Rajni A. Sethi · Igor J. Barani
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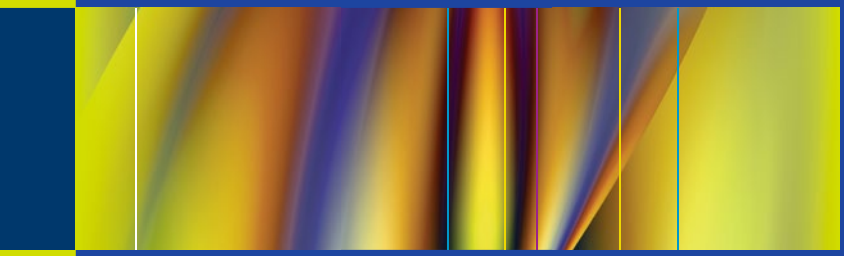
Editors



Handbook of Evidence-Based Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Springer

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Preface

Over the past decade, technical advancements in radiotherapy such as image guidance, highly modulated beams, improved patient immobilization, tumor tracking systems, beam gating, and complex treatment planning systems have enabled practitioners to accurately and precisely deliver highly conformal, large doses of radiation. As these technologies are more widely adopted worldwide, extreme hypofractionated and single fraction regimens using stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) are becoming more common. We developed this handbook in order to concisely summarize the state of the art including: (1) history of SRS and SBRT; (2) the biologic rationale; (3) typical practices; and (4) the reported results. In doing so, we hope that practitioners might be more aware of what has been published and what might be expected were they to similarly treat patients. However, we cannot and do not vouch for the safety of any of treatment practices reported. First, the follow-up in many cases is relatively short. Second, as with any recipe, there may be details or ingredients left out that may critically impact the results. In all cases clinical judgment is required, particularly in cases when dose-limiting structures are put at risk when adjacent to very high doses of radiation.

While several textbooks focus on SRS and SBRT, we specifically wanted to create a practical handbook on these techniques that could be referenced easily in the clinic. This handbook can inform decisions regarding the appropriateness

of SRS or SBRT, guide treatment technique, and summarize expected outcomes and toxicity.

We have developed the *Handbook of Evidence-Based Stereotactic Radiosurgery and Stereotactic Body Radiotherapy* as a companion book to our institution's prior publication, *Handbook of Evidence-Based Radiation Oncology*. As such, we have attempted not to replicate information between the two books. General information on anatomy, staging, work-up, and follow-up for each disease site can be referenced in the latter. The current handbook focuses on specific uses of SRS and SBRT, with chapters organized by disease site. We include a description of treatment techniques and recommended imaging. We also specifically address safety and quality assurance issues, which are especially important with extreme hypofractionation. In each chapter, we discuss toxicity and management issues specific to SBRT. We have also included chapters on the historical development of SRS and SBRT, biologic rationale for these techniques, and treatment delivery systems. Finally, in the appendix, we include a summary of normal tissue dose tolerances.

In order to maintain the nature of this publication as a handbook, we limited the amount of information included in each chapter. We encourage you to refer to original publications as listed in the reference section for more detailed information on clinical protocols and previously published data.

In many cases the contents of this book reflect the treatment approach at the University of California at San Francisco. We are privileged to employ a broad range of treatment machines and expertise that enables the use of SRS and SBRT in many settings. This book is meant to summarize our own experience and that of our colleagues who have reported separately in peer-reviewed journals and at national and international meetings. Individual practitioners must use their own clinical judgment and knowledge to guide use of SRS and SBRT in their own practice. Specifically, we caution against use of these highly skilled techniques in institutions without prior training or expertise.

We want to sincerely thank the contributing authors for the excellent chapters they have produced. We also wanted to specifically thank Keith Sharee for his stalwart and enthusiastic editorial review and for managing all of the references and abbreviations. This handbook would not have been possible without their hours of hard work and dedication. We want to acknowledge the pioneers in our field who have built the body of work that we are presenting here today and whose ingenuity and drive continues to move our field ahead with the constant goal of improving outcomes for our patients. And finally, we want to thank our patients, whose courage continues to inspire us every day.

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Abbreviations

AAPM	American Association of Physicists in Medicine
ABC	Active breathing control
ACTH	Adrenocorticotropic hormone
ADT	Androgen deprivation therapy
AFP	Alpha-fetoprotein (α-fetoprotein)
AMA	American Medical Association
AP/PA	Anteroposterior/posteroanterior
ASTRO	American Society for Radiation Oncology
ATM	Ataxia telangiectasia mutated
ATR	ATM-Rad3-related
AVM	Arterio-venous malformation
BED	Biologically effective dose
bPFS	Biochemical progression-free survival
BPL	Batho power-law correction
BRCA	Breast cancer risk genes BRCA1 and BRCA2
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CBC	Complete blood count
CBCT	Cone beam computed tomography
CEA	Carcinoembryonic antigen
CGE	Cobalt gray equivalent
CHF	Congestive heart failure
CK	CyberKnife
Cm	Centimeter
CMP	Comprehensive metabolic panel
CMS	Centers for Medicare and Medicaid Services
CN	Cranial nerve
CNS	Central nervous system

COPD	Chronic obstructive pulmonary disease
CPA	Cerebellopontine angle
CPT	Current procedural terminology
Cr	Creatinine
CR	Complete response
CRT	Conformal radiation therapy
CSF	Cerebrospinal fluid
CSS	Cause-specific survival
CT	Computerized tomography
CT A/P	CT abdomen pelvis
CT C/A/P	CT chest abdomen pelvis
ctDNA	Circulating tumor DNA
CTV	Clinical target volume
CXR	Chest X-ray
DBR	Distant brain recurrence
DLCO	Carbon monoxide diffusion in the lung
DNA	Deoxyribonucleic acids
DRE	Digital rectal examination
DRR	Digitally reconstructed radiograph
DSS	Disease-specific survival
EBRT	External beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EPID	Electronic portal imaging devices
EQD2	Equivalent dose in 2 Gy fractions
ERCP	Endoscopic retrograde cholangiopancreatography
ESR	Erythrocyte sedimentation rate
EUA	Exam under anesthesia
EUS	Endoscopic ultrasound
FCRT	Fractionated conformal radiotherapy
FDG	Fluoro-deoxy-glucose (fludeoxyglucose)
FEV1	Forced Expiratory Volume (In 1 s)
FFLP	Freedom from local progression
FFP	Freedom from progression
FLAIR	Fluid attenuation inversion recovery

FNA	Fine needle aspiration
FSH	Follicle-stimulating hormone
5FU	5-Fluorouracil
FVC	Forced vital capacity
GGO	Ground glass opacities
GH	Growth hormone
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
GKRS	Gamma knife radiosurgery
GS	Gleason score
GSM	Gold seed marker
GTR	Gross total resection
GTV	Gross tumor volume
GU	Genitourinary
Gy	Gray
H&P	History and physical
HCC	Hepatocellular carcinoma
HDR	High dose rate
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HR	Homologous recombination or Hazard ratio
ICRU	International Commission on Radiation Units and Measurements
IDL	Isodose line
IGRT	Image-guided radiation therapy
iGTV	Internal gross tumor volume
ILD	Interstitial lung disease
IMRT	Intensity modulated radiation therapy
INR	International normalized ratio
IORT	Intraoperative radiation therapy
ITV	Internal target volume
IV	Intravenous
IVC	Inferior vena cava
IVP	Intravenous pyelogram
JROSG	Japanese Radiation Oncology Study Group
KPS	Karnofsky performance scale
kV	Kilovolt

LC	Local control
LDH	Lactate dehydrogenase
LF	Local failure
LFT	Liver function test
LH	Luteinizing hormone
LPFS	Local progression-free survival
LQ	Linear quadratic
MDACC	MD Anderson Cancer Center
MeV	Mega electron volt
MFS	Metastasis-free survival
MLC	Multileaf collimator
Mm	Millimeter
MMEJ	Microhomology-mediated end joining
MMSE	Mini-mental state examination
MNLD	Maximal nonlethal dose
MRA	Magnetic resonance angiogram
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MRN	MRE11-Rad50-NBS1
MS	Median survival
MTD	Maximum tolerated dose
MTP	Mean target position
MU	Monitor units
MV	Megavolt
MVCT	Megavoltage CT
MVD	Microvascular decompression
NAA	*N*-acetyl-aspartic acid
NAGKC	North American Gamma Knife Consortium
NCCN	National Comprehensive Cancer Network
NED	No evidence of disease
NF2	Neurofibromatosis type II
NHEJ	Non-homologous end joining
NR	Not reported
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
OAR	Organs at risk
ODI	Optical distance indicator
OS	Overall survival

PALN	Para-aortic lymph nodes
PCP	Pneumocystis carinii pneumonia
PDD	Percent depth dose
PET	Positron emission tomography
PFP	Progression-free probabilities
PFS	Progression-free survival
PR	Partial response
PSA	Prostate-specific antigen
PTV	Planning target volume
QA	Quality assurance
QOD	Every other day
QOL	Quality of life
RBE	Relative biological effectiveness
RCC	Renal cell carcinoma
RECIST	Response evaluation criteria in solid tumors
RFA	Radiofrequency ablation
RILD	Radiation-induced liver damage
RP	Radical prostatectomy
RPA	Recursive partitioning analysis
RPL	Radiological path length algorithm
RS	Radiosurgery
RT	Radiotherapy or radiation therapy
RTOG	Radiation Therapy Oncology Group
RUC	AMA Specialty Society Relative Value Scale Update Committee
RVS	AMA Specialty Society Relative Value Scale
SABR	Stereotactic ablative radiotherapy or stereotactic ablative brain radiation or stereotactic ablative body radiotherapy
SAHP	Senescence-associated heterochromatin foci
SBRT	Stereotactic body radiotherapy
SD	Stable disease
SF	Surviving fraction
SMA	Superior mesenteric artery
SRS	Stereotactic radiosurgery
STR	Subtotal resection
STS	Soft tissue sarcoma
SUV	Standardized uptake value

TIA	Transient ischemic attack
TPS	Treatment planning system
TRUS	Transrectal ultrasound
TSH	Thyroid-stimulating hormone
TURBT	Transurethral resection of bladder tumor
TURP	Transurethral resection of prostate
TVT	Tumor vascular thrombosis
U/S	Ultrasound
UA	Urinalysis
USC	Universal survival curve
USPSTF	US Preventive Service Task Force
VCF	Vertebral body compression fracture
VEGF	Vascular endothelial growth factor
VMAT	Volumetric-modulated arc therapy
WBRT	Whole-brain radiation therapy
WHO	World Health Organization
XR	X-ray

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Chapter 1
Introduction to Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

David A. Larson

Stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) have an established but evolving role in the management of malignant and benign conditions. They have altered the way clinicians think about fractionation, and therefore they rank among the most important advances in radiation oncology, along with the development of megavoltage treatment machines, imaging-based treatment planning, and intensity-modulated radiation therapy. SRS and SBRT technologies were developed largely by dedicated medical physicists, (Benedict et al. 2008) with input from clinicians. Approximately 5–10 % of US radiotherapy courses are delivered with SRS or SBRT, and these technologies and their clinical outcomes are now a firmly established part of the educational curriculum for resident physicians in radiation oncology and neurosurgery.

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Historical Foundations

During the 1950s, neuroanatomists and neurophysiologists developed techniques to produce small, highly localized, ablative CNS radio-lesions in animals using a variety of radiation sources, including implanted radon seeds, implanted isotopes such as Au^{198} and Co^{60}, betatron X-rays, and cyclotron-produced protons and deuterons. Swedish neurosurgeon Lars Leksell, a pioneer in the development of stereotaxy, recognized that small, accurately placed radio-lesions could be produced in humans. In 1951 he coined the term "radiosurgery" and is recognized as the father of radiosurgery (Leksell 1951). He performed focal single-fraction experiments in the brains of goats, cats, and rabbits using multiple cross-fired proton beams as he sought an optimum dose to produce discrete CNS lesions of dimension 3–7 mm. He found that a suitable maximum dose for the production of a discrete lesion within 1–2 weeks was 20 Gy in a single fraction. In the 1950s and 1960s he pioneered X-ray and proton SRS for pain syndromes and movement disorders. In 1961 he used 3 mm cross-fired proton beams to perform thalamotomies for pain control. He invented the Gamma Knife and performed his first Gamma Knife procedure in 1967. In 1974 that first Gamma Knife was installed as an experimental tool at UCLA under the direction of neurosurgeon Bob Rand.

During the 1950s, in the USA, internist John Lawrence, often called the father of nuclear medicine, developed highly focal ablative radiation procedures with cyclotron-produced protons, deuterons, and helium ions at what is now called Lawrence Berkeley National Laboratory (where John's brother, Ernest, invented the cyclotron, for which he was awarded the Nobel Prize). He took great interest in pituitary disorders and performed multi-fraction dose/targeting studies in dogs, rats, and monkeys using bone landmarks to target and ablate the pituitary with multiple cross-fired beams. He initiated human studies in 1954, initially to suppress pituitary function in breast cancer patients and subsequently to treat acromegaly. He tried numerous fractionation schemes, eventually settling on 300 Gy

in six fractions over 2 weeks to ablate the pituitary without damage to the surrounding tissue.

In 1961, Massachusetts General Hospital neurosurgeons William Sweet and Raymond Kjellberg initiated treatment of pituitary tumors and arteriovenous malformations with single-fraction Bragg-peak protons. Kjellberg searched the literature for examples of brain radio-necrosis in humans, monkeys, and rats, and plotted his findings as log of dose sufficient to produce necrosis versus log of beam diameter, and connected the data points with a steep straight line demonstrating the strong relationship between treatment volume and likelihood of necrosis. His plot indicated that 10 Gy was sufficient to produce necrosis for a 10 cm beam diameter and 4000 Gy was sufficient to produce necrosis for a 10 μm beam diameter (Kjelberg 1979). Many of his initial SRS treatments involved doses considered just sufficient to cause radionecrosis, according to his necrosis plot.

Neurosurgeons in Europe, South America, and the United States subsequently developed SRS programs using modified linear accelerators or cobalt teletherapy units. One of the best known systems was the linac SRS system developed by neurosurgeon Ken Winston and physicist Wendel Lutz, stimulated by the work of Leksell and designed to be capable of delivering very high, single-fraction photon radiation doses in the range of 100–150 Gy to small, precisely located, volumes (0.5–2 cm^3) within the brain (Lutz et al. 1984).

Development of SRS and SBRT

Although the above historical foundations involved focally ablative lesioning, SRS as it developed in the late 1980s involved less aggressive single-fraction maximum doses, in the range of 20–50 Gy for most indications and for treatment volumes up to about 15 cc, with higher maximum doses in the range of 100–150 Gy reserved for pain syndromes or movement disorders and for treatment volumes less than about 0.1 cc. Selection of the less aggressive doses was strongly influenced by

radiation oncologists and neurosurgeons at the first North American SRS locations, including Boston (1/86, AVM), Montreal (12/86, AVM), Pittsburgh (8/87, acoustic neuroma), and San Francisco (3/88, AVM). Initial treatments at those facilities and others throughout the world were for benign rather than malignant indications, even though today the majority of SRS and nearly all SBRT procedures are for malignant processes. One of the first reported malignant indications receiving SRS was Sturm's 1987 report on brain metastasis (Sturm et al. 1987).

During the late 1980s and early 1990s, SRS grew rapidly. The first North American Radiosurgery conference was held in 1987 in Boston, organized by neurosurgeon Ken Winston and radiation oncologist Jay Loeffler, attracting 100 registrants. ASTRO's first "refresher" course on radiosurgery, attended by about 400 members, was presented by radiation oncologist David Larson at ASTRO's Annual Meeting in New Orleans in 1988. The yearly number of SRS patients in North America increased from about 600 in 1990 to about 12,000 in 2000, during which period the number of yearly publications on SRS increased from about 50 to about 200.

SBRT developed about a decade later than SRS, but was based on similar principles. Swedish physicist Ingmar Lax and radiation oncologist Henric Blomgren, both at the Karolinska Hospital in Stockholm, were very familiar with the brain SRS procedures being carried out in their institution. They reasoned that similar local control outcomes could be achieve at non-brain body sites with one or a few focally delivered fractions, even if targeting and immobilization issues for non-brain sites were more much complicated. They described their technique in 1994 (Lax et al. 1994) and in 1995 reported clinical outcomes in 31 patients with 42 malignant tumors of the liver, lung, or retroperitoneum, achieving local control in 80 % of targets, and prescribing at the 50 % isodose surface (Blomgren et al. 1995). David Larson visited the Karolinska Hospital in 1993 as an observer and brought their technique back to UCSF, where he treated 150 patients during 1993–1995. Thus the origins of both SRS and SBRT can be traced to the Karolinska Hospital.

Standard Fractionation Versus Hypofractionation

Prominent pioneers of standard fractionation include French radiation oncologists Henri Coutard and Francois Baclesse, who treated laryngeal and breast cancers in Paris with various fractionation schemes lasting from 2 weeks to 10 months during the 1920s–1940s. They found that the uncomplicated control rate, often called the therapeutic ratio, peaked at 6–8 weeks, a result championed by Gilbert Fletcher in the USA following his training in Paris and confirmed by years of clinical experience throughout the world. In 1997, radiation oncologist Eli Glatstein stated: "Had Coutard and Baclesse not pioneered fractionation, radiotherapy probably would have fallen into oblivion due to the morbidities of single shot treatment. Indeed, much of the first half of this century was spent learning that doses large enough to sterilize a mass of tumor cells (10 logs) cannot be predictably given safely. Instead, fractionation evolved which permitted us to exploit repopulation, redistribution, reoxygenation, and repair."

Despite the above, clinicians have found that SRS- and SBRT-based hypofractionation techniques can be effectively and safely used for benign and malignant conditions in the brain and for initial or recurrent non-small-cell lung cancer, prostate cancer, renal cell carcinoma, and hepatocellular cancer, and for oligometastases in the lung, liver, spine, and brain. To reconcile this with the established role of standard fractionation, one must recognize that with non-focal radiotherapy the number of normal cells irradiated to full dose was historically as much as several logs *greater* than the number of tumor cells irradiated. However, with SRS and SBRT, the number of normal cells irradiated to full dose is as much as a log *less* than the number of tumor cells irradiated. If few normal tissue cells receive full dose, any clinically observable benefits of standard fractionation that are attributable to repopulation and repair are necessarily diminished. Similarly, the clinically observable fractionation benefits attributable to reoxygenation and redistribution within tumors are diminished if BED within the target can be increased safely.

For small tumors such as acoustic neuromas, meningiomas, and brain metastases, the reported uncomplicated control rate curve appears to be relatively flat over the range of 1–30 fractions. For some slightly larger targets, perhaps up to 3–5 cm in maximum dimension, the rates may peak at about 5 fractions, possibly because of the increased importance of reoxygenation and the increased volume of irradiated normal tissue with larger targets. Nevertheless, it is recognized that for many targets at CNS and non-CNS sites, the precise optimum fraction number with highly focal SRS or SBRT is not known, even though it is almost certainly far less than 30.

Summary

In summary, clinical results indicate that for carefully selected small targets of most histologies and at most anatomic body sites, favorable uncomplicated control rates can be achieved with 1–5 SRS or SBRT fractions, as the following chapters demonstrate. Nevertheless, physician judgment remains paramount, and in that context it is appropriate to quote Professor Franz Buschke, ex-Chair of Radiation Oncology at UCSF, who wrote a letter to a referring physician in which he said: "Coutard taught us that the incidence of radiation sickness is related to the incompetence of the radiation therapist." (*Letter to a referring physician 1952*).

