Hypofractionated and Stereotactic Radiation Therapy

A Practical Guide

Orit Kaidar-Person
Ronald Chen
Editors

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Dr. Chen would like to dedicate this book to his wife Petronella Muresan, an incredible mother and outstanding statistician.

Preface

Radiation therapy (RT) continues to evolve rapidly as a result of improvements in imaging, advances in patient immobilization and treatment delivery technologies, and our understanding of radiobiology. There are currently two major trends in RT, shortening treatment (hypofractionation) and use of stereotactic radiosurgery and stereotactic body radiotherapy technologies. As published data continue to rapidly accumulate, these treatments are no longer exclusive to specialized centers. Shortening treatment is also appealing to patients because of increased convenience, less interference with planned systemic therapy, and is often less costly than conventionally fractionated (longer) RT courses.

This handbook was developed to summarize the data and techniques for hypofractionation and stereotactic radiation in a clinically accessible way, providing concise information ranging from commonly used dose-fractionation schemes to simulation and treatment specifications to published safety and efficacy data. While hypofractionation and stereotactic radiation are used in almost all cancer sites, we note where there are strong supportive data including randomized trials, and other areas where relatively little data are available to guide treatments. Further, we want to highlight that development of a stereotactic radiotherapy program requires specialized expertise and quality assurance procedures, which are described in Chap. 2.

We hope that you will enjoy the book as much as we enjoyed the process of developing it. This handbook was written to be practical, with usable information relevant for the clinician. We want to thank all the contributors of this book for their hard work and expertise.

Haifa, Israel — Orit Kaidar-Person
Chapel Hill, NC, USA — Ronald Chen

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Abbreviations

3D	3-Dimensional
3DCRT	3-Dimensional conformal radiotherapy
4D	4-Dimensional
4DCRT	4-Dimensional conformal radiotherapy
5-FU	5-Flourouracil
AA	Anaplastic astrocytoma
AAPM	American Association of Physicists in Medicine
Ab	Antibody
ABMT	Autologous bone marrow transplant
ABS	American Brachytherapy Society
abstr.	Abstract
ACOSOG	American College of Surgeon Oncology Group
ACS	American Cancer Society
ACTH	Adrenocorticotropic hormone
ADL	Activity of daily living
ADR	Adverse drug reaction
ADT	Androgen deprivation treatment
AE	Adverse event
AFP	Alpha fetoprotein
AIDS	Acquired immune deficiency syndrome
AJCC	American Joint Committee on Cancer
ALL	Acute lymphocytic leukemia
ALND	Axillary lymph node dissection
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMD	Dactinomycin
AML	Acute myeloid leukemia
AP	Anterior-posterior
APBI	Accelerated partial breast irradiation
APR	Abdominoperineal resection
ARC	Arc therapy

ASCO	American Society of Clinical Oncology
ASTRO	American Society for Therapeutic Radiology and Oncology
AUC	Area under the curve
AVM	Arteriovenous malformations
b.i.d	Twice a day (bis in die)
Bcc	Basal cell carcinoma
BCG	Bacillus Calmette-Guerin
BCS	Breast-conserving surgery
BCT	Breast-conserving treatment (lumpectomy and radiotherapy)
BED	Biological effective dose
BEV	Beam's eye view
BMJ	*British Medical Journal*
bPFS	Biochemical progression-free survival
BRCP	Borderline resectable pancreatic cancer
BUN	Blood urea nitrogen
Bx	Biopsy
c	Cycles (e.g., = for two cycles)
ca	Cancer
CALGB	Cancer and Leukemia Group B
CaSS	Cancer-specific survival
CBC	Complete blood count
CBCT	Cone beam CT
cc	Cubic centimeter
cCR	Clinical complete response
CEA	Carcinoembryonic antigen
CESS	German Cooperative Ewing's Sarcoma Study
cGy	CentiGray
Chemo	Chemotherapy
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Conformity index
CIS	Carcinoma in situ
cm	Centimeter
CN	Cranial nerve (e.g., CN X)
COG	Children's Oncology Group
CR	Complete response
Cr	Creatinine
CRC	Colorectal carcinoma
CRM	Circumferential resection margin
CRT	Chemo-radiotherapy
CSF	Cerebrospinal fluid
CSI	Craniospinal irradiation
CSS	Cause-specific survival
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CT-SIM	CT simulation

CTV_X	Clinical target volume x=1, 2, 3,…
Cu	Copper
CXR	Chest X-ray
CY	Cyclophosphamide
CyK	CyberKnife
D&C	Dilation and curettage
DCIS	Ductal carcinoma in situ
DES	Diethylstilbestrol
DFS	Disease-free survival
DIBH	Deep inspiration breath hold
dL	Deciliter
DLBCL	Diffuse large B cell lymphoma
DLCO	Diffusing capacity
DM	Distant metastases
Dmax	Maximum dose
DRE	Digital rectal exam
DRR	Digitally reconstructed radiograph
DSS	Disease-specific survival
DVH	Dose-volume histogram
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EBRT	External beam radiation therapy
EBUS	Endobronchial ultrasound
EBV	Epstein–Barr virus
ECE	Extracapsular extension
ECOG	Eastern Cooperative Oncology Group
ED	Erectile dysfunction
EDTA	Ethylendiaminetetraacetic acid
EFRT	Extended field radiotherapy
EFS	Event-free survival
EGD	Esophagogastroduodenoscopy
EGJ	Esophagogastric junction
ENT	Ear nose throat
EORTC	European Organisation for Research and Treatment of Cancer
EPID	Electronic portal imaging device
ER	Estrogen receptor
ERBB	Epidermal growth factor
ERCP	Endoscopic retrograde cholangiopancreatography
ESR	Erythrocyte sedimentation rate
ETE	Extra-thyroid extension
EtOH	Alcohol
EUA	Exam under anesthesia
EUS	Endoscopic ultrasound
F/U	Follow up
FDA	Food and Drug Administration
FDG	Fludeoxyglucose

FEV_1	Forced expiratory volume in 1 second
FFF	Freedom from failure
FFP	Freedom from progression
FFS	Failure-free survival
FH	Family history
FIGO	International Federation of Gynecology and Obstetrics staging system
FISH	Fluorescence in situ hybridization
FNA	Fine needle aspiration
FOBT	Fecal occult blood test
FSH	Follicle-stimulating hormone
FSRT	Fractionated stereotactic radiotherapy
FSU	Functional subunit
FWHM	Full width half maximum
fx	Fraction(s)
GaK	GammaKnife
GBM	Glioblastoma multiforme
GEC-ESTRO	Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology
GERD	Gastroesophageal reflux disease
GH	Growth hormone
GHSG	German Hodgkin's Study Group
GIST	Gastrointestinal stromal tumors
GITSG	Gastrointestinal Tumors Study Group
GOG	Gynecologic Oncology Group
GS	Gleason score
GTR	Gross total resection
GTV	Gross tumor volume
GU	Genitourinary
Gy	Gray
H&E	Hematoxylin and eosin
H&N	Head and neck
H&P	History and physical exam
HAART	Highly active retroviral therapy
Hb	Hemoglobin
Hcc	Hepatocellular carcinoma
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDR	High dose rate
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HNPCC	Hereditary nonpolyposis colon cancer
HNSqCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
HRT	Hormone replacement therapy

HSRT	Hypofractionated stereotactic radiotherapy
HT	Helical tomotherapy
HTN	Hypertension
HVL	Half-value layer
Hx	History
IC	Intracavitary
ICRU	International Commission of Radiation Units and Measurements
ICU	Intensive care unit
IDC	Invasive ductal carcinoma
IDL	Isodose line
IE	Ifosfamide and etoposide (VP-16)
IESS	Intergroup Ewing's Sarcoma Study
IFN	Interferon
IFRT I	Involved-field radiotherapy
IGRT	Image-guided radiotherapy
IJROBP	*International Journal of Radiation Oncology Biology Physics*
ILC	Invasive lobular carcinoma
IM	Internal margin
im	Intramuscular
IMN	Internal mammary nodes
IMRT	Intensity-modulated radiotherapy
INSS	International Neuroblastoma Staging System
Int	Intergroup
IORT	Intraoperative radiation therapy
IS	Interstitial
is	in situ
ISRT	Involved site radiotherapy
ITV	Internal target volume [ITV = CTV + IM]
iv	Intravenous
IVC	Inferior vena cava
IVP	Intravenous pyelogram
JCO	*Journal of Clinical Oncology*
JPA	Juvenile pilocytic astrocytoma
KPS	Karnofsky Performance Status
LAPC	Locally advanced pancreatic cancer
LAR	Low anterior resection
LC	Local control
LCIS	Lobular carcinoma in situ
LCSG	Lung Cancer Study Group
LDH	Lactate dehydrogenase
LDR	Low dose rate
LET	Linear energy transfer
LF	Local failure
LFFS	Local failure-free survival
LFTs	Liver function tests

LH	Luteinizing hormone
LINAC	Linear accelerator
LN	Lymph node(s)
LND	Lymph node dissection
LR	Local recurrence/relapse
LRC	Local-regional control
LRF	Local-regional failure
LRRFR	Locoregional recurrence-free rate
LVEF	Left ventricular ejection fraction
LVSI	Lymphovascular space invasion
m	Meter
MALT	Mucosa-associated lymphoid tissue
MFH	Malignant fibrous histiosarcoma
mg	Milligram
MHD	Mean heart dose
MLC	Multileaf collimator
MLD	Mean lung dose
mm	millimeter
mOS	Median overall survival
MRC	Medical Research Council
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MRSI	Magnetic resonance spectroscopy imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximal tolerated dose
MU	Monitor unit
MUGA	Multiple gated acquisition scan
N+	Node positive
N0	Node negative
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
NED	No evidence of disease
NEJM	*New England Journal of Medicine*
NHL	Non-Hodgkin's lymphoma
NPV	Negative predictive value
NPX	Nasopharynx
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSCLC	Non-small cell lung cancer
NSGCT	Nonseminomatous germ cell tumor
NTCP	Normal tissue complication probability
NWTS	National Wilms' Tumor Study
OAR	Organ at risk
OD	Oligodendroglioma
OPX	Oropharynx

ORN	Osteoradionecrosis
OS	Overall survival
PA	Posterior-anterior
PALN	Para-aortic lymph node
Pb	Lead
pCR	Pathologic complete response
PDR	Pulsed dose rate
PET	Positron emission tomography
PLAP	Placental alkaline phosphatase
PNET	Primitive neuroectodermal tumor
PNI	Perineural invasion
PORT	Postoperative radiotherapy
Post-op	Postoperative
PPV	Positive predictive value
pR	Partial response
PR	Progesterone receptor
Pre-op	Preoperative
PRL	Prolactin
prn	as required
PRV	Planning organ at risk volume [PRV = OAR + IM + SM]
PS	Performance status
PSA	Prostate-specific antigen
PTVx	Planning target volume x= 1,2…
PUVA	Psoralen and ultraviolet light A
q.d	Once daily
q.i.d	Four times a day (quater in die)
q.o.d	Every other day
QA	Quality assurance
QALY	Quality-adjusted life year
QC	Quality control
QOL	Quality of life
RAI	Radioactive iodine
RBE	Relative biological effectiveness
RCC	Renal cell carcinoma
Rct	Randomized controlled trial
RFA	Radiofrequency ablation
RFS	Relapse-free survival
RILD	Radiation-induced liver disease
RP	Radical prostatectomy
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
s/p	Status post
SBRT	Stereotactic body radiotherapy
SCID	Severe combined immunodeficiency
SCLC	Small cell lung cancer

SCV	Supraclavicular
SEER	Surveillance, Epidemiology, and End Results
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	Sacroiliac
SIADH	Syndrome of inappropriate antidiuretic hormone
SLNB	Sentinel lymph node biopsy
SM	Set up margin
SMA	Superior mesenteric artery
SMV	Superior mesenteric vein
SNUC	Sinonasal undifferentiated carcinoma
SOB	Shortness of breath
SPECT	Single-photon emission computed tomography
SPEP	Serum protein electrophoreses
SqCC	Squamous cell carcinoma
SRS	Stereotactic radiosurgery
STD	Sexually transmitted disease
STLI	Subtotal lymphoid irradiation
STR	Subtotal resection
SWOG	Southwest Oncology Group
T&O	Tandem and ovoid
t.i.d	Three times a day (ter in die)
TACE	Transarterial chemoembolization
TAH/BSO	Total abdominal hysterectomy/bilateral salpingo-oophorectomy
TBI	Total body irradiation
TBNA	Transbronchial needle aspiration
TCC	Transitional cell carcinoma
TCP	Tumor control probability
TG101	AAPM Task Force Group 101
TME	Total mesorectal excision
TMP/SMX	Trimethoprim/sulfamethoxazole
TMZ	Temozolomide
TNM	Tumor node metastasis
TPS	Treatment planning system
TRUS	Transrectal ultrasound
TSH	Thyroid-stimulating hormone
TTP	Time to tumor progression
TURBT	Transurethral resection of bladder tumor
UA	Urinalysis
UCSF	University of California, San Francisco
UKCCCR	United Kingdom Coordinating Committee on Cancer Research
UNC	University of North Carolina
UNC-CH	University of North Carolina Chapel Hill
UPEP	Urine protein electrophoreses
US	Ultrasound

USA	United States of America
USO	Unilateral salpingo-oophorectomy
UVB	Ultraviolet light B
VAC	Vincristine, actinomycin-D, and cyclophosphamide
VAIN	Vaginal intra-epithelial neoplasia
VCR	Vincristine
VDC	Vincristine, doxorubicin, cyclophosphamide
VDCA	Vincristine, doxorubicin, cyclophosphamide, and actinomycin-D
VEGF	Vascular endothelial growth factor
VM	Vincristine and melphalan
VMAT	Volumetric arc radiotherapy
VP-16	Etoposide
WART	Whole abdominal radiotherapy
Wbc	White blood cell count
WBI	Whole breast irradiation
WBRT	Whole brain radiotherapy
WHO	World Health Organization
WLE	Wide local excision

Chapter 1
The History and Radiobiology of Hypofractionation

Elaine M. Zeman

The use of hypofractionation in radiation therapy is not a new concept. In fact, it is a very old one, dating back to the first third of the twentieth century, the earliest days of the field that would evolve into today's specialty of radiation oncology. Since its earliest incarnation however, hypofractionation has been "repurposed" for today's use, thanks to more than a century of advances in physics and imaging that now allow most normal tissue to be excluded from the radiation field, something arguably inconceivable in 1900.

To better understand why hypofractionation was largely abandoned by the late 1920's, only to re-emerge at the beginning of the twenty-first century, an overview of the histories of both radiation therapy and radiation biology are in order. In many ways, these two disciplines evolved in parallel. With a few notable exceptions, for nearly 60 years advances in radiation therapy were empirically-based, and advances in radiobiology were seldom of clinical utility. This began to change during the 1950's.

1.1 Historical Context

1.1.1 The Early History of Fractionation in Radiotherapy

At the turn of the twentieth century, X-rays were discovered by German physicist Wilhelm Röentgen, who described them as invisible, "mysterious" emissions from energized vacuum tubes that were capable of producing fluorescence in platinocyanide salts [1]. The following year, French physicist Henri Becquerel identified similar emanations from natural substances—compounds of the element uranium—that didn't require an external energy source, yet like visible light,

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could expose photographic film [2]. Another year later, Pierre and Marie Curie identified and isolated some of the elements responsible for this "radioactivity" phenomenon, including radium, thorium and polonium [3]. That X-rays and radioactive sources (emitting γ−rays) had potential medical applications for both imaging and cancer treatment was immediately obvious, and between 1896 and 1900, the nascent field of radiation therapy, as practiced by dermatologists and surgeons of the day, had already claimed cures of both benign and malignant skin conditions [4–6].

In the earliest days of radiotherapy, both X-ray machines and radium applicators were used for cancer treatment, although the greater availability, convenience and portability of X-ray tubes afforded them a distinct advantage. Add to this the fact that X-ray machines offered, as the technology improved, much higher intensities of radiation output than low-activity radium sources, radiotherapy using X-rays (termed teletherapy) quickly became the international standard. Nevertheless, the use of radioactive sources continued to be developed and refined by the French, a practice that evolved into modern day brachytherapy.

Lacking an understanding at the time of the physical nature of ionizing radiation and how to quantify radiation dose, let alone an understanding of its biological effects, various "philosophies" developed as how best to treat patients. One fundamental radiotherapy principle was recognized from the outset however, and that was the concept of the therapeutic ratio, a risk-versus-benefit approach applied to treatment planning (Fig. 1.1).

In theory, any malignancy could be eradicated simply by delivering a sufficiently high radiation dose however in practice, injury to normal tissues that were necessarily irradiated along with the tumor limited the total dose that could be administered safely. Therefore, a balance had to be struck between what was considered an acceptable probability of radiation-induced damage to normal tissue, and the probability of tumor destruction.

Because surgeons were among the early practitioners of radiation therapy, from about 1900 into the 1920's a prevailing strategy was to view radiotherapy as akin to surgery, that is, to attempt to eradicate the tumor in a single procedure using a large, "tumoricidal" dose. This massive dose technique [7, 8] became a common way of administering radiation therapy, and a (somewhat arbitrary) biological interpretation was also provided: tumors would become increasingly resistant to radiotherapy if too many doses were given, and normal tissues would be preferentially damaged due to "cumulative injury", so it would be preferable to deliver the radiation therapy as one or a few large doses over no more than a few days [9]. However, it soon became obvious that this approach did not optimize the therapeutic ratio and that the biological rationale was incorrect; normal tissue complications were typically quite severe, and to make matters worse, the rate of local tumor recurrence was unacceptably high. An early example, in this case involving treatment of a benign lesion, is shown in Fig. 1.2.

As mentioned previously, radium therapy was used more extensively in France. Radium applications involved longer overall treatment times in order to reach total

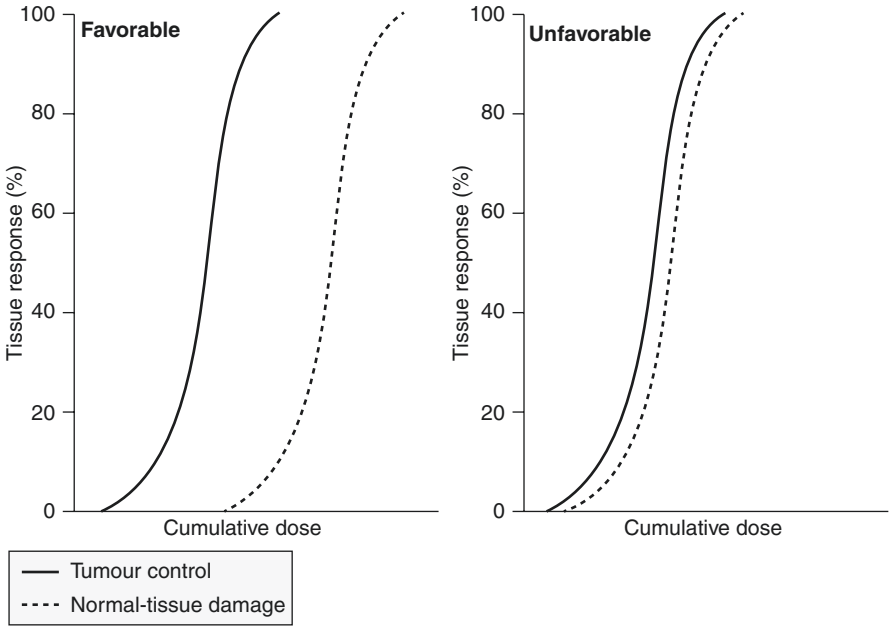

Fig. 1.1 The therapeutic ratio concept, depicted graphically. A favorable therapeutic ratio implies that the radiation response of the tumor is greater than that of the surrounding normal tissue (left panel). In the case of an unfavorable therapeutic ratio (right panel), there is no possibility of obtaining good tumor control without significantly damaging the normal tissue(s) at risk. (Adapted from Bernier et al. [7])

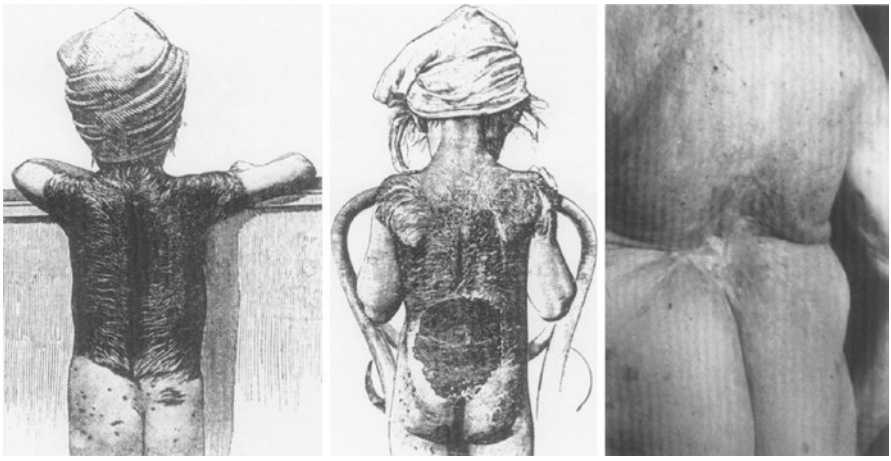

Fig. 1.2 Time course for radiation effects in the skin of a child treated during the "massive dose" era for an extensive hairy nevus before treatment (left), a week after the end of treatment (middle) and 75 years later (right). Acutely, the skin injury consisted of a large area of confluent moist desquamation, but over time, fibrosis, necrosis and poor wound healing was observed and persisted over the patient's lifetime. Few patients were cured using this large dose, large volume technique, and typically died long before normal tissue damage became manifest. In this particular case however, the (benign) hairy nevus was eradicated. (Adapted from Kogelnik [5])

doses comparable to those achieved with X-rays because of the low activity sources. Although multi-day treatments were less convenient in terms of patient throughput, clinical outcomes were often superior for skin and cervix cancers than for X-ray therapy. Brachytherapy proponents also offered a biological rationale, one that was better based on laboratory research than on theory or conjecture. As early as 1906, two French radiation biologists, Bergonié and Tribondeau, observed histologically that undifferentiated, rapidly-dividing spermatogonia of the rat testis showed evidence of damage at lower radiation doses than well-differentiated, non-dividing cells of the testicular stroma. Based on these observations, they put forth some basic "laws" stating that radiotherapy was selective for cells that were: (1) actively dividing; (2) capable of dividing for extended periods; and (3) poorly- or undifferentiated [10]. Based on the examination of surgical specimens, some tumors were already known to contain cells that were less differentiated and more proliferative than most normal tissues. Accordingly, Bergonié and Tribondeau reasoned that multiple radiation exposures would preferentially kill these tumor cells, while preserving their slowly-proliferating, differentiated counterparts in the normal tissues included in the radiation field.

During the 1920's, the massive dose technique began to fall out of favor, particularly in light of the pioneering experiments of Claude Regaud and colleagues, who built on Bergonié and Tribondeau's earlier work [11]. Regaud cleverly used the testes of the rabbit as a model system, reasoning that the process of sperm production (i.e., relatively undifferentiated cells proliferating rapidly and indefinitely) mimicked to a first approximation the behavior of tumors, and that the scrotum could be used as the dose-limiting normal tissue. Regaud showed that only through the use of multiple, smaller radiation doses could animals be completely sterilized without producing severe injury to the scrotum [12].

These principles were soon tested in the clinic by French physician Henri Coutard, who used multiple small X-ray doses delivered over extended periods in human patients [13]. Clinical outcomes for patients with head and neck cancer were improved to such an extent compared to patients receiving single, large doses that fractionated radiation therapy using many small dose increments spread over several weeks' time soon became the standard of care [13, 14], and has largely remained so to the present day.

Summary: Relevance to Today's Use of Hypofractionation

- During the early days of radiotherapy—the first 30 years of the twentieth century—extreme hypofractionation using one or a few very large doses was a treatment standard.
- It was subsequently abandoned when it became clear that tumor control was poor and normal tissue complications severe.
- Early research in radiation biology determined that the best way to optimize the therapeutic ratio was to deliver many small dose fractions over a period of weeks.
- Translating this information into the clinic, fractionated radiotherapy using small doses delivered over several weeks provided much improved outcomes, and became the new standard of care.

1.1.2 Isoeffect Relationships

Once fractionated radiotherapy became the new standard of care a different problem emerged, namely how different practitioners with somewhat different approaches to fractionation, e.g., how many fractions delivered, time between fractions, total dose, overall treatment duration, etc., could be inter-compared in terms of tumor control and normal tissue complication probabilities. One approach was to determine "equivalents", that is, treatment combinations that yielded similar outcomes. Time-dose equivalents for skin erythema were published by several investigators [15–18] and these formed the basis for the calculation of equivalents for other normal tissue and tumor responses. By plotting the total dose required for a particular equivalent in a particular tissue, as a function of one of the variable treatment parameters (overall treatment time, number of fractions, dose per fraction, etc.), a so-called "isoeffect" curve could be derived. Accordingly, all time and dose combinations that comprised an isoeffect curve for a certain endpoint would, theoretically, produce tissue or tumor responses of equal magnitude.

Also better appreciated during the 1930's was how and when normal tissue complications occurred after treatment, and their severity as a function of total dose. Presumably, these complications were the result (directly or indirectly) of the killing of critical cells within the tissue, so the higher the radiation dose, the more cells were killed and the more severe the complication. It was also clear that skin, the dose-limiting normal tissue in most cases, could manifest more than one complication and that each seemed to have its own threshold or tolerance dose before the complication occurred, a reflection of the tissue's radiosensitivity. However, the "earliness" or "lateness" of the clinical manifestation of that injury was a separate phenomenon more related to the cellular renewal pattern of the tissue.

The first published isoeffect curves were produced by Strandqvist in 1944 [19], and shown in Fig. 1.3. When plotted on a log-log scale of total dose versus overall treatment time, isoeffect curves for a variety of skin reactions, and the cure of skin cancer, were drawn as parallel lines.

As drawn, Stranqvist's isoeffect curves suggested that there would be *no* therapeutic advantage to using prolonged treatment times and multiple small dose fractions for the preferential eradication of tumors while staying within the tolerance of the normal tissue [20]. Ironically however, it was already known that the therapeutic ratio *did* increase with prolonged, as opposed to very short, overall treatment times. Nevertheless, the reliability of these curves at predicting skin reactions, which were the dose limiting factors at the time, made them quite popular.

Nearly 25 years after Strandqvist, Ellis [21, 22] revisited his popular isoeffect curves, and armed with new knowledge about the radiobiology underlying fractionation effects in pig skin [23, 24], formulated the NSD concept in 1969. The NSD equation,

$$D = \left(\mathrm{NSD}\right) N^{0.24}\, T^{0.11},$$

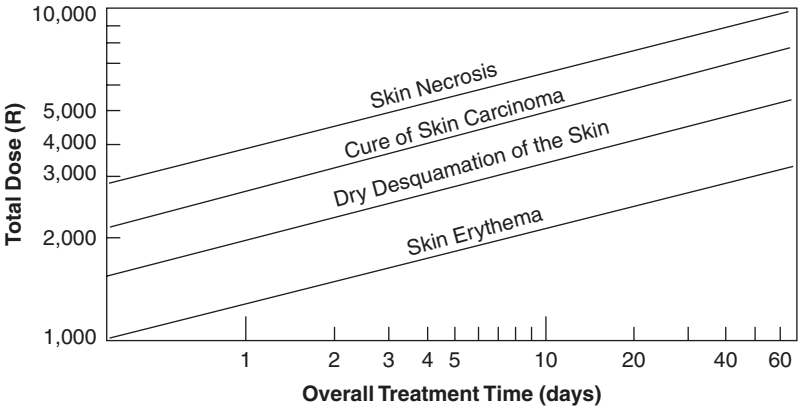

Fig. 1.3 Strandqvist's isoeffect curves, first published in 1944, plotted the log of the total dose to achieve the measured isoeffect as a function of the overall treatment time. The shorter the overall treatment time, the more hypofractionated the schedule, and the lower the dose required to produce the isoeffect. (Modified from Strandqvist [19])

where D is the total dose delivered, N the number of fractions used, T the overall treatment time, and NSD the nominal standard dose (a proportionality constant related to the tissue's tolerance), became widely used, particularly once mathematically simplified derivatives, such as the TDF equation [25] became available. The major innovation of the NSD model was that the influence of the fraction number had been separated from the influence of the overall treatment time, and in fact, the fraction number (and therefore, size) was the more important of the two.

The introduction of the NSD equation allowed radiotherapy treatment practices world-wide to be compared and contrasted with respect to putative "biological equivalence", provided it was not used for treatments involving extremes of fraction number or overall time outside the range of the data upon which the model was based (i.e., Strandqvist's curves). It also provided a means of revising treatment prescriptions in the event of unforeseen treatment interruptions. However, the NSD formula was ill-equipped to deal with some clinical issues, in particular the prediction of late effects in normal tissues, which, with the advent of megavoltage linear accelerators capable of treating deep-seated tumors, replaced skin as being dose-limiting [26]. In light of the growing frustration with the NSD model, there was a need for new, radiobiologically-based approaches to isoeffect modeling.

Summary: Relevance to Today's Use of Hypofractionation

- Isoeffect curves plot the total dose required for a particular tumor or normal tissue endpoint as a function of one of the variable treatment parameters, such as overall treatment time or number of fractions. All time-dose combinations that fell on a particular isoeffect curve were considered biologically equivalent.

- Isoeffects of interest included tumor control and various normal tissue complications, typically in skin, such as desquamation, necrosis or fibrosis.
- Some complications occurred during or soon after the completion of radiotherapy, "early effects", and others took months or years to manifest, "late effects".
- The total dose required to cause a particular complication was a reflection of the tissue's radiosensitivity, but the time it took for the complication to appear was related to the tissue's natural cell renewal process.
- A mathematical model derived from isoeffect curves, the NSD equation, allowed the calculation of biological equivalents for different treatment schedules. Yet because the model was based on early skin reactions, it was poorly-equipped to model late complications in normal tissues. With the advent of megavoltage radiotherapy equipment that allowed treatment of deep-seated tumors, damage to internal organs rather than skin became dose-limiting, and many of these expressed their injuries as late effects.

1.1.3 Tumor Hypoxia

As early as 1909, it was recognized that decreasing blood flow during radiotherapy lead to a reduction in the prevalence or severity of radiation-induced skin reactions [7, 8], although at the time, the mechanism for this effect was unclear. Decades later, chemists and biologists determined that the presence or absence of oxygen was the key, and that the mechanism of oxygen's action was to interact with free radicals produced during irradiation, thereby enhancing the damage to cellular macromolecules. In other words, oxygen acted as a radiation sensitizer. Thus, the relative *absence* of oxygen in an irradiated system meant less molecular damage, and therefore, greater radioresistance.

In 1955 however, Thomlinson and Gray [27] brought this idea to the forefront of radiation biology and radiation therapy by proposing that tumors contained a fraction of oxygen-starved yet still reproductively viable (i.e., "clonogenic") hypoxic cells and that if these persisted throughout the course of fractionated radiotherapy, they would adversely affect the therapeutic ratio. The oxygen enhancement ratio (OER) is a metric developed to quantify how much more radioresistant hypoxic cells were than well-aerated ones. For large, single radiation doses, OER values of 2.5–3.0 were typical, but for conventional radiotherapy using repeated, small dose fractions delivered over several weeks, the OER was lower, typically in the range of 1.5–2.0 [28].

Accordingly, if human tumors contained even a tiny fraction of clonogenic hypoxic cells, simple calculations suggested that tumor control would be nearly impossible [29], even for high doses. The total dose needed to control such tumors would become prohibitive because normal tissues are not hypoxic and therefore would experience higher complication rates if the total dose were increased. In fact, the only way that hypoxic tumor cells would *not* constitute a treatment impediment was if extended periods of hypoxia eventually led to their deaths and/or that they "reoxygenated" during the course of treatment (see below).

Hypoxia is a consequence of the abnormal vasculature characteristic of tumors. Such blood vessels are the product of abnormal angiogenesis and often are structurally, functionally, physiologically and/or spatially aberrant which, when combined with the tumor's high oxygen demand and tendency to outgrow its own blood supply, leads to both micro- and macro-regions of hypoxia.

Summary: Relevance to Today's Use of Hypofractionation

- Molecular oxygen interacts with free radicals produced during irradiation, enhancing cellular damage. Hypoxic cells that are low in oxygen, but not so low as to result in lethality, can be up to three times more radioresistant than well-aerated ones.
- Vascular abnormalities characteristic of tumors lead to both micro- and macro-regions of hypoxia. Hypoxia is largely absent in normal tissues.
- Simple calculations suggest that tumor control would be impossible—even for the high doses used today in extreme hypofractionation—if human tumors contained even a tiny fraction of clonogenic hypoxic cells, provided they persisted throughout the course of radiotherapy.

1.1.4 The Four R's of Radiotherapy

What was largely lacking during radiotherapy's first half-century was a biological basis for why dose fractionation spared normal tissue complications, and without this information it was very difficult to determine which biological characteristics of normal or tumor tissues might be exploited to improve the therapeutic ratio. This began to change with the publication in 1975 of a seminal paper entitled "*The Four R's of Radiotherapy*" [30]. The paper was an attempt to explain the biological basis of fractionation by describing in simple terms key radiobiological phenomena thought to affect radiotherapy outcome: *R*epair, *R*epopulation, *R*eoxygenation and *R*edistribution. In the ensuing years, a fifth "R" was added, *R*adiosensitivity [31], although in many respects, it is inextricably linked to repair. (Redistribution is difficult to measure, yet is assumed to occur in vivo during conventional fractionation. However, it is thought to play only a minor role in treatment outcome and likely has even less of a role for hypofractionation, so will not be discussed further.)

1.1.5 Repair/Radiosensitivity

The surviving fraction of cells following a moderate-to-high radiation dose is higher if that dose is split into two increments separated by a time interval than delivered as a single dose, suggesting that cells surviving the initial dose had repaired some of the damage during the radiation-free interval [32]. As such, this damage was no longer available to interact with the damage inflicted by the second dose, so a higher

cell surviving fraction resulted. This phenomenon is termed sublethal damage repair (SLDR). These "split-dose" experiments turned out to be crucial to the understanding of why and how fractionated radiation therapy works, that is, that SLDR was responsible for the greater radiation tolerance of tissues when a large total dose was divided into small dose fractions and protracted over time.

However, this sparing effect of dose fractionation does not continue indefinitely as smaller and smaller (and more numerous) doses are delivered. Instead, a limit is reached where further lowering of the dose per fraction does not produce a further decrease in toxicity. This finding is consistent with the idea that survival and dose response curves have negative initial slopes [33, 34], and that after many, sufficiently small dose fractions are delivered, a "trace" of this initial slope would be obtained.

One important clinical implication of repair and radiosensitivity phenomena is that small differences in shoulder regions of dose response curves for different dose-limiting normal tissues and tumors could be magnified into large differences when many small dose fractions are used compared to a single or a few large fractions. A tissue's radiosensitivity and repair capacity are critically important to the selection of the total dose, dose per fraction and interfraction interval used for radiation therapy, as they govern both the tumor control and normal tissue complication probabilities.

1.1.6 Repopulation

Repopulation is defined as an increase in cell proliferation in tissues in response to an injury that produces cell killing. Normal tissues and tumors containing stem or stem-like cells can begin to proliferate during and after a course of radiation therapy, with the timing of this response a function of the proliferation kinetics of the tissue [35, 36], typically during or within 3 months of treatment for "early-responding" normal tissues and most tumors, and more than 6–9 months (if at all) for "late-responding" tissues.

Repopulation is desirable in normal tissues because it facilitates the healing of common radiotherapy complications that develop during or soon after treatment, such as oral mucositis, for example. On the other hand, repopulation of tumor cells is undesirable because it would have the net effect of counteracting ongoing radiation therapy, which in turn would lead to the appearance of tumor "radioresistance" and accordingly, the attendant risk of recurrence. For tumors capable of rapid repopulation that begins during conventional radiotherapy, estimates are that as much as a third (and sometimes more) of the daily dose fraction is wasted simply trying to counteract the production new cells.

Although the killing of cells by ionizing radiation can stimulate repopulation, another radiation effect has the potential to slow or stop it, and that is that radiation exposure introduces blocks and delays in cell cycle transit, which, while transient for lower doses, could become permanent for higher ones. The principal

causes of this are dose-dependent blocks in the G_2-to-M phase transition and in the G_1-to-S phase transition, the latter typically more prominent in normal cells than malignant ones.

The critical clinical parameter that determines the influence of repopulation on treatment outcome is the overall treatment time. Shorter overall times—like those used for hypofractionation—would limit the potential for repopulation to negatively affect tumor control, albeit at the risk of exacerbating effects in early-responding normal tissues that depend on repopulation for healing.

1.1.7 Reoxygenation in Tumors

The identification of clonogenic, radioresistant hypoxic cells in rodent and human tumors suggests that tumor control with radiotherapy could be compromised, and yet obviously, many therapeutic successes do occur. This suggests that some form of reoxygenation must take place during the course of fractionated radiotherapy.

Are there different types of tumor hypoxia, and by extension, are there also different types of and time scales for reoxygenation? The type of hypoxia initially described by Thomlinson and Gray [27] is termed chronic, or diffusion-limited hypoxia, resulting from the tendency of tumors to have high oxygen consumption rates and to outgrow their own blood supply. Cells situated well beyond the diffusion distance of oxygen likely would be dead or dying (of nutrient deprivation and anoxia), yet in regions of chronically low oxygen—on the order of 0.5% oxygen tension, corresponding to about 10 ppm O_2 or less [37]—clonogenic and radioresistant hypoxic cells could persist. Should the tumor shrink as a result of radiation therapy, or, if the cells killed by radiation cause a decreased demand for oxygen, it is likely that this would allow some of the chronically hypoxic cells to reoxygenate. However, such a reoxygenation process would be slow—typically on the order of days or weeks—depending on the regression rates of tumors during treatment. Reoxygenation in some rodent tumors does occur over such time scales, but for others, reoxygenation is considerably faster, on a time scale of minutes to hours [38], and in the absence of either reduced oxygen utilization by tumor cells or tumor shrinkage.

During the late 1970's, Brown and colleagues [39] proposed that a second type of hypoxia must exist in tumors, an acute, intermittent type that occurred secondary to abnormal vascular physiology. Intermittent hypoxia has since been demonstrated unambiguously in rodent tumors [40], and, using hypoxia markers detected noninvasively using PET scanning, in human head and neck cancer patients [41]. There are multiple mechanisms to account for intermittent hypoxia including, but not limited to: temporary vessel blockage; vascular shunting; and vessel compression due to high interstitial fluid pressure in the tumor microenvironment [41]. Most of these would cause transient hypoxia of minutes to hours duration.

Regardless of type or mechanism, the clinical implication of reoxygenation of hypoxic tumor cells is that it would increase the therapeutic ratio, assuming that

normal tissues remained well-oxygenated. The overall treatment time would seem critical however, with overall times of several weeks in theory allowing "full" reoxygenation to occur and short overall treatment times running the risk of incomplete reoxygenation. Because of this, reoxygenation is thought to be a major factor in the radiosensitization of tumors during conventionally-fractionated radiation therapy. Unfortunately, this might not be the case for shorter, hypofractionated schedules.

Summary: Relevance to Today's Use of Hypofractionation

- The five R's of radiotherapy are radiosensitivity, repair, repopulation, reoxygenation and redistribution. These fundamental radiobiological phenomena provide a basis for how best to maximize tumor cell kill and avoid normal tissue toxicity during conventional radiotherapy.
- Radiosensitivity and repair are closely linked, and to best spare normal tissues, repair must be maximized.
- Accelerated repopulation in response to radiation injury is desirable for early-responding normal tissues, as it facilitates healing. In general, late-responding normal tissues cannot accelerate their proliferation in response to injury, and even among those that can, it would take months to occur, long after the completion of radiotherapy.
- Repopulation in tumors is undesirable, as it counteracts the toxicity of the radiotherapy, possibly culminating in treatment failure. Shorter overall treatment times, like those used for hypofractionation, would provide less time for tumor repopulation.
- Of the five R's, the only one unique to tumors is reoxygenation. In the absence of reoxygenation, tumors containing even a small fraction of clonogenic hypoxic cells would become nearly impossible to cure with radiotherapy. Depending on the type(s) of hypoxia present in tumors, reoxygenation can occur over timescales of minutes, hours or days.
- The shorter overall treatment times characteristic of hypofractionation may not allow sufficient time for tumor reoxygenation to occur, leading to treatment resistance.

1.1.8 The Linear-Quadratic Isoeffect Model

1.1.8.1 α/β Ratios

The beginnings of the linear-quadratic (LQ) isoeffect model can be traced to the ambitious multifractionation experiments in mice by Douglas and Fowler [42], where a broad range of fraction sizes, numbers and inter-fraction intervals was used and acute skin reactions in the mouse foot evaluated. They developed a novel method of interpreting their data by creating a new type of isoeffect curve, termed a "reciprocal dose plot", where the reciprocal of the total dose delivered was plotted as a function of the dose per fraction. From such a plot, a fractionation sensitivity metric could be derived for mouse skin which, borrowing the framework of the LQ

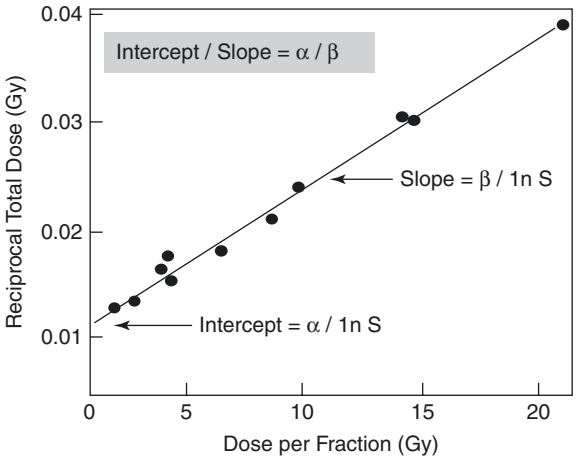

Fig. 1.4 The reciprocal dose plot technique of Douglas and Fowler {Douglas and Fowler, 1976, #231}, used to determine a normal tissue's or tumor's α/β ratio. Using this method, the reciprocal of the total dose necessary to reach a given isoeffect is plotted as a function of the dose per fraction. Assuming that the tissue's fractionation response can be modeled using the linear-quadratic expression, $S = e^{-(\alpha D + \beta D_2)}$, the α/β ratio can be obtained from the ratio of the isoeffect curve's intercept to its slope. See text for details. (Modified from Douglas and Fowler [42])

survival curve expression, was termed the skin's "α/β ratio". Fractionation data that adhered to the LQ formalism would produce a straight line on such a plot. The α/β ratio in turn was used to generate a pseudo dose response curve, the shape of which provided clues as to the tissue's overall radiosensitivity and repair competency. A representative reciprocal dose isoeffect curve is shown in Fig. 1.4.

More widespread use of this technique over time showed that in most cases, there was a systematic difference between early- and late-responding normal tissues in terms of their α/β ratios and significantly, that the majority of tumors behaved like early-responding tissues. The α/β ratios were typically low for late-responding tissues (about 1 to 6 Gy, with an average of about 3 Gy), and high for early-responding tissues and tumors (about 7 to 20 Gy, with an average of about 10 Gy). Select α/β ratios for human normal tissues are shown in Table 1.1. It is worth noting however that there are exceptions to these general trends, in particular that prostate cancer, and to a lesser extent breast cancer, have low rather than high α/β ratios, meaning that their fractionation sensitivities are more like those of late-responding normal tissues. This finding was a major impetus in the return of hypofractionation.

1.1.9 Steep vs. Shallow Isoeffect Curves

However, many found the use of reciprocal doses confusing and unwieldy, preferring more traditional isoeffect curves like those of Strandqvist. Accordingly, Thames, Withers, Peters and colleagues [44–46] replotted data obtained from

Table 1.1 α/β ratios for select human normal tissues and tumors

Tissue type (and endpoint)	α/β ratio (±95% confidence interval)
Early-responding normal tissues	
Skin:	
Erythema	10.6 (1.8; 22.8) Gy
Desquamation	11.2 (8.5; 17.6) Gy
Lung: Pneumonitis ≤90 days after radiotherapy	>8.8 Gy
Oral mucosa: Mucositis	8–15 Gy
Late-responding normal tissues	
Skin:	
Telangiectasia	~ 2.7 (−0.1; 8.1) Gy
Fibrosis	1.7 (0.6; 3.0) Gy
Breast:	
Cosmesis	3.4 (2.3; 4.5) Gy
Fibrosis	3.1 (1.8; 4.4) Gy
Lung:	
Pneumonitis >90 days after radiotherapy	4.0 (2.2; 5.8) Gy
Fibrosis	3.1 (−0.2; 8.5) Gy
Bowel:	
Perforation/stricture	3.9 (2.5; 5.3) Gy
Various other	4.3 (2.2; 9.6) Gy
Spinal cord: Myelopathy	<3.3 Gy
Tumors	
Head and neck:	
Vocal cord	~13 Gy
Tonsil	7.2 (3.6; ∞) Gy
Larynx	14.5 (4.9; 24) Gy
Lung: Squamous cell carcinoma	~50–90 Gy
Cervix: Squamous cell carcinoma	>13.9 Gy
Skin: Squamous cell carcinoma	8.5 (4.5; 11.3) Gy
Prostate	1.8 (−3.3; 5.6) Gy
Breast	4.6 (1.1; 8.1) Gy

Data from Joiner and van der Kogel [43]

fractionation experiments in rodents as the log of the total dose on the y-axis and the log of dose per fraction on the x-axis, with this axis reversed to better align with Stranqvist's original curves (where overall time rather than dose per fraction was used). When plotted in this manner, isoeffect curves for late-responding normal tissues were steeper than those for early-responding normal tissues, and significantly, most tumors. A steep isoeffect curve implied a greater sensitivity to changes in dose per fraction, experiencing greater sparing with decreasing fraction size (i.e., a higher tolerance dose for the isoeffect) and greater damage with increasing fraction size (i.e., a lower tolerance dose for the isoeffect). On the other hand, a shallow isoeffect curve suggested less sensitivity to changes in dose per fraction, that is, less "swing" in tolerance doses when the fraction size was changed. Isoeffect curves plotted in

this manner for several normal tissue complications, along with a few corresponding to tumor control doses, are shown in Fig. 1.5.

These authors also discussed in detail the various assumptions implicit in the "repurposing" of the LQ model for clinical use as a measure of fractionation sensitivity. Perhaps the most egregious of the assumptions was that an isoeffect in a tissue represented an isosurvival of the cells whose deaths precipitated the effect [44, 45]. This is clearly a gross oversimplification of what is now known (and was suspected even then) about the etiology of normal tissue complications, late effects in

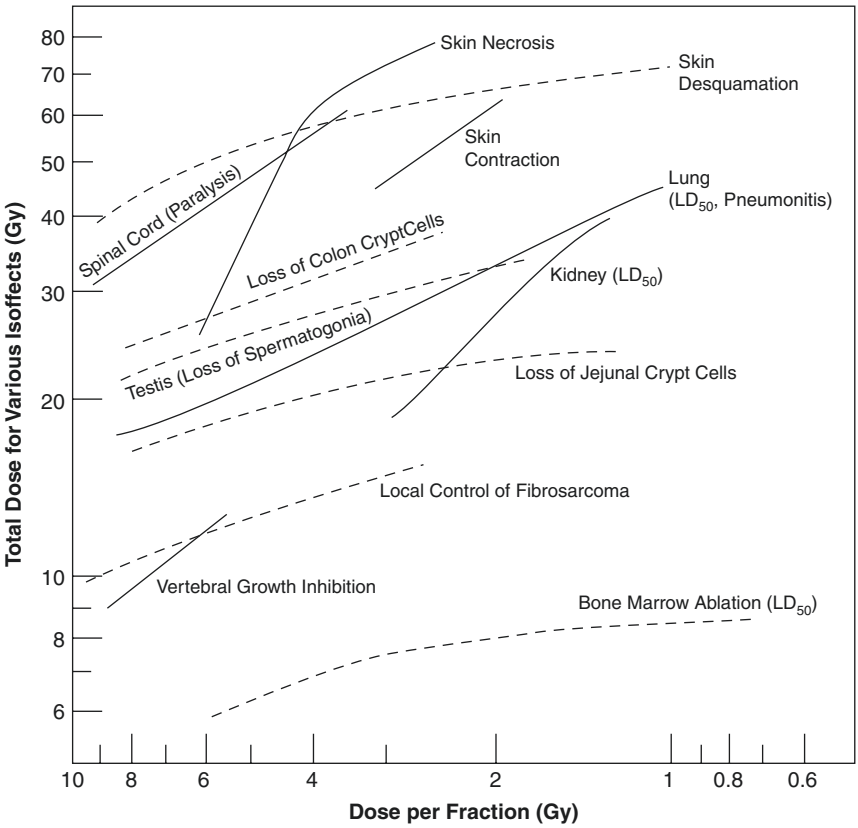

Fig. 1.5 Isoeffect curves in which the total dose necessary to produce a certain normal tissue or tumor endpoint (as indicated on graph) is plotted as a function of the dose per fraction, under conditions where cell proliferation is negligible. Isoeffect curves for late responding normal tissues (solid lines) tend to be steeper than those for early responding normal tissues and most tumors (dashed lines). This suggests that, for the same total dose, late reactions may be spared by decreasing the size of the dose per fraction used (hyperfractionation). However, in the case of a tumor with a steep isoeffect curve, it would be preferentially damaged by using higher doses per fraction ((hypofractionation). (Modified from Withers et al. [45])

particular. They develop over extended periods of time as a result of highly complex and dynamic molecular processes involving multiple, interacting cell types rather than a single putative "target cell". Nevertheless, this assumption was necessary, that is, that normal tissue complications were *initiated* by the killing of cells with unique radiosensitivities, in order to justify using a cell survival curve expression to model fractionation effects in vivo.

This assumption is also the probable source of a common misconception about the *LQ isoeffect model*, namely that the α/β ratios quoted for tumors and normal tissues are derived from cell survival curves fitted to the *LQ survival curve model*. This is not and never has been the case; α/β ratios used clinically are derived from multifraction experiments in vivo, and are a reflection of, at best, a composite dose response curve that likely has been further modified by the influence of the five R's. One important corollary is that these dose response curves are *not* quantitative in the same sense cell survival curves are, and treating them as such is, arguably, inappropriate.

Tissue dose response curve shapes consistent with the calculated α/β ratios and steep-vs.-shallow isoeffect curves are shown in Fig. 1.6.

The steeper initial slope in the low dose region for tissues with high α/β ratios (early-responding normal tissues and most tumors) accounts for their reduced sensitivity to changes in dose per fraction. Conversely, the shallower initial slope for late-responding normal tissues and the few tumors with low α/β ratios accounts for their high sensitivity to changes in dose per fraction. The use of low doses per fraction would preferentially spare these tissues, whereas high doses per fraction would be preferentially damaging.

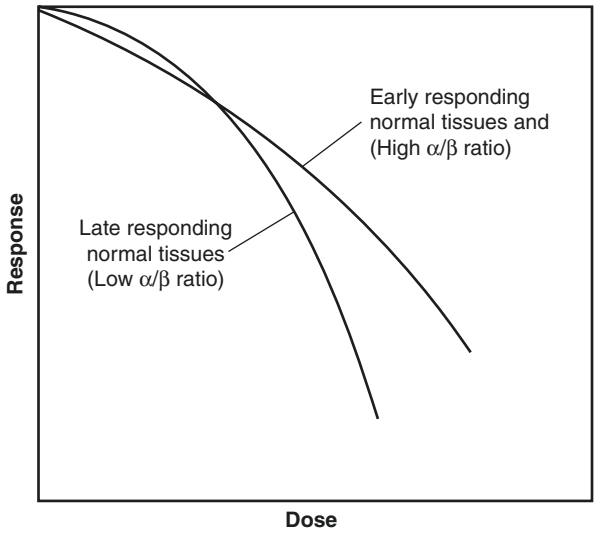

Fig. 1.6 Putative dose response curves for normal tissues and tumors generated from α/β ratios determined in fractionation experiments in vivo. Note that the shapes of these curves, particularly in the low dose region (governed mostly by the α-component), are assumed to account for the differences in fractionation sensitivity of the different tissues. (Modified from Zeman et al. [47])

1.1.10 Hyper- Vs. Hypofractionation

It was immediately evident that the differences in fractionation response between tumors and normal tissues could be exploited for clinical benefit. For example, it might be possible to increase the therapeutic ratio by sparing late normal tissue complications through the use of larger numbers of smaller fractions to a somewhat higher total dose than traditionally used [46, 48, 49], in the hopes that the higher total dose would be sufficient to control a tumor that is relatively insensitive to the change in the dose per fraction. This is termed hyperfractionation. The opposite strategy is also possible, namely to use fewer, larger dose fractions (typically to a lower total dose compared to conventional treatment) in order to preferentially damage those few tumors with low α/β ratios and steep isoeffect curves. This is called hypofractionation. At the time the LQ isoeffect model was first developed however, hypofractionation was strongly discouraged because it would likewise exacerbate late effects in incidentally irradiated normal tissues, as had been amply demonstrated during the early days of radiotherapy.

1.1.11 Biologically Effective Doses (BEDs)

The shapes of tissue and tumor isoeffect curves and their associated α/β ratios have a number of clinical applications. For example, α/β ratios can be used to equate treatment schedules employing different-sized doses per fraction in order to match the probability of causing a particular complication [45, 50, 51]. The equation,

$$D_2/D_1 = (\alpha/\beta + d_1)/(\alpha/\beta + d_2)$$

can be used for this purpose, where D_1 and d_1 are, respectively, the total dose and dose per fraction of one treatment prescription, and D_2 and d_2 are the total dose and dose per fraction for an alternate treatment plan designed to be biologically equivalent.

However, it is not sufficient to plan for biological equivalence based on a single normal tissue at risk with its α/β ratio, but rather, in keeping with the concept of therapeutic ratio, it should also be assessed for the tumor with its, presumably different, α/β ratio. In this way, the change in normal tissue tolerance dose *and* tumor control dose can be assessed simultaneously when considering a change in fractionation pattern.

The "biologically effective dose" or BED method [50, 52], another derivative of the LQ model, attempts to address this. Because tissue dose response curves have negative initial slopes, the question may be asked, *"In the limit, for an infinite number of infinitely small dose fractions, what total dose would correspond to normal tissue tolerance or tumor control?"* Clearly, this theoretical dose would be quite large for a tissue characterized by a dose response curve with a shallow initial slope and low α/β ratio, and appreciably smaller for a tissue characterized by a dose response curve with a steep initial slope and high α/β ratio.

The equation,

$$\mathrm{BED} = \mathrm{nd}\left(1 + \frac{d}{\alpha / \beta}\right)$$

is used to calculate the BED for tissues with different α/β ratios. In this equation, n is the number of fractions, d is the dose per fraction, and the α/β ratio is specific for the tissue at risk.

In using BEDs to compare likely outcomes for two different fractionation schedules, two important points need to be borne in mind. The first is to understand that BEDs are not real doses, but rather extrapolates based on the α-components of the dose response curves for the tissues at risk. For this reason, the units used to describe these extrapolated doses are, for example, "Gy_3's" and "Gy_{10}'s", rather than "Gy's", where the subscripts 3 and 10 refer to the α/β ratio (in Gy) of the tissue. Gy_3's can be compared qualitatively with Gy_3's for different fractionation schedules, and Gy_{10}'s with Gy_{10}'s, however, Gy_3's and Gy_{10}'s cannot be inter-compared.

Representative BED values for conventional, hyperfractionated and hypofractionated radiotherapy treatments are shown in Table 1.2.

The second important point is that BEDs are necessarily qualitative. By way of example from Table 1.2, a comparison of conventional fractionation (e.g., 30 fractions of 2 Gy) with a hypofractionated regimen (e.g., 3 fractions of 15 Gy), the BEDs for both early (Gy_{10}) and late (Gy_3) endpoints increase, suggesting that the hypofractionated schedule would be "hotter" in terms of complication likelihood, approximately 1.5 times hotter in the case of early effects (and tumor control, in most cases) and almost 3 times hotter for late effects (and a few tumors). However, this does not mean that the normal tissue complication or tumor control frequencies in this example would likewise increase exactly 1.5 or 3-fold, only that the probabilities of such complications might be expected to increase by using hypofractionation compared to standard fractionation. In fact, using head and neck cancer as an example, Fowler and colleagues [53, 54] suggested that only changes in BED of more than about 15–20% would yield clinically detectable changes in complication or tumor control frequency.

Table 1.2 Illustrating the use of BEDs to compare and contrast conventional, hyperfractionated and hypofractionated treatment schedules for tissues with α/β ratios of 10 Gy versus 3 Gy

30 × 2 Gy = 60 Gy	BED of 72 Gy_{10} and 100 Gy_3	Conventional
35 × 1.8 Gy = 63 Gy	BED of 74.3 Gy_{10} and 100.8 Gy_3	
68 × 1.2 Gy = 81.6 Gy	BED of 91.4 Gy_{10} and 114 Gy_3	Hyperfractionated
70 × 1.15 Gy = 80.5 Gy	BED of 89.8 Gy_{10} and 111.4 Gy_3	
20 × 2.8 Gy = 56 Gy	BED of 71.7 Gy_{10} and 108 Gy_3	Hypofractionated
16 × 3.4 Gy = 54.4 Gy	BED of 73 Gy_{10} and 116.1 Gy_3	
3 × 15 Gy = 45 Gy	BED of 112.5 Gy_{10} and 270 Gy_3	

Summary: Relevance to Today's Use of Hypofractionation

- The sensitivity of normal tissues and tumors to changes in dose per fraction can be expressed qualitatively either in terms of an α/β ratio (low for late-responding tissues and high for early responding ones) or isoeffect curve slopes (steep for late-responding tissues and shallow for early responding ones).
- Both metrics use the LQ survival curve model as a conceptual framework, but otherwise are derived solely from multifraction experiments conducted in vivo, not from cells irradiated in vitro.
- A third metric of interest is the biologically effective dose or BED, a theoretical, extrapolated total dose to achieve a particular isoeffect, pegged to a tissue's α/β ratio. BEDs are used to compare and contrast different radiotherapy treatment prescriptions with respect to how both normal tissue tolerance and tumor control change.
- Because BEDs are theoretical and not actual doses, they are expressed in a different dose unit, for example, Gy_3's or Gy_{10}'s, with the subscript identifying which α/β ratio was used to derive it. Gy_3's can be compared qualitatively with Gy_3's, and Gy_{10}'s with Gy_{10}'s, but not with each other.

1.2 Hypofractionation Today

The stereotactic delivery of radiation therapy has been considered for many decades, however only over the last decade has there been a marked increase in use of this approach thanks to advances in treatment technology. Stereotactic radiosurgery (SRS), limited to small primary and metastatic brain lesions, is generally delivered as a single, large dose of approximately 20 Gy or more. The term radiosurgery was first coined by neurosurgeon Lars Leskel in 1951 [55]. Stereotactic body radiation therapy (SBRT), sometimes called stereotactic ablative radiotherapy (SABR), is used in select cases for small, extracranial tumors and is typically delivered in 1–5 fractions of 7–20 Gy each [56]. Both of these approaches necessarily involve "extreme" hypofractionation.

The reader should be aware that there are other radiotherapy treatment regimens, more reminiscent of conventional radiotherapy, involving "milder" forms of hypofractionation using doses per fraction in the 2–4 Gy range [57]. However, these approaches are not necessarily intended to be ablative, involve larger treatment volumes than used in SRS and SBRT, and for some, overall treatment times extend several weeks.

One advantage of SRS and SBRT over conventional external beam radiotherapy is obvious, namely that overall treatment times are much shorter, which is not only of practical convenience for patients and facilitates multi-modality treatment, but also may offer radiobiological advantages as well.

The biological underpinnings associated with today's use of hypofractionation remain poorly defined however, and the subject of considerable controversy with some defending the use of "classical" radiation biology concepts and the LQ model (e.g., [58–61]), and others claiming that "new biology" uniquely associated with the

high doses used in SRS and SBRT isn't explained sufficiently by classical concepts and therefore invalidates the use of the LQ model (e.g., [62–66]). Part of the problem is that the *clinical* rationale for the use of SRS or SBRT/SABR is different from that of conventional and hyperfractionation. The goal of the former is to completely ablate small lesions, with the likelihood of producing normal tissue complications of lesser concern—with certain caveats—due to the more precise tumor targeting and small volumes of normal tissue incidentally irradiated. In contrast, both conventional and hyperfractionated radiation therapy are driven principally by the *avoidance* of normal tissue complications, particularly late complications, and within those constraints, a hopefully sufficient total dose to achieve good tumor control.

What isn't controversial however is that SRS and SBRT have been surprisingly successful for the treatment of small brain, lung, breast, liver, prostate and spine tumors, yielding high local control rates for tumors and usually, no worse normal tissue complications (e.g., [67–71]). This is the case regardless of any assumed, inferred or proposed biological underpinnings.

1.2.1 The Validity of the LQ Model

For more than 30 years, the LQ model has demonstrated its usefulness—for the relatively small dose fractions used in more conventional radiotherapy—for the calculation of isoeffective treatment schedules and to assess qualitatively how a change in fractionation pattern would affect both tumor control and normal tissue complication probabilities (i.e., comparison of BEDs). However, with the return of hypofractionation in the form of SRS or SBRT using high/very high doses per fraction, many radiation oncologists have continued to use the LQ model and BEDs despite such schedules being, for the most part, outside the range of the data sets used to formulate and validate the model in the first place. Are they justified in doing so, even in the face of BEDs often greater than 150 Gy_3's, suggesting an unacceptable risk for late complications [69]? Or, are these high BEDs overestimates of the actual biological effectiveness of hypofractionation? If so, is it possible that the LQ model is simply incorrect?

In the ensuing paragraphs, a number of radiobiological concepts are discussed, some that would argue against the continued use of the LQ model for hypofractionated radiotherapy, and others that would argue for the model's continued use. It is hoped that the reader can use this information in order to make better informed decisions about the use of hypofractionation.

1.2.2 Shapes of Dose Response Curves

Cell survival curves fitted to the LQ model are characterized by non-zero initial slopes represented by the α-component and, as the β-component becomes more prominent at increasing doses, a continuously bending curve. Could the

continuously bending curve account for the LQ model's apparent overestimation of the biological effectiveness of hypofractionation? In theory yes, if only because this is assumed to be the case in order to justify the use of the LQ model for measuring fractionation sensitivity in vivo. But what if the "real" dose response curve has a different shape?

Park and colleagues [72] proposed that the LQ model be modified in order to better align it with clinical results and expectations and to aid in determining isoeffective treatments using hypofractionation, by replacing the continuously-bending portion of the dose response curve with an exponential function. Fowler [73] maintained that the modification of the LQ formula to create such a "Universal Survival Curve" [72] was not necessary, when simply assigning a higher α/β ratio to the tissue would accomplish nearly the same thing, a "straightening" of the dose response curve at high doses. Both approaches—mixing and matching survival curve models and adjusting α/β ratios—seem rather arbitrary, although the latter does have some biological justification.

The LQ model and its derived α/β ratios (and therefore, BEDs) for different tissues are necessarily based on considerations of the tissue's inherent radiosensitivity and repair capacity. However it goes without saying that the other R's, repopulation and reoxygenation in particular, could very well be ongoing during treatment, and influence the measured α/β ratios. Accordingly, how might α/β ratios change?

In rodent tumors, Williams et al. [74] determined the effect on the measured α/β ratio with and without the influence of each R. For example, the persistence of hypoxia during treatment decreased the α/β ratio, whereas allowing reoxygenation to occur increased it. Repopulation had the net effect of decreasing the measured α/β ratio, suggesting that, at least to a first approximation, assigning a higher ratio for a tissue known to proliferate rapidly might better represent its "true" fractionation sensitivity.

1.2.3 Modes of Cell Death

The mechanism of radiation-induced death for most mammalian cells is mitotic catastrophe, which occurs secondary to chromosome aberrations and/or spindle defects that physically interfere with the cell division process [75, 76]. This type of cell death occurs during or soon after the cell next attempts to divide after irradiation. Cells killed in this manner initially appear intact, if multinucleated, but over several days are removed from the tumor.

Apoptosis, or programmed cell death, is a type of interphase death associated with embryonic development and normal tissue remodeling and homeostasis [77], and is an active and carefully-regulated process responsive to various stimuli. A modest subset of normal tissue and tumor cells undergo apoptosis after irradiation [78]. Cells undergoing apoptosis fragment into self-contained apoptotic bodies which ultimately are consumed by phagocytes and typically do not elicit an immune response [76].

Senescence refers to a type of genetically-controlled cellular growth arrest that, while not eliminating cells, does halt permanently their continued movement through the cell cycle [79]. It is a natural process associated with the shortening of DNA telomeres with each subsequent cell division as normal cells age. Radiation-induced senescence is similar, but to distinguish it from the natural process, it is more properly termed "radiation-induced permanent growth arrest" [80].

Necrosis is another form of cell death characterized by cell swelling followed by membrane rupture and the release of cellular contents into the extracellular space, eliciting inflammation and an immune response. Historically, necrosis was considered a relatively passive process that occurred secondary to prolonged nutrient deprivation or hypoxia, however under certain circumstances, it also can follow a molecular program akin to apoptosis. "Programmed" necrosis is more properly termed necroptosis [81].

Immunogenic cell death is a more recently identified mode of cell death observed after exposure to certain chemotherapy agents and ionizing radiation [82–84]. It is somewhat apoptosis-like, but due to some unique features, it *does* elicit an immune response to released tumor antigens, unlike apoptosis [83]. Of particular interest is that the immune response can act systemically as well as locally, and in theory, could elicit distant, abscopal effects.

There is a complicated interplay between the different modes of cell death, with several having biochemical features in common, some seeming to substitute for one another in cases where one pathway is downregulated or inhibited, and at other times some seeming to compete with each other [76]. These complex relationships make it difficult to predict which type or types of cell death might predominate in response to the high doses characteristic of SRS and SBRT, and whether the dose response for such would or would not be linear-quadratic.

1.2.4 The Role of the Tumor Vasculature

That vascular injury is responsible, at least in part, for radiation-induced complications in some normal tissues has long been appreciated [85], however the role vascular injury plays in tumors remains less well understood. Nevertheless, the targeting of tumor vasculature using radiation or other agents remains an attractive goal because the loss of a single microvessel has the potential to kill hundreds, if not thousands, of clonogenic tumor cells [86].

A loss or reduction in tumor vasculature could act as a radiosensitizer, that is, causing secondary ischemic death of tumor cells, reducing the tumor's overall growth rate, or leading to so-called "vascular normalization" [87, 88], the regression of small, inefficient vessels and the retention and promotion of more mature, larger vessels that would permit better access of chemotherapeutics. In addition, vascular normalization could lead to reoxygenation of hypoxic regions of the tumor. On the other hand, loss of small vasculature could also increase tumor hypoxia, which in turn could increase radioresistance as well as facilitate tumor progression [89, 90].

To complicate matters further, there is also evidence that radiation can *protect* tumor vasculature by causing the upregulation of proangiogenic factors [91].

Nearly 15 years ago, Fuks, Kolesnick and colleagues [92, 93] suggested that the radiation sensitivity of tumors, especially after large dose fractions such as those used in SRS/SBRT, was mediated by the apoptotic death of vascular endothelial cells. The proposed mechanism for this was that radiation activated the acid sphingomyelinase pathway—highly enriched in endothelial cells—which lead to the generation of ceramide, a potent mediator of apoptosis. In support of this idea was the finding that vascular endothelial cells in animal models lacking the acid sphingomyelinase pathway were resistant to radiation-induced apoptosis after large, single doses, but those with the pathway intact experienced a rapid wave of endothelial cell apoptosis within hours of irradiation, yet with little evidence of damage to the tumor cells themselves for 2–3 additional days [92]. On the other hand, others (e.g., [94]) have found no influence of the presence or absence of endothelial cell apoptosis on the overall radiation response of the tumor.

Further, albeit less direct, evidence supporting a role for vascular injury in tumor cell death was the finding that in select rodent tumors and human tumor xenografts irradiated with single doses of 10 or 20 Gy, the clonogenic cell survival (assessed using an in vivo-to-in-vitro assay) decreased for 2–3 days after irradiation [95–97] (left panel of Fig. 1.7).

The time scale for this additional tumor cell death was consistent with that observed for the loss of endothelial cells. Song and colleagues further suggested that the presence of indirect tumor cell death secondary to vascular injury could change the shape of the dose response curve for the tumor, and in so doing, potentially invalidate the LQ model. That said, there are also reports in the literature that do *not* demonstrate a further reduction in tumor clonogens in the days immediately following irradiation with a single dose of 20 Gy, a notable example being the work of Hermens and Barendsen [98] showing a steady increase in tumor clonogen number after irradiation of a rat rhabdomyosarcoma (right panel of Fig. 1.7).

The LQ model does not specifically address vascular injury as a distinct mechanism of radiation-induced cell killing, although in cases where it does play a role, use of the model might not be appropriate. However, the fact that there are multiple examples in the literature both supporting and refuting the role of the microvasculature in influencing tumor response to hypofractionation, and that it also remains unclear whether loss of vasculature would result in tumor radiosensitization or radioprotection, it is perhaps premature to conclude one way or the other about the applicability of the LQ model for hypofractionation.

1.2.5 The Role of the Immune System

An emerging paradigm is the use of radiation therapy as an immune system stimulant, e.g., [99–102]. Generally speaking however, most human tumors are not particularly immunogenic either before, during or after conventional radiation therapy

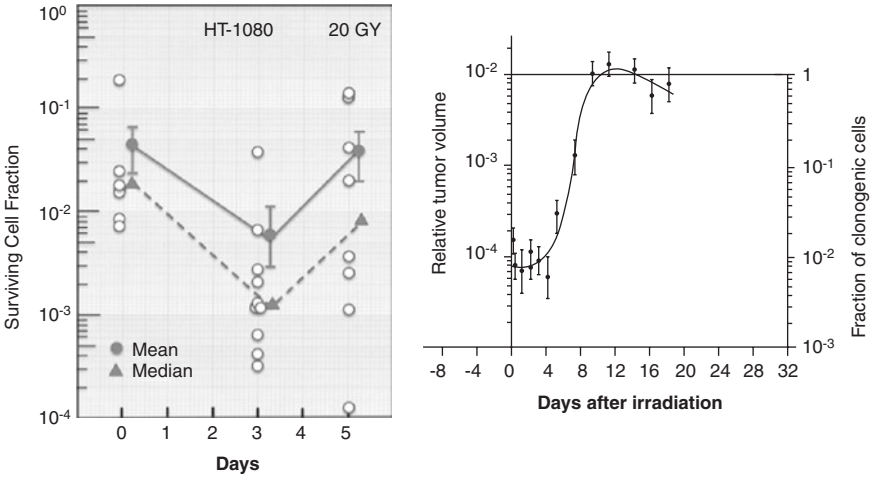

Fig. 1.7 Response of tumor clonogens as a function of time after a large, single dose of 20 Gy. Left panel: Mean and median surviving fractions of clonogens from a human HT-1080 fibrosarcoma xenograft assayed using an in vivo-to-in vitro excision assay. The surviving fraction of clonogens from tumors left in situ for the times indicated significantly decreased at 3 days after irradiation and then began to rebound. (From Song et al. [97].) Right panel: Fraction of clonogenic rat rhabdomyosarcoma cells, expressed as tumor volume relative to size-matched unirradiated tumors and assayed as above. Regrowth delay is evident for the first 4 days after irradiation before accelerated repopulation begins, however no significant decrease in surviving fraction is noted. (Adapted from Hermens and Barendsen [98])

[99], presumably because of an immunosuppressive tumor microenvironment. Immuno-stimulatory effects after the high radiation doses characteristic of SRS or SBRT could be different and potentially much greater however, although admittedly, there is still much to be learned about the time-dose-fractionation dependencies of these effects [100].

Some of the ways irradiated cells die (necrosis and immunogenic cell death especially) have the potential to release subcellular materials into the tumor microenvironment, liberating large quantities of tumor-associated antigens, eliciting a local inflammatory response and causing the release of inflammatory cytokines that in turn could enhance antigen presentation and processing by dendritic cells and macrophages. Taken together, these radiation-induced effects could convert the tumor milieu into an in situ vaccine, paving the way for non-local effector T cells bearing immune memory to be recruited to the tumor site [103, 104].

The use of immune checkpoint inhibitors in combination with hypofractionated radiotherapy has been proposed as a means of further overcoming the immunosuppressive tumor microenvironment and therefore augmenting the in situ vaccine, and there is a growing body of evidence that this can occur. This has already been observed in small subsets of patients with metastatic melanoma and non-small cell lung cancer receiving radiotherapy combined with the immune checkpoint inhibitor

ipilimumab [105, 106]. Such intriguing observations have spawned over a dozen Phase I and II clinical trials of combined radiotherapy and ipilimumab for patients with melanoma, lung, cervix and head and neck cancers [107]. Recent FDA approval of new checkpoint inhibitors targeting different immunosuppressive pathways used by tumors guarantee more trials of these drugs with radiation therapy in the future.

The existence of immune system effects unique to hypofractionation are not accommodated currently in the LQ isoeffect model, to the extent that increased tumor immunogenicity actually affects clinical outcome. If it does, the expectation would be that enhanced immunity would behave as a radiosensitizer, although it remains to be seen whether this radiosensitization would manifest as a change in dose response curve shape away from linear-quadratic.

1.2.6 The Role of Treatment Volume and Normal Tissue Organization

SRS and SBRT are critically dependent on very precise dose localization and delivery to the tumor, with as small a volume of surrounding normal tissue irradiated as currently feasible. Under such irradiation conditions, the likelihood of a clinically significant normal tissue complication should be quite low, provided the tissue at risk is not especially critical or in very close proximity to one that is (e.g., [108–111]). The tissue's structural and functional organization could also play a role.

A simplistic model for describing the structural/functional organization of normal tissues was proposed by Withers and colleagues [112], who envisioned tissues as being composed of functional subunits (FSUs), minimum anatomic entities capable of carrying out the function of the tissue or maintaining its structural integrity. By analogy with electrical circuits, the arrangement of FSUs in different tissues could be either "parallel" or "serial" (or some combination), and that this arrangement would dictate to a first approximation the tissue's radiation tolerance as a function of treatment volume. The spinal cord, the skin and many tubular or sack-like organs behave as if their FSUs are arranged in series, that is, that an injury to even a small volume of tissue potentially could inactivate it and produce a major functional loss. Conversely, for tissues such as the lung, liver and kidney, FSU's are arranged in parallel, meaning that provided the treatment volume is small, little or no functional loss would occur even for high or very high doses. As such, SRS and SBRT may be better suited for, and less likely to produce complications in, parallel tissues than serial ones.

At present, the LQ model does not make provisions for the volume of normal tissue irradiated (nor that tissue's structural/functional organization), but given that much of the advantage of SRS and SBRT lies in the small volumes irradiated overall and the exclusion of nearly all surrounding normal tissue, the LQ model should not be rejected on this basis alone.

1.2.7 The Role of the Five R's

Proponents of the continued used of the LQ model and the calculation of BEDs for SRS and SBRT [58–61] claim that the five R's of radiotherapy still apply for hypofractionation and can explain the excellent outcomes, even though the R's were initially proposed to describe the radiobiological underpinnings of conventional fractionation [30]. In the case of hypofractionation however, the roles and relative importance of the R's are likely to be different.

For example, when cells are irradiated with low-to-moderate doses of radiation, cell cycle arrest is temporary, so eventually survivors would resume proliferating and redistribute themselves around the cell cycle. However, after an exposure to high-to-very-high doses characteristic of SRS or SBRT, cells are much more likely to become permanently growth-arrested and undergo senescence, apoptosis and/or necrosis. This would effectively eliminate the possibility of cells either repopulating or redistributing, although the short overall treatment times characteristic of SRS and SBRT would limit their influence regardless.

These short overall treatment times could be problematic when it comes to reoxygenation however. In hypoxic tumors, short overall times could lead to incomplete reoxygenation which would have the net effect of making tumors more resistant, even to such high, ablative doses. Based on sample calculations of the effectiveness of commonly-used SBRT regimens in either the presence or absence of tumor hypoxia (20% hypoxic fraction and an OER of 2.8 assumed), Brown et al. [113] recommend therefore that hypoxic cell radiosensitizers be used in conjunction with SBRT, particularly single-dose SBRT.

In spite of presumed differences in the influence of the R's when hypofractionation is used, Brenner, Brown and colleagues [59, 60, 114, 115] have argued that use of the LQ model is not only still relevant, but relevant even for the high or very high doses used for SRS and SBRT. They cite two lines of evidence in support of this, first, that reciprocal dose isoeffect curves for different normal tissue endpoints generated from multifraction experiments in rodents are linear, and remain so up to doses of nearly 25 Gy, suggesting adherence to the LQ model (left panel of Fig. 1.8) [60, 115]. Second, using human data on the control of non-small cell lung cancers treated with either single fraction SBRT, 3–8 fraction SBRT or 3D conformal radiotherapy using greater than 10 fractions, these authors found a monotonic relationship between the tumor control probability (TCP) and the BED calculated using the LQ model (right panel of Fig. 1.8). In other words, a given TCP was achieved for a given BED *regardless* of whether the treatment was single or multi-fraction SBRT or more conventional 3D conformal therapy. This suggests that there is nothing unique about SBRT in terms of its biological effectiveness compared to more conventional treatment, and that its efficacy lies simply in the higher BED it delivers and not any new or unique biology.

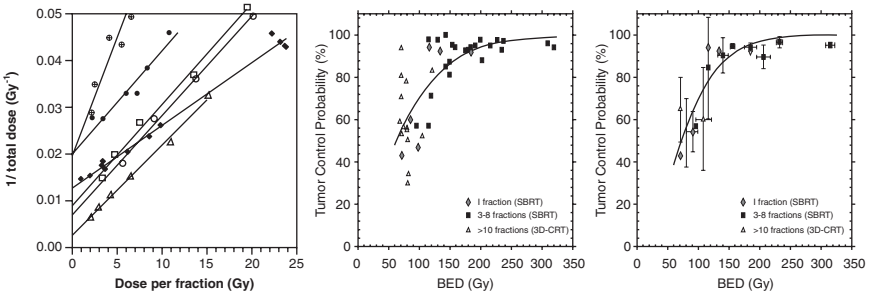

Fig. 1.8 Evidence for adherence of SBRT fractionation schemes to the LQ isoeffect model. Left panel: Reciprocal dose plot isoeffect curves for different normal tissue complications in rodents, including late effects in rat spinal cord (□, ○, △), early reactions in mouse skin (♦), and early (●) and late (⊕) murine intestinal injury. Isoeffect data that fall on a straight line on a reciprocal dose plot conform to the LQ model [60, 115]. (From Brenner et al. [115]) Right panel: Mean tumor control probability (TCP) as a function of BED (Gy_{10}) for Stage I non-small cell lung cancer in patients treated with either single fraction SBRT, 3–8 fraction SBRT or 3D conformal radiotherapy using greater than 10 fractions, weighted for the number of patients in each treatment group. A given TCP was achieved for a given BED regardless of how the dose was delivered, suggesting that SBRT was not different from more conventional treatment in terms of biological effectiveness [59, 60]. (From Brown et al. [60])

1.3 Conclusions

Thanks to technological advances in recent years allowing highly conformal treatment of small tumors, hypofractionation has made an impressive comeback compared to its use during the early days of radiotherapy at the turn of the twentieth century. In terms of the biology of hypofractionation, there are conflicting findings and still much to be learned, although in general, it appears that "old school" radiobiology in the form of the five R's of radiotherapy still applies, with the proviso that the R's may exert different influences in the case of hypofractionation than for conventionally fractionated radiotherapy. These influences could explain the impressive success of ablative radiotherapy in some settings, yet it is also clear that biological effects unique to hypofractionation also exist and could play a role, and, as some suggest, invalidate the use of the LQ model for the calculation of isoeffects.

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Chapter 2
The Physics of Hypofractionation and SRS/SBRT

Jason Matney, Alex Price, and Leith Rankine

The practice of SRS/SBRT and other hypofractionated radiation treatments relies on the accurate delivery of large doses in a limited number of fractions. To minimize normal tissue toxicities, radiation treatment is typically required to be highly conformal with rapid falloff of dose outside of the target volume. In SRS/SBRT cases, this requirement is achieved through a combination of specialized simulation, treatment planning, imaging, positional setup, motion management and delivery technologies. Since SRS/SBRT requires a hypofractionated regimen with little tolerance for error, establishing and following guidelines for rigorous quality assurance (QA) and quality control is extremely important. The quality of a SRS/SBRT program depends on the coordinated interactions of a team of skilled health care professionals.

This chapter outlines the physics of hypofractionation by starting with definitions, basic premise and reviewing some currently available delivery systems. This chapter includes a discussion of the basic SRS/SBRT strategy for simulation, motion management, treatment planning, and treatment delivery. Finally, the chapter concludes with a discussion of physics considerations for commissioning a clinical program and developing a comprehensive quality assurance program.