Nomenclature

The terms "SRS" and "SBRT," as used in this manual, apply to CNS and non-CNS anatomic sites, respectively, and in both cases involve delivery of a high biological effective dose (BED) in 1–5 fractions to small, focal, well-defined targets while minimizing nontarget dose. In the USA this terminology is recognized by the American Medical Association (AMA) Current Procedural Terminology (CPT) editorial panel, the AMA Specialty Society Relative Value Scale

(RVS) Update Committee (RUC), the Centers for Medicare and Medicaid Services (CMS), and most commercial payers. Alternative nomenclature such as "SABR" ("Stereotactic Ablative Radiotherapy" or "Stereotactic Ablative Brain Radiation" or "Stereotactic Ablative Body Radiotherapy") is favored by some marketers.

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Part I
Radiobiology of Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Chapter 2
Radiobiology of Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Andrew Vaughan and Shyam S.D. Rao

Historically, the radiation biology relevant to clinical treatment was developed in a pre-IGRT era where normal tissues received substantial, protracted irradiation. This conventional fractionated treatment, commonly involving 30–35 fractions of 1.8–2 Gy over 6–7 weeks, has been interpreted biologically with the parameters, repair, reoxygenation, redistribution, repopulation, and (less commonly) radiosensitivity. Hypofractionated treatment may modify the impact or significance of these factors.

Repair

It is widely assumed that irradiated normal tissue is better able to respond to repetitive cycles of DNA damage than tumors, linked to intrinsic aberrations in damage repair systems characteristic of transformation (Jackson and Bartek 2009). Thus multiple fractions of irradiation incrementally

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separate normal tissue toxicity from that seen in the tumor. *During SRS/SBRT the number of fractions delivered is much reduced, limiting the magnitude of this differential response, however offset by reduced normal tissue damage linked to precision dose delivery.* As the opportunity for repair is reduced the toxicity of the dose delivered is greater, a feature linked to the beta (quadratic) term of the linear quadratic equation discussed later. Individual DNA break sites are tagged with a modified histone, γ H2AX, over large, Mbp tracts of DNA surrounding the break, which can be visualized using labeled antibodies (Valdiglesias et al. 2013). The break itself is marked by the MRN complex of MRE11, Rad50, and Nibrin that holds the two broken ends together. Individual breaks may be repaired by one of the three systems, homologous recombination (HR), nonhomologous end joining (NHEJ) or microhomology-mediated end joining (MMEJ) also called backup NHEJ. In the order written these repair pathways offer an increasing chance of misrepair, thus generating lethal aberrations such as a dicentric rearrangement.

Reoxygenation

Tumors commonly exhibit localized hypoxia (≤10 mmHg). The lack of oxygen is a potent dose modifier increasing radiation resistance by up to a factor of three due to the lack of fixation of free radical damage. Conventional fractionation facilitates reoxygenation by reducing overall oxygen demand as the tumor mass shrinks under treatment. Residual hypoxic cells may become reoxygenated late in the treatment cycle, and thus be eradicated. *SRS/SBRT is at a theoretical disadvantage in that it offers both a reduced time frame and number of fractions to initiate and utilize reoxygenation. Further research will be required to determine the significance of this issue.* Hypoxic cell sensitizers, such as the nitroimidazoles, have been modestly effective in initial clinical trials but have not gained widespread clinical acceptance as more recent

data have shown minimal efficacy (Reddy and Williamson 2009; Rischin et al. 2010). *Their application to SRS/SBRT may be more appropriate in that the need for hypoxic sensitization may be greater and the reduced treatment time may limit patient exposure to toxic side effects*. Hypoxic tumor content alone is a negative predictor of outcome, independent of radiation effects, in that individuals with elevated hypoxia treated by surgery alone have a worse outcome in terms of loco-regional control and metastatic spread (Hockel et al. 1996). In an interesting approach it was shown that large fraction sizes (>10 Gy) activate a rapid endothelial apoptotic response via membrane located acid sphingomyelinase that releases the pro-apoptotic compound, ceramide, and that tumor cure with single-dose radiation was dependent on activation of this endothelial cell stress pathway (Fuks and Kolesnick 2005). *This raises the possibility that an initial large-dose fraction could affect the response to subsequent fractions* via *changes in tumor perfusion or hypoxia.* Such effects are subject to further modification including hypoxia triggered elevation in HIF1α/IF1β that transcriptionally activates VEGF—a proangiogenic factor, in addition to more broad effects such as ATM/ATR-mediated cell cycle checkpoint control and reduced ability to execute HR repair via suppression of RAD51 (Chan et al. 2008; Hammond et al. 2003).

Repopulation

In an early, but key, analysis of clinical data by Withers et al. it was found that after approximately 3 weeks of treatment, repopulation of tumor was observed that would require additional dose for control (Withers 1985). The continuous delivery of conventional fractionation to prevent treatment prolongation was the empirical answer to keep this expansion in check. *In the case of SBRT and SRS, the expedited delivery of a tumoricidal dose should mitigate any clonal expansion, offering a significant advantage, particularly for rapidly dividing tumors*.

Redistribution

Both conventional and hypofractionated regimes will selectively kill cells in the most sensitive part of the cell cycle, G2/M, leaving a cohort of relatively resistant cells. Thus far it has not proved possible to take advantage of this synchrony, due to the presence of subpopulations of tumor cells that cycle at different rates and the complexity of proactively measuring the ideal time for subsequent irradiation. However, reducing the number of fractions does alter the probability of irradiating a cohort of cells as they move into a radiosensitive phase.

Radiosensitivity

Tumor cells derived from radioresponsive tumors are more radiation sensitive than those, such as glioblastoma, that are harder to control (Malaise et al. 1987; Deacon et al. 1984). However, though the differential radiosensitivity observed between tumor types is significant at low (conventional fractionation) doses, at high doses, in the exponential part of the dose-response curve, no differential sensitivity is observed (Malaise et al. 1987). *Thus SRS/SBRT should mitigate differences in tumor kill that are directly attributable to variations in individual tumor cell radiation sensitivity*. Stem cells have been identified in solid tumors of breast, brain, and elsewhere (Al-Hajj et al. 2003; Singh et al. 2004). Such cells are notably more radiation resistant, likely through enhanced DNA repair secondary to increased CHK1/2 cell cycle checkpoint function (Bao et al. 2006). *The increased fraction size and shorter treatment time of SRS/SBRT may provide less opportunity for the selection and outgrowth of resistant stem cells*.

Cell Death

Assessment of radiation lethality is best demonstrated using the clonogenic assay: single, viable cells divide five or six times in culture forming a countable colony. Using this tool,

the shape of the dose-response survival curve for most human carcinoma cells exhibits an initial shoulder region, followed by a simple exponential when plotted as log survival against dose. This is a key feature in terms of estimating differences in lethality between conventional vs. SRS/SBRT treatments. For those cells that die, mitotic catastrophe is the most frequent lethal route for carcinomas. In this route, two chromosomes are fragmented by radiation and subsequently fuse. If the derivative structure contains two centromeres (a dicentric is one example) it may attach to both poles of the mitotic spindle and physically restrict cell division, killing the cell. Of the remainder, autophagy, necrosis, or senescence are likely minor components of radiation lethality; autophagy observed as sequestering of organelles, membrane, and cytoplasm into autophagosomes; necrosis releases cellular contents triggering inflammation; and in senescence, cells stop dividing, linked to an elevation in β [beta] galactosidase, senescence-associated heterochromatin foci (SAHP), and DNA fragmentation staining. However, a mitotic catastrophe may trigger an apoptotic phenotype (nuclear fragmentation, caspase 3 and 9 activation, elevation in bax, suppression of bcl2) secondary to mitotic arrest (Surova and Zhivotovsky 2013). As noted above the higher doses of SRS/SBRT *may selectively trigger apoptosis in endothelial cells that may impact tumor control* (Table 2.1).

Models of Cell Survival

The linear quadratic (LQ) interpretation of cell survival curves was developed in the conventional (non-IGRT) fractionation era to estimate the response of tumors and late reacting normal tissues to variations in fractionation schedules (Eq. 2.1). Here the surviving fraction (SF) is related to dose D through both linear and quadratic components:

$$\mathrm{SF} = e^{-\alpha D+\beta D2} \tag{2.1}$$

In its simplest form, differences in tissue or tumor responses can be calculated using BED, the biologically effective dose, obtained from a fraction size of dose d delivered n times (Eq. 2.2). Average values of the α/β ratio are often taken as 3 (Gy_3) for late reacting tissues, or 10 (Gy_{10}) for acute responses, including most tumors:

$$\text{BED} = nd\left(1+\frac{d}{\alpha/\beta}\right) \tag{2.2}$$

In the changing landscape provided by IGRT technology, SRS/SBRT incorporates increased fraction sizes and better tumor/normal tissue discrimination. This has led to inconsistencies when trying to identify biologically equivalent doses of conventional fractionation with that delivered by SRS/SBRT.

The major issue is that the LQ formula describes a continuously bending dose-response curve (the βD^2 component) whereas what is most commonly observed is a simple exponential response following an initial shouldered region. Thus using Eq. (2.2) to predict the BED of an SRS/SBRT treatment will potentially overestimate toxicity. A number of models have been proposed that counter this discrepancy. Of the many published models, the Universal Survival Curve (USC) of Park et al. offers a direct approach and grafts a multitarget dose-response model on to a standard LQ equation (Park et al. 2008). This has the benefit of better representing the biological reality of radiation lethality of simple survival curves, but does not address the many differences in clinical responses linked to SRS/SBRT that are discussed above. Many in the field are still divided on the issue, some suggesting that the LQ relationship is still valid, and others being less convinced (Park et al. 2008; Guerrero and Li 2004; Shibamoto et al. 2012). Sample calculations made using Eq. (2.2) illustrate the dramatic differences in calculated BED using the LQ formula for SRS/SBRT (Table 2.2). We would offer the following guidance: To generate an indication of the potency of a SRS/SRBT schedule compared to a conventional

TABLE 2.1 Advantages and disadvantages of SRS/SBRT from a radiobiological perspective, organized according to the five "R" principles of radiobiology

Parameter	SRS/SBRT disadvantage	SRS/SBRT advantage
Repair	Limits the number of cycles of damage and repair that separates the tumor response from normal tissue toxicity	Improved tumor targeting reduces the dose to normal tissues and the need for sparing by fractionation
Reoxygenation	Fewer treatment cycles potentially reduces inter-fraction reoxygenation and thus increases radioresistance	None
Repopulation	None	Much reduces or eliminates tumor repopulation during shorter treatment—specifically relevant to radiation resistant tumor stem cells
Redistribution	Reduced numbers of fractions will affect the cell cycle distribution of remaining viable cells. Though redistribution could favor fractionated RT which provides a higher probability of catching cells in their vulnerable cell cycle states, the clinical significance is unknown	
Radiosensitivity	None	Multi-log cell kill reduces the variability in tumor radiosensitivity primarily observed within the shoulder region of the cell survival curve. Single-tumor doses >10 Gy may trigger endothelial cell apoptosis

Table 2.2 BED calculation

Schedule	BED Gy_3	BED Gy_{10}
2 Gy × 30	72	100
20 Gy × 3	180	460

fractionation scheme, the LQ formula will provide appropriate estimates up to fractional doses in the range of 6–10 Gy. Above this, application of the LQ methodology will have reduced power to provide a comparison with conventional schedules. However, as in all applications of BED calculations, the result generated should only be considered as a guide. In the case of clinical questions related to normal tissue toxicity from SRS/SBRT schedules, empirically established dose limits and tolerances from relevant clinical literature should be respected for this increasingly used modality.

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Part II
Physics of Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Chapter 3
Physics of Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Angélica Pérez-Andújar, Martina Descovich, and Cynthia F. Chuang

Pearls

- High doses of radiation delivered over 1–5 fractions (high biological effective dose).
- High-precision radiation delivery techniques combining image guidance solutions and stereotactic coordinate systems.
- Very conformal dose distribution with steep dose gradients.

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- Margin reduction, but consider that a large source of uncertainty relates to target delineation.
- Requires a rigorous quality assurance program and end-to-end commissioning procedures incorporating imaging, simulation, treatment planning, image guidance, motion management, and treatment delivery systems.

Basic Principles

- Originally developed for the treatment of intracranial lesions (Leksell 1983), radiosurgery is rapidly evolving.
- Both intracranial (SRS) and extracranial (SBRT) treatment sites.
- Recommendations for normal tissue dose tolerances are reported in AAPM TG-101 (Benedict et al. 2010) (Table 3.1).
- Patient setup and immobilization devices vary depending on body site, treatment platform, and the capability of the delivery system to detect and correct for changes in patient position during treatment.
- The stereotactic coordinate system is provided either by an invasive fixation device (head frame) or by the imaging system (frameless radiosurgery).
  - SRS: Stereotactic head frame attached to the patient's skull using pins (Khan 2003). Frameless system could include thermoplastic mask with reflective markers and vacuum-assisted mouthpieces.
  - SBRT: body frames, body cast, and vacuum bags (Table 3.2).
- Imaging techniques for SRS/SBRT treatment verification (Murphy et al. 2007; German et al. 2001; Broderick et al. 2007; Li et al. 2008; Jin et al. 2008): 2D MV electronic portal imaging (EPID).
  - Orthogonal kV radiographs.
  - MV cone beam CT.

TABLE 3.1 General comparison of conventional radiotherapy treatment versus stereotactic therapy (SRS/SBRT)

Characteristic	Conventional RT	SRS/SBRT
Prescription dose per fraction	≤3 Gy	≥5 Gy
Number of fractions	≥10	≤5
Dose distribution	Homogeneous (max PTV dose ≈105–110 %)	Heterogeneous (max PTV dose ≈110–200 %)[a]
Dose gradient outside PTV	Shallow slope	Steep slope
Prescription isodose line	≈90–95 %	≈50–95 %[a]
Target definition	Tumor might not have a sharp boundary	Well-delineated target
PTV margin	≈cm	≈mm

Modified from Linda Hong's presentation (Benedict et al. 2010; Hong 2012)
[a]Heterogeneity of SRS/SBRT plans is highly dependent on the treatment technique used. The same applies to the prescription isodose lines

TABLE 3.2 Reported accuracy of commercially available SBRT immobilization devices (Taylor et al. 2011)

Site	System	Reported accuracy (mm)
Lung	Elekta body frame	1.8–5
	MI body fix	2.5–3
	Leinbinger body frame	2–4.4
Liver	Elekta body frame	≤4.4
	MI body fix	≤3.2
	Leinbinger body frame	1.8–4.4
Spine	MI body fix	≈1
	Body cast	≈3
	Fiducial marker tracking	2

  - kV cone beam CT.
  - MV helical CT.
  - In-room diagnostic CT.
  - 4DCBCT.
  - Infrared imaging.
  - Radiofrequency tracking.
- Management of respiratory motion for SBRT motion-encompassing techniques (4DCT—ITV delineation).
  - Abdominal compression—this method reduces the target excursion with breathing.
- Breath-hold—radiation is delivered when the patient is holding the breath.
- Gating—radiation is delivered only at a particular phase of respiration.
- Dynamic target tracking—beams are re-targeted in real time to the continuously changing target position—advantages: no need for ITV expansion; no treatment interruptions; accounts for changes in target motion and respiratory pattern during treatment.

SRS/SBRT Treatment Parameters

- Target volumes: The concept of GTV, CTV, PTV, and ITV described in ICRU 50 and 62 for SRS also applies to SBRT planning (Medin et al. 2010; ICRU 1993). PTV margins depend on body site, treatment device, localization technique, and imaging frequency. Typical margins range from 2 to 5 mm for SBRT.
- Dose conformity: the high-dose volume conforms tightly around the target.
- Dose heterogeneity: hot spots located within the target are often considered not only acceptable, but also desirable. The prescription dose is typically 50–90 % of the maximum dose depending on the treatment delivery and treatment planning systems.
- Dose gradient: the dose fall-off away from the target is steep. The volume of normal tissue receiving high doses of radiation is kept at a minimum. This is in comparison with other treatment techniques like 3D conformal.

- Beam energy: 6 MV photons offer the best compromise between beam penetration and penumbra characteristics. Many techniques use unflattened beams.
- Beam shaping: Radiation is collimated to a small field using heavy metal cones (circular field 4–60 mm diameters), multileaf collimator (MLCs), or microMLCs (2.5 mm leaves width). MLCs and micro MLCs are used to deliver treatments developed with conformal beams, intensity modulated fields, dynamic conformal arcs, or a combination of these (ICRU 1999).
- Treatments are delivered via coplanar and non-coplanar beam arrangements.
- Circular fields provide a sharper penumbra than microMLCs.
- Beam geometry: multiple non-overlapping beams concentrically pointing to the target; 5–12 coplanar or non-coplanar beams; 1 or 2 coplanar or non-coplanar arcs; a continuously rotating fan beam; hundreds of non-coplanar pencil beams pointing to different parts of the target (non-isocentric beam arrangement) or to the same point (isocentric beam arrangement).

Plan Optimization

- Forward planning: the user manually adjusts beam arrangement, field shapes, and weights until the desirable dose distribution is achieved.
- Inverse planning: the user specifies plan objectives for target and normal structures and a dose optimization algorithm calculates field shapes and weights based on the minimization of a mathematical cost function.

Plan Classification

- 3-Dimensional conformal radiation therapy (3D-CRT): typically forward planned. It might be advantageous for moving targets, as the target is always in the open radiation field.
- Intensity-modulated radiation therapy (IMRT): typically inverse planned (although the field-in-field technique is forward planned).
- Arc therapy (RapidArc, VMAT).

Dose Calculation Algorithms

- Pencil beam algorithms using radiological path length corrections to account for tissue heterogeneities. Not accurate in conditions of electronic disequilibrium. In these cases, heterogeneity corrections explicitly accounting for the transport of secondary electrons must be employed. While the most accurate technique for dose calculation is Monte Carlo, convolution-superposition methods are sufficiently accurate in most clinical situations.
- Calculation grid: should be less than $2 \times 2 \times 2$ mm^3.

Treatment Platforms and Cross-Platform Comparisons

- SRS/SBRT treatments can be performed using a variety of devices producing X rays, gamma rays or particle radiation (Tables 3.3 and 3.4) (Combs et al. 2012; Dieterich and Gibbs 2011; Soisson et al. 2006):
  - Robotic linac radiosurgery system (CyberKnife).
  - Helical TomoTherapy.
  - Gamma Knife.
  - Other linac-based systems.

Quality Assurance and Patient Safety

- AAPM Task Group 101, Section VII.B. states that "Specific tests should be developed to look at all aspects of the system both individually and in an integrated fashion (Benedict et al. 2010)."
- Systematic treatment accuracy verification is required for
  - CT/MR imaging.
  - Fusion uncertainties.
  - Planning calculation.

TABLE 3.3 Characteristics of various platforms for SRS/SBRT

Technology	Delivery system	Radiation	Dose rate	Beam shaping
CyberKnife	Compact linac mounted on a robotic arm	6 MV unflattened photon beam	Up to 1000 MU/min	12 Interchangeable tungsten cones; variable aperture collimator; MLC (not yet clinically available)
Tomotherapy	Helical, CT-like gantry equipped with a linac waveguide	6 MV unflattened photon beam	~850 cGy/min at isocenter	Binary MLC (64 leaves, 0.625 cm wide)
Gamma knife	192 (Perfexion) or 201 (models B-4C) ^{60}Co sources	1.17 and 1.33 MeV gamma rays	Initial source activity ~6000 Ci, dose-rate at focal point >3 Gy/min	Tungsten barrel subdivided into 8 sectors (Perfexion); 4 interchangeable helmets (models B-4C)
Linac-based systems	Gantry-based linac rotating about the isocenter	Multiphoton energies (6, 10, 15, 18 MV-flattened and unflattened) and electron energies	600 MU/min up to 2400 MU/min	MLC with standard (5 mm width) or micro (2.5 mm width) leaves

(continued)

TABLE 3.3 (continued)

Technology	Field sizes	Beam arrangements	Treatment time
CyberKnife	Circular fields: 5–60 mm diameter	Hundreds of non-coplanar beams. No posterior beams	Long (20 min–1.5 h)
Tomotherapy	Max field length 40 cm. Slices widths of 1, 2.5 and 5.0 cm	Treatments are delivered by synchronization of gantry rotation, couch translation, and MLC motion	Short (15–30 min)
Gamma knife	4, 8 and 16 mm (Perfexion); 4, 8, 14, 18 mm (models B-4C)	Multiple isocenters (shots)	Long (hours)
Linac-based systems	Standard MLC typically gives a 40×40 field, micro-MLC gives a smaller field (12×14 cm^2)	Multiple isocentric beams; coplanar or non-coplanar beams; coplanar or non-coplanar arcs	Fast (15–30 min)

TABLE 3.4 IGRT solutions

Technology	Imaging system	Imaging frequency	Image registration algorithms	Motion management
CyberKnife	2D orthogonal X-ray images at 45°	Every 15–150 s (typically 30–60 s)	Automatic registration of live camera images with DRR using site specific algorithms (skull, fiducial, spine, lung)	Synchrony respiratory motion tracking
TomoTherapy	3D MVCT	Prior to each treatment	Automatic registration of MVCT with planning CT based on bony and/or soft tissue anatomical landmarks	None
Linac-based systems (Varian-TrueBeam, Elekta-Versa)	2D kV or MV images, 2D fluoroscopy, 3D kV CBCT, 3D ultrasound, infrared system	Depending on imaging modality prior or during treatment	Automatic registration of CBCT with planning CT using either bony anatomy or soft tissue information. 3D ultrasound images are also automatically co-registered to the planning CT	Gated delivery verified by 2D real-time fluoroscopic imaging or 4D CBCT

  - Target localization.
  - Dose delivery.
- This section focuses on target localization, IGRT system quality assurance, and dosimetry quality assurance.

Target Localization Accuracy

- A top priority for SBRT/SRS treatments.
- The standard for dosimetric target localization accuracy is the "Winston-Lutz" test or a similar test for frameless SRS/SBRT procedures (Medin et al. 2010; Solberg et al. 2008).
- Patient treatment target localization is achieved with either stereoscopic localization X-rays or CBCT for the Cyberknife and the linac-based systems, and with stereotactic head frames for GK.

IGRT System Quality Assurance

- Daily imaging isocenter check and simple localization check should be done daily when SBRT treatments are to be performed.

IGRT Imaging Systems

- Both kV-CBCT and MV-CBCT systems need:
  - To calibrate for proper registration of the treatment beam isocenter.
  - To correct for accelerator and imaging component sags and flexes.
  - To certify the geometric accuracy of the imaged-guided procedures (Bissonnette 2007; Bissonnette et al. 2008).
- AAPM Task Group 142 on QA of Medical Accelerators, Table VI recommends QA tasks tolerance and

frequency for both planar and cone beam images. They include:

- Safety and functionality.
- Geometrical accuracy:
  - Imager isocenter accuracy.
  - 2D/2D match, 3D/3D registration accuracy.
  - Image magnification accuracy.
  - Imager isocenter accuracy with gantry rotation.
- Image quality:
  - Contrast resolution and spatial resolution.
  - Hounsfield Units linearity and uniformity.
  - In-slice spatial linearity and slice thickness (Klein et al. 2009).
- For a detailed list of the recommended tests and tolerances the reader is referred to TG-142.

IGRT Couch Shift Accuracy

- Need to verify the accuracy of the robotic couch movement.
  - To ensure proper operation of the IGRT device and workflow.
  - To assess communication between the image registration software and the remote-controlled couch.
  - Is determined using the "residual correlation error" method (for details, please refer to TG-179).
  - This value should be near 0 ± 2 mm, according to TG-179 (Bissonnette 2007).

Dosimetric Quality Assurance

Validation measurement vs. treatment planning output

- Validation measurements need to be conducted after commissioning of the treatment planning system (TPS) and before the start of SRS/SBRT programs.
- These ensure that the TPS is calculating the correct dose, and that the IGRT imaging system and the tracking/delivery system are delivering accurately.

Measurements Include

- Simple square field and/or circular cone outputs.
  - Percent depth dose (PDD) and energy measurements compared with treatment planning calculations.
- Simple 3D plans and some IMRT plans should be planned, delivered, and measured to verify the dose calculation and delivery accuracy.
- Measurements should cover the whole range of possible field sizes, and different tracking methods (i.e., kV imaging, cone beam, and for CK, different track algorithms).
- When treating multiple sites, double or multiple isocenter plans would need to be verified.
- Special care should be taken to verify small field dosimetry during these SRS/SBRT end-to-end validation tests, since this particular area is most prone to commissioning inaccuracy and also to dose planning uncertainty.

Routine Quality Assurance Program

- Routine quality assurance measurements are needed once the SRS/SBRT program has started, to ensure the continuing dosimetry accuracy for these treatments.
  - Beam stability test:
    - The output and energy of the beam should be checked daily (Table 3.5).
    - Tighter tolerance (constancy and accuracy to the sub mm) is needed for SBRT/SRS treatments delivered using micro-MLC or high-definition MLC (Klein et al. 2009).
    - For Cyberknife robotic radiosurgery, TG-135 on "Quality assurance for robotic radiosurgery" recommends individual component QA and overall system QA, with specific daily, monthly, and annual frequency and tolerance tables in IVB, C and D.

- End-to-end test: Including motion tracking/gating end-to-end test.
  - Each individual component of the SRS/SBRT process (imaging, localization, treatment delivery, etc.) has associated errors.
  - The cumulative system accuracy needs to be characterized through an end-to-end test using phantoms with measurement detectors and imaging on a routine basis.
  - For the CyberKnife system, an end-to-end test is conducted once a month, rotating among the different imaging/tracking modalities. Every month, one end-to-end will be done for the fixed cone and one for the Iris.
  - The end-to-end tests have to be repeated every time there is an upgrade to the system for all modalities.
  - Depending on the treatments, end-to-end tests could be done at the physicists' discretion to best reflect the delivery/imaging modalities used.
- Patient-specific QA.
  - Per TG-101, treatment-specific and patient-specific QA procedures should be established to govern both the treatment planning and delivery process as a whole, as well as to provide a sanity check of the setup.
  - For a new SRS/SBRT program, frequent patient-specific QA should be conducted until the physicist in charge is confident of the delivery accuracy of the modality.

- Extremely small fields warrant patient specific QA for all plans, since these cases involve both potential measurement uncertainty and positioning uncertainty:
  - The output factors measured carry certain uncertainties (cones <7.5 mm and MLC fields $<1 \times 1$ cm).
  - MicroMLC or IRIS positioning uncertainties, examples:
    - Cyberknife: IRIS 10 mm or lower.
    - For linac-based SRS/SBRT using micro-MLCs: any field size less than 1 cm.

TABLE 3.5 Daily, monthly, and annual tests for SRS and SBRT systems (recommendations based on TG-142) (Klein et al. 2009)

Daily QA	
Mechanical tests	*Tolerance*
Laser localization	1 mm
Distance indicator (ODI) @ iso	2 mm
Collimator size indicator	1 mm
Monthly QA	
Dosimetry tests	*Tolerance*
Typical dose rate output constancy	2 % (@ stereo dose rate, MU)
Mechanical tests	*Tolerance*
Treatment couch position indicators	1 mm/0.5°
Localizing lasers	<±1 mm
Annual QA	
Dosimetry tests	*Tolerance*
SRS arc rotation mode (range: 0.5–10 MU/deg)	Monitor units set vs. delivered: 1.0 MU or 2 % (whichever is greater) Gantry arc set vs. delivered: 1.0° or 2 % (whichever is greater)
X-ray monitor unit linearity (output constancy)	±5 % (2–4 MU) ±2 % ≧5 MU
Coincidence of radiation and mechanical isocenter	±1 mm from baseline
Stereotactic accessories, lockouts, etc.	Functional

- Need to use equipment that has the correct resolution for QA, i.e., film for isodose distribution, and either pinpoint chamber or diode for absolute measurement to avoid any volume averaging issues.

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Part III
Clinical Applications

Chapter 4
Intracranial Tumors

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Pearls

Brain Metastases

- Most common intracranial tumor (20–40 % of all cancer patients on autopsy); most often from lung cancer, breast cancer, or melanoma.
- "Solitary" metastasis: one brain lesion as the only site of disease; "single" metastasis: one brain metastasis, other sites of disease.
- Start dexamethasone up to 4 mg q6hrs for neurologic symptoms; no role for steroids in asymptomatic patients. Taper as tolerated once radiotherapy is complete; no evidence for seizure prophylaxis (Table 4.1).

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Table 4.1 RTOG RPA for brain metastases (Gaspar et al. 1997)

Class	Characteristics	Survival (months)
I	KPS 70–100 Age <65 Primary tumor controlled Metastases to brain only	7.1
II	All others	4.2
III	KPS <70	2.3

Table 4.2 Simpson grading system for meningioma resection

Grade I	Macroscopic complete removal with excision of dural attachment, any abnormal bone, and involved venous sinus(es)
Grade II	Macroscopic complete removal with coagulation of dural attachment
Grade III	Macroscopic complete removal of intradural component(s), without resection or coagulation of dural attachment or extradural extensions
Grade IV	Partial removal with residual intradural tumor in situ
Grade V	Simple decompression with or without biopsy

Meningioma

- Thirty-percent of primary intracranial neoplasms; two-fold more likely in women (although incidence is equal for anaplastic meningiomas) and linked to ionizing radiation, viral infection, sex hormones, NF2, and loss of chromosome 22q (Table 4.2).

Acoustic Neuroma

- Acoustic neuromas (i.e., vestibular schwannomas) arise from myelin sheath Schwann cells surrounding the vestibular nerve; 6–8 % of intracranial tumors, overall incidence ~1 % on autopsy studies.

- Risk factors include acoustic trauma and coincidence with parathyroid adenoma; bilateral acoustic neuromas pathopneumonic for NF2.
- Both CN VII and VIII may be affected (hearing loss, tinnitus, vertigo, and unsteady gait), and extension into the cerebellopontine angle may lead to dysfunction of CN V (trigeminal pain) and the facial nerve (facial paresis and taste disturbances), as well as compression of the posterior fossa (ataxia, hydrocephalus, and death).
- Mean growth rate ~2 mm per year, although may remain stable for years.

Paraganglioma

- Rare neuroendocrine tumors with incidence of ~1:1,000,000; sometimes called glomus tumors or chemodectomas as they arise from glomus cells which function as chemoreceptors along blood vessels.
- Can occur in the abdomen (85 %), thorax (12 %), and the head and neck (3 %); usually benign (<5 % malignant potential).

Pituitary Adenoma

- Approximately 10 % of intracranial tumors (5–25 % incidence on autopsy), almost all of which arise in the anterior lobe; 75 % functional (30–50 % prolactinoma, 25 % GH, 20 % ACTH, and <1 % TSH).
- Microadenoma <1 cm; macroadenoma ≥1 cm.
- Presenting symptoms include headaches, hydrocephalus from 3rd ventricle obstruction, cranial nerve palsies with extension to the cavernous sinus, and bitemporal hemianopsia and/or loss of color discrimination from optic chiasm compression.
- Forbes-Albright syndrome from prolactinoma: amenorrhea-galactorrhea in women, impotence and infertility in men.

- Both mass effect and radiation damage to the pituitary infundibulum can cause an elevation in prolactin due to loss of hypothalamic inhibition ("stalk effect").
- Hormone levels typically normalize within 1–2 years after radiotherapy.

Arteriovenous Malformation (AVM)

- Abnormal congenital communication between arterial and venous vasculature at a "nidus"; supraphysiologic hydrodynamic gradient.
- Low incidence in the US population (0.14 %), but 8 % coincidence with cerebral aneurysm.
- Annual rate of spontaneous hemorrhage ~2–6 %, with morbidity 20–30 % and mortality 10–15 % per event; after angiographic obliteration, lifetime risk of hemorrhage ≤1 %.
- SRS induces vascular wall hyperplasia and luminal thrombosis, but requires several years to achieve full effect.
- AVMs differ from cavernous malformations insofar as the latter are composed of sinusoidal vessels without a large feeding artery, and therefore have a low-pressure gradient (Table 4.3).

Table 4.3 Spetzler–Martin AVM grading system (1–5)

Size of nidus	<3 cm = 1
	3–6 cm = 2
	>6 cm = 3
Location	Adjacent to non-eloquent brain = 0
	Adjacent to eloquent cortex = 1
Venous drainage	Superficial = 0
	Deep = 1

Neuropathic Facial Pain

Trigeminal Neuralgia

- CN V sensory nucleus disorder resulting in episodic, provokable (i.e., shaving, brushing teeth, wind, etc.), paroxysmal, unilateral, severe, lancinating pain lasting seconds to minutes in the distribution of the trigeminal nerve.
- Predominantly idiopathic, although may be the result of trigeminal nerve compression by an aberrant artery or vein, or demyelination in multiple sclerosis. Secondary trigeminal neuralgia due to mass effect from meningioma, vestibular schwannoma, AVM, aneurysm, or other lesions.
- Diagnosis of exclusion; obtain MRI to rule out cerebellopontine angle neoplasm.
- Median time to pain relief after SRS is ~1 month; 50–60 % CR, 15–20 % PR; <10 % incidence of facial numbness after treatment.

Cluster Headache

- Sudden onset of unilateral pain typically along the distribution of CN V1; associated with ipsilateral autonomic activity including ptosis, meiosis, lacrimation, conjunctival injection, rhinorrhea, and nasal congestion.
- Etiology unclear; 6:1 male to female predominance.
- GKRS to the trigeminal nerve alone not successful, and is associated with much higher rate of toxicity than during SRS for trigeminal neuralgia (Donnet et al. 2006; McClelland et al. 2006). Investigation of SRS to the pterygopalatine ganglion +/– trigeminal nerve root is ongoing (Kano et al. 2011; Lad et al. 2007).

Sphenopalatine Neuralgia (Sluder's Neuralgia)

- Rare craniofacial pain syndrome with 2:1 female predominance associated with unilateral pain in the orbit, mouth, nose and posterior mastoid process as well as ipsilateral autonomic stimulation from vasomotor activity.

- Etiology unclear; perhaps related to pterygopalatine ganglion irritation from inflammation/infection of the sphenoid or posterior ethmoid sinuses.
- Radiosurgical data limited to case reports of sphenopalatine ganglion treatment (Pollock and Kondziolka 1997).

Other

- Small retrospective series of SRS for residual/recurrent pineal parenchymal tumors, craniopharyngiomas, and neurocytomas with high long-term local control and survival.
- SRS used as salvage treatment for certain functional disorders, including epilepsy, Parkinson disease, and essential tremor with varying efficacy.
- Stereotactic treatment of residual/recurrent glial tumors, medulloblastoma, and other aggressive CNS malignancies has been reported, but outcomes are discouraging. Hypofractionation of recurrent glial tumors effective as salvage.

Treatment Indications

- In general, SRS+WBRT is associated with longer survival than WBRT alone in patients with single metastases and KPS $\geq$70, improved LC and KPS preservation in patients with 1–4 metastases and KPS $\geq$70, and potentially, improved survival in patients with KPS <70.
- SRS alone may provide equivalent survival and LC, plus improved neurocognitive outcomes when compared to SRS+WBRT or WBRT alone in patients with $\leq$3 metastases; close surveillance and salvage treatment is essential.
- After resection, both SRS+WBRT and WBRT alone are acceptable adjuvant strategies, although SRS alone may be used in select cases with minimal intracranial disease and close surveillance (Linskey et al. 2010) (Tables 4.4 and 4.5).

TABLE 4.4 Radiosurgical treatment indications for brain metastases

Single lesion	Surgical resection + SRS to cavity
RPA class I–II	SRS alone for medically/surgically inoperable cases
2–4 Lesions RPA class I–II	SRS +/– surgical resection with excellent prognosis/KPS
KPS ≤60, extensive intracranial/extracranial disease, and in combination with SRS as described above	WBRT

TABLE 4.5 Radiosurgical treatment indications for benign intracranial neoplasms

Meningioma	■ Recurrent/residual disease after surgery ■ Recurrent disease after prior SRS/RT ■ Medically or surgically inoperable
Acoustic neuroma	■ STR (LF 45 % without adjuvant RT vs. 6 % with postoperative SRS) ■ Patient desire for greater preservation of useful hearing (30–50 % with surgery)
Pituitary adenoma	■ Adjuvant therapy after STR of macroadenoma with persistent postoperative hypersecretion or residual suprasellar extension ■ Consider medical management with bromocriptine or cabergoline for prolactin-secreting microadenoma
AVM	■ Medically inoperable, surgically inaccessible, or anticipated high morbidity due to Spetzler–Martin grade
Neurofacial pain	■ Failure of medical management (carbamazepine, phenytoin, gabapentin, baclofen, etc.) ■ Failure of surgical management (radiofrequency rhizotomy, balloon compression, microvascular decompression, etc.)

Workup

- H&P with emphasis on neurologic components
- Review of systems including any sensory changes, neurologic symtpoms, and endocrine abnormalities.
- Laboratories:
  - No routine serum tests necessary for the evaluation of brain metastases, meningioma, AVM, neurofacial pain syndromes, etc.
  - Acoustic neuroma: Audiometry is the best initial screening, and typically shows sensorineural hearing loss (as will the Rinne and Weber tests).
  - Pituitary adenomas: Endocrine evaluation with prolactin, basal GH, serum ACTH, free cortisol, dexamethasone suppression, TSH, T3, T4, FSH, LH, plasma estradiol, and testosterone levels.
- Imaging:
  - Thin-cut MRI with T1 pre- and post-gadolinium, T2, and FLAIR (fluid attenuation inversion recovery) sequences; tumor enhancement after gadolinium correlates with breakdown of the blood-brain barrier, abnormal T2 signal indicative of gliosis and/or edema.
  - Can consider increased dose gadolinium at the time of radiosurgery to improve sensitivity of detection of brain metastases.
  - Hemorrhagic metastases most often seen with renal cell cancer, choriocarcinoma, and melanoma.
  - Magnetic resonance spectroscopy: tumors characterized by increased choline (cellularity marker), decreased *N*-acetylaspartic acid (NAA; neuronal marker), and decreased creatinine (cellular energy marker); necrosis associated with increased lactate (anaerobic metabolism), and decreased choline/NAA/creatinine.
  - Dynamic magnetic resonance perfusion: relative cerebral blood flow (CBV) elevated in tumors (often in concert with grade), and decreased in areas of radiation necrosis and tumefactive demyelination.

- Post-operative MRI should be performed within 48 h of surgery to document residual disease; acute blood appears as increased intrinsic T1 signal pre-contrast.
- "Dural tail sign" can be indicative of either tumor extension or vascular congestion associated with tumors adjacent or intrinsic to the meninges (seen with 60 % of meningiomas).
- Meningiomas are isointense on T1 and T2, and intensely enhance with gadolinium; evidence of bony destruction or hyperostosis in 15–20 % of cases. Acoustic neuroma: Seen as enhancing "ice cream cone" in the internal acoustic canal or as "dumbbell" projecting into the foramen magnum.
- Pituitary adenomas: X-ray skeletal survey should be performed in cases of acromegaly to evaluate growth plates
- AVM: Co-registration of cerebral angiography and time of flight MRI sequences helpful for target delineation.
- Neuropathic facial pain: Thin slice (1 mm) MRI/MRA has sensitivity and specificity of 89 and 50 %, respectively, for identifying vascular compression of the trigeminal nerve.