- In the mid-twentieth century, stereotactic radiosurgery (SRS) was developed to treat intracranial sites [1].
- Stereotaxis is a method in neurosurgery for locating points within the brain using an external, three-dimensional frame of reference usually based on the Cartesian coordinate system.

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- The earliest use of the term "stereotactic radiosurgery" was reported by Lars Leksell in 1951 [2]. Typically, SRS is used to describe single fraction radiotherapy to intracranial targets, initially used as an alternative to neurosurgery.
- Stereotactic radiotherapy (SRT) is a term for fractionated SRS to localized sites within the brain or spine.
- The first combined use of x-rays with a stereotactic device (or frame) for immobilization and localization occurred in 1950 [2].
- SRS was first developed using orthovoltage X-rays, followed by protons, heavy charged particles, and gamma rays from Cobalt-60 treatment machines.
- Two broad categories have been used to immobilize and localize intracranial targets: Invasive and noninvasive systems [3].
  - Historically, skull fixation frames were used to immobilize and localize the head prior to simulation and treatment planning. These devices would remain in place until completion of treatment. These systems often used a physical frame affixed to the patient's skull, commonly using pins or screws.
  - Recently, frameless systems have been developed that uses radiographic imaging to verify and monitor patient alignment.
- The combination of clinical experience of SRS combined with developments in technology led to similar techniques over the past two decades in extracranial sites, stereotactic ablative radiation therapy (SABR) or stereotactic body radiation therapy (SBRT) [4].
- Both techniques (SRS/SBRT) differ from traditional radiotherapy in that large doses are delivered in 1–5 fractions.
- The goal of SRS/SBRT is to deliver a high biologically effective dose while minimizing dose to normal tissues using highly conformal treatment beams to achieve rapid dose fall-off outside the target.
- To achieve such highly conformal dose deliveries, it is imperative that the entire treatment process achieves accuracy and precision beyond that of conventional radiation therapy.
- Clinical patient outcomes of SBRT were first published in 1995, initially focusing on lung, liver and retroperitoneal disease sites [5].
- A 2011 survey of physicians found over 63% of physicians using SBRT, and over half had adopted SBRT in 2008 or later. Among SBRT users, the most common disease sites treated were lung (89.3%), spine (67.5%), and liver (54.5%) tumors. Overall, 76.0% of current users planned to increase their SBRT use, while 66.5% of nonusers planned to adopt the technology in the future [6].
- The clinical implementation recommendations including protocols, equipment, resources and QA procedures has been outlined in AAPM Task Group 101 publication [7]. Major features of SRS/SBRT adapted from AAPM TG-101 are summarized in Table 2.1.

Table 2.1 General Comparison of conventional (3D/IMRT) to stereotactic (SRS/SBRT) radiotherapy

Treatment	Conventional 3D/IMRT	SRS/SBRT
Dose/fraction	1.8–3 Gy	5–30 Gy
Fractions	10–30	1–5
Target definition	CTV/PTV (gross disease + subclinical extent). Tumor may not have sharp boundary	GTV/CTV/ITV/PTV Well defined tumors: GTV=CTV
Prescription Isodose line	~90–95%	~50–90%
Dose gradient outside PTV	Moderate falloff	Very steep falloff
Margin	~Centimeter	Millimeters
Beam arrangement	Typically coplanar beams	Typically include non-coplanar beams
Physics/dosimetry involvement & monitoring	Indirect	Direct
Primary imaging modality	Multi-modality: CT/MR/PET	Multi-modality: CT/MR/PET
Redundancy in geometric verification	No	Yes, imaging prior to each treatment, possibly during
Maintenance of target accuracy throughout treatment	Moderate patient positioning control and monitoring	High; strict immobilization and high frequency position monitoring
Need for respiratory motion management	Potentially	Necessary in sites with potential for respiratory motion
Staff training requirements	High	High + additional SBRT training

2.1 Treatment Systems for SRS/SBRT

2.1.1 GammaKnife

- The GammaKnife® Perfexion [8] system (Elekta, Crowley, UK) treats cranial sites with 192 Cobalt-60 sources in a conical configuration Older models used over 200 sources that were arranged in a hemispherical pattern and a helmet-type collimation system
- Primary and secondary collimation in the GammaKnife Perfexion® system is achieved by a single 12-cm thick tungsten collimator array, in which collimators are arranged in a series of five concentric rings around the patient, divided into independently moving eight regions.
- The collimation device produces individual beams of 4, 8 and 16 mm converging at the isocenter. Beam diameters are changed by moving the source tray over the selected collimator set.
  - Due to the pattern of source placements, the source to focus distance ranges from 374 to 433 mm.

- Each exposure is referred to as a "shot" of radiation where the circular beams intersect to produce a roughly spherical dose distribution.
  - Multiple spherical shots can be combined to "pack" a volume, leading to the term "sphere packing" to describe the method of treatment planning in GammaKnife.
- The patient is moved into the treatment unit using the couch. The only other main moving part on the GammaKnife unit is the drive which moves the source tray into position over the desired beam collimator holes.
- Patients are affixed in a head frame which is attached to the patient's skull with screws. This remains in place during imaging, planning and treatment.
  - This provides a rigid frame around the patient, but traditionally limits the GammaKnife to a single fraction, to avoid repeated placement of the head frame on to the patient.
  - The more recent GammaKnife® Icon (shown in Fig. 2.1) enables on-board CBCT and thus allows for frameless radiosurgery using a thermoplastic mask.
- Plans on the GammaKnife system are prescribed to the 50% isodose line. Thus, the maximum dose point is twice the prescription value.
- Advantages of GammaKnife include sharp penumbra and treatment planning with the ability to easily use multiple isocenters.

Fig. 2.1 Elekta GammaKnife® Icon unit, which collimates 192 Cobalt-60 sources to deliver multiple beams simultaneously

- Disadvantageous of GammaKnife include the need for source replacement approximately every 7 years due to the 5.26 year half-life of Cobalt-60, the ability to treat only intracranial lesions, and the limited field size/shaping available.

2.1.2 CyberKnife

- The CyberKnife system (Accuray, Sunnyvale, CA) shown in Fig. 2.2 is comprised of a 6 MV flattening filter free (FFF) linear accelerator mounted on a robotic arm and a robotic couch [9].
- The robotic arm can manipulate the accelerator into hundreds of predefined positions, called nodes. From each node, the system can produce non-coplanar, non-isocentric beams.
- Radiographic image guidance is performed with a two planar X-ray systems for patient alignment and intrafractional tracking.
- Initial CyberKnife treatments used fixed circular stereotactic cones with sizes 5–60 mm fields as measured at a reference source-to-axis distance of 800 mm.
- A variable aperture (IRIS) was later developed that can reproduce each of the fixed cones [10]. This allows for more field sizes to be used in a plan without the therapist needing to enter the room to physically exchange cones.

Fig. 2.2 Accuray CyberKnife system with a linear accelerator mounted on a robotic arm. Also shown are the ceiling and in-floor X-ray imaging system and robotic treatment couch

- Recently, a multileaf collimator system (InCise) was added that allows for MLC-defined step-and-shoot field shapes to be used.
  - This compact MLC is designed to achieve a maximum field size of 120×102.5 mm^2, using 41 leaf pairs with a width of 2.5 mm at the reference source-axis-distance (SAD) of 800 mm [11].
- Depending on the type/location of tumor, the CyberKnife allows for multiple frameless patient setup and tracking methods.
  - 6D skull tracking system: A frameless system using orthogonal x-rays to determine translation and rotation to align bony skull anatomy to the planned position using a series of digitally reconstructed radiographs (DRR).
  - Xsight Spine Alignment system: Similar to 6D skull tracking, spine tracking aligns the spine to the planned position using the X-ray imaging system and a series of DRRs from the treatment plan.
    - Options exist to treat patients in both prone and supine positions.
  - Synchrony Tracking System: The system synchronizes the beam delivery with the motion of internal fiducials.
    - The system continuously monitors external reflective markers placed on the patient's chest/abdomen.
    - By observing the fiducials through intermittent stereoscopic x-ray imaging, the system correlates the motion of the external reflective markers with the internal fiducials.
    - The CyberKnife system adjusts the treatment beam to track the position of the moving target in real time using the correlation model between the external markers and internal fiducials.

2.1.3 Linear Accelerators

- Two of the largest manufacturers, Varian and Elekta, have similar system configurations for their linear accelerators.
  - Both offer 6 and 10 MV beam energies, which are common for SRS/SBRT. Future versions of machines are likely to remain very similar in characteristics.
- Varian (Palo Alto, CA) accelerators that may be used for SRS/SBRT include the TrueBeam®, Trilogy®, and Clinac® platforms when used with the Varian On-Board Imaging® (OBI) kV imaging system.
- Elekta (Crowley, UK) accelerators that may be used for SRS/SBRT include the VersaHD®, Infinity®, and Synergy® platforms when used with the Elekta X-ray Volumetric Imaging (XVI) kV imaging system.

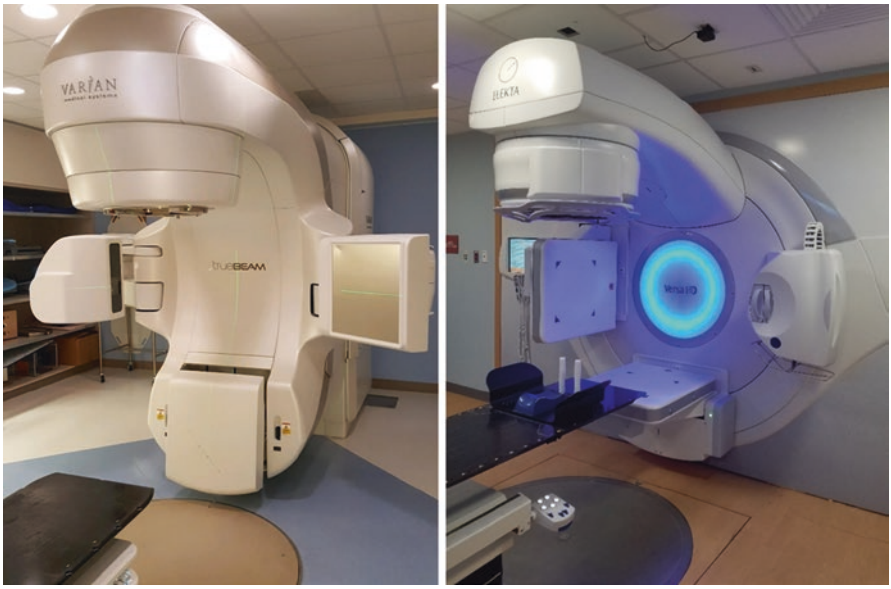

Fig. 2.3 Images of a two standard modern linear accelerators with IGRT capabilities: Varian TrueBeam® and Elekta VersaHD® which show the kV imaging source and panels, and carbon fiber couches on both systems

- A few design differences between Varian and Elekta linear accelerators, summarized in Table 2.2 and shown for comparison in Fig. 2.3:
  - Elekta uses a magnetron and a travelling wave guide to accelerate electrons, in contrast to Varian's klyston and standing wave guide.
  - Varian features a gridded triode electron gun. This grid allows the user to rapidly terminate the injection of electrons to the waveguide, which allows faster termination of the beam. This is an important feature for gated deliveries.
  - Recent Elekta machines are designed without x-direction jaws, instead using the MLC carriage with backup diaphragm to replace as the jaws.
  - Varian machines are designed with tertiary MLCs. Two sets of x-direction and y-direction jaws are still used.
- Both manufacturers offer high dose rate flattening filter free (FFF) modes. These modes remove the flattening filter from the beam. A cross-profile comparison of a flattened and FFF beam is shown in Fig. 2.4.
- For SRS & SBRT planning, the target dose is not meant to be uniform, thus FFF modes lend well to such treatments.
- The removal of the flattening filter for FFF mode results in a peaked profile, lower average photon energy (no beam hardening from the flattening filter), faster dose rate, lower head leakage, reduced scatter and less neutron production for 10+ MV beams.

Table 2.2 Comparison of two recent accelerator models from Varian and Elekta

Machine	Varian TrueBeam	Elekta VersaHD
Years of manufacture	2010-current	2013-current
Photon energy available	6&10/15/18	6&10/15/18
RF power source	Klystron	Magnetron
Maximum dose rate	6 MV FFF: 1400 MU/min 10 MV FFF: 2400 MU/min	6 MV FFF: 1400 MU/min 10 MV FFF: 2400 MU/min
Maximum field size	40×40 cm^2	40×40 cm^2
MLC	120 MLC 5 mm leaf width at isocenter 10 mm width on outside leaves at isocenter	160 MLC 5 mm leaf thickness at isocenter
Portal imager	Amorphous silicon: aS1000	Amorphous silicon: iViewGT
Treatment delivery	3D/IMRT/SRS/SBRT/Arc	3D/IMRT/SRS/SBRT/Arc
Arc therapy	Yes: RapidArc	Yes: VMAT
IGRT	OBI system with CBCT: kV planar Fluoroscopy Fiducial tracking algorithms	XVI system with CBCT: kV planar Fluoroscopy Online 4D CBCT
Couch	3D: Exact IGRT table or 6D: PerfectPitch	3D: Precise table or 6D: HexaPOD

- Both manufacturers include IGRT systems that incorporate both MV and kV energies. This includes the ability to acquire fluoroscopic studies for motion assessment and volumetric imaging which includes both CBCT and 4D CBCT capabilities.
  - Typical imaging kV energies range from 70–150 kVp.
- BrainLab Novalis™ Radiosurgery system features a high-definition MLC with 2.5 mm central leaves on a Varian linear accelerator with a 6D robotic couch and the ExacTrac® system that incorporates an infrared guidance with a stereoscopic X-ray system.
  - The combined kV/optical system allows for continuous monitoring of optical markers on the patient with x-ray verification of internal positioning.
- The Varian Edge™ radiosurgery system is the most recent SRS/SBRT machine by Varian. The machine has 6, 6 FFF & 10 FFF MV energies only, and 120 MLCs with 2.5 mm leaf width as isocenter with a maximum field size of 40×22 cm^2. This system also incorporates an optical surface monitoring system.
- Magnetic Resonance guided Radiation Therapy (MRgRT) is a recent development that combines MR imaging into patient setup and treatment delivery.
  - Cobalt therapy can be combined with MR guidance during treatment. One example is the ViewRay MRIdian® system (ViewRay, Oakwood Village, Ohio) that incorporates three independent, high activity cobalt sources mounted on a ring

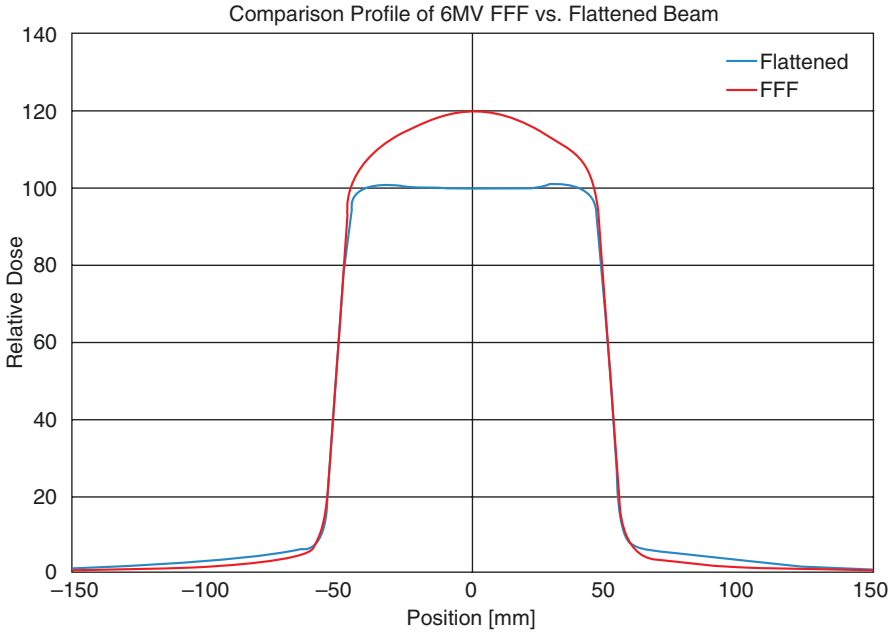

Fig. 2.4 Profile comparison of a 6 MV flattened beam (blue) with a flattening filter free (red) beam for a 10 × 10 cm^2 field at a depth of 10 cm in water

gantry with 120° separation with a 0.35 T MR system [12]. Each source has an independent MLC. The MR and cobalt therapy systems share a common isocenter, enabling simultaneous and continuous MRI during treatment delivery.

– The inclusion of MR imaging allows for continuous, non-ionizing imaging during treatment with superior soft tissue contrast.
– Disadvantages include the currently low MR field strength. Also with Cobalt-60 therapies, there is increased penumbra due to the source size and a limited dose rate: maximum 600 cGy/min which decays over time.
– Several institutions are commissioning recently designed linear accelerators with MR imaging capabilities. One example is the Elekta MR-linac which combines a 1.5 T Philips MRI with a ring based gantry system that houses a 6 MV accelerator [13].

2.1.4 Brachytherapy

- High Dose Rate Brachytherapy is a short course of radiation, usually ≤10 fractions where a high-activity Iridium-192 (5–10 Curies) source is placed into or near the tumor site using a remote afterloader to position the source.
- High dose rate is usually quantified as greater than 12 Gy/hr [14].

Fig. 2.5 Images of two common remote afterloaders for HDR brachytherapy: Varian Varisource® iX and Elekta MicroSelectron®. Both allow for the controlled placement of a sealed Iridium-192 source into a variety of applicators placed inside/on a patient

- Remote HDR afterloaders are an application of the "As Low as Reasonably Achievable" (ALARA) principle in radiation protection. By removing the need to hand place sources, remote afterloaders reduce exposure to all staff. Remote afterloading also allows for optimization of the source dwell time and position to optimize the dose distribution.
- Two common remote afteloaders are shown in Fig. 2.5.
- Various applicators are used to direct and separate the source from the patient. Different applicators exists for lung/bronchial, skin, gynecological, and breast treatments.

2.2 Patient Simulation

(a) Computed tomography (CT) is typically used for treatment planning. Recommendations from AAPM's Task Group 101 include:
   - Scan extent should include target and all relevant OARs.
   - Scan at least 5–10 cm in the superior-inferior direction beyond the OARs.
   - When using non coplanar beams, scan upwards to 15 cm in the superior-inferior direction to accurately model dose within the patient.
   - Slice thickness should be 1–3 mm.
   - Deep inspiration breath-hold CT scans can help reduce normal tissue dose during treatment for highly mobile tumors [15].

(b) Simulation for Respiratory Motion:

- Tumors in the thorax (lung, rib) or abdomen (liver, pancreas, kidney) can be affected by respiratory motion.
- Respiratory motion can induce artifacts in free-breathing planning CT, leading to target/normal-tissue delineation errors.
- Breath hold CT scans can be used to limit motion during a simulation/treatment.
- 4DCTs take advantage of time-resolved information of couch position and breathing motion to reconstruct a 4DCT.
- Inahle and exhale breath hold CTs may over-estimate tumor motion compared to 4DCTs as the patients may breathe more than normal tidal breathing.
- 4DCTs are imperative when treating free breathing treatment sites since it will demonstrate the extent of tumor motion to help aid in creating treatment margins [16].
- 4DCT should be acquired in addition to the planning CT at time of simulation
  - External surrogates often used to monitor breathing
    - Surface tracking (e.g. AlignRT®, Catalyst® systems)
    - Bellows device
    - Infra-red/optical reflective marker tracking
    - Spirometry
  - Breathing wave consistency and tag placement should be checked for errors by physics prior to reconstruction.
  - 4DCT imaging typically sorts CT images into ten different phases.
  - Amplitude-binning is generally less artifact-prone than phase-binning [17], but is only supported on modern CT scanners. Typically, amplitude values range from full-exhale (0%) to full-inhale (100%).
  - Maximum intensity projections (MIP) can be useful for lung planning; minimum intensity projections (MinIP) can be useful for liver planning; both projection images can cause target delineation errors if used near diaphragm
  - Most robust planning information is obtained by using all reconstructed 4DCT phases. Using only end-inhale and end-inhale imaging may underestimate respiratory motion due to tissue hysteresis.
- Inhale breath-hold and exhale breath-hold CT scans can be additionally attained to estimate extent of tumor motion; may over-estimate tumor motion compared to free-breathing motion 4DCT
- Some systems permit treatment during breath hold. However, variation in tumor location between breath holds should be quantified and included in margins.

(c) Immobilization devices

- Minimize inter-fraction and intra-fraction motion
- Currently available commercial immobilization systems include:

- Vacuum bag immobilization devices: (e.g. Vac-Lok Bag, Alpha Cradle)
  - Vacuum sealed bag with plastic beads or foam that conform to patient.
  - Patient in bag which hardens around patient to immobilize.
- Thermo-plastic masks and molds:
  - Plastic that is pliable when heated and formed to the patient where it is locked into anchors and hardens around patient.
- Compression belt/paddles:
  - Abdominal compression is used for lower lobe lung lesions or liver lesions to help reduce the respiratory motion.
- Body frames: (e.g. Elekta BodyFIX system)
  - Similar to a vacuum bag systems but also has a plastic wrap that suctions around the patient to help decrease motion of body areas not in contact with the bag.
- Full Body SBRT Frames:
  - Several vendors offer a complete body immobilization system that attaches to the simulation CT couch and accelerator couch that includes an immobilization bag, wingboard, head sponge, handles, abdominal compression device, knee sponge, and leg specific immobilization.

2.3 Image Registration

- Image registration has an important role in target delineation. Many different imaging modalities have been used in SRS/SBRT planning.
  - Magnetic Resonance Imaging (MRI) has better soft tissue and cerebral tissue delineation compared to CT. Task Group 101 considered MRI to be the gold standard for brain imaging.
  - When registering MRI and CT, one should be careful about:
    - The two scans are not always a complete match due to different patient positions between MR scan and simulation scan.
    - MRI does not provide electron density needed for the calculation of dose as is the case for CT.
    - One must be aware that MRI is prone to geometric distortions, especially at the periphery of a scan, which could cause limitations in the quality of a registration [18].
    - MRI can also have "ghost" artifacts which are the representation of more than one of the same object due to motion [18]

- Positron Emission Tomography (PET) scans are used in conjunction with CT scans to add biological information provided in the PET scan.
  - PET has attenuation corrections utilizing the CT taken concurrently and the attenuation corrected PET scan should be used for registration.
  - Fuse CT from PET/CT to planning CT to limit error since the PET/CT should already be registered. One must verify that the patient did not move between the CT and PET acquisitions.
  - Some disadvantages of a PET scan include [19]:

    PET is quantified in terms of standard uptake value of the PET radionuclide. One must work with standard update value (SUV) cautiously as visual appearance can change greatly from window and level, and SUV may not be reproducible from one scan to the next.

    Since PET scans take a longer time compared to CT, the PET scan is more prone to motion blurring and other artifacts.

2.4 Treatment Planning

(a) Unlike convention treatment planning, SRS/SBRT planning does not seek to achieve a uniform target dose coverage. Hot spots within the target volume are often considered acceptable as long as normal tissues are spared. This may have the benefit of delivering higher dose to what may be hypoxic regions at the center of some tumors.

(b) In SRS and SBRT, we continue to use GTV/CTV/ITV/PTV and OAR concepts that are covered in ICRU 50 [20] and ICRU 62 [21]. These margins are delineated by the radiation oncologist. Some anatomical sites may consider the GTV and CTV to be identical, due to well defined tumor edges.

(c) SRS: In cranial sites, the concept of PTV is not used. In such cases, plans are designed with GTV or CTV as the target.

(d) SBRT: The PTV concept, as in conventional radiotherapy, is a geometrical concept that is meant to account for all possible geometric variations of the CTV/GTV. Margins depend on treatment site, patient motion, and delivery system.

(e) To achieve a high dose gradient outside of the target, dose prescriptions in SRS/SBRT are often specified at a lower isodose, typically 50–90%. Often, little to no margin is used for block edge or beam penumbra.

- Typical brain isodose lines are around 80%, and spine/lung/liver are typically prescribed to the 60–80% isodose line. GammaKnife treatments (brain) are always prescribed to the 50% isodose line.

(f) Due to the high dose per fraction that is used in these treatments, the volume of normal tissue receiving high dose must be limited. Thus, the dose falloff around the target structure must be high.

(g) Non-coplanar beams are often used, and essentially required in some modalities such as GammaKnife and CyberKnife treatments.

(h) Beam selection: The use of multiple, non-overlapping beams and tight collimation is the primary means of achieving a high dose gradient outside the target. This practice increases the dose heterogeneity within the target.
(i) The use of multiple beams will also help to decrease the skin dose. One downside is the increased treatment time with more beams.
(j) Beam energy also affects the dose falloff around the target. For small beams, such as those used in SRS/SBRT, high energy photons will cause higher lateral scatter of secondary electrons. Thus, the beam penumbra will increase at high energy. This is why most SRS/SBRT accelerators use 6 MV, and 15–18+ MV is not used.

- For brain and thorax sites, 6 MV is used. For deep-seated sites outside of the thorax and head, 10 MV may be considered.

(k) The resolution of the beam shaping devices also affects the penumbra. Cones provide the sharpest penumbra, but are limited to discrete circular field sizes. The use of finer MLC leaves improves the conformity around the target. Several manufacturers now provide smaller MLC leaf sizes (<5mm) on linear accelerators, specifically designed for SRS/SBRT.
(l) Arc therapy: A single arc can be considered a collection of multiple beam angles. Thus, arc techniques are an excellent choice for SRS/SBRT delivery. The use of arc therapy has been supported in literature and can significantly improve delivery efficiency of lung and spine SBRT [22].

- In our experience, volumetric modulated arc therapy (VMAT) is useful for SBRT when respiratory motion is minimal (<5 mm). Planning methods that produce dynamic conformal arcs (or that limit beam modulation to low levels) provide plans that are equal to static beam plans, and can be delivered in the same, if not shorter, time frame.

(m) Isocenter placement is important to consider for treatments on conventional linear accelerators. At the time of simulation, it is important to understand the characteristics of the system that the patient is to be treated on. Accelerators used for SRS/SBRT will have imaging panels that may collide with the patient. This is especially important to consider when using couch kicks to deliver non-coplanar beams. The selection of the isocenter is important to minimize the potential for patient-machine collisions.
(n) The size of the TPS dose calculation grid will affect the accuracy of the calculation. For small targets with large dose gradients, a large dose grid may not be sufficient. For SRS/SBRT planning, AAPM Task Group 101 recommends an isotropic dose calculation grid size of 2 mm or less.
(o) Pencil beam or path-length-based algorithms accounting for one dimensional scatter are not recommended by Task Group 101 for accurate dose estimation in the lung. Furthermore, AAPM Task Group 65 [23] describes 1D algorithms as inaccurate in areas of electron disequilibrium, e.g. near lung-tumor interfaces or in beam penumbra regions, and recommends either superposition-convolution or Monte Carlo for lung dose calculation. More recent algorithms

that directly solve the Boltzmann Transport Equation (BTE) have been shown to have a high level of heterogeneity calculation accuracy and are suitable for lung SBRT [24].

(p) Planning for Respiratory Motion:

- Internal Target Volume (ITV):
  - From ICRU 62: Delineate CTV motion encompassing all phases of breathing cycle [21]
  - Results in a larger PTV compared to Mid-Position, gated, and breath-hold [25]
  - Abdominal compression has been shown to decrease motion (on average) in lower lung and liver targets; should be decided on a per-patient basis based on imaging with and without compression device [26, 27]
- Mid-Position with statistically generated PTV-margin [28]
  - Use 4DCT data to generate a Mid-Position CT for planning
  - Combine 4DCT estimate of respiratory motion with other uncertainties (i.e. target delineation uncertainty, machine mechanical tolerances, inter-treatment setup errors, intra-treatment baseline shifts) to create custom PTV margin
- Breath-hold, active breathing control, or free-breathing gated treatments are the most common methods to deliver gated therapy.
  - Free breathing gating: Requires minimal effort for patient as breathing should remain normal. Treatment beam typically enabled at exhale position of cycle due to increased duty cycle and more stable tumor position.
  - Breath-hold delivery is possible at full-inhale or full-exhale:
    - Inhale: larger lung volume and therefore better lung dosimetry; patients may be able to hold breath for longer than in exhale; less repeatable tumor positioning at inhale.
    - Exhale: stable and repeatable tumor baseline positioning; more difficult to hold breath for extended periods of time in exhale; smaller lung volume and therefore slightly worse DVH values
  - Active breathing control involves use of systems to limit or force respiration to desired state.
  - Respiratory gating is often not during a single phase, but over a finite period of time in which the tumor may be moving. Motion during the radiation delivery should be considered. One method is to generate partial-breathing-phase ITV to account for gating duty-cycle or differences in breath-hold position; can use phases of 4DCT surrounding inhale or exhale for free-breathing gated treatments.
- Dynamic tumor tracking

  - Active fiducial tracking via fluoroscopy and external surrogate (e.g. CyberKnife)
  - Must ensure that implanted fiducials move with tumor; i.e. provide a good surrogate for tumor motion

- For ITV or mid-Position treatments, IMRT/VMAT should be used with caution, as overly modulated fields may be subject to target/MLC interplay effects, which could result in hot/cold spots in the PTV

2.5 Patient Setup and Treatment Delivery

- Current SBRT systems rely on image guidance for patient setup before every fraction. The details of the IGRT available depend on the treatment machine.
- Typically simulation CT images or DRR are transferred to the treatment console to perform registration with kV and/or MV images acquired with the in-room imaging systems.
- It is important to consider the potential imaging dose to the patient over the course of SRS/SBRT. The management of imaging dose during IGRT is discussed in AAPM Task Group 75 [29].
  - The dose is dependent on technique of imaging. Overall kV imaging dose depends on many factors, such as energy
    - Planar imaging will deposit the high dose at the imaged entrance skin surface.
    - Volumetric imaging (e.g. CBCT) will deliver roughly uniform dose throughout the imaged volume.
  - To achieve ALARA, collimate radiographic imaging studies to the areas of interest to reduce imaging dose to the patient.
  - The imaging dose for a given imaging technique should be quantified by a qualified medical physicist.
- Resulting IGRT offsets in the co-registration signify setup shifts required to bring the patient into the planned position.
  - All SRS/SBRT systems have methods to align the patient after image guidance, typically by moving the treatment couch.
- In our clinic, after any patient shift, we repeat the imaging study to ensure that the patient positioning system performed as intended.
  - While all patient positioning systems should undergo daily quality assurance procedures, the high dose and limited number of fractions in SBRT/SRS warrant additional imaging to ensure proper patient alignment.
- Prior to the first treatment, our clinic's policies state that the in-room images must be reviewed by a physician.
- Additional delivery considerations to account for tumor motion

- Magnitude and frequency of tumor motion can vary [30]:
    - between simulation and treatment
    - day-to-day between treatments
    - during a treatment fraction
- For all approaches (ITV, Mid-Position, gating, breath-hold) daily pre-treatment dynamic imaging is vital to confirm estimated tumor motion and correlation with any external surrogates [31].
- Examples of pre-treatment respiratory motion assessment includes:
    - 4D-CBCT
    - CBCT or on-board fluoroscopy fiducial tracking
    - MRI (e.g. MRgRT real-target imaging)
- For extended treatment times encountered in SBRT, periodic monitoring of internal motion is recommended as patient respiration can vary over during a fraction.

2.6 Quality Assurance

2.6.1 Patient-Specific Physics Quality Assurance

- In our clinic, several additional tasks are performed for SBRT/SRS beyond that of conventional radiotherapy treatments.
- A physician and physicist is present throughout the simulation to assist with selection and usage of immobilization devices. The immobilization devices for SRS/SBRT are often more complex than traditional radiotherapy.
- A pretreatment physics chart check is performed to check relevant parameters such as treatment intent, simulation images, contouring, image registration, isocenter location (if applicable), and overall plan quality. An important check is the comparison of parameters in the patient's electronic chart against the TPS.
- A secondary monitor unit (MU) calculation is performed for every patient. Typically the second check and TPS MU are within 5% agreement per beam and 3% overall calculation point dose.
- Any patient treated with intensity modulated or arc therapy will have a measurement based QA performed. Often, this is similar to QA measurements performed for standard fractionation arc plans. This also serves to verify that the leaf position/sequencing from the TPS was correctly transferred to the record and verify system and the treatment machine control station.
- For cone defined fields (such as Cyberknife), our clinic does not perform patient-specific beam measurements. Each cone has been thoroughly measured and quantified during linear accelerator commissioning.
    - Beam data for a selection of cones is verified during annual QA

- For SBRT/SRS treated with MLC-based 3D conformal radiotherapy, the combination of irregular treatment field shapes and small treatment field areas (e.g. usually less than 4 cm × 4 cm) are an indication for individual field ion chamber output measurements. An ion chamber with small collecting volume dimensions must be used, so as not to succumb to partial volume effects. Additionally, we check the MLC transfer (from TPS to TMS to the linac) and positioning accuracy by way of diode array measurements or EPID-based port films of each field.
- Similarly, for VMAT/IMRT, with many irregular and small segments, the dose output is measured using a small ion chamber, and the relative dose distributions of each field/arc are measured through one plane of the treatment field, using either film or diode array.
  - Note: ion chamber and diode array measurements seldom test the accuracy of the dose calculation algorithm in heterogeneous media; this test should be performed during commissioning, and validated by way of a third-party heterogeneous phantom measurement (e.g. Imaging and Radiation Oncology Core [IROC], MD Anderson Cancer Center, Houston, TX).
- AAPM Task Group 101 [7] recommends that:
  - At least one qualified medical physicist is present from beginning to end of the first fraction and is available for therapists to consult for any subsequent fractions
  - A radiation oncologist approves the results of image guidance and verifies portal imaging before every fraction.
  - All systems to align the patient must be checked with specific quality assurance procedures. Daily imaging isocenter checks and simple localization checks are performed as part of routine morning QA in our clinic.

2.6.2 Machine-Specific Physics Quality Assurance

- Quality assurance programs for SRS/SBRT should be an extension of already existing tests.
  - The same format of daily, monthly and annual testing procedures is recommended.
  - These procedures should be designed to detect any deviations from the baseline performance determined at acceptance and commissioning
    - Daily QA should be designed to verify the basic functionality and safe usage of all delivery and IGRT systems.
    - Monthly QA should be designed to detect trends in performance away from the baseline and focus on tests most likely to affect patient treatment.
    - Annual QA should be a thorough retesting of all individual and combined systems used and sets a baselines for monthly comparisons.

- Our departmental linac quality assurance policies and procedures have been developed based on the following AAPM Task Group Reports:
  - TG-40 - Comprehensive QA for Radiation Oncology: This older report provides a comprehensive list of test, testing frequencies, and tolerance for linear accelerator based quality assurance [32].
  - TG-142 - Quality assurance of medical accelerators: This report is an update to TG-40 with increased testing recommendations for accelerators used for IGRT and SRS/SBRT techniques [33].
  - TG-104 - The Role of In-Room kV X-Ray Imaging for Patient Setup and Target Localization: This report outlines the different types of planar X-ray imaging systems available and recommends quality assurance tests for these systems [34].
  - TG-179 - Quality assurance for image-guided radiation therapy utilizing CT-based technologies: This report outlines available technology and general quality assurance testing and frequency of tests for kV CBCT and MV CBCT, and CT-on-rails units used for patient positioning [35].
  - TG-147 - Quality Assurance for nonradiographic localization and positioning systems: This report summarizes various systems and outlines quality assurance test and testing frequencies for non-radiographic systems used to align patients [16].
  - QA of robotic radiosurgery devices is covered by AAPM Task Group 135 [36]
  - AAPM Task Group 142 recommends daily, monthly and annual quality assurance tests that should be performed for all linear accelerators and additional tests for SRS/SBRT units.
  - In addition, an ASTRO executive summary recommended additional tests not mentioned in the earlier report [37].
  - Table 2.3 summarizes recommendations from ASTRO and Task Group 142.
  - Additional tests or more frequent testing may be appropriate depending on the treatment machine and technologies used.
- The Winston Lutz test is an important test of a linear accelerator used for SRS/SBRT.
  - This test was developed by Lutz et al., where a metal sphere is placed at isocenter. A film was acquired of the treatment beam, and the center of the sphere is compared to the center of the treatment field [38].
  - This test checks the gantry, table and collimator isocenter alignments in various angles.
    - Mechanical flex in the system as the gantry angles changes or variation in the center of the couch or collimator rotation can all be detected using this test.
  - Winston-Lutz films can now be acquired using the EPID imagers of most linear accelerators.
  - Typically, this test is performed daily to verify the imaging isocenter aligns to the treatment (MV) isocenter.

Table 2.3 Combined AAPM Task Group 142 and ASTRO Recommended Minimum Quality Assurance Testing Specifically for SRS/SBRT Linear Accelerators

Test Type	Procedure	Tolerance for SRS/SBRT accelerator
Daily tests (in addition to TG 142 guidelines)		
Dosimetric	X-ray output Constancy	3%
Mechanical	Laser localization	1 mm
	Optical distance indicator at isocenter	2 mm
	Collimator/jaw size indicator	1 mm
	Winston Lutz MV-kV isocenter coincidence (single angle)	≤1 mm, <0.75 mm average
	IGRT system couch positioning/repositioning	1 mm
Safety	Stereotactic interlocks/lockouts	Functional
	Collisional interlocks of kV/MV systems	Functional
	Imaging system interlocks	Functional
Monthly tests (in addition to TG 142 guidelines)		
Dosimetric	X-ray output	2%
	Dose rate output constancy	2%
Mechanical	Treatment couch positioning indicators	1 mm & 0.5°
	MV-kV isocenter coincidence (cardinal angles)	1 mm
Imaging	Hidden target test using frame or IGRT system	≤1 mm
	Planar kV and MV geometrical scaling	≤1 mm kV ≤2 mm MV
	CBCT contrast, spatial resolution, HU constancy, uniformity and noise	Baseline
	CBCT geometrical accuracy	≤1 mm
Annual tests (in addition to TG 142 guidelines)		
Dosimetric	SRS arc rotation	1 MU or 2%
	MU linearity	≤5% or 2–4 MU
	Spot check of small field beam data including output factors, depth dose and off-axis factors	≤1% from baseline
Mechanical	MV-kV isocenter coincidence	1 mm
Imaging	CBCT imaging dose	Baseline
	Planar kV or MV imaging dose	Baseline
	KV beam quality and energy	Baseline
	Imager position of full range of travel	±5 mm
	End-to-end localization assessment	≤1 mm
	End-to-end dosimetric measurement	≤2%

  - Figure 2.6 demonstrates typical Winston Lutz images.

- One recommended monthly QA addition is use of "hidden target" end-to-end test of the IGRT systems, in which the user aligns a phantom with an internal spherical target to the machine isocenter using the IGRT capabilities, and then verifies the target position using kV and MV imaging.

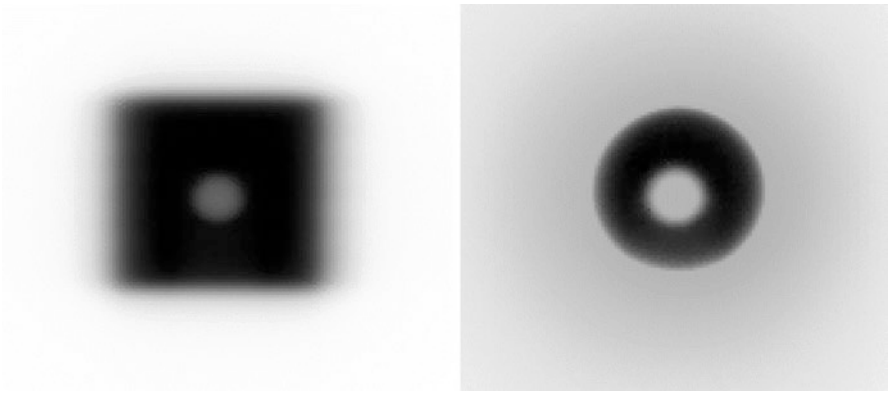

Fig. 2.6 Examples of Winston-Lutz tests for a MLC-defined field (left) and a cone-defined field (right) on a linear accelerator. The test compares the center of the radiation field to the center of a metal sphere placed at isocenter. In the image on the right, a small variation in the radiation field relative to the sphere is easily detected by the human eye

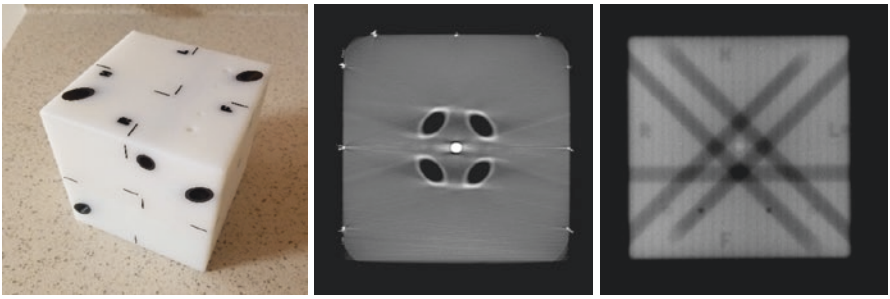

Fig. 2.7 A "hidden object" end-to-end test can be performed with commercial phantoms. Shown here are the MIMI phantom (left) and its resulting CBCT (center), which is used to align its central Winston-Lutz-style metal sphere to the kV isocenter. Finally, an MV portal image (right) can be taken to verify alignment of the metal sphere with the MV isocenter

- Intentionally misaligning the phantom initially by a known off-set, and then testing the IGRT system's ability to adequately correct the position, is a more thorough version of this recommended test.
- Several vendors have designed phantoms to facilitate this test for a variety of systems. These phantoms are able to test alignment of the laser, kV and MV isocenters.
- In our clinic, the "hidden target" test is performed using the "Multiple Imaging Modality Isocentricity" (MIMI) phantom (Fig. 2.7) from Standard Imaging (Middleton, WI)

    - The phantom has a hidden, metal sphere embedded at the center for Winston-Lutz testing and multiple open air columns assist with image registration.
    - Marked on the outside of the phantom are off-center lines to align the phantom with a known offset from the central sphere.
    - A CBCT of the phantom is acquired. The IGRT system automated registration algorithm aligns the phantom's center to isocenter and performs the couch shift. This tests the couch alignment capabilities of the system and should equal the known offset from sphere to external laser marking.
    - The previous step aligned the central sphere to the kV imaging isocenter. MV portal imaging is used to verify the central sphere aligns with the central axis of the radiation field.
  - Any ancillary imaging system isocenter, such as an optical surface tracking system, can also be tested with the hidden target test once the phantom is aligned to the MV isocenter.

2.7 Clinical Implementation and Commissioning

- AAPM Task Group 101 outlines the critical steps for initiating a clinical SBRT program
  - Establish the scope of the program including and goals for each treatment site.
  - Determine the treatment modality, dose, fractionation scheme, and treatment planning goals that support the clinical goals for each treatment site
  - Determine the equipment requirements for patient positioning, treatment delivery, and positional verification
  - Determine the personnel needs for implementation, including additional requirements on therapists, dosimetrists, physicists, and physicians.
  - Establish and perform acceptance testing and commissioning test procedures for all SBRT equipment
  - Establish quality assurance procedures for simulation, treatment planning, treatment delivery, and IGRT verification guidelines. Include reporting methodologies and action levels for these guidelines.
  - Conduct personnel training for all new equipment, procedures and guidelines.
- Acceptance testing is not the same as commissioning, but is only the first step of the process for physics.

  - Acceptance testing is generally performed with the vendor's personnel to ensure that the system is functional, operates within intended specifications, and in compliance with all regulatory requirements.

- Commissioning testing should be developed by the institution's physics team to establish a comprehensive baseline characterization of the SRS/SBRT system's performance. A time consuming but crucial portion of the commissioning process is the measurement and characterization of the radiation from the machine.
  - AAPM Task Group 106 provides guidelines and recommendations on standard linear accelerator beam data commissioning [39].
  - SBRT/SRS commonly use small treatment fields to achieve the necessary conformality. Accurate dosimetric measurement of small fields is complicated by several issues:
    - Detector volume averaging
    - Loss of lateral electronic equilibrium
    - Collimator effects (e.g. MLC leakage, leaf end transmission)
    - Detector position uncertainty
  - AAPM TG 101 recommends that the active diameter of the detector should be less than half of the full-width half maximum of the smallest beam measured.
- The TPS must be commissioned using beam data to ensure accurate calculation of dose and monitor units. This includes a systematic comparison of calculation and measurement ranging from simple configurations such as a single beam to sophisticated arrangements of beams replicating all potential SRS/SBRT clinical scenarios [37].
- There are large potential clinical consequences for incorrect beam data and machine calibration, especially in SRS/SBRT.
  - Due to the increased potential for errors, commissioning data should be compared to published data (often termed "golden data") and any inconsistencies should be investigated.
- Acceptance testing and commissioning should characterize each step of the SRS/SBRT process. Once the individual components of the SRS/SBRT planning and treatment technique are commissioned, it is recommended to perform an all-encompassing "end-to-end" test of the entire system [40].
  - The testing should mimic actual patient treatment and should use all of the same equipment used for treating the patient.

Table 2.4 Recommendations of comprehensive quality control measures from ASTRO

Appendix 1 – Recommendations to Guard Against Catastrophic Failures in SRS and SBRT			
Procedure and tests	Principal	Primary review	Secondary review
1. Commissioning Treatment Devices and Planning Systems			
Machine output calibrations and factors in accordance with relevant guidelines (TG-51, TG-101, TG-142).	Physicist	2nd Physicist	Independent assessment (RPC, etc.)
Treatment planning system commissioning should, include test cases similar to those encountered in SBRT (TG-53).	Physicist	2nd Physicist	Physicists and Dosimetrists
2. Patient Selection			
Patient selection should be in accordance with an approved clinical protocol.	Physician	Physicians and Physicists	ALL
3. Patient Simulation			
Patient simulated in accordance with approved protocol (immobilization and respiratory management) and supervised by physician.	Simulation Therapist	Physician	Physicists and Dosimetrists
4. Patient Treatment Planning			
Verify the patient information, treatment site, and prescription.	Dosimetrist	Physician	ALL
Verify correct positioning of the high dose and intermediate regions of isodose plan relative to targets.	Dosimetrist	Physician	Physicist
Verily the reference images and any shift information - physician determines KRT technique.	Dosimetrist	Physicist	ALL
5. Pre-Treatment Quality Assurance			
Verify that the correct version of the patient*s treatment plan is approved, sent to treatment management system, and used for patient-specific QA.	Dosimetrist	Physicist	ALL
Perform a thorough chart review.	Therapist	Physicist	ALL
Perform a complete chart check including review of information in treatment management system, field apertures in treatment management system, and check of dose to verify TPS calculation.	Dosimetrist	Physicist	ALL
Before the first treatment or for any change in treatment perform patient-specific QA to guarantee that data transfer between systems is correct before patient treatment begins.	Physicist	Physicist	ALL
6. Treatment Delivery			
Halt a procedure if the operator is unclear a bout what is being done.	ALL	ALL	ALL
Perform a check of treatment parameters before start of each treatment against a fixed version of the treatment plan.	Therapist	2nd Therapist	ALL

Table 2.4 (continued)

Appendix 1 – Recommendations to Guard Against Catastrophic Failures in SRS and SBRT			
Procedure and tests	Principal	Primary review	Secondary review
Perform a time out prior to treatment delivery.	Therapist	2nd Therapist	ALL
Assess patient clinically during course of SBRT to identify any acute effects	Physician, Therapist, and Nurse	Physician, Therapist, and Nurse	
7. Quality Performs nee and Improvement			
Perform end-to-end testing to guarantee transfer of data among all systems involved in imaging, planning and dose delivery (annually and after any software or hardware changes)	Physicist	2nd Physicist	Physicists and Dosimetrists

  - "End-to-end" testing using anthropomorphic phantoms is a recommended procedure prior to final commissioning and as part of on-going quality assurance.

- Prior to releasing the machine for clinical usage, it is recommended to independently verify the absolute machine calibration utilizing a remote dosimetric monitoring service.
  - One example is the MD Anderson IROC Houston Quality Assurance Center which provides dosimeters and phantoms via mail order service [41].
- Table 2.4 outlines recommendations of comprehensive quality control measures from ASTRO [37].

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Part I
Benign Central Nervous System Tumors

Chapter 3
Arteriovenous Malformation

Katelyn M. Atkins, Marc Bussière, and Helen A. Shih

Neurosurgeon Lars Leksell first described radiosurgery in 1951 [1] and the first clinical application involved GammaKnife-based treatment of benign conditions such as trigeminal neuralgia and arteriovenous malformations [2]. Importantly, the principles of SRS have been applied to fractionated stereotactic radiotherapy techniques for treatment of a variety of commonly treated benign tumors and functional disorders of the CNS. This chapter summarizes hypofractionated radiotherapy techniques, including SRS and FSRT, for arteriovenous malformations.

3.1 Pearls

- Cerebral AVMs are abnormal vascular lesions that bypass the capillary network by shunting blood from feeding arteries to draining veins via a tortuous nidus of vascular connections.
- The point prevalence is 18 in 100,000, accounting for 1–2% of all strokes and 9% of subarachnoid hemorrhages.
- The majority (80–90%) are supratentorial and isolated in nature, while up to 9% occur in multiple.

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- While generally considered sporadic congenital malformations, the presence of multiple AVMs is predictive of hereditary hemorrhagic telangiectasia (also termed Osler-Weber-Rendu syndrome).
- Brain AVMs generally present between the ages of 10 and 40 years.
- The most common presenting symptoms are:
  - Intracranial hemorrhage (usually intraparenchymal)
  - Seizure (more likely with large, cortical AVMs with superficial drainage)
  - Headaches
  - Focal neurologic deficits (secondary to mass effect, hemorrhage, or vascular steal)
- AVMs carry an estimated risk of hemorrhage of 1–4% per year:
  - The strongest predictors of hemorrhage include prior hemorrhage (at presentation, or clinically silent), deep location, exclusively deep drainage, and associated aneurysms.
- Medical workup: H&P, including assessment of performance status, with emphasis on preceding neurological symptoms (headaches, seizures, focal neurologic deficits) and thorough neurologic examination.
- Imaging workup:
  - CT: Lesions are typically identified on CT, which demonstrate strong contrast enhancement and appear as isodense or hyperdense tortuous vessels. There may be areas of hemorrhage surrounding the nidus. More sensitive imaging (see below) is usually required.
  - MRI/MRA: Increased sensitivity for evaluating the nidus, which demonstrate strong contrast enhancement and appear as hypointense flow voids on both T1- and T2-weighted series.
  - Angiography: The gold standard modality for AVM diagnosis and nidus delineation.
- Given the morbidity and mortality of hemorrhage, treatment is often considered for asymptomatic patients.
- Management strategies include observation, surgical resection, SRS, and embolization.
- For resectable lesions, surgery is the treatment of choice—as the risk of hemorrhage is immediately removed.
- For unresectable lesions or those with high associated surgical risk, SRS is a well-established alternative.
  - High-dose RT is presumed to result in a fibrointimal reaction with associated thrombosis and eventual obliteration of the AVM nidus often within the first 3 years (typical single-fraction SRS dose of 15–24 Gy with higher doses more effective but also with higher risk of morbidity).
- Endovascular treatment or embolization (while rarely curative as an isolated intervention) can be a useful adjuvant technique prior to surgery or SRS.

Table 3.1 Spetzler-Martin grading scale[a]

Size	
0–3 cm	1
3.1–6.0 cm	2
>6 cm	3
Brain location	
Non-eloquent	0
[b]Eloquent	1
Venous drainage	
Superficial	0
Deep	1

[a]Modified from Spetzler et al. [3]
[b]Involving or directly adjacent to primary motor or somatosensory cortex, primary visual cortex, Broca'a area, Wernicke's area, hypothalamus, thalamus, deep nuclei, brainstem, or cerebellar nuclei

3.2 Staging, Grading, and Other Classifications

Classically, the surgical risk associated with AVMs has been classified based on the 1986 Spetzler-Martin grading scale, which accounts for multiple or large lesions, those in eloquent brain regions, and superficial versus deep drainage, to predict surgical outcomes (Table 3.1, [3]). The total score is the sum in all categories (e.g., grade I = 1 point, grade V = 5 points), where the higher the score, the higher the risk of operative morbidity and mortality [4].

More recently, several radiosurgery-based AVM scoring systems have been developed to more effectively predict outcomes following AVM radiosurgery. The most commonly used is the modified radiosurgery-based AVM score that incorporates AVM nidus volume, patient age, and AVM location by the following equation: AVM score = (0.1) (volume, mL) + (0.02) (age, year) + (0.5) (location; hemispheric/corpus callosum/cerebellar = 0, basal ganglia/thalamus/brainstem = 1) [5].

3.3 Patient Selection

- Factors influencing treatment recommendations include patient age, medical comorbidities, cranial nerve deficits, AVM size and/or growth rate, presenting symptoms, competing symptoms (i.e., contralateral hearing or vision loss), and proximity to critical organs at risk (OAR, such as brainstem, cochlea, optic apparatus, and eloquent brain).
- Single-fraction SRS for low-grade or small-volume AVMs (SM Grade I–II, low AVM score, nidus volume <10–15 cc), including those in eloquent or deep locations not amenable to surgical resection.
- For single-fraction SRS, targets should generally be:

  - <3 cm.
  - Not directly abutting critical OARs.
  - >3–5 mm from the optic apparatus (optic chiasm, optic nerves) to achieve adequate dose falloff between the prescription dose and OAR tolerance (<8–10 Gy for single-fraction SRS).

- For FSRT, tumors may be larger (> 3–4 cm), in closer proximity to or involving OARs.
- For large or high-risk AVMs, the optimal treatment approach remains controversial, but includes FSRT versus volume-staged SRS:
  - FSRT: Total dose is divided into ≥2 equal fractions delivered approximately weekly [6].
  - Volume-staged SRS: The AVM nidus is divided into several regions based upon branches of vascular flow (typically 2–4), each of which is treated to an effective single-fraction dose, commonly with a 3–9-month break interval [7, 8].

3.4 Treatment Planning Considerations

Treatment planning considerations, including critical components of simulation, target delineation, coverage considerations, and planning strategies are described in (Table 3.2) and depicted in (Fig. 3.2).

Table 3.2 Treatment planning considerations

Simulation instructions	**Position**: Supine, arms at sides, head and neck neutral. **Immobilization**: A rigid (frame or frameless) stereotactic immobilization system[a]. – GaK: Head frame in conjunction with a metal collimator helmet. – Linac based: Various, including rigid frame with external skull fixation, noninvasive modified GTC frame (noninvasive fixation by use of a dental plate), or a three-point thermoplastic mask with a modified stereotactic frame (Fig. 3.1). **CT**: Thin-cut CT images (1.0–3.0 mm slice thickness) ideally with IV contrast spanning from vertex to mid-cervical spine. **Diagnostic imaging**: Co-registration of planning CT with the appropriate diagnostic imaging (contrast-enhanced MRI or CT) for target and OAR delineation. – MRI sequences should include pre- and post-contrast T1-weighted, pre-contrast T2-weighted and FLAIR, and multi-planar (axial, sagittal, and coronal) post-contrast T1-weighted images. Post-contrast T1-weighted images with thin (1 mm) sectioning ideally should be obtained.
Image guidance	Imaging options include CBCT, orthogonal KV X-rays; misalignment corrections via positional systems with four or six rotational axes of the patient couch/platform.

Table 3.2 (continued)

Target delineation	Target is the entire nidus (see Fig. 3.2a), delineated by co-registration with brain MRI/MRA and/or CT angiography. Draining veins best visualized during arterial phase of angiogram are not part of the target.
Margins	The target is the nidus (GTV = CTV). PTV = CTV plus 0–5 mm uniform expansion (depending on institutional setup error, including accuracy and reproducibility of immobilization). For standard thermoplastic mask, generally CTV plus 3–5 mm uniform expansion. For stereotactic frame, generally CTV plus 0–2 mm uniform expansion.
Tumor/target coverage considerations	≥98% of the GTV/CTV should receive the prescription dose. ≥95% of the PTV should receive the prescription dose.
Treatment modality	Linac, GaK, CyK, proton beam
Planning strategies/ assessment	Steep PTV to OAR dose gradients are generated using multiple beam arrangements or non-coplanar arcs together with dose prescription to the steepest portion of the beam profile (often the 50% IDL for GaK or the 80–90% IDL for linac based). For linac-based SRS, the standard beam profile is shaped by collimation with cones or MLCs. An example treatment plan is depicted in Fig. 3.2b. Notably, as target size increases, the dosimetric advantages of SRS tend to decline—as the sharp dose falloff becomes shallower and the higher doses to adjacent normal tissue become prohibitive, thereby generally precluding safe and effective SRS delivery to targets >3 cm in diameter. The following indices should be generated [9]: **Conformality index**: Prescription isodose volume/target volume (ideally ≤2). **Heterogeneity index**: Maximum dose to target volume/prescription dose (ideally ≤2). **Gradient index**: Volume receiving half the prescription isodose/ volume receiving the full prescription isodose (ideally ≥3).

[a]Based on delivery system and institutional protocol. *GaK* GammaKnife, *GTC* Gill-Thomas-Cosman, *FLAIR* fluid-attenuated inversion recovery, *CBCT* cone beam CT, *CyK* CyberKnife

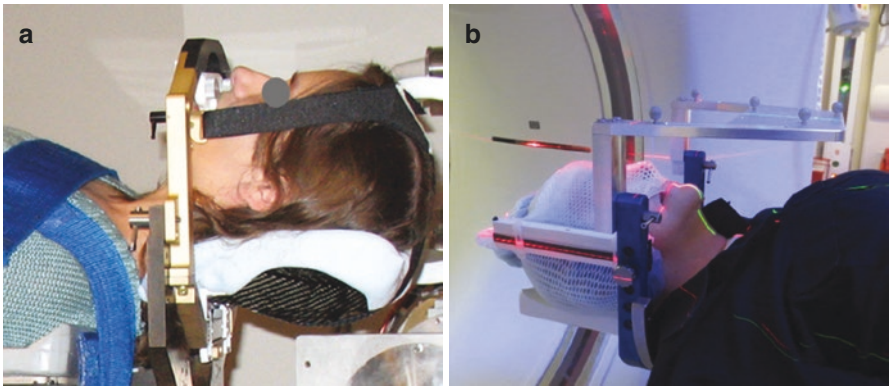

Fig. 3.1 Immobilization depicted using (**a**) a modified Gill-Thomas-Cosman (mGTC) frame (Integra NeuroSciences, USA) and (**b**) a thermoplastic mask (Brainlab, Germany)

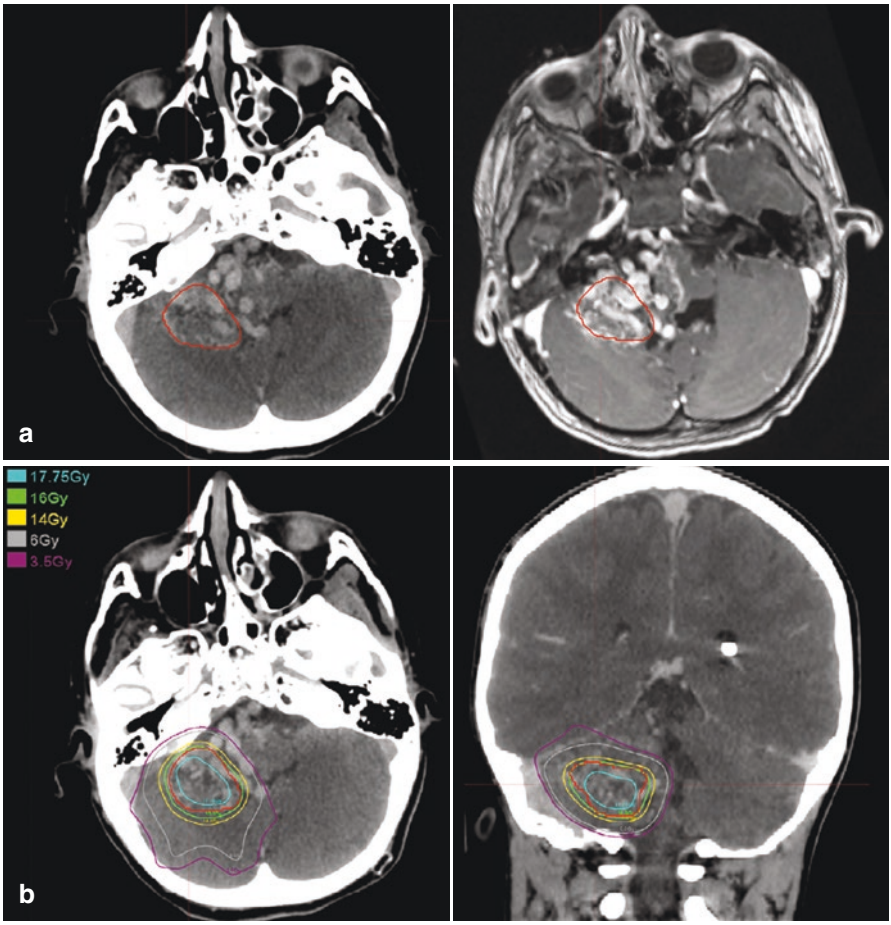

Fig. 3.2 A 6.5 cc right cerebellar AVM in a 12-year-old child; GTV target delineation in red. (**a**) Simulation CT (left), 3D FSPGR MRI sequence (right). (**b**) Treatment plans with prescription IDL in green, effective normalization 90%. SRS, 8 GyRBE protons × 2 fx (16 GyRBE total). Simulation CT axial (left) and coronal (right). *IDL* isodose line

3.5 Commonly Used Dose/Fractionation Schemes

Commonly utilized dose/fractionation schemes for SRS and FSRT are described in Table 3.3.

3.6 Normal Tissue Tolerances

Normal tissue tolerances for SRS and FSRT are described in Table 3.4. In particular, the estimated rates of radiation-induced optic neuropathy are very rare <8–10 Gy but reach >10% at single-SRS doses between 12 and 15 Gy [13, 14].

Table 3.3 Commonly used dose/fractionation schemes

Commonly used dose/fractionation schemes		
	Patient selection considerations	Dose/fractionation
SRS	SM Grade I–II, low risk	15–24 Gy × 1 fx [10, 11]
FSRT	Large lesion, high risk	12–28 Gy, in 2–4 fx ≥7 days apart [6, 12]
Volume staged	Large lesion, high risk	13–18 Gy, in 2–4 sessions, 3–9 months apart [7, 8]

SM Spetzler-Martin

Table 3.4 Normal tissue tolerances for SRS and FSRT

Dmax[a] (Gy) in critical structures for SRS and FSRT							
Organ	Authors' recommendations			TG101 [16]			QUANTEC [17]
Fractions	One	Three	Five	One	Three	Five	One
Brainstem	≤12 Gy	≤21 Gy	≤30 Gy	15 Gy	23.1 Gy	31 Gy	<12.5 Gy
Cochlea	<4.2Gy	–	–	9 Gy	17.1 Gy	25 Gy	≤14 Gy
Optic apparatus	≤8 Gy	≤16.5 Gy	≤25 Gy	10 Gy	17.4 Gy	25 Gy	–
Optic chiasm	≤8 Gy	–	–	–	–	–	<12 Gy
Optic nerve	≤8 Gy	–	–	–	–	–	–

[a]Maximum point dose

In a study by Kano et al., patients with vestibular schwannomas treated with GammaKnife SRS who received a central cochlea dose <4.2 Gy had better hearing preservation [15].

3.7 Patient Management Considerations

- Premedication/prophylactic medication:
  - There is no standard premedication regimen.
  - Consideration of steroids, benzodiazepines, and/or anticonvulsants is dependent on severity and tempo of symptoms or neurologic deficit(s), treatment volume/location and number of fractions, if known prior seizures, as well as patient age and/or medical comorbidities.
- Acute toxicity:
  - Generally well tolerated; expected higher risk of toxicity with high-grade AVMs requiring FSRT or volume-staged radiotherapy.
  - Headaches (<5–15%), transient neurologic changes (<1–10%) [10, 11, 18]:

    Consider short-course dexamethasone 2–4 mg QD (can increase to BID), taper, and/or discontinue as soon as feasible.
    Second line: Referral to neurology.
  - Seizures (<10–15%) [10, 11, 18]: Referral to neurology.

- Late toxicity:
  - Headaches (<10–15%), seizures (<5–10%), neurologic changes (<10%) [6, 7, 10–12, 19, 20].
  - To note, there remains an inherent risk of hemorrhage until obliteration occurs, including any hemorrhage (LG 0–6%, HG 2–22%) and fatal hemorrhage (LG 0–3%, HG 0–15%) [6, 7, 10–12, 19, 20].

3.8 Follow-Up

- H&P every 6–12 months, or as needed.
- MRI with contrast annually (CT with contrast if non-tolerant or MRI contraindicated).
  - At the time of apparent radiographic resolution, perform angiography to confirm obliteration.
- For base of skull locations, monitor for hypopituitarism with regular serum analyses annually.
  - Recommend endocrinologist for long-term management and monitoring of endocrine dysfunction.

3.9 Relevant Literature

- Low-grade AVMs (SM Grade I–II, low AVM score, nidus volume <10–15 cc) are effectively treated with single-fraction SRS (general dose 15–24 Gy). Typical reported obliteration rates are 70–90%, including those in eloquent or deep locations not amenable to surgical resection ([10, 11, 18] and see Table 3.5).
- For large or high-risk AVMs, the optimal treatment approach remains controversial, as delivery of effective single-fraction SRS doses is limited by increasing treatment volumes and associated risk of treatment-related toxicity. To mitigate this, there are two main strategies, FSRT or volume-staged SRS.
  - In FSRT, the total dose is divided into ≥2 equal fractions delivered weekly, with the rationale of improving tolerance of adjacent normal brain tissue to higher doses, however at the expense of obliteration rates (15–27%) [6, 12, 19].
  - For volume-staged SRS, the AVM nidus is divided into several regions (typically 2–4), for which each section is treated to an effective single-fraction dose, typically with a 3–9-month interval to allow for normal brain tissue recovery [7, 8, 21].

Table 3.5 Relevant literature

Study	Patients (*n*)	Median follow-up (months)	Median AVM vol (cm^3)	Modality, median marginal dose, fractionation	Obliteration rate (%)
Pan (2000) [22]	240	26 (12–73)	32% >10	GaK, 15–18 Gy × 1 fx	– vol 10–15 cm^3: 77% at 40 months – vol >15 cm^3: 25% at 40 months – 58% at 50 months
Flores (2011) [23]	213	48	2.1 (mean)	Linac, 14 Gy × 1 fx	– 66% at 3 years – 82% at 5 years
Kano (2012) [18]	217 (SM I-II)	64	2.3	GaK, 22 Gy × 1 fx	– 58% at 3 years – 87% at 4 years – 90% at 5 years – 93% at 10 years
Stark (2013) [24]	1012	96	3.5 (mean)	GaK, mean 21.1 Gy × 1 fx	69% overall
Hattangadi-Gluth (2014) [11]	248	35	3.5	Protons, 15 Gy (RBE) × 1 fx	– 65% at 2.9 years – 70% at 5 years
Ding (2014) [10]	502 (SM I-II)	48 (radiographic) 62 (clinical)	2.4	GaK, 23 Gy × 1 fx	– 66% at 5 years – 80% at 10 years
Silander (2004) [19]	26	NA	13	Protons, FSRT, 20–25 Gy (RBE) total in 2–4 fx	– vol <25 cm^3:70% – vol ≥25 cm^3: 30%
Vernimmen (2005) [25]	64	62	41% <14, 59% ≥14	Protons, FSRT, 2–3 fx – Volume <14 cm^3: Minimum target vol total dose—15 Gy (RBE) – Volume ≥14 cm^3: Minimum target vol total dose—10.4 Gy (RBE)	– vol <14 cm^3: 75% – vol ≥14 cm^3: 43%
Hattangadi (2012) [12]	59	56	22.9	Protons, FSRT, 8 Gy (RBE) × 2 fx	Total 15%, partial 34%, stable 51%
Blamek (2013) [6]	49 (37% SM III)	29	18	19.9 Gy total dose in 2–4 fx	1 year 7% 2 years 11% 3 years 21%

- Notably, a recent literature review by Moosa et al. suggests that the higher delivered BED in volume-staged SRS may result in higher obliteration rates compared to FSRT (47 vs. 22%), with the noted disadvantage that partial obliteration may result in altered blood flow patterns and an uncertain impact on the risk of hemorrhage, although rates of hemorrhage do not appear to be increased [20].

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Chapter 4
Trigeminal Neuralgia

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Lars Leksell reported the first clinical application of GammaKnife (GaK)-based treatment of trigeminal neuralgia in 1971 [1]. While GaK has been the gold standard modality for many decades, recent advances in linac-based SRS approaches have shown efficacy as an acceptable alternative modality. This chapter summarizes SRS treatment for trigeminal neuralgia.

4.1 Pearls

- Trigeminal neuralgia (also known as tic douloureux) is a rare condition characterized by paroxysmal facial pain with an annual incidence of 4–13 per 100,000 people.
- The incidence gradually increases with age, with most idiopathic cases occurring beyond age 50 and occurring more frequently in women than men (1.5–1.7:1).
- The vast majority is sporadic, while rare familial cases have been reported and hypertension may be a risk factor.
- While the precise cause is not well understood, the majority of classic cases are thought to result from aberrant vascular compression of the trigeminal nerve root at the entry to the pons (dorsal root entry zone, DREZ).

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  - Secondary, or non-classic, causes of trigeminal neuralgia may result from tumors (e.g., vestibular schwannoma or meningioma), multiple sclerosis, acute herpes zoster, postherpetic neuralgia, or trauma.

- Patients often present with brief, paroxysmal episodes of unilateral, shock-like pains that are abrupt in onset and termination, typically triggered by otherwise innocuous stimuli, and occur within the distribution of one or more divisions of the trigeminal nerve (CN V).
- Local anatomy:
  - The trigeminal nerve has three major divisions, ophthalmic (V_1), maxillary (V_2), and mandibular (V_3), which together supply sensory innervation to the face (V_1–V_3) and sensory and motor innervation to the muscles of mastication (V_3). The DREZ is at the midlateral surface of the pons and the sensory ganglion (gasserian ganglion) resides in Meckel's cave within the floor of the middle cranial fossa.
- Medical workup:
  - Detailed H&P, including assessment of performance status:

    Many secondary causes of trigeminal neuralgia, such as trauma, postherpetic neuralgia, acute herpes zoster, and multiple sclerosis, can be revealed by thorough history and physical examination.
- Imaging workup: MRI or CT is often obtained to rule out secondary or structural causes of trigeminal neuralgia symptoms.
  - MRI: The trigeminal nerve can be visualized on both T1- and T2-weighted images as it exits laterally from the pons and forms the trigeminal ganglion. Post-contrast T1-weighted images with thin (1 mm) sectioning through the skull base are ideal. High-resolution constructive interference in steady state (CISS) or 3D fast imaging employing steady-state acquisition (FIESTA) sequences can show enhanced visualization of the trigeminal nerve surrounded by CSF.
- First-line therapy for trigeminal neuralgia is pharmacologic management with carbamazepine, or second-line agents such as oxcarbazepine, lamotrigine, gabapentin, phenytoin, benzodiazepines, and baclofen—which can be used alone or in combination.
  - Patients with refractory symptoms may be considered for procedural intervention, including microvascular or balloon decompression, glycerol or radiofrequency rhizotomy, or SRS.

Table 4.1 The diagnostic criteria for trigeminal neuralgia

Trigeminal Neuralgia Diagnostic Criteria (ICHD-3)[a]	
A	At least three episodes of unilateral facial pain (fulfilling criteria B and C)
B	Occurring in at least one trigeminal nerve divisions (without radiation beyond the CN V distribution)
C	Pain harbors at least three of the following four characteristics: 1. Recurring, paroxysmal episodes (lasting from a fraction of a second to 2 min) 2. Severe intensity 3. Electric shock-like, shooting, stabbing, or sharp quality 4. At least three episodes are precipitated by innocuous stimuli to ipsilateral face (while some episodes may be spontaneous)
D	No clinically apparent neurologic deficit
E	Symptoms not better accounted for by another ICHD-3 diagnosis

[a]Modified from ICHD-3 (ICHD-3, [2]). *ICHD-3* International classification of headache disorder-third edition

4.2 Staging, Grading, and Other Classifications

The third edition of the International Classification of Headache Disorders (ICHD-3) describes the diagnostic criteria for trigeminal neuralgia [2] (Table 4.1).

4.3 Patient Selection

- Consider SRS for patients refractory to medical therapy, or who are not surgical candidates, and/or decline procedural intervention.
- Factors influencing treatment recommendations include patient age, medical comorbidities, trial and/or failure of medical therapies, and the severity and/or duration of symptoms.

4.4 Treatment Planning Considerations

Treatment planning considerations, including critical components of simulation, target delineation, coverage considerations, and planning strategies are described in (Table 4.2).

Table 4.2 Treatment planning considerations

Simulation instructions	**Position**: Supine, arms at sides, head and neck neutral. **Immobilization**: A rigid (frame or frameless) stereotactic immobilization system[a] – GaK: Head frame in conjunction with a metal collimator helmet. – Linac based: Various, including rigid frame with external skull fixation, noninvasive modified GTC frame (noninvasive fixation by use of a dental plate), or a three-point thermoplastic mask with a modified stereotactic frame (see Fig. 3.1). **CT**: Thin-cut CT images (1.0–3.0 mm slice thickness) ideally with IV contrast spanning from vertex to mid-cervical spine. **Diagnostic imaging**: Co-registration of planning CT with diagnostic MRI for target and OAR delineation. – MRI: Post-contrast T1-weighted images with thin (1 mm) sectioning through the skull base are ideal. High-resolution CISS or FIESTA sequences can show enhanced visualization of the trigeminal nerve surrounded by CSF [3].
Image guidance	Imaging options include CBCT, orthogonal KV X-rays; misalignment corrections via positional systems with four or six rotational axes of the patient couch/platform.
Target delineation	Target is the dorsal root entry zone (DREZ, or cisternal segment) of the trigeminal nerve at the level of the pons. The trigeminal nerve can be visualized on both T1- and T2-weighted images as it exits laterally from the pons and forms the trigeminal ganglion. *Note: Inferior results have been reported with SRS targeting the gasserian ganglion [4].
Margins	Target is the dorsal nerve root (GTV = CTV). PTV = CTV plus 0–5 mm uniform expansion (depending on institutional setup error, including accuracy and reproducibility of immobilization). Generally CTV plus 3–5 mm uniform expansion for standard thermoplastic mask or CTV plus 0–2 mm uniform expansion for a stereotactic frame.
Target coverage considerations	≥98% of the GTV/CTV should receive the prescription dose. ≥95% of the PTV should receive the prescription dose.
Treatment modality	GaK, CyK, linac
Planning strategies/ assessment	Steep PTV to OAR dose gradients are generated using multiple beam arrangements or non-coplanar arcs together with dose prescription to the steepest portion of the beam profile (often the 20–50% IDL for GaK or the 80–90% IDL for linac based). For linac-based SRS, the standard beam profile is shaped by collimation with cones. The treatment isocenter is generally based on the IDL touching the tangential surface of the brainstem. The following indices should be generated [5]: **Conformality index**: Prescription isodose volume/target volume (ideally ≤ 2). **Heterogeneity index**: Maximum dose to target volume/prescription dose (ideally ≤ 2). **Gradient index**: Volume receiving half the prescription isodose/ volume receiving the full prescription isodose (ideally ≥ 3).

[a]Based on delivery system and institutional protocol. *GTC* Gill-Thomas-Cosman, *FLAIR* fluid-attenuated inversion recovery, *CISS* constructive interference in steady state, *FIESTA* 3D fast imaging employing steady-state acquisition

Table 4.3 Normal tissue tolerances for SRS

Dmax (Gy) in critical structures for SRS			
Organ	Authors' recommendations	TG101 [8]	QUANTEC [9]
Fractions	One	One	One
Brainstem	≤12 Gy	15 Gy	<12.5 Gy

4.5 Commonly Used Dose/Fractionation Schemes

Commonly utilized dose/fractionation schemes are:
Medically refractory, not surgical candidate: 70–90 Gy × 1 fx [6, 7].

4.6 Normal Tissue Tolerances

Normal tissue tolerances for SRS are described in Table 4.3.

4.7 Patient Management Considerations

- Premedication/prophylactic medication:
  - There is no standard premedication regimen.
- Acute toxicity:
  - Generally well tolerated; increase in trigeminal neuralgia pain within the first few hours after SRS (<5%) [10].
- Late toxicity:
  - Paresthesia (6–42%), anesthesia dolorosa (0–1%) [10, 11].

4.8 Follow-Up

- H&P every 6–12 months.
- Recommend neurologist or primary care physician for long-term management of medical therapies.

4.9 Relevant Literature

- Stereotactic radiosurgery is a well-established technique for treatment of trigeminal neuralgia in medically refractory patients or those who are not surgical candidates.

Table 4.4 Summary of select series of SRS for trigeminal neuralgia

Study	Patients (*n*)	Median follow-up (months)	Modality, dose (SRS)	Outcomes
Riesenburger 2010 [13]	53	48	GaK, median maximum dose 80 Gy × 1 fx	59% achieved initial pain relief that was adequate or better, ± medications (equivalent to BNI scores I–IIIb)
Kondziolka 2010 [6]	503	24 (107 pts. >5-year follow-up)	GaK, maximum dose 80 Gy × 1 fx	89% achieved initial pain relief that was adequate or better, ± medications (BNI scores I–IIIb), BNI of I–IIIb: 80% 1 year, 71% 3 years, 46% 5 years, 30% 10 years
Smith 2011 [12]	179	NA	Linac, 70 Gy × 1 fx (1995–1999), 90 Gy × 1 fx (1999–2008)	Significant pain relief in 79%, mean time to relief 1.9 month
Régis 2016 [7]	737	44	GaK, median maximum dose 85 Gy × 1 fx	92% pain free in a median time of 10 days Pain free without medication at 3, 5, 7, and 10 years was 72%, 65%, 60%, and 45%, respectively

BNI Barrow Neurological Institute

- Historically, GaK has been the gold standard modality; however advances in linac-based SRS approaches over the past two decades have shown efficacy as an acceptable alternative modality [12] (Table 4.4).

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Chapter 5
Meningioma

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Meningiomas are the most frequent primary intracranial neoplasm, for which the treatment strategies range from observation to surgical resection and/or radiotherapy, depending on tumor size, location, histology, and growth pattern over time. Notably, stereotactic radiosurgery and conventionally fractionated radiotherapy are well-established techniques for the treatment of meningiomas with high local control rates and robust long-term follow-up data. Recent studies have applied the principles of SRS to fractionated stereotactic radiotherapy techniques, typically for patients with large tumors or those abutting critical OARs. Fractionation schemes are variable, though early data are promising. This chapter summarizes hypofractionated radiotherapy techniques, including SRS and FSRT, for meningiomas.

5.1 Pearls

- Arise from arachnoid cap cells of the arachnoid villi and are the most frequent primary intracranial neoplasm, accounting for one-third of all primary brain tumors.
- The average annual age-adjusted incidence is 7.86 per 100,000 people, with a median age at diagnosis of 65 years.
- More frequently diagnosed in women; female:male ratio of 2–3:1.

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- Risk factors include exposure to ionizing radiation (therapeutic or incidental) and genetic conditions such as type 2 neurofibromatosis (NF2) and schwannomatosis.
- The link between ionizing radiation exposure and risk for meningioma is well established from studies of therapeutic radiation, atomic bomb fallout, and historic use of cranial and scalp irradiation for tinea capitis.
- The role of sex hormones is less clear, although more than 70% of meningiomas express PR and nearly 40% express ER and androgen receptor.
- Meningiomas can arise from any location of the dura (see local anatomy below) and presenting symptoms depend largely on anatomic location, time course over which it developed, and presence of edema.
- While generally slow growing and clinically asymptomatic, there is a higher association with seizure in convexity and parasagittal/falcine locations and those with peritumoral edema.
- The WHO describes 3 grades (I–III) and 13 histologic subtypes (see Sect. 2).
- Local anatomy:
  - Meninges: Comprised of three membranes that envelop the brain and spinal cord, including the outer dura mater (including an outer endosteal and an inner meningeal layer), the middle arachnoid mater, and the inner pia mater. The arachnoid and pia mater form the leptomeninges and CSF flows between the two.