Radiosurgical Technique

- Simulation and treatment planning.
  - Simulation with stereotactic frame in place.
  - Primary MRI planning with thin cuts (1–2 mm) preferred for intracranial radiosurgery, with fusion of preoperative scans if available.
  - If necessary, CT slices no thicker than 2 mm should be obtained and co-registered with MRI images.
  - Target volumes:
    - Brain metastases: GTV alone for intact lesions. For resection cavities, a 1–2 mm margin may increase local control (Soltys et al. 2008).

    - Meningioma, acoustic neuroma, pituitary adenoma, and other benign intracranial tumors: GTV with 0–2 mm margin depending on degree of immobilization and stereotaxis.
    - Trigeminal neuralgia: Target ipsilateral trigeminal nerve adjacent to the pons in the retrogasserian cistern with a single, 4 mm shot. Retreatment isocenter should be located 2–3 mm away from initial target if possible.
- Dose prescription: See Table 4.6.
    - Consider hypofractionation in select cases if dose constraints to critical structures cannot be met with single-fraction treatment.
- Dose delivery.
    - Multiple treatment modalities available, but most centers employ GK SRS, frameless robotic radiosurgery, and/or linac-based SRS.

Toxicities and Management

- Stereotactic frame:
    - Mild headache immediately following frame removal, usually subsiding within 60 min.
    - Minimal bleeding from pin insertion sites requiring compression.
    - Peri-orbital edema resolving with head elevation and warm compress.
    - <1 % Risk of superficial skin infection.
- Acute (1 week to 6 months):
    - Alopecia and skin changes following treatment of superficial lesions.
    - Mild fatigue.
    - Transient worsening of neurologic symptoms due to edema potentially requiring steroids.
- Late (>6 months):
    - Radiation necrosis: Overall five-percent rate of symptomatic brain necrosis after SRS; typically resolves with steroids, but may require surgical intervention.

TABLE 4.6 Dose recommendations and outcomes for intracranial stereotactic radiosurgery

Presentation	Recommended dose	Outcomes
Brain metastases	■ 13–24 Gy/1 fraction depending on tumor volume/location	
	■ Dosereduction or hypofractionation (21–30 Gy/3–5 fractions) with larger lesions and/or resection cavities	
	■ Consider dose reduction (16 Gy) for brainstem lesions	
Meningioma	■ Individualize dose based on tumor volume/ location/surgical/ radiosurgical history	
	■ 15 Gy/1 fraction for WHO grade I–III lesions; hypofractionation to 25–30 Gy/5 fractions possible, although long-term results unknown (UCSF experience).	Long-term LC >90 % for WHO grade I lesions
	■ Grade III lesions may require higher dose	
Acoustic neuroma	■ 12–13 Gy/1 fraction	LC and preservation of CNs V and VII in excess of 95 %; hearing preservation ~75 %
	■ 18–25 Gy/3–5 fractions	Appears safe and effective, but long-term results are unknown
Paraganglioma	■ 15 Gy/1 fraction or hypofractionation to 25 Gy/5 fractions	LC ~100 %

(continued)

Table 4.6 (continued)

Presentation	Recommended dose	Outcomes
Pituitary adenoma	■ Nonfunctioning tumors: 12–20 Gy/1 fraction ■ Functioning tumors: 15–30 Gy/1 fraction (maximal safe dose); discontinue medical therapy 4 weeks prior to radiosurgery. ■ Single fraction optic apparatus tolerance: 8 Gy	
	■ 21–25 Gy/3–5 fractions	Appears safe and effective, but long-term results unknown
AVM	■ Individualize dose based on tumor volume; staged radiosurgery for larger lesions	2-Year obliteration rate for single-fraction treatment: <2 cm 90–100 %, >2 cm 50–70 %
	■ 18 Gy/1 fraction for 8 cm^3 target(s); dose escalation when feasible and safe (UCSF experience)	
Trigeminal neuralgia	■ Primary: 70–90 Gy (100 % isodose line)	Pain relief in ~30–80 % of patients, although retreatment common; dose related to both relief from symptoms and development of new symptoms
	■ Retreatment: 50–70 Gy (100 % isodose line)	
Pineal tumors	■ Fractioned neuraxial RT for high-grade lesion; 15 Gy SRS reserved for residual tumor or local recurrence after RT	

- Endocrine abnormalities.
- Cranial nerve dysfunction following treatment of skull base tumors.
- Rare: memory impairment and cavernous malformations.
- Isolated case reports of stroke, facial palsy/hyperesthesia, vision loss, and eye dryness after SRS for trigeminal neuralgia, all of which are very rare.

Recommended Follow-Up

- Brain metastases and other high-grade lesions:
  - MRI 4–12 weeks after treatment, then every 2–3 months for the first 2-years, followed by imaging every 6 months for the next 3 years, and yearly thereafter; imaging intervals should be individualized according to clinical symptoms and lesion trajectory.
- Low-grade lesions (meningioma, acoustic neuroma, paraganglioma, etc.):
  - MRI every 6–12 months for the first 2-years, then annually; imaging intervals should be individualized according to clinical symptoms and lesion trajectory.
- Pituitary adenoma and other peri-sellar lesions:
  - Endocrine testing every 6–12 months with visual field testing annually.
- Acoustic neuromas and cerebellopontine angle tumors:
  - Formal audiometry annually.
- AVM:
  - MRI up to once per year for 3 years after treatment, with angiogram to confirm response after 3 years.
- Neuropathologic facial pain and functional disorders:
  - Clinical follow-up only.

Evidence

Brain Metastases

SRS Boost with WBRT

- RTOG 95-08 (Andrews et al. 2004): Randomized, multi-institution trial including 333 patients with 1–3 brain metastases and KPS ≥70 treated with WBRT (37.5 Gy/15 fractions) plus SRS (15–24 Gy/1 fraction) vs. WBRT alone. Significant survival advantage with SRS in patients with a single metastasis on univariate analysis (6.5 vs. 4.9 months), RPA class I on multivariate analysis (11.6 vs. 9.6 months), and trends for advantage with lung histology (5.9 vs. 3.9 months), and tumor size >2 cm (6.5 vs. 5.3 months). WBRT+SRS also associated with significantly higher 1-year LC (82 % vs. 71 %), and improved KPS (13 % vs. 4 %) with decreased steroid use at 6 months. Minimal acute- and long-term toxicity.
- University of Pittsburgh (Kondziolka et al. 1999a, b): Randomized trial of 27 patients with 2–4 brain metastases and KPS ≥70 treated with WBRT (30 Gy/12 fractions) plus SRS (16 Gy/1 fraction) vs. WBRT alone. Study stopped early due to significant interim benefit in LC for WBRT+SRS (100 % vs. 8 %); median time to LF 6 months with WBRT vs. 36 months with WBRT+SRS. No difference in OS (8 vs. 11 months), and survival equal (~11 months) when accounting for SRS salvage in WBRT arm. No difference in OS or LC depending on histological type, number of brain metastases, or extent of extracranial disease.

SRS Alone or With WBRT

- RTOG 90-05 (Shaw et al. 2000): Dose escalation study including 156 patients (36 % recurrent primary brain tumors, median prior dose of 60 Gy; 64 % recurrent

brain metastases, median prior dose of 30 Gy). Maximum tolerated doses of 24 Gy, 18 Gy, and 15 Gy for tumors ≤ 20 mm, 21–30 mm, and 31–40 mm in diameter, respectively; MTD for tumors <20 mm likely higher, but investigators reluctant to escalate further. Tumor diameter ≥2 cm significantly associated with increasing risk of grade ≥3 neurotoxicity on multivariate analysis; higher dose and KPS also associated with greater neurotoxicity. Actuarial 24-month risk of radionecrosis 11 %. Patients with primary brain tumors and those treated on linear accelerators (as opposed to GKRS) had ~2.8-fold greater chance of local progression.

- JROSG 99-1 (Aoyama et al. 2006): Randomized, multi-institution trial including 132 patients with 1–4 brain metastases (diameter <3 cm) and KPS ≥70, treated with SRS (18–25 Gy/1 fraction) vs. WBRT (30 Gy/10 fractions) followed by SRS. Trial stopped early due to low probability of detecting a difference between arms. Addition of WBRT reduced rate of new metastases (64 % vs. 42 %) and need for salvage brain treatment, and improved 1-year recurrence rate (47 % vs. 76 %). No difference in OS (~8 months), neurologic or KPS preservation, or MMSE score.
- MDACC (Chang et al. 2009): Randomized trial including 58 patients with 1–3 brain metastases and KPS ≥70 treated with SRS (15–24 Gy/1 fraction) vs. SRS+WBRT (30 Gy/12 fractions) and followed with formal neurocognitive testing. Trial stopped early due to significant decline in memory and learning at 4 months with WBRT by Hopkins Verbal Learning Test (52 % vs. 24 %). However, WBRT also associated with improved LC (100 % vs. 67 %) and distant brain control (73 % vs. 45 %) at 1 year. Significantly longer OS with SRS alone (15 vs. 6 months), but patients in this arm received more salvage therapy including repeat SRS (27 vs. 3 retreatments).

- UCSF (Sneed et al. 1999): Retrospective review of GKRS ($n=62$) vs. GKRS+WBRT ($n=43$); treatment characteristics individualized according to physician preference. OS (~11 months) and 1-year local FFP (71 % vs. 79 %) equivalent. Although brain FFP significantly worse for SRS alone (28 % vs. 69 %), no difference when allowing for first salvage (62 % vs. 73 %) after 1 year.
- Sneed et al. (2002): Retrospective, multi-institution review of 569 patients with brain metastases treated with SRS alone ($n=268$) vs. WBRT+SRS ($n=301$); exclusion criteria included resection of brain metastasis and interval from end of WBRT to SRS >1 month. Median and overall survival no different among respective RPA statuses (I: 14 vs. 15 months; II: 8 vs. 7 months; class III: ~5 months). Twenty-four percent WBRT salvage rate in SRS patients.
- EORTC 22951-26001 (Kocher et al. 2011): Randomized, multi-institution trial of WBRT ($n=81$, 30 Gy/10 fractions) vs. observation ($n=79$) following either surgery or SRS for 1–3 brain metastases in patients with stable systemic disease and ECOG performance status 0–2. Median time to ECOG performance status deterioration >2: 10 months with observation and 9.5 months with WBRT. OS similarly equivalent (~11 months), although WBRT reduced 2-year relapse at both new and initial sites. Salvage therapies used more frequently in the observation arm.
- University of Cologne (Kocher et al. 2004): Retrospective review of patients with 1–3 previously untreated cerebral metastases treated with linac-based SRS ($n=117$, median dose 20 Gy/1 fraction) or WBRT ($n=138$, 30–36 Gy/10 fractions) stratified by RPA class. Rate of salvage WBRT: SRS group 22 %, WBRT group 7 %. Significantly longer survival after SRS in RPA class I (25 vs. 5 months) and class II (6 vs. 4 months) patients; no difference in RPA class III patients (4 vs. 2.5 months).

SRS for >4 Brain Metastases

- University of Pittsburgh (Bhatnagar et al. 2006): Retrospective review of 105 patients with ≥4 brain metastases (median 5, range 4–18) treated with single-session GKRS (median marginal dose 16 Gy/1 fraction) plus WBRT (46 %), after failure of WBRT (38 %), or alone (17 %). Median OS 8 months (RPA class I: 18 months, class II: 9 months, and class III: 3 months), 1-year LC 71 %, and median time to progression or new brain metastases 9 months. Total treatment volume, age, RPA classification, and median marginal dose (but not the total number of metastases treated) all significant prognostic factors on multivariate analysis.

SRS Boost After Resection

- Stanford (Soltys et al. 2008): Retrospective review of 76 resection cavities treated with SRS (median marginal dose 18.6 Gy, mean target volume 9.8 cm^3). Actuarial LC at 6 and 12 months: 88 and 79 %, respectively. Conformality index significantly correlated with improved LC on univariate analysis; LC 100 % for the least conformal quartile, and 63 % for all others. Target volume, dose, and number of fractions not significant. Recommendation for 2 mm margin around resection cavities.

Brainstem Lesions

- UCSF (Kased et al. 2008): Retrospective review of 42 consecutive patients with 44 brainstem metastases; median target volume 0.26 cm^3, median marginal dose 16 Gy/1 fraction. Brainstem FFP 90 % at 6 months, and 77 % at 1 year. Median survival after SRS 9 months; significantly longer in those with a single metastases, non-melanoma histology, and controlled extracranial disease. Poor outcomes with melanoma and renal cell

histology, as well as target volume ≥1 cm^3. Four complications following treatment including ataxia, disequilibrium, facial numbness, and hemiparesis, all of which were associated with lesion progression as well as potential radiation effect.

Salvage After SRS

- Zindler et al. (2014): Retrospective review of 443 patients with 1–3 brain metastases treated with RS alone. Salvage treatment for distant brain recurrence (DBR) in 25 % of patients, 70 % of which had ≤3 lesions. Actuarial DBR rates at 6, 12, and 24 months after primary SRS were 21, 41, and 54 %, respectively. Median time to DBR: 5.6 months. DBR-RPA classes: I = WHO 0 or 1, ≥6 months from RS (OS 10 months); II = WHO 0 or 1, <6 months from RS (OS 5 months); III = WHO ≥2 (OS 3 months).

Meningioma

- Mayo Clinic (Stafford et al. 2001): Retrospective review of 190 consecutive patients with 206 meningiomas treated by SRS (median marginal dose 16 Gy; median target volume 8.2 cm^3). Prior surgery in 59 % of patients; 12 % of lesions with atypical or anaplastic histology; 77 % of tumors involved the skull base. Five-year CSS for benign, atypical, and anaplastic tumors was 100, 76, and 0 %, respectively; LC 93, 68, and 0 %, respectively. Complications attributed to SRS in 13 % of patients (CN deficits in 8 %, symptomatic parenchymal changes in 3 %, carotid artery stenosis in 1 %, and cyst formation in 1 %); decrease in functional status related to radiosurgery in six patients.
- University of Pittsburgh (Kondziolka et al. 1999a, b): Retrospective review of 99 consecutive patients treated with SRS (43 %) or surgery followed by SRS (57 %). Median marginal dose 16 Gy; median target volume

4.7 cm^3. Five patients previously treated with conventional RT; 89 % of tumors adjacent to the skull base. At 10 years, 11 % LF; PFS worse in patients with prior resections and multiple meningiomas. New or worsening neurologic symptoms in 5 % of patients. By survey, 96 % of patients considered treatment a success.

Benign

- Germany (Fokas et al. 2014): Retrospective review of 318 patients with histologically confirmed (45 %) or radiographically presumed (55 %) benign meningioma treated with fractionated stereotactic RT (80 %; median dose 55.8 Gy/31 fractions), hypofractionated stereotactic RT (15 %; 40 Gy/10 fractions or 25–35 Gy/5–7 fractions), or SRS (5 %) based on tumor size and proximity to critical structures. With median follow-up 50 months, 5- and 10-year LC, OS, and CSS were 93, 89, and 97 %; and 88, 74, and 97 %, respectively. On multivariate analysis, tumor location and age >66 years were significant predictors of LC and OS, respectively. Acute worsening of neurologic symptoms and/or clinically significant acute toxicity after RT in 2 % of patients; no late grade ≥3 toxicity.
- University of Pittsburgh (Kondziolka et al. 2014): Retrospective review of 290 benign meningioma patients treated with GKRS (median marginal dose 15 Gy, median target volume 5.5 cm^3). Prior fractionated RT in 22 patients, STR in 126 patients, and recurrence after GTR in 22 patients. Overall tumor control 91 %; 10- and 20-year actuarial PFS from the treated lesion were both 87 %. Among symptomatic patients, 26 % improved, 54 % remained stable, and 20 % had a gradual worsening. No significant difference in control with prior craniotomy vs. primary GKRS; PFS worse in those with prior RT and higher-grade lesions.
- Santacroce et al. (2012): Retrospective, multicenter review of 4565 consecutive patients with 5300 benign

meningiomas treated with GKRS (median marginal dose 14 Gy; median target volume 4.8 cm^3). Results of 3768 lesions with >24 months follow-up reported. Tumor size decreased in 58 % of cases, remained unchanged in 34 %, and increased in 8 %; overall control rate 92 %. Five- and 10-year PFS 95 and 89 %, respectively. Tumor control higher for presumed meningiomas vs. histologically confirmed grade I lesions, female vs. male patients, sporadic vs. multiple meningiomas, and skull base vs. convexity tumors. Permanent morbidity in 6.6 %.

- Prague (Kollová et al. 2007): Retrospective review of 400 benign meningiomas in 368 patients treated with SRS (median marginal dose 12.5 Gy; median target volume 4.4 cm^3). With median follow-up of 5 years, 70 % of tumors decreased in size, 28 % remained stable, and 2 % increased in size. Actuarial LC 98 %; worse in men and with <12 Gy. Temporary toxicity in 10 % and permanent in 6 %. Peritumoral edema worse with >16 Gy, age >60 years, no prior surgery, preexisting edema, tumor volume >10 cm^3, and anterior fossa location.
- Mayo Clinic (Pollock et al. 2003): Retrospective review of 198 benign meningiomas <3.5 cm^3 in mean diameter treated surgically ($n = 136$) or with primary SRS ($n = 62$; mean marginal dose 18 Gy). No statistically significant difference in 3- and 7-year PFS for Simpson Grade I resections (100 and 96 %, respectively) and SRS (100 and 95 %, respectively). SRS associated with superior PFS relative to Simpson Grade ≥2 resections, and relative to surgery in general, fewer adjuvant treatments (3 % vs. 15 %) and fewer complications (10 % vs. 22 %).

Atypical and Anaplastic

- Northwestern University (Kaur et al. 2014): Systematic review from 1994 to 2011 analyzing 21 English-language studies reporting tumor characteristics,

treatment parameters, and clinical outcomes for atypical and malignant (anaplastic) meningiomas treated with adjuvant RT or SRS. Median 5-year PFS and OS for atypical lesions after adjuvant RT were 54 and 68 %, respectively; anaplastic lesions: 48 and 56 %, respectively. Outcomes data identified for only 23 patients treated with SRS (median marginal dose 18–19 Gy), generally with poor outcomes.

Skull Base

- NAGKC (Sheehan et al. 2014): Multi-institutional, retrospective review of 763 patients with sellar and/or parasellar meningiomas treated with GKRS (median marginal dose 13 Gy; median target volume 6.7 cm^3); 51 % prior resection, and 4 % prior RT. Median follow-up 67 months. Actuarial PFS at 5 and 10 years 95 and 82 %, respectively; significant predictors of progression included >1 prior surgery, prior RT, and tumor marginal dose <13 Gy. Stability or improvement in neurologic symptoms in 86 % of patients; CN V and VI improvement in 34 % with preexisting deficits. Progression of existing neurologic symptoms in 14 % of patients; new or worsening CN deficits in 10 % (most likely CN V dysfunction). New or worsening endocrinopathy in 1.6 % of patients.
- NAGKC (Starke et al. 2014): Multi-institution, retrospective review of 254 patients with radiographically presumed (55 %) or histologicially confirmed (45 %) benign petroclival meningioma treated with GKRS upfront ($n=140$) or following surgery (114). Mean marginal dose 13.4 Gy; mean target volume 7.5 cm^3. With mean follow-up of 71 months, 9 % of tumors increased in size, 52 % remained stable, and 39 % decreased; 94 % of patients had stable or improved neurologic symptoms. PFS at 5 and 10 years was 93 and 84 %, respectively. Multivariate predictors of favorable outcome included small tumor volume, female gender, no prior RT, and lower maximal dose.

- Park et al. (2014): Retrospective review of 74 patients with cerebellopontine angle (CPA) meningioma treated with GKRS; median marginal of dose 13 Gy, median target volume 3 cm^3. With median follow-up 40 months, 62 % of tumors decreased in size, 35 % remained stable, and 3 % increased. PFS at 1 and 5 years was 98 and 95 %, respectively. Neurological improvement in 31 %, stability in 58 %, and worsening of symptoms in 11 % of patients (most likely trigeminal neuralgia); rate of improvement 1, 3, and 5 years after GKRS was 16, 31, and 40 %, respectively. Asymptomatic peritumoral edema in 5 % of patients; symptomatic adverse radiation effects in 9 %.

Ongoing

- EORTC 26021-22021: Phase III, randomized study of observation vs. conventional RT or SRS for incompletely resected benign meningiomas. Trial closed 3/2006; results pending.
- RTOG 0539: Phase II trial of observation for benign meningiomas status post resection vs. conventionally fractionated RT or SRS for recurrent benign meningioma, and primary atypical or anaplastic meningioma. Large margins (1–2 cm) stipulated for fractionated RT of atypical and anaplastic meningiomas. Trial closed 6/2009; results pending.

Acoustic Neuroma

- University of Pittsburgh (Lunsford et al. 2005): Retrospective review of GKRS outcomes for 829 vestibular schwannoma patients; median marginal dose 13 Gy, mean target volume 2.5 cm^3. Ten-year tumor control rate 97 %; hearing preservation 77 %. Toxicity notable for <1 % facial neuropathy and <3 % trigeminal symptoms.

- University of Pittsburgh (Chopra et al. 2007): Retrospective review of 216 patients with acoustic neuroma treated with GKRS; median marginal dose 12–13 Gy, median target volume 1.3 cm^3. Median follow-up 5.6 years. Ten-year actuarial resection-free control rate 98 %; CN V preservation 95 %, and CN VII preservation 100 %. Preservation of hearing in patients with >3 years follow-up: 74 % for serviceable hearing, and 95 % for testable hearing.

Surgery vs. SRS

- Marseille, France (Régis et al. 2002): Non-randomized, prospective series of GKRS ($n=97$) vs. microsurgery ($n=110$) for vestibular schwannoma with preoperative and postoperative questionnaire assessment. Median follow-up 4 years. GKRS universally superior in terms of facial motor function (0 % vs. 37 %), CN V disturbance (4 % vs. 29 %), hearing preservation (70 % vs. 38 %), overall functionality (91 % vs. 61 %), duration of hospitalization (3 vs. 23 days), and mean time missed from work (7 vs. 130 days).

Hypofractionated Stereotactic RT vs. SRS

- Amsterdam (Meijer et al. 2003): Prospective trial of single-fraction ($n=49$) vs. fractionated linac-based SRS ($n=80$) for acoustic neuroma; mean tumor diameter ~2.5 cm. Dentate patients treated with 20–25 Gy/5 fractions, and edentate patients treated with 10–12.5 Gy/1 fraction to the 80 % isodose line. Median follow-up 33 months. Excellent tumor control (100 % vs. 94 %), preservation of hearing (75 % vs. 61 %), preservation of CN V (92 % vs. 98 %, statistically significant difference), and preservation of CN VII (93 % vs. 97 %) with both modalities.
- Japan (Morimoto et al. 2013): Retrospective review of 26 vestibular schwannomas treated with hypofractionated

robotic radiosurgery to 18–25 Gy/3–5 fractions (median target volume 2.6 cm^3). Progression defined as ≥2 mm 3D post-treatment tumor enlargement. Seven-year PFS and LC were 78 and 95 %, respectively. Six reports of late grade ≥3 toxicity. Formal audiometric testing demonstrated 50 % retention of pure tone averages.

Proton Beam Radiosurgery

- Harvard (Weber et al. 2003): Eighty-eight consecutive patients with vestibular schwannoma treated with 3 converging beams aligned to fiducial markers in the calvarium; maximum dose 13 Gy RBE, median target volume 1.4 cm^3. Actuarial 5-year tumor control 94 %, and preservation of CN's V and VII 89 and 91 %, respectively, but serviceable hearing preservation 33 %. Proton beam radiosurgery now only used for tumors <2 cm, and in patients without functional hearing.

Paraganglioma

- Pollock (2004): Retrospective, single-institution review of 42 patients with glomus jugulare tumors treated with single-session GKRS; mean marginal dose of 15 Gy, mean volume 13 cm^3. With median follow-up of 3.7 years, 31 % decreased in size, 67 % remained stable, and 2 % progressed. Seven- and 10-year PFS were 100 and 75 %, respectively. Hearing preservation 81 % at 4 years, with 15 % of patients developing new deficits including hearing loss, facial numbness, vocal cord paralysis, and vertigo.

Hypofractionation

- Chun et al. (2014): Retrospective, single-institution review of 31 patients with skull base paragangliomas treated with robotic radiosurgery to a total dose of

25 Gy/5 fractions. With median follow-up 24 months, OS and LC were both 100 %; tinnitus improved in 60 % of patients. Overall tumor volume decreased by 37 % (49 % when analyzing subset of patients with ≥24 month follow-up). No grade ≥3 toxicity.

Surgery vs. SRS

- Gottfried et al. (2004): Meta-analysis of 7 surgical series (374 patients) and 8 GKRS series (142 patients) of glomus jugulare tumors; mean follow-up 4 and 3 years, respectively. LC 92 % with surgery, 97 % with GKRS. Complications notable for 8 % morbidity from GKRS, 8 % CSF leak from surgery, and 1.3 % surgical mortality. Conclusion that both treatments are safe and efficacious, although inaccessibility of skull base limits selection of surgical candidates.

Pituitary Adenoma

- Sheehan et al. (2005a, b)): Systematic review of 35 peer-reviewed studies involving 1621 patients with pituitary adenoma treated with SRS. LC >90 % achieved in most studies, with mean marginal dose ranging from 15 to 34 Gy/1 fraction. Weighted mean tumor control rate for all published studies 96 %. Sixteen cases of damage to the optic apparatus with doses ranging from 0.7 to 12 Gy. Twenty-one new neuropathies from CN dysfunction, nearly half of which were transient. Risks of hypopituitarism, RT-induced neoplasia, and cerebral vasculopathy lower with SRS than historical rates with fractionated RT. Heterogeneous quantification of endocrinological remission for Cushing disease, acromegaly, prolactinoma, and Nelson syndrome, with wide variation of endocrine control. Hormone improvement anywhere from 3 months to 8 years after SRS, although levels typically normalize within 2 years.

Hypofractionation

- Iwata et al. (2011): Single institution retrospective review of 100 patients with recurrent/residual non-functioning pituitary adenomas without a history of prior RT treated with SRS to 21–25 Gy/3–5 fractions; median target volume 5.1 cm^3. Three-year OS and LC both 98 %. One case of visual disturbance after treatment, three cases of hypopituitarism in patients not previously on hormone replacement therapy, and three cases of transient cyst enlargement.

Hormone Control and Risk of Hypopituitarism

- Xu et al. (2013): Retrospective, single institution review of 262 pituitary adenoma patients treated by SRS with thorough endocrine assessments immediately before treatment, and then again at regular follow-up intervals. Tumor control 89 % and remission of endocrine abnormalities in 72 % of functional adenoma patients. Thirty percent rate of new hypopituitarism; increased risk with suprasellar extension and higher marginal dose, but not with tumor volume, prior surgery, prior RT, or age at SRS.

Vascular Malformations

Arteriovenous Malformation (AVM)

- Tokyo, Japan (Maruyama et al. 2005): Retrospective, single-institution review of 500 AVM patients status post definitive treatment with GKRS (mean dose 21 Gy; median Spetzler–Martin grade III). Pre-GKRS rate of spontaneous hemorrhage ~6 %; cumulative 4-year obliteration rate 81 %, 5-year rate 91 %. Hemorrhage risk reduced by 54 % during the latency period post-GKRS/pre-obliteration, and 88 % after obliteration; greatest risk reduction in those who initially presented with hemorrhage.

- University of Maryland (Koltz et al. 2013): Retrospective review of 102 patients treated with single- fraction or staged SRS for AVM's stratified by Spetzler–Martin Grade. With mean follow-up of 8.5 years, overall nidus obliteration was 75 % with 19 % morbidity, both of which correlated with Spetzler–Martin Grade. For Grade I–V lesions, obliteration achieved in 100, 89, 86, 54, and 0 % of cases. For AVMs that were not completely obliterated, the mean reduction in nidus volume was 69 %.
- University of Virginia (Ding et al. 2014): Retrospective review of 398 Spetzler–Martin Grade III AVMs treated with SRS (median target volume 2.8 cm^3, median prescription 20 Gy). With median 68 months clinical follow-up, complete obliteration in 69 % of lesions after median of 46 months from SRS. Significant predictors of response included prior hemorrhage, size <3 cm, deep venous drainage, and eloquent location. Annual risk for hemorrhage during the latency period was 1.7 %. Symptomatic radiation-induced complications in 12 % of patients (permanent in 4 %); independent predictors included absence of pre-SRS rupture and presence of a single draining vein. Conclusion: SRS for Spetzler–Martin Grade III lesions is comparable to surgery in the long-term.
- Harvard (Hattangadi-Gluth et al. 2014): Retrospective review of 248 consecutive patients with 254 cerebral AVMs treated with single-fraction proton beam stereotactic radiosurgery; median target volume 3.5 cm^3, 23 % in eloquent/deep locations, and median prescription dose 15 Gy RBE. With median 35 months follow-up, 65 % obliteration rate, median time to obliteration 31 months; 5- and 10-year cumulative incidence of total obliteration was 70 and 91 %, respectively. Univariate and multivariate analyses showed location and smaller target volume to be independent predictors of total obliteration; smaller volume and higher prescription dose also significant on univariate analysis.

- Harvard (Barker et al. 2003): Retrospective review of toxicity data in 1250 AVM patients treated with stereotactic proton beam radiosurgery. Median follow-up 6.5 years, median dose 10.5 Gy, median target volume 33.7 cm^3 (23 % <10 cm^3). Permanent radiation-related deficits in 4 % of patients; median time to complications 1.1 years. Complication rate related to dose, volume, deep location, and age; rate <0.5 % with <12 Gy.
- Nagasaki, Japan (Matsuo et al. 2014): Median 15.6-year results of 51 AVM patients treated with linear accelerator-based radiosurgery; median prescription 15 Gy, median target volume 4.5 cm^3, median Spetzler–Martin Grade II. Actuarial obliteration rates after 5 and 15 years were 54 and 68 %, which increased to 61 and 90 % when allowing for salvage treatments. Obliteration rate significantly related to target volume ≥4 cm^3, marginal dose ≥12 Gy, and Spetzler–Martin grade I (vs. others) on univariate analysis (target volume also significant on multivariate analysis). Post-treatment hemorrhage observed in 7 cases (14 %), predominantly within latency period; actuarial post-treatment bleeding rate ~5 % during the first 2 years, and 1.1 % upon final observation. Actuarial symptomatic radiation injury rates at 5 and 15 years were 12 and 19 %, respectively; target volume ≥4 cm^3 and location (lobular vs. other) were significantly associated with radiation injury on univariate and multivariate analysis. Cyst formation in five cases (9.8 % of patients; three asymptomatic, two treated with resection, and one resolved with steroids).

Staged AVM Treatment

- Yamamoto et al. (2012): Thirty-one patients retrospectively identified who underwent intentional 2-stage GKRS for 32 AVMs with nidus >10 cm^3 (mean target

volume 16 cm^3, maximum 56 cm^3). Low radiation doses (12–16 Gy) given to the lesion periphery during the first treatment; second session planned 36 months after the first. Complete nidus obliteration in 65 % of patients, and marked shrinkage in the remaining 35 %. Mild symptomatic GKRS-related complications in 2 patients.

- Ding et al. (2013): Eleven patients with large AVMs (31 ± 19 cm^3) divided into 3–7 cm^3 sub-targets for sequential treatment by robotic radiosurgery at 1–4 week intervals. Forward and inverse planning used to optimize 95 % coverage for delivery of 16–20 Gy; mean conformality index 0.65.

Cavernous Malformation

- Poorthuis et al. (2014): Systematic review and meta-regression analysis of 63 cohorts involving 3424 patients. Composite outcome of death, nonfatal intracranial hemorrhage, or new/worse persistent focal neurological deficit was 6.6 per 100 person-years after surgical excision ($n = 2684$), and 5.4 after SRS ($n = 740$; median dose 16 Gy). However, lesions treated with SRS significantly smaller than those treated surgically (14 mm vs. 19 mm).
- University of Pittsburgh (Hasegawa et al. 2002a, b): Retrospective review of 82 consecutive patients treated with SRS for hemorrhagic cavernous malformations; annual hemorrhage rate 34 %, excluding the first hemorrhage. Mean marginal dose 16.2 Gy, mean volume 1.85 cm^3. With mean follow-up of 5 years, average hemorrhage rate for the first 2 years after radiosurgery was 12 %, followed by <1 % from years 2 through 12. Eleven patients (13 %) had new neurological symptoms without hemorrhage after radiosurgery.

Trigeminal Neuralgia

Primary Treatment

- Marseille, France (Régis et al. 2006): Phase I prospective trial of GKRS (median dose 85 Gy) in 100 patients with trigeminal neuralgia; 42 % with history of prior surgery. At 12 months, 83 % pain free, 58 % pain free and off medication; salvage rate 17 %. Side effects included mild facial paresthesia in 6 % and hyperesthesia in 4 %.
- University of Virginia (Sheehan et al. 2005a, b): GKRS used to treat trigeminal neuralgia in 151 consecutive patients with median 19 months follow-up. Median time to pain relief was 24 days; at 3 years, 34 % of patients were pain free, and 70 % of patients had improvement in pain. Twelve patients experienced new onset of facial numbness after treatment, which correlated with repeat GKRS. Right-sided neuralgia and prior neurectomy correlated with pain-free outcomes on univariate analysis; multivariate analysis similarly significant for right-sided neuralgia.
- Brussels, Belgium and Marseilles, France (Massager et al. 2007): Retrospective stratification of 358 trigeminal neuralgia patients into 3 dosimetric groups: <90 Gy (no blocking), 90 Gy (no blocking), and 90 Gy with blocking. Excellent pain control in 66 % vs. 77 % vs. 84 %; good pain control in 81 %, 85 %, and 90 %. Mild trigeminal toxicity in 15 % vs. 21 % vs. 49 %; bothersome toxicity in 1.4 % vs. 2.4 % vs. 10 %.
- Brisman (2007): Review of 85 patients with trigeminal neuralgia treated with microvascular decompression (MVD, $n=24$) or GKRS ($n=61$) and followed prospectively. Complete pain relief at 12 and 18 months achieved in 68 % of MVD patients, and 58 and 24 % of GKRS patients; partial pain relief more equivalent. No permanent complications.

Retreatment

- UCSF (Sanchez-Mejia et al. 2005): Retrospective review of 32 patients retreated for trigeminal neuralgia with MVD ($n=19$), radiofrequency ablation (RFA, $n=5$), or SRS ($n=8$) from an initial cohort of 209 patients. Retreatment rate with RFA (42 %) significantly greater than the rate of retreatment with either MVD (20 %) or SRS (8 %).
- Columbia (Brisman 2003): Retrospective review of 335 patients with primary trigeminal neuralgia treated to a maximum dose of 75 Gy by GKRS, and then 45 re-treated to a maximum dose of 40 Gy GKRS (mean interval 18 months). Final pain relief was 50 % or greater in 62 % of patients; absence of prior surgery was an independent predictor of response to retreatment. Significant dysesthesias in 2 patients; no other serious complications.
- Zhang et al. (2005): Retrospective study of 40 trigeminal neuralgia patients initially treated with 75 Gy GKRS, and then retreated with 40 Gy GKRS. Landmark-based registration algorithm used to determine spatial relationship between primary and retreatment isocenters. Trend toward better pain relief with farther distance between isocenters; however, neither placing the second isocenter proximal or distal to the brainstem was significant. Mean distance 2.9 mm in complete or nearly complete responders vs. 1.9 mm in all others.
- Dvorak et al. (2009): Retrospective study of 28 trigeminal neuralgia patients initially treated to median 80 Gy GKRS, then retreated to median 45 Gy GKRS after a median 18 month interval. Univariate analysis showed no significant predictors of pain control or complication. However, when combining peer-reviewed retreatment series (215 total patients), both improved pain control and new trigeminal dysfunction were associated with greater dose: cumulative dose >130 Gy likely to result in >50 % pain control as well as >20 % risk of new dysfunction.

Pineal Tumors

- University of Pittsburgh (Hasegawa et al. 2002a, b): Retrospective review of 16 patients treated with SRS for pineal parenchymal tumors (10 pineocytomas, 2 mixed pineocytoma/pineoblastoma, and 4 pineoblastoma). Mean dose 15 Gy, mean target volume 5 cm^3. Actuarial 2 and 5 year OS 75 and 67 %, respectively; CR 29 %, PR 57 %, SD 14 %. LC 100 % although 4 patients died from leptomeningeal or extracranial spread. Two cases of gaze palsy 7 and 13 months after SRS attributed to treatment, one resolved with steroids and the other persisted until death.
- Marseille, France (Reyns et al. 2006): Retrospective review of 13 patients with pineal parenchymal tumors (8 pineocytomas and 5 pineoblastomas) treated with SRS (mean marginal dose 15 Gy). With mean follow-up 34 months, LC 100 %; 2 pineoblastomas progressed outside of SRS field resulting in death. No major mortality or morbidity related to SRS.
- England (Yianni et al. 2012): Retrospective review of 44 patients with pineal tumors treated with SRS (11 pineal parenchymal tumors, 6 astrocytomas, 3 ependymomas, 2 papillary epithelial tumors, and 2 germ cell tumors). Mean dose 18.2 Gy, mean target volume 3.8 cm^3. One- and 5-year PFS 93 and 77 %, respectively, but separating aggressive tumors from indolent lesions showed 5-year PFS 47 and 91 %, respectively. Tumor grade, prior RT, and radionecrosis associated with worse outcome.

Functional Disorders

Epilepsy

- UCSF (Chang et al. 2010): Prospective, randomized trial involving 30 patients with intractable medial temporal lobe epilepsy treated with 20 Gy/1 fraction vs. 24

Gy/1 by GKRS to the amygdala, 2 cm of the anterior hippocampus, and parahippocampal gyrus. Nonsignificant difference in seizure control between arms (59 % vs. 77 %), although early MRI alterations predictive of long-term seizure remission.

Parkinson Disease and Essential Tremor

- Japan (Ohye et al. 2012): Prospective, multicenter study of 72 patients with intractable Parkinson disease or essential tremor treated with selective thalamotomy by GKRS with a single 130 Gy shot to the lateral part of the ventralis intermedius nucleus (located 45 % of the thalamic length from the anterior tip). Excellent or good response with improved tremor in 43 of 53 patients (81 %) who completed 24 months of follow-up. No permanent clinical complications.
- University of Pittsburgh (Kondziolka et al. 2008): Retrospective review of GKRS thalamotomy in 31 patients with medically refractory essential tremor. Nucleus ventralis intermedius treated with 130–140 Gy in a single fraction. With median follow-up of 26 months, mean tremor score improved by 54 %, and mean handwriting score improved by 39 %, with the majority of patients (69 %) seeing improvement in both. Permanent mild right hemiparesis and speech impairment in 1 patient 6 months after radiosurgery; 1 patient with transient right hemiparesis and dysphagia.

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Chapter 5
Spine

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Pearls

- The spinal cord begins at the foramen magnum and, in adults, typically ends at the level of L1–L2. Below the termination of the cord, the spinal subarachnoid space extends to S2–S3, and the spinal canal continues inferiorly into the coccyx.
- Metastases to the vertebrae and epidural space compose the vast majority of tumors adjacent to the spinal cord (Linstadt and Nakamura 2010).
- Primary spinal cord tumors, such as chordoma and chondrosarcoma, account for 4–6 % of all CNS neoplasms and are slightly more common in pediatric patients.
- Primary tumors involving the spinal cord typically originate within the spinal canal (65 %), but may also

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arise from the spinal cord (10 %), or vertebral bodies (10 %).