    The dura has four areas of infolding to form the falx cerebri (separating the cerebral hemispheres), the tentorium cerebelli (separating the occipital lobes from the cerebellum), the falx cerebelli (separating the cerebellar hemispheres), and the diaphragma sellae (covering the pituitary gland and sella turcica).
  - Meningiomas develop in various regions: parasagittal/falcine (25%), convexity (19%), sphenoid ridge (17%), suprasellar (9%), posterior fossa (8%), olfactory groove (8%), middle fossa/Meckel's cave (4%), tentorial (3%), peritorcular (3%), lateral ventricle (1–2%), foramen magnum (1–2%), and orbit/optic nerve sheath (1–2%) [1]. Of those in the parasagittal region, 49% occur in the anterior one-third of the falx cerebri.
- Medical workup:
  - History: Assessment of performance status, potential risk factors (prior therapeutic radiation exposure, hormonal status), genetic predisposition syndromes (NF2, schwannomatosis), conditions that can also cause a dural-based lesion (sarcoidosis, hematologic and non-hematologic malignancy, infection/fungal/tuberculosis), and associated neurological symptoms (e.g., seizures, headaches, vision changes).
  - Physical examination: Thorough neurologic examination.
- Imaging workup:
  - CT: Meningiomas are well-circumscribed, extra-axial masses that display strong, homogenous contrast enhancement, and are iso- or hyper-dense to

normal brain parenchyma—which is often displaced adjacently. Approximately 20–30% of meningiomas harbor calcifications, while approximately 50% are associated with hyperostosis or osteolysis in the adjacent bone.
  - MRI: Meningiomas are typically iso- or hypo-intense to gray matter on T1-weighted images, and hyperintense to gray matter on FLAIR sequences, and may display associated peritumoral edema. More than 90% of meningiomas display strong, homogenous contrast enhancement and approximately two-thirds demonstrate an adjacent dural thickening or "dural tail."
- Management strategies include observation, surgical resection, and/or radiotherapy, depending on tumor size, location, histology, and growth pattern over time.

5.2 Staging, Grading, and Other Classifications

The WHO describes 3 grades (I–III) and 13 histologic subtypes of meningioma. The WHO grade is prognostic, with strong associations between grade, RFS, and OS (Table 5.1, [2]). Surgery is often an appropriate therapy for benign (WHO Grade I) meningiomas, with extent of resection based on the Simpson grade and correlating to the rate of tumor recurrence (Table 5.2, [3, 4]).

5.3 Patient Selection for SRS or FSRT

- Factors influencing treatment recommendations include patient age, medical comorbidities, cranial nerve deficits, tumor size and/or growth rate, presenting symptoms, competing symptoms (i.e., contralateral hearing or vision loss), and proximity to critical organs at risk (OAR, such as brainstem, cochlea, optic apparatus, eloquent brain).
- For single-fraction SRS, targets should generally be:
  - <3 cm.
  - Not directly abutting critical OARs.
  - >3–5 mm from the optic apparatus (optic chiasm, optic nerves) to achieve adequate dose falloff between the prescription dose and OAR tolerance (<8–10 Gy for single-fraction SRS).
- For FSRT, tumors may be larger (>3–4 cm), in closer proximity to or involving OARs.
- Case-by-case consideration of SRS for parasellar meningiomas (including cavernous sinus and medial sphenoid wing) given proximity to optic apparatus.
- Optic nerve sheath and tuberculum sellae meningiomas are generally a contraindication for SRS in patients with preserved vision given that the lowest therapeutic dose (12–13 Gy) exceeds optic apparatus tolerance (8–10 Gy).

Table 5.1 The 2016 WHO meningioma grading criteria[a]

Grade	Tumor histology/features
I (benign)	1. Any major histologic subtype, ***except*** clear cell, choroid, papillary, or rhabdoid 2. Does not otherwise meet the criteria for grade II or III
II (atypical)	1. Choroid or clear cell subtype, ***or*** 2. Presence of brain invasion, ***or*** 3. Increased mitotic index (4–19 per 10 hpf), ***or*** 4. Three or more of the following histologic features: Sheetlike or patternless architecture, increased cellularity (focal or diffuse), prominent nucleoli, small cells with high nuclear:cytoplasmic ratio, foci of spontaneous or geographic necrosis
III (anaplastic or malignant)	1. Papillary or rhabdoid subtypes, ***or*** 2. High mitotic index (≥20 per 10 hpf), ***or*** 3. Anaplastic by the following criteria: Focal or diffuse loss of meningothelial differentiation, resembling sarcomata, carcinomata, or melanoma

[a]Modified from Louis et al. [2]. Hpf, high-power field

Table 5.2 Simpson grade of resection and recurrence risk[a]

Grade	Extent of tumor resection	Recurrence rate (%)
I	Macroscopic complete resection of tumor, dural attachments, and abnormal bone	9
II	Macroscopic complete resection of tumor, coagulation of dural attachments	19
III	Macroscopic complete resection of tumor, without resection, or coagulation of dural attachments or extradural disease	29
IV	Subtotal resection of tumor	44
V	Decompression or biopsy only	N/A

[a]Modified from Simpson et al. [3]

5.4 Treatment Planning Considerations (Table 5.3)

Table 5.3 Treatment planning considerations

Simulation instructions	**Position**: Supine, arms at sides, head and neck neutral. **Immobilization**: A rigid (frame or frameless) stereotactic immobilization system[a]. – GaK: Head frame in conjunction with a metal collimator helmet. – Linac based: Various, including rigid frame with external skull fixation, noninvasive modified GTC frame (noninvasive fixation by use of a dental plate), or a three-point thermoplastic mask with a modified stereotactic frame (see Fig. 3.1). **CT**: Thin-cut CT images (1.0–3.0 mm slice thickness) ideally with IV contrast spanning from vertex to mid-cervical spine. **Diagnostic imaging**: Co-registration of planning CT with the appropriate diagnostic imaging (contrast-enhanced MRI or CT) for target and OAR delineation. MRI sequences should include pre- and post-contrast T1-weighted, pre-contrast T2-weighted and FLAIR, and multi-planar (axial, sagittal, and coronal) post-contrast T1-weighted images. Post-contrast T1-weighted images with thin (1 mm) sectioning should be obtained. High-resolution series, such as MP-RAGE, should be obtained for contrast-enhancing targets. Cranial nerves may be more readily visualized on a CISS or 3D FIESTA series as needed [5].
Image guidance	Imaging options include CBCT, orthogonal KV X-rays; misalignment corrections via positional systems with four or six rotational axes of the patient couch/platform.
Target delineation	For benign meningiomas, the tumor bed/GTV is defined as the enhancing lesion on the post-gadolinium T1-weighted MRI ([5], and see Fig. 5.1a). The GTV does not include any surrounding edema on T2-weighted images. The linearly enhancing dura adjacent to the primary meningioma is defined as the dural tail, which can be included in the GTV electively (the proximal component only) or if there is any enhancing nodularity [5]. Dural tail: Defined as presence of ≥2 consecutive slices and >1 imaging plane, tapering adjacently from the mass with increased contrast enhancement [6, 7]. This is most often an inflammatory effect of the tumor that does not require inclusion in grade I tumor target definition. For postoperative cases, the GTV is defined as the resection bed plus any residual nodular enhancement.
Margins	For benign meningiomas, GTV = CTV. May consider 0.5–1.0 cm margin for dural tail or uncertainty in contrast enhancement on T1-weighted images. PTV = CTV plus 0–5 mm uniform expansion (depending on institutional setup error, including accuracy and reproducibility of immobilization). Generally CTV plus 3–5 mm uniform expansion for standard thermoplastic mask or CTV plus 0–2 mm uniform expansion for a stereotactic frame.
Tumor/target coverage considerations	≥98% of the GTV/CTV should receive the prescription dose. ≥95% of the PTV should receive the prescription dose.

Table 5.3 (continued)

Treatment modality	Linac, GaK, CyK, proton beam
Planning strategies/ assessment	Steep PTV to OAR dose gradients are generated using multiple beam arrangements or non-coplanar arcs together with dose prescription to the steepest portion of the beam profile (often the 50% IDL for GaK or the 80–90% IDL for linac based). For linac-based SRS, the standard beam profile is shaped by collimation with cones or MLCs. An example treatment plan is depicted in Fig. 5.1a. Notably, as target size increases, the dosimetric advantages of SRS tend to decline—as the sharp dose falloff becomes shallower and the higher doses to adjacent normal tissue become prohibitive, thereby generally precluding safe and effective SRS delivery to targets >3 cm in diameter. The following indices should be generated [8]: **Conformality index**: Prescription isodose volume/target volume (ideally ≤2). **Heterogeneity index**: Maximum dose to target volume/prescription dose (ideally ≤2). **Gradient index**: Volume receiving half the prescription isodose/volume receiving the full prescription isodose (ideally ≥3).

[a]Based on delivery system and institutional protocol. *GTC* Gill-Thomas-Cosman, *FLAIR* fluid-attenuated inversion recovery, *MP-RAGE* magnetization-prepared rapid gradient echo, *CISS* constructive interference in steady state, *FIESTA* 3D fast imaging employing steady-state acquisition

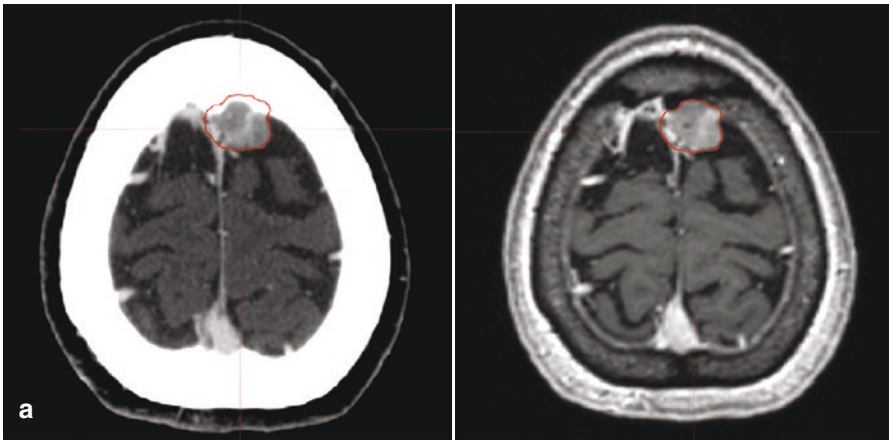

Fig. 5.1 A 2.6 cc left frontal meningioma; GTV target delineation in red. (**a**) Simulation CT (left), post-contrast T1-weighted MRI (right). (**b**) Treatment plans with prescription IDL in green, effective normalization 90%. FSRT, 3 GyRBE protons × 13 fx (39 GyRBE total). Simulation CT axial (left) and coronal (right). IDL, isodose line

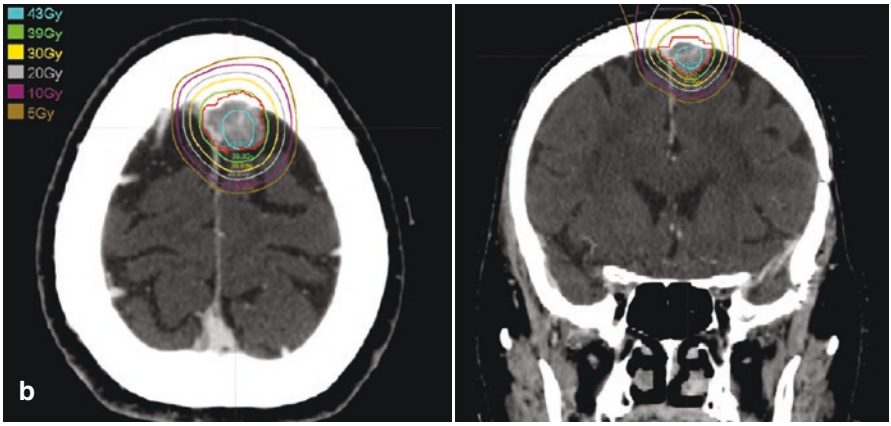

Fig. 5.1 (continued)

5.5 Commonly Used Dose/Fractionation Schemes (Table 5.4)

Table 5.4 Commonly used dose/fractionation schemes

Commonly used dose/fractionation schemes			
	Patient selection considerations	Dose/fractionation	Criteria for SRS
SRS	– More than 3–5 mm from optic apparatus – Optic nerve sheath and tuberculum sellae meningiomas are generally a contraindication to SRS (therapeutic doses exceed OAR tolerance)	WHO grade I: 12–15 Gy × 1 fx WHO grade II–III: 16–20 Gy × 1 fx	• Lesion <3 cm • Not directly abutting critical OARs • >3–5 mm from the optic apparatus
FSRT	Larger tumor and/or <2–3 mm from optic apparatus or other critical OAR	WHO grade I: 5–6 Gy × 5 fx [9], 2.5 Gy × 15 fx [10]	

Table 5.5 Relevant literature

Dmax[a] (Gy) in critical structures for SRS and FSRT							
Organ	Authors' recommendations			TG101 [14]			QUANTEC [15]
Fractions	One	Three	Five	One	Three	Five	One
Brainstem	≤12 Gy	≤21 Gy	≤30 Gy	15 Gy	23.1 Gy	31 Gy	<12.5 Gy
Cochlea	<4.2 Gy	–	–	9 Gy	17.1 Gy	25 (5 Gy/fx)	≤14 Gy
Optic apparatus	≤8 Gy	≤16.5 Gy	≤ 25 Gy	10 Gy	17.4 Gy	25 (5 Gy/fx)	–
Optic chiasm	≤8 Gy	–	–	–	–	–	<12 Gy
Optic nerve	≤8 Gy	–	–	–	–	–	–

5.6 Normal Tissue Tolerances

Rates of radiation-induced optic neuropathy are very rare <8–10 Gy but reach >10% at single-SRS doses between 12 and 15 Gy [11, 12] (Table 5.5). In a study by Kano et al., patients with vestibular schwannomas treated with GammaKnife SRS had improved serviceable hearing preservation if they received a central cochlea dose <4.2 Gy [13].

5.7 Patient Management Considerations

- Premedication/prophylactic medication:
  - There is no standard premedication regimen.
  - Consideration of steroids, benzodiazepines, and/or anticonvulsants is dependent on severity and progression of symptoms or neurologic deficit(s), treatment volume/location and number of fractions, if known prior seizures, as well as patient age and/or medical comorbidities.
- Acute toxicity: Side effects are tumor location dependent and include, but are not limited to, rare transient nausea, headache, alopecia, skin erythema, conjunctivitis, and fatigue.
- Late toxicity: Transient complications (3%), permanent neurologic deficits (5–9%), radionecrosis, or delayed CN deficits (<6%) [16, 17].

5.8 Follow-Up

- H&P every 6–12 months.
- Yearly imaging (ideally MRI, CT with contrast if non-tolerant, or MRI contraindicated) for 4–5 years, then every 2 years.
- For cavernous sinus or base of skull locations, monitor for hypopituitarism with regular serum analyses annually or as needed.
  - Recommend endocrinologist for long-term management and monitoring of endocrine dysfunction.

5.9 Relevant Literature

- Stereotactic radiosurgery and conventionally fractionated radiotherapy are well-established techniques for meningiomas with high local control rates and extensive long-term follow-up data.
- While FSRT is a promising treatment modality in patients with large tumors or those abutting critical OARs, more mature data are needed for robust evaluation of the long-term efficacy and toxicity profile for FSRT compared to SRS or conventionally fractionated radiotherapy (Table 5.6).

Table 5.6 Relevant literature

Study	Patients (*n*)	Median follow-up (months)	Median tumor vol (cm^3)	Modality, dose, fractionation	LC (%)
Torres, 2003 [18]	77	40.6	12.7	Linac, 15.6 Gy × 1 fx	– 92% 5 years
DiBiase, 2004 [19]	162	54	4.5	GaK, 14 Gy × 1 fx	– 86% 5 years
Kreil, 2005 [20]	200	95	6.5	GaK, 12 Gy × 1 fx	– 98.5% 5 years – 97% 10 years
Kollova, 2007 [21]	368	60	4.4	GaK, 12.5 Gy × 1 fx	– 98% 5 years
Feigl, 2007 [22]	214	24 (mean)	6.5 (mean)	GaK, mean 13.6 Gy × 1 fx	– 86% 4 years
Kondziolka, 2008 [17]	972	48 (mean)	7.4	GaK, mean 14 Gy × 1 fx	– 87% 10 years
Gorman, 2008 [10]	38	47	8.3	Linac, 2.5 Gy × 15 fx	100%
Mahadevan, 2011 [23]	16	22	10.5	CyK, mean 5.62 Gy × 5 fx	100%
Han, 2014 [9]	– SRS, 55 – FSRT, 22 – Conventional fx, 143	32	2.8 4.8 11.1	Linac, 12.5 Gy × 1 fx (SRS), 5 Gy × 5 fx (FSRT), 1.8 Gy × 28 fx (conventional fx)	– SRS 91% – FSRT 94% – Conventional fx 95%
Smith, 2014 [24]	28	32.6	14.7	CK, 4.5–6 Gy × 5 fx	100%
Navarria, 2015 [25]	26	24.5	13	Linac, 5 Gy × 5 fx	100%
Conti, 2015 [26]	25	17 (mean)	4.95	CyK, median 4.6 Gy × 5 fx	100%

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Chapter 6
Vestibular Schwannoma

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Stereotactic radiosurgery and conventionally fractionated radiotherapy have well-established track records with high local control rates and robust long-term follow-up data; recent studies utilizing FSRT in patients with large tumors or those abutting critical OARs have emerged. This chapter summarizes hypofractionated radiotherapy techniques, including SRS and FSRT, for vestibular schwannomas.

6.1 Pearls

- Incidence is estimated at 0.6–0.8 per 100,000 person-years and is increasing over time.
- Increased incidence is due (at least in part) to incidental diagnosis in asymptomatic patients in the setting of widespread MRI and CT imaging—as vestibular schwannomas are identified on 0.2% of MRIs in asymptomatic patients.
- Comprise 8% of adult intracranial tumors, 80–90% arise within the cerebellopontine angle, with more than 90% being sporadic and unilateral.
- The median age of diagnosis is 50 years; rare in children with the exception of patients with NF2.
- Both sporadic and NF2-associated vestibular schwannomas are routinely associated with biallelic inactivating mutations of the tumor-suppressor gene *NF2* (located on 22q12).

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  - Bilateral vestibular schwannomas are pathognomonic for NF2 and patients with NF2 commonly manifest symptoms by 20–30 years of age.

- For sporadic lesions, the estimated average growth rate is 1–2 mm per year, while for NF2-associated lesions it is 3 mm per year.
- The cystic schwannoma subtype displays a more aggressive growth pattern, but malignant transformation is rare.
- When tumors are symptomatic, the most common symptoms include hearing loss (95% objective, 66% subjective; usually gradual in tempo—but a subset present with sudden hearing loss), tinnitus (63%), imbalance or vertigo (61%, generally mild-to-moderate unsteadiness with ambulation, tilting, or veering, with true spinning vertigo unusual), facial paresthesias or pain (17%, typical onset more than 2 years since presence of hearing loss), facial paresis or taste disturbance (6%), and less commonly cerebellar symptoms or lower cranial nerve deficits.
- Local anatomy:
  - The cerebellopontine angle is bounded by the temporal bone laterally, the brainstem medially, the cerebellum superiorly and posteriorly, and the inferior cranial nerves inferiorly (CN IX-XI).

    Additional structures within the cerebellopontine angle include CN VII and the anterior inferior cerebellar artery.

  - The vestibular and cochlear nerve roots arise from the vestibular and cochlear apparatus, respectively, which together form the vestibulocochlear nerve, which travels through the internal auditory canal to the cerebellopontine angle.
  - The majorities of vestibular schwannomas arise within the internal auditory canal from the superior or inferior branches of the vestibular nerve, and rarely arise from the cochlear nerve.
  - The natural history is characterized by progressive growth within the internal auditory canal, extending to the cerebellopontine angle with associated compression of nearby cranial nerves—most notably the facial and trigeminal nerves—as well as the brainstem.

- Medical workup:
  - History and physical, including assessment of performance status, with emphasis on preceding neurological symptoms (e.g., hearing loss, tinnitus, imbalance, facial paresthesias, or weakness) and thorough neurologic examination including detailed examination of cranial nerves, balance, and ambulation.

    Weber and Rinne testing may suggest asymmetric sensorineural hearing loss. Romberg and Hall-Pike maneuvers are typically normal.

  - Audiometry: Initial screening test of choice, as 95% of patients will have an abnormal test, most commonly revealing asymmetric sensorineural hearing

loss, preferentially at higher frequencies with impaired speech discrimination scores out of proportion to the degree of hearing loss.
  - Vestibular testing: Not commonly performed as a screening modality given decreased sensitivity, but may show decreased or absent caloric response on the involved side.
  - Brainstem-evoked response audiometry is less commonly performed.

- Imaging workup:
  - CT: Appear as a well-defined isodense, contrast-enhancing mass within the internal auditory canal with variable extension into the cerebellopontine angle, and rarely harbor calcifications (as opposed to meningiomas).
  - MRI: Gold standard imaging modality; typically appear iso- or hypointense to the pons on T1-weighted images, heterogeneously hyperintense on T2-weighted images, and strongly and homogenously contrast enhancing.

    Purely intracanalicular vestibular schwannomas are usually round or oval in shape, while those extending into the cistern have a spherical extra-internal auditory canal component with a taillike taper into the internal auditory canal.

    Post-contrast T1-weighted images with thin (1 mm) sectioning through the internal auditory canal are ideal. High-resolution constructive interference in steady state (CISS) or 3D fast imaging employing steady-state acquisition (FIESTA) sequences can show enhanced visualization of structures surrounded by CSF, thereby assisting in delineation of the tumor and cranial nerves.

    High-resolution CT with and without contrast can be used as an alternative in patients who cannot tolerate MRI.

- Management options include surveillance, surgical resection, SRS, FSRT, or conventionally fractionated radiotherapy.
- Goals of therapy are to maximize local tumor and preservation of function (i.e., minimizing hearing loss and other cranial nerve deficits such as facial or trigeminal nerve dysfunction).
- Surgical resection is performed via a suboccipital (retrosigmoid), middle fossa, or translabyrinthine approach. Hearing preservation rates for suboccipital and middle fossa approaches range from 20 to 71% with smaller tumor size and extent of preoperative hearing level of variable prediction for hearing preservation; the general indications and limitations for each are as follows [1–3]:
  - Suboccipital (retrosigmoid):

    Indications: Any tumor size, can attempt hearing preservation, lower risk of facial nerve injury.

    Limitations: Increased incidence of headache and CSF leak, incomplete visualization of the internal auditory canal fundus.

  - Middle fossa:

Table 6.1 Koos Grading System for Vestibular Schwannomas

Koos grading system for vestibular schwannomas[a]	
Grade	Tumor localization/extension
I	Purely intracanalicular
II IIA IIB	Extension into the CPA (without contacting the brainstem): ≤ 10 mm from the porus acusticus 11–18 mm from the porus acusticus
III	Large tumor extending to the CPA cistern without brainstem displacement
IV	Very large tumor with displacement of brainstem and/or cranial nerves

[a]Modified from Koos et al. [4]. *CPA* cerebellopontine angle

Indications: Small tumors ≤1.5–2 cm and hearing preservation can be attempted (highest rates of hearing preservation among surgical approaches).

Limitations: Increased risk of facial nerve damage, incomplete visualization of the internal auditory canal fundus.

– Translabyrinthine:

Indications: Non-serviceable hearing in affected ear, any tumor size, and complete visualization of the internal auditory canal.

Limitations: Hearing is inevitably sacrificed.

6.2 Staging, Grading, and Other Classifications

Vestibular schwannomas are divided into four grades based on size and location according to the Koos grading system (Table 6.1, [4]).

6.3 Patient Selection for SRS or FSRT

- Factors influencing treatment recommendations include patient age, medical comorbidities, cranial nerve deficits, tumor size and/or growth rate, presenting symptoms, competing symptoms (i.e., contralateral hearing loss), and proximity to critical organs at risk (OAR, such as brainstem, cochlea).
- For single-fraction SRS, targets should generally be <3 cm.
- For FSRT, tumors may be larger (>3–4 cm), in closer proximity to or involving OARs.
- Patients with non-serviceable hearing (typically <50% speech discrimination at >50 dB) may not benefit from therapeutic approaches to preserve hearing [5].

6.4 Treatment Planning Considerations (Table 6.2)

Table 6.2 Treatment planning considerations

Simulation instructions	**Position**: Supine, arms at sides, head and neck neutral. **Immobilization**: A rigid (frame or frameless) stereotactic immobilization system[a]. – GaK: Head frame in conjunction with a metal collimator helmet. – Linac based: Various, including rigid frame with external skull fixation, noninvasive modified GTC frame (noninvasive fixation by use of a dental plate), or a three-point thermoplastic mask with a modified stereotactic frame (see Fig. 3.1). **CT**: Thin-cut CT images (1.0–3.0 mm slice thickness) ideally with IV contrast spanning from vertex to mid-cervical spine. **Diagnostic imaging**: Co-registration of planning CT with the appropriate diagnostic imaging (contrast-enhanced MRI or CT) for target and OAR delineation. MRI sequences should include pre- and post-contrast T1-weighted, pre-contrast T2-weighted and FLAIR, and multi-planar (axial, sagittal, and coronal) post-contrast T1-weighted images. Post-contrast T1-weighted images with thin (1 mm) sectioning should be obtained. High-resolution series, such as MP-RAGE, should be obtained for contrast-enhancing targets. Cranial nerves may be more readily visualized on a CISS or 3D FIESTA series [6].
Image guidance	Imaging options include CBCT, orthogonal KV X-rays; misalignment corrections via positional systems with four or six rotational axes of the patient couch/platform.
Target delineation	The tumor bed/GTV is defined as the enhancing lesion on the post-gadolinium T1-weighted MRI ([6], and see Fig. 6.1a).
Margins	GTV = CTV. PTV = CTV plus 0–5 mm uniform expansion (depending on institutional setup error, including accuracy and reproducibility of immobilization). Generally CTV plus 3–5 mm uniform expansion for standard thermoplastic mask or CTV plus 0–2 mm uniform expansion for a stereotactic frame.
Tumor/target coverage considerations	≥98% of the GTV/CTV should receive the prescription dose. ≥95% of the PTV should receive the prescription dose.
Treatment modality	Linac, GaK, CyK, proton beam
Planning strategies/ assessment	Steep PTV to OAR dose gradients are generated using multiple beam arrangements or non-coplanar arcs together with dose prescription to the steepest portion of the beam profile (often the 50% IDL for GaK or the 80–90% IDL for linac based). For linac-based SRS, the standard beam profile is shaped by collimation with cones or MLCs. An example treatment plan is depicted in Fig. 6.1b. Notably, as target size increases, the dosimetric advantages of SRS tend to decline—as the sharp dose falloff becomes shallower and the higher doses to adjacent normal tissue become prohibitive, thereby generally precluding safe and effective SRS delivery to targets >3 cm in diameter. The following indices should be generated [7]: **Conformality index**: Prescription isodose volume/target volume (ideally ≤2). **Heterogeneity index**: Maximum dose to target volume/prescription dose (ideally ≤2). **Gradient index**: Volume receiving half the prescription isodose/volume receiving the full prescription isodose (ideally ≥3).

[a]Based on delivery system and institutional protocol. *GTC* Gill-Thomas-Cosman, *FLAIR* fluid-attenuated inversion recovery, *MP-RAGE* magnetization-prepared rapid gradient echo, *CISS* constructive interference in steady state, *FIESTA* 3D fast imaging employing steady-state acquisition

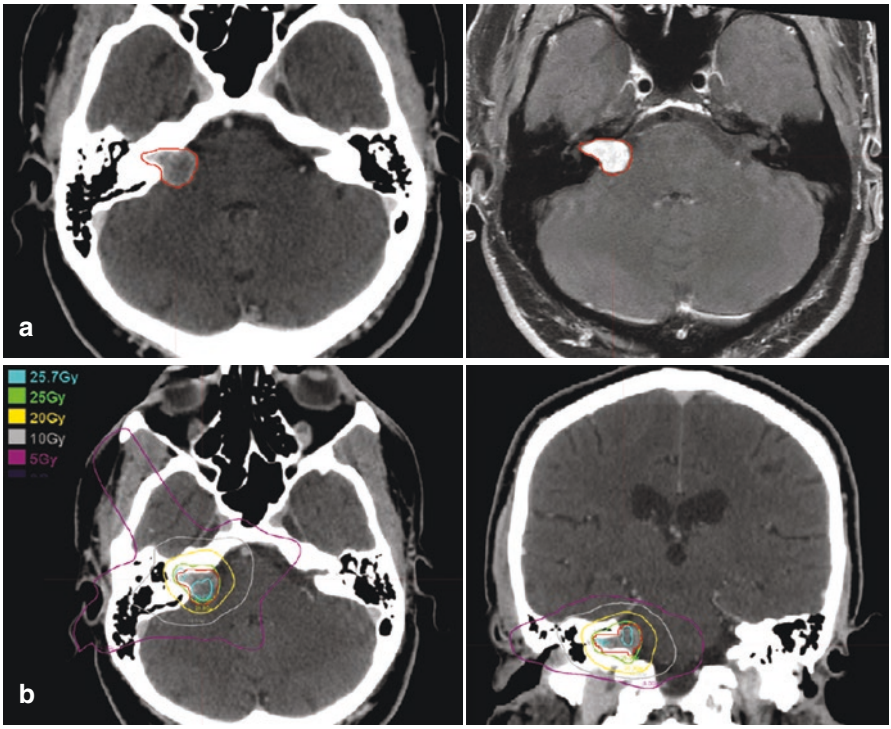

Fig. 6.1 A 1.9 cc right vestibular schwannoma; GTV target delineation in red. (**a**) Simulation CT (left), post-contrast T1-weighted MRI (right). (**b**) Treatment plans with prescription IDL in green, effective normalization 97%. HSRT, 5 Gy × 5 fx (25 Gy total) with 6 MV photon using VMAT. Simulation CT axial (left) and coronal (right). *IDL* isodose line

6.5 Commonly Used Dose/Fractionation Schemes

Commonly utilized dose/fractionation schemes for SRS and FSRT are described in Table 6.3.

6.6 Normal Tissue Tolerances

Improved serviceable hearing preservation has been reported in patients with vestibular schwannomas treated with GammaKnife SRS who received a central cochlea dose <4.2 Gy [10] (Table 6.4).

Table 6.3 Commonly utilized dose/fractionation schemes for SRS and FSRT

	Patient selection considerations	Dose/fractionation
SRS	Small, <3 cm	12–13 Gy
FSRT	Larger, >3–4 cm	5 Gy × 5 fx, 3 Gy × 10 fx [8, 9]

Fx fraction(s)

Table 6.4 Normal tissue tolerances

Dmax[a] (Gy) in critical structures for SRS and FSRT							
Organ	Authors' recommendations			TG101 [11]			QUANTEC [12]
Fractions	One	Three	Five	One	Three	Five	One
Brainstem	≤ 12 Gy	≤ 21 Gy	≤ 30 Gy	15 Gy	23.1 Gy	31 Gy	< 12.5 Gy
Cochlea	< 4.2 Gy	–	–	9 Gy	17.1 Gy	25 Gy	≤ 14 Gy

[a]Maximum point dose

6.7 Patient Management Considerations

- Premedication/prophylactic medication:
  - There is no standard premedication regimen.
  - Consideration of steroids is dependent on severity and tempo of symptoms or neurologic deficit(s), treatment volume, number of fractions, as well as patient age and/or medical comorbidities.
- Acute toxicity: Treatment is generally well tolerated, transient dizziness reported in ~17% [13].
- Late toxicity: Hearing loss (29–68%), CN V/VII neuropathy (<5%), dizziness (2%) [13, 14].

6.8 Follow-Up

- H&P every 6–12 months.
- Yearly imaging (ideally MRI, CT with contrast if non-tolerant, or MRI contraindicated) for 4–5 years, then every 2 years.
- Audiometry and vestibular testing as needed.

6.9 Relevant Literature

- The treatment of vestibular schwannomas with stereotactic radiosurgery and conventionally fractionated radiotherapy is well characterized with excellent local control rates and extensive long-term follow-up.
- In recent years FSRT has emerged as a promising treatment technique in patients with large tumors or those in close proximity to or involving critical OARs. However, more mature data are required for adequate evaluation of long-term local control rates as well as associated toxicity profiles for FSRT compared to SRS or conventionally fractionated radiotherapy (Table 6.5).

Table 6.5 Relevant literature

Study	Patients (*n*)	Median follow-up (year)	Mean tumor vol (cm^3)	Modality, dose, fractionation	PFS	Hearing preservation (%)
Prasad 2000 [15]	153	4.3, (mean)	2.6–2.8	GaK, 13 Gy × 1 fx	93%	58[a]
Hasegawa 2005 [16]	317	7.8	5.6	GaK, 13.2 Gy × 1 fx	– 93% 5 years – 92% 10 years	13(>13 Gy)[a] 68(≤13 Gy)[a]
Friedman 2006 [17]	295	3.3	2.2, (median)	Linac, 12.5 Gy × 1 fx	– 98% 2 years – 90% 5 years	NA
Chopra 2007 [18]	216	5.7	1.3	GaK, 13 Gy × 1 fx	– 98% 10 years	44, 10 years[a]
Fukuoka 2009 [13]	152	>5	2.0	GaK, 12 Gy × 1 fx	– 94% 5 years – 92% 8 years	71
Murphy 2011 [14]	103	3.1	1.95	GaK, 13 Gy × 1 fx	91%	NA
Kalapurakal 1999 [19]	19	5.4	3.5 cm (mean diameter)	Linac, 6 Gy × 6 weekly fx (*n* = −6); 5 Gy × 6 weekly fx (*n* = 13)	100%	100
Williams 2002 [8]	150	1.9	1.5 (≤3 cm), 8.7 (3–4 cm), 26.3 (≥4 cm)	Linac, 5 Gy × 5 fx (≤3 cm, *n* = 131), 3 Gy × 10 fx (3–4 cm, *n* = 18), 2 Gy × 20 fx (>4 cm, *n* = 1)	100%	72[a]
Meijer 2003 [20]	80	2.8	2.5 cm, (mean diameter)	Linac, 4 Gy × 5 fx (1992–1995), 5 Gy × 5 fx (1995–2000)	– 94% 5 years	61

Table 6.5 (continued)

Study	Patients (*n*)	Median follow-up (year)	Mean tumor vol (cm^3)	Modality, dose, fractionation	PFS	Hearing preservation (%)
Kapoor 2011 [9]	385	4.7	2.66, (mean)	Linac, 5 Gy × 5 fx (*n* = 340) or 3 Gy × 10 fx (*n* = 36)	– FFS 97% – FFRP 70% – 7.6 years median time to progression	NA

[a]Gardner-Robertson Class I–II.; *vol* volume, *FFS* freedom from surgery, *FFRP* freedom from radiologic progression

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Chapter 7
Pituitary Adenoma

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Pituitary adenomas represent a heterogeneous group of benign tumors that can present as an incidental radiographic finding or with a variety of neurologic and/or endocrine symptoms. The CNS goals of therapy are to maximize local control and preservation of normal function. Stereotactic radiosurgery and conventionally fractionated radiotherapy are well-established treatments for pituitary adenoma with high local tumor control rates and extensive long-term follow-up data. There has also been recent clinical interest in the application of FSRT in patients with large tumors or those abutting or involving the optic apparatus. This chapter summarizes hypofractionated radiotherapy techniques, including SRS and FSRT, for pituitary adenomas.

7.1 Pearls

- The third most common primary brain neoplasm, comprising 10–15%.
- The overall age-adjusted incidence is 2.94 per 100,000 persons. However, pooled meta-analyses of autopsy and radiological studies suggest that the estimated prevalence may be as high as one in six persons.
- Genetic predisposition has been identified in multiple endocrine neoplasia (MEN) type 1 syndrome, Carney's syndrome, and isolated familial somatotropinomas.

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- Pituitary adenomas can present with a variety of neurologic and/or endocrine symptoms, or as an incidental radiographic finding. Approximately 10% of asymptomatic adults have an MRI-detectable pituitary abnormality compatible with the diagnosis of asymptomatic pituitary adenoma.
- Symptomatic pituitary adenomas usually present with hypopituitarism, hyperpituitarism, and/or symptoms related to mass effect:
  - Hypopituitarism: Short stature in children (GH), failure of postpartum lactation (PRL), hypocortisolism (ACTH), hypogonadism (LH or FSH), or hypothyroidism (thyroid-stimulating hormone, TSH).
  - Hyperpituitarism: Acromegaly or gigantism (GH), galactorrhea or amenorrhea (PRL), Cushing's disease or Nelson's syndrome (ACTH), gonadal dysfunction (LH, FSH), or hyperthyroidism (TSH).
  - Mass effect: Visual impairment is the most common presenting symptom of a nonfunctioning pituitary adenoma due to suprasellar extension with associated optic chiasm compression, classically resulting in bitemporal hemianopsia.

    Other presenting neurologic symptoms: headaches, diplopia (due to lateral extension and oculomotor nerve compression).

    Onset of severe headache and diplopia may be a result of pituitary apoplexy following sudden hemorrhage.

  - A least one-third of pituitary tumors can result in mood disorders, infertility, sexual dysfunction, obesity or body disfigurement, visual impairment, hypertension, diabetes mellitus, and accelerated heart disease.
- Pituitary subtypes in order of frequency include prolactinomas, nonfunctioning adenomas, growth hormone (GH)-releasing adenomas, and adrenocorticotropic hormone (ACTH)-releasing adenomas, while TSH-releasing adenomas are the most rare.
- Local anatomy:
  - The pituitary gland is an 8–10 mm structure (in the superior-inferior dimension) located in the sella turcica.
  - Pituitary adenomas <10 mm = microadenomas, ≥10 mm = macroadenomas, and further divided into secretory and nonsecretory types.
  - Boundaries of the sella turcica:

    Anterior: tuberculum sellae and anterior clinoid process
    Posterior: dorsum sellae and posterior clinoid process
    Inferior: sphenoid bone (superior margin of sphenoid sinus)
    Superior: diaphragma sellae
    Lateral: cavernous sinuses bridging the superior orbital fissure to the petrous apex

  - Contents of the cavernous sinus: segment of internal carotid artery, and superiorly to inferiorly, CN III (oculomotor), CN IV (trochlear), CN V_1 (ophthalmic branch of trigeminal), CN V_2 (maxillary branch of the trigeminal nerve), and CN VI (abducens).

- Medical workup:
  - H&P with emphasis on thorough endocrine history and neurologic-ophthalmic examination, including visual field and acuity testing.
  - Complete serum endocrine evaluation including serum prolactin, insulin-like growth factor (IGF)-1, growth hormone (after glucose load), 24-h urine cortisol, ACTH, LH, FSH, free T4, T3, and TSH.
- Imaging workup:
  - Differential diagnosis for a sellar mass is broad, including pituitary adenoma, congenital lesions (craniopharyngioma or Rathke's cleft cyst), infiltrative or infectious process (e.g., granuloma, tuberculosis, lymphocytic hypophysitis), or non-adenoma neoplasm (e.g., meningioma, primary lymphoma, chordoma, germ cell tumor, or metastasis).
  - CT: Pituitary microadenomas are hypodense and less contrast enhancing than normal pituitary gland.
  - MRI: Pituitary microadenomas are typically hypointense to normal pituitary gland on T1-weighted images, while they can be iso-, hypo-, or hyperintense to normal pituitary on T2-weighted images. There may be hyperintensity on T1-weighted images in the setting of cystic lesions or a component of intralesional hemorrhage. In contrast to meningiomas, pituitary adenomas demonstrate partial, incomplete, or heterogenous contrast enhancement.

    The closest distance between the tumor and optic chiasm and optic nerves should be determined, particularly when a suprasellar extension is present.
- Management strategies include observation, surgical resection (standardly via transsphenoidal microsurgery), medical management, radiotherapy, or various combinations of these depending on tumor size and location, specific endocrine abnormalities, and response to initial therapies. For nonfunctioning pituitary adenomas that are symptomatic or causing mass effect, surgery is often the first-line option for pathologic confirmation and decompression, with variable local control rates ranging from 10 to 18% at 5 to 6 years and 44% at 10 years.

7.2 Staging, Grading, and Other Classifications

Pituitary adenomas are broadly classified by endocrine function, anatomic size, and extent of invasiveness. There is no universally accepted staging or classification system. The first devised system was the Hardy classification, whereby pituitary tumors were described based on the extent of invasiveness (Table 7.1, [1]). Additionally, pituitary tumors can be classified based on their endocrine activity as secretory or nonsecretory, and further categorized based on the pituitary cell type, tumor type, and associated endocrine syndromes (Table 7.2, [2]).

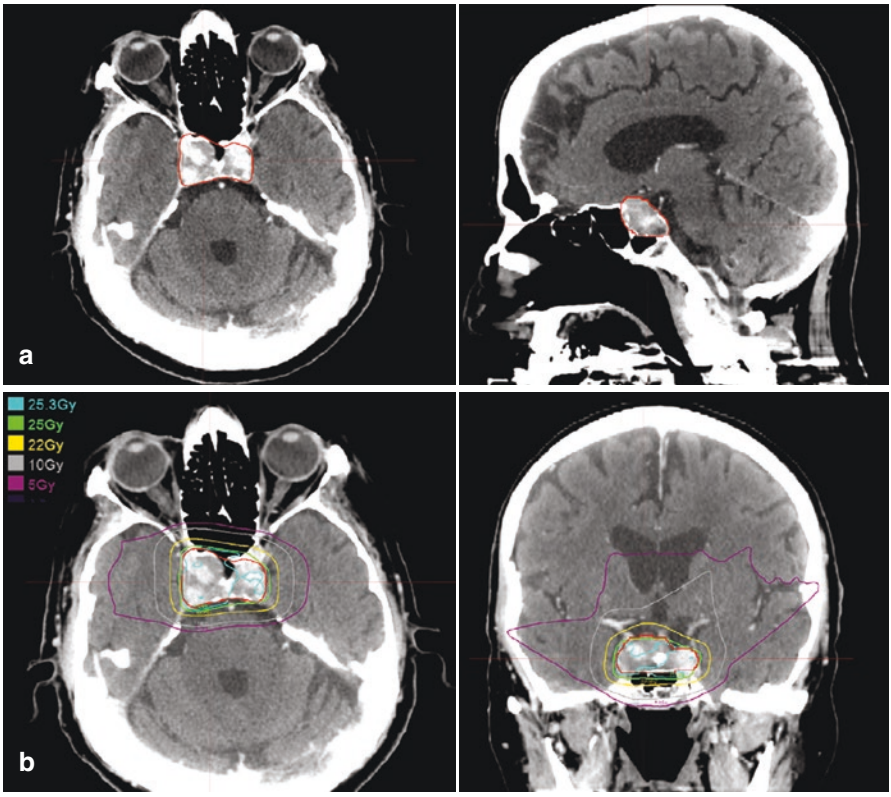

Fig. 7.1 A 9.7 cc postsurgical recurrent nonfunctioning macroadenoma; GTV target delineation in red. (**a**) Simulation CT axial (left) and sagittal (right). (**b**) Treatment plans with prescription IDL in green, effective normalization 97%. HSRT, 5 GyRBE protons × 5 fx (25 GyRBE total). Simulation CT axial (left) and coronal (right). *IDL* isodose line

Table 7.1 Hardy classification of pituitary adenomas[a]

Grade	Extent of invasiveness
Noninvasive	
0	Sella intact with normal contour
I	Sella intact, but with bulging of floor
II	Sella intact, with enlarged fossa
Invasive	
III	Sella with localized or focal destruction
IV	Sella with diffuse destruction

[a]Modified from Hardy [1]

Table 7.2 Pituitary classification based on cell type and endocrine syndrome

Pituitary cell type	Hormones	Endocrine syndrome	Percent of cases
Corticotroph	ACTH, POMC-derived peptides	Cushing's syndrome Nelson's syndrome	10%
Somatotroph	GH α-subunit	Gigantism (children) Acromegaly (adults)	15%
Lactotroph	Prolactin	Galactorrhea and amenorrhea (in females) Infertility, sexual dysfunction	30%
Thyrotroph	TSH α-subunit	Hypothyroidism, hyperthyroidism	<1%
Gonadotroph	FSH, LH α-subunit	Hypogonadism, hypopituitarism	10%
Nonsecretory	–	± Hypopituitarism due to mass effect	25%

[a]Modified from Stoller et al. 2009 [2]. *ACTH* adrenocorticotropic hormone, *POMC* pro-opiomelanocortin, *GH* growth hormone, *TSH* thyroid-stimulating hormone, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone

7.3 Patient Selection for SRS or FSRT

- Factors influencing treatment recommendations include patient age, medical comorbidities, cranial nerve deficits, tumor size and/or growth rate, presenting symptoms, competing symptoms (i.e., vision loss), and proximity to critical organs at risk (such as the optic apparatus).
- For single-fraction SRS, targets should generally be:
  - <3 cm.
  - Not directly abutting critical OARs.
- >3–5 mm from the optic apparatus (optic chiasm, optic nerves) to achieve adequate dose falloff between the prescription dose and OAR tolerance (<8–10 Gy for single-fraction SRS).
- For FSRT, tumors may be larger (> 3–4 cm), in closer proximity to or involving OARs.
- For secretory adenomas, SRS is associated with faster biochemical normalization [3, 4], with a mean time to normalization of 8.5 months for SRS versus 18 months for conventional fractionated radiotherapy [5].
- For nonfunctioning pituitary adenomas that are subtotally resected, multiply recurrent, or patients who are not good surgical candidates, consider fractionated radiation therapy or SRS, depending on proximity to the optic apparatus.
- For prolactinomas, the first-line therapy is a dopamine agonist such as bromocriptine or cabergoline, while surgery is second line, and radiation therapy is reserved for patients who do not respond to or tolerate medical therapy or are not surgical candidates [6].

7.4 Treatment Planning Considerations (Table 7.3)

Table 7.3 Treatment planning considerations

Simulation instructions	**Position**: Supine, arms at sides, head and neck neutral. **Immobilization**: A rigid (frame or frameless) stereotactic immobilization system[a]. – GaK: Head frame in conjunction with a metal collimator helmet. – Linac based: Various, including rigid frame with external skull fixation, noninvasive modified GTC frame (noninvasive fixation by use of a dental plate), or a three-point thermoplastic mask with a modified stereotactic frame (see Fig. 3.1). **CT**: Thin-cut CT images (1.0–3.0 mm slice thickness) ideally with IV contrast spanning from vertex to mid-cervical spine. **Diagnostic imaging**: Co-registration of planning CT with the appropriate diagnostic imaging (contrast-enhanced MRI or CT) for target and OAR delineation. MRI sequences should include pre- and post-contrast T1-weighted, pre-contrast T2-weighted and FLAIR, and multi-planar (axial, sagittal, and coronal) post-contrast T1-weighted images. Post-contrast T1-weighted images with thin (1 mm) sectioning should be obtained. High-resolution series, such as MP-RAGE, should be obtained for contrast-enhancing targets. Cranial nerves may be more readily visualized on a CISS or 3D FIESTA series [7].
Image guidance	Imaging options include CBCT, orthogonal KV X-rays; misalignment corrections via positional systems with four or six rotational axes of the patient couch/platform.
Target delineation	The tumor bed/GTV is defined as the enhancing lesion on the post-gadolinium T1-weighted MRI ([7], and see Fig. 7.1a).
Margins	GTV = CTV. PTV = CTV plus 0–5 mm uniform expansion (depending on institutional setup error, including accuracy and reproducibility of immobilization). Generally CTV plus 3–5 mm uniform expansion for standard thermoplastic mask or CTV plus 0–2 mm uniform expansion for a stereotactic frame.
Tumor/target coverage considerations	≥98% of the GTV/CTV should receive the prescription dose. ≥95% of the PTV should receive the prescription dose.
Treatment modality	Linac, GaK, CyK, proton beam
Planning strategies/ assessment	Steep PTV to OAR dose gradients are generated using multiple beam arrangements or non-coplanar arcs together with dose prescription to the steepest portion of the beam profile (often the 50% IDL for GaK or the 80–90% IDL for linac based). For linac-based SRS, the standard beam profile is shaped by collimation with cones or MLCs. An example treatment plan is depicted in Fig. 7.1b. Notably, as target size increases, the dosimetric advantages of SRS tend to decline—as the sharp dose falloff becomes shallower and the higher doses to adjacent normal tissue become prohibitive, thereby generally precluding safe and effective SRS delivery to targets >3 cm in diameter. The following indices should be generated [8]: **Conformality index**: Prescription isodose volume/target volume (ideally ≤2). **Heterogeneity index**: Maximum dose to target volume/prescription dose (ideally ≤2). **Gradient index**: Volume receiving half the prescription isodose/volume receiving the full prescription isodose (ideally ≥3).

[a]Based on delivery system and institutional protocol. *GTC* Gill-Thomas-Cosman, *FLAIR* fluid-attenuated inversion recovery, *MP-RAGE* magnetization-prepared rapid gradient echo, *CISS* constructive interference in steady state, *FIESTA* 3D fast imaging employing steady-state acquisition

7.5 Commonly Used Dose/Fractionation Schemes

Commonly utilized dose/fractionation schemes for SRS and FSRT are described in Table 7.4.

7.6 Normal Tissue Tolerances

The estimated rates of radiation-induced optic neuropathy are very rare <8–10 Gy but can be >10% at single-SRS doses between 12 and 15 Gy [11, 12] (Table 7.5).

7.7 Patient Management Considerations

- Premedication/prophylactic medication:
  - There is no standard premedication regimen.
  - For secretory adenomas, consider temporary discontinuation of centrally acting medical therapy to enhance radiotherapy response [15].

Table 7.4 Commonly used dose/fractionation schemes

	Patient selection considerations	Dose/fractionation
SRS	Small tumor (<3 cm), >3–5 mm from optic apparatus	Nonsecretory: 12–20 Gy × 1 fx (optimally 14–18 Gy × 1 fx) ACTH secreting: 15–30 Gy × 1 fx (optimally 20–25 Gy × 1 fx) GH secreting: 10–35 Gy × 1 fx (optimally 20–25 Gy × 1 fx) Other secretory: 15–25 Gy × 1 fx [9]
FSRT	Larger tumor and/or <2–3 mm from optic apparatus	7 Gy × 3 fx, 5–5.4 Gy × 5 fx [10]

Fx fraction(s), *ACTH* adrenocorticotropic hormone, *GH* growth hormone

Table 7.5 Normal Tissue Tolerances

Dmax[a] (Gy) in critical structures for SRS and FSRT							
Organ	Authors' recommendations			TG101 [13]			QUANTEC [14]
Fractions	One	Three	Five	One	Three	Five	One
Optic apparatus	≤8 Gy	≤16.5 Gy	≤25 Gy	10 Gy	17.4 Gy	25 Gy	–
Optic chiasm	≤8 Gy	–	–	–	–	–	<12 Gy
Optic nerve	≤8 Gy	–	–	–	–	–	–

[a]Maximum point dose

- Acute toxicity: Treatment is generally well tolerated; transient symptoms such as nausea, headache, alopecia, skin erythema, or fatigue are possible.
- Late toxicity: Hypopituitarism of single or multiple hormonal axes: 20% at 5 years; 80% by 10–15 years, 5–10% with panhypopituitarism [9].

7.8 Follow-Up

- H&P every 6–12 months.
- Yearly imaging (ideally MRI, CT with contrast if non-tolerant, or MRI contra-indicated) for 4–5 years, then every 2 years.
- Secretory adenomas: Monitor for biochemical normalization and hypopituitarism of other axes.
- Nonsecretory and secretory adenomas: Monitor for hypopituitarism with serum analysis every 6 months.
  - Recommend endocrinologist for long-term management and monitoring of endocrine dysfunction.

7.9 Relevant Literature

- Stereotactic radiosurgery and conventionally fractionated radiotherapy are well-established techniques for the treatment of secretory and nonsecretory pituitary adenomas with high local control rates and robust long-term follow-up data.
- While initial data reporting FSRT strategies show promising results in patients with large tumors or those abutting or involving critical OARs, more mature data are required for robust characterization of the long-term efficacy and toxicity profile for FSRT compared to SRS or conventionally fractionated radiotherapy (Table 7.6).

Table 7.6 Relevant Literature

Study	Patients (*n*)	Median follow-up (year)	Mean treatment vol (cm^3)	Modality, median marginal dose, fractionation	LC	Remission
Iwai, 2005 [16]	34 Nonsecretory	5	2.5	GaK, 14 Gy × 1 fx	93% 5 years	NA
Mingione, 2006 [17]	90 Nonsecretory	3.7	4.8	GaK, mean 18.5 Gy × 1 fx	92%	NA

Table 7.6 (continued)

Study	Patients (*n*)	Median follow-up (year)	Mean treatment vol (cm^3)	Modality, median marginal dose, fractionation	LC	Remission
Voges, 2006 [18]	175 – Nonsecretory ($n = 37$) – GH ($n = 64$) – ACTH ($n = 17$) – Nelson's ($n = 9$) – PRL ($n = 13$) – TSH ($n = 2$)	6.8 (mean)	4.3	Linac, mean 15.3 Gy × 1 fx	97%	– 34% 3 years – 51% 5 years
Liscak, 2007 [19]	140 Nonsecretory	5	3.45	GaK, 20 Gy × 1 fx	100%	NA
Pollock, 2008 [20]	62 Nonsecretory	5.3	4.0	GaK, 16 Gy × 1 fx	95% 7 years	NA
Sheehan, 2011 [21]	418 – Nonsecretory ($n = 152$) – GH ($n = 130$) – ACTH ($n = 82$) – Nelson's ($n = 22$) – PRL ($n = 32$)	2.6	1.9	GaK, 24 Gy × 1 fx	90%	49-month median time to remission
Iwata, 2011 [10]	100 Nonsecretory	2.7	5.1	CyK, 5.67–7 Gy × 3 fx or 4.4–5 Gy × 5 fx	97%	NA
Puataweepong, 2015 [22]	40 Secretory and nonsecretory	3.2	3.35	CyK, 5 Gy × 5 fx	98%	54%

Vol volume

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Part II
Malignant Central Nervous System Tumors

Chapter 8
Glioblastoma

Dominic H. Moon and Timothy M. Zagar

Glioblastoma multiforme (GBM) is the most common and most aggressive primary malignant brain tumor in adults. The median age at diagnosis is 64 with a peak incidence in the 75–84 age range. Because GBM is commonly a diagnosis of elderly patients, many with compromised performance status, balancing the therapeutic benefit with toxicity and quality of life is an especially important consideration. Hypofractionated RT has an important role in the treatment of many patients with GBM with best data supporting its use in the elderly population.

8.1 Pearls

- Glioblastoma is the most common adult primary malignant brain tumor accounting for about 55% of all gliomas.
- Incidence is approximately 3 per 100,000 adults per year in the USA with a male:female ratio of 3:2.
- Two-year survival is 25–30%.
- Median age at diagnosis is 64. The incidence rises with age and peaks at age 75–84.
- The vast majority of glioblastomas are sporadic. Genetic predisposition has been shown with *TP53* gene mutation, neurofibromatosis I, and Turcot syndrome.
- There is insufficient evidence that exposure to electromagnetic fields or cell phones increases the risk of brain tumors.

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- Median survival of glioblastoma patients is 12–15 months with a 2-year survival of 25–30%, but the prognosis varies based on age, performance status, extent of resection, and location of the tumor (refer to 8.2).
- Methylation of methyl guanine methyl transferase (MGMT) is both predictive for response to DNA-alkylating agents (e.g., temozolomide) and prognostic for survival.
- Presenting symptoms can include headaches, nausea/vomiting, neurologic deficits, and/or seizures.
- Brain tumors are classified based on the World Health Organization (WHO) classification system. Glioblastoma is grade IV.
- MRI brain with contrast is part of a standard workup. Glioblastoma is typically ring enhancing or heterogeneously enhancing. Postoperative MRI brain helps to evaluate the extent of resection and the tumor bed for treatment planning.
- Tissue diagnosis is required and can be obtained via stereotactic biopsy, open biopsy, or gross resection.

8.2 Prognosis Based on Recursive Partitioning Analysis (RPA)

Simplified RPA based on RTOG glioma database [1].

RPA class	Defining variables	Median survival (months)	Overall survival		
			1 year	3 years	5 years
III	Age <50, KPS ≥90	17.1	70%	20%	14%
IV	Age <50, KPS <90 Age ≥50, KPS ≥70, resection, working	11.2	46%	7%	4%
V + VI	Age ≥50, KPS ≥70, resection, not working Age ≥50, KPS ≥70, biopsy only Age ≥50, KPS <70	7.5	28%	1%	0%

Abbreviations: *KPS* Karnofsky performance status

RPA of patients ≥70 years of age [2].

RPA subgroup	Defining variables	Median survival (months)	
		US data	French data
I	GTR/PR, age <75.5	9.3	8.5
II	GTR/PR, age >75.5	6.4	7.7
III	Biopsy, KPS ≥70	4.6	4.3
IV	Biopsy, KPS <70	2.3	3.1

Abbreviations: *GTR* gross total resection, *PR* partial resection, *KPS* Karnofsky performance status

8.3 Tumor/Patient Selection

- First step in management is maximal surgical resection as feasible.
- In general, patients aged 65 and younger with Karnofsky performance status (KPS) ≥60 should receive standard fractionation RT (e.g., 60 Gy in 30 fractions) + concurrent and adjuvant temozolomide.
- Patients older than 65–70 with KPS ≥60 can be considered for hypofractionated RT ± concurrent and adjuvant temozolomide.
- Patients of any age with KPS <60 can be considered for hypofractionated RT alone, temozolomide alone, or palliative/best supportive care based on MGMT methylation status, comorbidities, and overall clinical picture.

8.4 Treatment Planning Considerations

Simulation instructions	– Timing: Simulate patient 10–14 days after surgery/biopsy – Position: Supine – Immobilization: Customized head cast (Fig. 8.1) – 3D CRT vs. IMRT should be used – 3D CRT: Better dose homogeneity – IMRT: Better sparing of critical structures (e.g., optic structures, brainstem), increased low-dose radiation scattering – Fuse postoperative brain MRI to help delineate target volume
Image guidance	3D CRT: Weekly port films IMRT: Cone beam CT or kV onboard imaging as appropriate (1–5 times a week)
Margins	GTV: T1 post-contrast volume (resection bed and any residual tumor) CTV1*: T2 or FLAIR volume (edema) + 1–2 cm margin CTV2*: GTV + 1–2.5 cm margin PTV: CTV + 0.3–0.5 cm margin * CTV expanded as above excluding brainstem, chiasm, nerve, and bone (Figs. 8.2 and 8.3)
Dosimetric considerations	95% of the PTV receives 100% of the Rx ≤1% of non-PTV tissue receives >110% of the Rx

Fig. 8.1 CT simulation with a customized head cast

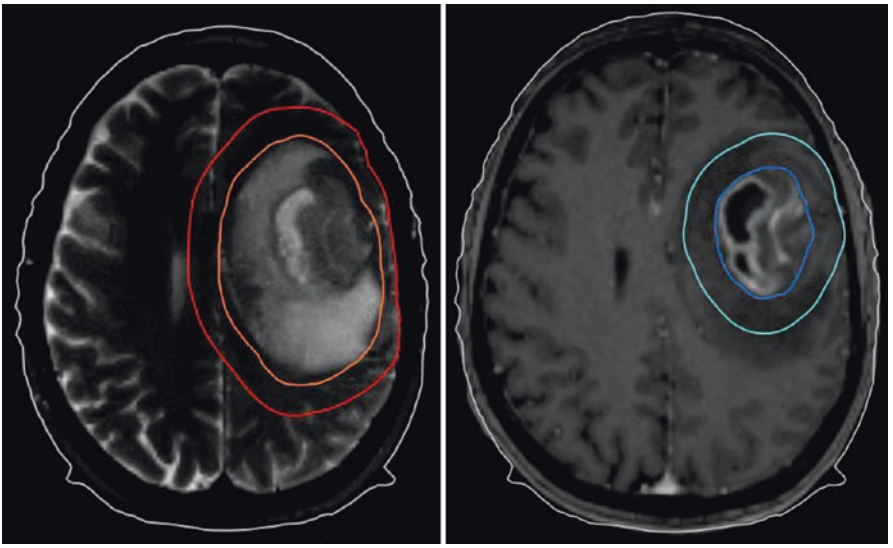

Fig. 8.2 Target delineation. CTV1 based on the volume of edema (orange) with a 1 cm margin excluding the skull (red) on MR T2 sequence (left image). GTV volume (blue) with a 1 cm margin for CTV2 (turquoise) based on post-contrast MR T1 sequence (right image). For hypofractionated RT, CTV1 volume is used for the entire treatment course

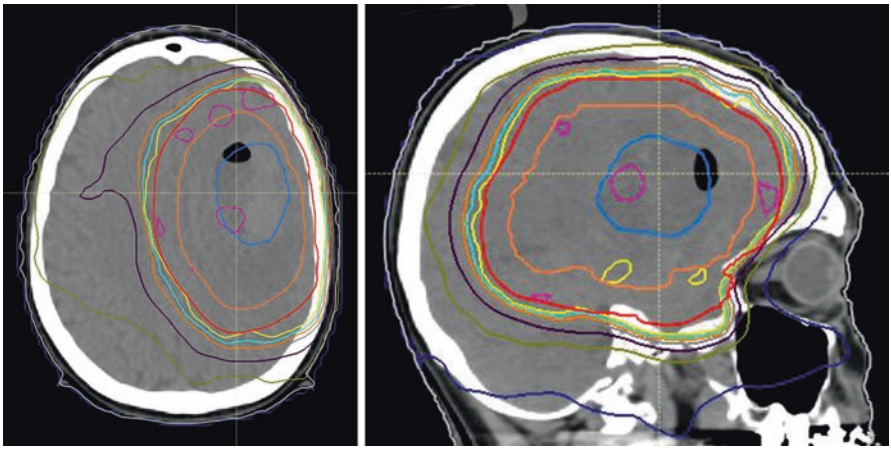

Fig. 8.3 Treatment plan using IMRT to spare optic structures, brainstem, and normal brain in the setting of a large treatment volume

8.5 Commonly Used Dose/Fractionation Schemes

Target	Dose per fraction (Gy)	# of fractions	Total dose (Gy)	Notes
Standard fractionation				
PTV1	2	23	46	Age ≤65, KPS ≥60
PTV2	2	7	14	Generally with concurrent temozolomide
Total	2	30	60	Either fractionation schedule is acceptable
PTV1	1.8	25	45	
PTV2	1.8	8	14.4	
Total	1.8	33	59.4	
Hypofractionation				
PTV1 [3, 4]	2.67	15	40.05	Age >65–70, KPS ≥60, ±temozolomide Any age, KPS <60
PTV1 [5]	3.4	10	34	
PTV1 [6]	5	5	25	In elderly and/or frail patients, if longer course is not feasible
Whole brain [7]	3	10	30	Alternative to involved-field radiation for elderly patients with poor performance status

At our institution, patients older than 70 with good performance status (KPS ≥60) receive hypofractionated RT (2.67 Gy × 15 = 40.05 Gy) with concurrent and adjuvant temozolomide, unless concurrent temozolomide is considered inappropriate by our multidisciplinary team. Patients aged 65–70 with good performance status receive standard RT (2 Gy × 30 = 60 Gy) or hypofractionated RT with concurrent and adjuvant temozolomide. Patients with poor performance status (KPS <60) regardless of age receive hypofractionated RT alone (especially if MGMT unmethylated), temozolomide alone (only if MGMT methylated), or best supportive care.

8.6 Normal Tissue Tolerances (QUANTEC)

Organ	QUANTEC (constraint and endpoint)	Our institutional practice
Brain parenchyma	Dmax = 72 Gy 5% symptomatic necrosis	No standard constraints have been established in the setting of hypofractionated RT to doses ≤40 Gy
	Dmax <60 Gy <3% symptomatic necrosis	
Brainstem	Dmax <54 Gy Point dose Dmax <64 Gy <5% permanent cranial neuropathy or necrosis	
Optic nerve/ chiasm	Dmax >60 Gy >7% optic neuropathy	
	Dmax = 55–60 Gy 3–7% optic neuropathy	
	Dmax <55 Gy <3% optic neuropathy	
Spinal cord	Dmax = 69 Gy 50% myelopathy	
	Dmax = 60 Gy 6% myelopathy	
	Dmax = 50 Gy 0.2% myelopathy	
Cochlea	Mean dose ≤45 Gy <30% sensory neural hearing loss	
Parotid (bilateral)	Mean dose <25 Gy <20% parotid function reduced to <25% of pre-RT	
Parotid (unilateral)	Mean dose <20 Gy <20% parotid function reduced to <25% of pre-RT	

8.7 Patient Management Considerations

- Premedication: Patients should be evaluated for steroids as appropriate based on symptoms. Routine premedication is not indicated.
- Acute toxicity: Acute symptoms are generally self-limited and mild. Pain and nausea medications are used as needed.
  - Fatigue: Up to 90% of patients. Many patients recover over several weeks, but some may experience chronic fatigue.
  - Nausea: Approximately 30% of patients. Generally well controlled on anti-emetics (e.g., ondansetron 4–8 mg q8h prn).
  - Headaches: Symptoms may occur due to inflammation and potential transient increase in cerebral edema. Headaches can be managed with over-the-counter pain medications as needed. Patients with significant pretreatment cerebral edema should be placed on dexamethasone (4 mg BID-QID) prior to RT.

  - Scalp erythema: Generally mild and treated with moisturizing cream (e.g., calendula cream) as needed.
  - Alopecia: Hair loss occurs at the site of radiation treatment. Severity and permanence are dose dependent.
- Late toxicity: Difficult to attribute to treatment due to multiple confounding factors including disease progression, medications (e.g., anticonvulsants), and comorbidities.
  - Neurocognitive decline: Patients receiving RT may experience decline in memory and executive functioning. Retrospective and small prospective studies suggest that bevacizumab may improve or preserve neurocognitive function in poor-prognosis glioblastoma patients [8].
  - Radiation necrosis: Radiation necrosis typically occurs 1–3 years after RT at or adjacent to the original tumor, which can cause neurologic symptoms based on the location. It is often difficult to distinguish recurrence with radiation necrosis. Radiation necrosis is managed conservatively if asymptomatic or with moderate-dose steroids (e.g., dexamethasone 4 mg BID) if symptomatic. Surgical resection for palliation may be needed in severe cases.

8.8 Follow-Up

- According to NCCN guidelines [9]:
  - First MRI brain 2–6 weeks after RT.
  - Follow-up q2–4 months with MRI brain for the first 2–3 years.
  - Follow-up less frequently as appropriate after 3 years.

8.9 Relevant Literature

Study	Patients	Treatment	Median f/u	Outcomes
Randomized trials				
Roa 2004 [3]	*N* = 100 Age ≥60 KPS ≥50	1. 2 Gy × 30 = 60 Gy 2. 2.67 Gy × 15 = 40 Gy	Not reported	**1. Standard fx:** – 5.1-month median OS – 49% requiring post-RT steroid dose increase **2. Hypofx:** – 5.6-month median OS (p = NS) – 23% requiring post-RT steroid dose increase (p = 0.02)
Souhami 2004 (RTOG 93–05) [10]	*N* = 206 GBM ≤4 cm KPS ≥60	1. Post-op SRS (15–24 Gy × 1) + EBRT (60 Gy) + carmustine 2. EBRT (60 Gy) + carmustine	61 months	**1. Post-op SRS:** – 13.5-month median OS **2. No post-op SRS:** – 13.6-month median OS (p = NS)

Study	Patients	Treatment	Median f/u	Outcomes
Malmstrom 2012 [5]	*N* = 342 Age ≥60 WHO PS 0–2	1. Temozolomide 2. 3.4 Gy × 10 = 34 Gy 3. 2 Gy × 30 = 60 Gy	Not reported	**1. Temozolomide:** – 8.3-month median OS – 9.0-month median OS (age > 70) **2. Hypofx:** – 7.5-month median OS – 7.0-month median OS (age > 70) **3. Standard fx:** – 6-month median OS (p = NS vs. hypofx, p = 0.01 vs. temozolomide) – 5.2-month median OS (age >70) (p = 0.02 vs. hypofx, p < 0.0001 vs. temozolomide)
Roa 2015 [6]	*N* = 98 Frail: age ≥50 and KPS 50–70% Elderly and frail: age ≥65 and KPS 50–70% Elderly: age ≥65 and KPS 80–100%	1. 5 Gy × 5 = 25 Gy 2. 2.67 Gy × 15 = 40 Gy	6.3 months	**1. 5 Gy × 5** – 7.9-month median OS – 4.2-month median PFS **2. 2.67 Gy × 15** – 6.4-month median OS (p = NS) – 4.2-month median PFS (p = NS)
Perry 2017 [4]	*N* = 562 Age ≥65 ECOG 0–2	1. EBRT (2.67 Gy × 15 = 40 Gy) 2. EBRT + temozolomide	17 months	**1. Hypofx** – 7.6-month median OS – 7.7-month median OS (MGMT methylated) – 7.9-month median OS (MGMT unmethylated) – 3.9-month median PFS **2. Hypofx + temozolomide** – 9.3-month median OS (p < 0.001) – 13.5-month median OS (MGMT methylated) (p < 0.001) – 10-month median OS (MGMT unmethylated) (p = 0.055) – 5.3-month median PFS (p < 0.001)

Study	Patients	Treatment	Median f/u	Outcomes
Prospective non-randomized studies				
Bauman 1994 [7] (phase II)	$N = 29$ Age ≥65 KPS ≤50	3 Gy × 10 = 30 Gy (whole-brain RT)	Not reported	– 6-month median OS

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Chapter 9
Secondary Malignant (Metastases)

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Brain metastasis is the most common indication for stereotactic radiosurgery (SRS). SRS is a safe and effective treatment modality for patients with good performance status and limited number of brain metastases. In addition, SRS serves as an adjuvant therapy for resected brain lesions. Accumulating studies also support the use of hypofractionated stereotactic radiotherapy (HSRT) delivering 27–35 Gy in 3–5 fractions for relatively large brain lesions and resection beds.

9.1 Pearls

- Brain metastases are the most common intracranial tumors in adults.
- Incidence of brain metastases has been increasing due to improvement in detection with MRI and improvement in extracranial disease control with systemic therapy.
- Up to 30% of patients with cancer develop brain metastases.
- Common primary malignancies metastasizing to the brain include lung cancer, breast cancer, melanoma, and renal cell cancer.
- Metastases are most commonly located at the grey-white matter junction.
- Distribution of metastases is approximately proportional to the blood flow to the different parts of the brain: cerebral hemispheres (80%), cerebellum (15%), and brainstem (5%).
- Patients commonly present with headaches, focal neurologic dysfunction, cognitive dysfunction, seizures, and/or stroke.

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- The imaging study of choice is a contrast-enhanced brain MRI. Brain metastases are suspected by the presence of multiple lesions, localization at the grey-white matter junction, circumscribed margins, and presence of vasogenic edema.

9.2 Prognosis Based on Diagnosis-Specific Graded Prognostic Assessment (DS-GPA)

Non-small cell lung cancer (Lung-molGPA) [1].

	GPA scoring criteria		
Prognostic factor	0	0.5	1.0
Age (years)	≥70	<70	–
KPS	≤70	80	90–100
ECM	Present	–	Absent
No. of BM	>4	1–4	–
Gene status	*EGFR* neg/unk and *ALK* neg/unk	–	*EGFR* pos or *ALK* pos
Median survival (months) by GPA score	Adenocarcinoma: 0–1.0 = 6.9; 1.5–2.0 = 13.7; 2.5–3.0 = 26.5; 3.5–4.0 = 46.8 Non-adenocarcinoma: 0–1.0 = 5.3; 1.5–2.0 = 9.8; 2.5–3.0 = 12.8		

Abbreviations: *KPS* Karnofsky performance score, *ECM* extracranial metastases, *BM* brain metastases, *neg/unk* negative or unknown, *pos* positive

Melanoma (Melanoma-molGPA) [2].

	GPA scoring criteria		
Prognostic factor	0	0.5	1.0
Age (years)	≥70	<70	
KPS	≤70	80	90–100
ECM	Present	–	Absent
No. of BM	>4	2–4	1
BRAF gene status	Negative/unknown	Positive	
Median survival (months) by GPA score	0–1.0 = 4.9; 1.5–2.0 = 8.3; 2.5–3.0 = 15.8; 3.5–4 = 34.1		

Abbreviations: *KPS* Karnofsky performance score, *ECM* extracranial metastases, *BM* brain metastases

Breast cancer [3].

Prognostic factor	GPA scoring criteria				
	0	0.5	1.0	1.5	2.0
KPS	≤50	60	70–80	90–100	–
Subtype[a]	Basal	–	LumA	HER2	LumB
Age (years)	≥60	<60	–	–	–
Median survival (months) by GPA score	0–1.0 = 3.4; 1.5–2.0 = 7.7; 2.5–3.0 = 15.1; 4.5–4.0 = 25.3				

Abbreviations: *KPS* Karnofsky performance score
[a]Breast cancer subtype: Basal—triple negative; LumA—ER/PR positive, HER2 negative; HER2—ER/PR negative, HER2 positive; LumB—triple positive

Renal cell carcinoma [3].

Prognostic factor	GPA scoring criteria		
	0	1	2
KPS	<70	70–80	90–100
No. of BM	>3	2–3	1
Median survival (months) by GPA score	0–1 = 3.3; 2 = 7.3; 3 = 11.3; 4 = 14.8		

Abbreviations: *KPS* Karnofsky performance score, *BM* brain metastases

GI cancers [3].

Prognostic factor	GPA scoring criteria				
	0	1	2	3	4
KPS	≤60	70	80	90	100
Median survival (months) by GPA score	0–1 = 3.1; 2 = 4.4; 3 = 6.9; 4 = 13.5				

Abbreviations: *KPS* Karnofsky performance score

9.3 Tumor/Patient Selection

- SRS is generally recommended for patients with good performance status (KPS ≥70).
- Patients with brain metastases and a KPS <70 have poor overall prognosis, and should be considered for whole-brain radiotherapy (WBRT) versus best supportive care [4].
- Indications for SRS:
  - 1–4 brain metastases and surgery are not feasible secondary to location, comorbidities, or patient preference.
  - Status post-resection of a dominant or a few brain metastases (postoperative RT).

- SRS can also be considered for patients with good performance status and 4–10 brain metastases with low tumor burden (i.e., total volume of disease in the brain is low) [5].
- For patients with limited number of brain metastases, adding WBRT to SRS is generally not recommended. Although SRS + WBRT improves local and distant brain control, it leads to significant cognitive decline without improvement in overall survival [6, 7].
- Dose and fractionation are selected based on size and setting (refer to 9.5 and 9.9 for details):
  - For lesions ≤40 mm, a single-fraction SRS is given with doses of 15–24 Gy based on size.
  - For larger lesions or lesions near critical structures such as the brainstem and optic apparatus, a lower dose (12–14 Gy) can be used in a single-fraction SRS or Fractionated stereotactic radiotherapy (FSRT) with doses of 24–35 Gy in 3–5 fractions.
  - In the postoperative setting, SRS/HSRT to the surgical bed in 1–5 fractions is an alternative to WBRT.
- Re-irradiation with SRS is used in some institutions as salvage therapy for local failure after initial SRS. Several retrospective series report good local control rates but relatively high risk of radiation necrosis [8]. For select patients (surgically inaccessible local recurrence, small and limited number of lesions, etc.), repeat SRS may be an option, but the authors urge caution.

9.4 Treatment Planning Considerations

Simulation instructions	– Position: Supine – Immobilization: Customized head cast – 1 mm thick CT slices – Fuse MR brain (1 mm slices preferred) to help delineate target volume – Fuse pre- and postoperative MR for surgical bed treatment
Image guidance	Linac: Daily cone beam CT CyberKnife: Continuous skull tracking
Margins	– The authors use no CTV or PTV expansions for intact brain metastasis (Figs. 9.1 and 9.2) – Consider 1–2 mm expansion of postoperative bed CTV for resected brain metastasis (Fig. 9.3)
Tumor coverage considerations	– 100% of GTV (or CTV for postoperative cases) receives 100% of Rx (if GTV/CTV ≤20 mm) – ≥95% of GTV (or CTV for postoperative cases) receives 100% of Rx (if GTV/CTV >20 mm)

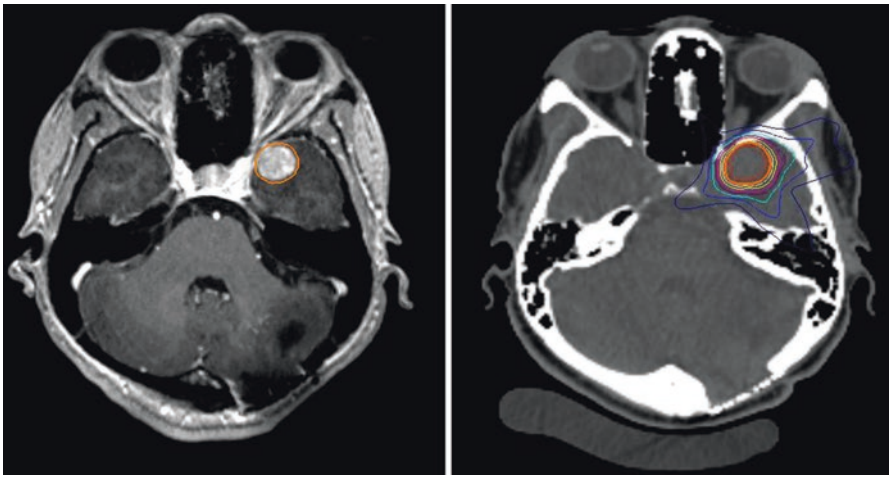

Fig. 9.1 Contouring of a left temporal lobe metastasis based on contrast-enhanced MR brain (left) and the treatment plan sparing optic structures (right)

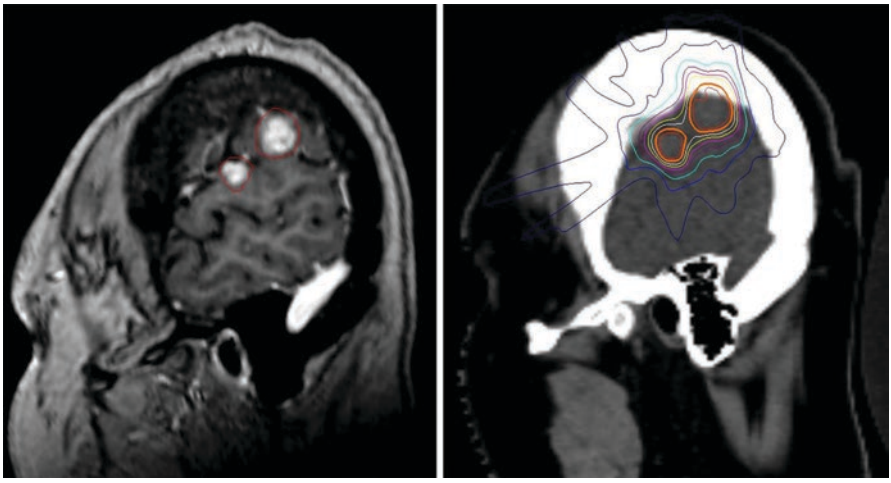

Fig. 9.2 Sagittal view of two adjacent left temporal brain metastases (left) and the treatment plan targeting both lesions (right)

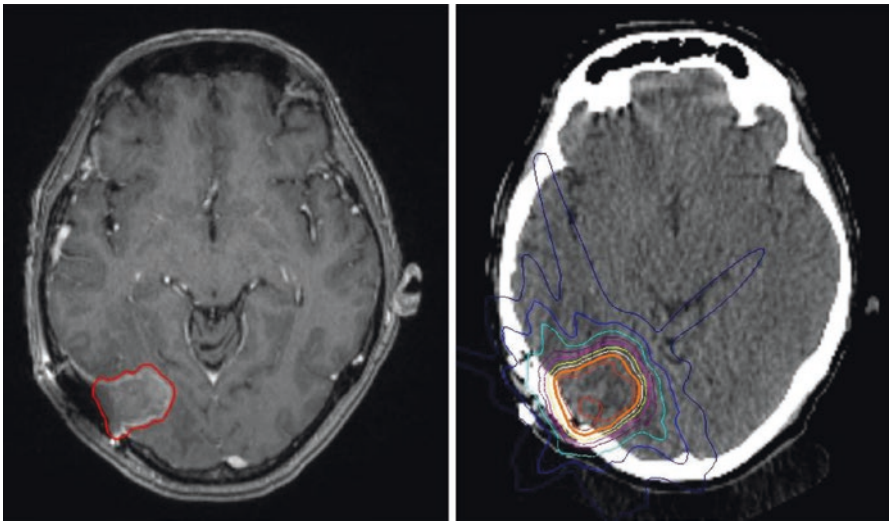

Fig. 9.3 Contouring of a right occipital surgical bed following a resection of a renal cell metastasis based on the postoperative contrast-enhanced MR brain (left) and the treatment plan (right)

9.5 Commonly Used Dose/Fractionation Schemes

Dose per fraction (Gy)	# of fractions	Total dose (Gy)	Notes
SRS for intact lesions			
RTOG 90–05 [9]			
20–24	1	20–24	≤20 mm
18	1	18	21–30 mm
15	1	15	31–40 mm
Hypofractionated stereotactic radiotherapy			
Manning 2000 [10]			
9	3	27	≤3 brain mets, median dose
Aoyama 2003 [11]			
8.75	4	35	≤4 brain mets, median dose
Ernst-Stecken 2006 [12]			
6	5	30	If combined with WBRT
7	5	35	All others
Murai 2014 [13]			
9–10	3	27–30	25–39 mm
6.2–7	5	31–35	≥40 mm
Postoperative SRS			
Minniti 2013 [14]			
9	3	27	>30 mm
N107C/CEC.3 [15]			

Dose per fraction (Gy)	# of fractions	Total dose (Gy)	Notes
20	1	20	<4.2 cc
18	1	18	≥4.2 and <8.0 cc
17	1	17	≥8.0 and <14.4 cc
15	1	15	≥14.4 and <20 cc
14	1	14	≥20 and <30 cc
12	1	12	≥30 cc and <5 cm
Mahajan 2016 [16]			
16	1	16	≤10 cc
14	1	14	10.1–15 cc
12	1	12	>15 cc

For intact lesions, the authors use 20 Gy × 1 = 20 Gy if ≤20 mm, 18 Gy × 1 = 18 Gy if 21–30 mm, and 6 Gy × 5 = 30 Gy if >30 mm. In general, postoperative CTV is >30 mm and 6 Gy × 5 = 30 Gy is used

9.6 Normal Tissue Tolerances

	TG101	QUANTEC	Our institutional practice
Brain parenchyma			
One fraction	NA	V12 <5–10 cc	V12 <10 cc
Toxicity	NA	<20% symptomatic necrosis	<20% symptomatic necrosis
Brainstem			
One fraction Three fractions Five fractions	Dmax ≤15 Gy, V10 <0.5 cc Dmax ≤23.1 Gy, V18 <0.5 cc Dmax ≤31 Gy, V23 <0.5 cc	Dmax <12.5 Gy	Same as TG101
Toxicity	≥grade 3 cranial neuropathy	<5% permanent cranial neuropathy or necrosis	≥grade 3 cranial neuropathy
Optic pathway			
One fraction Three fractions Five fractions	Dmax ≤10 Gy, V8 <0.2 cc Dmax ≤17.4, V15.3 <0.2 cc Dmax ≤25, V23 <0.2 cc	Dmax <12 Gy	Same as TG101
Toxicity	≥grade 3 neuritis	<10% optic neuropathy	≥grade 3 neuritis
Spinal cord			
One fraction Three fractions Five fractions	Dmax ≤14 Gy, V10 <0.35 cc, V7 <1.2 cc Dmax ≤21.9 Gy, V18 <0.35 cc, V12.3 <1.2 cc Dmax ≤30 Gy, V23 <0.35 cc, V14.5 <1.2 cc	Dmax = 13 Gy	Same as TG101

	TG101	QUANTEC	Our institutional practice
Toxicity	≥grade 3 myelitis	1% myelopathy	≥grade 3 myelitis
Cochlea			
One fraction Three fractions Five fractions	Dmax ≤9 Gy Dmax ≤17.1 Gy Dmax ≤25 Gy	Dose ≤14 Gy (prescription dose)	Same as TG101
Toxicity	≥grade 3 hearing loss	<25% sensory neural hearing loss	≥grade 3 hearing loss

9.7 Patient Management Considerations

- Premedication: If the patient is not already on steroids, premedicate with dexamethasone 4 mg PO prior to each fraction. Lorazepam 0.5–1 mg PO can be used prior to each fraction.
- Acute toxicities can include mild nausea, headaches, and in rare cases, new-onset seizures.
- The main dose-limiting late toxicity of SRS is radiation necrosis, which occurs in 5–10% of cases, 6 months to years after treatment.
  - Factors associated with increased risk of radiation necrosis include larger size of the brain metastasis and a history of prior radiation to the same region. Other tumor biology characteristics including renal cell or lung adenocarcinoma histology, HER2 amplification, and ALK/BRAF mutation may increase the risk of radiation necrosis [17].
  - Radiation necrosis is managed conservatively if asymptomatic or with moderate-dose steroids (e.g., dexamethasone 4 mg BID) if symptomatic. Surgical resection for palliation may be needed in severe cases.