- Presentation ranges from incidental discovery on surveillance imaging (especially in patients on high-dose steroids) to full paralysis, but the most common complaint is pain.
- Brown-Sécquard syndrome: Ipsilateral motor and fine touch impairment, and contralateral loss of pain and temperature sensation.
- Crude local control (LC) after spine SBRT for spine metastases ranges from 80 to 100 % (Lo et al. 2010); LC with conventional radiotherapy is approximately 86 % for non-mass-type metastases, but falls to 46 % for bulky lesions (Mizumoto et al. 2011).
- The risk–benefit ratio for SBRT treatment of meningioma, schwannoma, and malignant tumors of the spinal cord (glioblastoma, ependymoma, and metastases) relative to standard fractionation is not known.
- SBRT should be performed before cement kyphoplasty to prevent extravasation of active tumor into the epidural space (Cruz et al. 2014).

Treatment Indications

ASTRO guidelines for general spine SBRT (2011)	■ Life expectancy ≥3 months ■ Limited disease burden ■ Previously radiated location(s) ■ Postoperative radiation ■ Favor enrollment on a clinical trial
Spinal cord compression	■ Limited compression (1–2 segments) ■ Sub-acute presentation (outcome unlikely to be impacted by protracted SBRT planning) ■ Re-irradiation
Primary spinal cord neoplasms	■ Postoperative adjuvant setting ■ Salvage

Workup

- H&P with emphasis on neurologic components.
- Review of systems, including:
  - Focal weakness.
  - Focal sensory changes.
  - Bowel or bladder incontinence, and perianal numbness which could indicate cauda equina involvement.
  - Back pain.
- Laboratories not typically required, except in cases where adjacent viscera may be invaded or if there is concern for hematologic malignancy (then CBC, CMP, LFTs, etc.).
- Imaging.
  - MRI spine with gadolinium remains the gold standard for assessment of spinal cord neoplasms, and is also critical for SBRT targeting.
  - CT myelogram (standard or metrizamide-enhanced) is often useful in patients with metallic vertebral implants or a permanent pacemaker. At some institutions, CT myelograms are standard practice for spine SBRT planning.
  - MRI neurogram may be used to assess for nerve root involvement but has limited utility in SBRT planning.

Radiosurgical Technique

Simulation and Treatment Planning

- Invasive stereotactic frames that attach to spinous processes (Hamilton and Lulu 1995; Hamilton et al. 1995) have fallen out of favor with the advent of noninvasive immobilization devices that allow for targeting accuracy within 1–2 mm and 1–2° (Ryu et al. 2003; Yenice et al. 2003).

- Fluoroscopic placement of percutaneous gold fiducial markers into vertebral pedicles can be used to enhance intrafraction tumor targeting and tracking, but spinal tracking is most often sufficient.
- Insertion of a percutaneous balloon into pre-sacral space may be considered to displace the rectum if needed for definitive treatment of complex sacral lesions.
- CT simulation with slice thickness ≤3 mm (1–1.5 mm recommended).
- MRI and/or CT myelogram should be used in patients with vertebral hardware.
- Co-registration with MRI or PET/CT images when available.
- Target volumes:
  - GTV: Residual disease on CT/MRI.
  - CTV: GTV plus postoperative bed at high risk for recurrence.
  - PTV: CTV + 1.5–2 mm margin excluding critical neural structures.

Dose Prescription

- No randomized studies are available to provide firm recommendations for dose selection, and a clear dose-response relationship for pain control has not been established. However, there is a trend for symptomatic improvement (Ryu et al. 2003, 2007; Gerszten et al. 2006) and improved control of radioresistant histologic subtypes with increased dose (Gerszten et al. 2005a, b; Yamada et al. 2008).
- Limited disease in patients without prior radiation: 16–24 Gy in 1 fraction.
- Multi-segment disease without prior radiation: 20–27 Gy in 2–3 fractions.
- Multi-segment disease in previously irradiated field: 20–25 Gy in 5 fractions.
- Chordoma: 40 Gy in 5 fractions (UCSF experience).

Dose Delivery

- For multifraction regimens, doses are delivered every other day or twice weekly.
- Initial verification by kV X-ray or CBCT, aligned to spine or surrogate fiducial markers of position.
- Interval verification during treatment delivery with repeat kV X-ray films or CBCT for longer treatments or patients unable to remain immobile (Figs. 5.1, 5.2, and 5.3).

Toxicities and Management

- Acute toxicities (≤6 weeks):
  - Low risk of acute, self-limited esophagitis, nausea/vomiting, and loose stool with treatment of cervicothoracic, lumbar, and sacral spinal lesions, respectively; manage with antiemetic and antidiarrheal agents.
  - Cutaneous toxicities are rare, mild, and generally limited to treatment of lesions extending into the posterior paraspinous space.
- Late toxicities (>6 weeks):
  - Vertebral body compression fracture is a fairly low-risk adverse event after conventional radiotherapy (~5 %), but estimates range from 11 to 39 % after spine SBRT (*vide infra*).
  - Serious late effects to the esophagus and bronchi, such as necrosis and ulceration, are rare but may require surgical intervention.
  - Late toxicity to the brachial plexus, lumbar plexus and spinal cord, including both self-limited myelopathy and chronic progressive myelopathy, are similarly uncommon and may be mitigated with hyperbaric oxygen treatment.

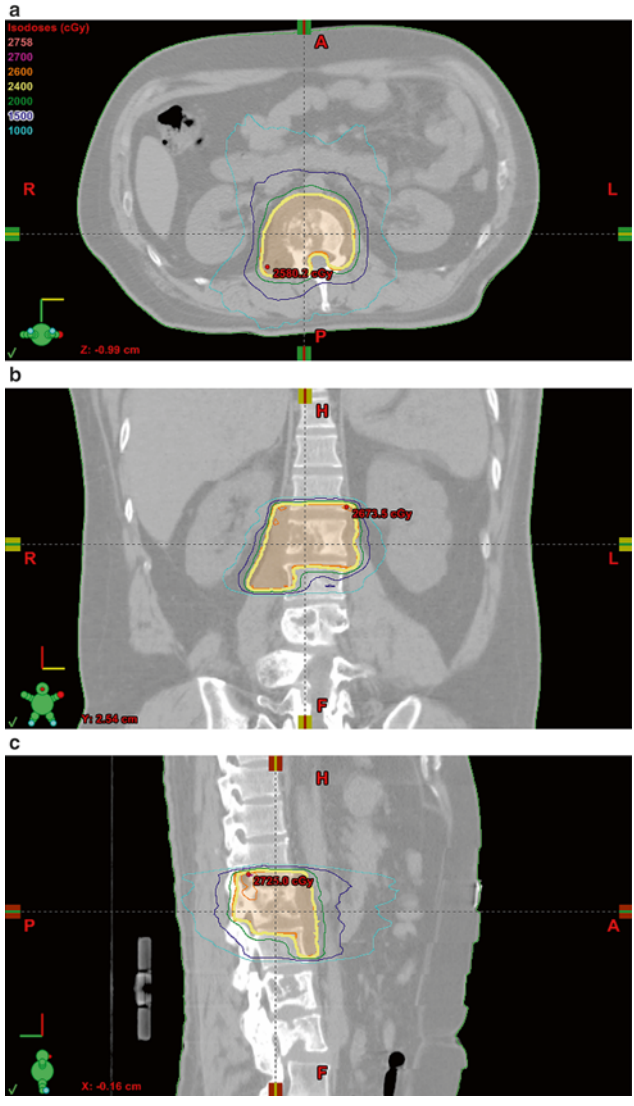

FIG. 5.1. SBRT for vertebral body metastasis. (**a**–**c**) Thirty-nine year-old male with stage IVC nasopharyngeal carcinoma and a painful L1 vertebral body metastasis extending to the bilateral epidural space and right psoas muscle. The metastasis was treated with rapid arc stereotactic radiosurgery to a total dose of 2400 cGy in a single fraction with 6 MV photons prescribed to the 87 % isodose line

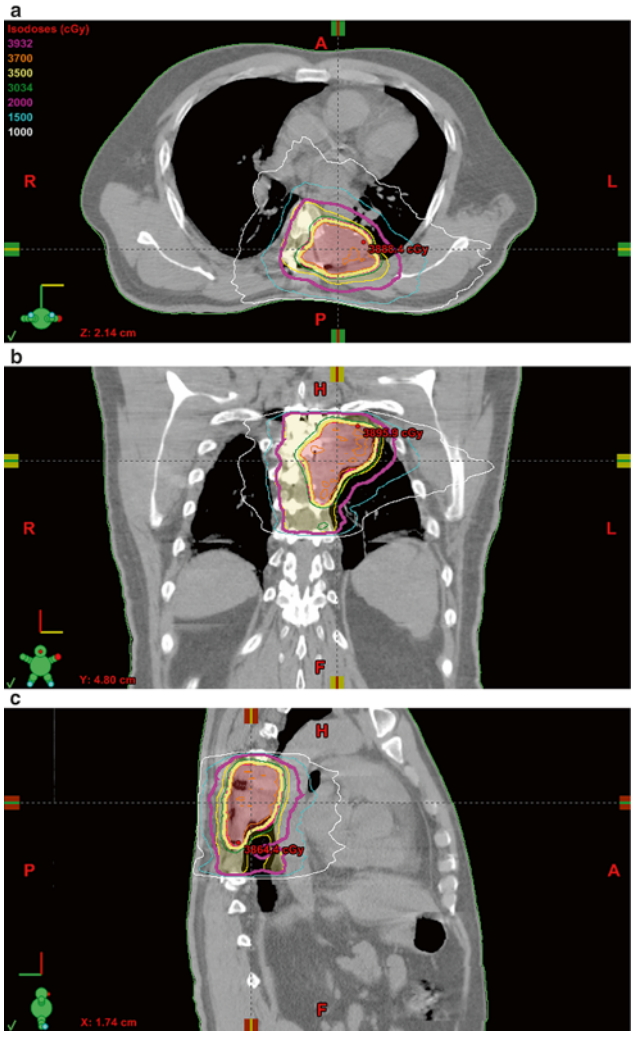

FIG. 5.2. Postoperative SBRT for primary spine tumor. (**a**–**c**) Forty-nine year-old male with a remote history of medullary thyroid cancer who subsequently developed a painful left posterior 7th rib lesion that was treated with a course of palliative radiotherapy to 3300 cGy in 11 fractions at an outside institution. The lesion continued to grow over the following 2 years, and a biopsy demonstrated chondrosarcoma. Following gross total resection and two subsequent recurrences, the GTV was treated with rapid arc stereotactic radiosurgery to a total dose of 3500 cGy in 5 fractions, with 2000 cGy to the postoperative bed, using 6 MV photons prescribed to the 88 % isodose line

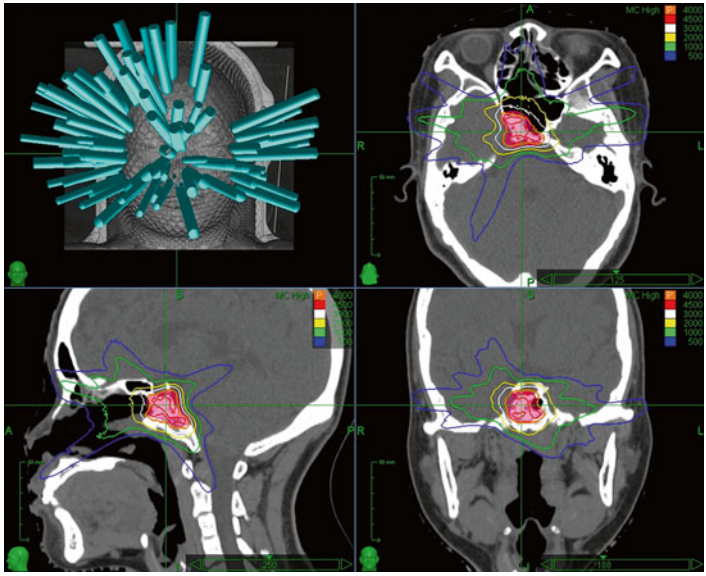

FIG. 5.3. Clival chordoma SBRT. Thirty year-old female with a clival chordoma status post gross total endoscopic endonasal transsphenoidal resection, followed by repeat gross total resection for a recurrence 1 year later. The tumor was treated with adjuvant robotic radiosurgery to a total dose of 4000 cGy in five daily sequential fractions with 6 MV photons prescribed to the 83 % isodose line. Beam angles are shown at the *top left*, and proceeding clockwise are axial, coronal, and sagittal CT images with isodose lines and the PTV in *red* color wash

- Lhermitte's syndrome, an electric sensation running down the back into the limbs, often precedes frank neurologic deficits of radiation myelopathy.

Recommended Follow-Up

- H&P and MRI spine every 2–3 months or as clinically indicated for the first 2-years, followed by imaging every 6 months for the next 3 years, and yearly imaging thereafter.

Evidence

Dose and Technique

- Yamada et al. (2005): Noninvasive immobilization for paraspinal stereotactic or image-guided radiotherapy with setup accuracy within 2 mm. Thirty-five patients (14 primary tumors and 21 metastases) with gross disease involving the spinal canal who were either previously irradiated or treated with doses beyond conventional spinal cord tolerance. PTV = gross disease with a 1 cm margin, excluding the spinal cord. For primary treatments, median PTV dose 7000 cGy in 33 fractions with V100 of 90 %; median cord Dmax 68 %. In re-irradiation cases, median PTV dose 20 Gy in 5 fractions with V100 of 88 %; median cord Dmax 34 %. Median follow-up 11 months; no radiation myelopathy. Palliation from pain, weakness, or paresis in 90 % of patients with >3 months of follow-up. LC 75 and 81 % for secondary and primary malignancies, respectively.
- Chang et al. (2007): Prospective phase I/II study of SBRT for spinal metastases in 63 patients with 74 tumors treated at MDACC (30 Gy in 5 fractions or 27 Gy in 3 fractions; spinal cord Dmax ≤10 Gy). In previously radiated patients ($n = 35$, 56 %), prior dose ≤45 Gy. Median follow-up 21.3 months; no neuropathy or myelopathy. Actuarial 1-year PFS 84 %. Primary mechanisms of failure limited to recurrence in adjacent bones (i.e., pedicles and posterior vertebral elements), and epidural space. Narcotic usage declined from 60 to 36 % at 6 months.
- Ryu et al. (2008): Forty-nine patients with 61 separate spinal metastases treated with single-session SBRT from 10 to 16 Gy. Spinal cord limited to ≤10 Gy for ≤10 % of the cord volume 6 mm superior and inferior to the treated segment. Median time to pain relief 14 days (earliest within 24 h). Complete pain relief in

46 % and partial relief in 19 %. Overall pain control rate for 1 year was 84 %; median duration of relief 13.3 months. Trend toward increasing pain relief with ≥14 Gy. No clinically detectable late toxicity.

- Yamada et al. (2008): One-hundred three consecutive spinal metastases in 93 patients treated with 18–24 Gy in 1 fraction (median 24 Gy) prescribed to the 100 % isodose line; spinal cord Dmax ≤14 Gy. Patients with high-grade cord compression, mechanical instability, and prior history of RT excluded. Median follow-up and OS both 15 months; actuarial LC 90 % with median time to LF 9 months. Radiation dose, but not histologic subtype, was a significant predictor of LC. Acute toxicity limited to grade ≤2 events; no late toxicity. All patients without local failure reported durable palliation of symptoms.
- Amdur et al. (2009): Prospective phase II study of SBRT for spinal cord metastases involving 25 sites in 21 patients treated with 15 Gy in 1fraction. Primary endpoint was toxicity; spinal cord Dmax ≤12 Gy in patients with no prior radiotherapy ($n=9$), and ≤5 Gy for salvage cases ($n=12$). With median follow-up 11 months, 95 % LC and 43 % pain improvement, but 1-year OS 25 % and PFS 5 %. Acute toxicity limited to grade ≤2 dysphagia or nausea; no late toxicity.

Spinal Cord Compression and Retreatment

- Milker-Zabel et al. (2003): Eighteen patients with 19 previously irradiated spinal cord metastases (median dose 38 Gy) re-treated due to progressive pain ($n=16$) or neurologic symptoms ($n=12$). Median time to re-treatment 17.7 months. Five patients treated with fractionated conformal radiotherapy (FCRT), 14 treated with IMRT; all immobilized for extracranial stereotaxy. Median re-treatment dose 39.6 Gy in 2 Gy fractions. After median of 12 months of follow-up, OS 65 %, LC 95 %, pain relief 81 %, and neurologic

improvement 42 %. Tumor size unchanged in 84 % of cases. No clinical late toxicity.

- Gerszten et al. (2007): Single institution cohort of 393 patients with spinal cord compression treated with 12.5–25 Gy robot-assisted SBRT in 1 fraction (mean 20 Gy) and followed prospectively. Five hundred metastases, 67 % previously treated with EBRT. Long-term improvement in pain for 86 % of patients; 84 % (30 of 35) with progressive neurological deficit experienced clinical improvement. LC was 90 and 88 % for primary and salvage SBRT, respectively. No reports of radiation myelopathy.
- Sahgal et al. (2009): Single institution retrospective review of 39 consecutive patients with 60 paraspinal metastases treated with robot-assisted SBRT. Median dose 24 Gy in 3 fractions prescribed to the 60–67 % isodose line. Sixty-two percent of lesions previously treated with EBRT. Median OS 21 months; 1- and 2-year PFP was 85 and 69 %, respectively. For re-irradiation cases, 1-year PFP was 96 %. No significant differences in OS or PFP between salvage and *de novo* treatments. No reports of radiation-induced myelopathy or radiculopathy in the 39 cases with ≥6 months follow-up. All patients with local failure experienced worsening of pain; all others stable at best, but no standardized pain quantification used.

Chordoma and Other Primary Tumors of the Spine and Skull Base

- Martin et al. (2007): Twenty-eight patients with chordoma ($n=18$) or chondrosarcoma ($n=10$) of the skull base treated with Gamma Knife SRS as either primary ($n=2$) or adjuvant treatment. Twenty-two patients previously received fractionated radiotherapy prior to radiosurgery (mean dose 65 Gy and 75 CGE). Mean tumor volume at SRS 9.8 cm^3. Median dose to the tumor margin 16 Gy in 1 fraction (range 10.5–25 Gy)

prescribed to the 50 % isodose line in all but 1 patient. Transient acute toxicity in 1 patient. Median follow-up 7.7 years. Five-year actuarial LC for chondrosarcoma 80 ± 10 %; chordoma actuarial LC and survival 63 ± 10 % at both 5- and 10-years. No significant factors identified for tumor control.

- Henderson et al. (2009): Eighteen chordoma patients treated with stereotactic robotic radiosurgery; 44 % mobile spine, 39 % clivus, and 17 % sacral tumors. Median tumor volume 128 cm^3 treated with a median dose of 35 Gy in 5 fractions; salvage cases treated with 28 Gy in 4 fractions. Five-year LC 59 %, OS 74 %, and DSS 89 %. No improvement in pain or quality of life. Recommendation for 40 Gy in 5 fractions to gross tumor and at least a 1 cm margin based on modeling with α/β of 2.45 for chordoma.
- North American Gamma Knife Consortium (Kano et al. 2011): Seventy-one patients status post SRS for chordoma from six institutions. Median target volume 7.1 cm^3, and median marginal dose 15 Gy. Five-year actuarial OS 80 %; 93 % for patients with no prior fractionated RT ($n = 50$), and 43 % for prior RT group ($n = 21$). Younger age, longer interval between initial diagnosis and SRS, no prior RT, <2 cranial nerve deficits, and smaller tumor volume were significantly associated with longer survival. Five-year overall LC 66 %; 69 % for no prior RT, and 62 % for prior RT. Older age, prior RT, and large tumor volume all significantly associated with worse tumor control. Thirty percent of patients with pretreatment neurologic deficits experienced improvement; median time to response 4.6 months.
- Jiang et al. (2012): Twenty patients with chordoma treated with stereotactic robotic radiosurgery (11 primary adjuvant therapy, 9 salvage); 65 % clival lesions. Average tumor volume 16 cm^3; mean marginal dose of 32.5 Gy in 1–5 fractions to the 79 % isodose line. With median follow-up 34 months, LC 55 %; 82 % in

primary adjuvant cases, and 29 % in salvage cases. Five-year OS 52.5 %. Status of symptoms not reported.

- Yamada et al. (2013): Twenty-four patients with chordoma of the sacrum ($n=10$) and mobile spine ($n=14$) treated with single-fraction SRS (median dose 24 Gy, with median V100 95 %). Treatment given in both the adjuvant ($n=7$) and neoadjuvant setting ($n=13$), although only six patients proceeded to surgery. Seven patients treated for postoperative recurrence. With median follow-up 24 months, LC 95 %; 1 case of progression 11 months after SRS. Toxicity limited to 1 case sciatic neuropathy and 1 case vocal cord paralysis. Status of symptoms not reported.

Vertebral Body Compression Fracture (VCF)

- Rose et al. (2009): 62 patients with 71 spinal metastases treated with single-fraction SBRT (median 24 Gy); predominance of lytic spinal lesions (65 %). With median follow-up of 13 months, VCF occurred in 27 (39 %) treated sites after a median time of 25 months. HR for VCF: osteolytic tumors 3.8; >40 % vertebral body involvement 3.9; and lesions located from T10 through the sacrum 4.6.
- Sahgal et al. (2013): Pooled retrospective study of 252 patients with 410 spinal segments treated with SBRT at MDACC, Cleveland Clinic, and University of Toronto. Median follow-up and OS of 11.5 and 16 months, respectively. Twenty-seven new VCFs and 30 cases of VCF progression (overall incidence 14 %). Median time to VCF 2.46 months, with 65 % of events occurring in the first 4 months. Dose per fraction identified as a significant predictor of VCF on univariate and multivariate analysis; baseline VCF, lytic tumors, and spinal deformity all significant on multivariate analysis. Relative to ≤19 Gy per fraction, the HR for VCF with ≥24 Gy and 20–23 Gy per fraction was 5.25 and 4.91, respectively.

Late Toxicity

- Ryu et al. (2007): Retrospective analysis of 230 lesions treated with single-fraction SBRT to the gross tumor plus vertebral body and pedicles, and/or posterior elements in 177 patients without a history of prior radiotherapy to the spine. Prescription ranged from 8 to 18 Gy to the 90 % isodose line; no PTV margin; spinal cord volume defined as 6 mm superior and inferior to the target. Among the patients treated with 18 Gy, the average dose to the 10 % spinal cord volume was 9.8 ± 1.5 Gy. Median follow-up 6.4 months; 1-year survival 49 %. One case of radiation myelopathy among the 86 patients alive >1 year after treatment.
- Gomez et al. (2009): Retrospective analysis of 119 paraspinal thoracic sites treated with single-fraction SBRT (median dose 24 Gy) in 114 patients. Median Dmax to esophagi and bronchi were 12.5 Gy and 11 Gy, respectively. At a median follow-up of 11.6 months, seven episodes of grade ≥2 esophageal toxicity (one of which required gastric pull-up for fistula formation), and two cases of grade ≥2 bronchial toxicity; no cases of pneumonitis.
- Sahgal et al. (2010): Dosimetric report of radiation-induced myelopathy in five patients after primary SBRT for spinal tumors. Radiation myelopathy observed with Dmax of 10.6–14.8 Gy in 1 fraction, 25.6 Gy in 2 fractions, and 30.9 Gy in 3 fractions to the thecal sac. When compared to dosimetric data from 19 patients without spinal cord myelopathy after SBRT, there was a significant interaction between patient subsets based on normalized BED. Modeling with α/β value of 2 for spinal cord late effect and 10 for tumor effect suggests that 10 Gy in 1 fraction and up to 35 Gy_2 in 5 fractions carries a low risk of radiation-induced myelopathy.
- Sahgal et al. (2012): Dosimetric report of radiation-induced myelopathy after salvage SBRT in five

patients who initially received conventional EBRT to the spine (median 40 Gy in 20 fractions). When compared to a group of 14 salvage patients without radiation myelopathy, the mean EQD2 maximum point dose (P_{max}) to the thecal sac was significantly higher in those with radiation myelopathy (67.4 Gy vs. 20 Gy), as was the total P_{max} (105.8 Gy vs. 62.3 Gy). Modeling suggests that SBRT given at least 5 months after conventional palliative radiotherapy with a re-irradiation thecal sac P_{max} EQD2 of 20–25 Gy appears to be safe provided the total P_{max} EQD2 does not exceed 70 Gy, and the thecal sac P_{max} EQD2 comprises no more than one-half of the total EQD2.

Ongoing

- RTOG 0631: Randomized, prospective, multicenter trial of single fraction spine SBRT to 8 Gy vs. 16–18 Gy (1:2 randomization), based on the equivalent results of 30 Gy in 10 fractions vs. 8 Gy in 1 fraction AP/PA from RTOG 97–14 (Hartsell et al. 2005). Patients stratified by number of spine metastases, tumor histology, and intended SBRT dose. Primary endpoint was pain control; target enrollment 380 patients.

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Chapter 6
Head and Neck

Sue S. Yom

Pearls

- ~52,140 cases/year and 11,460 deaths in the USA from head and neck cancer (M:W, ~3:1), comprising 6.5 % of new cancer diagnoses in the USA (Jemal et al. 2010).
- 5-year survival rates range between 50 and 75 % but for local-regionally advanced disease (60 % of new diagnoses), they are as low as 30 % (Ries et al. 1988; Vokes et al. 1993).
- 5-year survival for early local recurrence ~25–35 % and for more advanced recurrence, ~15–20 % (Lee & Esclamado 2005).
- At present SBRT has no clearly established or widely accepted role in the definitive management of newly diagnosed, non-metastatic disease or for curative intent multimodality reirradiation.
- The potentially serious risks of SBRT should be cautiously weighed against the competing risks of symptomatic tumor progression and the feasibility and efficacy of alternative treatment options.

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Work-Up

- H&P, including performance status, HPV status, smoking and alcohol history, prior history of treatment to the head and neck.
- Review of symptoms, including
  - Bleeding.
  - Pain.
  - Weight loss/nutritional status.
  - Pre-existing dysphagia.
  - Neuropathies.
- Laboratories
  - CBC, BUN, Cr, LFTs, alkaline phosphatase, and LDH.
- Imaging
  - MRI of the primary site and neck ± upper mediastinum.
  - CT chest with contrast ± CT abdomen and pelvis or PETCT as indicated.
- Pathology
  - FNA or ultrasound/CT-guided biopsy for accessible lesions.

Treatment Indications

- Early-stage head and neck cancers are definitively managed by local therapy, with single-modality surgical resection or external beam radiation therapy (EBRT) as usual standard of care. EBRT is more frequently employed for medically inoperable, high-risk, or elderly patients.
- Multimodal therapy, nearly always including EBRT combined with surgery, chemotherapy, or both, is frequently employed for locally or regionally advanced head and neck cancer.
- SBRT is now selectively employed at a limited number of centers for small-volume recurrence or palliation.

- SBRT has been reported as a fractionated stereotactic boost following definitive (chemo)radiation for locally advanced nasopharyngeal cancers.
- A few reports exist combining SBRT with concurrent targeted therapy or cytotoxic chemotherapy but these combinations remain investigational.

Radiosurgical Technique

Simulation and Treatment Planning

- Thin-cut CT (1–1.5 mm) thickness recommended.
- GTV contoured from fusion of MRI with/without gadolinium contrast, merged in the area of interest to the planning CT.
- CTV margins may range from 0 to 10 mm depending on clinical scenario:
  - For recurrent disease, margins up to 5–10 mm may be considered depending on the degree of tumor infiltration into surrounding tissues.
  - For well-delineated disease at the skull base, where high-stability or real-time localization of the setup is expected, 0–3 mm margins could be considered.
  - For palliation, no margin may be prudent to minimize toxicity.
- PTV = CTV + 1–5 mm (dependent upon available center-specific image guidance and site-specific motion considerations).
- State of the art tracking localization or frequent IGRT are recommended to reduce setup uncertainty and margins.
- Goal should be for low-dose to proximal OARs, achieved by use of an increased number of beams and angles, as well as minimization of margins.
- Phantom-based QA on all treatment plans prior to delivery.

Dose Prescription

- Dose and fractionation outside of the range of conventional fractionation for head and neck cancer (1.8–2.0 Gy/fraction/day) are not clearly defined in terms of alterations in safety profile or gains in efficacy.
- Planning should be determined with a high level of attention to potential adjacent normal tissue toxicity.
- For SBRT-based single-modality reirradiation and SBRT boost following EBRT, prescriptions vary widely depending on the clinical scenario; practitioners are advised to consult the primary literature to identify applicable solutions. For reirradiation, the most commonly reported dose range is 30–50 Gy over 5 fractions.
- Ideally prescribe to ≥80 % isodose line (IDL), ≥95 % PTV coverage with prescription dose; depending on characteristics of treatment planning system, 50–60 % IDL is acceptable only if high-dose heterogeneity and fall off are thoroughly reviewed for safety.
- Composite planning should be employed in cases of reirradiation, with appropriate BED conversion for dose summation.

Dose Limitations

- Dose and fractionation schemas largely empirically determined.
- Almost no reports address normal organ tolerances for hypofractionated regimens in any detail.
- A dose-escalation study of SBRT-based reirradiation at the University of Pittsburgh used the following general constraints for a 5-fraction regimen: spinal cord ≤ 8 Gy, brain stem ≤ 8 Gy, larynx ≤ 20 Gy, and mandible ≤ 20 Gy. Doses given to the oral cavity and parotid glands were based on patient-specific factors.

- A prospective phase II French study restricted the repeat dose to a fully previously radiated spinal cord to ≤6 Gy point dose over 6 fractions.
- In general, the dose per fraction should be less than 2.5 Gy per fraction to as much tissue as possible, with special attention to pharyngeal, vascular, or other reir-radiated structures prone to late complications. Tissue receiving above 4 Gy per fraction should be strictly minimized.

Dose Delivery

- Dose often delivered in fractions given every other day; consecutive daily treatments should warrant additional caution.
- Setup may be isocentric or non-isocentric depending upon SBRT delivery system.
- Verification by kV XR or CBCT, aligned to visualized tumor or surrogate markers of position.
- Flexion of the cervical neck can result in interfractional variability of setup of a few millimeters.
- Intrafractional tumor motion may be as much as several millimeters in areas affected by jaw opening or laryngeal/swallowing motions.

Toxicities and Management

- Common acute toxicities (<6 weeks):
  - Fatigue: Generally early-onset and self-limiting.
  - Dermatitis: Entrance and exit doses can be reduced with increased numbers of beams to minimize radiation dermatitis. Mild-to-moderate: skin reaction treated with supportive care, including topical moisturizers, analgesics, low-dose steroids, and antimicrobial salves.

- Mucositis: Critical to minimize target volumes to reduce pain and dysphagia related to this toxicity. Treated with topical preparations including lidocaine-based solutions and pain medications. Nutritional status should be carefully monitored.

- Severe late toxicities (>6 weeks)
  - Brachial plexopathy: May present with neuropathic pain or with motor/sensory changes in the upper extremities. MRI of brachial plexus and upper spine may be diagnostic and rule out tumor recurrence. Limited treatment options include supportive care and occupational therapy.
  - Skin or soft tissue necrosis: For persistent non-healing lesions, consider hyperbaric oxygen therapy and tocopherol pharmacotherapy.
  - Esophageal stricture or fistula: Can occur after treatment of hypopharyngeal or cervical esophageal inlet. More possible in the reirradiation setting. Treatment options include dilation or stent placement.
  - Vasculopathy: Vascular erosion may lead to limited hemoptysis or massive hemorrhage and death (especially seen in reirradiation setting).
  - Osteoradionecrosis: May occur in the jaw, skull base, or spine. Worsened by infectious complications and in proximity to vascular structures, may raise the risk of hemorrhage.
  - Brain necrosis: Highest risk within areas of high cumulative dose. May require neurosurgical intervention and potentially fatal.

Recommended Follow-Up

- CT or PETCT every 3–4 months × 3 years, every 6 months × 2 years, every 12 months thereafter for routine follow-up.

- Neurologic/vascular status should be carefully followed; symptoms of headache, dizziness, or TIA should be investigated immediately.
- Infectious complications of the soft tissue or bone must be vigorously addressed due to high potential for osteoradionecrosis, soft tissue necrosis, and/or vascular exposure and blowout.

Evidence

Boost/Recurrence for Nasopharyngeal Carcinoma

- Stanford University reported mature results for 82 patients given a median EBRT dose of 66 Gy followed by single-fraction 7–15 Gy SBRT boost. Most had concurrent cisplatin. 5-year freedom from local relapse was 98 % and overall survival was 75 %. Four patients had acute facial numbness. Late toxicities included three patients with retinopathy, one with carotid aneurysm, and ten cases of temporal lobe necrosis especially in those with T4 tumors (Hara et al. 2008).
- Taiwanese investigators reported on 54 patients given 64.8–68.4 Gy followed by 12–15 Gy SBRT boost, most with concurrent cisplatin. Local control at 3 years was 92 % and overall survival was 85 %. Three patients with large primary tumors had vascular bleeding resulting in death (Chen et al. 2006).
- Investigators from Hong Kong reported results for 45 patients who were offered either 20 Gy intracavitary brachytherapy boost or fractionated SBRT following EBRT to 66 Gy. Patients were selected due to suspicion for persistent localized disease at several weeks after EBRT completion. Median boost dose was 15 Gy, at 6–8 Gy per fraction for 2–3 weekly fractions vs. 2.5 Gy for 8 daily fractions. At 3-year follow-up, local failure-free control rates in the no boost, brachytherapy, and SBRT groups were 43, 71, and 82 % (Yau et al. 2004).

- Investigators in Guangzhou, China delivered SBRT to 90 patients with either persistent or recurrent disease. For persistence, the median dose was 18 Gy in 3 fractions; for recurrence, it was 48 Gy in 6 fractions. 3-year local failure-free survival and disease-specific survival rates were 89.4 % and 80.7 % for persistence, and 75.1 % and 45.9 % for recurrence. 17 (19 %) patients developed severe late complications: 6 with mucosal necrosis, 3 with brain stem necrosis, 6 with temporal lobe necrosis, and 2 with fatal hemorrhage (Wu et al. 2007).

Locoregionally Recurrent Head and Neck Cancer (Reirradiation)

- University of Pittsburgh conducted a phase I dose-escalation study of reirradiation for recurrent unresectable head and neck squamous cell carcinoma (HNSCC). 31 patients with oropharynx, oral cavity, larynx, nasopharynx, and unknown primary cancers were treated in 5 tiers ranging from 25to 44 Gy in 5 fractions over 2 weeks. Median prior dose of EBRT was 64.7 Gy and 56 % had received prior concurrent chemoradiation. 25 patients were evaluable for toxicity, in whom no grade 3 complications were reported; the maximally tolerated dose was not reached (Heron et al. 2009).
- Turkish investigators reported on 46 patients with nasopharynx, oral cavity, paranasal sinus, larynx, and hypopharynx cancers reirradiated with SBRT to doses from 18 to 45 Gy over 1–5 fractions. 1-year local control and survival rates were 84 and 46 %. Eight patients had carotid artery blowout and died. This occurred only in patients receiving 100 % of the dose to the carotid artery and in whom tumor surrounded the carotid artery by at least 180° (Cengiz et al. 2011).

Reirradiation with Concurrent Systemic Therapy

- University of Pittsburgh published a 70-patient matched-cohort retrospective study reporting SBRT results with or without cetuximab in previously radiated HNSCC patients. Addition of cetuximab resulted in an overall survival of 24.5 months versus 14.8 months for patients who had SBRT alone. No grade 4–5 complications occurred in either group (Heron et al. 2011).
- A French (Lilly, Nancy, Nice) multi-institutional phase II study included 60 patients with inoperable recurrence or new primary HNSCC (size $\leq$65 mm) in a previously irradiated area. 80 % were oropharyngeal tumors. 48 % had prior chemotherapy and 93 % had more than 20 pack-year smoking history. The mean time between prior RT and SBRT was 38 months. The SBRT dose was 36 Gy in 6 fractions in 11–12 days, prescribed at the 85 % IDL, given with 1 loading and 4 concurrent cycles of concurrent cetuximab. If the spinal cord had received $\geq$45 Gy previously, the maximum allowed point dose was $\leq$6 Gy. Tumors with skin infiltration or invading more than 1/3 of the carotid artery were "avoided." Among 56 patients who completed SBRT-cetuximab with a follow-up of 11.4 months, 18 had grade 3 toxicities including mucositis, dysphagia, fistula, induration, and fibrosis. One patient died from hemorrhage and malnutrition. At 3 months, response and disease control rates were 58.4 % and 91.7 %. Median survival was 11.8 months, median progression free survival was 7.1 months, and 1-year overall survival was 47.5 %. Per intention to treat analysis, 33 % had progressive disease (Lartigau et al. 2013).
- Georgetown University investigators reported on 65 patients who were treated with SBRT, of whom 33 received concurrent chemotherapy or cetuximab. Patients receiving <30 Gy over 5 fractions had a 29 % response rate versus 69 % for higher doses. 2-year local control and survival rates were 30 and 41 %. 19

patients experienced grade 1–3 toxicity and 7 experienced severe toxicity including one death. Chemotherapy did not improve outcomes on multivariable analysis, attributable to the small sample size and heterogeneity of agents used (Unger et al. 2010).

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Chapter 7
Lung

Steve E. Braunstein, Sue S. Yom, and Alexander R. Gottschalk

Pearls

- ~224,000 cases/year and 159,000 LUNG cancer deaths in the USA (M:F ~ 1:1).
- Lung cancer is the most common noncutaneous with the greatest cancer mortality rate worldwide.
- Risk of lung cancer in current smokers is 24×, and in former smokers 6×, as compared to never smokers.
- Historically, presentations were largely advanced (symptomatic): stage I (10 %), II (20 %), III (30 %), IV (40 %). This may shift to early stage I–II (60 %), III (20 %), IV (20 %) with low-dose CT screening.
- Low-dose CT screening currently recommended by USPSTF for adults 55–80 years old with ≥30 pack-year smoking history, currently smoking or having quit within the past 15 years.
- Poor outcomes for untreated stage I NSCLC: median OS 9 months, 5 years OS 7 %.

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- Lobectomy has been considered standard of care for early-stage, medically operable NSCLC, with 5 years OS 60–70 %. However, recent studies suggest equivalent efficacy of sublobar resection, including wedge resection for small peripheral tumors, in the era of CT-based diagnosis.
- Of note, historically ~15 % of cT1-2 N0 have + LN, which may be underappreciated by nonsurgical management approaches. However, with PET and CT staging this may be diminished.
- Conventionally fractionated EBRT approaches to early-stage lung cancer associated with poor LC (20–70 %) and OS (20–60 %) at 3 years.
- Improved outcomes with dose escalation and hypofractionation suggested by multiple studies in EBRT, though continues to be an area of uncertainty for locally advanced disease.
- Current studies of SBRT for early-stage NSCLC show LC ~85–95 % and OS ~60–80 % at 3 years. Distant failure rate ~20 %.
- NSCLC dose calculations for tumor control employ [alpha]/[beta] = 10
- Improved early-stage NSCLC outcomes associated with SBRT dose and fractionation schemas achieving $BED_{10} \geq 100$ Gy.
- Metachronous primary NSCLC arises in 4–10 % of early-stage patients within 5 years of initial treatment.
- Stage III patients treated with conventional chemoradiation experience 25 % rate of in-field recurrence.
- Complete metastasectomy of lung lesions of various malignant primary histologies is associated with 5 years OS 20–40 %.