9.8 Follow-Up

- According to NCCN guidelines [18]:
  - Brain MRI q2–3 months for the first year
  - Follow-up and imaging as clinically indicated after 1 year

9.9 Relevant Literature

Study	Patients	Treatment	Median f/u	Outcomes
Dose escalation				
RTOG 90–05 [9] (phase I trial)	*N* = 156 Patients previously treated with WBRT	SRS dose escalation: ≤ 20 mm: 18 –> 21 –> 24 Gy 21–30 mm: 15 –> 18 –> 21 –> 24 Gy 31–40 mm: 12 –> 15 –> 18 Gy	3 years	– Maximum tolerated dose: ≤ 20 mm: 24 Gy 21–30 mm: 18 Gy 31–40 mm: 15 Gy – Total grade 3–5 toxicity: ≤ 20 mm: 18 Gy (8%), 21 Gy (11%), 24 Gy (10%) 21–30 mm: 15 Gy (13%), 18 Gy (20%), 21 Gy (38%), 24 Gy (58%) 31–40 mm: 12 Gy (10%), 15 Gy (14%), 18 Gy (50%)
WBRT ± SRS boost				
RTOG 95–08 [19] (randomized trial)	*N* = 333 KPS ≥70, 1–3 mets ≤40 mm	1. WBRT (37.5 Gy) 2. WBRT + SRS boost (15–24 Gy per RTOG 90–05)	Not reported	1. **WBRT** – 5.7-month median OS – 4.9-month median OS (single met) – 71% 1-year LC – 27% stable/improved KPS at 6 months 2. **WBRT + SRS** – 6.5-month median OS (p = NS) – 6.5 months (single met) (p = 0.039) – 82% 1-year LC (p = 0.013) – 43% stable/improved KPS at 6 months (p = 0.03)
SRS ± WBRT				
JROSG 99–1 [20] (randomized trial)	*N* = 132 KPS ≥70, 1–4 mets ≤30 mm	1. SRS (18–25 Gy) 2. SRS (30% reduction) + WBRT (30 Gy)	7.8 months (entire study) 49.2 months (survivors)	1. **SRS** – 8-month median OS – 73% 1-year LC – 76% 1-year brain tumor recurrence 2. **SRS + WBRT** – 7.5-month median OS (p = NS) – 89% 1-year LC (p = 0.002) – 47% 1-year brain tumor recurrence (p < 0.001)

Study	Patients	Treatment	Median f/u	Outcomes
Chang 2009 [6] (randomized trial)	*N* = 58 KPS ≥70, 1–3 mets	1. SRS (15–20 Gy) 2. SRS + WBRT (30 Gy)	9.5 months	1. **SRS** – 15.2-month median OS – 67% 1-year LC – 24% mean probability of neurocognitive decline at 4 months 2. **SRS + WBRT** – 5.7-month median OS ($p = 0.003$) – 100% 1-year LC ($p = 0.01$) – 52% mean probability of neurocognitive decline at 4 months
EORTC22952–26001 [21] (randomized trial)	*N* = 359 ECOG 0–2, 1–3 mets ≤35 mm	1. SRS (14–25 Gy) 2. SRS + WBRT (30 Gy)	1. **SRS:** 40 months 2. **SRS + WBRT:** 49 months	1. **SRS:** – 10.7-month median OS – 69% 2-year LC 2. **SRS + WBRT** – 10.9-month median OS (p = NS) – 81% 2-year LC ($p = 0.04$)
Brown 2016 [7] (randomized trial)	*N* = 213 ECOG 0–2, 1–3 mets < 30 mm	1. SRS (20–24 Gy) 2. SRS (18–22 Gy) + WBRT (30 Gy)	7.2 months	1. **SRS** – 10.4-month median OS – 73% 1-year LC – 64% cognitive deterioration at 3 months – 0.1 mean decline from baseline in overall quality-of-life score 2. **SRS + WBRT** – 7.4-month median OS (p = NS) – 90% 1-year LC ($p = 0.003$) – 92% cognitive deterioration at 3 months ($p < 0.001$) – 12 mean decline from baseline in overall quality-of-life score ($p = 0.001$)

Study	Patients	Treatment	Median f/u	Outcomes
Number of metastases				
Likhacheva 2013 [22] (retrospective study)	*N* = 251 brain mets (median 2, range 1–9)	– SRS alone (62% of patients, median dose: 20 Gy) – SRS + salvage SRS (22%), WBRT (13%), or surgery (3%)	9.4 months	– 11.1-month median OS – 94.6% 1-year LC – Factors associated with OS on multivariable analysis: Total tumor volume >2 cc, age ≥60, diagnosis-specific graded prognostic assessment, and extracranial disease – Number of brain mets not associated with OS
JLGK0901 [5] (prospective observational cohort study)	*N* = 1194 KPS ≥70, 1–10 brain mets < 3 cm each, <10 cc each, ≤15 cc total volume	SRS: <4 cc: 22 Gy 4–10 cc: 20 Gy	20.9 months (survivors)	1. **1 metastasis** – 13.9 median OS – 7% any grade toxicity 2. **2–4 metastases** – 10.8 median OS – 9% any grade toxicity 3. **5–10 metastases** – 10.8 median OS (p = NS vs. 2–4 metastases) – 9% any grade toxicity (p = NS vs. 2–4 metastases)
Hypofractionated stereotactic radiotherapy				
Manning 2000 [10] (phase II)	*N* = 32 ≤3 brain mets	HSRT with a linac Median 9 Gy × 3 = 27 Gy to the 80–90% isodose line	37 weeks (survivors)	– 11.8-month median OS – Acute toxicity: None – Late toxicity: Seizures (13%), radionecrosis (6%)
Ernst-Stecken 2006 [12] (phase II)	*N* = 51 KPS ≥60, ≤3 brain mets	HSRT with a linac 7 Gy × 5 = 35 Gy to the 90% isodose line 6 Gy × 5 = 30 Gy if additional WBRT	7 months	– 11-month median OS – 76% 1-year LC – Acute toxicity: None – Increasing rates of edema and necrosis if V4 ≥23 cc
Ammirati 2014 [23] (phase II)	*N* = 40 KPS ≥60, ≤3 brain mets	HSRT with a linac 6 Gy × 5 = 30 Gy Definitive or adjuvant following a surgical resection	16 months	– 16-month median OS – 11-month median PFS – 13% neurological death rate – Acute toxicity: None – Late toxicity: 8% radiation necrosis

Study	Patients	Treatment	Median f/u	Outcomes
Aoyama 2003 [11] (retrospective)	*N* = 87 ≤4 brain mets	HSRT with a linac Median 35 Gy/4 fx to the 80–90% isodose line	6.3 months (entire study) 7.6 months (survivors)	– 8.7-month median OS – 81% 1-year LC – Acute toxicity: 2% nausea, 1% hypomnesia, 1% seizure – Late toxicity: 1% nausea, 1% hemiparesis
Murai 2014 [13] (retrospective)	*N* = 54 brain mets ≥2.5 cm	HSRT with a linac Dose escalation: 3fx (2.5–3.9 cm): 18–22 Gy to 27–30 Gy 5 fx (≥ 4 cm): 21–25 Gy to 31–35 Gy	Not reported	– 6-month median OS – 78% 1-year LC – No ≥grade 3 toxicity at every level of dose
Postoperative SRS				
Mahajan 2016 [16] (randomized trial)	*N* = 131 1–3 mets, ≥1 met with complete resection, ≤4 cm resection cavity	1. SRS (12–16 Gy) 2. observation of the resection cavity	11.1 months	1. **SRS** – 17-month median OS – 72% 1-year LC 2. **Observation** – 18-month median OS (p = NS) – 43% 1-year LC (p = 0.015)
N107C/CEC.3 [15] (randomized trial)	*N* = 194 1–4 mets, s/p surgical resection of 1 met, <5 cm resection cavity	1. SRS (12–20 Gy) 2. WBRT (30 or 37.5 Gy) Unresected mets treated with SRS in both arms	11.1 months	1. **SRS** – 12.2-month median OS – 3.7-month cognitive deterioration-free survival – 60.5% 1-year surgical bed control – 36.6% 1-year overall brain control 2. **WBRT** – 11.6-month median OS (p = NS) – 3.0-month cognitive deterioration-free survival (p < 0.0001) – 80.6% 1-year surgical bed control (p = 0.00068) – 72.1% 1-year overall brain control (p < 0.0001)
Brennan 2014 [24] (phase II)	*N* = 49 1–2 brain mets s/p resection	SRS with a linac ≤ 2 cm: 22 Gy 2.1–3 cm: 18 Gy 3.1–4 cm: 15 Gy	12 months	– 78% 1-year LC – 56% 1-year distant brain control – Toxicity: 17.5% with radionecrosis

Study	Patients	Treatment	Median f/u	Outcomes
Jensen 2011 [25] (retrospective)	*N* = 106 s/p surgical resection, no prior WBRT	SRS with GammaKnife Median dose of 17 Gy to the 50% isodose line	Not reported	– 10.9-month median OS – 80.3% 1-year LC – 35.4% 1-year distant brain control – 37% received salvage WBRT at a median of 12.6 months
Choi 2012 [26] (retrospective)	*N* = 112 s/p surgical resection	SRS with CyberKnife Median dose of 20 Gy in 1–5 fx to a median 79% isodose line, 2 mm margin	11 months	– 17-month median OS – 90.5% 1-year LC – 46% 1-year distant brain control – 28% received salvage WBRT at a median on 7 months
Minniti 2013 [14] (retrospective)	*N* = 101 s/p surgical resection (resection cavity >3 cm)	SRS with a linac 9 Gy × 3 = 27 Gy to a median 83% isodose line, 2 mm margin	16 months	– 17-month median OS – 93% 1-year LC – 50% 1-year distant brain control – 24% received salvage WBRT

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Part III
Head and Neck Tumors

Chapter 10
Nasopharynx

Gregory D. Judy and Bhishamjit S. Chera

10.1 Pearls [1, 2]

- ~86,000 annual cases worldwide. Distinct geographic distribution with high incidence in southern China and Hong Kong (25–50 cases/100,000 people), while more uncommon in the USA and Western Europe (0.2–0.5 cases/100,000 people).
- More common in men (2–3:1). Two age peaks: 15–25 years and 50–60 years.
- Strong association with EBV (70–80% of patients); other risk factors include tobacco, alcohol, and preserved or fermented food consumption.
- Higher incidence with known first-degree relative.
- Most common presenting symptoms include headache, diplopia, facial numbness (from cranial nerve involvement), and neck mass (from nodal involvement). Other symptoms can include nasal pain/obstruction, epistaxis, serous otitis media, tinnitus, hearing loss, or other cranial nerve involvement (III, IV, V, VI most common).
- Local anatomy:
  - Arises from epithelial lining of the nasopharynx.
  - Three histological subtypes: WHO I (keratinizing SCC, ~25% of US cases), WHO II (nonkeratinizing, differentiated SCC, ~12% of US

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cases), and WHO III (nonkeratinizing, undifferentiated, ~63% US of cases vs. 95% of Chinese cases). There is also a basaloid SCC, noted to be more aggressive with poor survival.
  - Anatomical borders of nasopharynx:
  - Anterior—posterior nasal septum and nasal apertures
  - Posterior—pharyngeal mucosa
  - Superior—sphenoid bone
  - Inferior—roof of the soft palate
  - The lateral wall contains pharyngeal opening of the Eustachian tubes; a protuberance (torus tubarius) is created at the posterior aspect of the orifice. Posterior to the torus tubarius is the fossa of Rosenmüller (most common primary site).
- Common pathways of local spread include along the walls of the nasopharynx, superiorly through sphenoid bone (can involve CN III, IV, V, VI), and laterally to involve parapharyngeal space (including CN IX–XII).
- High incidence of lymph node metastases at diagnosis—70–80% clinical, 90% subclinical, and up to 50% bilateral. Cervical levels II and V most commonly involved.
- Distant metastases present in 5–10%; most common sites are bone, lung, and liver.
- Medical workup:
  - H&P, focusing on assessment of cranial nerves. Physical exam requires thorough CN exam and cervical lymph node assessment
  - Fiber-optic nasopharyngolaryngoscopy
  - Basic lab work (CBC, metabolic panel, liver function tests, TSH, and EBV DNA viral load)
  - Dental and baseline speech/swallowing evaluations
- Imaging workup: Crucial to determine the extent of tumor invasion and detecting nodal metastases.
  - MRI head/neck w/wo contrast, CT neck w/ contrast, chest CT wo contrast. Additionally, strongly consider PET/CT (to assess distant metastases).
    MRI: Appear as heterogeneous enhancing mass on T1 post-contrast image; T1 pre- and T2 images reveal isointense tumor compared to muscle; also good to delineate PNI and medullary bone invasion.
    CT: Appear as soft-tissue mass; will show heterogeneous enhancement post-contrast; optimal for assessing cortical bone involvement.
    PET/CT: Both primary and nodal metastases will show FDG avidity.
- Pathology workup:
  - EBV FISH or PCR.
  - HPV and p16 can also test positive, but no prognostic/predictive value in nasopharynx cancer.
- Treatment strategies: Radiation therapy with EBRT alone for early-stage tumors (stage I). Radiation with EBRT + concurrent chemotherapy for locally advanced tumors (stage 2–4). SBRT can be used as a boost following EBRT for primary treatment, or as sole therapy in the re-irradiation setting. Surgery not typically recommended due to anatomic location.

10.2 AJCC Staging (AJCC 8th ed., 2017)

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor, but EBV+ cervical node(s) involved
Tis	Carcinoma in situ
T1	Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension
T2	Tumor with parapharyngeal extension* and/or adjacent soft-tissue invasion (medial, lateral pterygoid, prevertebral muscles)
T3	Tumor involves bony structures of skull base and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extension beyond lateral surface of lateral pterygoid muscle
*Note: Parapharyngeal extension denotes posterolateral infiltration of tumor	
Regional lymph nodes (N)	
NX	No regional lymph node metastasis can be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
N3	Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Stage grouping	
0	TisN0M0
I	T1N0M0
II	T1N1M0, T2N0-1M0
III	T1-2N2M0, T3N0-2M0
IVA	T4N0-2M0, any T, N3, M0
IVB	Any T, any N, M1

10.3 Patient Selection

- Definitive setting: EBRT (5–7 weeks) followed by SBRT boost (1–6 weeks later):
  - Radiographically residual tumor.

- Re-irradiation setting:
  - Small (≤3.5 cm diameter or ≤5 cc tumor volume), single lesion preferred; node negative.
  - Biopsy or radiographic proven local persistence or recurrence.
  - Not directly encasing cavernous sinus and/or internal carotid artery or within 9 mm of optic chiasm/optic nerve (or use multiple fractions to reduce late complications).

10.4 Treatment Planning

Simulation instructions	SBRT boost • 1–6 weeks post-standard chemoradiation (EBRT) • Repeat diagnostic MRI w/wo contrast • Use adaptive planning: – Re-simulate patient—Supine, immobilized with head and neck thermoplastic mask or stereotactic frame • Planning CT performed with IV contrast, 1–3 mm slices • Fuse pretreatment MRI to adaptive CT and MRI to delineate residual tumor after initial EBRT • Post-EBRT GTV is the target (residual tumor). Re-irradiation: • Simulate supine immobilized with head and neck thermoplastic mask or stereotactic frame • Planning CT performed with IV contrast, 1–3 mm slices • Fuse updated diagnostic MRI (should be within 2 weeks of CT simulation) to planning CT to delineate recurrent tumor
Image guidance	• CyberKnife: Skull and spine tracking • Linac: CBCT
Margins	PTV = GTV + 3–5 mm
Dosimetric considerations	Dose prescribed to periphery of lesion. Goal = 95% of PTV covered by 80% IDL Depending upon technique, target shape, or proximity to critical structures, prescribing to lower IDL may be necessary. Conformity index for the PTV should be ≤2 (preferably ≤1.5).

Use T1 post-contrast MRI to aid in tumor delineation and planning. T2 sequences are helpful to distinguish between inflammation/fluid and gross tumor.

10.5 Common Dose/Fractionation Schemes

Definitive boost (EBRT + SBRT boost)

There are a range of doses used in the literature. EBRT doses typically range from 2Gy × 25 to 35 fx with SBRT boost doses ranging from 7–15 Gy × 1 fx to 12–15 Gy/3–5 fx.

Dose/Fx	Number of fx	Total dose	Notes
EBRT—2 Gy SBRT boost—11–12 Gy	EBRT—33 SBRT boost—1	EBRT—66 Gy SBRT boost—11–12 Gy	Use SBRT boost for small amount of residual tumor, away from critical OAR(s) [3]
EBRT—2 Gy SBRT boost—4–5 Gy	EBRT—33 SBRT boost—3	EBRT—66 Gy SBRT boost—12–15 Gy	For use when nearby critical OAR(s); treat boost QOD [4, 5]
EBRT—2 Gy SBRT boost—5 Gy	EBRT—25 SBRT boost—3	EBRT—50 Gy SBRT boost—15 Gy	Alternative for use when nearby critical OAR(s); treat boost QOD [4, 5]

Definitive EBRT: Hypofractionated RT-alone regimen has also been described.

Dose/Fx	Number of fx	Total dose	Notes
2.34 Gy	30	70.2 Gy	Treat QD [6]

Re-irradiation (SBRT alone)

Wide range of fractionation schedules in the literature, and depend on tumor size, dose to nearby OARs, cumulative RT already received, and time interval from previous RT.

Dose/Fx	Number of fx	Total dose	Notes
9 Gy	2	18 Gy	Treat QOD [7]
11 Gy	3	33 Gy	Treat QOD [8]
12 Gy	4	48 Gy	Treat QOD [7]
6 Gy	5	30 Gy	Treat QOD [9]
6 Gy	8	48 Gy	Treat QOD [7]
8 Gy	6	48 Gy	Treat QOD [10]

10.6 Normal Tissue Tolerances

	TG101[a] [11]	
Organ	Dmax	Volumetric
Brainstem		
• 1 fx	15 Gy	<0.5 cc
• 3 fx	23 Gy	<0.5 cc
• 5 fx	31 Gy	<0.5 cc
• DLT	Cranial neuropathy	
Optic nerves/chiasm		
• 1 fx	10 Gy	<0.2 cc

Organ	TG101[a] [11]	
	Dmax	Volumetric
• 3 fx	17 Gy	<0.2 cc
• 5 fx	25 Gy	<0.2 cc
• DLT	Neuritis	
Spinal cord		
• 1 fx	14 Gy	<0.35 cc
• 3 fx	22 Gy	<0.35 cc
• 5 fx	30 Gy	<0.35 cc
• DLT	Myelitis	
Cochlea		
• 1 fx	9 Gy	NA
• 3 fx	17 Gy	NA
• 5 fx	25 Gy	NA
• DLT	Hearing loss	

[a]At UNC we follow TG101 constraints. However, TG101 dose constraints were *not* created from nasopharynx patients who received SBRT following EBRT or SBRT alone. Thus while the constraints may not directly apply to nasopharynx patients, they are a good reference

10.7 Patient Management

1. Premedicate for SBRT with single-dose 4 mg PO dexamethasone. May consider premedicating with antiemetic (e.g., zofran 4 mg PO × 1, phenergan 12.5 mg PO × 1, 30 min before treatment) for nausea or anxiolytic (e.g., ativan 0.5-1 mg PO × 1, 30 min before treatment) for claustrophobia and/or anxiety.
2. Toxicity

   (a) Definitive (EBRT + SBRT boost)

   - Acute:
     - Skin/soft tissue (dermatitis, alopecia, xerostomia, mucositis, dysgeusia, dysphagia, odynophagia)

       Emollients (aquaphor, calendula): Remove prior to RT treatment.
       Baking soda/salt rinses up to 12x/day.
       Oral solutions (first BLM, magic mouthwash): Use prior to meals.
       Pain medication (long-acting example: fentanyl patch 25–100 mcg q72 h; short-acting example: oxycodone 5–20 mg q4-6 h).
     - Nausea/vomiting

       Zofran 4 mg q8 h: Can increase to 8 mg q8 h.
       Phenergan 12.5 mg q4–6 h: Can increase to 25 mg q4–6 h.
       Compazine 5 mg q6 h: Can increase to 10 mg q6 h.
   - Subacute/late:
     - Skin/soft tissue (ulceration, fistula, necrosis, <10%)

- Tinnitus/hearing loss (variable, worse when receiving cisplatin chemotherapy)

  Discontinue offending drug.
  Refer to neurology.

- Trismus (<10%)
- Cranial nerve neuropathy (<10%)
- Nasopharyngeal hemorrhage (<5%)
- Pharyngeal stricture/stenosis (<10%)
- Temporal lobe necrosis/ORN of skull base (<15%)
- Carotid aneurysm/blowout (~1%)

  Emergent surgery

****For above late complications, recommend referral to appropriate specialty for management (ENT, surgery, neurology, etc.).*

(b) Re-irradiation (SBRT alone)

- Acute:
  - Patients unlikely to experience symptoms during treatment.
  - In the 2–4 weeks posttreatment, patients can experience dysphagia, odynophagia, dysgeusia, fatigue, or nausea/vomiting.

Management similar to definitive treatment setting (above).

- Subacute/late:
  - Mucosal necrosis (<10%)
  - Trismus (<10%)
  - Nasopharyngeal hemorrhage (10%)
  - Pharyngeal stricture/stenosis (<15%)
  - Temporal lobe necrosis/ORN skull base (<15%)
  - Carotid aneurysm/blowout (5–10%)
  - CN neuropathies [9–12] (<15%)

****For above late complications, recommend referral to appropriate specialty for management (ENT, surgery, neurology, etc.).*

3. Recommend follow-up 1 month posttreatment to assess acute toxicity.
4. Systemic therapy:

(c) There is minimal to no data addressing the use of concurrent chemotherapy/systemic therapy with SBRT boost, in either the definitive setting or the re-irradiation setting. When used in the definitive setting, neo-adjuvant, concurrent, or adjuvant chemotherapy was frequently given with EBRT; however, its use was held during the SBRT boost. When used in the re-irradiation setting, chemotherapy is typically not given concurrently with radiation; if given at all, typically following completion of radiation.

(d) We recommend against the use of concurrent systemic therapy off-study due to the concern of increasing toxicity and lack of data on the safety of this combination.

10.8 Follow-Up

- H&P, fiber-optic nasopharyngoscopy every 2–3 months for first 2 years, q6 months years 3–5, then annually.
- PET/CT and MRI w/wo contrast at 3 months posttreatment, then q6 months for first 2 years, then as clinically indicated. Chest CT w/o contrast annually.
- If pretreatment EBV viral load is elevated, follow posttreatment EBV DNA plasma levels at 3 and 6 months, then as clinically indicated.

10.9 Relevant Literature

- There are no published guidelines as to the recommended dosing/fractionation of SBRT for both definitive boost following chemoradiation or in the re-irradiation setting; however, there are several studies demonstrating its efficacy.
- There is wide variation in these trials with regard to dose, fraction size, prescribed IDL, use of concurrent chemotherapy, and timing of when boost is delivered. Overall promising results with small, but concerning late toxicity reports.

Definitive boost setting.

Study	Patients	Treatment	Median f/u	Outcomes
Prospective studies				
Hara 2008 [3]	*n* = 82, stage IIA-IVb 85% w/ concurrent cisplatin chemotherapy during EBRT	EBRT to 66Gy + single fx SRS boost Boost 2–6 weeks post-EBRT (reimaged prior to boost) Boost: Median 11 Gy (range 7–15 Gy) × 1 fx Dose Rx to 80% IDL	40 months	98% 5-year LC 69% 5-year OS Late toxicity: Carotid aneurysm (1%), temporal lobe necrosis (12%)
Chen 2006 [4]	*n* = 64, majority stage III–IVb 60% w/ concurrent cisplatin chemotherapy during EBRT	EBRT 64–68Gy + fractionated SBRT boost Boost 1 week post-EBRT Boost: 4–5 Gy × 3 fx GTV + 2-3 mm Dose Rx to 85% IDL	31 months	93% 3-year LC 84% 3-year OS Late toxicity: No G4 toxicity; 3 pts. Died from nasal bleeding, unclear if related to SBRT

Study	Patients	Treatment	Median f/u	Outcomes
Retrospective studies				
Yamazaki 2014 [5]	*n* = 25, stage IIA–IVb Majority w/ concurrent cisplatin or 5FU chemotherapy during EBRT	EBRT to 50Gy (median) in 1.8–2Gy/fx + SBRT boost Boost: 5Gy × 3fx (median) Dose Rx to 80% IDL	28 months	71% 5-year LC 70% 5-year OS Late toxicity: G2 ulcerations, >G3, fistula (8%)
Yau 2004 [12]	*n* = 52, majority stage II–IV 23% w/ concurrent cisplatin chemotherapy during EBRT	EBRT to 66Gy + either brachytherapy or SBRT boost Boost: 7.5 Gy × 2 fx or 2.5 Gy × 8 fx Brachytherapy: ^{192}Ir HDR, median 4–10 Gy × 2–5 fx, twice weekly GTV + 3–5 mm Dose Rx to 100% IDL	36 months	**Overall**: 71% 3-year LC 82% 3-year OS **Brachytherapy**: 71% 3-year LC **SBRT**: 82% 3-year LC Late toxicity: Transient soft-tissue necrosis (3%)

Definitive EBRT

Study	Patients	Treatment	Median f/u	Outcomes
Prospective study				
Bakst 2011 [6]	*n* = 25	Dose painting EBRT w/ chemotherapy 2.34 Gy × 30 fx PTV = GTV + 1 cm	33 months	91% 3-year LC 89% 3-year OS Late toxicity: 12% temporal lobe necrosis

Re-irradiation setting

Study	Patients	Treatment	Median f/u	Outcomes
Retrospective studies				
Chua 2009 [7]	*n* = 125 Previous EBRT 66–70 Gy. ~25% concurrent chemo Tx recurrent disease w/ single vs. multiple fx SBRT Median time between recurrence 10 months	Single: 12.5 Gy median Multiple: 18 Gy/2–4 fx qod (48 Gy/4–6 fx for recurrent dx) PTV = GTV + 2-3 mm Dose Rx to 80% IDL (single fx) or 90% IDL (multiple fx) Median tumor volume 5.2 cc	40 months	**Single fraction**: 51% 3-year LC 66% 3-year OS 33% late toxicity (16% brain necrosis, 2% hemorrhage) **Multiple fraction**: 83% 3-year LC 61% 3-year OS 21% late toxicity (12% brain necrosis, 4% hemorrhage)

Study	Patients	Treatment	Median f/u	Outcomes
Seo 2009 [8]	*n* = 35 Previous EBRT + cisplatin. Median RT dose 70 Gy Median time between recurrence 26 months	Median 33 Gy/3 or 5 fx qd PTV = GTV + 2 mm Dose Rx to 80% IDL Median tumor volume 8 cc	25 months	84% 5-year LC 60% 5-year OS 5 pts. with late G4/5 toxicity (mucosal necrosis (5%) and hemorrhage (9%))
Ozyigit 2011 [9]	*n* = 51 Previous EBRT 67–70Gy + ~60% concurrent chemotherapy Tx recurrent disease w/ 3DCRT vs. SBRT Median time between recurrence 36 months	30 Gy/5 fx (SBRT) qd 60 Gy/30 fx (3D) PTV = GTV (SBRT) Dose Rx to 95–99% IDL Median tumor volume 63 cc	24 months	**SBRT**: 82% 2-year LC 64% 2-year CSS 21% late toxicity (17% carotid blowout, 12% neuropathy, 4% brain necrosis) **3D**: 80% 2-year LC 47% 2-year CSS 48% late toxicity
Wu 2007 [10]	*n* = 90 (majority had single lesion, ≤4 cm) Previous EBRT 60–74 Gy Tx w/ SBRT (7 pts. received 3D + SBRT) Median time between recurrence 23 months	Persistent dx = median 6 Gy × 3 fx qd Recurrent = median 8 Gy × 6 fx qd PTV = GTV + 2–3 mm Dose Rx to 90% IDL Tumor volume 5–6 cc	20 months	**Persistent dx**: 89% 3-year LFFS 81% 3-year DMFS 72% 3-year PFS **Recurrent dx**: 75% 3-year LFFS 67% 3-year DMFS 43% 3-year PFS Late toxicity: Mucosal necrosis (7%), G5 hemorrhage (2%), and brainstem necrosis (3%)
Pai 2002 [13]	*n* = 36 Previous EBRT 64–81Gy Tx recurrent disease w/ 3DCRT + SBRT Median time between recurrence 16 months	SBRT = median 12 Gy × 1 fx 3D = median 2 Gy × 25 fx PTV = GTV Dose Rx to 80% IDL Median tumor volume 16.8 cc	22 months	57% 3-year LC 54% 3-year OS Late toxicity: Mucosal necrosis (11%) and nasal bleeding (8%)

10.10 Summary

Again, there is wide variation in published studies with regard to dose, fraction size, prescribed IDL, use of concurrent chemotherapy, and volume irradiated. Results are promising; however, there remains a relatively high rate of grade 3/4 toxicity, including some grade 5.

10.11 UNC Experience

At our institution, we do not routinely perform SBRT boost in the definitive setting, as the LC and OS rates are similar to those of definitive EBRT alone with chemotherapy, but with a higher risk of severe late effects (carotid blowout, hemorrhage, ORN).

For patients with persistent/recurrent local disease, we re-irradiate with SBRT at 600 cGy/fx for five fractions for a total dose of 3000 cGy. Radiation is given every other day using the CyberKnife radiosurgery system. The GTV is expanded 3–5 mm to make a PTV (no CTV is created). We typically track on the skull base and prescribe to the 80% IDL.

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Chapter 11
Larynx

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11.1 Pearls [1, 2]

- 13,000 annual estimated cases in the USA (~3.4 cases/100,000 people).
- Predominately affects men; median age at diagnosis is 65.
- Etiologies include tobacco, alcohol, betel nut consumption, and deficiencies in vitamins/nutrients (iron, vitamin B12, and vitamin C).
- Common presenting symptoms include hoarseness, dysphagia, odynophagia, chronic cough, and referred otalgia; can be location dependent.
- 90–95% are SCC; can also see verrucous carcinoma, adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinomas.
- Local anatomy:
  - Divided into three subsites:

    Supraglottis: includes supra- and infrahyoid epiglottis, aryepiglottic folds, arytenoids, ventricles, and false vocal cords.
    Glottis: true vocal cords, infraglottis (free edge of true vocal cord to within 5 mm inferior), and mucosa of the anterior and posterior commissures.
    Subglottis: lower border of glottis to inferior border of cricoid cartilage.

  - Intrinsic muscles of the larynx are innervated by recurrent laryngeal nerve, except for cricothyroid muscle, which is innervated by the superior laryngeal nerve and is solely responsible for producing tension of the vocal cords.

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- Lymph node drainage:
  - Glottis has sparse lymphatic supply, and thus rarely spreads to lymph nodes (T1–2: <5%; T3–4: ~20%). If involved, typically bilateral levels II, III, IV, and VI.
  - Supraglottis has richer lymphatic supply and is thus more common to have nodal metastases at presentation (~50%); drains to bilateral levels II, III, IV, and VI.
  - Subglottis typically drains to levels II, III, IV, VI, and VII.
- Incidence of distant metastases is low (≤10%); common sites include lungs>liver>bone.
- Medical workup:
  - H&P, physical exam requires thorough cervical lymph node assessment.
  - Fiber-optic nasopharyngolaryngoscopy.
  - Biopsy and basic lab work (CBC, metabolic panel, liver function tests, TSH).
  - Dental and baseline speech/swallowing evaluations.
- Imaging workup:
  - CT neck w/wo contrast: look for enhancing mass at level of laryngeal sides (supraglottis), true vocal fold (glottis), or cricoid cartilage (subglottis).
  - CT chest w/wo contrast.
  - Additionally may consider PET/CT: look for primary and nodal metastases with FDG avidity.
- Treatment strategies: radiation therapy alone or surgery for early-stage, T1–2 tumors. Radiation therapy with concurrent chemotherapy or surgical resection for locally advanced T3 tumors. Surgical resection recommended for advanced T4 tumors.

11.2 AJCC Staging (AJCC 8th Ed., 2017)

Primary tumor (T)	
Larynx	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of the base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx

Primary tumor (T)	
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: Postcricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease. Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility T1a: Tumor limited to one vocal cord T1b: Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Regional lymph nodes (N)[a]	
NX	No regional lymph node metastasis can be assessed
N0	No regional lymph node metastasis

Primary tumor (T)	
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE (−)
N2	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−) or Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−) or Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−); or Metastasis in any lymph node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any lymph node(s) with clinically overt ENE(+)
[a]Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+)	
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Stage grouping	
0	Tis N0 M0
I	T1 N0 M0
II	T2 N0 M0
III	T3 N0 M0 T1-3 N1 M0
IVA	T4a N0-2 M0 T1-3 N2 M0
IVB	T4b, any N, M0 Any T, N3, M0
IVC	Any T, any N, M1

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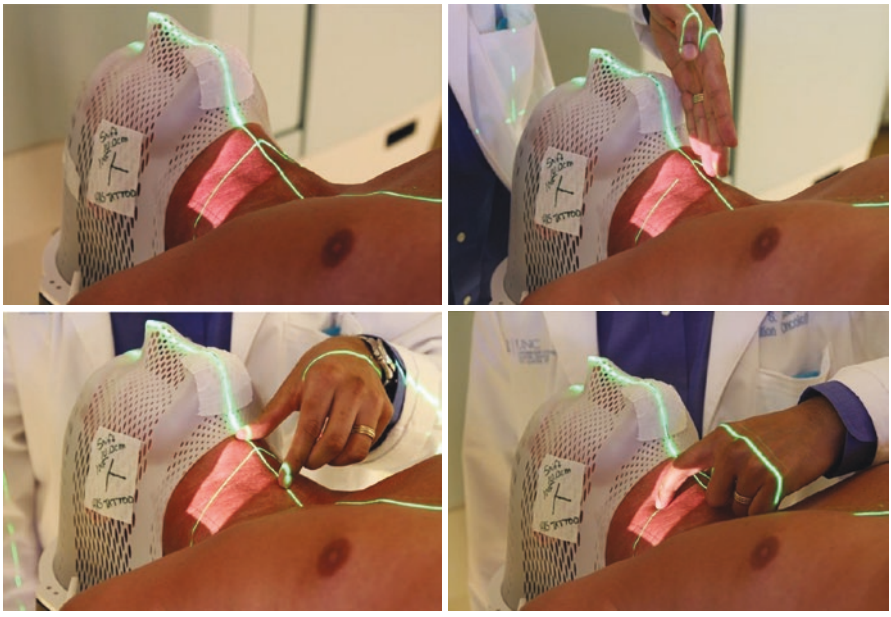
11.3 Patient Selection for Hypofractionation Treatment

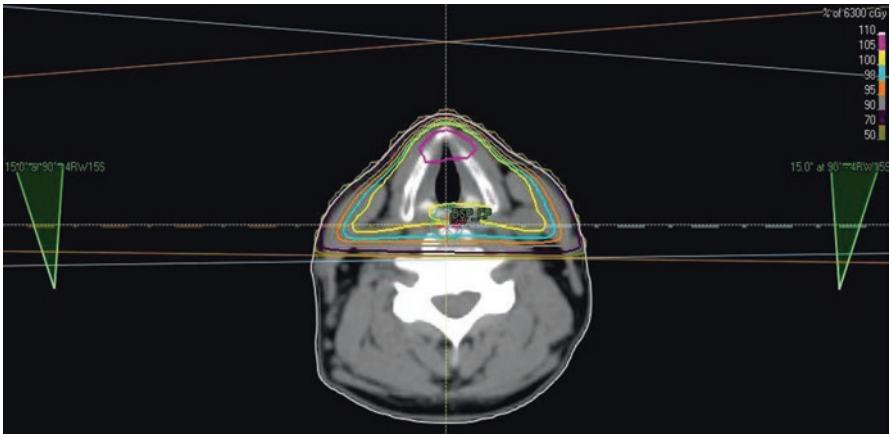
- T1–2 tumors of the glottic larynx

11.4 Treatment Planning

Simulation instructions	– Supine, immobilized with head and neck thermoplastic mask – Head/neck hyperextended – Autotraction straps to immobilize and pull shoulders down – Opposed lateral fields typically utilized – 3DCRT plan utilized to minimize normal tissue injury – Daily bolus—Over anterior larynx in thin neck patients and anterior commissure involvement to ensure adequate coverage. 2 cm wide × 5 cm long
Image guidance	– At least weekly portal imaging – Daily clinical verification of light field in the treatment room (palpate thyroid notch = superior field border, cricoid = inferior field border, thyroid alae = posterior field border)
Margins	– T1 tumors: 4 × 4 cm or 5 × 5 cm (preferred) field – T2 tumors: 5 × 5 cm (preferred) or 6 × 6 cm field – Borders: *Superior*: Bottom/mid-thyroid notch (top of notch if there is supraglottic extension) *Inferior*: Bottom of cricoid cartilage (1 cm inferior to cricoid cartilage if subglottic extension) *Posterior*: Anterior edge of vertebral body (split vertebral body if there is posterior commissure involvement) *Anterior*: 2 cm skin flash IMRT (unproven benefit) – CTV = entire larynx (includes anterior/posterior commissures, arytenoids from top of thyroid cartilage to inferior cricoid cartilage) – PTV = CTV + 0–10 mm (wide range in literature)



Light field images showing treatment field.



Plan design showing isodose lines.

11.5 Common Dose/Fractionation Schemes

Dose/Fx	Number of fx	Total dose	Notes
2.25 Gy	28	63 Gy	T1 tumors; treat daily [3–6]
2.25 Gy	29	65.25 Gy	T2 tumors; treat daily [3, 5, 6]

11.6 Normal Tissue Tolerances

- The main relevant dose constraint is to ensure that overall plan is not too hot (goal of 105% of the prescription with a max of 110%) to minimize the risk for laryngeal edema and necrosis.
- Several studies have reported increased risk of carotid artery-related adverse events after radiation therapy.
  - We interpret the studies on cerebrovascular disease to show that the risk of moderate and severe carotid complications from neck radiotherapy is so low that very few patients will end up with a better clinical outcome as a result of changing the radiotherapy (e.g., using carotid-sparing IMRT).
  - There is no specific study associating dose volume data with clinical outcomes of carotid artery stenosis/stroke.

11.7 Patient Management

(a) No premedications required.

- Tobacco cessation important—smoking during treatment increases acute toxicities and decreases local control.

(b) Toxicity

- Acute:
  - Skin/soft tissue (dermatitis, mucositis, dysphagia, laryngeal edema)

    Emollients (aquaphor, calendula): Remove 4 h prior to RT treatment.
    Baking soda/salt rinses up to 12×/day.
    Oral solutions (first BLM, magic mouthwash): Use TID prior to meals.
    Pain medication (fentanyl patch 25–100 mcg q72 h, oxycodone 5–20 mg q4–6 h).

  - Late:

    Skin/soft tissue (fibrosis, laryngeal edema, fistula) (<10%)
    Hypothyroidism (20–30%)
    Osteoradionecrosis (ORN) (<5%)
    Carotid blowout (1.7%)

    ****For above late complications, recommend referral to appropriate specialty for management (ENT, surgery, PCP, etc.).*

11.8 Follow-Up

- H&P, fiber-optic nasopharyngoscopy every 3 months for first 2 years, q6 months years 3–5, then annually.
- Chest CT w/o contrast, TSH q6–12 months.

11.9 Relevant Literature

Study	Patients	Treatment	Median f/u	Outcomes
Randomized controlled trials				
Moon (2014) [3]	*n* = 156, T1–2 N0 glottic SCC RT alone conventional vs. hypofractionation	1) 2 Gy × 33–35 fx 2) 2.25 Gy × 28–30 fx Opposed laterals	67 months	**2.25Gy/fx**: 94% 5-year LC 88% 5-year LPFS **2Gy/fx**: 89% 5-year LC 77% 5-year LPFS Toxicity: No difference between arms

Study	Patients	Treatment	Median f/u	Outcomes
Yamazaki (2006) [4]	*n* = 180, T1 glottic SCC RT alone conventional vs. hypofractionation	1) 2 Gy × 30–33 fx 2) 2.25 Gy × 25–28 fx	64 months	**2.25Gy/fx**: 92% 5-year LC 100% 5-year CSS **2Gy/fx**: 77% 5-year LC 97% 5-year CSS Toxicity: No difference between arms
Retrospective studies				
Chera (2010) [5]	*n* = 585, T1/2 N0 glottic SCC Retrospective RT alone, hypofractionated	2.25 Gy × 28–29 fx (T2 lesions offered 1.2 Gy/fx BID) Opposed laterals	144 months	**Local control**: 93% 10 years (T1a) 91% 10 years (T1b) 80% 10 years (T2a) 67% 10 years (T2b) **Overall survival**: 62% 10 years (T1a) 57% 10 years (T1b) 51% 10 years (T2a) 49% 10 years (T2b) Toxicity: 10 pts. with G4/5; one fatal RT-induced carotid artery angiosarcoma
Gowda (2003) [7]	*n* = 200, T1 N0 glottic SCC Retrospective RT alone, hypofractionated	3.12 or 3.28 Gy × 16 fx Opposed laterals	72 months	93% 5-year LC 80% 5-year OS Toxicity: No severe acute toxicity; 1 pt. with severe late toxicity (continued to smoke following tx)
Le (1997) [6]	*n* = 398, T1–2 glottic SCC RT alone, opposed laterals	Total dose: T1 63Gy, T2 65Gy Fx sizes: <1.8 Gy 1.8–1.99 Gy 2–2.24 Gy ≥2.25 Gy	116 months	**T1 tumors** ≥ 2.25Gy/fx: 94% 5-year LC <1.8Gy/fx: 79% 5-year LC **T2 tumors** ≥ 2.25 Gy/fx: 100% 5-year LC <1.8Gy/fx: 44% 5-year LC

11.10 Summary

Hypofractionation has been shown to improve LC versus standard fractionation schedules with low rates of severe complications. Currently there is no data on the use of stereotactic ablative doses.

11.11 UNC Experience

Our standard is to treat with 5 × 5 cm opposed lateral fields with daily clinical verification of the light field by the physician. Our interpretation of the published literature on the potential increase in carotid artery-related adverse events is that the risk, if any, is small. We do not treat with carotid-sparing EBRT.

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Chapter 12
Other Head and Neck Sites

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Definitive brachytherapy or SBRT boost literature.

Study	Patients	Treatment	Median f/u	Outcomes
Retrospective studies				
Al-Mamgani 2013 [1]	*n* = 250, oropharynx SCC, T1-2 N0-3 Chemotherapy given for N2c/N3	Definitive EBRT + brachytherapy or SBRT boost (SBRT boost initiated in 2005) EBRT: 2 Gy × 23 fx Brachytherapy: ^{192}Ir source; PDR—total dose 22 Gy given in 8 fx/day SBRT boost: 5.5 Gy × 3 fx	66 months	**Brachytherapy**: 94% 3-year LC 86% 3-year DFS 83% 3-year OS 31% acute G3 toxicity 4% late G3 toxicity **SBRT**: 97% 3-year LC 92% 3-year DFS 81% 3-year OS 23% acute G3 toxicity 5% late G3 toxicity
Lee 2012 [2]	*n* = 26 locally advanced H&N SCC (NPX, OPX, paranasal sinus, tongue) EBRT + boost Median f/u 56 months	EBRT: Median 50.4 Gy in 2 Gy/fx SBRT: 5 Gy × 2-5 fx (median 21Gy/ median 5 fxs)	56 months	100% response rate (21 CR, 5 PR) 86% 2-year LRRFR ~35% late G ≥ 3 toxicities; boost volume significant predictor

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12.1 Summary

There are variable dose fractionation schemes and responses to treatment, with limited numbers of subjects. Overall, complication rates are high and require long-term follow-up. We do not typically utilize brachytherapy at UNC for treatment of head and neck tumors.

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Chapter 13
Intraoral Cone (IOC)

Gregory D. Judy and Bhishamjit S. Chera

13.1 General Utilization

1. Mainly for floor of mouth, oral tongue, buccal mucosa, gingiva, and retromolar trigone.

   (a) Indications:
   - Small, superficial, early-stage disease.

   (b) Technique:
   - Administered with orthovoltage X-rays or electrons.
   - Orthovoltage preferred due to less beam constriction and higher surface dose.
   - If electrons are utilized, bolus is needed for adequate surface dose and a larger margin is necessary due to beam constriction.
   - Daily setup verification is necessary to ensure position of tumor relative to the cone.

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13.2 Specific Disease Sites

1. Floor of mouth
   (a) Indications:
      - Superficial (≤4 mm thick), well-differentiated tumors.
      - Alone or as a boost with EBRT:
        – If used as a boost, IOC will precede EBRT (can optimally define the extent of tumor and procedure is difficult when following EBRT due to patient discomfort).
   (b) Dose:
      - Sole treatment = 45 Gy over 3 weeks (55 Gy over 4 weeks if palpable induration or positive margins).
      - Boost w/ EBRT = 15–24 Gy in 10 fx followed by 45–50 Gy EBRT.
2. Oral tongue
   (a) Indications:
      - Early T1 and superficial T2 N0 tumors if patient declines or is at surgical risk.
      - Typically used as a boost with EBRT
      - Daily setup/reproducibility can be an issue due to difficulty with immobilization of the lesion.
   (b) Dose:
      - 21–27 Gy in 7–9 fx followed by 30–50 Gy EBRT.

Study	Patients	Treatment	Outcomes
Wang 1989 [1]	*n* = 142, oral tongue SCC (93 tx w/ IOC)	EBRT + brachytherapy or IOC boost IOC: 24–27 Gy in 8–9 fx EBRT: 51.4 Gy/32 fx BID	**Brachytherapy boost**: 54% 5-year LC **IOC boost (orthovoltage)** 50% 5-year LC **IOC (electrons)**: 86% 5-year LC Toxicity: ORN, ulceration
Million and Cassisi 1994 [2]	N/A	EBRT + IOC boost IOC: 21–27 Gy in 7–9 fx EBRT: 30–32 Gy	Common dose fractionation schemes for oral tongue SCC

13.3 Summary

IOC is no longer commonly used. It has variable LC rates, and the literature is limited. The types of severe complication are similar to brachytherapy (ORN, ulceration) and generally acceptable, but, like brachytherapy, are also likely related to clinician experience and expertise in performing the procedure.

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Chapter 14
Brachytherapy

Gregory D. Judy and Bhishamjit S. Chera

14.1 Disease-Site Utilization

1. Oral Cavity
   (a) Lip
      - Indications:
        – Sole treatment for T1–T2 tumors (but often performed as a boost after initial 50 Gy EBRT)
        – Boost treatment following EBRT in low-volume T3–T4 tumors
        – Use of EBRT necessary to treat lymphatics for upper lip lesions, poorly differentiated lesions, presence of PNI, or recurrent disease
      - Technique:
        – Typically performed under local anesthesia.
        – Uses single-plane plastic tube technique—sources arranged horizontally (10–12 mm apart) with crossing sources over lateral aspect; the number of sources used depends on tumor size.
        – Place gauze between lip and gum to increase distance between alveolar ridge and sources (to minimize ORN).

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- Dose:
  - Definitive, implant alone: 60–70 Gy at dose rate of 0.4–0.5 Gy/h (~5-day implant)
  - Implant boost: 35–40 Gy at dose rate 0.4–0.5 Gy/h (EBRT dose 45–50 Gy/2Gy/fx)
    Duration: approximately 2–3-day implant
- Complications: dermatitis, mucosal necrosis (10%), ORN (<10%), or acute hemorrhage

Study	Patients	Treatment	Median f/u	Outcomes
Retrospective studies				
Guinot 2003 [1]	*n* = 39, SCC lip T1–4	^{192}Ir HDR brachytherapy BID Total doses 40.5–45 Gy in 8–10 fx	18 months	88% 3 years LC 91% 3 years CSS Very good cosmetic result
Tombolini 1998 [2]	*n* = 57, SCC of lower lip T1–3, N+	^{192}Ir LDR brachytherapy alone (cN+ received EBRT) Median dose 62 Gy (range 44–96 Gy)	Not specified	90% 5 years LC 81% 5 years DFS 76% 5 years OS
Orecchi 1991 [3]	*n* = 47, SCC of lower lip T1–2 N0	^{192}Ir LDR brachytherapy alone 60–80 Gy	Not specified	94% 5 years LC 92% 5 years DFS 85% 10 years DFS Toxicity: 10% mucosal necrosis Excellent/good cosmetic result 92%

(b) Floor of the Mouth
- Indications:
  - Sole treatment for well-differentiated, superficial (≤4 mm) T1–T2 tumors
  - Boost treatment following EBRT in T1–2 tumors with thickness > 4 mm and/or poorly differentiated (higher risk for nodal spread)
  - Not recommended when tumor extends to mandibular alveolar ridge due to increased risk of ORN
- Technique:
  - Plastic tube technique (discussed above)
- Dose:
  - Implant alone: 60–70 Gy at dose rate of 0.4–0.5 Gy/h
  - Implant boost: 10–25 Gy at dose rate 0.4–0.5 Gy/h (EBRT dose 46–50/2Gy/fx)
- Complications: mucosal necrosis (<5%), ORN (2.5%), or acute hemorrhage

Study	Patients	Treatment	Median f/u	Outcomes
Retrospective studies				
Marsiglia 2002 [4]	*n* = 160, SCC of FOM T1–2, N0–1	^{192}Ir LDR brachytherapy alone (cT2 or N1 received surgery) Median 70 Gy (58–80 Gy)	108 months	93% LC (T1) 88% LC (T2) Toxicity: mucosal necrosis and ORN (2.5% G3 ORN)
Lapeyre 2000 [5]	*n* = 36, SCC tongue, FOM T1–2 N0	Surgery ± ^{192}Ir brachytherapy (if close or + margins) Mean 60 Gy (50–67.4 Gy)	80 months	88.5% 2 years LC Toxicity: G2/3 in 16% FOM cases
Pernot 1995 [6]	*n* = 207, SCC FOM T1–4, N0–3	EBRT + ^{192}Ir brachytherapy or brachytherapy alone 50 Gy EBRT + boost	60 months	**T1 tumors**: 97% 5 years LC 88% 5 years CSS **T2 tumors**: 72% 5 years LC 47% 5 years CSS **T3 tumors**: 51% 5 years LC 36% 5 years CSS Toxicity: 1% ≥G3 soft tissue necrosis; 6% ≥G3 bone necrosis

(c) Oral Tongue
- Indications:
  - Sole treatment for well-differentiated, superficial (≤3 mm) T1–2 tumors
  - Boost treatment following EBRT for T1–2 tumors with thickness >3 mm and/or poorly differentiated
- Technique:
  - Plastic tube technique (discussed above)
- Dose:
  - Implant alone: 65–70 Gy at dose rate of 0.4–0.5 Gy/h over 5–7 days
  - Implant boost: 25–30 Gy at dose rate 0.4–0.5 Gy/h (EBRT dose 40–45 Gy/2Gy/fx)
- Complications: mucosal necrosis (<5%), ORN (<5%), or acute hemorrhage

Study	Patients	Treatment	Median f/u	Outcomes
Prospective studies				
Inoue 1996 [7]	*n* = 29, SCC tongue T1–2, N0	^{192}Ir LDR vs. HDR brachytherapy alone LDR: 70 Gy, 4–9 days HDR: 60 Gy, 6 days	24 months	**LDR**: 86% 2 years LC **HDR**: 100% 2 years LCR Toxicity: ulcer (3%), necrosis (3%)
Retrospective studies				
Matsuura 1998 [8]	*n* = 173, SCC tongue T1–3, N0–3	EBRT + ^{192}Ir LDR brachytherapy or brachytherapy alone Brachytherapy alone—60–84 Gy EBRT dose 30–50 Gy	24 months	**T1 tumor**: 93% 5 years LC **T2 tumor**: 78% 5 years LC Tumor thickness <8 mm: 92% 5 years LC Tumor thickness >8 mm: 28% 5 years LC
Wendt 1990 [9]	*n* = 103, SCC tongue T1–2, N0	EBRT + ^{192}Ir LDR brachytherapy or brachytherapy alone EBRT + brachytherapy—50 + 20–40 Gy	159 months	**Brachytherapy alone**: 67% 2 years LC **EBRT + brachytherapy**: 92% 2 years LC (EBRT dose >40 Gy) 65% 2 years LC (EBRT dose <40 Gy) Toxicity: moderate-severe complications ~15%

(d) Buccal Mucosa

- Indications:
  - Combination therapy with EBRT in T1–2 tumors
- Technique:
  - Plastic tube technique—single plane of 3–5 horizontal tubes (10–12 mm apart); crossing tubes at either end of the horizontal tubes
- Dose:
  - 25–30 Gy at dose rate 0.4–0.5 Gy/h following EBRT (45–50 Gy/2Gy/fx)
- Complications: mucosal necrosis, trismus, and acute hemorrhage

Study	Patients	Treatment	Median f/u	Outcomes
Retrospective studies				
Nair 1988 [10]	*n* = 52, majority buccal mucosa T1–4, N0–3 (33% T1–2, N0)	^{192}Ir LDR brachytherapy alone—65 Gy over 6 days	36 months	85% 3 years OS Toxicity: mucositis, mild-moderate xerostomia in most patients. No ORN in this study

(e) Oropharynx
- Indications:
  - Combination therapy with EBRT for small (<5 cm), node-negative tonsillar fossa, base of tongue, or soft palate tumors
  - Contraindicated if tumor invades underlying structures or the bone
- Technique:
  - Plastic tube technique (described above)
- Dose:
  - LDR—25–35 Gy at dose rate 0.4–0.5 Gy/h following EBRT (45–50 Gy/2Gy/fx)
  - HDR—21–30 Gy/3 Gy fx or 21–24 Gy/4 Gy fx following EBRT (45–50 Gy/2Gy/fx)
- Complications: ulceration (10–20%), mucosal necrosis (<5%), pain (20%), trismus (<2%), and acute hemorrhage (3%)

Study	Patients	Treatment	Median f/u	Outcomes
Prospective studies				
Levendag 2004 [11]	*n* = 248, SCC tonsillar fossa, soft palate T1–3, N0–N+	EBRT + brachytherapy boost (if brachytherapy not possible, underwent surgery) EBRT 46 Gy/2 Gy/fx ^{192}Ir LDR/HDR brachytherapy—20–36 (LDR) or 15–30 (HDR)	24 months	88% 5 years LC Brachytherapy toxicity: mucosal ulcer (39%), pain (20%), trismus (1%)
Harrison 1998 [12]	*n* = 68, SCC BOT T1–3, N0–N+	EBRT + brachytherapy boost (+neck dissection if N+) EBRT 54 Gy/2 Gy/fx ^{192}Ir LDR brachytherapy—20–30 (LDR)	36 months	89% 5 years LC 80% 5 years DFS Toxicity: soft tissue ulceration (13%), ORN (3%), hemorrhage (3%)

(f) Nasopharynx
- Indications:
  - Alone or in combination with EBRT for small, superficial, well-circumscribed T1–2 tumors and/or in re-irradiation setting
  - Contraindicated if tumor extends into nasal cavities or the oropharynx
- Technique:
  - Intracavitary or interstitial techniques.
  - Applicator should be used. The Rotterdam nasopharyngeal applicator is commonly used with HDR afterloading device.
  - Shaped to conform to nasopharynx, guided through oral cavity to correct position; once immobilized, X-rays are performed to confirm location and define anatomy for planning.

- Dose
  - Implant boost: 5–6 Gy in 2 fx (5–6 h apart) following EBRT (40–50 Gy)
- Complications: hemorrhage (<5%), CN neuropathies (<10%), trismus (10–20%), ORN (<5%), and soft tissue necrosis (10–15%)

Study	Patients	Treatment	Median f/u	Outcomes
Retrospective studies				
Koutcher 2010 [13]	*n* = 29, recurrent T1–4 NPX Median 3.9 years between primary and re-XRT	EBRT alone = median 59.4 Gy Chemotherapy given to all patients EBRT + ^{125}I or ^{192}Ir LDR brachytherapy: 40 Gy median (20 EBRT, 20 brachytherapy)	45 months	52% 5 years LC 69% 5 years OS Toxicity: hemorrhage (4%), CN neuropathy (9%), trismus (17%), soft tissue necrosis (13%)
Lee 1997 [14]	*n* = 654, recurrent T1–3 NPX Median 2 years between primary and re-XRT	EBRT alone = median 46.5 Gy EBRT + brachytherapy: 40 Gy EBRT, 20 Gy brachytherapy Intracavitary ^{137}Cs alone = median 40 Gy	1.4 years	23% 5 years LC 16% 5 years OS Toxicity: trismus/soft tissue necrosis (16%), ORN (3%), neuropathies (7%), fatal hemorrhage (<1%)

(g) Paranasal Sinuses

- Indications:
  - Nasal vestibule and nasal cavity tumors
    Nasal vestibule: monotherapy for small lesions (<2 cm) or in combination with EBRT for larger (<2 cm) lesions
    Nasal cavity: monotherapy for small (≤1.5 cm) anteroinferior septal lesions (better cosmetic outcome vs. surgery)
- Technique:
  - Interstitial technique with 192Ir wire implant typically used.
  - Afterloading needles inserted under general anesthesia (to visualize tumor and protect airway in case of hemorrhage).
  - For HDR, custom mold of nasal vestibule is made.
  - Tumor is marked and 2–4 plastic tubes with 1 cm spacing inserted.
  - Lateral vestibule tumors—two tubes placed on inner aspect of vestibule.
  - Medial tumors—2–4 tubes placed on both sides of tumor.
- Dose
  - LDR

Sole treatment: 60–65 Gy over 5–7 days (dose rate 0.4–0.6 Gy/h)
Boost: 20–25 Gy at 0.4–0.6 Gy/hr. following EBRT 50 Gy/2Gy/fx
– HDR:
Boost: 18 Gy at 3 Gy/fx BID following EBRT 50 Gy/2 Gy/fx

- Complications: hemorrhage (<5%), rhinorrhea (40%), nasal dryness (40–50%), and ORN (<5%)

Study	Patients	Treatment	Median f/u	Outcomes
Retrospective studies				
Langendijk 2004 [15]	*n* = 56, T1–2 nasal vestibule SCC	EBRT or EBRT + brachytherapy EBRT alone = median 52.5 Gy EBRT + brachytherapy: ^{137}Cs IDR: 16 Gy at 2.7 Gy/h ^{192}Ir HDR: 18 Gy/3 fx, BID	24 months	80% 2 years LC 95% 5 years LC (can be salvaged w/ surgery) **Tumor diameter <1.5 cm**: 83% 2 years LC **Tumor diameter ≥1.5 cm**: 74% 2 years LC 74% Toxicity: rhinorrhea (45%), nasal dryness (39%), epistaxis (15%), adhesions (4%)
Chobe 1988 [16]	*n* = 32, SCC nasal vestibule	EBRT or brachytherapy alone EBRT: 55–70 Gy LDR brachytherapy: 60–75 Gy	Not specified	**Brachytherapy**: 100% LC **EBRT**: 95% LC Toxicity: ORN (3%), hemorrhage (3%)

14.2 Summary: Brachytherapy

Overall, while brachytherapy is no longer commonly utilized, it does offer good local control in a variety of disease sites of the head and neck (with exception of the nasopharynx, where control rates are more variable). Complication rates are generally acceptable but are likely also related to clinician experience and expertise in performing the procedure.

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Chapter 15
Intraoperative Radiotherapy (IORT)

Gregory D. Judy and Bhishamjit S. Chera

15.1 IORT Using Electrons

- Technique:
  (a) Sterile applicator and cone required.
  (b) Attaches to the head of linac.
  (c) Collimate the electron beam to define treatment field and retract normal tissue.
  (d) Typical margin 1–2 cm. A 5 mm water equivalent bolus is used.
  (e) The target area should be defined with the surgeon, as it is typically the high-risk, postoperative bed where the tumor was in close proximity to normal tissue structures (and likely where there is a positive margin).
  (f) Must be performed in shielded OR or special IORT suite.
- Dose:
  (a) Ranges between 10 and 25 Gy × 1 fx prescribed to 80–100% IDL.
- Advantages: area at risk directly visible, better sparing of normal tissue/overlying tissue.
- Complications: major organ at risk is the spinal cord.

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15.2 Intraoperative Brachytherapy

- Use of radioactive source (^{192}Ir, ^{125}I) to deliver RT in or <5 cm from the tumor.
- Technique:
  (a) ^{192}Ir—requires afterloading catheters to be placed in applicator
  (b) ^{125}I—permanently inserted at time of surgery
- Dose:
  (a) HDR 10–20 Gy × 1 fx
  (b) LDR 40–50 Gy over 4–10 days
- Advantages: meticulous placement of catheters or implants within tumor bed (ability to conform to irregular surfaces), sparing of normal tissue
- Disadvantage: if LDR, catheters remain in place for several days = increase risk of infection (HDR can be done the same day in the OR); additional hospital personnel exposed to radiation
- Complications: ORN (up to ~15%), fistula (1–2%), hemorrhage, and infection (<5%)

Study	Patients	Treatment	Median f/u	Outcomes
Prospective studies				
Nag 1996 [1]	*n* = 29, recurrent SCC	Surgery + intraoperative brachytherapy (additional adjuvant EBRT given in RT naïve areas) ^{192}Ir HDR: 15 Gy (if previous RT given) 7.5–12.5 Gy to RT naïve areas + EBRT 45–50 Gy	21 months	67% 2 years LC 72% 2 years OS No intraoperative complications; delayed toxicity = CSF leak (3%), septicemia (3%), otitis media (3%), xerostomia (3%)
Retrospective studies				
Perry 2010 [2]	*n* = 34, recurrent SCC (majority in the neck) All pts received definitive EBRT previously—median 63 Gy)	Surgery + IORT ^{192}Ir HDR: 10–20 Gy (median 15)/1 fx	23 months	Median time to recurrence 16 months 66% 2 years LC 55% 2 years OS Toxicity: fibrosis (30–40%), fistula (<10%), wound infection (<10%), ORN (<5%)
Chen 2007 [3]	*n* = 137, recurrent SCC	Surgery + IORT Electrons: 10–18 Gy (median 15 Gy)/1 fx Median cone size 5 cm Rx 90% IDL	41 months	61% 3 years LC 36% 3 years OS Toxicity: no perioperative complications; Delayed complications included wound infection (<5%), fistula (1–2%), necrosis (<1%), neuropathy (<1%), trismus (<1%)

Study	Patients	Treatment	Median f/u	Outcomes
Rate 1991 [4]	$n = 126$, recurrent SCC (majority in the neck); 47 recurred in area w/ previous RT	Surgery + IORT (for R1, R2 resections) Electrons: 15, 20, 25 Gy/1 fx Rx to Dmax	14 months	Median time to recurrence 18 months 62% 2 years LC 55 2 years OS Toxicity: ORN (1%), fistula (2%)
Vikram 1985 [5]	$n = 21$, recurrent SCC	Surgery + intraoperative brachytherapy ^{192}Ir LDR: 40–56 Gy over 4–10 days	35 months	Median time to recurrence 36 months 81% 2 years LC 55% 2 years DFS Toxicity: ORN (14%)

15.3 Summary: IORT

Most studies have small sample sizes and LC rates vary from 60 to 80%. Complication rates are generally low, with intraoperative brachytherapy showing a higher complication rate with regard to fistula, ORN, and wound infection.

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Chapter 16
Re-irradiation

Gregory D. Judy and Bhishamjit S. Chera

16.1 Re-irradiation Literature

Study	Patients	Treatment	Median f/u	Outcomes
Prospective studies				
Vargo 2015 [1]	*n* = 50, recurrent H&N SCC, inoperable (majority OPX) Previous EBRT median 70 Gy Median time between recurrence 26 months Median tumor volume 36 cc	SBRT + concurrent cetuximab 40–44 Gy/5 fx, qod CTV = GTV PTV = CTV + 3–5 mm Rx dose: 95% PTV	18 months	60% 1 year local PFS 40% 1 year OS Toxicity: 6% G3 acute/late toxicity
Comet 2012 [2]	*n* = 40, recurrent H&N SCC, inoperable Previous EBRT (median 66 Gy) Median time between recurrence 31 months Median PTV volume 64 cc	SBRT + concurrent cetuximab 6 Gy × 6 fx, qod CTV = GTV + 5 mm PTV = CTV + 1 mm Rx dose: 85% IDL	25 months	79% response rate 24% 2 years OS Late toxicity: no G4+ late toxicity

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Study	Patients	Treatment	Median f/u	Outcomes
Vargo 2012 [3]	*n* = 34, recurrent H&N cancer, inoperable (majority salivary gland, oral cavity) Previous EBRT median 61 Gy Median time between recurrence 53 months Median tumor volume 19 cc	SBRT Median 5 Gy × 8 fx, qod PTV = GTV Rx dose: 80% IDL (95% PTV coverage)	10 months	59% 1 year LC 59% 1 year OS Toxicity: 6% G3 late toxicity; no G4/G5 toxicity
Heron 2009 [4]	*n* = 25, recurrent H&N SCC, inoperable (majority larynx) Previous EBRT median 65 Gy Median time between recurrence 13 months Median tumor volume 45 cc	SBRT 5 Gy × 5–9 fx, qod Rx dose: 80% IDL	Not specified	76% response rate 6 months Median OS Late toxicity: no G3+ late toxicity
Retrospective studies				
Ling 2016 [5, 6]	*n* = 291, recurrent H&N cancer Previous EBRT median 68 Gy Median tumor volume 29 cc	SBRT ± concurrent cetuximab (~50% received) Median 44 Gy/5 fx, qod CTV = GTV PTV = CTV + 3–5 mm Rx dose: 80% IDL	53 months	Toxicity: 11% ≥G3 acute; 19% ≥G3 late Larynx/ hypopharynx: 50% ≥G3 late toxicity vs. 6–20% all other sites
Owen 2015 [7]	*n* = 184, recurrent H&N cancer, majority SCC (heterogeneous population) Median tumor volume 16 cc	SBRT Majority tx with EBRT + SBRT boost Median EBRT dose 61 Gy Boost: median 14 Gy × 1 fx Rx dose: 50% IDL	17 months	82% 1 year LC 41% 1 year OS Toxicity: 32% experienced late toxicity, including temporal lobe necrosis, CN palsy, facial numbness, and pain
Rwigema 2011 [8]	*n* = 96, recurrent H&N cancer, inoperable Previous EBRT median 68 Gy Median tumor volume 24 cc	SBRT: Grp 1: 15–28 Gy/5 fx Grp 2: 30–36 Gy/5 fx Grp 3: 40 Gy/5 fx Grp 4: 44–50 Gy/5 fx	14 months	Improved response rate with >40 Gy and tumor volume ≤25 cc

16.2 Summary

There are variable disease sites, doses used, dose fractionation schemes, IDL prescription, and systemic therapy used in all of these studies. Severe toxicity was also somewhat variable, with frequencies as high as 50% in some studies. Long-term follow-up is needed to monitor for these late toxicities.

Several studies have looked at the combination of SBRT with cetuximab in the recurrent setting with good results. However, we recommend against the use of concurrent systemic therapy due to the concern of increasing toxicity, but it would be reasonable to study on a prospective trial.

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Part IV
Skin

Chapter 17
Skin (Melanoma and Nonmelanoma Skin Cancers)

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17.1 Pearls

- NMSC is the most common malignancy with an estimated 5.4 million cases annually in the United States.
- The incidence of melanoma doubled from 1982 to 2011 and continues to rise; estimated incidence in 2018 is 91,270 cases.
- NMSC is more common in males (4:1); melanoma is site dependent (men = trunk; women = extremities).
- Caucasians are at highest risk for both melanoma and NMSC skin cancers.
- Risk factors:
  - NMSC: Most common risk factor is UV exposure. Other risk factors include chronic irritation, chronic arsenic exposure, immunosuppression, radiation exposure, occupational exposure, and genetic disorders (e.g., basal cell nevus syndrome, xeroderma pigmentosum).
  - Melanoma: UV exposure, atypical nevi/high nevus count, familial, immunosuppression, and phenotypic traits (light skin, blond hair, light-colored eyes, and high freckle density).
- Histology:
  - NMSC: basal cell carcinoma (BCC, ~65%), squamous cell carcinoma (SCC, ~30%), Merkel cell carcinoma (MCC), and adnexal (<5%).

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BCC subtypes include nodulo-ulcerative, superficial, morpheaform, infiltrative, pigmented, fibroepithelial tumor of Pinkus, and basosquamous

SCC subtypes include invasive, Bowen's disease (carcinoma in situ), erythroplasia of Queyrat (Bowen's of penis), Marjolin's ulcer (arises within chronic wound/scar), verrucous (typically anogenital or plantar of foot), and spindle cell (sun-exposed areas, Caucasian, >40 age)

  - Melanoma: superficial spreading (65%), nodular (25%), lentigo maligna (~7%), and acral lentiginous (<5%; most common type among dark-skinned individuals). Also desmoplastic (typically occurs in H&N, low likelihood for nodal metastases)

- Presenting symptoms:
  - NMSC:

    BCC: pearly papule, pruritic plaque, or bleeding ulcer (waxes/wanes). Typical slow growing.

    SCC: in situ typically soft, erythematous, scaly, well-circumscribed patch. Invasive SCC, firm, ulcerative mass with elevated border; signs of PNI include pain, tingling, and hypesthesia.
  - Melanoma: ABCDEs = A, asymmetry; B, irregular borders; C, color; D, diameter >6 mm; E, evolving lesion (color, shape, size). Acral lentiginous typically presents on palms, soles, or subungual
- Local anatomy:
  - BCC and SCC typically arise in sun-exposed areas on H&N.
  - H zone of the face (periauricular, glabella, medial canthus, nose, nasolabial region, and columella) is a high-risk area (disease extent often underestimated).
- Areas of spread:
  - NMSC:

    Spreads laterally and deep

    BCC: low propensity for PNI (~1–2% usually in setting of recurrent or locally advanced disease), nodal spread, and distant metastases (<0.01%—regional nodes > lung > liver > bone)

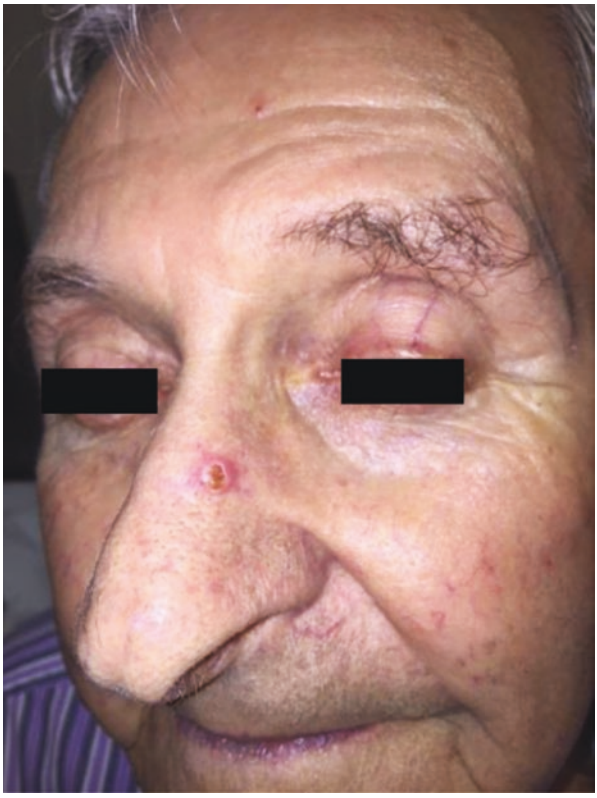
    SCC: more aggressive, with ~7% PNI, nodal spread up to 10–20% in poorly differentiated, recurrent, >3 cm or > 4 mm depth; distant metastases remain low, <5%, to the lungs, liver, and bones
  - Melanoma:

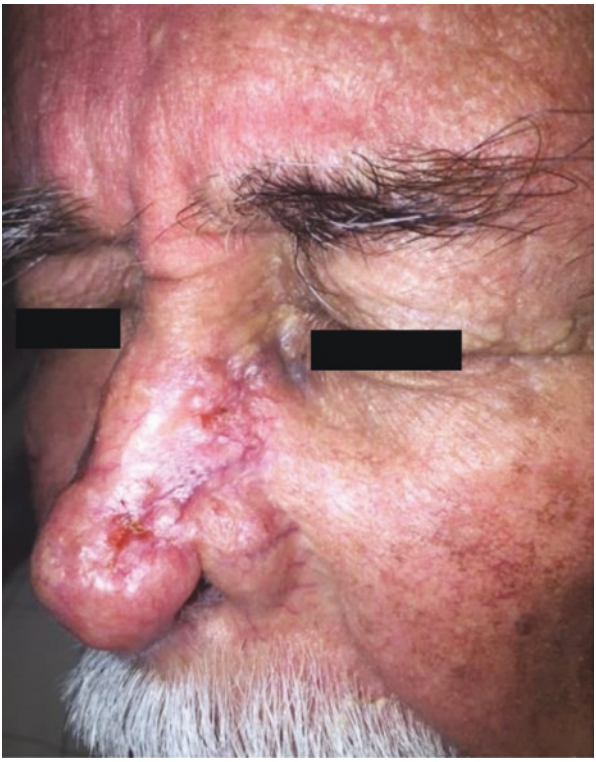
    Regional nodal metastases at presentation: <10% for T1 lesions, ~25–30% > T1

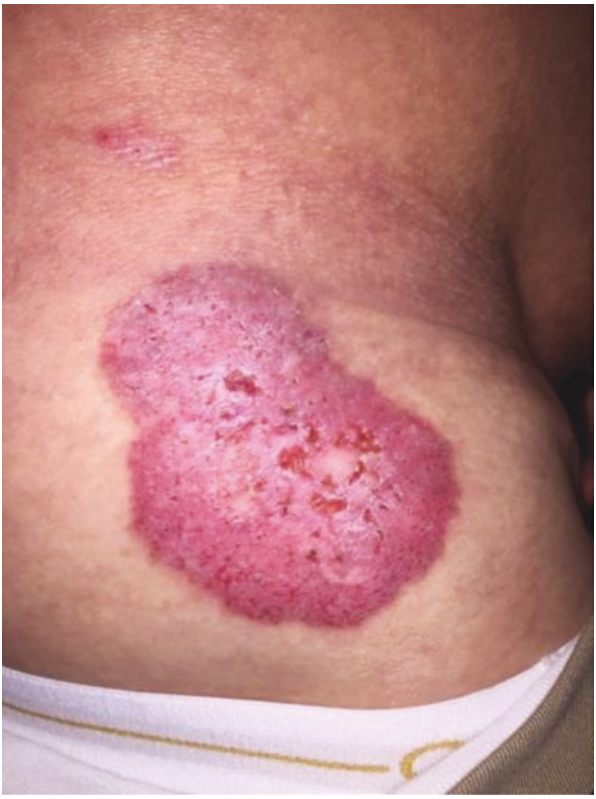
    Sentinel lymph node status best prognostic factor for recurrence and survival; ulceration and tumor thickness best prognostic factors when node negative

    ~5% with distant metastases at presentation
- Medical workup:
  - H&P: thorough CN exam for head/face tumors and regional nodal evaluation

  - Biopsy
  - Basic lab work (CBC, metabolic panel, liver function tests)
- Imaging workup:
  - CT or MRI w/wo contrast for suspected/known nodal involvement
  - MRI w/wo contrast for suspected PNI or medial/lateral canthi lesions (rule out orbital involvement)
    CT: best to assess nodal or bone involvement
    MRI: best to assess PNI; seen as enhancement of nerve on post contrast scan; can also see thickening along nerve or loss of fat surrounding nerve
- Treatment strategies: surgical resection and/or RT, depending on location, disease extent, performance status [1–4].







17.2 AJCC Staging (AJCC 8th ed., 2017)

Nonmelanoma skin carcinoma

Primary tumor (T)[a]	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor smaller than 2 cm in greatest dimension
T2	Tumor 2 cm or larger, but smaller than 4 cm in greatest dimension
T3	Tumor 4 cm or larger in maximum dimension or minor bone erosion or perineural invasion or deep invasion*
T4	Tumor with gross cortical bone/marrow, skull base invasion, and/or skull base foramen invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement
Regional lymph nodes (N)	
NX	Regional lymph node metastasis cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−) Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−) In bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−) dimension
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−) Metastasis in any node(s) and clinically overt ENE [ENE(+)]
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) and ENE(+)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Stage grouping	
0	Tis N0 M0
I	T1 N0 M0
II	T2 N0 M0
III	T3 N0 M0 T1–3 N1 M0

IV	T1–3 N2 M0 Any T N3 M0 T4 any N M0 Any T and N M1

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[a]Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression

Melanoma

Primary tumor (T)	
TX	Primary tumor thickness cannot be assessed
T0	No evidence of primary tumor
Tis	Melanoma in situ (thickness and ulceration N/A)
T1	Melanoma ≤1 mm, with or without ulceration
T1a	<0.8 mm thick without ulceration
T1b	<0.8 mm thick with ulceration or 0.8–1 mm with or without ulceration
T2	Melanoma 1.01–2 mm thick, with or without ulceration
T2a	>1 to 2 mm thick, without ulceration
T2b	>1 to 2 mm thick with ulceration
T3	Melanoma 2.01–4 mm thick, with or without ulceration
T3a	>2 to 4 mm without ulceration
T3b	>2 to 4 mm with ulceration
T4	Melanoma >4 mm thick, with or without ulceration
T4a	>4 mm thick without ulceration
T4b	>4 mm thick with ulceration
Regional lymph nodes (N)	
NX	Regional lymph node metastasis cannot be assessed
N0	No regional lymph node metastasis
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes
N1a	One clinically occult node (i.e., detected by SLN biopsy)
N1b	One clinically detected node
N1c	No regional lymph node disease with presence of in-transit, satellite, and/or microsatellite metastases
N2	Two or three tumor-involved nodes OR in-transit, satellite, and/or microsatellite metastases with one tumor-involved node
N2a	Two or three clinically occult (i.e., detected by SLN biopsy)
N2b	Two or three, at least one of which was clinically detected
N2c	One clinically occult or clinically detected WITH presence of in-transit, satellite, and/or microsatellite metastases

N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes WITH presence of in-transit, satellite, and/or microsatellite metastases
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis to the skin, soft tissue including the muscle, and/or nonregional lymph node
M1a(0)	LDH not elevated
M1a(1)	LDH elevated
M1b	Distant metastasis to the lung with or without M1a sites of disease
M1b(0)	LDH not elevated
M1b(1)	LDH elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease
M1c(0)	LDH not elevated
M1c(1)	LDH elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease
M1d(0)	LDH not elevated
M1d(1)	LDH elevated
Stage grouping	
Clinical staging[a]	
0	Tis N0 M0
IA	T1a N0 M0
IB	T1b N0 M0 T2a N0 M0
IIA	T2b N0 M0 T3a N0 M0
IIB	T3b N0 M0 T4a N0 M0
IIC	T4b N0 M0
III	Any T, N1–3, M0
IV	Any T any N M1
Pathologic staging[b]	
0	Tis N0 M0
IA	T1a N0 M0
IB	T1b N0 M0 T2a N0 M0
IIA	T2b N0 M0 T3a N0 M0
IIB	T3b N0 M0 T4a N0 M0

IIC	T4b N0 M0
IIIA	T1–4a N1a M0 T1–4a N2a M0
IIIB	T1–4b N1a M0 T1–4b N2a M0 T1–4a N1b M0 T1–4a N2b M0 T1–4a N2c M0
IIIC	T1–4b N1b M0 T1–4b N2b M0 T1–4b N2c M0 T1–4b N3 M0 Any T N3 M0
IV	Any T any N M1

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[a]Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases

[b]Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes

17.3 Patient Selection for Hypofractionated RT

1. NMSC: in general—T1–2 tumors, node negative; exact fractionation scheme utilized depends on lesion location, patient age/functional status, and cosmetic outcome considerations.
   (a) Cosmesis improved with more protracted course.
   (b) Close proximity to the eye, eyelid, nose, or ear = lower dose/fraction.
   (c) Dorsum of hands/feet = generally avoid RT (elevated risk of necrosis).
   (d) Hypofractionation not suited for larger lesions or locally advanced disease (T3/4, N+, PNI) due to large treatment fields.
   (e) Postoperative treatment = indications include gross residual disease, close or positive margins, PNI, pT3/4, node positive, or recurrent disease.
   (f) Treatment of lymphatics = indications include positive nodes, PNI, T3/4, recurrent disease, or primary in close proximity to the lip.
2. Melanoma:
   (a) Primary site: Postoperative indications include desmoplastic/neurotropic features, >4 mm thick (especially if ulcerated), and close/positive margins.
   (b) Nodal basin: post-op indications include positive nodes (≥2 cervical, ≥3–4 axillary/inguinal), ECE, size ≥3 cm, recurrent disease, or SLNB+ without plan for completion dissection.

17.4 Treatment Planning

Simulation instructions	• Location dependent: – H&N: Clinical setup in treatment room for superficial lesions; may need CT scan w/ immobilization mask when treating deep lesions/nodes – Axilla: Supine, arm akimbo, or above head (use wingboard) – Groin: Unilateral frog leg • Lead shields (lens, nasal septum, oral cavity, ear, etc.) as needed if near OAR. Use beeswax coating to minimize backscatter
Image guidance	• Weekly port films • CBCT for pelvic nodes • Weekly clinical verification for electrons
Margins	• NMSC: GTV + 1–2 cm • Melanoma: Primary site +2–3 cm margin
Tumor coverage	NMSC—Treat with orthovoltage or electrons • Orthovoltage Rx = Dmax • Electrons Rx = 90–95% IDL • Daily bolus (0.5–1 cm) to achieve adequate skin dose • If PNI present, include nerve retrograde to skull base. Treat with EBRT and conventional or BID fractionation Melanoma—Nodal volume, location dependent • H&N: Cover ipsilateral levels 1–5 + SCV fossa. For scalp/high facial lesions, cover pre-/postauricular nodes • Axilla: Levels 1–3 + SCV (for high axillary disease) • Groin: Include all confirmed locations; if positive inguinal nodes can treat back to external iliac

17.5 Common Dose/Fractionation Schemes

NMSC

Dose/fx	Number of fx	Total dose	Notes[a]
15–20 Gy	1	15–20 Gy	Palliative (symptom relief); older pts., poor health [5]
8 Gy	4	32 Gy	QD; older pts., poor health [5]
7 Gy	3	21 Gy	QD; older pts., poor health [5]
6 Gy	5	30 Gy	QD; older pts., poor health [5]
4 Gy	10	40 Gy	QD; older pts., poor health [5]
3 Gy	15	45 Gy	QD; older pts., poor health [5]
2.5 Gy	20	50 Gy	QD; larger lesions or lesions near the ear, nose, eye/eyelid [5]

[a]Lesions with PNI need to treat the affected nerve back to skull base. In these situations, recommend using EBRT and more conventional or BID fractionation schemes (e.g., 2 Gy × 30–35 fx, QD or 1.2 Gy × 38–64 fx, BID) to minimize late normal tissue side effects

Melanoma

Melanoma is conventionally thought of as a more radioresistant tumor, potentially benefiting from higher dose/fraction.

Dose/fx	Number of fx	Total dose	Notes[a]
6 Gy	4	24 Gy	Twice weekly [6]
6 Gy	5	30 Gy	Twice weekly [6–8]
2.4 Gy	20	48 Gy	QD [9, 10]

[a]Daily conventional fractionation can be used (2 Gy × 25–35 fx). However, many believe hypofractionation is more efficacious

17.6 Normal Tissue Tolerances

	TG101[a] [11]		
Organ	Dmax	Volumetric	OTHER[a] [12]
Cartilage			<3 Gy/day
• DLT			Chondritis
Spinal cord			Max <45–50 Gy
• 1 fx	14 Gy	<0.35 cc	
• 3 fx	22 Gy	<0.35 cc	
• 5 fx	30 Gy	<0.35 cc	
• DLT	Myelitis		Myelitis
Small bowel – Duodenum			Max <45–50 Gy
• 1 fx	12.4 Gy	<5 cc	
• 3 fx	22 Gy	<5 cc	
• 5 fx	32 Gy	<5 cc	
• DLT	Ulceration		
Small bowel – Jejunum/ileum			
• 1 fx	15.4 Gy	<5 cc	
• 3 fx	25 Gy	<5 cc	
• 5 fx	35 Gy	<5 cc	
• DLT	Enteritis/obstruction		
Skin			Max 30 cc 60 Gy Max 10 cc 70 Gy
• 1 fx	26 Gy	<10 cc	
• 3 fx	33 Gy	<10 cc	
• 5 fx	39.5 Gy	<10 cc	
• DLT	Ulceration		Ulceration

[a]At UNC we follow the above constraints

17.7 Patient Management

1. No premedication required
2. Toxicity
   (a) Acute:
      - Dermatitis ± desquamation (~100%; desquamation less likely (5–10% but will depend on location and dose).
        – Manage with emollients (e.g., aquaphor, calendula, aloe).
        – If moist desquamation occurs, use 1% Silvadene cream on affected area.

   (b) Late:
      - Skin (hypo–/hyperpigmentation, telangiectasia, skin atrophy, fibrosis up to 50% G1/2, <10% G3/4).
        – Vast majority do not cause problems.
        – Continue use of emollients.
        – Refer to dermatology and/or surgery if causing symptoms.
      - Lymphedema (especially groin and axilla) (~10%)
        – Refer to lymphedema physical therapy.
        – Compression sleeve.
        – Avoid vaccinations, BP readings in affected arm/leg.
      - Osteoradionecrosis (site dependent, <5%)*
      - Cartilage (site dependent, chondritis <5%, cartilage necrosis <5%)*
      - Neuropathy (site dependent, 2–3%)*

**For above late complications, recommend referral to appropriate specialist for management (dermatology, ENT, surgery, neurology,* etc.*).*

3. Systemic therapy
   (a) Limited data regarding combined radiation and systemic treatments.
      - *B*RAF inhibitors—can act as radiosensitizers/increase acute radiation toxicity. Recommend holding systemic therapy at least 3 days before and after fractionated radiation and at least 1 day before and after SBRT/SRS.
      - *Immunotherapy* (PD-1/PDL-1 or CTLA-4 inhibitors)—abscopal effects have been seen when given concurrently with radiation; however, there are no prospective data to guide decisions. Recommend sequential (giving before or after radiation therapy) rather than concurrent treatment.

17.8 Follow-Up

- H&P with skin exam every 3 months for first year, q6 months years 3–5, and then annually.
- Melanoma: PET/CT at 3 months posttreatment and then restaging CT scans as clinically indicated
- NMSC with PNI, can repeat MRI at 3 months posttreatment with subsequent scans as clinically indicated

17.9 Relevant Literature

- NMSC—The use of 2.5 Gy/fx generally gives better cosmetic result compared to larger fractionation schemes.

Study	Patients	Treatment	Median f/u	Outcomes
Retrospective studies				
Van Hezewijk 2010 [13]	*n* = 333, skin cancers, majority head/face	Electrons to primary site 3 Gy × 18 fx, 4×/week 4.4 Gy × 10 fx, 4×/week GTV + 1 cm margin	43 months	**54 Gy**: 98% 3 years LRC (BCC) 97% 3 years LRC (SCC) 62% good cosmetic result **44 Gy**: 97% 3 years LRC (BCC) 94% 3 years LRC (SCC) 62% good cosmetic result
Abbatucci 1989 [14]	*n* = 675, facial skin cancers (excluding lips, ears, eyelids, melanoma, and stage IV disease) Mostly elderly population	Superficial RT to primary lesion 10.2 Gy × 3 fx; once/week	24 months	96% 2 years LC 90% good cosmetic result 3% complication rate = ulcerations (2–3%), epiphora (<1%)

17.10 Summary

Overall excellent tumor control with good cosmetic outcomes and low rates of complications.

- Melanoma

Study	Patients	Treatment	Median f/u	Outcomes
Randomized controlled trials				
Burmeister 2012 [9]	*n* = 217; one nodal basin, completely resected High risk of relapse = ≥1 parotid node, ≥2 cervical/axillary nodes, ≥3 inguinal nodes, ECE, nodal size (≥3 cm cervical, ≥4 cm ax/ing)	Lymphadenectomy then randomized to: (1) 2.4 Gy × 20 fx (2) observation	40 months	**RT**: LN field failure improved w/ adjuvant RT (20 vs 34 relapses, HR 0.56) **Observation**: No difference in RFS/OS Toxicity: 22% grade 3/4 toxicity; mainly skin/subcutaneous

Study	Patients	Treatment	Median f/u	Outcomes
Sause 1991 [15]	*n* = 126, definitive treatment Measurable lesions	(1) 8 Gy × 4 fx, 1×/week (2) 2.5 Gy × 20 fx/daily	24 months	**32Gy**: 24% complete remission rate 4% ≥grade 3 toxicity **50Gy**: 23% complete remission rate 3% ≥grade 3 toxicity
Prospective studies				
Burmeister 2006 [10]	*n* = 234, N+ melanoma Phase II study Nodal ECE, ≥1 LN+, or recurrent disease	Resection + adjuvant RT (1 pt. received systemic therapy) 2.4 Gy × 20 fx	58 months	91% 5 years LRC 27% 5 years PFS 36% 5 years OS Grade 3 lymphedema 9% in axillary pts, 19% in ilioinguinal pts
Ang 1990 [6]	*n* = 83, melanoma (>1.5 mm or cLN+) of H&N region Three groups: 1 = WLE + adjuvant RT 2 = pre- vs. post-op RT w/ WLE 3 = recurrent disease s/p node dissection + adjuvant RT or preoperative RT	6 Gy × 4 fx, 2×/week (RT given prior to surgery) 6 Gy × 5 fx, 2×/week (RT given after surgery)	16 months	**Group 1**: 95% 2 years LC 80% 2 years OS **Group 2**: 90% 2 years LC 71% 2 years OS **Group 3**: 83% 2 years LC 69% 2 years OS
Retrospective studies				
Chang 2006 [7]	*n* = 56, high-risk melanoma (gross disease, close/+ margins, recurrent disease, satellitosis, nodal metastases, ECE) 87% were H&N pts	WLE, node dissection, adjuvant RT (hypofractionation vs. conventional) Hypofractionation: 6 Gy × 5 fx, 2×/week Conventional: 2 Gy × 30 fx/daily	52 months	**Hypofractionation**: 87% 5 years LC 3% late toxicity (osteoradionecrosis of temporal bone and RT plexopathy) **Conventional**: 87% 5 years LC
Ballo 2006 [8]	*n* = 466, N+ melanoma Nodal ECE, ≥4 LN+, size ≥3 cm, or recurrent disease indications for RT	Lymphadenectomy + adjuvant RT (33% had systemic therapy) RT: 6 Gy × 5 fx, 2×/week	48 months	89% 5 years LC 49% 5 years DSS Lymphedema main toxicity (10 years symptomatic edema 11%)

17.11 Summary

Hypofractionated regimens offer good rates of tumor control with relatively low rates of toxicity. The likelihood of common toxicities such as lymphedema is related to which lymph node chains are irradiated.

17.12 UNC Experience

At our institution, we typically treat melanoma with either the 6 Gy × 5 fx or 2.48 Gy × 20 fx regimen. For NMSC it will depend on location, patient's age, PS, presence of PNI, etc. If it is an older patient who has transportation issues and a poor PS, we will often treat with 4 Gy × 10 fx or 15–20 Gy × 1 fx. If PNI is present, we will treat with conventional dosing (2 Gy × 30–35 fx) and treat involved nerve back to the base of skull.

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Part V
Lung Tumors

Chapter 18
Hypofractionation for Lung Tumors (Primary Malignant, Secondary Malignant)

Joseph M. Caster, Achilles J. Fakiris, Michael V. Lawrence, Eric C. Scheriber, and Lawrence B. Marks

18.1 Introduction

Surgery has traditionally been the standard of care for early-stage (T1–T2 N0) NSCLC and lung metastases as local control with conventionally fractionated EBRT was clearly inferior to surgical resection. However, the emergence of SBRT (1–5 fractions of >5 Gy/fx) for lung lesions is challenging this standard as local control rates of >80–95% can be achieved with either modality. Less extreme hypofractionation (15–25 fractions of 2.5–3.5 Gy/fx) regimens have also been utilized in an attempt to escalate the BED of radiation for more advanced (stages III–IV) NSCLC. Clinical experience has demonstrated that while these approaches can produce encouraging tumor control rates, they are not without the risk of severe, even fatal complications as a result of damage to the many critical structures located in the thorax. This chapter will review the sizeable literature for lung SBRT and hypofractionation regimens and highlight the technical considerations that are necessary to properly utilize these techniques.

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18.2 Primary Non-small Cell Lung Cancer Pearls

- Incidence: 234,030 new US cases of lung cancer (small cell and non-small cell lung cancer combined) in 2018, and 154,050 deaths
  - Incidence peaked in the early 1990s (70 per 100,000 individuals).
  - Slow decline to current level (57 per 100,000 individuals).
  - Approximately 15–20% present with stage I (T1–T2 N0) disease.
- Demographics
  - Median age at diagnosis: 70
  - 1.2:1 M–F ratio
- Potential causes or risk factors
  - Smoking (10–20-fold increased risk)
  - Radon, secondhand smoke, prior radiation, asbestos, inhaled chemicals (polycyclic aromatic hydrocarbons), heavy metals, and pulmonary fibrosis
- Genetic risk factors
  - Only a handful of identified hereditary predisposition syndromes.
  - First-degree relatives have twofold increased incidence of lung cancer.
  - Identified hereditary conditions (<1% of all NSCLCs):
    α1-Antitrypsin deficiency
    Li-Fraumeni syndrome
    Hereditary lung cancer syndrome (EGFR T790 M)
  - Acquired mutations are very common; some can be actionable (i.e., pharmacologically targetable):
    Frequently mutated/rearranged genes: ALK, PIK3C, EGFR, FGF, MEK1, MET, KRAS, NRAS, RET, PTEN, BRAF, DDR2, and ROS1
- Presenting symptoms
  - Cough, dyspnea, chest pain, weight loss, hoarseness, and recurrent lung infections
  - Less commonly paralysis, headaches, seizure, and pathologic fracture
- Pathology subtypes
  - Adenocarcinoma
  - Approximately 50% of new NSCLC diagnoses
  - Most common histology in never/minimal smokers
  - Most likely histology to harbor actionable mutation (EGFR, ALK)
  - Squamous cell carcinoma
  - 60–80% centrally located
  - Strongly associated with smoking
  - Large cell NCSLC
    Large cell neuroendocrine tumors: less aggressive than SCLC
- Local anatomy
  - Right lung divided into three lobes: RUL, RML, and RLL
    RUL and RML separated by horizontal fissure
    RLL separated from RML and RUL by oblique fissure

  - Left lung divided into two lobes: LUL and LLL
    Separated by oblique fissure
    Lingula is projection of LUL
  - Closely associated mediastinal structures include:
    Heart, great vessels, esophagus, trachea, and thymus
  - Nerves at risk: clinical presentation
    Recurrent laryngeal nerve: hoarseness and vocal cord paralysis
    Diaphragmatic nerve: elevated hemidiaphragm
    Sympathetic ganglion (apical tumors): Horner's syndrome
    Vagus nerve: varied, hoarseness, and pain are most common
  - Regional nodal areas of likely spread
    Intralobar/peribronchial/perihilar nodes (N1)
    Mediastinal nodes (N2 ipsilateral, N3 contralateral)
    Supraclavicular nodes (N3)
- Common sites of distant spread
  - Brain, liver, bone, adrenal, ipsilateral lung lobes, and contralateral lung
  - Less commonly the skin, muscle, kidney, bladder, and GI organs
- Medical work-up
  - Blood tests
    Complete chemistry
    CBC
    LFTs
    Coagulation studies
  - PFTs
    Spirometry
    DLCO
  - Pathologic confirmation (unless contraindicated for medical reasons or previously confirmed metastatic disease)
    Histologic diagnosis
    Mutational analysis (if applicable)
    Consider placement of fiducials at time of biopsy if applicable and suspicion for malignancy is high
  - Imaging work-up: imaging needed
    CT chest/abdomen/pelvis or PET-CT
    Brain MRI for stage III and IV or if neurologic symptoms are present
    Consider bone scan if no PET and osseous pain is present
  - Additional work-up
    Surgical evaluation
    Pathologic nodal evaluation recommended for NSCLC
    Bronchoscopic FNA
    Mediastinoscopy
    Chamberlain procedure
- Treatment options include surgical resection, SBRT, concurrent chemoradiation, sequential chemotherapy and radiation, palliative radiation, palliative chemotherapy, and observation.

18.3 AJCC 8th Edition Staging Tables

Primary tumor (T)	
TX	Primary cannot be assessed, tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or on bronchoscopy
Tis	Carcinoma in situ Squamous cell carcinoma in situ (SCIS) Adenocarcinoma in situ (AIS): Adenocarcinoma with pure lepidic pattern, <3 cm in greatest dimension
T1Mi	Minimally invasive adenocarcinoma ≤3 cm in greatest diameter with pure lepidic pattern, ≤5 mm depth of invasion
T1	3 cm or less, surrounded by lung or visceral pleura, not invading into a main bronchus
T1a	Tumor ≤1 cm in greatest dimension
T1b	>1 but ≤2 cm
T1c	>2 cm but ≤3 cm
T2	3–5 cm, involves MSB (without carina), involves visceral pleura, associated with atelectasis or obstructive pneumonitis that extends to the hilar region Tumors meeting above criteria <4 cm are considered T2a; >4 but <5 cm are considered T2b
T2a	>3 cm but ≤4 cm (also includes T2 tumors smaller than 3 cm)
T2b	>4 cm but ≤5 cm
T3	>5 but ≤7 cm; or tumor that directly invades one of the following: Parietal pleura (PL3), chest wall, phrenic nerve, parietal pericardium; or separate tumor nodules in the same lobe
T4	>7 cm; or tumor invades one of the following: Diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; or separate tumor nodule(s) in a different ipsilateral lobe

Regional lymph nodes (N)	
NX	Regional lymph nodes not assessed
N0	No nodal involvement
N1	Intraparenchymal, peribronchial, hilar nodal involvement
N2	Ipsilateral mediastinal or subcarinal involvement
N3	Contralateral hilar or mediastinal, ipsilateral or contralateral scalene, or supraclavicular involvement

Distant metastases (M)	
M0	No mets
M1a	M1a—Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion
M1b	Single extrathoracic metastasis in a single organ (including involvement of a single non-regional node)
M1c	Multiple extrathoracic metastases in a single or multiple extrathoracic organs

Stage grouping	
Occult	Tx N0
0	Tis N0
IA1	T1mi or T1a N0
IA2	T1b N0

Stage grouping	
IB	T2a N0
IIA	T2bN0
IIB	T1a–T1c N1, T2a–T2b N1, T3 N0
IIIA	T3 N1, T1–T2 N2, T4 N0–N1
IIIB	T1–T2 N3, T3–T4 N2
IIIC	T3–T4 N3
IVA	M1a or M1b
IVB	M1c

1. Tumor/patient selection:
    - NSCLC or lung metastases:
        - One to three thoracic lesions, < 5–7 cm combined maximal diameter [1, 2]
        - For NSCLC: either T1–T2 and N0 or N1–N2 and small primary distant (>5–7 cm) from nodal disease
        - Can consider for localized recurrence/residual disease of SCLC after definitive therapy [3]
    - Peripheral:
        - Tumors ≤5–7 cm
        - At least 2 cm from the hilum, major bronchus, heart, great vessel, and esophagus
        - Organs potentially at risk: chest wall, brachial plexus, lungs, heart, and major airways
    - Central:
        - Tumors ≤5 cm
        - Within 2 cm of the hilum, major bronchus, heart, great vessels, and esophagus [2, 4]
        - Organs potentially at risk: lungs, chest wall (anterior), heart, cord, esophagus, trachea, and great vessels
    - Re-irradiation:
        - Solitary lesion <3–5 cm.
        - Strongest predictors of treatment failure are tumor size >2 cm and time to recurrence <18 months [5, 6].
        - Re-irradiation with SBRT for centrally located failures appears feasible with fraction sizes <10–12 Gy [7].
    - Baseline symptoms or patient characteristics:
        - Comorbidities and concomitant lung disease very common.
        - Many patients would not be surgically fit.
        - No official minimal PFTs; continuous supplemental 02 is not an absolute contraindication to treatment.
        - Must be able to tolerate some deterioration in lung function:
          If PFS 2 or greater *because* of baseline lung dysfunction, then worsened lung function from treatment may be unacceptable.

Consider deferring biopsy and/or fiducial placement if complications of pneumothorax are unlikely to be tolerated and clinical suspicion of malignancy is sufficiently high to proceed without tissue.

– Patient-specific factors (e.g., esophageal Crohn's, systemic connective tissue disorder, pulmonary fibrosis, immunosuppression, prior radiation, etc.) can increase risk of unacceptable toxicity.

18.4 Treatment Planning Considerations[1]

Simulation instructions	**SBRT** Patient supine and scanned head first Patient scanned in a Vaclock bag Abdominal compression recommended (unless other respiratory gaiting or motion management systems utilized) 4D scan 0–90% used to assess tumor motion and create an ITV (when applicable) **Hypofractionation** Patient supine and scanned head first with arms over the head Patient scanned in a Vaclock bag 4D scan 0–90% used to assess tumor motion and create and ITV Abdominal compression or other forms of respiratory gaiting or motion management can be considered
Image guidance	**SBRT conventional linac:** • Daily CBCT for patient setup • 4D CBCT used for targets with >1 cm motion • Second CBCT to confirm correct patient shifts **SBRT CyberKnife:** • **Fiducial-based tracking** – Wait at least 7 days between fiducial placement and sim – Ideally 3 markers implanted in order to track translation and rotation – Perform a 4DCT 0% and 50% scan to assess how well fiducials track tumor movement – Use Accuray software to build a synchrony model correlating target motion with external respiratory markers – kV planar imaging every 60 s to confirm tracking alignment and update synchrony model • **Spine tracking** – Appropriate for tumors within 6 cm of the center of the vertebral body – Used for patients that are not candidates for fiducial placement • **Tumor tracking** – Solid nodules that are "floating" in the lung and easily distinguished from the lung **Hypofractionated conventional linac:** • CBCT recommended before first treatment for most tumors • 4D-CBCT may be needed for tumors with >1 cm motion • Weekly PORT films thereafter may suffice if PTV is >1 cm from spinal cord and minimal tumor motion • Daily or weekly CBCT recommended if PTV is close (<5 mm) to spinal cord

[1] Based on delivery system and institutional protocols.

Margins	CTV, PTV, ITV—Recommendations dependent on type of image guidance or motion management systems utilized **SBRT conventional linac:** ITV: Delineated based upon tumor motion assessed during 4DCT • Combination of GTV on 0% and 50% scans CTV: Not typically recommended PTV: At least a uniform 5 mm expansion of the ITV • Larger expansion (frequently 8 mm) in direction of greatest motion • Example: For a tumor with 1 cm superior-inferior displacement, consider 5 mm radial expansion with 8 mm superiorly and inferiorly **SBRT CyberKnife fiducial:** No ITV or CTV PTV: 5 mm expansion of GTV with 8 mm in direction of maximal displacement (see above example) **SBRT CyberKnife spine tracking:** ITV: Union of the inspiration, expiration, and simulation GTV PTV: 5 mm uniform expansion of the ITV with 8 mm expansion in direction of maximal displacement (see above example) **Hypofractionated conventional linac:** ITV: Delineated based upon tumor motion assessed during 4DCT • Combination of GTV on 0 and 50% scans (or MIP and FB) CTV: 5–8 mm uniform expansion around ITV • CTV is not expanded into the bone or esophagus • Elective nodal regions are generally not included in CTV PTV: Generally a 3–5 mm uniform expansion around CTV • PTV is expanded into OAR including the esophagus and bone
Dosimetric consideration	GTV: 100% CTV: 100% (if applicable) PTV: 95% CI (SBRT, conventional linac) <1.5–1.8 CI (SBRT, CyberKnife, spine tracking) <1.3–1.5 CI (SBRT, CyberKnife, fiducial-based tracking) <1.2–1.4

Contouring/Planning Considerations

1. 4D conventional linac SBRT (Fig. 18.1)

   (a) Utilize windowing tools (A–C)
   - Extent of parenchymal lesion best visualized on lung windowing (A).
   - Soft-tissue windowing allows for improved visualization of adjacent structures such as chest wall (B) but can underestimate the extent of parenchymal disease (C).

   (b) Delineate on different phases of breathing (A, D, E)
   - Contour GTV on free breathing and MIP (or 0 and 50%, etc.) (A, D).
   - Combine GTVs to form ITV (E, F).
   - Evaluate tumor motion and generate PTV (E, F).
     – PTVs do expand into critical structures including chest wall (E)

  - Non-isotropic expansion of 5 mm anterior/posterior, medial/lateral, and 8 mm superior/inferior commonly utilized as lung tumors generally show more superior/inferior displacement with breathing (F).
  - Always review 4D tumor movement. Consider changing PTV expansions based on principle direction and extent of tumor displacement with breathing.

(c) Evaluate plan in multiple planes (G–H)
- Make sure lower (10–20%) isodose lines are visible.
- Evaluate for hot spots or dose streaking.
- Review DVHs for critical structures.
- Consider changing isodose prescription line based on proximity to organs/structures at risk.

2. Non-fiducial-based CyberKnife SBRT (Fig. 18.2)

(a) Obtain 4D CT and delineate GTV on multiple phases (0%, 50%, free breathing, breath-hold, etc.) (B–C):
- Use lung windows to delineate parenchymal disease.
- Evaluated for bony or soft-tissue involvement on appropriate window levels.
- PTV expansion of ITV should be based on extent and direction of tumor motion—8 mm superior/inferior with 5 mm in all other directions is common but may not be appropriate for tumor with substantial axial displacement.

(b) Evaluate plan in multiple planes (D–E):
- Check for hot spots, dose distribution, and dose streaking.

3. Fiducial-based CyberKnife SBRT (Fig. 18.3)
4. Requires 4D scan to evaluate tracking but only requires delineating in one phase:

(a) Yellow arrow highlights fiducial marker in the tumor (A).
(b) PTV expansion of GTV is based on tumor motion as above.
(c) Plan evaluation in multiple planes (C–D).

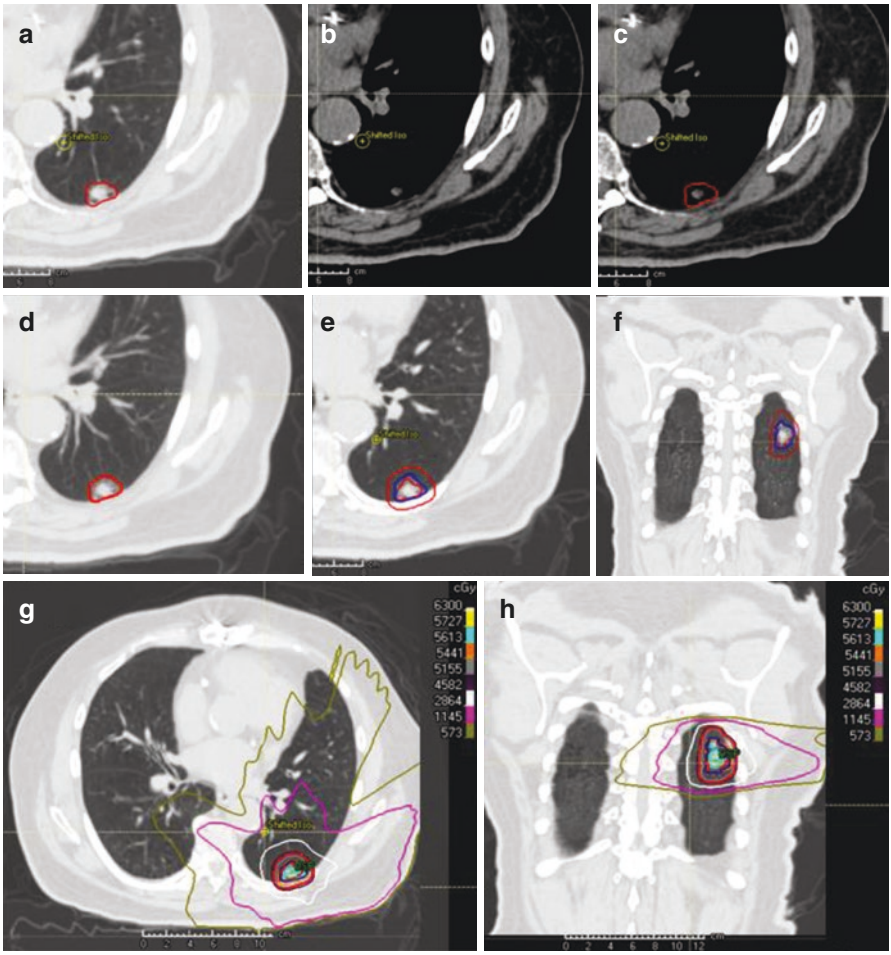

Fig. 18.1 Contouring and planning considerations for conventional linac-based lung SBRT

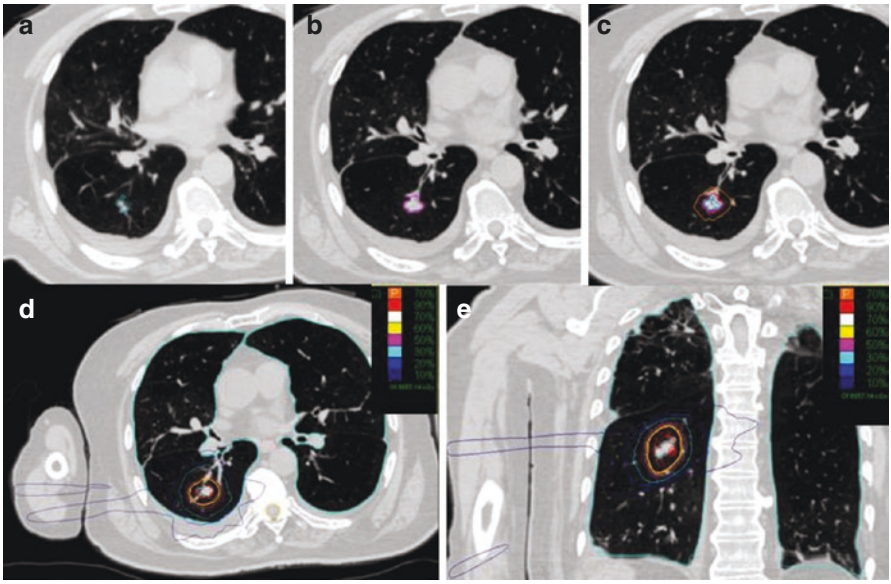

Fig. 18.2 Contouring and planning considerations for non-fiducial-based lung SBRT with CyberKnife radiosurgery

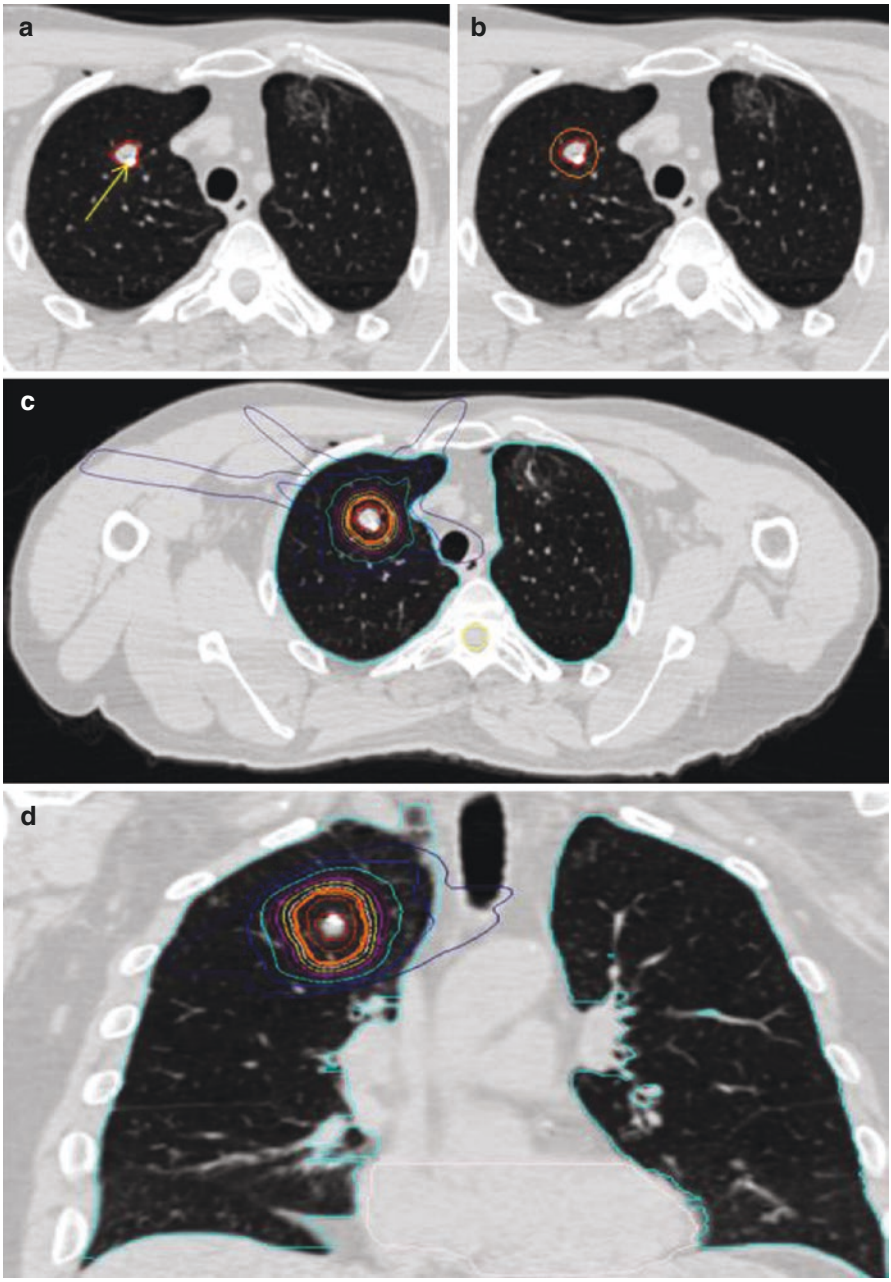

Fig. 18.3 Contouring and planning considerations for fiducial-based lung SBRT with CyberKnife

18.5 Commonly Used Dose/Fractionation Schemes

Dose/fx	# of fx	Total dose	Notes
SBRT			
5–7.5 Gy	8–10 QD	45–50 Gy	Re-irradiation, central location, patient-specific factor concerning for excess toxicity [8, 9]
10 Gy	5 QD or QOD	50 Gy	Centrally located (within 2 cm of major bronchus), re-irradiation [10–12]
12 Gy	4 QD or QOD	48 Gy	Peripherally located (within 2 cm of chest wall or plexus) [13–15]
15–20 Gy	3 QOD	45–60 Gy	>2 cm from central structures, chest wall, and plexus [16–19]
34 Gy	1	34 Gy	Small (<2–3 cm), >2 cm from central structures, chest wall, and plexus and minimal tumor motion
Hypofractionation			
2.5–3.0 Gy	15–20 QD without concurrent chemotherapy	60–66 Gy	Peripheral (>2 cm from central structures) T1–T3 N0 NSCLC or metastases where SBRT is not available [20]
2.4–3.0 Gy	15–25 QD ± concurrent chemotherapy	60–75 Gy	Inoperable, stage IIIa–IV NSCLC, limited to tumors where total PTV (no ENI, involved nodes and primary tumor only) is <200–250 cc to achieve V20 < 20–30% [21–24]

18.6 Normal Tissue Tolerances

TG101 (Benedict et al. 2010) [25]		Other	Institutional practice
Lungs **End point: Grade 3 pneumonitis**			
1 fx SBRT	7 Gy < 1500 cc 7.4 Gy < 1000 cc	–	–
3 fx SBRT	11.6 Gy < 1500 cc 12.4 Gy < 1000 cc	–	24Gy < 15 cc 12.4Gy < 1000 cc 11.6Gy < 1500 cc Mean < 6Gy
4 fx SBRT	–	–	27Gy < 0.01 cc 20Gy < 15 cc Mean < 6Gy
5 fx SBRT	12.5 Gy < 1500 cc 13.5 Gy < 1000 cc	–	32Gy < 15 cc 19.5Gy < 5 cc 13.5Gy < 1000 cc 12.5Gy < 1500 cc Mean < 6Gy

TG101 (Benedict et al. 2010) [25]		Other	Institutional practice
15–25 fx hypofractionated	–	V20 < 30% if total RT dose <60–66 Gy [26, 27] V20 < 20% if total RT dose >66 Gy	–
Heart **End point: Pericarditis**			
1 fx SBRT	16 Gy < 15 cc 22 Gy max	–	–
3 fx SBRT	24 Gy < 15 cc 30 Gy max	–	24 Gy < 15 cc 30 Gy max
4 fx SBRT	–	–	28 Gy < 15 cc 34 Gy max
5 fx SBRT	32 Gy < 15 cc 38 Gy max	–	32 Gy < 15 cc 38 Gy max
15–25 fx hypofractionated	–	V40 < 40% [26]	–
Esophagus **End point: Stenosis/fistula (SBRT), grade 3 esophagitis/perforation (Hypofrx)**			
1 fx SBRT	11.9 Gy < 5 cc 15.4 Gy max	–	–
3 fx SBRT	17.7 Gy < 5 cc 25.2 Gy max	–	17.7 Gy < 5 cc 25.2 Gy max
4 fx SBRT	–	–	18.5 Gy < 5 cc 30 Gy max
5 fx SBRT	19.5 Gy < 5 cc 35 Gy max	–	19.5 Gy < 5 cc 35 Gy max
15–25 fx hypofractionated	–	V60 Gy < 10 cc 70 Gy max [26]	–
Spinal cord **End point: Neuropathy**			
1 fx SBRT	10 Gy < 0.35 cc 14 Gy max	–	–
3 fx SBRT	18 Gy <0.35 cc 21.9 max	–	18 Gy <0.35 cc 21.9 Gy max
4 fx SBRT	–	–	20.4 Gy <0.35 cc 24 Gy max
5 fx SBRT	23 Gy < 0.35 cc 30 Gy max	–	27 Gy < 0.35 cc 30 Gy max
15–25 fx hypofractionated	–	45 Gy max [26, 27]	–
Brachial plexus **End point: Neuropathy**			
1 fx SBRT	14 Gy < 3 cc 17.5 Gy max	–	–
3 fx SBRT	20.4 Gy < 3 cc 24 Gy max	–	20.4 Gy < 3 cc 24 Gy max
4 fx SBRT	–	–	24 Gy < 3 cc 27 Gy max

TG101 (Benedict et al. 2010) [25]		Other	Institutional practice
5 fx SBRT	27 Gy < 3 cc 30.5 Gy max	–	27 Gy < 3 cc 30.5 Gy max
15–25 fx hypofractionated	–	NR	–
Large bronchus **End point: Stenosis/fistula**			
1 fx SBRT	10.5 Gy < 4 cc 20.2 Gy max	–	–
3 fx SBRT	15 Gy < 4 cc 30 Gy max	–	15 Gy < 4 cc 30 Gy max
4 fx SBRT	–	–	16.5 Gy < 4 cc 40 Gy max
5 fx SBRT	16.5 Gy < 4 cc 40 Gy max	–	20 Gy < 5 cc 52.5 Gy max
15–25 fx hypofractionated	–	No max[a]	–
Small bronchus **End point: Stenosis/atelectasis**			
1 fx	12.4 Gy < 0.5 cc 13.3 Gy max	–	12.4 Gy < 0.5 cc 13.3 Gy max
3 fx	18.9 Gy < 0.5 cc 23.1 Gy max	–	18.9 Gy < 0.5 cc 23.1 Gy max
4 fx	–	–	20 Gy < 0.5 cc 26 Gy max
5 fx	21 Gy < 0.5 cc 33 Gy max	–	21 Gy < 0.5 cc 33 Gy max
15–25 fx hypofractionated	–	No max[a]	–
Chest wall/rib **End point: Pain/fracture[b]**			
1 fx	22 Gy < 1 cc 30 Gy max	–	–
3 fx	28.8 Gy < 1 cc 30 Gy < 30 cc 36.9 Gy max	–	28.8 Gy < 1 cc 36.9 Gy max
4 fx	–	–	30 Gy < 10 cc 50 Gy max
5 fx	35 Gy < 1 cc 43 Gy max	–	30 Gy < 10 cc 50 Gy max

[a]No maximum value reported. Major and minor airways are frequently included in the PTV for patients with advanced NSCLC

[b]Maximum values for chest wall/rib toxicity relate to incidence of pain which is generally self-limited and/or medically manageable. Of the OAR in this table, the chest wall/ribs are the only ones that these authors will regularly exceed the above dose limits to achieve optimal tumor coverage

1. Patient Management Considerations

(a) Premedication/prophylactic medication
- Patient-specific, and many patients require no premedication.
- Medications to consider as needed:
  - Benzodiazepines
    Lorazepam (Ativan) 0.5–1 mg before treatment
    Diazepam (Valium) 10–20 mg before treatment
  - Oral analgesics
    Oxycodone 5–10 mg before treatment
    Percocet 5–10/325 mg before treatment
    Vicoden 5–10/300 before treatment
  - Oral steroids
    Dexamethasone 4–8 mg before treatment
  - Antiemetics
    Zofran 8 mg before treatment
    Promethazine 25 mg before treatment
      Should consider prescribing q8–12 hours for 24–72 hours after treatment if nausea during treatment is problematic
  - Cough suppressants
    Morphine
      10–20 mg oral before treatment
      4 mg IV before treatment
    Tessalon Perles (benzonatate) 200–300 mg before treatment

(b) Common acute and late toxicities

- General acute toxicities:
  - Fatigue: 50%+ [18, 24, 28]
  - Dyspnea: 10–30% [7, 11, 29]
  - Cough: 10–30% [7, 14, 30]
  - Nausea: 10–20%
  - Chest pain: 5–10% [9, 31, 32]
  - Odynophagia: 5–10% [33, 34]
- Mild-moderate late toxicities
  - Chest wall pain:
    5–10% incidence for non-peripheral (>2–3 cm from chest wall) lesions [29, 35]
    Up to 30–50% incidence if abutting chest wall [34, 36]
    50–75% of cases are transient
    Management
      Observation
      Non-narcotic pain medications (e.g., NSAIDs)
        Ensure patients do not overuse OTC analgesics
        Have low threshold for narcotics if there is a history of comorbidities (upper GI ulcers, hepatic dysfunction, renal disease, etc.) which increase the risk of non-narcotic pain medications

Narcotic pain medications including:
Oxycodone 5–10 mg q4–6 hours prn
Percocet 5–10/325 mg q4–5 prn
Vicoden 5–10/300 mg q4–6 prn
OxyContin 10–20 mg q12 hours
Duragesic (fentanyl) patches 25–75 mcg q72 hours
Neuropathic medications
Gabapentin 100 mg TID (can be titrated up to 1800 mg TID)
Lyrica 75 mg BID (can be titrated up to 300 mg BID)
Orthopedic/interventional referral if fracture present

- Rib fracture:

Up to 20% incidence if proximal to chest wall [36]
Roughly half will be symptomatic [32]
Management: same as chest wall pain

- Pneumonitis:
Radiographic only: 50–80% incidence
Symptomatic: 10–20% incidence [13, 15, 18]
Management:
Rule out other causes (e.g., COPD exacerbation)
Observation
Oral prednisone, 60 mg daily for 2 weeks followed by slow taper over 2–4 weeks
- Worsening dyspnea:
10–20% incidence [26, 37]
Management
Rule out other causes
Optimize management of concomitant lung diseases
Symptomatic therapies
Short acting beta-agonists
Opioids
Steroids
Supplemental oxygen
Pulmonary rehab

• Severe late toxicities: overall incidence <5%, dependent on tumor location [2, 18, 28, 34, 38]
- Bronchial/tracheal stenosis
Stenting
Surgical management
- Bronchial/tracheal necrosis
Surgical management
- Esophageal perforation
Emergency surgical management
- Massive hemoptysis
Emergency surgery or embolization
- Impaired cardiac function
Medical optimization

ACEi/ARB
Beta-blockers
Loop diuretics
Pacemaker or AICD implantation
Cardiac rehabilitation
– Pulmonary necrosis
Surgical options:
Lobectomy
Pneumonectomy
Debridement
Bronchoscopy for culture
Long-term (4–12 weeks) antibiotic therapy, preferably driven by culture-detected sensitivity analysis
– Bacterial superinfections
Antibiotics, initially broad spectrum followed by culture-directed sensitivity for 10–14 days. Examples include:
Vancomycin + zosyn
Meropenem
Ceftriaxone + metronidazole
Esophageal-aortic and tracheal-esophageal fistulas
Surgical management
Cord injury/myelitis
Generally irreversible
Symptomatic therapies include:
Neuropathic medications
Gabapentin 100 mg TID (can be titrated up to 1800 mg TID)
Lyrica 75 mg BID (can be titrated up to 300 mg BID as needed)
Physical medicine/rehabilitation

2. Follow-Up[2]

(a) NSCLC
- CT chest
  - Every 3–6 months for 2 years
  - Every 6 months years 3–5
  - Consider annual after year 5
- PET-CT
  - Not indicated unless clinical suspicion for recurrence (e.g., growing mass on CT or symptomatic worsening) or metastatic spread
- Blood tests
  - No routine blood work unless clinically indicated

(b) Lung metastases

- CT chest/abdomen/pelvis
  - Every 3–6 months for 2 years
  - Long-term surveillance determined by histology and clinical setting

[2] Based on NCCN guidelines and authors institutional practice.

- PET-CT
  - Regular PET-CT (every 3–6 months) may be reasonable to assess for new metastatic lesions
- Blood tests
  - Tumor-specific biomarkers (CEA, CA19–9, CA-125, PSA, etc.) as indicated after treatment of oligometastases

3. Relevant Literature

Summary of three-fraction lung SBRT trials

Study	Patients	Treatments	Median FU (month)	Outcomes
Prospective				
Lindberg 2015 [39]	*N* = pts T1–T2 N0 Peripheral tumors only	15 Gy × 3	NR	5-year LC: 79% 5-year OS: 30% Grade 3+ toxicity: 30% No grade 5 toxicity
Bral 2011 [4]	*N* = 40 <6 cm	20 Gy × 3 (peripheral tumors) 15 Gy × 5 (central tumors)	16	2-year LC: 84% Grade 3+ toxicity: 20% One grade 5 toxicity bronchial stenosis (central)
Ricardi 2010 [40]	*N* = 62 <5 cm Peripheral tumors only	15 Gy × 3	28	3-year LC: 88% 3-year OS: 57% Grade 3 toxicity: 10% Rib fracture: 1.6%
Bauman 2009 [41]	*N* = 57 T1–T2 N0	15 Gy × 3	35	3-year LC: 92% 3-year OS: 60% Grade 3+ toxicity: 38% No grade 5 toxicity
Fakiris 2009 [18]	*N* = 70 <7 cm	20–22 Gy × 3	50	3-year LC: 88% 3-year OS: 42% Grade 3+ toxicity: 10% for peripheral tumors 27% for central tumors
Rusthoven 2009 [1]	*N* = 38 metastases 1–3 with total diameter <7 cm	16–20 Gy × 3	15	2-year LC: 96% 2-year OS: 38% Grade 3: 7.8% No grade 4 or 5 toxicities
Koto 2007 [42]	*N* = 31 <5 cm	15 Gy × 3 7.5 Gy × 8	32	3-year LC: 78% T1 tumors 40% T2 tumors 3-year OS: 72% Grade 3 pneumonitis 1/31 patients

Study	Patients	Treatments	Median FU (month)	Outcomes
Timmerman 2006 [2]	*N* = 70 <7 cm	20–22 Gy × 3	18	2-year LC: 95% 2-year OS: 55% Grade 3+ toxicity 17% for peripheral tumors 40% for central tumors
Retrospective				
Shen 2015 [43]	*N* = 50 <5 cm Peripheral	16–20 Gy × 3	35	2-year LC: 92% 2-year OS: 74% Grade 3 toxicity: 10% No grade 4 or 5
Timmerman 2010 [16]	*N* = 59 <5 cm Peripheral tumors only	18 Gy × 3	34	3-year LC: 91% Med OS: 4 year Grade 3+ toxicity: 17% No grade 5
Vahdat 2010 [17]	*N* = 20 T1 N0 Peripheral tumors only	18–20 Gy × 3	18	2-year LC: 95% 2-year OS: 90%
Kopek 2009 [29]	*N* = 88 <6 cm	15–22.5 Gy × 3	44	4-year LC: 89% 4-year OS: 24% Grade 3 dyspnea: 12.5% Grade 3–4 pain: 12.5% Rib fractures: 8%
Song 2009 [44]	*N* = 32 <5 cm	10– 20 Gy × 3–4	25	2-year LC: 85% 2-year OS: 38% Grade 3+ toxicity: 0% (peripheral) 33% (central) Bronchial stricture in 8/9 central tumors
Baumen 2008 [41]	*N* = 60 T1–T2 N0 Peripheral tumors only	15 Gy × 3	23	2-year LC: 96% 2-year OS: 65% Grade 3 toxicity: 21% No grade 4 or 5 toxicities
Hoopes 2007 [45]	*N* = 58 T1–T2 N0	8–24 Gy × 3	42	3-year LC: 75% 3-year OS: 49%
Nyman 2006 [35]	*N* = 45 <5 cm Peripheral tumors only	15 Gy × 3	43	3-year LC: 80% 3-year OS: 30% 4.5% rib fracture 6.5% symptomatic pneumonitis

Summary of 4+ fraction lung SBRT regimens

Study	Patients	Treatments	Median FU (month)	Outcomes
Prospective				
Nagata 2015 [13]	169 T1 N0 Medically operable and inoperable	12 Gy × 4	47–67	3-year LC: 90% 3-year OS: 76% operable 60% inoperable Grade 3+ toxicity: Inoperable 10.6% Operable 6.2% (no grade 4–5)
Niibe 2015 [46]	34 metastases	5–12.5 Gy × 4–10 fractions	28	2-year LC: 90% 2-year OS: 66% Grade 3+ toxicity: 3%
Modh 2014 [37]	125 Central NSCLC or metastases	9 Gy × 5	17	2-year LC: 79% Grade 3 toxicity: 8% (esophagitis, dyspnea) 2 grade 5 toxicities (hypoxia)
Shibamoto 2012 [15]	180 <5 cm Medically operable and inoperable	11–13 Gy × 4	40	3-year LC: 86% if <3 cm 74% if >3 cm 3 year OS: 74% operable 59% inoperable Grade 2+ pneumonitis: 13% (44–48 Gy) 21% (52 Gy)
Baba 2010 [31]	124 <5 cm	11–13 Gy × 4	26	3-year LC: 91% (IA) 74% (IB) 3-year OS: 79% (IA) 56% (IB) Grade 3 toxicity: 2.5% 8 rib fractures note, only 1 symptomatic
Baba 2009 [47]	53 T1–T2 N0 or metastases <5 cm	11–13 Gy × 4	32	3-year LC: 80% 3-year OS: 76% No grade 3+ toxicity Only 1 symptomatic rib fracture

Study	Patients	Treatments	Median FU (month)	Outcomes
Nagata 2005 [14]	45 T1–T2 N0	12 Gy × 4	30	5-year LC: 98% 5-year OS: 72–83% No grade 3 toxicity Grade 2 pneumonitis (requiring steroids): 4%
Retrospective				
Haseltine 2016 [30]	108 Central NSCLC or mets	9 Gy × 5 (median)	23	2-year LC: 77% 2-year OS: 64% Grade 3+ toxicity: 30.7% if within 1 cm of central airway 7.9% if >1 cm of central airway
Aibe 2014 [48]	30 T1–T3 N0	10 Gy × 5	36	3-year LC: 86% 3-year OS: 77% No grade 3 or 4 toxicity noted 2/30 patients with fatal pneumonitis
Harkenrider 2014 [49]	34 T1–T2 N0	5–15 Gy × 3–10 fractions (median 10 Gy × 5 fractions)	17	2-year LC: 97% 2-year OS: 85% Grade 3 toxicity: 8.8% No chest wall pain or fractures No grade 4 or 5 toxicities
Li 2014 [8]	82 Within 2 cm of central structures or chest wall	7 Gy × 10	21	2-year LC: 96% 2-year OS: 66% Grade 3 toxicity: 3.2% 1 grade 5 hemoptysis
Baschnagel 2013 [50]	47 metastases <5 cm	5–18 Gy × 4–10	28	3-year LC: 85% 3-year OS: 63% Grade 3 toxicity: 10% No grade 4 or 5
Ricardi 2012 [51]	61 metastases <5 cm	26 Gy × 1 15 Gy × 3 9 Gy × 4	20	3-year LC: 84% 3-year OS: 52% 1 grade 3 toxicity (1.6%) (pneumonitis)

Study	Patients	Treatments	Median FU (month)	Outcomes
Haasbeek 2011 [9]	63 T1–T2 N0 central hilar, or abutting mediastinal structures	7.5 Gy × 8	35	3-year LC: 93% 3-year OS: 64% Grade 3 chest wall pain 2/63 and dyspnea 2/63 Nine cardiopulmonary deaths
Grills 2010 [32]	124 T1–T2 N0	12 Gy × 4–5	30	2.5-year LC: 96% 2.5-year OS: 72% Grade 3 toxicity: 10.5% 12 rib fractures, 6 symptomatic (grade 2)
Videtic 2010 [11]	26 <5 cm	10 Gy × 5	30	3-year LC: 94% 3-year OS: 52% Grade 3 dyspnea (1/26) Grade 2 chest wall pain (1/26)
Okunief 2006 [12]	50 metastases	10 Gy × 5	18	2-year LC: 93% 2-year OS: 48% Grade 2 toxicity: 6.1% Grade 3 toxicity: 2%

Clinical outcomes of lung re-irradiation with SBRT

Study	Patients	Treatments	Median FU (month)	Outcomes
Patel 2015 [52]	*N* = 26 Previous med RT dose: 61.4 Gy	6 Gy × 5 (med)	NR	2-year OS: 80% 2-year OS: 37% No grade 3+ toxicity 55% grade 1–2
Hearn 2014 [10]	*N* = 10 Previous med RT dose: 50 Gy (SBRT)	10 Gy × 5 (med)	14	2-year LC: 60% 2-year OS: 30% Grade 1–2 CW toxicity: 50% No grade 3+ toxicity

Study	Patients	Treatments	Median FU (month)	Outcomes
Kilburn 2014 [7]	*N* = 33 Previous med RT dose: 66 Gy	5 Gy × 10 (med)	17	2-year LC: 67% Median OS: 21 months Grade 3 pneumonitis: 23% 2 grade 5 toxicities (1 pneumonitis, 1 hemoptysis)
Owen 2014 [6]	*N* = 18 Previous med RT dose: 60 Gy	18 Gy × 3 12 Gy × 4 10 Gy × 5	21	2-year LC: 90% 1-year OS: 88% Grade 2 toxicity: 27% No grade 3+ toxicity
Trovo 2014 [19]	*N* = 17 Previous RT: Med BED 87.5	6 Gy × 5 (med)	15	1-year LC: 67% 1-year OS: 80% No grade 2+ pneumonitis Chest wall pain: 6.7%
Reyngold 2013 [53]	*N* = 39 Previous med RT dose: 61 Gy	10– 12 Gy × 3–5	12	1-year LC: 64% 1-year OS: 45% Grade 3 toxicity: 17% Grade 2 toxicity: 65%
Trakul 2012 [5]	*N* = 17 Previous RT: BED 87.5	20–25 Gy × 1 10 Gy × 3–5	15	1-year LC: 67% 1-year OS: 80% No grade 2+ pneumonitis Chest wall pain: 6.7%
Kelly 2010 [34]	*N* = 36 Previous med RT dose: 61.4 Gy	12.5 Gy × 4	15	1-year LC: 92% 1-year OS: 59% Chest wall pain: 30% Grade 3 esophagitis: 8% No grade 4–5
Coon 2008 [38]	*N* = 12	20 Gy × 3	12	1-year LC: 92% 1-year OS: 67% No grade 3+ toxicity One symptomatic pneumonitis (grade 2)

Summary of studies using hypofractionated radiation for lung cancer

Study	Patients	Treatments	Median FU (month)	Outcomes
Prospective				
Walraven 2016 [24]	*N* = 102 Stage II–III NSCLC	2.75 Gy × 24 + concurrent cisplatin ± weekly cetuximab	60	5-year OS: 37%
Maguire 2014 [54]	*N* = 130 Inoperable stage III NSCLC	2.75 Gy × 20 with concurrent or sequential cisplatin + vinorelbine	35	2-year OS: 50% Grade 3+ esophagitis: 8% Grade 5 toxicity: 5%
Cheung 2014 [20]	*N* = 80 T1–T3 N0	3 Gy × 20	49	2-year LC: 88% 2-year OS: 68% Grade 3 dyspnea: 14% Grade 3 pneumonitis: 10%
Cannon 2013 [27]	*N* = 79 Stage III NSCLC	Dose escalation 2.2–3.4 Gy × 25	17	No grade 3+ esophagitis or pneumonitis 6 patients died from damage to central structures, all treated with >2.5 Gy/fx
Liu 2013 [26]	*N* = 26 IIIa or IIIb NSCLC	3 Gy × 20–25 with concurrent vinorelbine and carboplatin	11.5	Absolute response rate: 80% mPFS 11.5 months Any esophagitis: 88% Grade 3 esophagitis: 15% Grade 3 pneumonitis: 7%
Osti 2013 [55]	*N* = 30 IIIa–VI NSCLC	3 Gy × 20	13	2-year PFS: 36% 2-year OS: 38% Grade 3 esophagitis: 7% Grade 3 pneumonitis: 3.5%
Cho 2009 [56]	*N* = 49 Unresectable stage III NSCLC	2.4 × 25 Gy	37	3-year LC: 54% 3-year OS: 44% Grade 2+ esophagitis: 60% 2 grade 5 toxicities (hemoptysis)

Study	Patients	Treatments	Median FU (month)	Outcomes
Belderbos 2007 [23]	*N* = 158 Stage III NSCLC	Induction gem + Cis followed by 2.75 Gy × 24 vs. 2.75 Gy × 24 with concurrent cis	39	mOS 16 months (both arms) Grade 3 esophagitis: 14% (C) 5% (S) Grade 3 pneumonitis: 18% (C) 14% (S)
Retrospective				
Jiang 2016 [57]	*N* = 65 Stage I NSCLC	4–6 Gy × 12–15	24	3-year LC: 90% 3-year OS: 88% Symptomatic pneumonitis: 17%
Agolli 2015 [21]	N = 60 IIIa–IV NSCLC	3 Gy × 20	30	mPFS: 12 months mOS: 13 months Grade 3 esophagitis: 6% Grade 3 pneumonitis: 5% No grade 4–5 toxicities
Chang 2012 [22]	*N* = 33 Lung metastases or NSCLC	4.5–7.0 Gy × 8–16 (50 Gy median total dose)	26	mOS: 32 months (NSCLC) mOS: >40 months (metastases) Grade 3+ pneumonitis: 6%

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Part VI
Breast Cancer

Chapter 19
Breast Cancer

Kevin Pearlstein and Ellen Jones

The benefit of post-lumpectomy and postmastectomy RT in improving local control and overall survival has been demonstrated through multiple randomized trials. The conventional fractionation scheme has evolved to be 25 RT treatments (2 Gy/fraction) to the whole breast with an additional RT boost to the lumpectomy cavity or mastectomy scar. However, multiple randomized studies have subsequently explored hypofractionated whole breast RT in specific populations. Another approach, APBI, has been explored in the post-lumpectomy setting to target only the lumpectomy cavity. These alternative approaches to conventional whole breast RT are viable options in certain patient populations.

19.1 Pearls

- Breast cancer is the most commonly diagnosed cancer, with 230,000 new cases in the United States annually.
- Median age at diagnosis is 62 years.
- There is a strong female predominance, and <1% of new cases are in men.
- Risk factors include older age, estrogen exposure (high natural estrogen levels, hormone replacement), early menarche, late menopause, nulliparity, and obesity (in postmenopausal women).
- Known genetic risk factors include mutations in BRCA1/2, p53 (Li-Fraumeni syndrome), STK11 (Peutz-Jeghers syndrome), and PTEN (Cowden syndrome).

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- Abnormal screening mammogram is the most common presentation in developed countries. The most common physical exam finding is a firm palpable mass, while more advanced findings include palpable axillary or supraclavicular lymphadenopathy. Indications of inflammatory breast cancer include breast erythema, skin thickening, nipple changes, and peau d'orange (skin dimpling).
- Core biopsy should be performed to confirm diagnosis.
  - Proliferative lesions that are not necessarily precursors to invasive cancer but do increase risk of malignancy include lobular carcinoma in situ (LCIS) and atypical hyperplasia (AH).
  - Ductal carcinoma in situ (DCIS) is considered a precursor to invasive cancer. Higher nuclear grade and comedo subtype are associated with higher risk of invasion and recurrence.
  - Invasive carcinomas include infiltrating ductal carcinoma (70–80% of invasive cancer) and infiltrating lobular carcinoma (more often bilateral and multicentric). More rare types (<5%) include mucinous, tubular, medullary, and papillary subtypes.
  - Invasive cancers can be classified according to ER, PR, HER2 status and Ki67%.
- Breast tissue generally lies between 2nd and 6th ribs and extends from the edge of the sternum to midaxillary line.
  - Axillary lymph nodes are divided into anatomic groups based on relation to pectoralis minor: level I (lateral), level II (posterior), and level III (medial).
  - Internal mammary lymph nodes are located in intercostal spaces near internal mammary vessels from retroclavicular area to fifth intercostal space.
- Lymph node drainage is predominantly to axillary lymph nodes but also to IMN and supraclavicular lymph nodes. The inner quadrant lesions are more likely to drain to IMN compared to outer quadrant lesions.
- Most common sites of distant spread include the bone, lung, brain, and liver.
- Diagnostic evaluation can include different imaging studies.
  - Diagnostic mammogram, which includes mediolateral oblique (MLO) and craniocaudal (CC) views.
  - Ultrasound of the breast can further characterize mass, is very sensitive for breast cancer, and can help identify target for core needle biopsy.
  - Breast MRI is very sensitive (>90%) but has lower specificity (~70%). It can be used to evaluate young women with dense breast tissue and further evaluate inconclusive breast masses seen on mammogram or ultrasound.
- Treatment options
  - Surgery is used as treatment for both in situ and invasive breast cancer and can be lumpectomy or mastectomy. Axillary lymph node dissection can be performed in the clinically positive axilla, whereas sentinel lymph node biopsy is more commonly used in the clinically negative axilla.
    - The equivalency of lumpectomy followed by whole breast RT and mastectomy has been demonstrated in multiple clinical trials.

    - The omission of post-lumpectomy RT can be considered in older women (>65–70) with early-stage (T1–2, N0) hormone-positive breast cancers.
    - RT alone and/or endocrine therapy if ER/PR positive can be considered for patients with poor performance status or who are otherwise unfit for surgical management.
- Five to ten years of endocrine therapy (tamoxifen or aromatase inhibitor) is generally recommended for ER-/PR-positive patients.
- Neoadjuvant systemic therapy is appropriate in some situations including triple negative cancer, HER2 cancers, and inoperable disease.
- Adjuvant systemic therapy can be used for those at high risk for locoregional or distant recurrence (triple negative, large tumors, positive lymph nodes). Genetic tests such as Oncotype DX can help guide decision for node-negative, ER-positive cancers.

19.2 AJCC 8th Edition Staging

Primary Tumor (T Stage)

The same staging is used for clinical and pathologic staging. Clinical staging is denoted by the prefix "c," and pathologic staging has the prefix "p." The prefix "yc" or "yp" is added to denote clinical or pathologic T staging following administration of neoadjuvant treatment.

Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis	Tis (DCIS)	Ductal carcinoma in situ
	Tis (Paget)	Paget's disease of the nipple not associated with invasive carcinoma and/or carcinoma in situ (DCIS) in the underlying breast parenchyma
T1	T1mi	Tumor ≤1 mm in greatest dimension
	T1a	Tumor >1 mm but ≤5 mm in greatest dimension
	T1b	Tumor >5 mm but ≤10 mm in greatest dimension
	T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2		Tumor >20 mm but ≤50 mm in greatest dimension
T3		Tumor >50 mm in greatest dimension
T4	T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
	T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which does not meet the criteria for inflammatory carcinoma
	T4c	Both T4a and T4b
	T4d	Inflammatory carcinoma

Regional Lymph Nodes (N Stage)

Clinical Lymph Node Staging

cNX		Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0		No regional lymph node metastases
cN1		Metastases to movable ipsilateral level I, II axillary lymph node(s)
cN2	cN2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
	cN2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
cN3	cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
	cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
	cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Pathologic Lymph Node Staging

pNX		Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0	pN0(i−)	No regional lymph node metastases histologically, negative IHC
	pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
	pN0(Mol−)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
	pN0(Mol+)	Positive molecular findings (reverse transcriptase/polymerase chain reaction), but no regional lymph node metastases detected by histology or IHC
pN1	Pn1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
	pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
	pN1b	Metastases in internal mammary nodes detected by sentinel lymph node biopsy but not clinically detected
	pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes detected by sentinel lymph node biopsy but not clinically detected
pN2	pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
	pN2b	Metastases in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
pN3	pN3a	Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm) or metastases to the infraclavicular (level III axillary lymph) nodes
	pN3b	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes or in more than three axillary lymph nodes and in internal mammary lymph nodes detected by sentinel lymph node biopsy but not clinically detected
	pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Distant Metastasis (M Stage)

M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissues that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
cM1	Distant detectable metastases as determined by clinical and radiographic means
pM1	Histologically proven distant metastases, larger than 0.2 mm

Anatomic Staging Groups

Stage	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0	N1mi	M0
	T1[a]	N1mi	M0
Stage IIA	T0	N1[b]	M0
	T1[a]	N1[b]	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1[a]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

- M0 includes M0(i+)
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered stage IV and remains stage IV regardless of response to neoadjuvant therapy
- No stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0

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[a]T1 includes T1mi

[b]T0 and T1 tumors with nodal micrometastases only are excluded from stage IIA and are classified stage IB

19.3 Tumor and Patient Selection

Hypofractionated Whole Breast RT

- As part of the Choosing Wisely campaign, ASTRO recommends against initiating post-lumpectomy RT in women ≥50 with early-stage invasive breast cancer without considering hypofractionation [1].
- 2011 ASTRO guidelines to assist in patient selection for hypofractionated approach include [2]:
  - Age > 50 years
  - Treated with breast-conserving surgery
  - T stage pT1–2
  - Chemotherapy (either neoadjuvant or adjuvant) not used
  - Final RT plan with ≤±7% dose heterogeneity along central axis using 2D treatment planning
- Criteria for patient selection based on ASTRO guidelines and available clinical evidence are as follows [3]:

Clinical characteristic		Suitable	Cautionary	Unsuitable
Patient factors	Age	≥50 <50 with boost	<50 without boost	–
	Breast size	Small/medium (breast separation <25 cm)	Large (breast separation >25 cm)	–
Pathologic factors	T stage	T1–2	T3	T4
	Histology	Invasive ductal carcinoma	DCIS	Inflammatory
	ER status	ER/PR Pos, HER2 neg	HER2 pos (no concurrent trastuzumab) Triple negative	HER2 pos (with concurrent trastuzumab)
	Path margins	Negative	Positive	–
	Grade	1–2, 3 (with boost)	3 (without boost)	–
	N stage	N0	N1	N2–3
Treatment factors	Surgery	Breast-conserving	Mastectomy	Breast reconstruction
	Chemotherapy	None	Neoadjuvant chemo	Concurrent chemo
	Dose inhomogeneity	≤±7% at midplane	± 7–10% at midplane with 3DCRT	>10% at midplane

*Modified from Eblan et al. [3]

Accelerated Partial Breast Irradiation

Multiple groups have released guidelines to assist in patient selection for APBI following lumpectomy, which can be delivered using multiple techniques including brachytherapy, external beam RT, and intraoperative RT with low-energy X-rays or electrons.

ASTRO Guidelines (2009, updated 2016) [4, 5]

Clinical characteristic		Suitable	Cautionary	Unsuitable
Patient factors	Age	≥50	40–49 (all other factors "suitable") ≥50 (with other "cautionary" factor	<40 40–49 with "cautionary" factor
	BRCA 1/2 mutation	Not present	–	Present
Pathologic factors	Tumor size	≤2 cm	2.1–3 cm	>3 cm
	T stage	T1, tis	T2	T3–4
	Histology	Invasive ductal,screen-detected DCIS ≤2.5 cm	Invasive lobular, DCIS ≤3 cm	DCIS>3 cm
	ER status	Positive	Negative	–
	Path margins	Invasive: Neg (≥2 mm), DCIS: Neg (≥3 mm)	Close (<2 mm)	Positive
	Grade	Invasive: Any, DCIS: Low/intermed	–	–
	N stage	pN0	–	pN1–3
	LVSI	No	Limited/focal	Extensive
	EIC	No	≤3 cm	>3 cm
	Multicentricity	Unicentric	–	Multicentric
	Multifocality	Unifocal	–	Multifocal
	Associated LCIS	Allowed	–	–
Treatment factors	Neoadjuvant therapy	Not allowed	–	Yes
	Nodal surgery	SLN Bx, ALND	–	None performed

Note: 2016 ASTRO recommendations for intraoperative RT include:
- Limit treatment with electrons to women with invasive cancer and only "suitable" factors.
- Low-energy X-ray IORT should not be used for treatment outside of registry or clinical trial.

Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology (GEC-ESTRO) Guidelines [6]

Clinical characteristic		Suitable	Cautionary	Unsuitable
Patient factors	Age	>50	>40–50	<40
Pathologic factors	Tumor size	≤3 cm	≤3 cm	>3 cm
	T stage	pT1–2	pT1–2	pT3–T4
	Histology	Invasive ductal	Invasive lobular, DCIS	–
	ER/PR status	Any	–	–
	Path margins	Neg (≥2 mm)	Close (<2 mm)	Positive
	Grade	Any	–	–
	N stage	pN0	pN1mi, pN1 (by ALND)	pNx, ≥pN2a
	LVI	Not present	–	Present
	EIC	Not present	–	Present
	Multicentricity	Unicentric	–	Multicentric
	Multifocality	Unifocal	Multifocal (limited to within 2 cm of index lesion)	Multifocal (>2 cm from index lesion)
	Associated LCIS	Allowed	–	–
Treatment factors	Neoadjuvant therapy	No	No	Yes

Women who experience local recurrence following breast-conserving therapy and wish to have repeat breast-conserving surgery can be considered for re-irradiation with APBI. Studies have examined this approach in women with:

- Unicentric recurrence >1 year from initial treatment
- Refusal of mastectomy
- Repeat breast-conserving surgery with negative margins

19.4 Treatment and Planning

Hypofractionated Whole Breast

Simulation instructions	• Patients placed in supine position with immobilization device • Bilateral arms externally rotated with hands placed behind head using wingboard • Head tilted to opposite direction of the involved breast • Prone positioning can be considered as an alternative. This positioning can be particularly useful for women with large pendulous breasts • Markers should be placed over scar, below clavicle, 2 cm below palpable breast tissue, midsternum, midaxilla • A single isocenter is generally placed below the bottom edge of the clavicle • For left-sided cancers, deep inspiration breath hold can be used to minimize heart dose

Image guidance	• At a minimum, weekly verification films should be obtained, while the patient is under treatment • For left-sided breast cancers, deep inspiratory breath hold or respiratory gating can be used with each fraction to minimize cardiac dose
Tumor target/ margins	• Target is whole breast treated using opposed tangents (Fig. 19.1) – Whole breast CTV: Superior border is variable but approximately level of 2nd rib insertion, inferior border is where CT apparent breast is lost, medial border is sternal-rib junction, lateral border is midaxillary line, anterior border is skin, and posterior border is pectoralis/chest wall muscles or ribs • If used, tumor boost can be delivered with en face electrons or photons (wedge pair or mini-tangent) to target lumpectomy cavity (including surgical clips and seroma) + 1.5–2 cm margin • There is limited data for safety and efficacy of a hypofractionated schedule to treat locoregional LN (axillary, supraclavicular, internal mammary). Locoregional LN can be treated depending on clinical scenario—Usually with single AP field, but may need PA boost for deeper targets – Superior border is cricoid cartilage, inferior border is bottom edge of clavicle (matched non-divergent to tangent), medial border is pedicle, and lateral border is humeral head (more inferior can be extended to at least surgical clips, and potentially further in lieu of ALND)
Dosimetric considerations	• Keep max 3D point dose in the breast <110% prescription • Limit amount of breast receiving 105% prescription • Homogeneity may be suboptimal for breast separation >25 cm • An IMRT plan is not mandatory; however, multiple field-in-field segments can be used to improve homogeneity and reduce hot spots (Fig. 19.2)

Accelerated Partial Breast Irradiation

There are multiple techniques for delivering APBI that are used in clinical practice following breast-conserving surgery including brachytherapy, IORT, and EBRT. Standard management after in-breast recurrence for patients treated with lumpectomy and whole breast RT would be salvage mastectomy; however, there is developing evidence that these local recurrences after breast-conserving therapy can

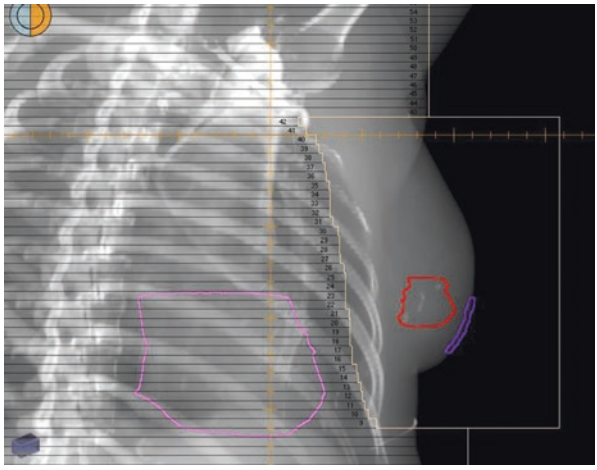

Fig. 19.1 DRR of L medial tangent field covering the whole breast using deep inspiratory breath hold technique. Lumpectomy cavity contoured in red, surgical scar in purple, heart in pink

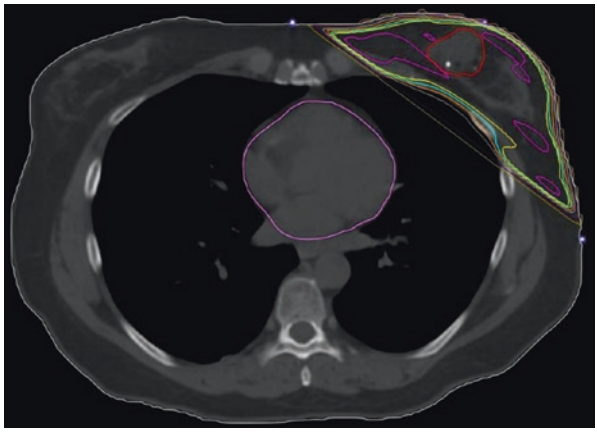

Fig. 19.2 Final treatment plan using field-in-field technique to optimize plan homogeneity

be treated with repeat lumpectomy followed by re-irradiation with APBI. This is generally done with hyperfractionated external beam RT (BID treatment, as in RTOG 1014) or brachytherapy.

Brachytherapy

Technique	Multiple techniques exist for catheter placement around lumpectomy cavity either at the time of lumpectomy or as a separate procedure: • Interstitial catheter brachytherapy (Fig. 19.3) • Intracavitary balloon brachytherapy using single or multiple catheters (e.g., MammoSite) • A combination of the two approaches (e.g., SAVI) Source location, number of positions, dwell times determined by CT-based 3D treatment planning
Tumor target/margins	• GTV: Lumpectomy cavity (defined by preoperative imaging and clinical exam, surgical procedure and postoperative surgical clips, seroma and pathology report) • CTV/PTV: Lumpectomy cavity with 1–1.5 cm expansion (at least 5 mm inside the skin, excluding chest wall and pectoralis major)
Interstitial brachytherapy dosimetric considerations	≥90% PTV coverage by ≥90% prescription
	Dose homogeneity index $(1 - V_{150\%}/V_{100\%}) \geq 0.75$
	$V_{150\%} \leq 70$ cm^3
	$V_{200\%} \leq 20$ cm^3
	Skin $D_{max} \leq 100\%$
	Ipsilateral breast $V_{\geq 50\%} \leq 60\%$
Intracavitary brachytherapy dosimetric considerations	≥90% PTV coverage by ≥90% prescription
	Tissue-balloon conformance (volume of trapped air/PTV) < 10%
	Balloon symmetry deviation of ≤2 mm from expected
	Balloon surface-skin distance Ideal: ≥7 mm Acceptable: 5–7 mm if skin $D_{max} \leq 145\%$
	Ipsilateral breast $V_{150\%} \leq 50$ cm^3
	Ipsilateral breast $V_{200\%} \leq 10$ cm^3
	Ipsilateral breast $V_{\geq 50\%} \leq 60\%$

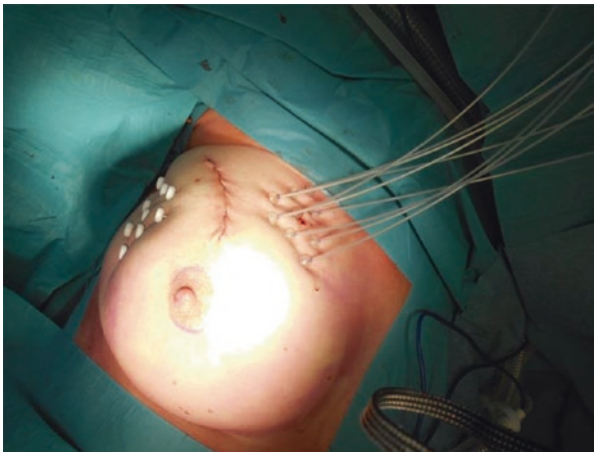

Fig. 19.3 Interstitial brachytherapy catheter placement [7]. **Image used with permission of Elsevier publishing*

Intraoperative RT

A single fraction of RT can be delivered with multiple techniques at the time of surgery.

- For all techniques, appropriate shielding of thoracic wall should be used to minimize heart, lung, and chest wall exposure.

Low-energy photons	• Appropriately sized applicator placed into lumpectomy cavity after resection • Ensure adequate separation of the applicator and skin • RT delivered using low-energy (50 kV) photons
Electrons	• Appropriately sized applicator (1.5–2 cm larger than target) placed into lumpectomy cavity after resection (Fig. 19.4) • Appropriate electron energy selected based on depth measurement to chest wall (generally 4–12 MeV) • Dose delivered to 90% depth
HDR brachytherapy	• Applicator and catheters placed into the lumpectomy cavity after tumor resection • Dwell time calculated to deliver prescription dose to lateral margin of the resection cavity

External Beam RT [4]

Simulation	See simulation section for hypofractionated whole breast RT
Target/margins	• GTV: Lumpectomy cavity (including surgical clips and seroma) (Fig. 19.5) • CTV: GTV+ 1–1.5 cm expansion (at least 5 mm inside skin, excluding chest wall and pec major) • PTV: CTV+ 1 cm expansion
Dosimetric constraints	• ≥90% of prescription dose covering ≥90% of PTV • Maximum breast dose ≤120% prescription dose • Minimize dose delivered to uninvolved ipsilateral breast • Ideally <35% of the breast should receive prescribed dose

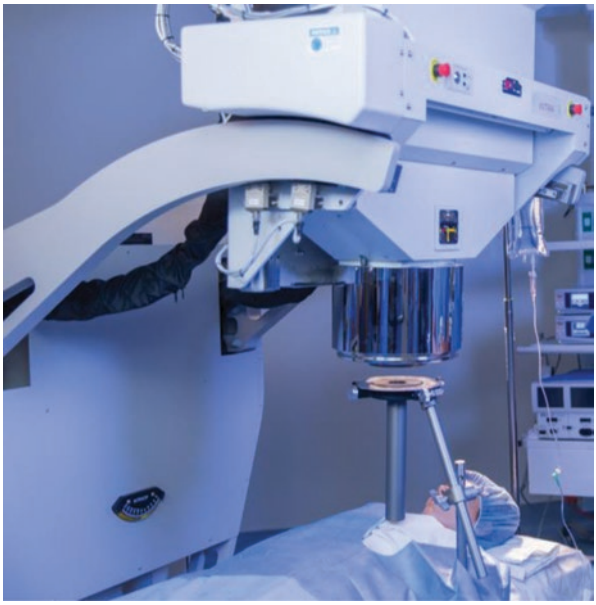

Fig. 19.4 Intraoperative electron treatment with applicator in place—Mobetron in docked position. **Image used with permission of IntraOp Medical Corporation*

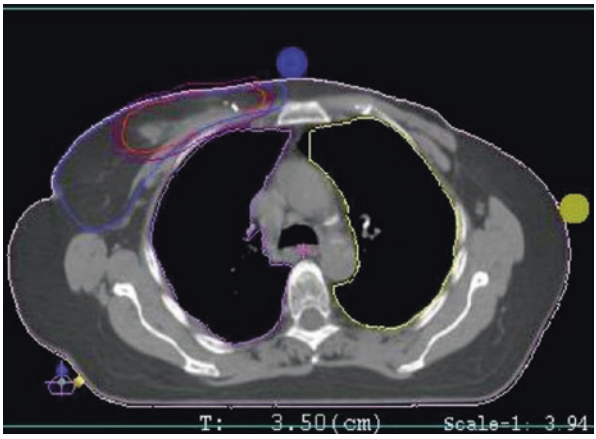

Fig. 19.5 Target identification for partial breast external beam RT using surgical clips to help delineate lumpectomy cavity. **Image used with permission of Dr. Icro Meattini, Oncology Institute, Florence University Hospital, Florence, Italy*

19.5 Doses

Hypofractionated Whole Breast RT

Multiple treatment regimens have been evaluated in prospective trials.

- α/β estimated ~3–4 [8]

Dose per fraction	Number fractions	Total dose	Duration of treatment	Notes
3 Gy	13	39 Gy	5 weeks, qod	Fractionation from START A [9], RMH/GOC [10]
2.66 Gy	15	40 Gy	3 weeks, daily	Fractionation from START B [11]
3.2 Gy	13	41.6 Gy	5 weeks, qod	Fractionation from START A
2.66 Gy	16	42.5 Gy	3 weeks, daily	Fractionation from OCOG [12]
3.3 Gy	13	42.9 Gy	5 weeks, qod	Fractionation from RMH/GOC

START: UK Standardisation of Breast Radiotherapy
RMH/GOC: Royal Marsden Hospital/Gloucestershire Oncology Centre
OCOG: Ontario Clinical Oncology Group

- An ASTRO task force favored a dose schedule of 42.5Gy in 16 fractions using the OCOG regimen [12].
- A tumor bed boost was not consistently used in clinical trials evaluating hypofractionated whole breast RT.
  - A boost is routinely incorporated at our institution, generally 10 Gy delivered in 5 fractions.
- There is limited data for the safety and efficacy of a hypofractionated schedule to treat locoregional LN.
  - START A and B trials did include small proportion of patients who received supraclavicular treatment without increased rate of late brachial plexopathy.
  - If locoregional LN coverage is planned at our institution, a separate SCV field using a standard dose schedule (46–50 Gy delivered in 23–25 fractions) is run concurrently with hypofractionated whole breast fields.

Accelerated Partial Breast Irradiation

A number of different techniques have been used to deliver APBI, including external beam RT, brachytherapy, and intraoperative RT. Common fractionations include:

Treatment modality	Dose per fraction	Number fractions	Total dose	Duration of treatment	Notes
External beam RT	6 Gy	5	30 Gy	2 weeks, QOD	From Florence trial [13]
	3.75 Gy	10	37.5 Gy	1 week, BID	From Barcelona trial [14]
	3.85 Gy	10	38.5 Gy	1 week, BID	From NSABP B39, RAPID [15], RTOG 0319 [16]
	2 Gy	25	50 Gy	5 weeks, daily	From Hungary trial [17]
Intra-op RT (IORT)	20 Gy	1	20 Gy	Intra-op	From TARGIT [18]
	21 Gy	1	21 Gy	Intra-op	From ELIOT [19]

Treatment modality	Dose per fraction	Number fractions	Total dose	Duration of treatment	Notes
Brachytherapy	5.2 Gy	7	36.4 Gy	4 days, BID	From Hungary trial
	4 Gy	8	32 Gy	4 days, BID	From GEC-ESTRO trial [20]
	4.33 Gy	7	30.3 Gy	4 days, BID	From GEC-ESTRO trial
	3.4 Gy	10	34 Gy	4–6 days, BID	From NSABP B39, MammoSite study [21], RTOG 9517 [22]

RAPID: randomized trial of accelerated partial breast irradiation
TARGIT: targeted intraoperative radiotherapy
ELIOT: intraoperative radiotherapy with electrons

19.6 Normal Tissue Constraints

Hypofractionated Whole Breast

ASTRO task force noted optimal dose-volume parameters for the lung and heart when using hypofractionated approach are not known [2].

Constraints used at our institution and in the RTOG 1005 hypofractionation trial include:

Structure	RTOG 1005 constraint	Our institutional practice
Heart	$V_{10Gy} < 30\%$ (L) $V_{10Gy} < 10\%$ (R) $V_{20Gy} < 5\%$ (L) $V_{20Gy} = 0\%$ (R) Mean < 4Gy	$V_{10Gy} < 35\%$ $V_{20Gy} < 5\%$ Mean < 4 Gy
Ipsilateral lung	$V_{5Gy} < 50\%$ $V_{10Gy} < 35\%$ $V_{20Gy} < 15\%$	$V_{5Gy} < 50\%$ $V_{20Gy} < 15\%$ Mean < 16 Gy
Contralateral lung	$V_{5Gy} < 10\%$	–
Contralateral breast	$V_{1.86Gy} < 5\%$ $D_{max} < 3.1$ Gy	–
Thyroid	$D_{max} < 2\%$ prescription	–
Spinal cord	–	$D_{max} < 45$ Gy
Brachial plexus	–	$D_{max} < 66$ Gy

APBI

Dose constraints vary by study and modality

ASTRO's most recent guidelines recommend following the dosimetric constraints in the NSABP B39/RTOG 0413 trial. These include [4]:

Technique	Normal tissue	Constraint
Brachytherapy	Skin	$D_{max} \leq 100\%$
	Ipsilateral breast	$V_{\geq 50\%} \leq 60\%$
MammoSite	Ipsilateral breast	$V_{150\%} \leq 50\ cm^3$ $V_{200\%} \leq 10\ cm^3$ $V_{\geq 50\%} \leq 60\%$
External beam	Ipsilateral breast	$V_{\geq 50\%} \leq 60\%$ $V_{100\%} \leq 35\%$
	Contralateral breast	$D_{max} \leq 3\%$
	Ipsilateral lung	$V_{30\%} < 15\%$
	Contralateral lung	$V_{5\%} < 15\%$
	Heart (R)	$V_{5\%} < 5\%$
	Heart (L)	$V_{5\%} < 40\%$
	Thyroid	$D_{max} \leq 3\%$

19.7 Patient Management

- **Acute Toxicity**
  - Skin reaction: common and can range from mild skin erythema to more significant dry or wet desquamation. The rate appears similar or lower with hypofractionation as compared to conventional fractionated in most studies [23].

    Prevention: Various approaches have been explored for prevention of acute skin reaction with mixed results. General precautions include avoidance of skin irritants (alcohol-based or fragrant lotions and soaps), use of moisturizing agent (Aquaphor, aloe, *Calendula*, etc.), and maintenance of a dry environment particularly in inframammary fold.
    Skin erythema: symptomatic management only.
    Folliculitis: consider use of topical steroids (1% hydrocortisone cream).
    Dry desquamation: symptomatic management only.
    Moist desquamation: consider use of physical barrier (Mepilex) or 1% Silvadene cream. These should be applied after RT treatments.
  - Pain: OTC pain medications are often adequate, but prescription pain medications may be needed.
- **Late Toxicity**
  - Breast cosmesis: can include fibrosis, edema, and telangiectasias. Mild changes are seen in majority of patients. More significant late toxicity is less common (<5%).

Late cosmetic outcomes appear similar (or slightly better) with hypofractionation compared to conventional fractionation.

  - Use of pentoxifylline (400 mg tid or 800 mg qd) and vitamin E (300–1000 IU daily) for 6 months has been found to reduce risk of fibrosis [24], as well as improve cosmetic outcomes in those who develop fibrosis [25].
  - If patient has undergone breast reconstruction prior to RT, cosmetic issues such as asymmetry, hardness, or capsular contraction can occur following RT.

- **Rare Late Toxicities**
  - Cardiac toxicity: There does not appear to be a threshold dose. The absolute increase in risk of coronary event is small if RT dose to the heart is limited (likely <1% if mean heart dose <3 Gy) [26].
  - Radiation pneumonitis: risk of clinically significant pneumonitis is <1% but depends on lung volume in field.

    If symptomatic, it can be treated with course of steroids tapered over 6–12 weeks.

  - Lymphedema: risk is <5% with breast RT alone and 10–12% if locoregional LNs are treated as well. The rate is higher if axillary surgery was performed.
  - Brachial plexopathy: <1% risk with conventional RT doses; similar rates seen in hypofractionated trials [27].
  - Rib fracture: <2% in hypofractionated trials [27].

- Patient's treated with brachytherapy APBI can experience additional side effects:
  - Infection (risk <10%)
  - Fat necrosis (risk <5%)

19.8 Follow-Up

ASCO and NCCN recommendations for breast cancer follow-up include [28, 29]:

- Clinical evaluation, including breast exam and assessment of acute/late toxicities.
  - Year 1–3 every 3–6 months
  - Year 4–5 every 6–12 months
  - Year >5 annually
- First mammogram no earlier than 6 months following treatment completion. Subsequent mammograms every 6–12 months.

  - In certain high-risk patients (BRCA population), breast MRI may be appropriate for surveillance.

- Bone density evaluation is recommended for woman receiving aromatase inhibitors at baseline and periodically thereafter.

19.9 Relevant Literature

Hypofractionated Whole Breast RT

Study	Patients	Treatment	Median follow-up	Outcomes
Randomized trials				
OCOG [12]	*N* = 1234, pT1–2, pN0 following ALND. 75% >50yo. 80% T1	**Arm 1:** 42.5 Gy/16 fractions **Arm 2:** 50 Gy/25 fractions No tumor bed boost	12 years	**Arm 1:** – 6.2% 10 year LR, 84.6% 10 year OS – 70% good/excellent cosmesis – 2.5% G3 skin toxicity **Arm 2:** – 6.7% 10 year LR (NS), 84.4% 10 year OS (NS) – 71% good/excellent cosmesis (NS) – 2.7% G3 skin toxicity (NS)
START A [9]	*N* = 2236, pT1–3, N0–1. 77% >50yo. 29% N+, 70% G1/2. BCS (85%) or mastectomy (15%)	**Arm 1:** 39 Gy/13 fractions **Arm 2:** 41.6 Gy/13 fractions **Arm 3:** 50 Gy/25 fractions Note: All tx delivered over 5 weeks 61% received boost	9 years	**Arm 1:** – 8.8% 10 year LRR, 10.7% 5 year all-cause mortality – 10 year cosmesis: 3% telangiectasia, 7% breast edema, 22% breast induration **Arm 2:** – 6.3% 10 year LRR, 11.3% 5 year all-cause mortality – 10 year cosmesis similar to arm 3 **Arm 3:** – 7.4% 10 year LRR (NS), 11.1% 5 year all-cause mortality (NS) – 10 year cosmesis: 7% telangiectasia ($p < 0.01$ vs. arm 1), 14% breast edema ($p < 0.01$), 27% breast in duration ($p = 0.03$)

Study	Patients	Treatment	Median follow-up	Outcomes
START B [11]	*N* = 2215, pT1–3, pN0–1 79% >50yo. 23% N+, 75% G1/2. BCS (92%) or mastectomy (8%)	**Arm 1**: 40 Gy/15 fractions **Arm 2**: 50 Gy/25 fractions Note: Hypofx tx delivered over 3 weeks 43% received boost	10 years	**Arm 1:** – 4.3% 10 year LRR – 10 year cosmesis: 25% breast shrinkage, 4% telangiectasia, 5% breast edema **Arm 2:** 5.5% 10 year LRR – 10 year cosmesis: 31% breast shrinkage ($p = 0.02$), 6% telangiectasias ($p = 0.03$), 9% breast edema ($p < 0.01$)
RMH/ GOC [10]	*N* = 1410, pT1–3, ≤1 pos LN. 70% >50yo. 94% T1–2, 16% cN+, 33% pN+	**Arm 1:** 39Gy/13 fractions **Arm 2:** 42.9 Gy/13 fractions **Arm 3:** 50 Gy/25 fractions Note: All tx delivered over 5 weeks 75% received boost	10 years	**Arm 1:** – 15% 10 year IBTR – 5 year cosmesis: 43% breast shrinkage, 11% breast edema, 45% fair/ poor cosmesis **Arm 2:** – 10% 10 year IBTR ($p = 0.03$ vs. arm 1) – 5 year cosmesis: 53% breast shrinkage, 20% breast edema, 62% fair/ poor cosmesis **Arm 3:** – 12% 10 year IBTR – 5 year cosmesis: 50% breast shrinkage ($p = 0.03$), 12% breast edema ($p < 0.01$), 56% fair/poor cosmesis ($p < 0.01$)
MD Anderson [23]	*N* = 287, DCIS or pT1–2, pN0-N1	**Arm 1**: 42.6 Gy/16 fractions + boost (10–12.5 Gy/4–5 fractions) **Arm 2**: 50 Gy/25 fractions + boost (10–14 Gy/5–7 fractions)	NA	6-month outcomes **Arm 1:** – 47% ≥ G2 acute toxicity – 23% patient-reported fatigue **Arm 2:** – 78% ≥ G2 acute toxicity ($p < 0.01$) – 39% patient-reported fatigue ($p < 0.01$)

Study	Patients	Treatment	Median follow-up	Outcomes
UK FAST [30]	$N = 915$, age > 50, tumor size <3 cm, pN0	**Arm 1**: 28.5 Gy/5 fractions (weekly tx) **Arm 2**: 30 Gy/5 fractions (weekly tx) **Arm 3**: 50 Gy/25 fractions (daily tx)	37 months	3 year moderate/marked adverse cosmesis **Arm 1:** – 11% **Arm 2:** – 17% ($p < 0.01$) **Arm 3:** – 10% (NS vs. arm 1)
Metanalysis				
Cochrane review [31]	$N = 8228$[a], early-stage breast cancer treated with breast-conserving surgery	Hypofractionated regimens vs. 50 Gy/25 fractions	NA	– No difference in recurrence-free survival (HR 0.94, 0.77–1.15) – No difference in cosmetic outcome (RR 0.90, 0.81–1.01) – Less acute skin toxicity with hypofractionation (RR 0.32, 0.22–0.45)

START: UK Standardisation of Breast Radiotherapy
RMH/GOC: Royal Marsden Hospital/Gloucestershire Oncology Centre
OCOG: Ontario Clinical Oncology Group
[a]>98% patients from OCOG, START A, START B, RMH/GOC, MD Anderson, UK FAST trials

Accelerated Partial Breast Irradiation

Brachytherapy

Two randomized studies and several non-randomized studies have evaluated APBI delivered via brachytherapy following breast-conserving surgery [17, 20–22, 32].

Study	Patients	Treatment	Median follow-up	Outcomes
Randomized trials				
GEC-ESTRO [20]	$N = 1184$, age > 40, size ≤3 cm (89% T1), 95% pN0	**Arm 1:** APBI multicatheter interstitial HDR (32 Gy/8fx or 30.3 Gy/7fx, BID) or PDR (50 Gy, pulses 0.6–0.8 Gy/h) **Arm 2:** Whole breast 50 Gy/25fx or 50.4 Gy/28fx + 10 Gy boost	6.6 years	**Arm 1:** – 1.4% 5-year LR – 3.2% G2/3 late side effects **Arm 2:** – 0.9% 5-year LR (NS) – 5.7% G2/3 late side effects ($p = 0.08$)

Study	Patients	Treatment	Median follow-up	Outcomes
National Institute of Oncology-Hungary [17]	$N = 258$, age > 40 (median 49), T1, pN0-N1mi, grade 1–2, no ILC, 68% received hormonal therapy (89% ER pos)	**Arm 1:** APBI multicatheter interstitial HDR (36.4 Gy/7fx) or EBRT with electrons (see EBRT APBI) **Arm 2:** Whole breast 50 Gy/25 fx	5.5 years	**Arm 1:** – 4.7% 5 year LR – 81% with good/excellent cosmesis **Arm 2:** – 3.4% 5 year LR (NS) – 63% with good/excellent cosmesis ($p < 0.01$)
Other prospective trials				
MammoSite [21]	$N = 1449$, 91% age > 50, 94% T1, 83% N0	APBI: Single lumen HDR (34 Gy/10 fx)	5.3 years	– 3.8% 5 year IBTR – 91% with excellent/good cosmesis at 5 year
RTOG 9517 [22]	$N = 98$, size <3 cm, 0–3 pos LN	APBI: Multicatheter HDR (34Gy/10fx) or LDR (45Gy/3.5–6 days)	11.3 years	– 13% G3 skin toxicity – 66% with patient-reported good/excellent cosmesis
Non-prospective studies				
Smith 2012 [32]	SEER-Medicare analysis, $N = 93{,}000$ (age ≥ 67)	**Group 1:** APBI w/ brachytherapy **Group 2:** Whole breast RT	3 years	**Group 1:** – 88% 5 year OS – 4% 5 year mastectomy rate – 16% infectious complications – 16% noninfectious complications **Group 2:** – 87% 5 year OS (NS) – 2.2% 5 year mastectomy rate ($p < 0.01$) – 10% infectious complications ($p < 0.01$) – 9% noninfectious complications ($p < 0.01$)

Brachytherapy for Local Recurrence

Several small prospective studies and retrospective studies have evaluated APBI brachytherapy for individuals with local recurrence following initial breast-conserving therapy who choose to have repeat lumpectomy [33–35].

Study	Patients	Treatment	Median follow-up	Outcomes
Prospective trials				
Guix 2010 [34]	*N* = 36, >1 year from initial BCT with IBTR <3 cm	APBI with HDR brachytherapy (30 Gy/12 fx with bid treatment)	7.4 years	– 89% 10 year LC – No G3/4 complications – 90% with satisfactory cosmesis
Kauer-Dorner 2012 [35]	*N* = 39, unicentric IBTR, repeat lumpectomy with neg margins, not suitable for interstitial brachy	APBI with PDR brachytherapy (mean dose 50.1 Gy, 0.8 Gy in hourly intervals)	4.8 years	– 93% 5 year LC – 15% late G3/4 toxicity – 76% with fair to excellent cosmesis
Non-prospective studies				
GEC-ESTRO [33]	*N* = 217, median time to IBTR 10 years, median size 1.2 cm	APBI with HDR brachytherapy (median dose 32 Gy/8 fractions)	3.9 years	– 7% 10 year LR rate – 11% G3/4 skin toxicity – 85% good/ excellent cosmesis

IORT

Study	Patients	Treatment	Median follow-up	Outcomes
Randomized trials				
ELIOT [19]	*N* = 1305, age 48–75, tumor size <2.5 cm, 74% N0	**Arm 1:** IORT 21 Gy to tumor bed with electrons **Arm 2:** Whole breast: 50 Gy/25 fractions + 10 Gy boost	5.8 years	**Arm 1:** – 4.4% 5 year IBTR – 97% 5 year OS – 1% acute skin toxicity – 1% late skin toxicity **Arm 2:** – 0.4% 5 year IBTR ($p < 0.01$) – 97% 5 year OS (NS) – 7% acute skin toxicity ($p < 0.01$) – 1% late skin toxicity

Study	Patients	Treatment	Median follow-up	Outcomes
TARGIT-A [18]	*N* = 3451, age ≥ 45, IDC, 86% <2 cm in size, 82% N0[a]	**Arm 1:** IORT low-energy photons (keV), 20 Gy to surface of tumor bed **Arm 2:** Whole breast, 40–56Gy ± boost	2.4 years	**Arm 1:** – 2.1% 5 year LR (IORT at time of surgery) 5.4% 5 year LR (IORT delivered as second procedure) – 0.5% G3/4 skin toxicity **Arm 2:** – 1.1–1.7% 5 year LR (NS vs IORT at time of surgery, $p = 0.07$ vs. IORT as second procedure) – 2.1% G3/4 skin toxicity ($p = 0.002$)

[a]Patients randomized pre-surgery (*N* = 1482, IORT delivered at time of surgery) or post-surgery (*N* = 672, wound re-opened to deliver IORT)

External Beam RT

The use of external beam RT to deliver APBI has been examined in multiple randomized and non-randomized trials [13–15, 17, 36].

Study	Patients	Treatment	Median follow-up	Outcomes
Randomized trials				
National Institute of Oncology-Hungary [17]	*N* = 258, age > 40 (median 49), T1, pN0-N1mi, grade 1–2, no ILC, 68% received hormonal therapy (89% ER pos)	**Arm 1:** APBI with HDR (see brachy section) or EBRT with electrons 50 Gy/25 fx **Arm 2:** Whole breast: 50 Gy/25 fx	5.5 years	**Arm 1:** – 4.7% 5 year LR – 70% with good/ excellent cosmesis **Arm 2:** – 3.4% 5 year LR (NS) – 63% with good/ excellent cosmesis

Study	Patients	Treatment	Median follow-up	Outcomes
University of Florence [13]	$N = 520$, age > 40, size <2.5 cm, 86% pN0	**Arm 1:** APBI 30 Gy/5 fx over 2 weeks **Arm 2:** Whole breast: 50 Gy + 10 Gy boost with IMRT	5 years	**Arm 1:** – 1.5% 5 year IBTR 95% with excellent cosmesis – 2% grade ≥2 acute toxicity **Arm 2:** – 1.5% 5 year IBR (NS) – 90% with excellent cosmesis ($p = 0.05$) – 38% grade ≥2 acute toxicity ($p = 0.02$)
Barcelona [14]	$N = 102$, age ≥ 60, tumor size ≤3 cm (90% T1), pN0, grade 1 or 2	**Arm 1:** APBI: 37.5 Gy/10 fractions (BID) **Arm 2:** Whole breast: 48 Gy/24 fractions ±10 Gy boost	5 years	**Arm 1:** – No local failures – 18% acute grade ≥ 2 toxicity **Arm 2:** – No local failures – 75% acute grade ≥2 toxicity
RAPID [15]	$N = 2135$, 88% over age > 50, 18% DCIS, size ≤3 cm, pN0	**Arm 1:** APBI: 38.5 Gy/10 fractions (BID) **Arm 2:** Whole breast: 42.5 Gy/16 fx or 50 Gy/25 fx ± boost	3 years	**Arm 1:** – 33% 5 year adverse cosmesis **Arm 2:** – 13% 5 year adverse cosmesis ($p < 0.01$)
Other prospective trials				
RTOG 0319 [36]	$N = 52$, size ≤3 cm, ≤3 Pos LN	APBI: 38.5 Gy/10 fractions (BID over 5 days)	5.3 years	– 82% with patient-reported good/ excellent cosmesis – 56% with G2/3 skin toxicity

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Part VII
Gastrointestinal Cancer

Chapter 20
Hepatobiliary Malignancies

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Historically, the radiosensitivity of hepatocytes and risk for radiation-induced liver disease (RILD) precluded the use of RT for liver tumors using older techniques. CT-based planning, SBRT, and IMRT have generated renewed interest in the treatment of liver malignancies due to the new ability to deliver high doses to tumors with good normal tissue sparing. Though surgery is the primary treatment modality for liver tumors, RT provides previously unavailable opportunities for durable local control in patients who are inoperable or not candidates for other ablative approaches. Here, we review hypofractionated RT (focusing on SBRT) for hepatocellular carcinoma (HCC), cholangiocarcinoma (predominantly intrahepatic and perihilar types), and liver metastases. Though distinct clinical entities, the principles of SBRT delivery are similar, though cirrhosis commonly impacts dose delivery in patients with HCC.

20.1 Pearls: Hepatocellular Carcinoma (HCC)

- 6 cases per 100,000 in the United States. Second leading cause of cancer mortality worldwide. Most common in males. Median age of diagnosis 65 years.
- The major risk factor is cirrhosis due to any cause, most commonly viral hepatitis, but also hemochromatosis, alcohol, and nonalcoholic steatohepatitis. Hepatitis C is the dominant factor in the United States, though hepatitis B is more common worldwide.
- Clinical presentation often reflects underlying liver disease and may include symptoms of portal hypertension and/or impaired metabolism such as ascites, GI bleeding, and hepatic encephalopathy.

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- Arise from hepatocytes and may be well, moderately, or poorly differentiated, with rarer subtypes including small cell, giant cell, and spindle cell variants.
- May present anywhere in the liver as circumscribed solitary or multifocal nodules.
- May spread regionally to portohepatic, peripancreatic, gastroduodenal, portocaval, and para-aortic nodes. Most common distant site of spread is the lung.
- Medical work-up: LFTs including tests of synthetic function such as PT-INR and albumin, total bilirubin, HBV/HCV viral serologies, CBC, chemistries, and AFP.
- Imaging work-up: Ultrasound is used for screening in high-risk patients. Three-phase CT and MRI are used for definitive diagnosis. Biopsy is not required if imaging is conclusive.
- Treatment: Options include surgery (transplant/partial hepatectomy), microwave/radiofrequency ablation, RT, embolization (bland−/chemo−/radio-), and chemotherapy.

20.2 Pearls: Cholangiocarcinoma

- Include intrahepatic, perihilar (Klatskin tumors), and distal types. Incidence is 1–2 per 100,000 in the United States and increases with age (median 60–70) and male sex, with roughly an equal distribution of intrahepatic and extrahepatic (including perihilar) varieties.
- Intrahepatic cholangiocarcinoma in the past was often thought to represent metastatic disease to the liver of unknown primary. With increasing recognition of its etiology as a distinct bile duct cancer, the reported incidence has risen in recent decades.
- Risk factors include primary sclerosing cholangitis, cystic liver disease, hepatolithiasis, and parasitic infections. Some association with cirrhosis and hepatitis.
- Genetic predisposing conditions include Lynch syndrome and biliary papillomatosis.
- Present with signs/symptoms of biliary obstruction, abdominal pain, and weight loss. Intrahepatic varieties are less likely to present with biliary obstruction.
- Most are adenocarcinomas and are divided into nodular, sclerosing, and papillary types.
- Intrahepatic cholangiocarcinomas are further subdivided into mass-forming, periductal invasion, and intraductal growth types.
- 30–40% of patients with intrahepatic cholangiocarcinoma have nodal involvement at time of surgical treatment.
- Medical work-up: CA 19-9 (elevated in 75%), CEA (less sensitive and specific than CA 19-9), AFP (more likely HCC if elevated), and LFTs.
- Imaging work-up: MRI is the most informative. Other modalities include CT, abdominal and endoscopic ultrasound, and biliary tract imaging including ERCP and MRCP. Therapeutic biliary stents may be deployed during work-up for distal tumors.
- Treatment: Surgery with postop chemotherapy ± RT if resectable, RT ± chemotherapy if unresectable.

20.3 Pearls: Liver Metastases

- Common site of distant metastasis for many malignancies, especially colorectal cancer but also lung, breast, and others.
- Usually detected with staging scans or elevated tumor markers, though can present with symptoms of abdominal pain, jaundice, and laboratory abnormalities.
- Medical work-up: Liver synthetic function tests including PT-INR, albumin, and platelet count are helpful in assessing the ability of the patient to tolerate aggressive locoregional therapy.
- Imaging work-up: Includes contrast-enhanced CT, MRI, and PET scans.
- Treatment: For limited metastatic disease (usually from colorectal cancer), aggressive locoregional treatment such as surgery, ablation, and/or RT may be used.

20.4 AJCC Staging Table: Hepatocellular Carcinoma

Primary tumor (T)	
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 ≤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)	
NX	Regional lymph nodes cannot be assessed
N0	No regional nodal metastasis
N1	Regional nodal metastasis present
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present
Stage grouping	
IA	T1aN0M0
IB	T1bN0M0
II	T2N0M0
IIIA	T3N0M0
IIIB	T4N0M0
IVA	Any T, N1, M0
IVB	Any T, any N, M1

20.5 Barcelona Clinic Liver Cancer (BCLC) [1] Staging Table: Hepatocellular Carcinoma

0: Very early	Solitary <2 cm tumor, Child-Pugh A, ECOG 0
A: Early	Single or ≤3 nodules <3 cm, Child-Pugh A-B, ECOG 0
B: Intermediate	Large multinodular, Child-Pugh A-B, ECOG 0
C: Advanced	Portal invasion, extrahepatic spread, Child-Pugh A-B, ECOG 1–2
D: Terminal	Child-Pugh C, ECOG 3–4

20.6 AJCC Staging Table: Intrahepatic Cholangiocarcinoma

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (intraductal tumor)
T1	Solitary tumor of any size without vascular invasion
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
T3	Tumor perforating the visceral peritoneum
T4	Tumor involving local extrahepatic structures by direct invasion
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional nodal metastasis
N1	Regional nodal metastasis present
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present
Stage grouping	
0	TisN0M0
IA	T1aN0M0
IB	T1bN0M0
II	T2N0M0
IIIA	T3N0M0
IIIB	T4N0M0 *or* any T, N1, M0
IV	Any T, any N, M1

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20.7 AJCC Staging Table: Perihilar Cholangiocarcinoma

Primary tumor (T)	
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ/high-grade dysplasia
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, or tumor invades adjacent hepatic parenchyma
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades the main portal vein or its branches bilaterally or the common hepatic artery or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional nodal metastasis
N1	Metastasis in 1–3 lymph nodes (typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreaticoduodenal, and/or portal vein lymph nodes)
N2	Metastasis in ≥4 regional lymph nodes (from the sites described for N1)
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present
Stage grouping	
0	TisN0M0
I	T1N0M0
II	T2a-bN0M0
IIIA	T3N0M0
IIIB	T4N0M0
IIIC	Any T, N1, M0
IVA	Any T, N2, M0
IVB	Any T, any N, M1

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20.8 AJCC Staging Table: Distal Cholangiocarcinoma

Primary tumor (T)	
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ/high-grade dysplasia
T1	Tumor invades the bile duct wall with a depth less than 5 mm
T2	Tumor invades the bile duct wall with a depth of 5–12 mm
T3	Tumor invades the bile duct wall with a depth greater than 12 mm
T4	Tumor involves the celiac axis, SMA, and/or common hepatic artery
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional nodal metastasis
N1	Metastasis in 1–3 lymph nodes
N2	Metastasis in ≥4 regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present
Stage grouping	
0	TisN0M0
I	T1N0M0
IIA	T1N1M0 *or* T2N0M0
IIB	T2N1M0 *or* T3N0-1M0
IIIA	T1-3N2M0
IIIB	T4, any N, M0
IVB	Any T, any N, M1

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20.9 Tumor/Patient Selection

(a) Due to substantial diversity of diagnoses, clinical context, and types of liver-directed therapy, it is challenging to select appropriate candidates for RT or other ablative treatment options. Treatment decisions should be made with multidisciplinary input from liver surgeons, interventional radiologists, and radiation and medical oncologists.

(b) SBRT is used in patients with limited disease, alone or in combination with surgery or RFA, for:

- Inoperable patients (e.g., due to disease extent, surgically difficult sites, and/or comorbidities)
- Lesions located in areas precluding the use of other ablation techniques, such as RFA (e.g., major vessels that act as a heat sink, bile ducts prone to heat injury, and liver capsule where RFA may cause pain)
- Positive surgical margins
- Salvage for patients with progression in isolated sites

(c) In addition to the above patient selection criteria, the combination of tumor size and total liver volume must meet liver dose volume constraints (see Toxicities).

(d) For patients with large tumors or compromised liver function, dosimetric studies suggest advantages of charged particle therapy such as carbon ion and protons in reducing the low-dose volume, which is of particular importance in a radiosensitive, "parallel" organ such as the liver [2, 3].

(e) Disease-specific considerations (**HCC**):

- In patients ineligible for other treatments, SBRT and other conformal hypofractionated RT techniques lead to impressive local control, even for large tumors with adverse features such as tumor vascular thrombi.
- RT may also be used as a bridge to transplant.
- SBRT should not be used concurrently with sorafenib based on a recent Phase I study reporting unacceptably high rates of GI toxicity [4].
- Both EBRT or SBRT are category 2 recommendations for locoregional treatment in the NCCN guideline for inoperable HCC [5].
- The frequent presence of cirrhosis reduces liver "reserve" and requires the use of more stringent dose volume criteria during patient selection and radiation planning for patients with compromised liver function, e.g., Child-Pugh B patients (see Toxicities).

(f) Disease-specific considerations (**cholangiocarcinoma**):

- Similar to HCC, standard management is surgical resection but many tumors/patients are inoperable.
- The use of SBRT or hypofractionated conformal RT provides an opportunity for durable local control and sometimes cure.

(g) Disease-specific considerations (**liver metastases**):

- For patients with limited colorectal cancer liver metastases, aggressive locoregional therapy is warranted in the absence of extrahepatic disease.
- The use of RT for patients ineligible for resection of liver metastases is a category 3 recommendation in the NCCN guidelines [6].

20.10 Treatment Planning Considerations (Fig. 20.1)

Simulation instructions	– Position: Supine with arms overhead (for CyberKnife, patients are simulated with arms at side for comfort during long treatments) – Immobilization: Vac-Lok or similar device – 4D CT to assess tumor motion – Abdominal compression devices may reduce respiratory variation – We usually administer IV contrast to aid tumor delineation, but obtaining proper timing can be difficult, especially for HCC (where diagnostic triphasic CT may be needed for proper visualization)
Image guidance	Linac: – Daily cone beam for alignment – Fiducials are helpful for daily alignment given the difficulty of visualizing the actual tumor using CT – Respiratory gating techniques may help account for motion CyberKnife: – Fiducial markers for tumor tracking, typically placed by interventional radiology at least 7 days prior to simulation
Tumor delineation	– We obtain MRI with contrast for all patients (due to variation in ability to visualize tumors with contrast-enhanced simulation CT) – HCCs show enhancement on the immediate post-contrast MRI, with later sequences showing washout of the lesion compared to the rest of the liver. We select the series and sequence with the best subjective visualization of the tumor for fusion to the CT – Accurate image fusion is difficult and should be based on structures and liver contours close to the target and verified – We contour the GTV on the MRI and verify its accuracy (when possible) on the planning CT itself
Margins	Linac: – An ITV is generated by combining the GTVs at various respiratory phases (if 4D scan is obtained) – Based on the degree of tumor motion and uncertainty, a total CTV + PTV margin of 5–10 mm is added around the ITV CyberKnife: – With tumor tracking using fiducials, we typically add a 5 mm radial and 8 mm superior/inferior total CTV + PTV margin around the GTV – In cases where motion is greater or MRI fusion is suboptimal, we use total CTV + PTV margins up to 1 cm
Dosimetric considerations	– Goal: 95% of PTV receives 100% prescription dose – To meet constraints of critical nearby structures, especially small bowel, decreased coverage may be accepted, and/or CTV/PTV margins selectively reduced

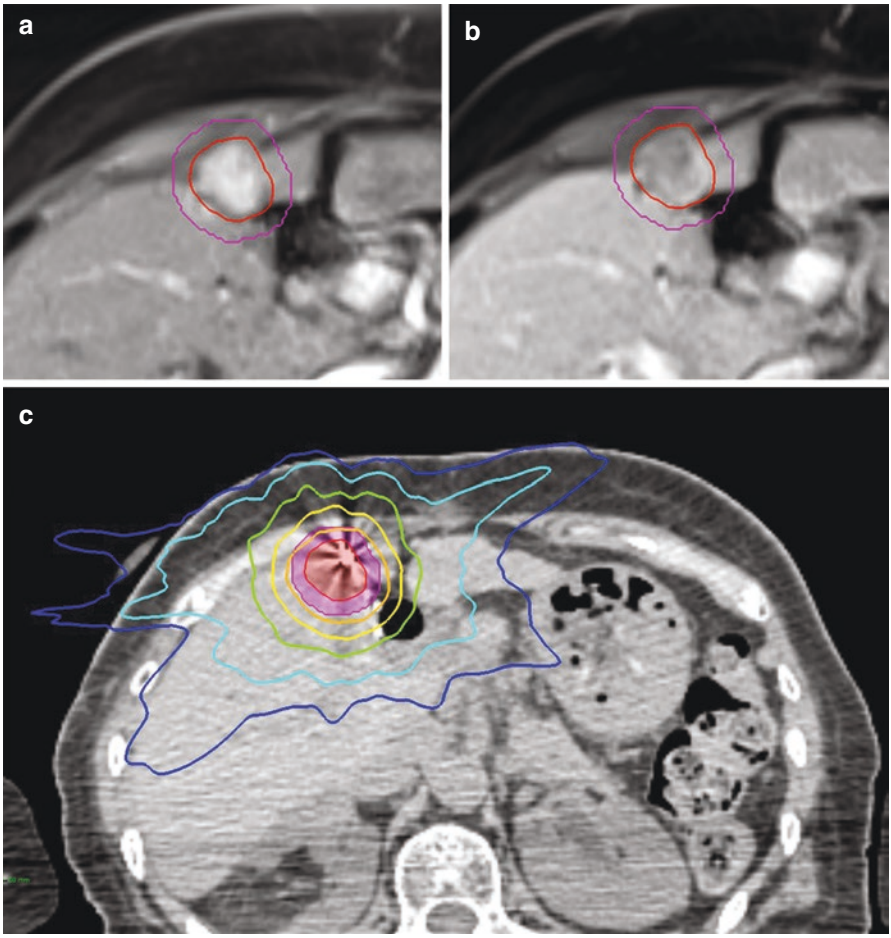

Fig. 20.1 A patient with HCC treated with SBRT using CyberKnife, prescribed 45 Gy in three fractions. Two different gadolinium-enhanced MRI sequences (**a** and **b**) were selected based on good visualization of tumor and fused to treatment planning CT for tumor delineation, with the GTV delineated in red and PTV in purple generated using 5 mm radial expansions. (**c**) Doses shown as calculated on planning CT with the GTV shaded red and PTV shaded purple. Orange, 45 Gy; yellow, 30 Gy; green, 20 Gy; light blue, 10 Gy; dark blue, 5 Gy

20.11 Commonly Used Dose/Fractionation Schemes

Dose/fx	# of fx	Total dose	Notes
15–20 Gy	3	45–60 Gy	HCC (typically Child-Pugh A) and metastases, typically 1–5 cm [7–12]
7–8 Gy	5	35–40 Gy	HCC, Child-Pugh A or B, typically 1–5 cm [13, 14]
10–15 Gy	3	30–45 Gy	Cholangiocarcinoma, size variable [15, 16]
10–12 Gy	4	48 Gy	HCC (typically Child-Pugh A) and metastases, typically 1–5 cm [11, 17]
6–7 Gy	6	36–42 Gy	HCC (Child-Pugh A), cholangiocarcinoma, and metastases, up to ≈15 cm [18–20]
4.5 Gy	15	67.5 Gy	Cholangiocarcinoma, up to ≈15 cm [21]

Authors' Recommendations
– At our institution, we generally use three fraction treatments for liver SBRT
– For patients who meet liver constraints, we typically use 15 Gy × 3 fx
– For liver metastases, we typically use slightly higher doses, e.g., 18 Gy × 3 fx
– Great care must be taken when deciding to treat Child-Pugh B patients. We only treat patients in the lowest echelon of Child-Pugh B (Child-Pugh 7) with adequate liver volume. Dose/fractionation is variable but ranges between 15 Gy × 3 fx and 7 Gy × 5 fx to more aggressively meet constraints and minimize toxicity
– We deliver SBRT treatments every other day

20.12 Normal Tissue Tolerances

<table>
<tr><th colspan="2">TG101 [22]</th><th>Other(s)</th><th>Our institutional practice</th></tr>
<tr><td colspan="4">Liver (minus GTV)
Endpoint: Grade 3 toxicity</td></tr>
<tr><td>1 fx</td><td>≥700 cc ≤ 9.1 Gy</td><td rowspan="3">Quantec [23]:
Endpoint: 5% RILD
(3–5 fx) ≥ 700 cc ≤ 15 Gy
– Liver cancer (Child-Pugh A):
(3 fx) mean < 13 Gy
(6 fx) mean < 18 Gy
– Liver cancer (Child-Pugh B):
(4–6 Gy/fx) mean < 6 Gy
– Metastases:
(3 fx) mean < 15 Gy
(6 fx) mean < 20 Gy</td><td rowspan="3">(3 fx)
Mean < 15 Gy
≥700 cc ≤ 15 Gy (Child-Pugh A)
≥700 cc ≤ 13 Gy (Child-Pugh B)</td></tr>
<tr><td>3 fx</td><td>≥700 cc ≤ 19.2 Gy</td></tr>
<tr><td>5 fx</td><td>≥700 cc ≤ 21 Gy</td></tr>
</table>

TG101 [22]		Other(s)	Our institutional practice
Small bowel (duodenum) Endpoint: Ulceration			
1 fx	*V* 11.2 Gy < 5 cc D max ≤12.4 Gy	Goldsmith et al. [24] Endpoint: 5% Grade 3 hemorrhage/stricture (1 fx) D 5 cc < 11.2 Gy (3 fx) D 5 cc < 21 Gy (5 fx) D 5 cc < 25.8 Gy (1 fx) D 0.035 cc < 16 Gy (3 fx) D 0.035 cc < 30 Gy (5 fx) D 0.035 cc < 32 Gy	(3 fx) < 1 cc > 30 Gy (5 fx) < 1 cc > 32 Gy
3 fx	*V* 16.5 Gy < 5 cc D max ≤22.2 Gy		
5 fx	*V* 18 Gy < 5 cc D max ≤32 Gy		
Stomach Endpoint: Ulceration/fistula			
1 fx	*V* 11.2 Gy < 10 cc D max ≤12.4 Gy		(3 fx) < 1 cc > 30 Gy
3 fx	*V* 16.5 Gy < 10 cc D max ≤22.2 Gy		
5 fx	*V* 18 Gy < 10 cc D max ≤32 Gy		
Esophagus Endpoint: Stenosis/fistula			
1 fx	*V* 11.9 Gy < 5 cc D max ≤15.4 Gy		(3 fx) < 1 cc > 30 Gy
3 fx	*V* 17.7 Gy < 5 cc D max ≤25.2 Gy		
5 fx	*V* 19.5 Gy < 5 cc D max ≤35 Gy		
Kidney (bilateral) Endpoint: Grade 3 toxicity			
1 fx	≥200 cc ≤ 8.4 Gy		We do not have strict unilateral kidney guidelines provided that the patient has adequate bilateral renal function
3 fx	≥200 cc ≤ 16 Gy		
5 fx	≥200 cc ≤ 17.5 Gy		
Colon Endpoint: Colitis/fistula			
1 fx	*V* 14.3 Gy < 20 cc D max ≤18.4 Gy		
3 fx	*V* 24 Gy < 20 cc D max ≤28.2 Gy		
5 fx	*V* 25 Gy < 20 cc D max ≤38 Gy		
Lungs (total) Endpoint: Grade 3 pneumonitis			
1 fx	≥1000 cc ≤ 7.4 Gy		
3 fx	≥1000 cc ≤ 12.4 Gy		
5 fx	≥1000 cc ≤ 13.5 Gy		
Rib Endpoint: Pain/fracture			

TG101 [22]		Other(s)	Our institutional practice
1 fx	*V* 22 Gy < 1 cc D max ≤30 Gy		
3 fx	*V* 28.8 Gy < 1 cc *V* 30 Gy < 30 cc D max ≤36.9 Gy		
5 fx	*V* 35 Gy < 1 cc D max ≤43 Gy		

20.13 Patient Management Considerations

- Premedications are optional and the data behind their use lacking but include dexamethasone (4 mg, once prior to treatment) to reduce acute edema and antiemetics (e.g., ondansetron, 8 mg, once prior to treatment) to prevent nausea. For patients who may have difficulty tolerating long treatments, we consider administering a single small dose of a benzodiazepam (e.g., lorazepam, 0.5–1 mg) 30 min prior to treatment.
- Toxicities: Nausea, abdominal pain, and fatigue may occur acutely but are rare. Other acute toxicities include transient thrombocytopenia and elevation in transaminases, as well as RILD, which can also be a late toxicity. Overall, Grade 3 toxicities are higher in patients with HCC and worse baseline liver function (typically 10–15%) [12, 17, 18, 25] vs. liver metastases (typically <5%) [26, 27].
- "Classic" RILD occurs within 4 months of RT and is manifested by anicteric hepatomegaly, ascites, and elevated LFTs (especially alkaline phosphatase) often leading to liver failure and death. The pathophysiology is thought to be inflammation leading to venous congestion, which may worsen portal hypertension. Reports are rare in modern series utilizing highly conformal RT.
- "Nonclassic" RILD includes decline in liver function or transient LFT elevation in the absence of classic RILD; though many patients have progression of preexisting liver disease after treatment, RT may accelerate this process and lead to worsening of Child-Pugh score and/or class, which is observed in 10–20% of HCC patients according to recent SBRT series [9, 13, 14, 18].
- Biliary stenosis in the absence of disease progression is rare (<5%), even after treatment for centrally located tumors [21, 28]. Patients with signs of biliary obstruction should receive ERCP.
- Patients with tumors located near esophagus and bowel are at risk for ulceration, stenosis, and bleeding, though reports of severe non-hepatic toxicities are rare.
- A prospective assessment of QOL in 222 patients treated with SBRT for liver tumors showed an acute worsening of appetite and fatigue at 1 month posttreatment but recovery by 3 months. Overall QOL appeared to be stable at 3 and 12 months posttreatment [29].

- Management of toxicity is usually supportive and/or directed at the underlying liver disease, with close monitoring of LFTs. Patients with GI bleeding or disproportionate pain after treatment should receive an urgent upper endoscopy.

20.14 Follow-Up

(a) Abdominal MRI for surveillance every 3 months posttreatment, along with LFTs (including PT/INR and albumin).
(b) For patients with HCC, decline of a pretreatment elevated AFP may also have prognostic significance.

20.15 Relevant Literature: Toxicity

(a) **Classic RILD**: The University of Michigan and others have published guidelines using the Lyman NTCP model for classic RILD with fraction sizes of 1.5–6 Gy. Mean liver dose in patients experiencing RILD was ≈25 Gy, leading to Quantec's recommendation of mean liver dose <13–18 Gy when using SBRT-level hypofractionation [23, 30–32]. The incidence of RILD in these series was much higher among Child-Pugh B patients, and several authors recommended limiting mean liver dose to as low as 6 Gy for these higher-risk patients [23, 32].
(b) **Nonclassic RILD**: A parallel dosimetric guideline seeks to prevent nonclassic RILD (e.g., worsening of liver function) by ensuring that a minimum volume of effective "functional" liver remains after RT. Based on partial hepatectomy series, the most common recommendation is that ≥700 cc of normal liver receives less than a certain threshold dose (usually 15 Gy), at least for Child-Pugh class A patients [23]. A more ambitious criterion is likely prudent for Child-Pugh B patients, though no common volumetric guidelines exist.
(c) **Biliary Toxicity**: There is concern for increased biliary toxicity with centrally located tumors. However, in an analysis of 50 patients receiving significant central biliary system dose (≥20 Gy, prescription dose 35–50 Gy in 5 fx), there were only two cases of bile duct stenosis (both asymptomatic), and no patients experienced cholangitis or obstructive jaundice [28]. This has also been confirmed in unpublished data from our institution. SBRT to these doses therefore appears to be safe for tumors adjacent to the central biliary system. For cholangiocarcinoma (especially perihilar variants), many studies used either prophylactic or therapeutic pre-RT biliary stents and appeared to have higher biliary complications after RT. However, it is unclear whether complications were due to RT vs. tumor progression or issues related to the stent itself [16, 21, 33, 34].

20.16 Relevant Literature: Hepatocellular Carcinoma

(a) Studies for hepatocellular carcinoma have been highly variable. Doses range from 24 to 60 Gy in 3–6 fractions. The size of treated tumors has also varied greatly. Most have included patients with small (2–3 cm) tumors, with results indicating excellent control and acceptable toxicity.
(b) The study by Bujold et al. [18] was unique in that it included very large (10 cm) tumors, half of which were associated with tumor vascular thrombosis. With a median dose of 36 Gy in six fractions, control was excellent, though there were seven deaths (7%) potentially attributed to treatment. Overall results appeared favorable given the tumor burden and poor prognosis of these patients.
(c) The recent report by Wahl et al. [25] retrospectively compared SBRT to RFA and found comparable rates of control and toxicity, establishing SBRT as an acceptable first-line modality treatment for inoperable HCC.
(d) Most patients in the following series received extensive prior treatment (surgery, RFA, and/or chemotherapy).

Study	Patients	Treatments	Median f/u	Outcomes
Prospective trials				
Takeda 2016 [13] Phase II	– 90 pts – 90% size ≤2 cm – 91% Child-Pugh A	– 89%: 40 Gy (5 fx) – 11%: 35 Gy (5 fx)	41.7 months (55.9 months in survivors)	– 96% 3-year LC – 67% 3-year OS – 9% had 2-point worsening of Child-Pugh score
Bujold 2013 [18] Phase I/II	– 102 pts – 55% with tumor vascular thrombosis – Median size 10 cm – Median GTV 117 cc – All child-Pugh A	– 24–54 Gy (6 fx) – Median: 36 Gy (6 fx)	31.4 months	– 87% 1-year LC – 17 months Median OS – 29% had worsening Child-Pugh class at 3 months – 7 deaths at least partially related to treatment (5 due to liver failure)
Kang 2012 [9] Phase II	– 47 pts – Median size 2.9 cm – Median GTV 15 cc – 87% Child-Pugh A	– 42–60 Gy (3 fx)	17 month (22 montha in survivors)	– 95% 2-year LC – 69% 2-year OS – 2 pts, gastric ulcer perforation – 13% had worsening Child-Pugh class at 3 month
Retrospective studies				

Study	Patients	Treatments	Median f/u	Outcomes
Wahl 2016 [25]	– 224 pts, 332 lesions – RFA (161 pts, 249 lesions, median 1.8 cm) vs. SBRT (63 pts, 83 lesions, median 2.2 cm) – RFA pts had worse baseline liver function	**(SBRT)** – 27–60 Gy (3 or 5 fx)	**RFA** 20 months (50.9 months in survivors) **SBRT** 13 months (27 months in survivors)	**RFA** – 84% 1-year LC – 80% 2-year LC – 11% Acute G3 tox. **SBRT** – 97% 1-year LC – 84% 1-year LC – 5% Acute G3 tox.
Huertas 2015 [8]	– 77 pts – Median size 2.4 cm – Median GTV 12 cc – 85% Child-Pugh A	– 45 Gy (3 fx)	12 months	– 99% 2-year LC – 57% 2-year OS – 23% 2-year hepatic tox. (any grade)
Kimura 2015 [17]	– 64 pts – Median size 1.6 cm – 86% Child-Pugh A	– 48 Gy (4 fx)	26 months	– 100% 2-year LC – 76% 2-year OS – 23% 1-year ≥G3 hepatic tox
Yoon 2013 [12]	– 93 pts – Median size 2 cm – 74% Child-Pugh A	– 30–60 Gy (3–4 fx)	25.6 months	– 92% 3-year LC – 54% 3-year OS – 7% had ≥G3 hepatic tox
Andolino 2011 [14]	– 60 pts – Median size 3.2 cm – 60% Child-Pugh A	Median: – Child-Pugh A: 44 Gy (3 fx) – Child-Pugh B: 40 Gy (5 fx)	27 months	– 90% 2-year LC – 67% 2-year OS – 20% had worsening Child-Pugh class at 3 months – 23 pts received subsequent transplant

20.17 Relevant Literature: Cholangiocarcinoma

(a) Given the rarity of cholangiocarcinoma, most of these studies are very small. Studies included a mix of small to large tumors, but most showed moderate to good local control with acceptable toxicity.

(b) The study by Tao et al. [21] was unique in that patients had very large tumors (median 8 cm). In these patients, high doses were delivered using hypofractionated conformal RT, with doses further escalated in the geometric "center" of tumors. This approach produced impressive outcomes, with excellent local control and survival despite the size of these tumors, with no documented cases of RILD.

Study	Patients	Treatments	Median f/u	Outcomes
Prospective trials				
Tse 2008 [20] Phase I	– 10 pts – Intrahepatic – Median GTV 172 cc	– 24–54 Gy (6 fx) – Median: 36 Gy (6 fx)	17.6 months	– 65% 1-year LC – 57% 1-year OS – 2 pts, transient biliary stenosis; 2 pts, worsening in Child-Pugh class; 1 pt, small bowl obstruction
Retrospective studies				
Tao 2016 [21]	– 79 pts – Intrahepatic – Median size 8 cm – median GTV 198 cc – 89% had pre-RT chemo	– 35–100 Gy (3–30 fx) – Most common hypofx regimens: – 58.05 Gy (15 fx) – 67.5 Gy (15 fx) – 75 Gy (25 fx)	24 months (33 months in survivors)	– 44% 3-year OS – Higher OS and LC if BED >80.5 Gy – No cases of RILD despite large tumors – 9% biliary stenosis (most also had tumor progression)
Mahadevan 2015 [16]	– 34 pts – Intrahepatic – Median GTV 64 cc	– 30 Gy (3 fx) – 62% had biliary stent	38 months	– 88% 1-year LC – 58% 1-year OS – 12% G3 toxicity (duodenal ulcer, cholangitis, abscess)
Welling 2014 [34]	– 12 pts – Perihilar, unresectable – Mean size 1.4 cm	– 50–60 Gy (3–5 fx) – Xeloda post-RT until transplant	14 months	– 6 pts received liver transplant: 1-year OS 83% in these pts – 6 pts (50%) had cholangitis, attributed to stent dysfunction
Barney 2012 [35]	– 10 pts (12 lesions) – 6 intrahepatic, 3 perihilar – Median PTV 79 cc	– 45–60 Gy (3–5 fx)	14 months in survivors	– 100% LC (med. f/u 14 months) – 73% 1-year OS – 1 pt, G3 biliary stenosis; 1 pt, G5 liver failure
Polistina 2011 [33]	– 10 pts – Perihilar, unresectable	– 30 Gy (3 fx) – Weekly gemcitabine – All pts had biliary stent	35.5 months	– 30 months median TTP – 80% 2-year OS – No ≥G3 acute or late toxicities
Kopek 2010 [15]	– 27 pts – Perihilar – Median CTV 32 cc	– 45 Gy (3 fx) – All pts had biliary stent	5.4 years	– 84% 1-year LC – 11 months median OS – 6 pts, duodenal ulceration; 3 pts, duodenal stenosis – Mean duodenum D1cc was 37 Gy in pts with ≥G2 ulceration or stenosis

20.18 Relevant Literature: Liver Metastases

(a) There is substantial variation in these studies in dose, size, and number of treated metastases.
(b) Patients with liver metastases are often "healthier" with better baseline liver function than patients with HCC who often have comorbid cirrhosis. This is reflected in the higher allowable dose constraints published in Quantec [23] and perhaps also by the higher doses prescribed. Though 45 Gy in three fractions is perhaps most common, several studies have also delivered 60–75 Gy in three fractions, reporting greater than 90% 2-year LC [10, 36]. There is a suggestion that patients with liver metastases require higher doses for local control than HCC.
(c) Two significant studies are pooled analyses, one with patients from Stanford University, Princess Margaret Hospital, and the University of Colorado, and the other from Case Western University, University of Rochester, Memorial Sloan Kettering, and Cleveland Clinic [26, 27]. The Chang et al. study appeared to show improved local control with doses ≥42 Gy, which may justify dose escalation in these patients, as described by Scorsetti and Rusthoven.
(d) Most patients in the following series received extensive prior treatment (surgery, RFA, and/or chemotherapy).

Study	Patients	Treatments	Median f/u	Outcomes
Prospective trials				
Scorsetti 2015 [36] Phase II	– 42 pts, 52 lesions – Colorectal – Median size 3.5 cm – Median CTV 19 cc	– 75 (3 fx)	24 months	– 91% 2-year LC – 65% 2-year OS – No ≥G3 toxicity
Rusthoven 2009 [10] Phase I/II	– 47 pts, 63 lesions – 32% colorectal – Median size 2.7 cm – Median GTV 15 cc	– 36–60 Gy (3 fx) – Most: 60 Gy (3 fx)	16 months	– 92% 2-year LC – 30% 2-year OS – 2% ≥G3 toxicity
Lee 2009 [19] Phase I	– 68 pts – 59% colorectal – Median GTV 75 cc	27.7–60 Gy (6 fx) – Median: 41.4 Gy (6 fx)	10.8 months	– 71% 1-year LC – 47% 18-month OS – 3 pts, late ≥ G4 GI toxicity (duodenal bleed, bowel obstruction) – 6% had worsening Child-Pugh class at 3 mo

Study	Patients	Treatments	Median f/u	Outcomes
Hoyer 2006 [7] Phase II	– 64 pts (44 liver), 141 lesions – Colorectal – Median size 3.5 cm	– 45 Gy (3 fx)	4.3 years	– 86% 2-year LC (per lesion) – 19% 2-year PFS – 38% 2-year OS – 4 pts had ≥G3 GI toxicity
Retrospective studies				
[a]Berber 2013 [26]	– 153 pts, 363 lesions – 56% colorectal – Mean GTV 139 cc	– Mean 37.5 Gy (2–8 fx)	25.2 months	– 62% LC – 51% 1-year OS – 3% ≥G3 toxicity
[b]Chang 2011 [27]	– 65 pts, 102 lesions – Colorectal, – Median GTV 30 cc	– 22–60 Gy (1–6 fx) – Median: 42 Gy (3 fx)	1.2 years (1.4 years in survivors)	– 55% 2-year LC (per lesion) – 38% 2-year OS – Higher LC with ≥42 Gy (84%) vs. <42 Gy (43%) – 6% ≥ G2 late GI toxicity
Vautravers-Dewas [11]	– 42 pts, 62 lesions – 67% colorectal – Median size 2.5 cm – Median GTV 13 cc	– 64%: 40 Gy (4 fx) – 36%: 45 Gy (3 fx)	14.3 months	– 86% 2-year LC – 48% 2-year OS – 1 pt, liver failure; 1 pt, gastric ulceration
Katz 2007 [37]	– 69 pts, 174 lesions – 29% colorectal – Median size 2.7 cm	– "Preferred" 50 Gy (10 fx)	14.5 months	– 57% 20-month LC – 37% 20-month OS – No ≥G3 toxicity

[a]Pooled results from Case Western, Rochester, Memorial Sloan Kettering, and Cleveland Clinic
[b]Pooled results from Stanford, Princess Margaret, and Colorado

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Chapter 21
Pancreas Cancer

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The use of RT for pancreatic cancer is controversial. Though RT increases local control, this has not usually translated to an OS benefit, likely due to the high competing risk of distant metastases. Selection of appropriate candidates for RT is therefore challenging. The use of hypofractionated techniques such as SBRT has been investigated to potentially increase local control, to increase resectability, and to decrease the overall treatment time, minimizing patient burden and delay of systemic therapy. In this chapter, we will review the use of SBRT for pancreatic malignancies.

21.1 Pearls

- Over 50,000 cases per year in the United States, median age 70, and the fourth leading cause of cancer mortality. Only 15–20% are candidates for curative surgery at diagnosis.
- Risk factors include chronic pancreatitis, pancreatic cysts, cigarette smoking, obesity, alcohol, and genetic causes.
- Up to 10% of cases have hereditary causes, and risk is increased with some inherited syndromes including BRCA, Peutz-Jeghers syndrome, and hereditary pancreatitis.

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- Patients typically present with weight loss, abdominal pain, nausea, new onset of type 2 diabetes, and signs of biliary obstruction including jaundice and dark urine.
- The majority are exocrine pancreatic adenocarcinoma originating in the ductal epithelium.
- Most commonly located in the pancreatic head. Resectability is determined by the degree of involvement of the superior mesenteric and celiac arteries and to a less extent by the involvement of the superior mesenteric and portal veins.
- Commonly spread to regional lymph nodes around the common hepatic, celiac, and splenic arteries. Distant spread is very common, especially to the liver and peritoneum.
- CA 19-9 has a relatively high sensitivity for pancreatic cancer and may be used to monitor response to treatment and as a marker for recurrence (10% of the population lack the Lewis antigen and do not express CA 19-9).
- Imaging: Ultrasound, pancreatic protocol "triple-phase" CT, MRI, and PET are all employed. Endoscopic biopsy may be used for obtaining tissue, and ERCP may be employed for therapeutic biliary stenting.
- Treatment: For M0 patients, surgery with chemotherapy ± postoperative RT if resectable, neoadjuvant chemotherapy ± RT if borderline resectable, and chemotherapy ± RT if unresectable.

21.2 AJCC Staging Table (Exocrine Pancreatic Cancer)

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, including high-grade pancreatic intraepithelial neoplasia (PanIN-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 cm and ≤1 cm in greatest dimension
T1c	Tumor >1 cm and ≤2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor of any size involving celiac axis, SMA, and/or common hepatic artery

Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional nodal metastasis
N1	Metastasis in 1–3 regional lymph nodes
N2	Metastasis in ≥4 regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present
Stage grouping	
0	TisN0M0
IA	T1N0M0
IB	T2N0M0
IIA	T3N0M0
IIB	T1-3N1M0
III	T1-3N2M0 *or* T4, any N, M0
IV	Any T, any N, M1

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21.3 Tumor/Patient Selection

(a) RT of any type is most likely to benefit patients without distant metastatic disease and who retain a good performance status after initial chemotherapy. The 2016 ASCO guideline for locally advanced, unresectable pancreatic cancer [1] recommends either conventional RT or SBRT in such patients: ECOG PS ≤ 2, adequate comorbidity profile, no distant metastases, and with either local progression after chemotherapy or stable disease but poor chemotherapy tolerance.

(b) SBRT may also be used as a planned preoperative or adjuvant treatment (to areas at high risk of residual disease such as vasculature), as well as for reirradiation.

(c) Patients ideal for SBRT are those with comparatively small, well-visualized tumors that are not abutting or adjacent to the duodenum (though the majority of tumors are close to the duodenum).

21.4 Treatment Planning Considerations

Simulation instructions	– Position: Supine with arms overhead (for CyberKnife, patients are simulated with arms at side for comfort during long treatments) – Immobilization: Vac-LoK or similar device – To minimize stomach distension and maximize reproducibility, patients should be instructed to fast at least 3 h before simulation and each treatment – 4D simulation CT is helpful to assess tumor motion – Abdominal compression devices may reduce respiratory variation – Oral contrast given 10–20 min before simulation is helpful for delineation of the duodenum (if the patient has not had a Whipple resection) – IV contrast is used at simulation to aid in tumor delineation and more importantly to accurately define the position of vasculature
Image guidance	Linac: – Fiducial markers (typically placed by gastroenterology at least 7 days prior to simulation) in most patients given the difficulty of aligning to soft tissue alone in the pancreatic region – Daily cone beam CT to align to implanted fiducial markers CyberKnife: – Fiducial markers for tumor tracking
Tumor delineation	– Though contrast administered during a CT scan may be adequate, delineation may be aided by fusion of a diagnostic CT, MRI, or PET. Typically, the tumors themselves are *hypo*-enhancing – Typically the entire tumor is delineated, though some regimens utilize an integrated boost to the posterior tumor-vessel interface – The fusion should prioritize (in addition to gross tumor) neighboring vessels such as the celiac artery, SMA, and portal/SMV complex
Margins	Linac: – An ITV is generated by combining the GTVs at various respiratory phases (if 4D scan is obtained), though there is typically minimal pancreatic motion – Based on the degree of tumor motion and uncertainty, a total CTV + PTV margin of 5–10 mm is added around the ITV (generally with a greater superior/inferior margin) CyberKnife: – With tumor tracking using fiducials, we typically add a 5 mm radial and 8 mm superior/inferior total CTV + PTV margin around the GTV
Dosimetric considerations	– Goal: 95% of PTV receives 100% prescription dose – To meet constraints of critical nearby structures (such as duodenum and stomach), decreased coverage may be accepted, and/or CTV/PTV margins selectively reduced – Dose distribution is usually heterogeneous in the tumor in order to decrease the duodenal dose

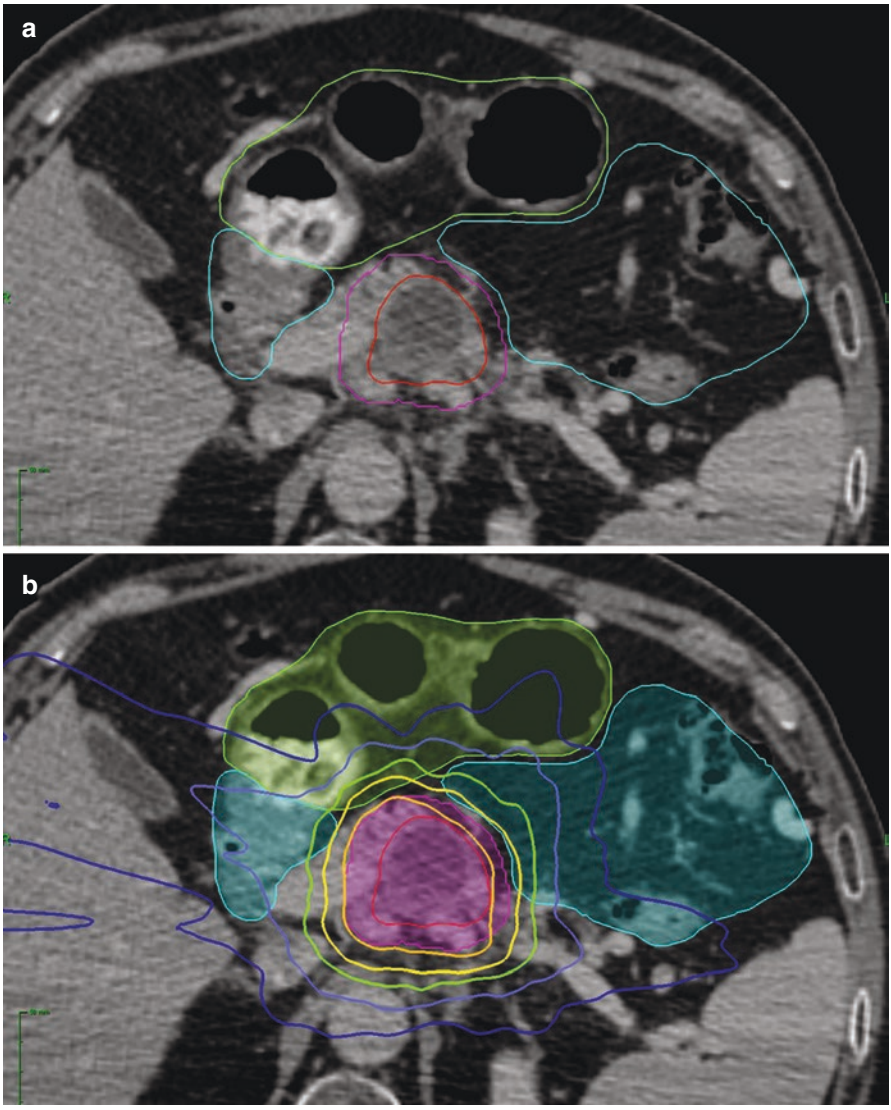

Fig. 21.1 A patient with unresectable pancreatic adenocarcinoma treated with SBRT using CyberKnife, prescribed 30 Gy in three fractions, an ideal SBRT candidate due to distance and dose fall off between duodenum and tumor. (**a**) Delineation on contrast-enhanced CT of the hypo-enhancing GTV (red) with a PTV expansion (purple) covering the posterior tumor-vessel interface and celiac artery. The bowel contour is shown in blue and stomach in green. (**b**) Target and organs are shown shaded with doses displayed as lines, orange, 30 Gy; yellow, 20 Gy; green, 15 Gy; light blue, 10 Gy; dark blue, 5 Gy (Note the 30 Gy isodose curve covers the entire GTV but not the PTV to minimize the bowel dose)

21.5 Commonly Used Dose/Fractionation Schemes

Dose/fx	# of fx	Total dose	Notes
6–10 Gy	5	30–50 Gy	Series investigating planned preoperative SBRT with doses of 25–36 Gy in 3–5 fractions for the entire tumor, with a simultaneous integrated boost of 6–20 Gy delivered to the posterior margin (tumor-vessel interface) [2–5]
7.5 Gy	6	45 Gy	Unresectable tumors [6]
8–12 Gy	3	24–36 Gy	Unresectable tumors [7] or preoperative [8]

– At our institution, we generally use three or five fraction treatments for pancreatic SBRT. We do not recommend single fraction pancreatic SBRT due to the risk of duodenal toxicity [5].
– At our institution, we deliver SBRT treatments every other day.

21.6 Normal Tissue Tolerances

TG101 [9]		Other(s)	Our institutional practice
Small bowel (duodenum) Endpoint: Ulceration			
1 fx	V 11.2 Gy < 5 cc D max ≤ 12.4 Gy	Goldsmith et al. [10] Endpoint: 5% Grade 3 hemorrhage/stricture (1 fx) D 5 cc < 11.2 Gy (3 fx) D 5 cc < 21 Gy (5 fx) D 5 cc < 25.8 Gy (1 fx) D 0.035 cc < 16 Gy (3 fx) D 0.035 cc < 30 Gy (5 fx) D 0.035 cc < 32 Gy	(3 fx) < 1 cc > 30 Gy (5 fx) < 1 cc > 32 Gy
3 fx	V 16.5 Gy < 5 cc D max ≤ 22.2 Gy		
5 fx	V 18 Gy < 5 cc D max ≤ 32 Gy		
Stomach Endpoint: Ulceration/fistula			
1 fx	V 11.2 Gy < 10 cc D max ≤ 12.4 Gy		(3 fx) < 1 cc > 30 Gy
3 fx	V 16.5 Gy < 10 cc D max ≤ 22.2 Gy		
5 fx	V 18 Gy < 10 cc D max ≤ 32 Gy		
Esophagus Endpoint: Stenosis/fistula			

TG101 [9]		Other(s)	Our institutional practice
1 fx	V 11.9 Gy < 5 cc D max ≤ 15.4 Gy		(3 fx) < 1 cc > 30 Gy
3 fx	V 17.7 Gy < 5 cc D max ≤ 25.2 Gy		
5 fx	V 19.5 Gy < 5 cc D max ≤ 35 Gy		
Kidney (bilateral) Endpoint: Grade 3 toxicity			
1 fx	≥200 cc ≤ 8.4 Gy		We do not have strict unilateral kidney guidelines provided that the patient has adequate bilateral renal function
3 fx	≥200 cc ≤ 16 Gy		
5 fx	≥200 cc ≤ 17.5 Gy		
Colon Endpoint: Colitis/fistula			
1 fx	V 14.3 Gy < 20 cc D max ≤ 18.4 Gy		
3 fx	V 24 Gy < 20 cc D max ≤ 28.2 Gy		
5 fx	V 25 Gy < 20 cc D max ≤ 38 Gy		
Spinal cord Endpoint: Myelitis			
1 fx	V 10 Gy < 0.35 cc D max ≤ 14 Gy		We generally follow the TG101 guidelines for spinal cord
3 fx	V 18 Gy < 0.35 cc D max ≤ 21.9 Gy		
5 fx	V 23 Gy < 0.35 cc D max ≤ 30 Gy		

21.7 Patient Management Considerations

(a) Premedications are optional and the data behind their use lacking but include dexamethasone (4 mg, once prior to treatment) to reduce acute edema and antiemetics (e.g., ondansetron, 8 mg, once prior to treatment) to prevent nausea. For patients who may have difficulty tolerating long treatments, we consider administering a single small dose of a benzodiazepam (e.g., lorazepam, 0.5–1 mg) 30 min prior to treatment.

(b) Acute toxicities most commonly include nausea, abdominal pain, and fatigue. Most are minor and self-limiting, with Grade 1/2 toxicities reported in 30–40% of patients [4, 7, 11]. Management is supportive.

(c) Late toxicities may occur with high doses to duodenum and stomach, but these complications can be minimized by meeting normal tissue constraints in these organs. These toxicities are potentially severe, including ulceration, stenosis, bleeding, and perforation, and have been reported to occur in 5–10% of patients [2–4, 7]. Late liver dysfunction is rare.
(d) Patients should be closely followed for signs of gastrointestinal toxicity. Patients with disproportionate pain, GI bleeding, or signs of bowel obstruction should receive an urgent upper endoscopy for evaluation/intervention.

21.8 Follow-Up

(a) Follow-up after SBRT for pancreatic cancer depends on the context and intent of treatment. All patients should be followed closely to monitor for adverse events, particularly GI toxicity. Patients are generally evaluated every 3 months.
(b) Patients with unresectable disease should be followed for progression and candidacy for other treatments.
(c) Patients with borderline resectable disease may proceed to an attempted resection.
(d) Routine CT is usually sufficient to follow both response to local treatment and monitor for distant metastases, though imaging is very insensitive in defining response. CA 19-9 is also used.

21.9 Relevant Literature

(a) For unresectable disease, contemporary SBRT regimens use fractionated approaches (3–6 fractions) delivering 24–45 Gy, recognizing the potential for severe small bowel toxicity. Local control rates appear favorable, in the order of 80–90% at 1–2 years, though survival is poor. Older series utilized single fraction delivery of 18–25 Gy, though this approach has largely been abandoned because of toxicity [5].
(b) For patients receiving SBRT as a planned preoperative treatment, doses of 25–36 Gy in 3–5 fractions are used for the entire tumor, with a simultaneous integrated boost of 6–20 Gy delivered to the posterior margin (tumor-vessel interface).
(c) Reirradiation series are small but demonstrate similarly high rates of local control with potentially acceptable toxicity.

Study	Patients	Treatments	Median f/u	Outcomes
Prospective trials				
Comito 2016 [6] Phase II	– 45 pts – Unresectable – Median PTV 65 cc	– 45 Gy (6 fx) – Chemo: 78% pre-RT, 48% post-RT	13.5 months (23.5 months in survivors)	– 87% 2-years LC – 18% 2-years OS – No late G3 toxicity
Herman 2016 [3] Phase II	– 49 pts – Unresectable – Median PTV 71 cc	– 33 Gy (5 fx) – Chemo: Pre- and post-RT gemcitabine	13.9 months in survivors	– 78% 1-year LC – 18% 2-year OS – 4 pts had R0 surgery – 6% late ≥G3 toxicity (1 fistula, 2 GI bleed) – Significant improvement in pain-related QoL
Shaib 2016 [8] Phase I	– 13 pts – Preoperative intent (BRPC) – Mean tumor size 2.6 cm	– PTV: 30–36 Gy (3 fx) – Simultaneous boost: 6–9 Gy (3 fx) – Total: 36–45 Gy (3 fx) – Chemo: pre-RT FOLFIRINOX	18 months	– 11 months Med. OS – 5 pts: No surgery – 8 pts: R0 surgery (med. PFS 30 months, med. OS not reached) – No ≥G3 toxicity
Retrospective studies				
Pollom 2014 [5]	– 167 pts – Unresectable – Median PTV 50 cc	– 25 Gy (1 fx), $n = 76$ – 25–45 Gy (5 fx), $n = 91$ – Compared fractionation schemes	7.9 months	– 90% 1-year LC – 33% 1-year OS – More G2 GI toxicity with single fraction: 26% (1 fx), 8% (5 fx)
Mahadevan 2011 [7]	– 39 pts – Unresectable – Median PTV 64 cc	– 24–36 Gy (3 fx) – Chemo: pre- and post-RT gemcitabine	9.1 months (21 months in survivors)	– 85% LC (med. f/u 21 mo.) – 20 months median OS – 9% late ≥G3 toxicity (GI bleeding, bowel obstruction) – Significant improvement in pain-related QoL
Rwigema 2011 [11]	– 71 pts – Mixed population, most LAPC, 12 postop – Median GTV 17 cc	– 18–25 Gy (1 fx)	6 months (12.7 months in survivors)	– 49% 1-year LC – 41% 1-year OS – 4% acute G3 tox. (1 SMV thrombosis, 1 nausea, thrombosis, 1 gastroparesis), no late ≥G3 toxicity

Study	Patients	Treatments	Median f/u	Outcomes
Didolkar 2010 [12]	– 85 pts – Unresectable – Reirradiation in 34% – Median GTV 60 cc	– 15–30 Gy (1–4 fx) (median 26 Gy, 3 fx) – Chemo: 56% pre-RT, 100% post-RT	n/a	– 92% LC – 19 months median OS – 22% acute or late ≥G3 GI toxicity (duodenitis, gastritis, and diarrhea)
Chang 2009 [13]	– 77 pts (pts were included in subsequent Pollom 2014 analysis) – Unresectable	– 25 Gy (1 fx) – chemo: most received pre-RT	6 months (12 months in survivors)	– 84% 1-year LC – 21% 1-year OS – 9% late ≥G3 toxicity (three ulcers, three duodenal/biliary stricture, one bowel perforation)
Mellon 2015 [4]	– 159 pts (110 BRPC, 49 LAPC) – Preoperative intent	– PTV: 30 Gy (5 fx) – Simultaneous boost: 10–20 Gy (5 fx) – Total: 30–50 Gy (5 fx) – Chemo: 100% pre-RT	14 months	– BRPC: 19 months med. OS, 49% R0 resection – LAPC: 15 months med. OS, 10% R0 resection – 7% ≥G3 toxicity (6 pts, GI bleeding due partly to tumor)
Chuong 2013 [2]	– 73 pts (57 BRPC, 16 LAPC) – Preoperative intent – Median PTV 111 cc	– PTV: 25–30 Gy (5 fx) – Simultaneous boost: 10–20 Gy (5 fx) – Total: 35–50 Gy (5 fx) – Chemo: 100% pre-RT, 84% post-RT	13.8 months	– BRPC: 1-year OS 72%, 54% R0 resection, 16% pCR or near pCR – 5% ≥G3 late toxicity (GI bleeding)
Dagoglu 2016 [14]	– 30 pts – Reirradiation (prior SBRT or EBRT) – Median 18 months from prior RT – Median GTV 41 cc	– 24–36 Gy (3–5 fx)	11 months	– 78% 2-years LC – 50% 1-year OS – 1 point, G3 GI bleed; 1 point, G3 pain; 2 pts, G3 bowel obstruction
Lominska 2012 [15]	– 28 pts – Reirradiation (most had prior EBRT to 50.4 Gy) – Median GTV 44 cc	– 20–30 Gy (3–5 fx)	5.9 months	– 86% LC (med. f/u 6 months) – 18% 1-year OS – 2 pts, ≥G3 late GI toxicity (obstruction, perforation)

Abbreviations: *BRPC* borderline resectable pancreatic cancer, *LAPC* locally advanced pancreatic cancer

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Chapter 22
Rectal Cancer

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For locally advanced (e.g., T3 or N+) rectal cancer, RT is conventionally delivered with concurrent chemotherapy over a course of 5–6 weeks, 4–8 weeks before or after surgery. However, numerous randomized trials have utilized a "short course" technique, where RT is delivered in five fractions, without concurrent chemotherapy, and with surgery taking place within 1 week. In this section we will focus on the use of short course RT in the treatment of rectal cancer. In contrast to other gastrointestinal malignancies, SBRT does not have an established role in the treatment of rectal cancer; hypofractionation for rectal cancer is delivered to conventional large pelvic volumes usually with 3D-CRT.

22.1 Pearls

- There are approximately 140,000 cases of colorectal cancer in the USA per year (median age 70). Around 40,000 of these are rectal cancers.
- Most cases are sporadic rather than familial, and general risk factors include obesity, diabetes, tobacco, and alcohol use.
- Several genetic disorders increase risk, including familial adenomatous polyposis and Lynch syndrome (hereditary nonpolyposis colorectal cancer). Risk is substantially increased in patients with long-standing IBD, particularly ulcerative colitis.
- Rectal cancers (vs. colon cancer) more frequently present with symptoms including hematochezia, rectal pain, tenesmus, and decreased stool caliber.

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- Most are adenocarcinomas and similar in appearance to colonic adenocarcinomas. The dentate line forms an anatomic boundary below which squamous cell epithelium predominates (characteristic of anal cancer).
- Lymphatic spread is common. Beyond the immediate perirectal nodes, lower rectal tumors commonly spread to internal iliac nodes via the middle and inferior rectal vasculature, and upper rectal tumors commonly spread to inferior mesenteric nodes via the inferior mesenteric vasculature. Tumors below the dentate line (usually anal squamous cell carcinoma) often spread to inguinal and external iliac nodes.
- The liver and lung are the most common sites of distant metastasis. Similar to colon cancer, patients with metastases limited to the liver may be cured with aggressive locoregional therapy.
- Workup:
  - Colonoscopy to evaluate local tumor and look for synchronous tumors
  - MRI and/or endoscopic ultrasound to evaluate regional lymph nodes and involvement of the circumferential resection margin (CRM)
  - Total body CT for staging
  - Baseline CEA for prognostic purposes and to use during follow-up
- Treatment:
  - Surgery is integral for treatment of most patients and ideally involves a total mesorectal excision (TME). The location within the rectum is specified based on distance from the anal verge or dentate line, which has important implications on whether anal sphincter-sparing low anterior resection (LAR) is possible vs. abdominoperineal resection (APR).
  - Neoadjuvant RT ± chemotherapy in patients with Stage T3–4 or N+ disease.
  - Patients presenting with clinical symptoms of bowel obstruction (not endoscopic "obstruction") due to tumor should receive a palliative diverting ostomy if planned for conventional neoadjuvant RT.

22.2 AJCC Staging Table

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)

T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to adjacent organs or structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes (tumor in lymph nodes measuring ≥0.2 mm) or presence of tumor deposits (without involvement of regional lymph nodes)
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumor deposits in the subserosa, mesentery, nonperitonealized pericolic, or perirectal/mesorectal tissues (without involvement of regional lymph nodes)
N2	Metastasis in ≥4 regional lymph nodes
N2a	Metastasis in 4–6 regional lymph nodes
N2b	Metastasis in ≥7 regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Metastasis confined to one organ or site without peritoneal metastasis
M1b	Metastases to two or more organs or sites without peritoneal metastasis
M1c	Metastasis to peritoneum
Stage grouping	
0	TisN0M0
I	T1-2N0M0
IIA	T3N0M0
IIB	T4aN0M0
IIC	T4bN0M0
IIIA	T1-2N1M0 *or* T1N2aM0
IIIB	T3-4aN1M0 *or* T2-3N2aM0 *or* T1-2N2bM0
IIIC	T4aN2aM0 *or* T3-4aN2bM0 *or* T4bN1-2M0
IVA	Any T, any N, M1a
IVB	Any T, any N, M1b
IVC	Any T, any N, M1c

22.3 Tumor/Patient Selection

(a) Numerous randomized trials have studied short course preoperative RT vs. surgery alone and vs. conventionally fractionated RT. However, due to patient heterogeneity, it is unclear who optimal patients are for this hypofractionated approach. Though short course fractionation has become standard of care in many European countries, there has been relatively little adoption in the USA. With further emerging evidence, longer follow-up, and the increasing emphasis on value-based care, there is likely to be increased uptake of this approach. A discussion on short course RT must include its impact on surgery, patient selection, the role of chemotherapy, and toxicity.

(b) **Summary**:

- Short course preoperative RT is a convenient, effective, and well-tolerated treatment for rectal cancer.
- Ideal patients are those with proximal tumors and minimal concern for sphincter preservation and/or mesorectal fascia involvement.
- Patients who may benefit from downstaging may be more suited for conventionally fractionated preoperative CRT.
- In patients with low volume metastatic disease, definitive treatment of all sites of disease may be curative. Short course RT may be preferable when there are competing priorities of isolated distant metastases and symptomatic locoregional disease to minimize time to surgery and/or chemotherapy.

(c) **Surgical considerations:** A key question for all rectal cancer patients is whether patients can retain a functional anal sphincter and avoid permanent colostomy. Most short course RT trials have shown a lower rate of downstaging and pathologic complete response compared to conventional CRT, likely due to the timing of surgery within 1 week of RT and lack of chemotherapy. In cases borderline for sphincter preservation, a more protracted preoperative course may be preferable.

(d) **Patient selection:** Likely due to the above surgical considerations, most short course RT trials (see Relevant Literature) have therefore included tumors of all stages, with many patients having Stage I–II disease or tumors >5 cm from the anal verge, though recent series include more advanced tumors.

(e) **Role of chemotherapy:** The addition of chemotherapy to conventionally fractionated preoperative RT has been shown to increase downstaging and local control [1]. Chemotherapy is not used concurrently with short course RT due to concern for excess toxicity. However, a recently published Polish random-

ized trial compared conventional preop CRT to sequential short course RT and preoperative chemotherapy for advanced tumors and reported not only similar control but similar rates of pathologic downstaging and complete response. However, this approach effectively nullifies several of the purported advantages of short course RT, namely, convenience and minimization of therapy [2].

(f) **Toxicity:** Randomized trials have not shown an increased rate of toxicity using the short course regimen when compared to conventional fractionation, but longer follow-up may be needed to exclude the possibility of late toxicity due to hypofractionation.

(g) **Guidelines:** The use of neoadjuvant short course RT is included in the NCCN guidelines, though the guideline recommends against its use for T4 tumors [3]. A recently published ASTRO appropriateness guideline for treatment of Stage II–III rectal cancer rated conventional neoadjuvant CRT as appropriate for all patients, whereas short course RT was rated as appropriate for patients with non-threatened mesorectal fascia margins and lower risk disease [4].

(h) An area of current research is the intensification of preoperative treatment (whether RT or chemotherapy) with the aim of selective rectal preservation and avoidance of surgery altogether. Patients receiving short course RT are not candidates for this approach; surgery should not be omitted in these patients.

22.4 Treatment Planning Considerations

Simulation instructions	Depending on body habitus, the patient may be simulated either prone or supine. Patients with a larger girth may benefit from prone simulation with a belly board to remove bowel from the field
Image guidance	For conventional 3D-CRT, weekly portal films are adequate
Field size	The fields for short course fractionation for rectal cancer are typically similar or identical to those used for conventional fractionation, including the anal canal (with the exception of proximal tumors) plus presacral, mesorectal, obturator, and internal iliac lymph nodes with a superior border at the lower edge of the fifth lumbar vertebra. No “cone-down” is used for short course RT
Dosimetric considerations	Maximum allowed dose: 110–115% of prescription

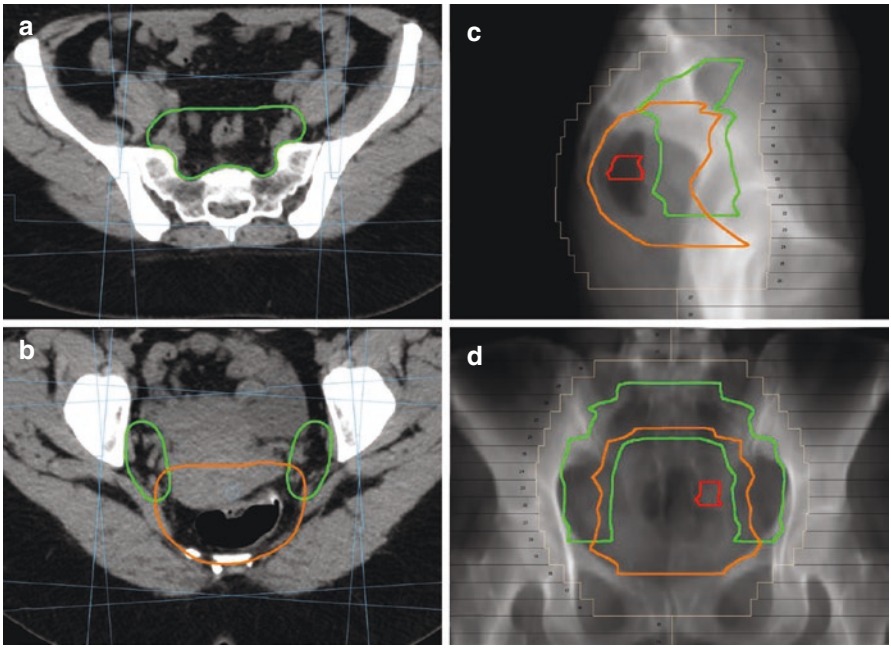

Fig. 22.1 Example of standard rectal cancer treatment planning. This patient had limited metastatic disease and received initial chemotherapy with a good local response. The GTV is red; mesorectum is orange, and nodal volume is green. (**a**) Coverage of presacral and high internal iliac nodes. (**b**) Coverage of mesorectum and low internal iliac nodes. (**c**) Lateral field view showing a generous posterior field edge to ensure coverage of the presacral space, superior field edge at the inferior border of L5, and limited anterior field edge to spare bowel. (**d**) Anterior field view. The anal canal was not covered due to proximal location of tumor

22.5 Commonly Used Dose/Fractionation Schemes

Dose/fx	# of fx	Total dose	Notes
5 Gy	5	25 Gy	Standard short course preop RT fractionation, delivered daily, which utilizes the same field design as conventionally fractionated RT, without concurrent chemotherapy

22.6 Normal Tissue Tolerances

– Most protocols and trials publishing on short course RT have not reported on normal tissue tolerance goals but rather described beam arrangements and design.

Washington University [5]	Our institutional practice
Small bowel	
Dmax <25 Gy	Though we do not have strict criteria, we recommend minimizing the volume of small bowel in the RT field and considering standard fractionation in patients with large volumes of small bowel within the pelvis
V 20 Gy < 50 cc	
Colon	
"Minimize" V 20 Gy	
Femoral heads (bilateral)	
"Minimize" V 20 Gy	Standard rectal fields deliver substantial femoral head dose only with the lateral beams, so the extent of the V 20 Gy will be related to the additional dose from the lateral borders of the anterior/posterior beams

22.7 Patient Management Considerations

(a) Patients receiving short course preop RT typically finish treatment within 1 week and proceed to surgery the following week. Because of the short duration of treatment, the rates of reported acute toxicity are low and perhaps manifest during the perioperative period. Management is supportive.
(b) Rates of late toxicity appear comparable to patients receiving conventional fractionation (albeit with limited follow-up) and usually involve gastrointestinal changes including increased frequency of bowel movements and incontinence. Late Grade 3 gastrointestinal toxicities have been reported to occur in around 5–10% [6, 7], though low-grade toxicities may occur in up to 50% [8]. Though challenging to manage, these late symptoms can be reduced by alteration of diet and use of anti-motility agents.

22.8 Follow-Up

(a) Patients receiving preoperative short course RT typically proceed to surgery within 1 week of completing RT.
(b) Following surgery, patients should be evaluated every 3–6 months with rectal examination and CEA. Patients should also receive a colonoscopy at 1 year and annual CT scans.

22.9 Relevant Literature

(a) **Toxicity:** Late gastrointestinal toxicity has been reported to be higher than surgery alone in the Swedish and Dutch short course trials [8, 9]. However, studies randomizing patients to short course vs. conventional RT have shown similar rates of late toxicity, albeit with follow-up of only around 5 years [2, 6, 7]. Longer follow-up is likely necessary to accurately compare late toxicity, as many patients in the Swedish and Dutch trials experienced late toxicity more than 5 years post-RT. Acute toxicity appears to be lower with short course RT vs. conventional CRT, but this comparison may be subject to ascertainment bias and the masking of acute toxicities by the subsequent perioperative period in patients receiving short course RT [6, 10].

(b) The following trials are organized by clinical question and roughly by chronologic order. The first three trials (Swedish, Dutch, UK) compare short course preop RT vs. surgery alone in rectal cancer patients of all stages. The initial Swedish short course trial [11] demonstrated feasibility and effectiveness of short course RT. The Dutch [12] and UK [13] trials confirmed this benefit when standardizing surgery to TME.

(c) The next two trials (Polish I and TROG) compared short course preop RT to conventional preop CRT and included only advanced tumors. These trials show comparable survival and control outcomes, similar late toxicities, but significantly greater rates of pathologic complete response and possibly sphincter preservation in the conventionally treated patients [6, 7]. However, the Stockholm III trial (not listed below as primary endpoint results have not been published) showed pathologic complete response rates comparable to conventionally treated patients when surgery is delayed to 4–8 weeks after short course preop RT [14].

(d) The final trial (Polish II) intensified preop treatment for advanced tumors by comparing conventional preop CRT to sequential short course preop RT followed by preop chemotherapy. This strategy showed not only comparable control and late toxicities but also similar rates of pathologic complete response and sphincter preservation [2].

Study	Patients	Treatments	Median f/u	Outcomes
Randomized trials				
Swedish 1997 [11]	**Surgery ± short course RT** – 908 pts – Dukes' stage A (30%), B (33%), C (37%)	**Arm 1**: 25 Gy (5 fx, daily), surgery within 1 week **Arm 2:** Surgery alone (TME not reported)	6.25 years in survivors	**Arm 1** – 11% 5-year LR – 58% 5-year OS **Arm 2** – 27% 5-year LR ($p < 0.001$) – 48% 5-year OS ($p = 0.004$)
Kapiteijn 2001 [12] Peeters 2007 (long-term f/u) [15] Dutch	**Surgery ± short course RT** – 1805 pts – Stage I (28%), II (29%), III (35%) – 28% ≤5 cm from anal verge	**Arm 1**: 25 Gy (5 fx, daily), surgery **Arm 2:** Surgery alone (TME both arms)	6.1 years in survivors	**Arm 1** – 6% 5-year LR – 64% 5-year OS **Arm 2** – 11% 5-year LR ($p < 0.001$) – 64% 5-year OS (NS)
Sebag-Montefiore 2009 [13] UK	**Surgery ± short course RT** – 1350 pts – Stage I (26%), II (30%), III (40%) – 34% ≤5 cm from anal verge	**Arm 1**: 25 Gy (5 fx, daily), surgery 1-week post-RT **Arm 2:** Surgery (10% received conventional post-op CRT) (TME both arms)	4 years in survivors	**Arm 1** – 5% 5-year LR – 70% 5-year OS **Arm 2** – 12% 5-year LR ($p < 0.001$) – 68% 5-year OS (NS)
Bujko 2006 [6] Polish I	**Short course vs. conventional** – 312 pts – T3/4	**Arm 1**: 25 Gy (5 fx, daily), surgery 1-week post-RT **Arm 2:** 50.4 Gy (28 fx), concurrent 5-FU, surgery 4–6 weeks post-RT (TME for low-lying tumors, both arms)	4 years in survivors	**Arm 1** – 11% 4-year LR – 67% 4-year OS – 1% pCR, 13% pos. CRM – Toxicity: 3% ≥G3 acute, 10% severe late **Arm 2** – 16% 4-year LR (NS) – 66% 4-year OS (NS) – 16% pCR, 4% pos. CRM – Toxicity: 18% ≥G3 acute, 7% severe late

Study	Patients	Treatments	Median f/u	Outcomes
Ngan 2012 [7] TROG	**Short course vs. conventional** – 323 pts – T3 – 37% node pos. – 24% ≤5 cm from anal verge	**Arm 1**: 25 Gy (5 fx, daily), surgery 1-week post-RT **Arm 2:** 50.4 Gy (28 fx), concurrent 5-FU, surgery 4–6 weeks post-RT (TME both arms)	5.9 years	**Arm 1** – 8% 5-year LR – 74% 5-year OS – 1% pCR, 37% APR – 6% Late G3/4 toxicity **Arm 2** – 6% 5-year LR (NS) – 70% 5-year OS (NS) – 15% pCR, 31% APR – 8% Late G3/4 toxicity
Bujko 2016 [2] Polish II	**Short course + chemo vs. conventional** 515 pts – fixed T3/4 – 56% ≤5 cm from anal verge	**Arm 1**: 25 Gy (5 fx, daily), sequential FOLFOX4 ×3 cycles, surgery 6 weeks post-chemo **Arm 2:** 50.4 Gy (28 fx), concurrent 5-FU + weekly oxaliplatin, surgery 6 weeks post-RT (TME both arms)	2.9 years in survivors	**Arm 1** – 22% 3-year LR – 73% 3-year OS – 16% pCR, 37% APR – 20% Late complications **Arm 2** – 21% 3-year LR (NS) – 65% 3-year OS ($p = 0.046$) – 12% pCR, 41% APR – 22% Late complications

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Part VIII
Genitourinary Cancer

Chapter 23
Prostate Cancer Hypofractionation

Jordan A. Holmes and Ronald Chen

23.1 Introduction

Prostate cancer is the most common malignancy diagnosed in men in the USA, and in 2018 it is estimated that over 164,690 men will be diagnosed with prostate cancer. Treatment options for prostate cancer are based on risk stratification with Gleason score, clinical stage, and PSA. Of interest to the radiation oncologist, prostate cancer is hypothesized to have an alpha/beta ratio of <2 offering a potential therapeutic benefit for hypofractionation. In addition to biological reasons, the frequency of prostate cancer and the high health-care cost of treatment have led to significant interest in shortening radiation treatment time. Recently several large randomized trials of hypofractionation have been published providing high quality level I evidence for the safety and efficacy of modest hypofractionation. There has been a more recent interest in SBRT for prostate cancer with many single and multiinstitutional studies reporting safety and efficacy.

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23.2 Pearls

- Prostate cancer is the most common non-cutaneous malignancy in men and the second leading cause of cancer mortality in the USA. An estimated 164,690 men will be diagnosed with prostate cancer in 2018. The incidence of prostate cancer is decreasing as screening has decreased.
- The median age at diagnosis is 70 years. African Americans are more likely to be diagnosed with prostate cancer than Caucasian men. But there has been no clear causal relationship determined between a risk factor and development of prostate cancer. Diet (high-fat diet), tobacco use, and higher BMI have been correlated with increased risk of prostate cancer.
- No clear driving genetic mutation has been identified, but increased incidence of prostate cancer in some families suggest a heritable risk for development of prostate cancer
- Most prostate cancers are diagnosed while asymptomatic due to PSA screening. However, more advanced disease can present with urinary obstruction and/or hematuria, and metastatic patients can present with bone pain.
- Prostate cancer is graded using the Gleason grading system. More recently there has been a movement toward grade groupings ranging from 1 to 5 (Group 1 = Gleason 6; Group 2 = Gleason 3 + 4; Group 3 = Gleason 4 + 3; Group 4 = Gleason 8; Group 5 = Gleason 9–10).
- Over 95% of prostate cancers are adenocarcinoma. Uncommon variants include small cell, mucinous, and ductal prostate cancers. These rare variants are almost always found in a background of adenocarcinoma.
- The peripheral zone of the prostate makes up about 70% of the glandular tissue in an adult and contains almost all prostate cancers. The central zone makes up most of the remaining glandular tissue; the transitional zone surrounding the urethra (the site of BPH) and the anterior fibromuscular stroma are rarely sites of cancer.
- The apex of the prostate is involved in over half of cancers, and because the prostatic capsule is not well-defined at this level, extracapsular spread can be difficult to identify. Extracapsular extension is most frequently identified in the posterior and lateral portions of the gland along the neurovascular bundle.
- The seminal vesicles are superior to the prostate and can be involved by cancers involving the base of the gland by local extension.
- Prostate cancer typically follows a stepwise pattern of spread first to the internal iliac or obturator nodes, then to the common iliac and para-aortic nodes. Less commonly, presacral and perirectal nodes can be involved (<20% of node + patients). When the seminal vesicles are involved, the risk of spread to the external iliac chain is increased.
- Risk of nodal spread is related to tumor volume, PSA, and Gleason score. Risk of adverse pathology (i.e., node positive, extracapsular extension, seminal vesicle invasion) can be estimated using prediction tools.
  - Roach formula for risk of LN+: 2/3 × PSA + ([Gleason-6] × 10)
  - Partin nomograms: http://urology.jhu.edu/prostate/partintables.php
  - MSKCC nomograms: https://www.mskcc.org/nomograms/prostate/pre-op

- The overwhelming majority of prostate cancer metastases are to the bone (>80%). Metastatic disease to the lung and liver is more common in later stages of disease.
- Medical workup should include PSA, prostate biopsy (Gleason score), and digital rectal exam (to asses clinical T stage) to complete risk stratification. Basic labs including a CBC and basic chemistry panel should be obtained for any patients considering surgical intervention, and LFTs should be obtained for patients who are being considered for ADT.
- Imaging workup (Per NCCN guidelines):
  - Bone scan if any of the following: T1 and PSA > 20, T2 and PSA > 10, Gleason ≥8, T3/4, or symptomatic
  - CT/MRI pelvis if any of the following: T3/4 disease, T1/2 disease with nomogram predicted probability of lymph node involvement >10%.
  - All others no imaging
- Treatment options
  - Low risk: Active surveillance, brachytherapy, SBRT, conventional fractionated or hypofractionated external beam RT, or radical prostatectomy
  - Intermediate risk: External beam RT ± brachytherapy ± ADT, SBRT in select patients, brachytherapy in select patients, and radical prostatectomy
  - High risk: External beam RT ± brachytherapy + ADT, radical prostatectomy
  - Limited life expectancy: Watchful waiting

23.3 AJCC Clinical Staging Table

Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable or visible by imaging
T1a	Tumor incidental histologic finding in ≤5% of tissue resected
T1b	Tumor incidental histologic finding in >5% of tissue resected
T1c	Tumor identified by needle biopsy (because of elevated prostate-specific antigen [PSA] level)
T2	Tumor confined within prostate; tumors found in one or both lobes by needle biopsy but not palpable or reliably visible by imaging
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invading seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Regional lymph nodes	
NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph nodes(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

23.4 AJCC Pathologic Staging Table

Primary tumor	
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Regional lymph nodes	
NX	Regional lymph nodes not sampled
N0	No positive regional lymph nodes
N1	Metastasis in regional lymph node(s)

23.5 Gleason score and grade grouping

Gleason score	Grade grouping
3 + 3 = 6	1
3 + 4 = 7	2
4 + 3 = 7	3
8	4
>8	5

23.6 NCCN risk stratification

Low risk	T1-T2a *AND* Gleason ≤6 *AND* PSA <10
Intermediate risk	T2b-T2c *OR* Gleason 7 *OR* PSA 10–20
High risk	T3/T4 *OR* Gleason 8–10 *OR* PSA >20

23.7 CAPRA score calculation

Variable	Corresponding points
PSA at diagnosis, ng/mL	
<6.0	0
6.0–10	1
10.01–20	2
20.01–30	3
>30	4
Gleason score at biopsy examination, primary/secondary pattern	
1–3/1–3	0
1–3/4–5	1
4–5/1–5	3
Age at diagnosis, year	
<50	0
≥50	1
Clinical tumor stage	
T1a–T2c	0
T3a	1
Percent of biopsy cores positive for cancer	
≤33	0
>33	1

CAPRA score risk groups

Low risk	CAPRA score 0–2
Intermediate risk	CAPRA score 3–5
High risk	CAPRA score 6–10

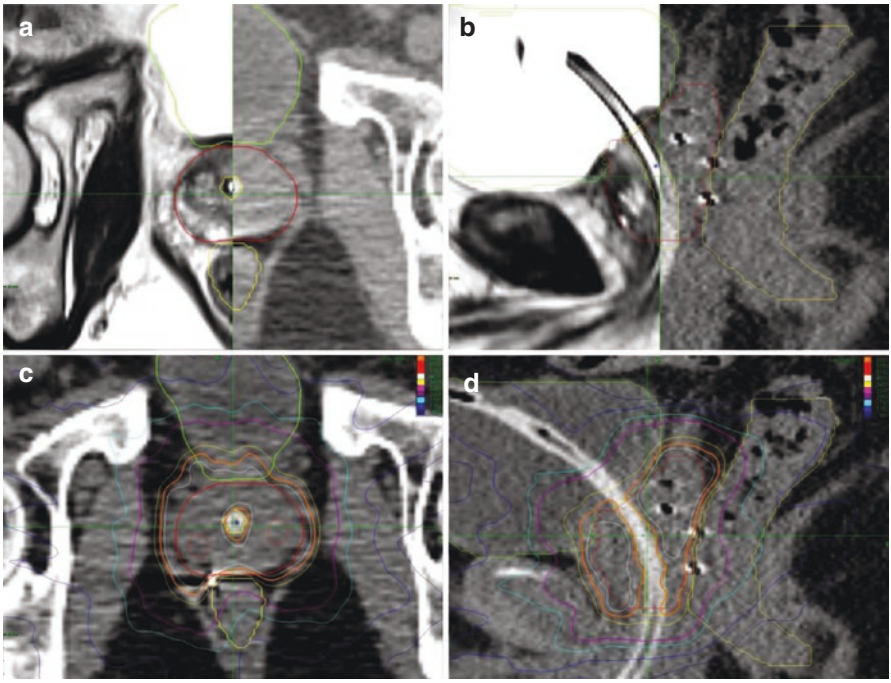
23.8 Tumor/Patient Selection

1. Intact prostate hypofractionation
   (a) No history of proctitis, diverticulitis, or inflammatory bowel conditions
2. Post-radical prostatectomy hypofractionation
   (a) No history of proctitis, diverticulitis, or inflammatory bowel conditions
3. SBRT:
   (a) Low-risk or low volume intermediate-risk disease
   (b) No history of proctitis, diverticulitis, or inflammatory bowel conditions
   (c) Prostate volume <100 ccs (UNC practice)

23.9 Treatment Planning Considerations

Simulation instructions	*Intact prostate hypofractionation*: **Per RTOG 0415:** A urethrogram is encouraged to establish the inferior portion of the prostate. Patients should be simulated supine with CT slice thickness ≤5 mm. Extreme bladder or rectal filling should not be present at the time of the planning CT scan. **UNC practice:** Patients simulated supine with urethrogram. 1.5 mm CT slices are obtained from the mid abdomen through the mid-thigh. A urethrogram is used to establish the inferior portion of the prostate. We do not routinely fuse MRI images for prostate delineation. *Intact prostate SBRT*: **Per RTOG 0938:** Patients should adhere to a low gas, low motility diet commencing 1 day prior to the treatment. One tablespoon of milk of magnesia will be taken the night before the simulation and the night before each treatment. One Fleet's enema will be administered 2–3 h before the simulation and each treatment. Patients will be asked to have a full urinary bladder both during simulation and treatment for all techniques except where treatment time exceeds 30 minutes when patients may be treated with an empty bladder. Consistent bladder filling procedure should be used for an individual patient for simulation and for each treatment. **UNC practice:** Patients are instructed to perform a Fleets enema at home 2 h before simulation and treatments. Simulate patients supine with a Foley catheter in place and 50 ccs of water instilled in the bladder. Patients are immobilized in a vac-loc. MRI is performed immediately after CT simulation with the Foley catheter still in place. Patient does not have Foley catheter for treatments. *Post-radical prostatectomy hypofractionation*: **UNC practice:** Patients are simulated supine. 3 mm CT slices are obtained from the mid abdomen through the mid-thigh. A urethrogram is used.
Image guidance	Intact prostate linac: – Daily image guidance with either real-time tracking (Calypso transponders, ultrasound) or daily 3D imaging (CT on rails, KV-CBCT) Intact prostate CyberKnife: – Fiducial markers, need at least 3 for translational and rotational tracking Post-radical prostatectomy: – Daily image guidance with 3D imaging (CT on rails, KV-CBCT)

Margins	Intact prostate hypofractionation: – **RTOG 0415:** Prostate = CTV, CTV+ at least 4 mm for PTV. Sup/Inf PTV margin of 4–10 mm – **UNC practice:** Prostate +5 mm (0 mm posterior) = CTV, CTV+ 3–5 mm = PTV. The authors do not routinely plan pelvic radiation unless patient has known node-positive disease Intact prostate SBRT: – **RTOG 0938:** Prostate = CTV; CTV + 5 mm (3 mm posterior) = PTV – **UNC practice:** Prostate = CTV; prostate +2–5 mm (0 mm posterior) = PTV the side of the prostate with Gleason 7 disease is expanded 5 mm, otherwise 2 mm expansion Post-radical prostatectomy hypofractionation [1]: – *Prostatic bed*: – Superior: Should include entire seminal vesicle remnant – Inferior: 8–12 mm inferior to the vesicourethral anastomosis – Anterior: Posterior aspect of the pubic symphysis, above the symphysis include 1–2 cm of posterior bladder wall – Posterior: Anterior rectal wall – Prostatic bed = CTV; CTV + 5 mm = PTV – The authors do not routinely plan pelvic radiation unless patient has known node-positive disease
Dosimetric considerations	Intact prostate hypofractionation (RTOG 0415): – Prostate PTV V100% prescription ≥98% – Prostate PTV D95% prescription = 100% – Dmax 107% Intact prostate SBRT (RTOG 0938): – Prostate PTV V100% prescription ≥95% – Prostate PTV D95% prescription = 100% – DMax 107% (120% for CyberKnife) Postoperative hypofractionation: – Prostatic bed PTV V100% prescription ≥95% – DMax <115%



Representative axial (**a**) and sagittal (**b**) sections of the prostate, rectum, and bladder with CT (right half of image) and T2-weighted MRI (left half of image) in a patient planned to receive CyberKnife SBRT. The same axial (**c**) and sagittal (**d**) slices showing the final radiation plan

23.10 Commonly Used Dose/Fractionation

Dose per fraction	Fractions	Total dose	Duration	Notes
Intact				
Hypofractionation				
2.5 Gy	28	70 Gy	Daily	RTOG 0415 [2]
3 Gy	20	60 Gy	Daily	CHHiP [3] and PROFIT trials [4]
3.4 Gy	19	64.6 Gy	Every other day	HYPRO trial [5]
SBRT				
9.5 Gy	4	38 Gy	Daily	
7.25 Gy	5	36.25 Gy	Twice a week	RTOG 0938 [6] (off protocol, published studies have used daily or every other day treatment)
8 Gy	5	40 Gy	Every other day	

Dose per fraction	Fractions	Total dose	Duration	Notes
Postoperative hypofractionation				
2.5 Gy	25–26	62.5–65 Gy	Daily	

23.11 Normal Tissue Tolerances

Organ	TG101	Other	Our institutional practice for 9.5 Gy × 4 = 38 Gy
Bladder			
SBRT			
−3 fractions	DMax: 28.2 Gy V16.8 < 15 cc		
−4 fraction			DMax <45.6 Gy D10cc <41.8 Gy
−5 fractions	DMax: 38 Gy V18.3 < 15 cc	RTOG 0938 [6] DMax <105% prescription 90% of bladder <90% prescription 50% of bladder <50% prescription	
Limiting toxicity	≥Grade 3 cystitis		
Intact hypofractionation			
−70 Gy/28 fractions		RTOG 0415 [2] V79 < 15% V74 < 25% V69 < 35%	
Limiting toxicity			
Post-op hypofractionation			
−65 Gy/26 fxs		Lewis et al. 2016 [7] V43 < 50% V62.4 < 25%	
Limiting toxicity			
Rectum			
SBRT			
−3 fractions	DMax: 28.2 Gy V24 < 20 cc		
−4 fraction			DMax <38 Gy
−5 fractions	DMax: 38 Gy V25 < 20 cc	RTOG 0938 [6] DMax <105% prescription <3 cc at 95% prescription 90% of rectum <90% prescription 50% of rectum <50% prescription	

Organ	TG101	Other	Our institutional practice for 9.5 Gy × 4 = 38 Gy
Limiting toxicity	≥Grade 3 proctitis		
Intact hypofractionation			
−70 Gy/28 fractions		RTOG 0415 [2] V74 < 15% V69 < 25% V64 < 35%	
Limiting toxicity			
Post-op hypofractionation			
−65 Gy/26 fxs		Lewis et al. 2016 [7] V53.8 < 50% V66.8 < 25%	
Limiting toxicity			
Urethra			
SBRT			
−3 fractions			
−4 fraction			DMax: 40 Gy
−5 fractions		RTOG 0938 [6] DMax <107%	
Limiting toxicity			
Penile bulb			
SBRT			
			Mean < 50 Gy
Intact hypofractionation			
−70 Gy/28 fractions		RTOG 0415 [2] Mean ≤ 51 Gy	
Limiting toxicity			

23.12 Patient Management Considerations

1. Premedication/prophylactic medication
   (a) Moderate hypofractionation: None
   (b) SBRT:
   - Patients are started on prophylactic alpha-blocker (0.4 mg tamsulosin QD) at the time of simulation. Therapy is continued through at least first follow-up at 1 month after treatment.
   - Dexamethasone 4 mg is given before each fraction of SBRT.

2. Common acute and late toxicity
   (a) Obstructive urinary symptoms (frequency, incomplete emptying, poor flow) occur in 7–54% of patients [8, 9].
   - Start with tamsulosin 0.4 mg once a day, can increase to twice a day if inadequate response.
   - Second-tier symptom management with silodosin 8 mg (Rapaflo).

(b) Incontinence/urgency ≥grade 3 occurs in ~11% of patients [9].
- Start with Ditropan 10 mg QD, can increase to 5 mg TID if inadequate response.
- Second-line mirabegron 25 mg QD (Myrbetriq), can increase to 50 mg QD (Myrbetriq).

(c) Macroscopic/gross hematuria is rare (<2%) [9]: referral to urology for workup including cystoscopy.
(d) Rectal bleeding is uncommon [9]: referral to gastroenterology for workup including endoscopy.
(e) Fecal incontinence is very rare (~2%): referral to gastroenterology.
(f) Erectile dysfunction is a common side effect after any treatment for prostate cancer. Medical management includes sildenafil (Viagra) 50–100 mg or tadalafil (Cialis) 10–20 mg. If medical management fails, additional options include penile pump, injectable medications, and surgery (prosthesis). Referral to a specialist is often necessary beyond medical management.

23.13 Follow-Up

(a) Frequency: every 6–12 months PSA for year 1–5, then yearly. Every 3 months monitoring may be appropriate for patients at high risk of recurrence. Follow up for both intact and post prostatectomy (NCCN guidlines) [10].
(b) Tests needed: PSA, DRE (optional if PSA undetectable)

23.14 Relevant Literature

Guidelines: NCCN 2016 Guidelines for Intact Prostate [10]:

(a) Moderately hypofractionated image-guided IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) can be considered as an alternative to conventionally fractionated regimens when clinically indicated.
(b) Extremely hypofractionated image-guided IMRT/SBRT regimens (6.5 Gy per fraction or greater) can be considered as a cautious alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.

Study	Patients	Treatment	Median FU	Outcomes
Intact hypofractionation				
Randomized trials				
Low risk				
RTOG 0415 [2] Non-inferiority study	*n* = 1115 T1b-T2c PSA <10 Gleason 2–6 PS 0–1 (78% T1c)	73.8 Gy 41 fxs 70 Gy/28 fxs ADT not allowed	5.8 years	5-year disease-free survival 73.8 Gy: 85.3% 70 Gy: 86.3% (non-inferior) No difference in overall survival No difference in early GI or GU toxicity Increased late grade 2 GI (18.3% vs. 11.4%, $p = 0.005$) and late grade 2 GU (26.2% vs. 20.5%) toxicity in the hypofractionation arm
Intermediate risk				
Pollack 2013 [11]	*n* = 307 Intermediate (66%) and high-risk (34%) patients	76 Gy/38 fxs 70.2 Gy/27 fxs 0–4 months ADT intermediate risk, 24 months high risk	5.6 years	5-year biochemical disease-free survival 76 Gy: 21.4% 70.2 Gy: 23.3% ($p = 0.745$) No difference in overall survival No difference in acute or late GI/GU toxicity On multivariable analysis hypofractionated patients with baseline IPSS > 12 more likely to develop late GU toxicity
CHHiP [3, 12, 13] Non-inferiority study	*n* = 3216 T1b-T3a PS 0–1 73% intermediate risk	74 Gy/37 fxs 60 Gy/20 fxs 57 Gy/19 fxs 3–6 mo ADT	5.2 years	5 year DFS 74 Gy: 88.3% 60 Gy: 90.6% (non-inferior to 74 Gy) 57 Gy: 85.9% (inferior to 74 Gy) No difference in overall survival More acute grade ≥2 bowel toxicity in hypofractionated groups (38% combined 57/60 Gy vs. 25% for 74 Gy), resolved by 2 years No difference in QOL scores through 5 years

Study	Patients	Treatment	Median FU	Outcomes
PROFIT [4, 14] Non-inferiority study	*n* = 1206 T1a-T2c PSA ≤20 Gleason ≤7 Intermediate risk by Canadian consensus criteria	78 Gy/39 fxs 60 Gy/20 fxs Allowed pre-randomization ADT up to 90 days, no post randomization ADT	6 years	5 year biochemical failure 78 Gy: 79% 60 Gy: 79% (non-inferior) No difference in OS No difference in acute grade ≥3 GI or GU toxicity No difference in late grade ≥ 3 GI or GU toxicity No difference in QOL scores at 48 months
High risk				
HYPRO [5, 9, 15]	*n* = 820 T1b-T4a PSA <60 PS 0–2 26% intermediate risk, 74% high risk	78 Gy/39 fxs 64.6 Gy/19 fxs ADT at physician discretion (67%)	5 years	5-year relapse-free survival 78 Gy: 77.1% 64.6 Gy: 80.5% (p = 0.36) No difference in cumulative incidence of acute (<120 days) ≥ grade 2 GU toxicity (57.8% standard vs. 60.5% hypofractionated) Increase in cumulative incidence of acute (<120 days) ≥grade 2 GI toxicity (31.2% standard vs. 42.0% hypofractionated) Increase in cumulative incidence of late ≥grade 2 GI toxicity at 5 years (12.9% standard vs. 19.0% hypofractionated) No difference in cumulative incidence of late ≥grade 2 GU toxicity at 5 years (2.6% standard vs. 3.3% hypofractionated)
Intact prostate SBRT				
Prospective phase I–II				
King 2013 [16] Multiinstitutional, combined data of several prospective phase II studies. All patients treated with CyberKnife SBRT	*N* = 1100 58% low risk 30% intermediate risk 11% high risk	35–40 Gy/5 fxs Daily treatment for >95% of patients	36 months	5-year biochemical relapse-free survival: 93% – Low risk: 95% – Intermediate risk: 83% – High risk: 81%

Study	Patients	Treatment	Median FU	Outcomes
King 2013 [17] Multiinstitutional, combined data of several prospective phase II studies. All patients treated with CyberKnife SBRT	*n* = 864	Median dose 36.25 Gy/5 fxs Median dose 39 Gy/4 fxs	36 months	Significant decrease in GU quality of life at 3 months, return to baseline at 6–9 months Significant decrease in GI quality of life at 3 months, return to baseline at 6–9 months
RTOG 0938 Randomized phase II (Abstract only)	*n* = 240	36.25 Gy/5 fxs 51.6 Gy/12 fxs	12 months	Worsening of EPIC bowel score: 5 fractions, 23.5%; 12 fractions, 23.1% Worsening of EPIC urinary score: 5 fractions, 35.3%; 12 fractions, 34.7%
Boike 2011 [18] Phase I	*n* = 45	Dose-escalation study 45 Gy/5 fxs 47.5 Gy 5 fxs 50 Gy/5 fxs	30 months 18 months 12 months	97% biochemical control (varying follow-up by dose level) Toxicity – No ≥grade 3 toxicity in 45 Gy dose level. – One patient with grade 2 GU toxicity – One patient with ≥grade 3 toxicity in 47.5 Gy dose level – Two patients with ≥grade 3 toxicity in 50 Gy dose level
Retrospective				
Katz 2014 [18] All patients treated with CyberKnife SBRT	*n* = 515	36.25 Gy/5 fxs 35 Gy/5 fxs	72 months	7-year actuarial freedom from biochemical failure: – Low risk: 95.8% – Intermediate risk: 89.3% – High risk: 68.5% No acute grade 3 or 4 toxicity Late grade 2 rectal toxicity 4%, late grade 2 GU toxicity 9.1% Mean EPIC urinary and bowel QOL declined at 1 month, returned to baseline by 2 years

Study	Patients	Treatment	Median FU	Outcomes
Postoperative hypofractionation				
Prospective phase I–II				
Cozzarini 2008 [19]	*n* = 50 T3 or positive margins and N0	58 Gy/20 fxs	2.2 years	Acute ≥grade 2 toxicity GI, 4%; GU, 10%
Massaccesi 2013 [20]	*n* = 49 Positive margins or ECE or SVI AND > 7% risk of nodal involvement (Roach), OR positive pelvic nodes, OR PSA failure after RP	62.5 Gy/25 fxs using simultaneous integrated boost Pelvic nodes treated to 45 Gy in 25 fxs	Not reported	Acute ≥grade 2 toxicity GI, 32.6%; GU, 11.5%
Katayama 2014 [21]	*n* = 39 T3 or positive margins or PSA recurrence	54 Gy/18 fxs	Not reported	Acute ≥ grade 2 toxicity GI, 18%; GU, 0%
Gladwish 2015 [22]	*n* = 30 T3 or positive margins or PSA recurrence	51 Gy/17 fxs	2 years	Acute ≥ grade 2 toxicity GI, 0%; GU, 6%
Retrospective series				
Kruser 2011 [23]	*n* = 108 Biochemical recurrence after RP 87% pathologic Gleason ≤7	65 Gy/26 fxs	2.7 years	4-year actuarial failure from biochemical progression: 67% Acute ≥grade 2 toxicity GI, 14%; GU, 7% Late ≥grade 2 toxicity GI, 4%; GU,15%
Lewis 2016 [7]	*n* = 56	57.5–65 Gy/23–26 fxs	4 years	4-year biochemical progression-free survival: 75% Acute ≥grade 2 toxicity GI, 3.6%; GU, 16% Late ≥grade 3 toxicity GI, 12.5%; GU, 27%

Abbreviations: *Gy* Gray, *PSA* prostate-specific antigen, *PS* performance status, *Fxs* fractions, *ADT* androgen deprivation therapy, *GI* gastrointestinal, *GU* genitourinary, *QOL* quality of life, *ECE* extracapsular extension, and *RP* radical prostatectomy

23.15 Summary

(a) Intact prostate hypofractionation: Hypofractionation is now an established standard of care for men with localized prostate cancer based on level 1evidence from multiple randomized controlled trials. Hypofractionation is non-inferior to conventional dose-escalated radiation for disease control.
(b) Intact prostate SBRT: SBRT can be considered a treatment option for low- and low-intermediate-risk prostate cancer based on multiple prospective phase II trials. Results from these studies have shown favorable disease control and long-term toxicity outcomes compared to historical controls, but there is no randomized data comparing SBRT to conventional fractionation or hypofractionated external beam radiotherapy.
(c) Post-radical prostatectomy hypofractionation: This is an area of active investigation. Preliminary single-institution studies have shown promising results. An upcoming NRG trial will compare hypofractionated to conventionally fractionated radiotherapy in this setting.

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Chapter 24
Kidney Cancer

Jordan A. Holmes and Ronald Chen

24.1 Introduction

Surgery remains the standard of care for patients with primary renal cell carcinoma, which has classically been considered radioresistant; however, there is growing evidence that SBRT with high-dose per fraction might be able to overcome the previously described radioresistance. In limited literature SBRT has shown promising safety and local control outcomes for primary renal cell carcinomas in patients who are not eligible or refuse surgery.

24.2 Pearls

- Renal cell carcinoma (RCC) is one of the 10 most common malignancies in the developed world compromising approximately 4% of new cancer diagnosis each year. An estimated 14,970 deaths are expected in 2018 from RCC. The incidence

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of RCC has been increasing in the USA at a rate of 2–3% per year mostly due to incidental early detection on abdominal imaging.
- RCC incidence is the highest in North America and Scandinavia, and African Americans and Whites have the highest rates of diagnosis.
- The median age at diagnosis is 65 years, and men are twice as likely to develop RCC as women.
- Smoking and obesity have both been suggested as risk factors for developing RCC based on meta-analyses.
- Inherited forms of RCC have been linked to VHL, TSC1, TSC2, and Met1 gene alterations, but in cases with a family history and no identifiable mutations, the risk of developing RCC can still be increased by as much as twofold.
- Most early stage RCCs are diagnosed incidentally on abdominal imaging. However more advanced disease can present with abdominal pain, hematuria, or a palpable abdominal mass. Rarely male patients can present with a varicocele from impaired testicular drainage. Paraneoplastic symptoms can include fevers, hypercalcemia, hypertension, and liver dysfunction.
- Greater than 90% of all primary kidney cancers are renal cell carcinoma and of these >80% are clear cell. The remaining RCCs are classified as chromophobe, papillary, or collecting duct types. Clear cell tumors have a worse prognosis than the other subtypes.
- Direct extension of RCCs can include invasion into the perinephric fat, adrenal gland, or inferior vena cava.
- Nodal drainage and metastasis can spread to the renal hilar, paracaval, aortic, and retroperitoneal lymph nodes. Blood-borne metastatic disease has a predilection for the lungs, brain, and bone.
- Medical workup should include basic labs to establish renal function and surgical suitability (CBC, metabolic panel), LDH, and urinalysis. Imaging should include chest staging (X-ray or CT) and contrasted imaging of the abdomen and pelvis (CT or MRI). If clinically indicated imaging of the brain for neurologic symptoms (MRI) or bones for pain (bone scan, PET/CT) is appropriate.
- Surgical resection remains the gold standard treatment for nonmetastatic renal cell carcinoma. For those who refuse or cannot undergo resection, SBRT or other local ablative treatments (cryotherapy, HIFU) have been studied.

24.3 AJCC Staging Table

Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but ≤7 cm in greatest dimension, limited to the kidney
T2	Tumor >7 cm in greatest dimension, limited to the kidney

Primary tumor	
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumor >10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond the Gerota fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond the Gerota fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

24.4 Tumor/Patient Selection

(a) For patients who refuse or are not candidates for surgery, limited published data have shown that SBRT can be effective.

24.5 Treatment Planning Considerations

Simulation instructions	**UNC practice** – Fiducials are placed in or around the tumor at least 7 days before simulation – Patients are simulated supine immobilized in a vac-loc with 3 mm CT slices – CT should include non-contrast and contrast enhanced phases – 4D imaging should be obtained to assess tumor motion – Consider MRI for difficult to visualize tumors
Image guidance	Linac – Daily image guidance with either real-time tracking (transponders, USA) or daily 3D imaging (CT on rails, KV-CBCT) CyberKnife – Fiducial markers, need at least three for translational and rotational tracking

Tumor movement	Because renal tumors can potentially move significantly with respiration [1], real-time tracking, breath hold, and/or abdominal compression are preferred [2, 3]
Margins	– GTV=CTV – CTV + 3 mm = PTV – PTV margins may need to be larger depending on image guidance technique
Dosimetric considerations	SBRT – 100% of prescription to 95% of PTV – 95% of prescription to 100% of PTV – DMax <107% prescription (<120% for CyberKnife) – CI: <1.5

24.6 Treatment Planning Images

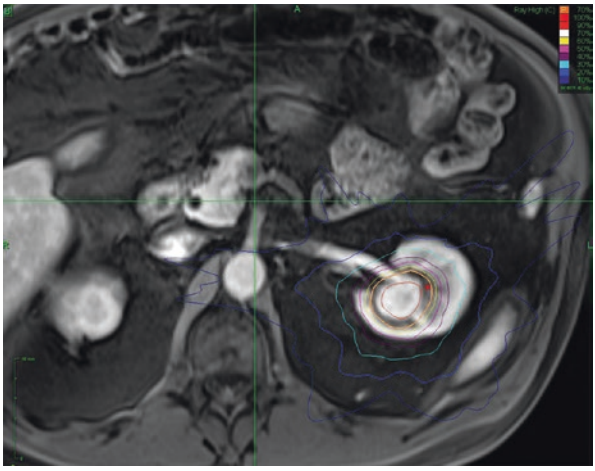

Fig. 24.1 Representative axial T2-weighted MRI of a CyberKnife SBRT plan for a primary renal cell carcinoma. Total dose delivered was 13 Gy × 3 fractions

24.7 Commonly Used Dose/Fractionation

Small series have been published using many dosing regimens. Some of these regimens are summarized below:

Dose per fraction	Fractions	Total dose	Duration
13 Gy	3	39	Every day
16 Gy	3	48 Gy	Every other day
12 Gy	4	48 Gy	Every other day
8 Gy	5	40 Gy	Every other day

24.8 Normal Tissue Tolerances

Organ	TG101 [4]	Other	Our institutional practice
Stomach			
−1 fraction	DMax: 12.4 Gy V11.2 < 10 cc		Our institution follows TG101 guidelines for all organs at risk
−3 fractions	DMax: 22.2 Gy V16.5 < 10 cc		
−4 fraction		Ponsky 2015 [5] ≤1 cc at 22 Gy	
−5 fractions	DMax: 32 Gy V18 < 10 cc		
Limiting toxicity	≥Grade 3 ulceration/ fistula		
Duodenum			
−1 fraction	DMax: 12.4 Gy V11.2 < 10 cc		
−3 fractions	DMax: 22.2 Gy V16.5 < 10 cc		
−5 fractions	DMax: 32 Gy V18 < 10 cc	Chang 2016 [6] DMax: 32 Gy V18 Gy <5 cc	
Limiting toxicity	≥Grade 3 ulceration		
Small bowel			
−1 fraction	DMax: 15.4 Gy V11.9 < 5 cc	Pham 20,147 30 cc <12.5 Gy	
−3 fractions	DMax, 25.2 Gy; V17.7 < 5 cc	Pham 2014 [7] DMax: 30 Gy Svedman 2008 [8] DMax: 21 Gy	
−4 fraction		Ponsky 2015 [5] ≤1 cc at 24 Gy Svedman 2008 [8] DMax: 28 Gy	
−5 fractions	DMax: 35 Gy V19.5 < 5 cc	Chang 2016 [6] DMax: 35 Gy V19.5 < 5 cc	
Limiting toxicity	≥Grade 3 enteritis/ obstruction		
Colon			
−1 fraction	DMax: 18.4 Gy V14.3 < 20 cc		
−3 fractions	DMax: 28.2 Gy V24 < 20 cc		
−4 fraction		Ponsky 2015 [5] ≤1 cc at 24 Gy	

Organ	TG101 [4]	Other	Our institutional practice
−5 fractions	DMax: 38 Gy V25 < 20 cc	Chang 2016 [6] DMax: 38 Gy V25Gy <20 cc	
Limiting toxicity	≥Grade 3 colitis/fistula		
Liver			
−1 fraction	700 cc <9.1 Gy	Pham 2014 [7] 700 cc ≤15 Gy	
−3 fractions	700 cc <19.2 Gy	Pham 2014 [7] 700 cc ≤15 Gy	
−4 fraction		Ponsky 2015 [5] ≤2/3 of liver <17 Gy ≥800 ccs at ≤15 Gy	
−5 fractions	700 cc <21 Gy		
Limiting toxicity	Decline in liver function		
Skin			
−1 fraction	DMax: 26 Gy V23 < 10 cc	Pham 2014 [7] DMax: 18 Gy	
−3 fractions	DMax: 33 Gy V30 < 10 cc	Pham 2014 [7] DMax: 24 Gy	
−5 fractions	DMax: 39.5 Gy V36.5 < 10 cc	Chang 2016 [6] DMax: 39.5 Gy V36.5Gy < 10 cc	
Limiting toxicity	≥Grade 3 ulceration		
Spinal cord			
−1 fraction	DMax: 14 Gy	Pham 2014 [7] DMax: 12 Gy	
−3 fractions	DMax: 21.9 Gy	Pham 2014 [7] DMax: 18 Gy	
−4 fraction		Ponsky 2015 [5] <0.3 cc at 24 Gy	
−5 fractions	DMax: 30 Gy	Chang 2016 [6] DMax: 25.3 Gy	
Limiting toxicity	Myelitis		

24.9 Patient Management Considerations

1. Premedication/prophylactic medication: Dexamethasone 4 mg is given before each fraction of SBRT.
2. Common acute and late toxicity
   (a) The most common acute side effects are fatigue, nausea, and enteritis.
   (b) Patients with baseline chronic kidney disease may experience a worsening in kidney function after treatment in 5–10% of cases [5, 9].

24.10 Follow-Up (Per NCCN Guidelines) [10]

(a) Follow-up schedule: H&P every 6 months for 2 years, then annually up to 5 years after treatment
(b) Imaging: Abdominal CT or MRI with contrast 3–6 months after treatment, then annually for 5 years. CT chest or CXR once a year for 5 years
(c) Lab tests: Comprehensive metabolic panel with every follow-up to assess kidney function and electrolyte balance

24.11 Relevant Literature

Study	Patients	Treatment	Median FU	Outcomes
Prospective series				
Svedman 2006 [11] Phase I trial	*n* = 5 Medically inoperable	8 Gy × 4 every other day 10 Gy × 4 every other day 15 Gy × 2 every other day 15 Gy × 3 every other day	52 months	Crude LC 80% Estimated 2-year LC: 91%
Kaplan 2009, McBride 2013 (abstracts only) [12, 13] Phase I trial	*n* = 15 Medically inoperable Stage IA/B Median age 75 Biopsy not mandatory Lesion ≤5 cm (mean 3.4 cm) KPS ≥70 60% with baselines CKD	Dose-escalation study 7 Gy × 3 every other day 9 Gy × 3 every other day 11 Gy × 3 every other day 13 Gy × 3 every other day 16 Gy × 3 every other day	37 months	Crude LC: 87% (both failures in low-dose arms 7–9 ×3, both failures at 31 months) No dose-limiting toxicity 1 pt with worsening CKD stage[a]
Ponsky 2015 [5] Phase I trial	*n* = 19 Medically inoperable KPS ≥60 Median age 78 Median tumor volume 58 cc	Dose-escalation study 6 Gy × 4 every other day 8 Gy × 4 every other day 10 Gy × 4 every other day 12 Gy × 4 every other day	14 months	6-month crude local control 95% No dose-limiting toxicity 1 pt with grade 4 duodenal ulcer 3 pts with worsening CKD stage[a]

Study	Patients	Treatment	Median FU	Outcomes
Siva 2017 [9] Phase I trial	*n* = 37 Median PTV – Fractionated (*n* = 17): 172 cc – Single fraction (*n* = 17): 77.2 cc Median age 78	14 Gy × 3 (≥5 cm) every other day 26 Gy × 1 (<5 cm)	24 months	100% freedom from local progression at 2 years Mean decrease in GFR at 1 year of 11 mL/min 3% grade 3 toxicity (fatigue) No ≥grade 4 toxicity
Retrospective series				
Qian 2003 [14]	*n* = 27 Mean age 62 Mean tumor volume 367 cc	8 Gy × 5	12 months	Crude control rate 93%
Beitler 2004 [15]	*n* = 9 Median tumor volume 97 cc	8 Gy × 5 every other day	27 months	Crude local control 100%
Wersall 2005 [16]	*n* = 8 Medically inoperable KPS ≥60	8 Gy × 5 (>4 cm) every other day 10 Gy × 3 (≤4 cm) every other day	37 months	Crude local control 100%
Gilson 2006 [17]	*n* = 14 Mean 62 years Mean tumor volume 356 cc	40–50 Gy/5 fxs	17 months	Crude local control 88%
Teh 2007 [18]	*n* = 2 Medically inoperable	24–48 Gy/3–6 fxs	9 months	Crude local control 100% Pain improved in both patients No change in kidney function
Nomiya 2008 [19]	*n* = 10 Carbon-ion therapy Median diameter 43 mm	Median 4.5 Gy × 16 every day	58 months	5-year local control 100% 5-year progression-free survival 100% 1 pt with late grade 4 skin toxicity No change in kidney function in patients with normal baseline function
Svedman 2008 [8]	*n* = 7 Only patients with one kidney Mean age 64	10 Gy × 3 every other day 10 Gy × 4 every other day	49 months	Crude local control 86% No change in kidney function

Study	Patients	Treatment	Median FU	Outcomes
Chang 2016 [6]	$n = 16$ Medically inoperable Median age 73 Median diameter 40 mm	8 Gy × 5 every other day 7 Gy × 5 every other day 6.5 Gy × 5 every other day 6 Gy × 5 every other day	19 months	Crude local control 100% 1 pt with change in CKD stage
Kaidar-Person 2017 [1]	$n = 6$ Tumors ≥4 cm	13 Gy × 3 every day	29.5 months	No clinical evidence of disease progression 2 patients with acute grade 1 nausea 1 patient with acute grade 2 colitis No worsening of renal function No late toxicity

[a]CKD Stages: Stage 1 GFR > 90 mL/min; Stage 2 GFR = 60–89 mL/min; Stage 3 GFR = 30–59 mL/min; Stage 4 GFR = 15–29 mL/min; Stage 5 GFR <15 mL/min

24.12 Summary

SBRT for renal tumors is an emerging treatment option, but to date clinical experience is limited to small series with relatively short follow-up. Published series have used many different dosing regimens. Initial local control and tolerability results are promising, but longer-term follow-up and larger studies are needed.

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Part IX
Spine Tumors and Non-Spine Bone Metastases

Chapter 25
Spine Tumors and Non-Spine Bone Metastases

Simon S. Lo, Yolanda Tseng, Lia M. Halasz, and Edward Y. Kim

25.1 Spine

Spine tumor is a broad term including primary and metastatic tumors. Only a minority of spine tumors are primary tumors. They include the vertebral column (bone) tumors, intradural-extramedullary tumors, and intramedullary tumors.

For most primary spine tumors, the mainstay of treatment is maximal safe resection followed by conventional radiotherapy (RT). For intramedullary tumors, hypofractionated RT is seldom used as the target volume is located within the spinal cord, rendering delivery of a tumoricidal dose to the tumor more difficult without resulting in a higher risk for radiation myelopathy (RM), which is the most feared complication in spine RT. For intradural-extramedullary and vertebral column primary tumors, there are scarce data on the use of hypofractionated RT, most in the form of stereotactic body radiotherapy (SBRT).

Examples of primary spine tumors

Location	Examples of primary tumors
Vertebral column	Osteogenic sarcoma (malignant) Hemangioma (benign) Giant cell tumors (benign in most cases) Chordoma (malignant) Chondrosarcoma (malignant)
Intradural-extramedullary	Meningioma (benign) Nerve sheath tumors including schwannomas and neurofibromas (benign) Ependymoma
Intramedullary	Astrocytoma Ependymoma

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The spine or vertebra is a common site of involvement in patients with bone metastases. Left untreated, progressive spinal metastases can lead to severe pain, hypercalcemia, pathologic fracture, and spinal cord compression. The standard treatment, depending upon patient and disease factors, is RT with or without surgical intervention. Factors determining the need for consideration for surgery include the Bilsky grade for metastatic epidural spinal cord compression (MESCC), neurologic status, and spinal instability neoplastic score (SINS).The traditional RT utilizes conventional fractionation, but the amount of radiation that can be delivered is limited by the spinal cord tolerance. With the sophistication of radiation technology, stereotactic body radiotherapy (SBRT) has emerged as a means to deliver higher biologically effective doses to the metastatic tumor and one of the standard treatments for spine bone metastases in the setting of newly diagnosed disease, recurrent or progressive disease after prior RT, postoperative situation, and MESCC (rare).

This chapter will focus on the use of SBRT for intradural-extramedullary and vertebral column primary tumors and vertebral (spine bone) metastatic tumors. Hypofractionated RT delivering low doses of radiation has been standard of care for spine bone metastatic tumors, and interested readers should seek details from references, including the American College of Radiology Appropriateness Criteria [1] and American Society for Radiation Oncology (ASTRO) guideline documents [2], at the end of this chapter.

25.1.1 Pearls: Primary Spine Tumors

- Benign tumors of the spine represent a wide variety of histologies that occur within the intradural space, and epidural, paraspinal, and vertebral body locations.
- Common benign tumors include meningiomas, schwannomas, and neurofibromas.
- Malignant tumors include malignant nerve sheath tumors, osteogenic sarcomas, chondrosarcomas, and chordomas.
- Symptoms include back pain, extremity weakness, and loss of bladder or bowel function.
- Pathology workup:
  - Biopsy to confirm pathologic diagnosis when a radiographic diagnosis cannot be confidently made.
  - Tissue can be obtained when surgery is done for tumor resection or debulking.
- Medical workup:

  - H&P, focusing on assessment of pain symptoms and neurologic function. Physical exam requires thorough neurological examination to detect any motor and sensory deficits in the upper and lower extremities or any sensory level in the torso.
  - Basic lab work (CBC, metabolic panel, and liver function tests).

- Imaging workup: Crucial to determine extent of tumor invasion, pathologic fracture, and tumor compression of spinal cord, cauda equina, and nerve roots.

  - MRI of the spine w/wo contrast

MRI: Sagittal T1 and STIR to evaluate marrow replacement, axial T2 to evaluate epidural disease, volumetric T1 with gadolinium, and T2 for treatment planning.

- Treatment strategies:

  - Surgical resection is the mainstay of treatment for primary spine tumors.
  - Observation can be offered in patients with benign primary spine tumors if a gross total resection is achieved.
  - Observation or postoperative conventional RT or SBRT can be offered to patient with subtotally resected benign primary spine tumors (excluding intramedullary tumors).
  - Postoperative RT ± systemic therapy is offered to patients with malignant primary spine tumors regardless of extent of resection. Postoperative SBRT is offered in rare situations.

25.1.2 Pearls: Spinal Metastasis

- Spinal metastases are diagnosed in approximately 40% of cancer patients during their disease course and are the most common spinal tumors.
- In postmortem studies, up to 90% of cancer patients may have microscopic spinal metastases.
- Most common presenting symptom is back pain. Other symptoms can include upper or lower extremity weakness or numbness, sensory level in the torso, and loss of bladder or bowel control.
- Local anatomy:

  - Based on the International Spine Radiosurgery Consortium anatomic classification system, each vertebra is divided into six sectors: Sector 1, vertebral body; Sector 2, left pedicle; Sector 3, left transverse process and lamina; Sector 4, spinous process; Sector 5, right transverse process and lamina; and Sector 6, right pedicle [3] (Fig. 25.1).

- Progressive metastatic spine tumors can lead to spinal cord or nerve compression.
- Medical workup:

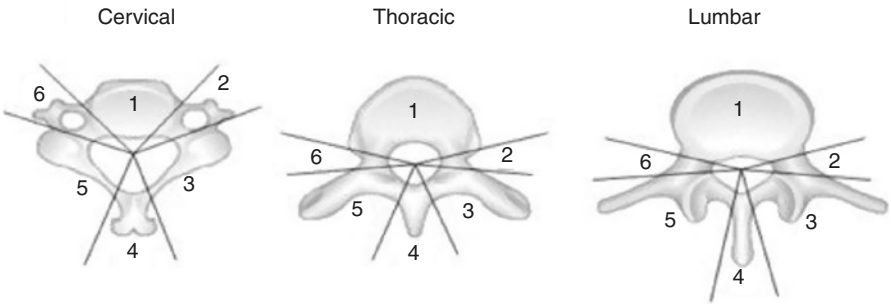


Fig. 25.1 International Spine Radiosurgery Consortium anatomic classification system for consensus target volumes for spine radiosurgery. Reprinted from Int J Radiation Oncol Biol Phys, Vol. 83, No. 5, Cox et al., International Spine Radiosurgery Consortium Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiosurgery, pp. e597ee605, Copyright (2012), with permission from Elsevier [3]

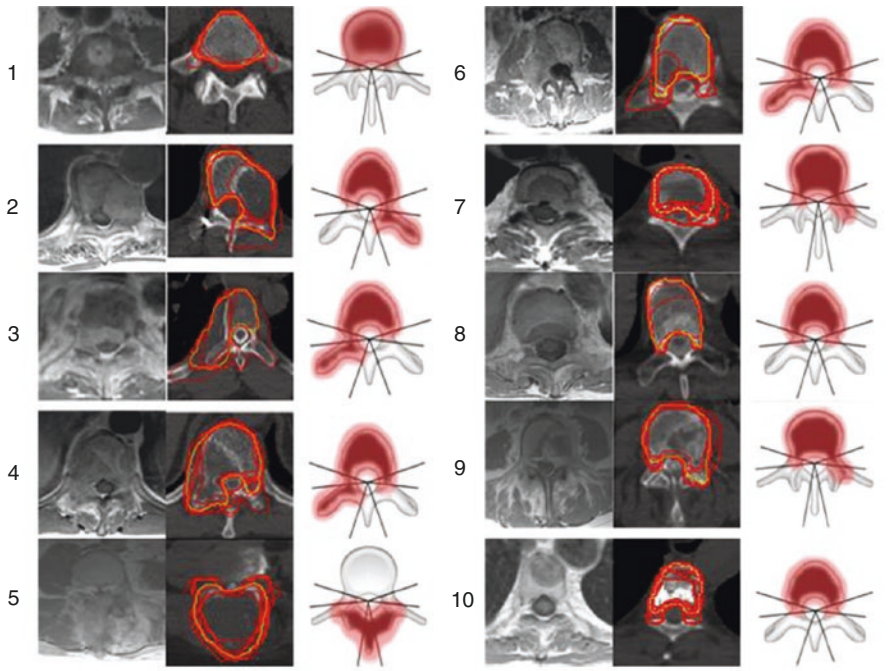


Fig. 25.2 Consensus clinical target volume contours for spine stereotactic radiosurgery. Red indicates individual contours, and orange indicates consensus contours. Reprinted from Int J Radiation Oncol Biol Phys, Vol. 83, No. 5, Cox et al., International Spine Radiosurgery Consortium Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiosurgery, pp. e597ee605, Copyright (2012), with permission from Elsevier [3]

- H&P, focusing on assessment of pain symptoms and neurologic function. Physical exam requires thorough neurological examination to detect any motor and sensory deficits in the upper and lower extremities or any sensory level in the torso.
- Basic lab work (CBC, metabolic panel, and liver function tests).

- Imaging workup: Crucial to determine extent of tumor invasion, bone retropulsion, and tumor compression of spinal cord, cauda equina, and nerve roots.
  - MRI of the spine w/wo contrast and/ or CT myelogram.

    MRI: Sagittal T1 and STIR to evaluate marrow replacement, axial T2 to evaluate epidural disease, volumetric T1 and T2 for treatment planning, and gadolinium enhanced MRI to evaluate leptomeningeal disease.

    CT myelogram: To evaluate epidural disease, especially in postoperative patients with metallic hardware.
- Pathology workup:
  - Biopsy to confirm metastatic disease if no prior pathologic diagnosis.
  - Tissue can be obtained when surgical decompression for spinal cord compression is performed.
  - Radioresistant histologies including renal cell carcinoma, melanoma, and sarcoma, and there may be a benefit utilizing SBRT to improve local control.
- Treatment strategies:
- Conventional RT or SBRT for uncomplicated spinal metastases, surgery + conventional RT or SBRT for patients with bony retropulsion, high-grade MESCC, or mechanical instability.

25.1.3 Staging

For spine bone metastases, there are two commonly used systems that objectively evaluate patients with regard to the extent of MESCC (Bilsky grade) and spinal stability (spinal instability neoplastic score). These tools are being used to evaluate the need for surgical intervention and the suitability for SBRT for spinal metastases.

Bilsky grading system for epidural disease [4]

Bilsky grade	Details
0	Absence of epidural disease
1a	Impingement but no deformation of thecal sac
1b	Impingement and deformation of thecal sac
1c	Deformation of thecal sac and abutment of spinal cord
2	Epidural spinal cord compression with visible cerebrospinal fluid (CSF)
3	Epidural spinal cord compression with visible CSF

The *Spinal Instability Neoplastic Score (SINS)* was developed by the Spine Oncology Study Group and was validated in terms of interobserver and intraobserver reliability among spine oncologic surgeons and radiation oncologists [5].

There are six parameters in the system:

1. Location: three points for occiput-C2, C7-T2, T11-L1, L5-S1; 2 points for C3-C6, L2-L4; 1 point for T3-T10; 0 for S2-S5.
2. Pain: 3 points for pain relief with recumbency and/or pain with movement/loading of the spine; 1 point for occasional nonmechanical pain; 0 points for absence of pain.
3. Bone lesion characteristic: 2 points for lytic lesion; 1 point for mixed lytic/blastic; 0 points for blastic.
4. Radiographic spinal alignment: 4 points for subluxation/ translation; 2 points for de novo deformity (kyphosis/scoliosis);0 points for normal alignment.
5. Vertebral body collapse: 3 points for greater than 50% collapse; 2 points for less than 50% collapse; 1 point for no collapse but with greater than 50% body involved; 0 points for absence of the above.
6. Posterolateral involvement of the spinal elements (facet, pedicle, or costovertebral joint fracture or replacement withtumor): 3 points for bilateral; 1 point for unilateral; 0 points for neither.

Patients with 0–6 points, 7–12 points, and 13–18 points are designated to have stable, potentially unstable, and unstable spine, respectively. In a patient with an unstable spine, surgical stabilization should be considered before SBRT.

25.1.4 Patient Selection

1. For primary spine tumors:
   (a) Benign spine tumors—Postoperative radiographically residual tumors or medically inoperable spine tumors, ideally at least 1–2 mm from the spinal cord.
   (b) Malignant spine tumors—The standard postoperative treatment is conventional RT or proton therapy. If SBRT is offered in postoperative or medically inoperable setting, there should be ideally at least 1–2 mm from the CTV to the spinal cord.
   (c) Reirradiation—Ideally, the last course of RT should be at least 5–6 months; there should be ideally at least 1–2 mm from the CTV to the spinal cord (can be achieved by reoperation upon recurrence).
2. For spinal metastases:
   (a) The American Society of Radiation Oncology (ASTRO) (see table below) and American College of Radiology guidelines have detailed appropriate inclusion and exclusion criteria for spine SBRT [1, 2].

(b) In broad terms, the inclusion criteria include spinal or paraspinal metastatic non-radiosensitive solid tumor histology in three or less contiguous segments, a reasonably stable spinal column, low-grade epidural disease based on Bilsky grading system, a life expectancy of 3 months or longer, and relatively limited extraspinal systemic disease.

Suggested inclusion and exclusion criteria for patients enrolled in trials to evaluate stereotactic body radiotherapy for spinal bone metastases from ASTRO guidelines [2].

Characteristic	Inclusion	Exclusion
Radiographic	(1) spinal or paraspinal metastasis by MRI (2) no more than two consecutive or three noncontiguous spine segments involved	(1) Spinal MRI cannot be completed for any reason (2) Epidural compression of spinal cord or cauda equina (3) Spinal canal compromise >25% (4) Unstable spine requiring surgical stabilization (5) Tumor location within 5 mm of spinal cord or cauda equina (relative[a])
Patient	(1) Age ≥ 18 years (2) KPS of ≥40–50 (3) Medically inoperable (or patient refused surgery)	(1) Active connective tissue disease (2) Worsening or progressive neurologic deficit (3) Inability to lie flat on table for SBRT (4) Patient in hospice or with <3-month life expectancy
Tumor	(1) Histologic proof of malignancy (2) Biopsy of spine lesion if first suspected metastasis (3) Oligometastatic or bone only metastatic disease	(1) Radiosensitive histology such as MM (2) Extraspinal disease not eligible for further treatment
Previous treatment	Any of the following (1) Previous EBRT <45-Gy total dose (2) Failure of previous surgery to that spinal level (3) Presence of gross residual disease after surgery	(1) Previous SBRT to same level (2) Systemic radionuclide delivery within 30 days before SBRT (3) EBRT within 90 days before SBRT (4) Chemotherapy within 30 days of SBRT

Abbreviations: *MRI* magnetic resonance imaging, *KPS* Karnofsky performance status, *SBRT* stereotactic body radiotherapy, *MM* multiple myeloma, *EBRT* external beam radiotherapy

Reprinted from Int J Radiation Oncol Biol Phys, Vol. 79, No. 4, Lutz et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline, pp. 965–76, Copyright (2011), with permission from Elsevier [2]

[a]Relative indicates that optimally tumor >5 mm from spinal cord; if this distance is closer, case-by-case discussion required because published data suggest risk of failure is greater

25.1.5 Treatment Planning

Simulation instructions	SBRT – Immobilization using a long head and neck thermoplastic mask for lesions above T4 – Immobilization using a dual vacuum system (Body FIX) for LINAC-based system or a vacuum cushion for CyberKnife system for lesions T4 or below – Arms must be down for CyberKnife to avoid possible collision of robotically mounted LINAC with the arms – Repeat diagnostic volumetric MRI T1 w/wo contrast and T2 ± CT myelogram (if metallic hardware hinders visualization of the spinal cord) – Planning CT performed without IV contrast, if possible, 1.0–1.25 mm slices – Fuse the treatment planning CT to the new MRI and preoperative MRI (for postoperative cases) ± CT myelogram at the index spinal segments for target delineation Reirradiation – Same as radiation naïve cases
Target delineation	– Primary benign spinal tumors—Contrast-enhanced tumor defined as GTV = CTV – Primary malignant spinal tumors—Tumor bed + contrast-enhanced tumor defined as GTV = CTV – Spinal metastases—CTV is defined as the whole vertebral body ± pedicles ± posterior elements except for metastases located mainly in the posterior elements; need to include all epidural and paraspinal involvement; for postoperative case, need to take into account the preoperative extent of involvement; interested readers are advised to go to the consensus guidelines for contouring by Cox et al. (Fig 25.2) and Redmond et al. (Fig. 25.3) published in IJROBP
Image guidance	– Cyberknife: Spine tracking – Linac: Daily pretreatment, post-shift, and midway CBCT
Margins	PTV = CTV + 2.0–3.0 mm minus PRV cord PRV cord = spinal cord +1.5–3.0 mm (typically 2.0 mm) (Thecal sac can also be used as PRV cord)
Dosimetric considerations	Dose prescribed to PTV. Goal = ≥90% of PTV and ≥80% of CTV covered by the prescribed IDL (typically 75–85%)

Treatment planning with linear accelerator

- 4–8 MV photons
- Utilize 7–9 static, coplanar beams (IMRT) or 2–4 rotational arcs (VMAT)
- Beams shaped using multi-leaf collimators

Treatment planning with CyberKnife

- Composed of hundreds of pencil beams.
- For thoracic spine tumors, use Monte Carlo instead of ray tracing for treatment planning as Okoye et al. discovered that when ray tracing was used for thoracic spine lesions, the coverage of the PTV would be overestimated, and the doses to the critical structures such as the spinal cord might be underestimated significantly [7].
- Beams shaped using collimators of various sizes dosimetry
- Prescription dose typically prescribed to 75–85% IDL.
- Limits dose outside of the PTV to ≥105% of the prescription dose to a volume of less than or equal to 2.0 cc and dose of ≥105% of the prescription dose to a region within 1.0 cm from the edge of the PTV.

25.1.6 Common Dose/Fractionation Schemes

Primary Spine Tumors

Dose/Fx	Number of fx	Total dose	Notes
Benign: 12–18 Gy Malignant: 16–24 Gy	1	Benign: 12–18 Gy Malignant: 16–24 Gy	Dose schemes for benign spine tumors are based on literature on meningiomas, schwannomas, and neurofibromas, whereas those for malignant spine tumors are based on literature on chordomas
Benign: 6–8 Gy Malignant: 8–12 Gy	3	Benign: 18–24 Gy Malignant: 24–36 Gy	Dose schemes for benign spine tumors are based on literature on meningiomas, schwannomas, and neurofibromas, whereas those for malignant spine tumors are based on literature on chordomas
Benign: 5–6 Gy Malignant: 6–8 Gy	5	Benign: 25–30 Gy Malignant: 30–40 Gy	Dose schemes for benign spine tumors are based on literature on meningiomas, schwannomas, and neurofibromas, whereas those for malignant spine tumors are based on literature on chordomas

Spinal Metastases (Figs. 25.4, 25.5, and 25.6)

Dose/Fx	Number of fx	Total dose	Notes
16–24 Gy	1	16–24 Gy	Based on data from high volume institutions [8, 9]
10–12 Gy	2	20–24 Gy	Based on data from high volume institutions [8, 9]
9 Gy	3	27 Gy	Based on data from high volume institutions [8, 9]
6 Gy	5	30 Gy	Based on data from high volume institutions [8, 9]

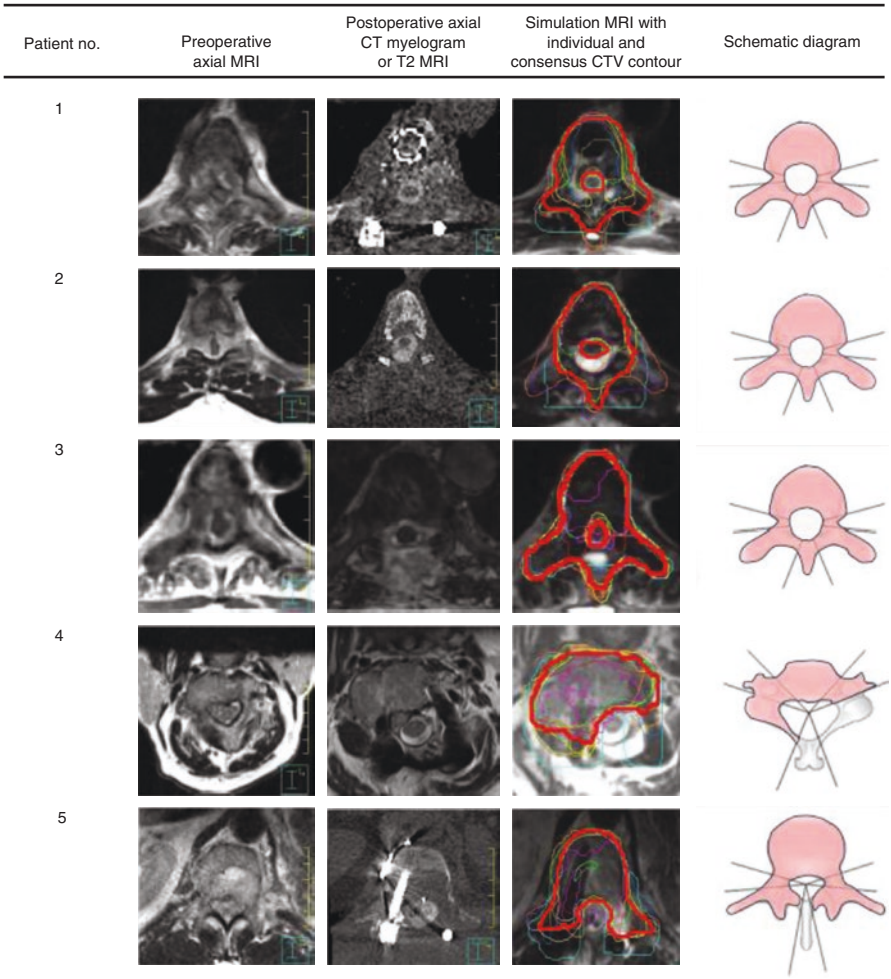
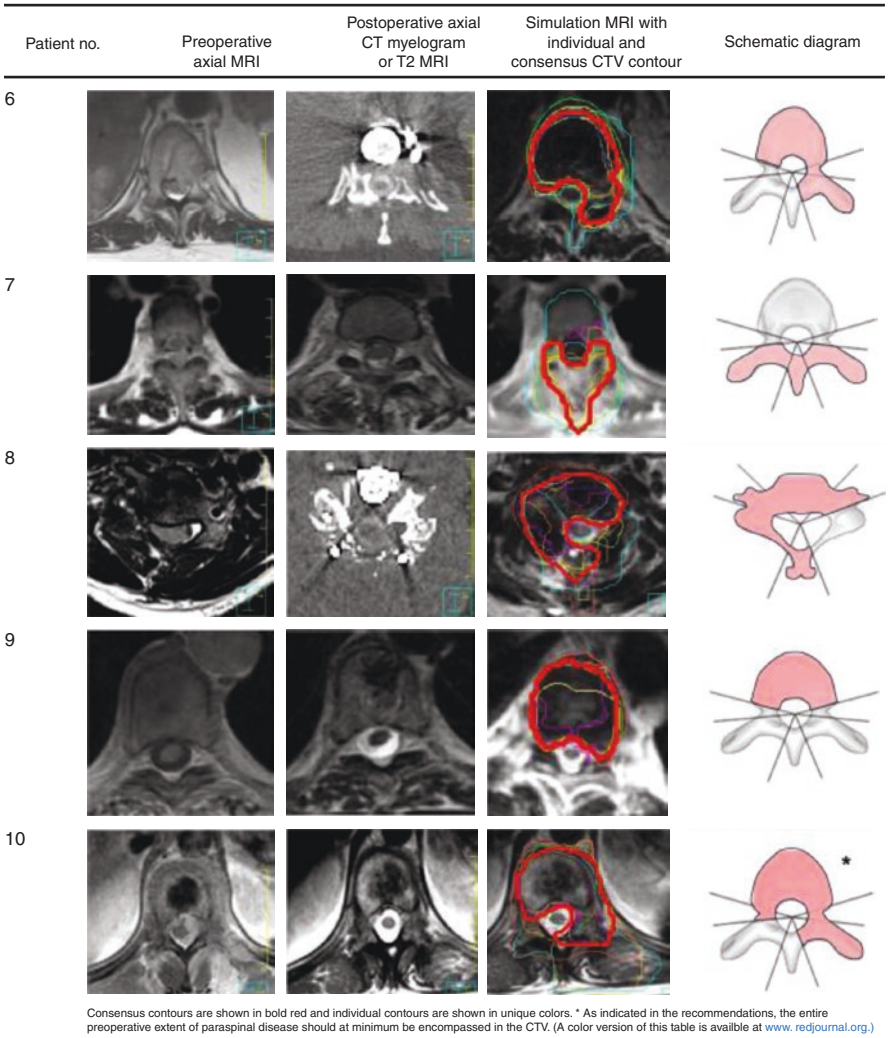


Fig. 25.3 Consensus CTV contours for postoperative SBRT for spine metastases. Reprinted from Int J Radiation Oncol Biol Phys, Vol. 97, No. 1, Redmond et al., Consensus Contouring Guidelines for Postoperative Stereotactic Body Radiation Therapy for Metastatic Solid Tumor Malignancies to the Spine, pp. 64–77, Copyright (2017), with permission from Elsevier [6]



Consensus contours are shown in bold red and individual contours are shown in unique colors. * As indicated in the recommendations, the entire preoperative extent of paraspinal disease should at minimum be encompassed in the CTV. (A color version of this table is availble at www. redjournal.org.)

Fig. 25.3 (continued)

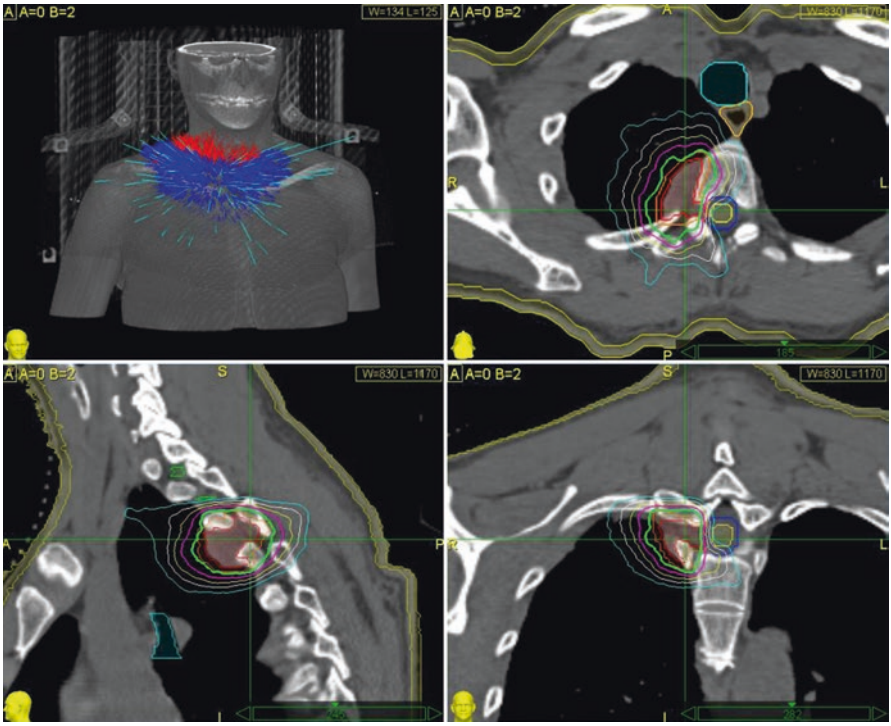


Fig. 25.4 A patient with a right T3 schwannoma treated with SBRT to a dose of 21 Gy in 3 fractions prescribed to the 80% isodose line (green)

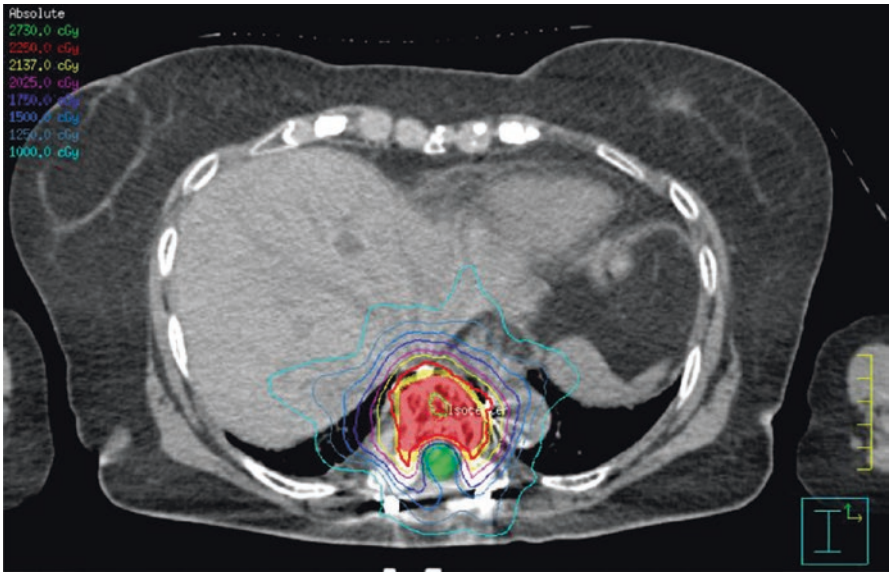


Fig. 25.5 A patient with a T9 hemangioma treated with SBRT to a dose of 22.5 Gy in 3 fractions after surgical decompression of spinal cord compression. The residual tumor regressed, and there was no evidence of recurrence 4 years after treatment

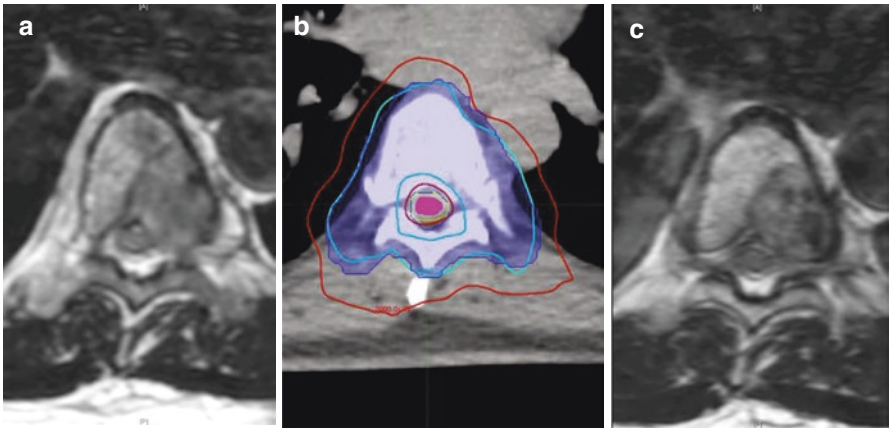


Fig. 25.6 A 61-year-old gentleman with metastatic thyroid cancer to T7 with Bilsky grade 2 metastatic spinal cord compression (left panel); he received SBRT delivering 27 Gy in 3 fractions (cyan) with PRV cord limited to 20.3 Gy (based on Sahgal et al. data) (middle panel); MRI after 3 months showed regression of epidural disease (Bilsky grade 1a disease)

25.1.7 Normal Tissue Tolerances

Organs at risk (OARs)	Dmax	Volumetric	Notes
Brachial plexus			
– 1 fx	17.5 Gy 14 Gy	Maximum point <3 cc	RTOG 0631
– 3 fx	24 Gy 20.4 Gy	Maximum point <3 cc	RTOG 1021
– 5 fx	32 Gy 30 Gy	Maximum point <3 cc	RTOG 0813
– DLT	Brachial plexopathy		
Cauda equina			
– 1 fx	16 Gy 14 Gy	Maximum point <3 cc	RTOG 0631
– 3 fx	24 Gy 20.4 Gy	Maximum point <3 cc	Extrapolation from brachial plexus constraints (based on RTOG 1021)
– 5 fx	32 Gy 30 Gy	Maximum point <3 cc	Extrapolation from brachial plexus constraints (based on RTOG 0813)
– DLT	Neuropathy		
Spinal cord (no prior RT)[a]			

Continued

Organs at risk (OARs)	Dmax	Volumetric	Notes
– 1 fx	12.2 Gy	Point max	Based on study by Sahgal et al. [10]
– 3 fx	20.3 Gy	Point max	Based on study by Sahgal et al. [10]
– 5 fx	25.3 Gy	Point max	Based on study by Sahgal et al. [10]
– DLT	Radiation myelopathy		
Esophagus			
– 1 fx	16 Gy 11.9 Gy	Maximum point <5 cc	RTOG 0631
– 3 fx	25.2 Gy 17.7 Gy	Maximum point <5 cc	RTOG 1021
– 5 fx	105% of PTV prescription 27.5 Gy	Maximum point <5 cc	RTOG 0813
– DLT	Esophageal injury		

[a]The spinal cord constraints from the study Sahgal et al. were based on real patient data. RTOG constraints for spinal cord for three and five fractions should not be applied to spine SBRT as those constraints were for non-spine SBRT trials where the spinal canal was used as the surrogate for spinal cord

Prior conventional RT	One fraction: SBRT dose to PRV cord or thecal sac (maximum point dose)	Three fraction: SBRT dose to PRV cord or thecal sac (maximum point dose)	Five fraction: SBRT dose to PRV cord or thecal sac (maximum point dose)
20 Gy/5 fractions, 30 Gy/10 fractions, or 37.5 Gy/15 fractions	9 Gy	14.5 Gy	18 Gy
40 Gy/20 fractions or 45 Gy/25 fractions	No information	14.5 Gy	18 Gy
50 Gy/25 fractions	No information	12.5 Gy	15.5 Gy

Recommended dose constraints for reirradiation with SBRT from Sahgal et al. Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. 107–116, 2012 [11]. SBRT must be at least 5 months after prior conventional RT with a reirradiation PRV cord or thecal sac nBED of 20–25 $Gy_{2/2}$ or less

25.1.8 Patient Management

1. Premedicate patient with antiemetic medication if the CTV is close to the stomach (e.g., ondansetron 4 mg PO × 1 30 min before treatment).
2. For patients with severe back pain, premedicate with narcotic medication.
3. Consider premedicating with Medrol Dosepak or dexamethasone 4 mg during and up to 4 days after completion of SBRT (or slower taper) for prophylaxis against pain flare.

4. Toxicity
   (a) Acute:
      - Skin/esophagus (dermatitis, odynophagia)
        – Emollients (aquaphor, calendula). Remove 4 h prior to SBRT.
        – Oral solutions (first BLM, magic mouthwash). Use TID prior to meals.
        – Pain medication (fentanyl patch 25–100 mcg q72 hrs, oxycodone 5–20 mg q-–6 hrs).
      - Nausea/vomiting
        – Start with Zofran 4 mg q8hrs. Can increase to 8 mg q8hrs.
        – Phenergan 12.5 mg q4–6 hrs. Can increase to 25 mg q4–6 hrs.
        – Compazine 5 mg q6hrs. Can increase to 10 mg q6hrs.
      - Pain flare
        – Medrol Dosepak or dexamethasone 4 mg (up to 4 days after SBRT or slower taper)

   (b) Subacute/late:
      - Skin/soft tissue (discoloration, fibrosis)
      - Vertebral compression fracture (fraction size-dependent, higher risk if ≥20 Gy/fraction, peak incidence 2–3 months after SBRT)
        – Pain medication.
        – Refer to spine surgeon.
      - Radiation myelopathy (permanent, very rare <1%)
      - Radiation plexopathy (rare)
      - Esophageal stricture/stenosis (rare)

5. Recommend follow-up 1-month posttreatment completion to assess acute toxicity.
6. Systemic therapy
   (a) There is minimal data addressing the use of concurrent chemotherapy/systemic therapy with spine SBRT. One study from Cleveland Clinic Foundation showed that addition of concurrent tyrosine-kinase inhibitor to SBRT for spine metastases appeared to be safe and improve local control [12].
   (b) Interested readers are encourage to refer to the systemic review of concurrent targeted/immune therapy with SBRT by Kroeze et al. [13]

25.1.9 Follow-Up (Please Refer to SPINO Published in Lancet Oncology [14])

- H&P, neurologic examination every 2–3 months for the first 2 years, q6 months for years 3–5, and then annually.
- Spine MRI every 2–3 months after SBRT for the first 1–2 years and every 3–6 months thereafter.

25.1.10 Relevant Literature

- There are a range of dose regimens used for SBRT for primary spine tumors and radiation naïve; previously irradiated and postoperative spine metastases and promising results have been demonstrated.

SBRT for Primary Spinal Tumors

Series	Study type/tumor type	No. of patients/ tumors	Prescribed dose	Follow-up	Local control (%)
Gerszten et al. [15]	Retrospective/ benign spine tumors	Meningiomas: 8/8 Schwannomas: 15/15 Neurofibromas: 7/7	18–21 Gy/3 fxs	26 months	100%
Gerszten et al. [16]	Retrospective/ benign spine tumors	Meningiomas: 13/13 Schwannomas: 35/35 Neurofibromas: 25/25	17.31 Gy/1 fx	37 months	100%
Yamada et al. [17]	Retrospective/ chordoma of spine and sacrum	21 primary and 3 metastatic	24 Gy/1 fx	24 months	95%
Lockney et al. [18]	Retrospective/ chordoma of mobile spine	12/12	24 Gy/1 fx, 24–36 Gy/3 fxs	Postoperative: 65.9 months Salvage: 10.7 months	Postoperative: 80% Salvage: 57.1%

SBRT for Spinal Metastases

Series	Study type/ patient population/ tumor type	No. of patients/ tumors	Prescribed dose	Follow-up	Local control (%)	Pain control (%)
Wang et al. [19]	Prospective/ mixed/spinal metastases	149 (79 with prior RT ± surgery)/166	27–30 Gy/3 fxs	15.9 months	1 year: 80.5% 2 years: 72.4%	BPI: 26% (baseline) to 54% (6 months)
Garg et al. [20]	Prospective/ RT naïve/ spinal metastases	61(16 had prior surgery)/63	16–24 Gy/1 fx	20 months (mean)	18 months: 88%	18 patients pain-free at 3 and 6 months compared to 13 at baseline
Yamada et al. [21]	Retrospective/ RT naïve/ spinal metastases	93/103	18–24 Gy/1 fx	15 months	15 months: 90%	N/A

Series	Study type/ patient population/ tumor type	No. of patients/ tumors	Prescribed dose	Follow-up	Local control (%)	Pain control (%)
Guckenberger et al. [22]	Retrospective/ mixed/spinal metastases	301/387	24 Gy (10–60 Gy)/3 fxs (1–20)	11.8 months	1 year: 89.9% 2 years: 83.9%	N/A
Sahgal et al. [23]	Retrospective/ RT naïve/ spinal metastases	14/23	24 Gy (7–40 Gy)/ 3 fxs [1–5]	9 months	1 year: 85% 2 years: 69%	N/A
Gerszten et al. [24]	Retrospective/ postoperative	26/26	18 Gy (16–20 Gy)/1 fx	16 months	N/A	92%
Laufer et al. [25]	Retrospective/ postoperative/ spinal metastases	186/186	24 Gy/1 fx, or 24–30 Gy/3 fxs, Or 18–36 Gy/5–6 fxs	7.6 months	1 year: 83.6%	N/A
Al-Omair et al. [26]	Retrospective/ postoperative/ spinal metastases	80/80	24 Gy (18–40 Gy)/2 fxs [1–5]	8.3 months	1 year: 84%	N/A
Bate et al. [27]	Retrospective/ postoperative/ spinal metastases	21/ 21	16–22 Gy/1 fx, or 20–30 Gy/2–5 fxs	13.7 months	1 year: 90.5%	N/A

25.1.11 Summary

There is wide variation in these studies with regard to dose, fraction size, and prescribed IDL. Overall, the results were promising with very low incidence of radiation myelopathy for both primary spine tumors and spinal metastases.

25.2 Non-spine Bone

Bone metastases are a common occurrence in patients with cancer, and when they progress, they can cause severe pain and pathologic fracture. Conventional radiotherapy using hypofractionated regimens with or without prophylactic fixation is the standard treatment. In patients with bone oligometastases or progressive bone metastases after prior conventional radiotherapy, SBRT may be considered. However, the data on SBRT for limited non-spine bone metastases are scarce overall and cannot be regarded as the standard of care. For guidelines regarding conventional radiotherapy for bone

metastases, readers are strongly encouraged to refer to the ASTRO bone metastasis guideline and guideline update and the ACR Appropriateness Criteria documents for non-spine bone metastasis [28, 29]. This chapter will focus on SBRT for non-spine bone metastases.

25.2.1 Pearls

- A substantial proportion of cancer patients will develop bone metastases.
- Bone metastases can cause severe pain and pathologic fracture. The treatment options for painful uncomplicated bone metastases include analgesics, bisphosphonates, surgical intervention, and radiotherapy.
- Patients with metastases in weight-bearing bone with significant cortical erosion are at higher risk for pathologic fractures and should be evaluated by an orthopedic surgeon for the consideration for prophylactic fixation.
- Medical workup:
  - H&P, physical exam requires assessment of painful sites and associated soft tissue mass.
  - Basic lab work (CBC, metabolic panel, liver function tests).
- Imaging workup:
  - Plain X-rays and CT w/w/o contrast for evaluation of soft tissue mass.
  - MRI if CT cannot show the lesion well.
  - Additionally may consider PET/CT.

    PET/CT: For determination of the extent of disease systemically and in the involved bone.
- Treatment strategies: Radiation therapy alone ± prophylactic fixation (please refer to ASTRO and ACR documents). SBRT may be considered in limited non-spine bone metastases or reirradiation.

25.2.2 AJCC Staging (AJCC 7th ed., 2010)

- All patients with bone metastases are designated as having M1 and stage IV disease.

25.2.3 Patient Selection for Hypofractionation Treatment

- Oligometastatic disease in the bone
- Progressive bone metastases after prior conventional radiotherapy to the same site

25.2.4 Treatment Planning (Fig. 25.7)

Simulation instructions	– Supine, immobilized with body cradle; arms must be down for CyberKnife to avoid possible collision of robotically mounted LINAC with the arms – Planning CT performed without IV contrast, if possible, 1.0–1.25 mm slices – Fuse diagnostic MRI T1 with and without contrast and/or PET with treatment planning CT – IMRT or VMAT planning for LINAC-based SBRT – CyberKnife SBRT—Multiplan
Target delineation and margins	– GTV—Contrast enhanced tumor on T1 with gadolinium ± PET uptake – CTV—GTV + 0–5 mm – PTV—CTV + 2–3 mm
Image guidance	– Daily CBCT or stereoscopic X-rays recommended
Dosimetric considerations	– Goals—95% of PTV covered by the prescribed IDL (typically 75–85%)

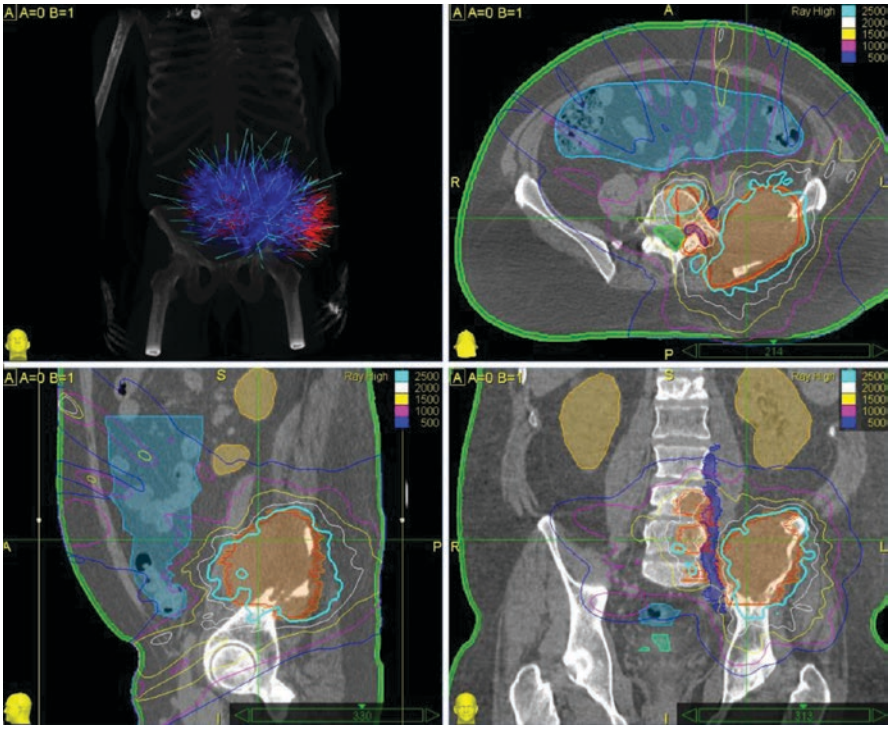


Fig. 25.7 A 42-year-old male with malignant fibrous histiocytoma, status post external beam radiotherapy to the left ilium (37.5 Gy/15 fractions). He developed progressive disease in the left iliac metastasis. A course of SBRT delivering 25 Gy in five fractions was given to the left iliac metastasis. The pain score decreased from 10 to 1 based on Brief Pain Inventory. The small bowel dose was limited to 15 Gy

Treatment planning with linear accelerator

- 4–8 MV photons
- Utilize 7–9 static, coplanar beams (IMRT) or 2–4 rotational arcs (VMAT)
- Beams shaped using multi-leaf collimators

Treatment planning with CyberKnife

- Composed of hundreds of pencil beams

25.2.5 Common Dose/Fractionation Schemes [30]

Dose/Fx	Number of fx	Total dose	Notes
15–24 Gy	1	15–24 Gy (authors' preference: 15–18 Gy)	Based on limited literature [3]; normal tissue constraint permitting
6–12 Gy	3	18–36 Gy (authors' preference: 24–27 Gy)	Based on limited literature [3]; normal tissue constraint permitting
5–10 Gy	5	25–50 Gy (authors' preference: 25–35 Gy)	Based on limited literature [3]; normal tissue constraint permitting

25.2.6 Normal Tissue Tolerances

- For non-spine bone metastases, the organs at risk depend on the location of the bone treated.
- The normal tissue constraints of various organs at risk for hypofractionated radiotherapy are covered elsewhere in this book.
- For reirradiated cases, the prior radiation dose delivered has to be factored in when setting the dose constraints.

25.2.7 Patient Management

1. Similar to SBRT for spinal metastases
2. Toxicity

   (a) Acute:

   - Skin/soft tissue/bone (dermatitis, pain flare)
     - Emollients (aquaphor, calendula). Remove 4 h prior to RT treatment.
     - Medrol Dosepak or dexamethasone 4 mg QD until 4 days after completion of SBRT
     - Pain medication (fentanyl patch 25–100mcg q72hrs, oxycodone 5–20 mg q4-6 hrs)

(b) Late:

- Skin/soft tissue (discoloration, fibrosis)
- Pathologic fracture
- Chronic chest wall pain after SBRT for rib metastases

25.2.8 Follow-Up

- Repeat CT or MRI every 3 months
- PET-CT every 3 months
- Bone scan every 3 months

25.2.9 Relevant Literature

Study	Patients	Treatment	Median f/u	Outcome
Owen et al. 2014 [31]	74 patients with 85 bone metastases	18–24 Gy/1 or 30 Gy/3	7.6 years	1 yr. LC 91.8% median OS: 9.5 months Median PFS, 9.7 toxicity: 1 grade 3 pain flare
Jhaveri et al. 2012 [32]	18 patients with 24 renal cell carcinoma bone metastases	18–40 Gy/3–5	38 weeks	78% symptomatic toxicity: No grade 2 or higher

25.2.10 Summary

SBRT for non-spine bone metastases is an emerging area of practice and research but is currently not yet the standard of care in most circumstances.

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Part X
Gynecologic Malignancies

Chapter 26
Uterine Cervix Cancer

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Hypofractionation has a selective and important role in the radiotherapeutic management of gynecological malignancies, primarily in the use of brachytherapy. High-dose rate (HDR) intracavitary brachytherapy is the most common brachytherapy technique used for cervical cancer, although interstitial brachytherapy can be utilized in advanced cases. Brachytherapy (in combination with external beam radiotherapy) is an integral component in the curative management of advanced cervical cancer, and survival rates are poorer when external beam radiation techniques (intensity-modulated radiotherapy or stereotactic body radiotherapy) are utilized instead of brachytherapy [1, 2].

26.1 Pearls

- Thirteen thousand women are diagnosed with cervical cancer each year in the USA, while another 4210 women will die from the disease.
- In the past 40 years, both the incidence of and the mortality from cervical cancer have decreased significantly in the USA due to screening programs.

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- Cervical cancer remains most common gynecologic malignancy and 4th leading cause of cancer-related death in women worldwide. Eighty-five percent of cervical cancer diagnoses occur in developing countries and are commonly diagnosed in advanced stages.
- In the USA, the mean age of diagnosis is 48 years; however, cervical cancer has a bimodal disease distribution with peaks at ages 35–39 and 60–64 years.
- HPV infection is the greatest risk factor (mostly types 16 and 18) and is detected in 99.7% of cervical cancers.
- Other risk factors include young age at first intercourse, multiple sexual partners (>4), high-risk sexual partners, history of other STDs (e.g., chlamydia trachomatis, genital herpes), high parity, smoking, history of precancerous lesions or cancer, and prenatal DES exposure (clear-cell carcinoma), and immunosuppression (immunodeficiency syndrome, chronic steroid usage, organ transplantation). Cervical cancer is an AIDS-defining malignancy in patients living with HIV.
- Currently, there are no known genetic abnormalities/germline mutations that are associated with a higher risk for cervical cancer.
- The most common presenting symptoms are irregular vaginal bleeding/discharge or postcoital bleeding. Pelvic pain, bowel/bladder symptoms, and lower extremity lymphedema are symptoms of advanced disease.
- The two most common histologic types are squamous cell carcinoma (69%) and adenocarcinoma (25%).
- Over the past three decades, the incidence of adenocarcinoma has increased secondary to increased exposure to estrogen. Other uncommon histologic types (6%) are clear-cell carcinoma, small-cell carcinoma (neuroendocrine), melanoma, and lymphoma.
- **Local anatomy and patterns of spread:**
  - The uterine cervix is located at the junction between the lower uterus and apical vagina. It consists of the endocervix and ectocervix, which are lined by stratified squamous and glandular epithelia, respectively. HPV infection causes malignant transformation at the transition zone between the two types of epithelia.
  - Cervical cancer progresses by direct contiguous spread to adjacent structures, most frequently to the parametria, vagina, or uterine corpus. More advanced disease may extend to the pelvic sidewalls or invade the peritoneal cavity, bladder, and/or rectum.
  - There is increasing frequency of lymph node (LN) involvement with advancing stage: <5% of patients with stage IA disease will have pelvic LN involvement. This increases to 15% of stage IB patients, 30% of stage II patients, 50% of stage III patients, and 60% of stage IV patients. Roughly one-third of the patients with pelvic LN involvement will have involved para-aortic LNs.
  - In early-stage patients, the depth of invasion below the basement membrane is also related to the risk of LN involvement: for <3 mm invasion, there is <1% risk of pelvic LN involvement. With invasion ≥3 mm or LVI (stage IA2), the risk of LN spread increases to 2–8%.

  - Lymphatic dissemination typically occurs in a predictable manner with initial pelvic LN involvement followed by dissemination to the para-aortic and then supraclavicular LNs.
  - Hematogenous dissemination is less common. When it occurs, the common sites are the lungs and, to a lesser extent, to the liver and bone.

- **Medical workup:**
  - H&P including examination of vagina, vulva, and anal region to exclude other HPV-associated malignancies. A full gynecologic examination (including speculum, bimanual, and recto-vaginal examination) is essential for staging and for choosing the appropriate brachytherapy applicator for a patient's anatomy.
  - Laboratory tests include CBC, LFTs, BUN/creatinine, and urine pregnancy test in women of reproductive age. Consider HIV testing. CBC is important to assess for anemia as many cervical cancer patients have several months' history of vaginal bleeding, and correction of anemia is important for treatment with surgery, chemotherapy, and optimizing radiation treatment outcomes.
  - Fertility consultation should be considered for patients of childbearing age.
  - Smoking cessation and counseling intervention advised.

- **Imaging workup:**
  - Optional for patients with ≤stage IB1 and recommended for more advanced disease.
  - Pelvic MRI with contrast is a preferred method for the detection of parametrial involvement, estimation of tumor size, and delineating uterine and cervical anatomy to guide subsequent brachytherapy.
  - CT and ultrasound can be used if MRI is not available.
  - PET-CT is recommended for detection of LN metastasis. CT of chest, abdomen, and pelvis with IV contrast can be used if PET-CT is unavailable.
  - Examination under anesthesia including cystoscopy/proctoscopy is indicated if bladder or rectum involvement is suspected.
  - Advanced imaging (CT, PET-CT, MRI) is used for guiding treatment decisions but does not impact FIGO staging.
  - If hydronephrosis is noted on imaging studies, stenting is recommended prior to initiation of therapy.

- Treatment strategies depend on the stage of disease, desired for fertility and ovarian hormonal function preservation. Surgery is preferred choice for early-stage disease (e.g., fertility-sparing surgery such as radical hysterectomy/pelvic node dissection for preserving ovarian function), reserving postoperative radiation therapy with/without chemotherapy for pathologic risk factors noted below. Advanced-stage patients are treated with definitive chemoradiation with brachytherapy. Patients with distant metastatic disease are treated with chemotherapy and palliative radiation therapy.
- Brachytherapy is an integral part of primary radiation treatment and has been shown to increase local control and overall survival in comparison with external beam radiotherapy alone [1, 2].

- Brachytherapy should be incorporated into treatment as early as the tumor shrinks to a size that allows adequate applicator placement, to allow completion of all treatments within 8 weeks. Prolonged treatment duration leads to a decrease in local control and survival of approximately 1% per day [3].

26.2 AJCC and FIGO Staging: Cervix Uteri

Primary tumor (T)		
T category	FIGO stage	T criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion of 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm, with a horizontal spread of 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2. Includes all macroscopically visible lesions, even those with superficial invasion
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invading beyond the uterus but not to the pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extending to the pelvic wall[a] and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involving the lower third of the vagina but not extending to the pelvic wall
T3b	IIIB	Tumor extending to the pelvic wall and/or causing hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invading the mucosa of the bladder or rectum and/or extending beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4)

[a]The pelvic sidewall is defined as the muscle, fascia, neurovascular structures, and skeletal portions of the bony pelvis. On rectal examination, there is no cancer-free space between the tumor and pelvic sidewall

Regional lymph nodes (N)		
N category	FIGO staging	N criteria
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1		Regional lymph node metastasis

Distant metastasis (M)		
M category	FIGO staging	M criteria
M0		No distant metastasis
M1	IVB	Distant metastasis (including peritoneal spread or involvement of the supraclavicular, mediastinal, or distant lymph nodes, lung, liver, or bone)

Prognostic stage groups			
When T is…	And N is…	And M is…	Then the stage group is…
T1	Any N	M0	I
T1a	Any N	M0	IA
T1a1	Any N	M0	IA1
T1a2	Any N	M0	IA2
T1b	Any N	M0	IB
T1b1	Any N	M0	IB1
T1b2	Any N	M0	IB2
T2	Any N	M0	II
T2a	Any N	M0	IIA
T2a1	Any N	M0	IIA1
T2a2	Any N	M0	IIA2
T2b	Any N	M0	IIB
T3	Any N	M0	III
T3a	Any N	M0	IIIA
T3b	Any N	M0	IIIB
T4	Any N	M0	IVA
Any T	Any N	M1	IVB

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26.3 Patient Selection

- For patients undergoing definitive radiation, brachytherapy is indicated in conjunction with EBRT for locally advanced disease (stages IB2–IVA); brachytherapy alone may be considered as primary treatment for patients with very early-stage disease (IA) that are not candidates for surgical therapy [1, 4].

- Patients with stage IB1/IB2 disease not suitable for brachytherapy should be evaluated for interval hysterectomy after EBRT.

26.4 Treatment Planning Considerations

Timing	Start brachytherapy after 10–20 Gy EBRT or as soon as possible. We recommend once a week intracavitary brachytherapy during EBRT and twice a week treatments after EBRT is completed
Analgesia	Analgesia options for cervical cancer brachytherapy include general, spinal, intravenous sedation. And/or oral pain medication. Our practice is to use titrated doses of fentanyl, starting with 50 μg IV, and lorazepam with 1 mg IV, 20–30 min prior to start of the procedure
Position	Dorsal lithotomy position
Pelvic exam	Examination under anesthesia—a bimanual examination to document any residual nodularity, the cervix size, and the size of the vaginal fornices (i.e., disease extension/response to treatment). The uterus is sounded to aid in selection of the appropriate tandem applicator. Insertion of radiopaque markers in the cervix aids localization of the cervix on imaging. We generally avoid inserting the seed at 3, 6, 9, and 12 o'clock positions on the cervical os so that the seeds are not masked by the applicator on AP and lateral orthogonal images
Preparation and procedure	• A Foley catheter is inserted into the bladder, and the balloon is inflated with dilute contrast • The ABS/GEC-ESTRO recommendations can be used for guidance in choosing the appropriate applicator according to patient's anatomy and target geometry, but familiarity and experience with the applicator are essential for providing appropriate treatment [5, 6]. Applicator options include tandem and ovoids, tandem and ring, tandem and cylinder, and tandem and ovoid or ring with guides for interstitial needles. Interstitial catheters can be used to allow full coverage in cases such as poorly fitting intracavitary applicators, parametrial involvement, and lower vaginal involvement • After selection of appropriate applicators (including angle of the intrauterine tandem and size of ring or ovoids), the applicators are placed. A tenaculum may be placed on the cervix to provide countertraction for placement of the intrauterine tandem • Radiopaque vaginal packing is used to displace the bladder base anteriorly and the anterior rectal wall posteriorly away from the intracavitary applicator. Packing also serves to prevent the displacement of the tandem from the uterus and to secure the positioning of the entire applicator • We do not routinely use a Smit sleeve, but they can be useful for anatomically difficult implants • Imaging (CT, MRI, or plain radiographs) is done for each implant immediately following the placement of the applicator and is essential for treatment planning of each procedure • 3D imaging allows for accurate contouring of the tumor, cervix, uterus, and OAR. While the OARs can be readily visualized on CT, MRI is superior for delineating the tumor for image-guided brachytherapy, particularly in the setting of parametrial involvement [7]

Treatment planning	**Image-guided brachytherapy** • Requires planning of dwell according to 3D images (CT or MRI) • We recommend using the GEC-ESTRO guidelines for target delineation/definition (Fig. 26.1) [5, 7] with prescription to the high-risk CTV (HR-CTV) • OARs that should be contoured include the bladder, rectum, and sigmoid **2D (X-ray) planning** Prescribe to point A: 2 cm superior to external cervical os and 2 cm lateral to central canal/tandem • Point B: 5 cm lateral from a point 2 cm superior to the cervical os along the patient's midline (represent parametria /obturator nodes) • Bladder point: The posterior surface of Foley balloon on lateral X-ray and center of balloon on AP film • Rectal point: 5 mm posterior to the posterior vaginal wall between ovoids • Vaginal point: The mid-ovoid on lateral X-ray film and the lateral edge of ovoid on AP film
Documentation	Documentation of brachytherapy is essential and should include the type of isotope and source; description of the target (including size and shape), target dose, dose per fraction, and the fractionation plan; the applicator type and size and the treatment plan documentation (dose distribution to the target and OAR). Even if 3D planning is used, the dose for point A should be recorded per ICRU system [7]

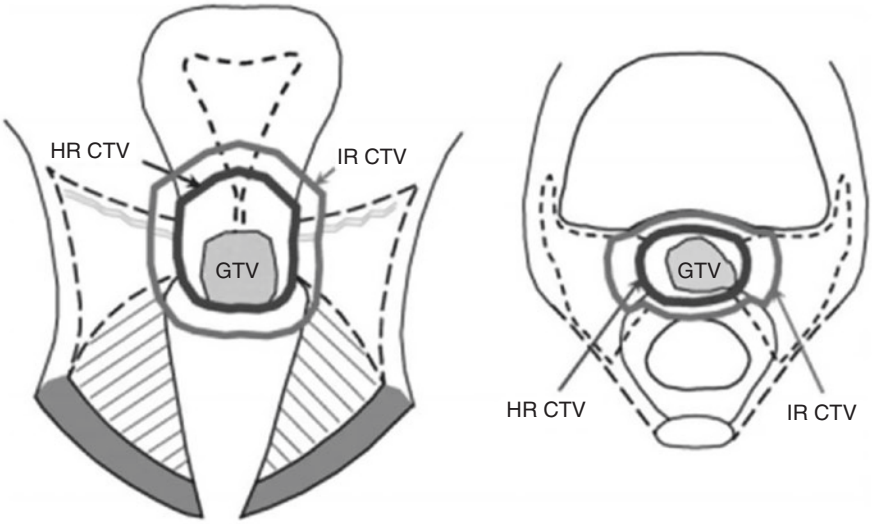

Fig. 26.1 GEC-ESTRO guidelines for 3D target delineation for cervix cancer. Coronal view (**a**) and transverse view (**b**) of limited disease with partial remission after EBRT. A high-risk CTV (HR-CTV) includes the whole cervix and presumed residual disease at the time of brachytherapy (determined by visualization, palpation, and MRI). An intermediate-risk CTV (IR-CTV) encompassing the HR-CTV with directional margins (usually 5–15 mm) and at least the initial volume at diagnosis [5, 7]

Modified ABS checklist for brachytherapy [6]

*Procedure checklist for brachytherapy	Checklist for an adequate implant
▫ Consents present in the chart ▫ IV access obtained ▫ "Timeout" to identify the patient treatment prescription and session number ▫ Anesthesia administered ▫ Examination under anesthesia ▫ Document disease extension in drawing ▫ Dilation of cervical os; ultrasound use if insertion is difficult ▫ Smit sleeve placement, if preferred ▫ Applicator placement ▫ Caution that applicator does not slip ▫ Packing ▫ Imaging (CT, MRI, plain radiographs) ▫ Prescription ▫ Treatment planning ▫ Documentation of OAR (sigmoid, rectum, bladder) doses in chart ▫ QA checks ▫ Timeout to confirm treatment prescription and session number prior to treatment delivery ▫ Treatment delivery ▫ Dictation of treatment administered ▫ Applicator removed ▫ Posttreatment care ▫ Follow-up scheduled	▫ The tandem should bisect the ovoids on an AP and lateral image ▫ On a lateral image, the ovoids should not be displaced inferiorly from the flange (cervical stop) and should overlap one another ▫ The tandem should be approximately 1/2 to 1/3 the distance between the symphysis and the sacral promontory ▫ The superior tip of the tandem should be located below the sacral promontory within the pelvis ▫ Radiopaque packing will be visible on radiographic images and should be placed anterior and posterior to the ovoids, with no packing visible superior to the ovoids (superior packing represents an unwanted inferior displacement of the applicator)

26.5 Commonly Used Dose/Fractionation Schemes

Definitive treatment

- **EBRT + intracavitary brachytherapy:** EBRT to pelvis (using either a four-field technique or IMRT). Daily dose of 1.8–2 Gy × 25–28 fx to a total of 45–50.4 Gy. A split pelvis field with midline block can be considered (with higher dose delivered by brachytherapy). If there is common iliac or para-aortic LN involvement, an extended treatment field is utilized with IMRT. Pelvic sidewall boost to a total dose of 50–54 Gy can be considered for stage IIB and higher. Gross nodal disease can be boosted to a total dose of 60–70 Gy [4, 6]. Concurrent

chemotherapy with weekly cisplatin is recommended for stages IB2-IVA in patients with adequate renal function. The ABS recommends that chemotherapy be administered day that EBRT is delivered but not on a day of a brachytherapy treatment [4, 6].

- Dose reporting for cervical brachytherapy is typically converted to a biologically equivalent dose in 2-Gy fractions (EQD2). This aids in conversion between different fractionation regimens and in summing EBRT and brachytherapy doses.
- Classic tandem and ovoid geometry is based on the dose to point A and should be recorded even when 3D planning is used.
- The DVH parameter typically used to describe target coverage is the dose received by at least 90% of the target volume (HR-CTV by GEC-ESTRO definition, see Fig. 26.1).
- In cases of complete response or a partial response (<4 cm residual disease) to EBRT, the target D90 should be greater than 80 Gy (EQD2).
- In cases of residual tumors ≥4 cm at the time of brachytherapy, the target D90 of at least 85–90 Gy EQD2 is recommended. Interstitial needle application may be needed to provide optimal coverage.

Common intracavitary brachytherapy-HDR doses (combined with EBRT, 1.8 Gy × 25 fx) [41]

Fractionation to point A	EQD2(Gy) to the tumor, inclusive of EBRT dose (point A with α/β = 10 Gy)	Comments
5.5 Gy × 5	79.8	Complete response or <4 cm of residual disease after chemoradiation
5 Gy × 6	81.8	
7 Gy × 4	83.9	
6 Gy × 5	84.3	Patients with tumors >4 cm after EBRT

Postoperative treatment:
Postoperative pelvic radiation with EBRT to a total dose of 45–50.4 Gy should be considered in high-risk cases [4]. Vaginal brachytherapy (as a vaginal cuff boost) is not routinely given but should be considered in patients with less than radical hysterectomy, close or positive margins, large or deeply invasive tumors, parametrial or vaginal involvement, or extensive LVI. Vaginal brachytherapy dosing ranges from 5 Gy × 5 fx to 7 Gy × 3 fx (total dose to vaginal mucosa 45–80 Gy) [8].
Recurrent disease:
In the case of small volume recurrence, SBRT can be considered, with promising safety and efficacy (though limited to retrospective series) [9].

Palliative treatment:
In the setting of metastatic disease, a single fraction (10 Gy) of EBRT can be delivered to the pelvis using AP-PA fields or a four-field arrangement for palliation of pelvic pain or bleeding [10–12].

26.6 Normal Tissue Tolerance

Organ at risk	Radiographic (ICRU point)	3D imaging (D2cc)	Comments
Bladder	5x < 3.7 Gy	<90 Gy[a]	
Rectum	5x < 3.7 Gy	<70–75 Gy[a]	Dose-volume effect relationship for late rectal morbidity was recently published by the EMBRACE collaborative group [5, 13]. Rectal D2cc ≥ 75 Gy was associated with grade 2–4 rectal toxicity (fistula) in 3 years A D2cc ≤ 65 Gy was associated with more minor and less frequent rectal morbidity [5, 13]
Sigmoid	–	<70–75 Gy[a]	–
Ureters	–	<70 Gy	–
Uterus	–	<100 Gy	–
Ovaries			Sterilization after 2–3 Gy, ovarian failure with 5–10 Gy, patients, who are over 35 years or receive chemotherapy, are at greater risk for ovarian failure
Vagina		<50–60 Gy	Doses above 50–60 Gy can cause fibrosis and stenosis. High doses (>100 Gy) may cause fistulization with adjacent organs. High doses to the vagina mucosa are often inevitable; dose to vaginal should be limited according to extent of disease. Upper vaginal mucosa limit usually <120 Gy, mid-vaginal mucosa <80–90 Gy, lower vaginal mucosa <60–70 Gy The EMBRACE study reported that a higher recto-vaginal reference point dose, EBRT dose more than 45 Gy in 25 fractions, and tumor extension in the vagina were risk factors for vaginal stenosis [8]. Based on the model curve, the risk for vaginal stenosis was 20% at 65 Gy, 27% at 75 Gy, and 34% at 85 Gy (recto-vaginal reference point dose). Therefore, the authors recommended to keep the EBRT dose ≤45 Gy in 25 fractions and planning aim of ≤65 Gy EQD2 (EBRT+ brachytherapy dose) to the recto-vaginal reference point is therefore proposed [6, 14]

[a]Max point dose defined as <0.035 cc

The cumulative dose delivered by EBRT and brachytherapy need to be integrated during treatment planning to avoid significant overexposure to midline structures, particularly the bladder and rectum.

26.7 Patient Management Considerations

Acute Toxicity

- Acute urinary symptoms such urgency and frequency occur in more than 40% of patients and are usually minor [7]. Urinary tract infection should be excluded and, if present, treated according to culture sensitivity.
- Mild or occasional diarrhea can be managed with loperamide. Initial: 4 mg orally once followed by 2 mg orally after each loose stool, not exceeding 16 mg per 24-h. Loperamide maintenance: daily dosage between 4 and 8 mg.
- For persistent and/or severe diarrhea, evaluate patient for *C. difficile* infection. Patient should undergo dietary consultation. If infectious diarrhea excluded, patients can be treated with loperamide.
- At time of intracavitary applicator placement, uterine perforation can occur. It typically occurs in the posterior cervix, but it may also occur at the fundus. If a uterine perforation is suspected, the applicator should be removed immediately without initiating treatment, and the applicator should be reinserted to obtain proper positioning. The patient should be started on a broad-spectrum antibiotic [6]. An unrecognized uterine perforation with subsequent radiation treatment delivery with the tandem outside the uterus and close to or in the bowel or bladder may result in significant toxicity [6].
- In patients with absolute neutrophil counts, less than 500 mm^3 brachytherapy should be held until count recovery [7].

Late Toxicity

- Possible complications include vaginal stenosis (minimized by vaginal dilator use and resumption of sexual activity), vaginal dryness (treat with topical estrogen), urethral stricture (<3%), vesico-vaginal or recto-vaginal fistulae (<2.5%), and femoral head fracture (risk after EBRT to pelvis).
- The risk of developing major urinary toxicity is the greatest in the first 3 years following radiation (0.7% per year) [7, 15].
- Rate of grade ≥3 of late vaginal morbidity (at 2 years) in patients treated by IGRT-brachytherapy in the EMBRACE study was 3.6%. The majority of the patients experienced mild and moderate vaginal symptoms (grade ≥ 1, 89%; grade ≥ 2, 29%), of which the majority developed within 6 months. The most frequent vaginal toxicity observed was vaginal stenosis, followed by vaginal dryness [14].

26.8 Follow-Up

- H&P including bimanual, pelvic, and rectal examination every 3 months for the first 2 years, every 6 months for 3–5 years, and then annually.
- At UNC we recommend performing cervical and/or vaginal cytology annually for detection of genital tract malignancies. However, the value may be limited due to post-radiation changes. Abnormal cytology should be followed by colposcopy and biopsy for histologic confirmation.
- Posttreatment imaging with PET-CT is routinely performed 3 months following completion of definitive chemoradiotherapy. If there is a metabolic complete response on this exam, further imaging is typically performed only with abnormal pelvic examinations or symptoms.

26.9 Relevant Literature

- A Cochrane collaboration review of HDR versus LDR for locally advance uterine cervix cancer did not find significant differences between HDR and LDR intracavitary brachytherapy when considering overall survival, disease-free survival, recurrence-free survival, and local control rate, metastasis, or treatment-related complications [16]. The authors recommend the use of HDR intracavitary brachytherapy for all clinical stages of cervical cancer due to the potential advantages of HDR intracavitary brachytherapy: outpatient treatment, patient convenience, accuracy of source and applicator positioning, and individualized treatment.

Brachytherapy is an integral component of therapy and should be part of all definitive treatments. Cervical SBRT (or other EBRT technique) boost in lieu of brachytherapy is not considered standard of care and lacks rigorous data comparing outcomes vs. brachytherapy. Most earlier randomized trials for advanced cervical cancer (i.e., RTOG 9001 [17] and GOG 120 [18]) utilized LDR brachytherapy (which is beyond the scope of this chapter).

Small series using SBRT as a boost and for recurrent gynecologic cancers are summarized in the Table below. Given the small numbers of patients, varied treatments, and relatively short follow-up, the authors do not make any clinical recommendations based on this limited literature.

Select retrospective and prospective studies of hypofractionation for gynecological malignancies

Study	Patients	Treatments	Median follow-up	Outcome
SBRT as boost to definitive RT ***Note that the authors do not recommend SBRT in lieu of brachytherapy**				
Jorcano 2010 [19]	26 – 9 cervix – 17 uterine	EBRT 45–50.4 Gy SBRT boost 7 Gy × 2 fx	47 months	– 3 year OS, 95% – 3 year LC, 96% – Grade ≥ 2 toxicity GU-4% GI-12% Sexual function disturbances 29.4%
Haas 2012 [14]	6	EBRT 45–50.4 Gy SBRT boost 4Gy × 5 fx or 6.5 Gy × 3 fx	14 months	– LC, 100% – OS, 100% – No grade 4 toxicity
SBRT for recurrence				
Kunos 2012 [20] Prospective phase II	50 – 9 cervix – 18 uterine – 25 ovary – 2 vulva	SBRT sites PALN (38%), pelvis (28%) 8 Gy × 3 fx	15 months	– LC, 100% – Grade 3–4 toxicity (6%): Diarrhea, fistula
Dewas 2011 [21]	16 – 4 cervix – 1 uterine – 11 non-gyn ca	SBRT sites Pelvic sidewall 6 Gy × 6 fx	10.6 months	– 1 year LC, 51% – mPFS—8.3 months – No grade 3 toxicity
Choi 2009 [22]	28 – 26 cervix – 2 uterine	SBRT sites PALN 11–15Gy × 3 fx (24 pts) EBRT+SBRT boost (4 pts) Chemotherapy sequencing varied	–	– 4 year OS, 50% – 4 year LC, 68% – 4 year PFS, 45% – Grade 3–4 toxicity: 21%
Mesko 2017 [23]	28 (47 targets) −2 cervix −8 uterine −15 ovary −2 vagina −1 uterine carcinosarcoma	SBRT sites 17% liver, 21% lung, 17% PALN, 26% other LNs, 19% pelvic soft tissue Median 8 Gy (range, 5–18) in 5 fractions (range, 1–10)	12.8 months	– OS, 86% – mPFS 10.8 months – No failures occurred in lung or nodal targets – Grade 3 toxicity: 3%, GU toxicity in a previously irradiated site

Study	Patients	Treatments	Median follow-up	Outcome
Re-irradiation setting brachytherapy				
Badakh 2009 [24]	22	HDR ISBT 4–6 Gy × 6–10 fx, BID	9.2 months	– mOS—9.2 months – Grade 4 toxicity: 18%, fistulas, soft tissue
Zolciak-Siwinska 2014 [25]	20	HDR BT—interstitial, cylinder or IORT With/without EBRT and/or hyperthermia	31 months	– 3 year OS, 68% – 3 year LC, 45% – 3 year DFS, 42% – Acute toxicity: No grade ≥3 toxicity – Late toxicity: Grade ≤ 3 toxicity GU (10%), GI (5%); grade 4 obliteration of the vagina (40%)
Mabuchi 2014 [26]	52	HDR ISBT 6 Gy × 7 fx = 42 Gy; BID	55.6 months	– 5 year OS, 52.6% – Late grade 3–4 toxicity 25%: Fistulas, bowel obstruction and ulceration
Palliation				
Kim 2013 [27]	17	EBRT 5 Gy × 4–5 fx daily	12.2 months	– mOS—7.8 months – Vaginal bleeding control—93.8% – Pelvic pain control—66.7% – Acute toxicity: Grade 3 diarrhea (5.9%)
Grigsby 2002 [28]	15	Cervical ring brachytherapy (HDR) 5 Gy × 2 fractions prescribed to surface administered 1 week apart for emergent bleed prior to definitive EBRT/intracavitary brachytherapy Mean rectal dose 1.75 Gy, mean bladder dose 1.65 Gy, mean point A dose 0.85	32 months	– Vaginal bleeding control—93% – No acute toxicity – All patients went on to complete definitive therapy (chemotherapy with EBRT and brachytherapy)

Study	Patients	Treatments	Median follow-up	Outcome
Halle 1986 [10]	42	10 Gy × 1–2 fractions EBRT delivered monthly	12.8 months	– Vaginal bleeding control—90% – Pelvic pain control—44% – Five late toxicities: Fistulas, ulceration, tissue necrosis

Abbreviations: *PALN* para-aortic lymph nodes, *ISBT* interstitial brachytherapy, *IORT* intraoperative radiotherapy

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Chapter 27
Endometrial Cancer

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Hypofractionation in the radiotherapeutic management of endometrial cancer has an important but selective role, mainly in terms of postoperative vaginal cuff HDR brachytherapy. SBRT is used for oligometastatic disease, rarely as a boost technique with EBRT and for palliation. These data have mostly been reported from retrospective cohort studies that include other gynecological malignancies as discussed in the cervical cancer chapter. Surgery [total hysterectomy with bilateral salpingo-oophorectomy (BSO)] with or without nodal assessment (sentinel lymph node biopsy or nodal dissection) is the primary treatment of endometrial cancer. Recommendations for adjuvant radiotherapy are based on surgical pathology. Factors considered include depth of invasion, grade, lymphovascular space invasion, and nodal involvement. The use of postoperative vaginal cuff brachytherapy for high-intermediate-risk early-stage endometrial cancer is increasing in the recent years after reports indicating its efficacy in local control and favorable toxicity profile compared to pelvic EBRT.

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27.1 Pearls

- Uterine cancer is the most common gynecologic malignancy in the USA and the sixth most common cancer diagnosis in women worldwide.
- Mostly diagnosed in postmenopausal women (median age 63 years); 4% of the women are younger than 40 years.
- It is most common in white women followed by African-Americans, Hispanics, and Asian women. Notably, African-American women experience poorer prognosis, regardless of stage, pathology, socioeconomic status, and treatment.
- Risk factors include excess (unopposed) estrogen exposure: early age at menarche, nulliparity, late age at menopause, obesity, estrogen-secreting tumors, tamoxifen therapy, and estrogen-progestin postmenopausal hormone therapy. Diabetes mellitus and high-fat diet are also considered risk factors.
- Genetic predisposition: Lynch syndrome, BRCA1 mutation.
- The most common presenting symptom is postmenopausal uterine bleeding (75–90%).
- Most diagnoses occur at an early stage: disease confined to the uterus (67–80%), spread to regional lymph nodes and organs (21%), and distant metastases (12%).
- Histology: Adenocarcinoma (i.e., endometrioid cancer) is the most common subtype (90–95%). Type 1 cancers (75–80%) are estrogen-dependent, low-grade, and uterus-confined cancers that typically occur in postmenopausal women and have favorable prognosis. Type 2 cancers (10–20%) are estrogen-independent, non-endometrioid (serous, clear cell, mixed histology, undifferentiated, carcinosarcoma) cancers with poorer prognosis. Uterine sarcoma ~ 5%.
- **Patterns of spread:**
  - Local spread is through invasion of the myometrium or the cervix and less commonly to uterine serosa, parametria, or vagina.
  - Extrauterine spread of endometrioid cancer primarily occurs through lymphatic drainage to locoregional lymph nodes (pelvic, iliac, obturator, presacral, and para-aortic) and the adnexa.
  - Surgical series have described several pathologic risk factors for lymphatic spread including depth of invasion, tumor grade [1], tumor sizes [2], and lymphovascular space invasion (LVSI) [3].
  - Hematogenous dissemination to the lungs and liver is less common. Uterine sarcoma can spread to the lungs.
- **Medical workup:**
  - Physical exam including a pelvic exam with speculum and bimanual examination. For women with postmenopausal vaginal bleeding, the American College of Obstetricians and Gynecologists recommends initial evaluation with either endometrial biopsy or transvaginal ultrasonography. Endometrial thickness of greater than 4 mm on ultrasound requires a biopsy. Non-diagnostic endometrial biopsy should be followed by dilation and curettage.
  - Laboratory tests: CBC, serum chemistries, LFTs, and renal function tests. CA-125 is optional for high-grade endometrioid histology, advanced stage, and serous or clear cell histology.

  - Though the majority of women diagnosed are postmenopausal, fertility consultation should be considered for patients of childbearing age.

- **Imaging studies:**
  - For patients, who will have surgical staging and primary treatment, preoperative imaging is reserved for those with high-grade or non-endometrioid cell types or suspected advanced stage on clinical evaluation.
  - Suspected/gross cervical involvement: contrast abdomen and pelvis MRI is recommended to evaluate extent of disease.
  - Suspected extrauterine disease: MRI/CT/PET as clinically indicated.

- Operable patients undergo initial hysterectomy (open, laparoscopic, or robotic) with BSO ± adjuvant treatment based on age, stage, and pathologic risk factors.
- The highest-risk site of disease recurrence after surgery is at the vaginal cuff.
- Adjuvant therapy primarily includes EBRT and/or vaginal brachytherapy (VBT). Chemotherapy may be administered for advanced disease. Recent data showed that VBT is as effective as EBRT in reducing vaginal recurrences in select FIGO stage I intermediate- to high-intermediate-risk patients, who have a low risk of lymph node involvement [4].
- Patients with FIGO stage II endometrial cancer may be candidates for VBT ± EBRT based on other pathologic risk factors.
- Patients with FIGO stage III endometrial cancer typically receive chemotherapy with pelvic EBRT.
- Medically inoperable patients with early-stage disease without risk factors per MRI (positive LN, deep myometrium involvement) can be treated by intracavitary brachytherapy alone or EBRT + brachytherapy [5]. Hormone therapy (either systemic or via a hormonal intrauterine device) alone can be considered for unfit patients [6].
- Patients with unresectable disease (e.g., invasion of the vagina, bladder, rectum) or with extrauterine pelvis disease are candidates for EBRT + brachytherapy ± chemotherapy, or neoadjuvant chemotherapy or chemoradiotherapy followed by surgical resection or chemotherapy alone.
- Treatment for locoregional recurrences is dependent on primary cancer treatment as well as site of recurrence. Patients without prior RT are treated with EBRT ± brachytherapy. Recurrences at the vaginal cuff are amenable to intracavitary or interstitial brachytherapy, while nodal or pelvic sidewall recurrences are typically treated with EBRT alone. Patients, who recur in or adjacent to a prior RT field, are treated with surgical exploration with resection ± intraoperative radiotherapy (IORT) and/or systemic therapy.
- Limited nodal recurrence may be amenable to hypofractionated radiotherapy using SBRT with good efficacy and favorable toxicity in retrospective review [7] and in single-institution prospective evaluation [8], though further evaluation of this strategy may be warranted.
- Regardless of tumor type, the estimated 5-year OS is 85–90% for stage I, 75–85% for stage II, 50–65% for stage III, and 20–25% for stage IV (FIGO 26th report).

27.2 AJCC and FIGO Staging

Primary tumor (T)		
T category	**FIGO stage**	**T criteria**
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to the corpus uteri, including endocervical glandular involvement[a]
T1a	IA	Tumor limited to the endometrium or invading less than half the myometrium
T1b	IB	Tumor invading one half or more of the myometrium
T2	II	Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus. Does NOT include endocervical glandular involvement
T3	III	Tumor involving serosa, adnexa, vagina, or parametrium
T3a	IIIA	Tumor involving the serosa and/or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	IVA	Tumor invading the bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)
Regional lymph nodes (N)		
N category	**FIGO stage**	**N criteria**
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	IIIC1	Regional lymph node metastasis to pelvic lymph node
N1mi	IIIC1	Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to pelvic lymph nodes
N1a	IIIC1	Regional lymph node metastasis (greater than 2.0 mm in diameter) to pelvic lymph nodes
N2	IIIC2	Regional lymph node metastasis to Para-aortic lymph nodes, with or without positive pelvic lymph nodes
N2mi	IIIC2	Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to Para-aortic lymph nodes, with or without positive pelvic lymph nodes
N2a	IIIC2	Regional lymph node metastasis (greater than 2.0 mm in diameter) to Para-aortic lymph nodes, with or without positive pelvic lymph nodes
Suffix (sn) is added to the N category when metastasis is identified only by sentinel lymph node biopsy		

Distant metastasis (M)			
M category	**FIGO stage**	**M criteria**	
M0		No distant metastasis	
M1	IVB	Distant metastasis (including metastasis to inguinal lymph nodes, intraperitoneal disease, lung, liver, or bone) (it excludes metastasis to pelvic or Para-aortic lymph nodes, vagina, uterine serosa, or adnexa)	
Prognostic state groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
T1	N0	M0	I
T1a	N0	M0	IA
T1b	N0	M0	IB
T2	N0	M0	II
T3	N0	M0	III
T3a	N0	M0	IIIA
T3b	N0	M0	IIIB
T1-T3	N1/N1mi/N1a	M0	IIIC1
T1-T3	N2/N2mi/N2a	M0	IIIC2
T4	Any N	M0	IVA
Any T	Any N	M1	IVB
Histologic grade (G)			
G	**G definition**		
GX	Grade cannot be assessed		
G1	Well differentiated		
G2	Moderately differentiated		
G3	Poorly differentiated or undifferentiated		
Histopathology: Degree of differentiation			
Cases or carcinoma of the corpus uteri should be grouped according to the degree of differentiation of the endometrioid adenocarcinoma			
G	**G definition**		
G1	5% or less of nonsquamous or nonmorular solid growth pattern		
G2	6–50% of a nonsquamous or nonmorular solid growth pattern		
G3	More than 50% of a nonsquamous or nonmorular solid growth pattern. Papillary serous, clear cell, and carcinosarcoma are considered high grade		

NOTES on pathologic grading

1. Notable nuclear atypia exceeding that which is routinely expected for the architectural grade increases the tumor grade by 1 (i.e., 1 to 2 and 2 to 3)
2. Serous, clear cell, and mixed mesodermal tumors are *high risk* and considered grade 3

Adenocarcinomas with benign squamous elements (squamous metaplasia) are graded according to the nuclear grade of the glandular component

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[a]Endometrial intraepithelial carcinoma (EIC) should be considered a T1 cancer

27.3 Patient Selection

Adjuvant setting (after hysterectomy/BSO) : FIGO stage I–II

- Surgical pathology must be fully assessed to determine recommendations for adjuvant radiotherapy.
- For patients with FIGO stage I endometrioid cancer, three risk factors are considered: high grade (grade 2–3), deep (>66%) myometrial invasion, and LVSI. Adjuvant treatment is recommended for patients with age <50 years with all three risk factors; 50–70 years with two risk factors; and 70 years and older with any one risk factor. These risk factors for recurrence were initially described in GOG 99 [9].
- Low-risk patients, who do not meet the above criteria, need only close surveillance.
- Patients meeting the above "high-intermediate"-risk criteria are recommended to receive adjuvant EBRT or VBT.
- Many of these patients are candidates for VBT alone; however, some patients have substantial risk of occult nodal involvement (i.e., G3 disease with deep myometrial invasion, extensive LVSI) warranting EBRT to target the at-risk nodal basins in addition to the vaginal cuff.
- Occasionally, a patient may have risk factors that warrant EBRT but have additional risk factors for recurrence at the vaginal cuff (positive surgical margins, FIGO stage II – cervical stromal invasion), and a VBT boost is administered.
- Initiate brachytherapy after the vaginal cuff is healed, usually at least 4–6 weeks postsurgery (within 12 weeks postoperatively).
- Brachytherapy dose depends on whether EBRT is indicated.

FIGO stage IIIC1/2

- Patients with lymph node involvement will typically receive 6 cycles of chemotherapy and pelvic EBRT. EBRT will generally occur between cycles 3 and 4 of chemotherapy ("sandwich") or after completion of chemotherapy. VBT boost may be warranted if there are additional risk factors for vaginal cuff recurrence.

Definitive radiotherapy in patients who are not surgical candidates:

- Patients with early stage but medically inoperable disease are treated with EBRT and/or intracavitary brachytherapy or hormone therapy.
- Patients with unresectable disease (e.g., invasion of the vagina, bladder, rectum) or extrauterine pelvic disease are candidates for EBRT + brachytherapy ± chemotherapy, chemoradiotherapy followed by surgical resection, neoadjuvant chemotherapy, or chemotherapy alone.

Recurrent disease:

- Patients with recurrent disease should only be considered for surgery if gross tumor resection can be achieved [4, 6]. RT with curative intent is indicated in

patients with isolated pelvic relapse after surgery alone for initial disease (no prior RT) [8].

- Brachytherapy technique for vaginal cuff recurrence (intracavitary vs. interstitial) is based on the depth of vaginal wall invasion and the distribution of the disease. In cases of superficial (<5 mm) recurrences, VBT may be selected. For lesions invading ≥5 mm, VBT provides inadequate dose at depth compared with interstitial techniques [10–13]. For recurrences in the pelvic lymph nodes or pelvic sidewall not amenable for brachytherapy, EBRT is given with a boost to the region of gross involvement. SBRT can be considered for low volume recurrences.

27.4 Treatment Planning

Vaginal brachytherapy:

Timing	Brachytherapy should be started within 12 weeks after surgery. We recommend once weekly intracavitary brachytherapy if administered during EBRT. VBT can be administered twice weekly as a monotherapy or after EBRT completion
Analgesia	Consider premedication with anxiolytics, pain medication, or mild sedation [11]. However, these are often not necessary with VBT
Position	Dorsal lithotomy position
Pelvic exam	Perform a visual inspection and manual examination with care to ensure that the vaginal cuff is well healed and that there is no recurrence at the vaginal apex or vaginal cuff dehiscence. In a subset of patients, the placement of a vaginal applicator may be difficult (postoperative changes, pain, etc.)
Preparation and procedure	• Placement of a radiopaque marker at the vaginal cuff can assist in verifying that the applicator is in contact with the vaginal mucosa. Typically three markers are placed – One at the apex and two laterally • A vaginal cylinder is commonly used for postoperative VBT. The choice of applicator depends on patient's anatomy and physician's experience. In many patients, the postoperative vagina is cylindrical, and it can be treated adequately with a properly sized vaginal cylinder. In some situations, ovoids may provide better dosimetry due to the remnants of the vaginal fornices. The applicator should be lubricated prior to placement. After placement of the applicator, a visual check is done to verify that the applicator is midline and not tilted laterally, anteriorly, or posteriorly • The treatment target is the submucosal lymphatics of the vagina, and in most situations only the proximal vagina must be targeted [11, 14–16]. The proximal vagina is limited to the upper 1/3–1/2 of the vagina (upper 3–5 cm of the vagina) [11, 15]. Increased treatment length can result in increased toxicity • To allow an optimal dose distribution, the vaginal mucosa needs to be in contact with the applicator surface (no air pockets). The ABS recommends use of the largest diameter cylinder that can comfortably fit into the apex of the vagina [6, 11] to reduce mucosal dose

Treatment planning	Treatment planning can be 2D (x-ray) and/or 3D (CT, MRI) based. For treatment planning optimization, points should be placed around both the apex and the lateral aspects of the applicator [11, 15]
Documentation	Documentation of brachytherapy is essential and should include the type of isotope and source; description of the target (including size and shape); prescription depth, target dose, dose per fraction, and the fractionation plan; the applicator type and size, and the treatment plan documentation (dose distribution to dose the target and OAR)

Intact uterus:

Timing	Brachytherapy should be started as soon as possible. We recommend once weekly intracavitary brachytherapy if administered during EBRT. Brachytherapy can be administered twice weekly as a monotherapy or after EBRT completion
Analgesia	Analgesia options include general, spinal, intravenous sedation and/or oral pain medication. Our practice is to use titrated doses of fentanyl, starting with 50 micrograms IV, and lorazepam with 1 mg IV, 20–30 min prior to start of the procedure
Position	Dorsal lithotomy position
Pelvic exam	Examination under anesthesia – a bimanual examination to document any residual nodularity, the cervix size and, the size of the vaginal fornices (i.e., disease extension/response to treatment). The uterus is sounded to aid in selection of the appropriate tandem applicator. Insertion of radiopaque markers in the cervix aids localization of the cervix on imaging. We generally avoid inserting the seed at 3, 6, 9, and 12 o'clock position on the cervical os so that the seeds are not masked by the applicator on AP and lateral orthogonal images
Procedure	• A Foley catheter is inserted into the bladder, and the balloon is inflated with dilute contrast • Tandem and ovoids are commonly used for brachytherapy in this setting. Other applicators include tandem and ring applicator. Simon-Heyman capsules can be used to further distribute dose to the uterus • After selection of appropriate applicators (including angle of the intrauterine tandem and size of ring or ovoids), cervical os is dilated to enable accommodation of Simon-Heyman capsules (if used). Ultrasound guidance can be used during applicator insertion to help guide dilation of the endocervical canal and evaluate placement of the uterine applicators. A tenaculum may be placed on the cervix to provide countertraction for placement of the intrauterine tandem. A ring or ovoids can be used if lateral cervical dosing is needed • It is important that the tandem extends to the uterine fundus to ensure that the entire endometrial lining is treated • Radiopaque vaginal packing is used to displace the bladder base anteriorly and the anterior rectal wall posteriorly away from the intracavitary applicator. Packing also serves to prevent the displacement of the tandem from the uterus and to secure the positioning of the entire applicator • We do not routinely use a smit sleeve, but they can be useful for anatomically difficult implants • Imaging (CT, MRI, plain radiographs) is done for each implant immediately following the placement of the applicator and is essential for treatment planning of each procedure • 3D imaging allows for accurate contouring of the tumor, cervix, uterus, and OAR

Treatment planning	Treatment planning can be 2D (X-ray) and/or 3D (CT, MRI) based. Brachytherapy is prescribed to the uterine serosa
Documentation	Documentation of brachytherapy is essential and should include the type of isotope and source; description of the target (including size and shape), target dose, dose per fraction, and the fractionation plan; the applicator type and size and the treatment plan documentation (dose distribution to dose the target and OAR)

27.5 Common Dose/Fractionation Scheme

Vaginal brachytherapy alone:

- At UNC, VBT is typically prescribed to a dose of 7 Gy at 0.5 cm depth × 3 fractions for VBT alone after hysterectomy. The goal is to achieve an LDR equivalent of 30 Gy at 0.5 cm depth and 65 Gy at the surface.

Common vaginal brachytherapy doses [11, 15]

Dose and fractionation	Prescription depth
7 Gy × 3	0.5 cm depth
4 Gy × 6	Vaginal surface
6 Gy × 5	Vaginal surface
5.5 Gy × 4	0.5 cm depth

EBRT followed by vaginal brachytherapy:

- If EBRT is given, the total dose is 45–50.4 Gy. Midline block (at ~40 Gy) can be used [11].
- Involved unresected lymph nodes can be boosted during EBRT with 1.8 Gy daily fractions for a total of 59.4 Gy [11].
- At UNC, VBT is typically prescribed to a dose of 5 Gy to the vaginal surface x 3 fractions when administered in conjunction with EBRT.

Common vaginal brachytherapy doses (combined with EBRT, 1.8 Gy × 25–33 fx) [6, 12]

Dose and fractionation	Prescription depth
5 Gy × 3	Vaginal surface or 0.5 cm depth
6 Gy × 2	Vaginal surface or 0.5 cm depth
6 Gy × 3	Vaginal surface

RT for inoperable patients:

Inoperable patients with stage I grade 1–2 endometrial cancer with minimal myometrial invasion can be treated with brachytherapy alone. All other patients should receive EBRT in conjunction with brachytherapy. The CTV encompassing

the whole uterus extending to the serosal surface should receive an EQD2 of at least 48 Gy for tandem/ovoids (intracavitary brachytherapy alone) and at least 65 Gy for combination of EBRT plus VBT. A GTV may also be defined using T2-weighted MRI and may be prescribed a dose of ≥80 Gy [5].

Common brachytherapy doses (without EBRT) for inoperable endometrial cancer [5]

Fractionation prescribed to uterine serosa	EQD2(Gy) to the tumor (point A with $\alpha/\beta = 10$ Gy)
6 Gy × 6	48
6.4 Gy × 6	52.5
7.3 Gy × 5	52.6
8.5 Gy × 4	52.4

Common brachytherapy doses (combined with EBRT, 1.8 Gy × 25 fx) [5].

Fractionation prescribed to uterine serosa	EQD2(Gy) to the tumor (point A with $\alpha/\beta = 10$ Gy)
6.5 Gy × 3	71.1
5.2 Gy × 4	70.6
5 Gy × 5	75

27.6 Normal Tissue Tolerance

- EBRT + VBT:
  - Upper vagina mucosa 150 Gy, mid-vagina mucosa 80–90 Gy, lower vagina mucosa 60–70 Gy. *NOTE: the proximal vagina is a target in VBT
  - Small bowel <45–50.5 Gy
  - Rectal point dose <70 Gy
  - Bladder <75 Gy

Dose constraints to organs at risk for brachytherapy

Organ at risk	Radiographic (ICRU point)	3D imaging (D2cc)
Bladder	5× < 3.7 Gy	<90 Gy[a]
Rectum	5× < 3.7 Gy	<70–75 Gy[a]
Sigmoid	–	<70–75 Gy[a]
Ureters	–	<70 Gy

[a]Max point dose defined as <0.035 cc

27.7 Patient Management Considerations

- After completion of treatment, patients should be given a vaginal dilator to prevent scar tissue and adhesions within the vagina. Patients are instructed to place the dilator within the vagina for 10–15 min several times per week.

Acute toxicity

Due to the conformal dosimetry of vaginal cuff brachytherapy, toxicity to bowel, bladder, and rectum are low. There are generally minimal acute toxicities during treatment with vaginal cuff brachytherapy alone.

Late toxicity

Late toxicity is also rare with vaginal cuff brachytherapy alone. The most common side effect is stenosis and atrophy of the vagina, which can result in vaginal shortening or narrowing. Incidences of severe bowel, rectum, and bladder toxicity have been reported including rectovaginal fistula, radiation colitis or cystitis, and vaginal or bladder necrosis, but these reports are rare and appear to be more common when VBT is administered with EBRT.

27.8 Follow-Up

- H&P including pelvic exam should be completed every 3–6 months for the first 2–3 years, then every 6 months for 5 years, and then annually.
- Ca-125 is optional, useful for follow-up if preoperative level was elevated.
- Imaging only if clinically indicated and/or if extrauterine spread was present at initial surgery.

27.9 Relevant Literature

PORTEC-1 and GOG-99, which established the role of postoperative EBRT (conventional fractionation), are outside the scope of this chapter.

Postoperative vaginal brachytherapy vs. vaginal brachytherapy + EBRT				
Randomized control trials				
Study	**Arm 1: VBT alone**	**Arm 2: VBT + EBRT**	**Median follow-up**	**Outcomes**
Onsrud (2013) [17] Stage I	(n = 280) 60 Gy LDR	(n = 288) 60 Gy LDR + 40 Gy EBRT	20.5 years	Median OS 20.48 years (VBT) vs. 20.5 years (EBRT+VBT) (p = 0.186)

Aalders (1980) [18] Stage I	(n = 277) 60 Gy LDR	(n = 263) 60 Gy LDR + 40 Gy EBRT	3–10 years	5-year OS 91% (VBT) vs. 89% (EBRT+VBT) (p = NS) Vaginal/pelvic recurrences 6.9% (VBT) vs. 1.9% (EBRT+VBT) ($p < 0.01$) Grade 3+ toxicity 0.7% (VBT) vs. 1.1% (EBRT+VBT)
Sorbe (2012) [19] Stage I	(n = 263) 3 Gy × 6 fx (HDR) 5.9 Gy × 3 fx (HDR) , or 20 Gy (LDR)	(n = 285) VBT + 46 Gy EBRT	62 months	5-year OS 90% (VBT) vs. 89% (EBRT+VBT) (p = NS) Pelvic recurrences 5.3% (VBT) vs. 0.4% (EBRT+VBT) ($p < 0.001$) Vaginal recurrences 2.7% (VBT) vs. 1.9% (EBRT +VBT) ($p = 0.55$) Grade 3 toxicity 0.8% (VBT) vs. 1.9% (EBRT+VBT)
Postoperative vaginal brachytherapy vs. EBRT				
Randomized control trial				
Study	**Arm 1: VBT**	**Arm 2: EBRT**	**Median follow-up**	**Outcomes**
Nout (2010) [20] (PORTEC-2) Stage I–II	(n = 213) 7 Gy × 3 fx at 0.5 cm (HDR) or 30 Gy at 0.5 cm (LDR)	(n = 214) 46 Gy EBRT	45 months	5-year OS 84.8% (VBT) vs. 79.6% (EBRT) (p = NS) Pelvic recurrences 3.8% (VBT) vs. 0.5% (EBRT) ($p = 0.02$) Vaginal recurrences 1.8% (VBT) vs. 1.6% (EBRT) (p = NS) Grade 3 toxicity <1% (VBT) vs. 3% (EBRT)

Selected studies of postoperative HDR-VBT alone

Study	Patients	Treatments	Median follow-up	Outcomes
Prospective				
Sorbe (1990) [21] Stage I	404	5.0 Gy × 6 fx 4.5 Gy × 6 fx 6.0 Gy × 5 fx 9.0 Gy × 4 fx	NA	5-year OS 92% Pelvic/vaginal recurrences 1.7% Vaginal recurrences 0.7% Acute toxicity 30.9%, late toxicity 15.8% The high-dose group 9 Gy × 4 had a higher rate and grade of late complications
Retrospective				
Weiss (1998) [22] Stage IA–II	122	7.0 Gy × 3 fx	25.6 months	Pelvic recurrence 4.1% Vaginal recurrence 1.6% Recurrence occurred in 3.8% of patients with moderate risk and in 20.5% of patients with high risk No grade 3–4 toxicity
Petereit (1999) [23] Stage IB	191	16.2 Gy × 2 fx prescribed to surface	38 months	4-year OS 95% Pelvic recurrence 0.5% Vaginal recurrence 0% 0.5% developed colo-vaginal fistula 4% asymptomatic vaginal cuff necrosis
Horowitz (2002) [24] Stage IB–II	164	7 Gy × 3 fx at 0.5 cm	65 months	5-year OS 87% Pelvic recurrence 0.6% Vaginal recurrence 1.2% No grade 3–4 toxicity
Alektiar (2005) [16] Stage IB–IIB	382	6.0–7.0 Gy × 3 fx	48 months	5-year OS 93% Pelvic recurrence 3% Vaginal recurrence 0.8% No grade 3–4 toxicity
Diavolitsis (2012) [25] Stage IA	169	7.0 Gy × 3 fx 5.5 Gy × 4 fx at 0.5 cm	103 months	5-year OS 95.5% 5-year RFS 94.4% Pelvic recurrence 0.5% Vaginal recurrence 0.5% No grade 3–4 toxicity

Selected studies of postoperative pelvic EBRT and HDR-VBT

Study	Patients	Treatments	Median follow-up	Outcomes
Retrospective				
Lybeert (1989) [26] Stage I–IV	291	40 Gy EBRT + 5Gy × 4 fx at 0.5 cm HDR	NA	5-year RFS Stage I:88% Stage II:68% Stage III/IV:50% Pelvic recurrence 2.7% Vaginal recurrence 2.7% No grade 3–4 toxicity
Nori (1994) [27] Stage I	300	40 Gy EBRT + 7Gy × 3 fx at 0.5 cm HDR	12 years	PFS 96.6% Pelvic recurrence 0.3% Vaginal recurrence 2% No grade 3–4 toxicity
Algan (1996) [28] Stage I/II	81	45 Gy EBRT + 4 Gy × 3 fx at 0.5 cm HDR Or 30 Gy LDR to surface	NA	5-year OS 83% Pelvic recurrence 3% Vaginal recurrence 4% Grade 3 toxicity 3%
Cannon (2009) [29] Stage II	50	45–51 Gy EBRT + more than 4 different fractionations for HDR (most common 5 Gy × 5 fx or 7.8 Gy × 2 fx)	5.2 years	5-yearr OS 82% 5-year DFS 82% Pelvic recurrence 4% Vaginal recurrence 0% Grade 3 toxicity 2%, grade 4 toxicity 2%

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