Workup

- H&P, including performance status, weight loss, and smoking status.
- Review of symptoms

- Most early-stage NSCLC are asymptomatic.
- More advanced presentations include cough, dyspnea, hemoptysis, post-obstructive pneumonia, pleural effusion, pain, hoarseness (left recurrent laryngeal nerve), SVC syndrome, clubbing, superior sulcus (Pancoast) tumor triad of shoulder pain, brachial plexopathy, and Horner's syndrome.

- Laboratories
  - CBC, BUN, Cr, LFTs, alkaline phosphatase, and LDH.
- Imaging
  - Chest, abdomen, and pelvis staging CT with contrast (r/o liver and adrenal metastases).
  - PETCT (>90 % negative predictive value for nodal involvement, but low sensitivity for adenocarcinoma in situ (AIS); unclear association of max SUV with SBRT outcomes).
  - MRI brain for LN+, stage III-IV, and/or if neurologic symptoms on presentation.
  - MRI thoracic inlet for superior sulcus tumors for assessment of brachial plexus and vertebral involvement.
- Pathology
  - CT-guided biopsy of peripheral N0 lesions.
  - Mediastinoscopy or bronchoscopic biopsy for central tumors and/or N+ disease.
  - Thoracentesis for pleural effusions.
  - Molecular testing for Kras activation, EGFR mutation, ROS and ALK gene rearrangements.
- Pulmonary function testing for presurgical and preradiotherapy evaluation.
  - Medically inoperable is generally FEV1 <40 % or <1.2 L, DLCO <60 %, FVC <70 %.

Treatment Indications

- SBRT is currently employed in NSCLC. SBRT has no established role in small cell lung cancer.
- Early-stage NSCLC managed by local therapy, with surgical resection as standard of care historically, and SBRT approaches most frequently employed for node-negative, medically inoperable and increasingly for select (high-risk and elderly) operable candidates.
- The role of adjuvant chemotherapy in SBRT-treated T2N0 disease is not established in any way.
- Multimodal therapy is employed for locally advanced disease.
- Most established SBRT criteria include N0 patients with <5 cm, peripherally located tumors, but tumors may be more cautiously treated with expanded criteria of larger size (<7 cm), central location, multiple synchronous lesions, and chest wall invasion (T3N0) with historically inferior results.
- SBRT has a developing role as a boost following definitive chemoradiation in management of locally advanced NSCLC, for re-irradiation of locally recurrent disease, and for treatment of intrathoracic oligometastases from various primary histologies (commonly stage IV NSCLC, sarcoma, renal cell carcinoma, thyroid, or colorectal cancer) (Table 7.1).

Radiosurgical Technique

Simulation and Treatment Planning

- Tumor motion may be 2–3 cm in peri-diaphragmatic regions of the lower lung. Motion management strategies include respiratory gating, coaching with audio-visual feedback, breath-hold techniques, abdominal compression, and intrafraction tumor tracking real-time imaging techniques with dynamic beam and/or couch compensation.

TABLE 7.1 Treatment recommendations for NSCLC and pulmonary oligometastases

Presentation	Resectability	Recommended treatment
T1-2N0	Operable	Lobectomy (preferred over segmentectomy or wedge resection) or SBRT
	Inoperable	SBRT (may consider RFA/Cryotherapy)
II (T2bN0, T1-2N1, T3N0)	Operable	Surgery → chemo (>4 cm)
	Inoperable	ChemoRT → ±chemo or hypofx EBRT → ±chemo
IIIA	Operable	ChemoRT → restage → surgery → chemo or Chemo → restage → surgery → chemo ± RT
	Inoperable	ChemoRT → ±chemo
IIIB	Inoperable	ChemoRT → ±chemo
Recurrent	Operable	EBRT/SBRT/resection for limited local recurrence → systemic therapy
	Inoperable	EBRT/SBRT/RFA/cryo for limited recurrence → systemic therapy
Pulmonary oligometastases	Operable	Lobectomy/wedge resection or SBRT or hypofractionated EBRT (for larger lesions, >5 cm) → systemic therapy
	Inoperable	SBRT, RFA, cryo, or hypofx EBRT (preferred for larger lesions, > 5 cm) → systemic therapy

- Thin-cut CT (≤1.5 mm) thickness recommended. 4DCT or maximal inspiratory and expiratory phase CTs or slow CT recommended to assess target and critical structure internal motion. Free-breathing helical or mean intensity projection CT should be used for dose calculation.
- iGTV contoured from Maximum Intensity Projection (MIP) generated from 4DCT. MIP should be used judiciously in tumors adjacent to diaphragm or chest wall, with additional imaging as needed to fully discriminate the target from surrounding normal tissue with similar CT tissue density.

- GTV/iGTV = tumor visible on CT lung window.
- CTV/ITV = GTV/iGTV + 0–10 mm (in RTOG protocols, GTV and CTV have been considered identical on CT planning with zero expansion margin added).
- PTV = CTV/ITV + 3–10 mm (dependent upon available center-specific IGRT and motion management capabilities). Current RTOG guidelines are:
  - Non-4DCT planning, PTV = GTV + 5 mm axial and 10 mm longitudinal anisotropic margins.
  - 4DCT planning, PTV = ITV + 5 mm isotropic margin.
- Dose to proximal OARs attributed to compact intermediate dose region outside of the CTV/ITV region, generally reduced with increased beams and angles, as well as minimization of margins on target.
- Treatment planning guidelines (adapted from RTOG 0618).
  - V_{Rx} dose ≥95 % PTV, V90 ≥99 % PTV.
  - High dose region (≥105 % Rx dose) should fall within the PTV.
  - Conformality Index goal ≤1.2.
- Heterogeneity correction algorithms are increasingly routinely used for planning (anisotropic analytical algorithm, collapsed cone convolution, Monte Carlo, etc.). Pencil-beam algorithms that overestimate dose in heterogeneous tissue are generally not recommended.
- Phantom-based QA on treatment plans.

Dose Prescription

- Dose and fractionation directed by adjacent normal tissue RT toxicity constraints with goal tumor $BED_{10} > 100$. Adaptive dosimetry for histology-, volume-, location-, and context-based lesions (primary vs. metastatic) are under investigation.
- Current dose fractionation schema largely employs 1–5 fractions.

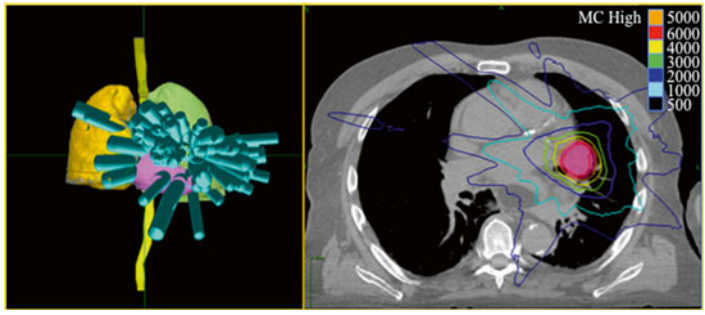

FIG. 7.1. SBRT planning for a central early-stage NSCLC. Beam distribution shown on 3D anatomy reconstruction (*left*) and dose distribution for 50 Gy given in 5 fractions (*right*)

- Peripheral Lung Tumors
  - Common accepted schemas: 25–34 Gy × 1 fraction, 18 Gy × 3 fractions, 12 Gy × 4 fractions, 10 Gy × 5 fractions.
- Central Lung Tumors
  - We recommend: 10 Gy × 5 fractions (BED_{10} dose limited to reduce toxicity of central structures: large airways, heart, esophagus, and spinal cord). See Fig. 7.1.
- Dose typically prescribed 60–90 % IDL, with ≥95 % PTV coverage by prescription dose.
- Composite planning should be employed in cases of regional lung re-irradiation with appropriate BED conversion for dose summation.

Dose Limitations

- See Table 7.2, assuming no prior regional radiotherapy (TG101, Benedict et al., 2010; RTOG 0618).

Table 7.2 Recommended dose constraints for SBRT lung lesion target planning

Structure	Fractions	Constraints
Lung	1	V7 < 1500 cc
	3	V11.6 < 1500 cc
	5	V12.5 < 1500 cc
Central airway	1	V10.5 < 4 cc, Dmax 20.2 Gy
	3	V15 < 4 cc, Dmax 30 Gy
	5	V16.5 < 4 cc, Dmax 40 Gy
Chest wall	1	V22 < 1 cc, Dmax 30 Gy
	3	V28.8 < 1 cc, Dmax 36.9 Gy
	5	V35 < 1 cc, Dmax 43 Gy
Heart	1	V16 < 15 cc, Dmax 22 Gy
	3	V24 < 15 cc, Dmax 30 Gy
	5	V32 < 15 cc, Dmax 38 Gy
Esophagus	1	V11.9 < 5 cc, Dmax 15.4 Gy
	3	V17.7 < 5 cc, Dmax 25.2 Gy
	5	V19.5 < 5 cc, Dmax 35 Gy
Brachial plexus	1	V14 < 3 cc, Dmax 17.5 Gy
	3	V20.4 < 3 cc, Dmax 24 Gy
	5	V 27 < 3 cc, Dmax 30.5 Gy
Spinal cord	1	V10 < 0.35 cc, Dmax 14 Gy
	3	V18 < 0.35 cc, Dmax 21.9 Gy
	5	V23 < 0.35 cc, Dmax 30 Gy
Skin	1	V23 < 10 cc, Dmax 26 Gy
	3	V30 < 10 cc, Dmax 33 Gy
	5	V36.5 < 10 cc, Dmax 39.5 Gy

Dose Delivery

- Dose delivered in consecutive daily or every other day fractions as per current NRG protocols.
- Setup may be isocentric or non-isocentric depending upon SBRT delivery system.
- Verification by kV XR or CBCT, aligned to visualized tumor or surrogate.
- Intrafraction dose delivery adjustment by motion management and IGRT systems as discussed above.

Toxicities and Management

- Common acute toxicities (<6 weeks):
  - Fatigue
    Generally early-onset and self-limiting.
    Sustained fatigue may be related to cardiopulmonary dysfunction (CHF, CAD, COPD, etc.) and warrants further work up.
  - Cough/dyspnea
    Low-grade cough common secondary to RT-related intrapulmonary inflammation. Antitussive pharmacotherapy for mild symptoms.
    Severity of shortness of breath may be related to baseline lung function and associated comorbidities. For patients with moderate to severe symptoms or significant baseline comorbidities (COPD, ILD, CHF, etc.), recommend follow-up with pulmonology and/or cardiology.
  - Chest pain
    May be related to regional pleuritis and/or pericarditis and is generally self-limited.
    Analgesic pharmacotherapy recommended.
  - Pneumonitis
    Associated with increased dose volume (V20 <10 %), smoking history (current/former), age, prior use of steroids, and comorbidity index on multiple studies.
    Generally subacute onset (>2 weeks), associated with cough, dyspnea, hypoxia, and fever.
    If symptomatic, treat with prednisone (1 mg/kg/d) or 60 mg/d and trimethoprim/sulfamethoxazole for PCP prophylaxis. Symptomatic relief may be rapid but slow steroid taper is critical for durable symptom resolution.

- Esophagitis
  Increased risk with treatment centrally located tumors, and is generally self-limited to several weeks after treatment.
  Local or systemic analgesic pharmacotherapy (lidocaine, NSAIDs, opioids) ± proton pump inhibitor based on severity of symptoms.
- Dermatitis
  Chest wall entrance and exit doses can be reduced with increased numbers of beams to minimize radiation dermatitis.
  Mild to moderate skin reaction treated with supportive care, including topical moisturizers, analgesics, low-dose steroids, and antimicrobial salves.

- Common late toxicities (>6 weeks):
  - Persistent cough/dyspnea
    Recommend consultation with pulmonary medicine for consideration of long-term bronchodilator and anti-inflammatory therapy.
  - Radiation pneumonitis
    Most commonly observed at ~6 weeks.
    As above, recommend steroids with gradual taper for symptomatic patients
  - Brachial plexopathy
    Apical lung tumors associated with greater risk of brachial plexus injury.
    May present with neuropathic pain as seen in Lhermittes syndrome or with motor/sensory changes in the upper extremities.
    MRI of brachial plexus and upper spine may be diagnostic and rule out tumor recurrence.
    Limited treatment options include supportive care and occupational therapy.
  - Chest wall pain and rib fracture
    More common in patients with peripheral lesions.
    Supportive care indicated.

- Radiation skin ulcer
  For persistent non-healing skin lesions, consider hyperbaric oxygen therapy and tocopherol pharmacotherapy.
- Esophageal stricture and tracheoesophageal fistula
  Historically rare complication observed with treatment of mediastinal lymphadenopathy in locally advanced lung cancer.
  Even less likely with SBRT, if airway and esophageal constraints maintained, with exception of re-irradiation setting.
- Vasculopathy
  Vascular erosion may lead to limited hemoptysis or massive hemorrhage and death (seen in re-irradiation setting of central lesions).

Recommended Follow-Up

- CT or PETCT every 3–4 months × 3 years, every 6 months × 2 years, every 12 months thereafter for routine follow-up.
- Assessment with RECIST criteria of limited utility due to wide spectrum of evolving radiographic features following SBRT including diffuse and patchy GGO, consolidation, and/or fibrosis.
- In general, radiographic changes include early inflammatory response (≤3 months) followed by resolution of FDG activity and late fibrosis (>6 months) in area of treated lesion which is often dynamic and may evolve over several years.
- Persistent increase in size and density of treated tumor on interval CTs in the early post-treatment setting (<12 months) or new densities at later times (>12 months) should be considered suspicious for recurrence, with recommendation for increased frequency of CT, interval PET scan, and consideration of biopsy and/or surgical or radiotherapy salvage procedure.
- Role of molecular imaging and circulating tumor markers is under investigation.

Evidence

Primary Lung Cancer

- Evidence widely supports efficacy and safety of SBRT in early-stage NSCLC, with optimal patient selection criteria and dose schema emerging as studies mature.
- CALGB 39904 (Bogart et al. 2010). Phase I dose-escalation study of 39 stage I (≤4 cm) NSCLC patients. 70 Gy in 29 decreased to 17 fractions. 92.3 % actuarial control, 82.1 % actuarial distant control. No late grade 3 or 4 toxicity.
- Onishi et al. (2004). Initial report of retrospective Japanese multi-institutional series of 245 patients with stage I NSCLC treated with SBRT 18–75 Gy in 1–22 fractions with a median follow-up of 24 months. Grade ≥3 toxicity 2.4 %. LR at 3 years for BED ≥ 100 vs. BED < 100 was 8.1 % vs. 26.4 %, $p < 0.05$ and OS was 88.4 % vs. 69.4 %, $p < 0.05$, establishing BED ≥ 100 as prescribing criterion.
- Nordic Study Group (Baumann et al. 2009). Phase II study of SBRT in 57 patients with medically inoperable early-stage peripheral tumors (40 stage IA, 17 stage IB), treated with 45–66 Gy in 3 fractions. Estimated 3 year LC and OS were 88.4 % and 59.5 %, respectively. Distant metastatic rate 16 %. Risk of any failure increased in T2 vs. T1 tumors (41 % vs. 18 %, $p = 0.027$).
- RTOG 0236 (Timmerman et al. 2010, Stanic et al. 2014). Phase II multicenter trial of 55 patients with medically inoperable early-stage (<5 cm) peripheral NSCLC (44 stage IA, 11 stage IB), treated with 54 Gy in 3 fractions SBRT. Three year primary tumor and involved lobe control was 98 %. Rate of distant failure 22 % at 3 years. OS 56 % at 3 years. Grade 3 and 4 toxicities were 12.7 % and 3.5 %, respectively. Poor baseline PFT not predictive of SBRT-related toxicity.

- Timmerman et al. (2006), Farikis et al. (2009). Phase II study of SBRT at Indiana University for T1-2N0 medically inoperable NSCLC patients ($n = 70$), 60–66 Gy in 3 fractions. LC and OS at 3 years were 88.1 % and 42.7 %, respectively. Grade ≥3 toxicity rates of 10.4 % peripheral vs. 27.3 % central over a median follow-up of 50.2 months ($p = 0.088$).
- JCOG 0403 (Nagata et al. 2012). Phase II trial of SBRT in early-stage NSCLC, stratified by medically operable/inoperable. In medically inoperable arm, 100 patients with stage IA disease received 48 Gy in 4 fractions. LC and OS at 3 years were 88 % and 59.9 %, respectively. For 64 medically operable patients, LC and OS at 3 years were 86.0 % and 76.0 %, respectively. Grade 3 pneumonitis 7 %, overall grade 4 toxicity 2 %.
- RTOG 0618 (Timmerman et al. 2013). Phase II trial of 33 patients with medically operable early-stage peripheral NSCLC (<5 cm), treated with 60 Gy in 3 fractions. Completed accrual in 2010 with results presented at ASCO 2013 showing estimated 2 years primary tumor failure rate of 7.8 %, with a median follow-up of 25 months. Local failure, including ipsilateral lobe, was 19.2 %. PFS and OS at 2 years were estimated at 65.4 % and 84.4 %. Grade 3 toxicity was 16 %.
- RTOG 0813. Phase I/II dose-escalation trial of medically inoperable centrally located (<2 cm of proximal bronchial tree) early-stage NSCLC (<5 cm). At the time of accrual completion, dose escalated to 60 Gy in 5 fractions. Closed to accrual at 120 patients in 2013. Results are pending.
- RTOG 0915 (Videtic et al. 2013). Phase II randomized trial of 34 Gy in 1 fraction vs. 48 Gy in 4 fractions for medially inoperable early-stage peripheral NSCLC (<5 cm). Study completed accrual in 2011 with 94 patients. At 1 year, LC 97.1 % vs. 97.6 %; OS 85.4 % vs. 91.1 %, and PFS 78.0 % vs. 84.4 %. Adverse events were 9.8 % vs. 13.3 %. Based on the favorable toxicity, the

34 Gy in 1 fraction arm will be compared to the 54 Gy in 3 fractions arm of RTOG 0236 in a phase III setting.

- Hoppe et al. (2008). Study of 50 stage I NSCLC patients treated with SBRT 60 Gy in 3 fractions or 44–48 Gy in 4 fractions with a median follow-up of 6 months. Skin toxicity was 38 % grade 1, 8 % grade 2, 4 % grade 3, and 2 % grade 4. Reduced number of beams, proximal distance to chest wall, and skin dose ≥50 % prescription dose were associated with increased risk of skin toxicity.
- Mutter et al. (2012). Retrospective study of 128 early-stage NSCLC patients receiving SBRT 40–60 Gy in 3–5 fractions. With a median follow-up of 16 months, grade ≥2 chest wall toxicity was 39 % estimated at 2 years. On dosimetric analysis, grade ≥2 chest wall pain was associated with a V30Gy >70 cm^3 within a 2 cm 2D-ipsilateral chest wall expansion.
- ACOSOG Z4099/RTOG 1021. Phase III trial of SBRT vs. sublobar resection for high-risk operable, early-stage peripheral NSCLC (<3 cm). Terminated for poor accrual.
- ROSEL Trial (VUMC, NCT00687986). Phase III trial of SBRT (60 Gy in 3 or 5 fractions) vs. surgery for stage IA peripheral NSCLC. Terminated for poor accrual.
- STARS Trial (MDACC, NCT00840749). Phase III trial of SBRT 60 Gy in 3–4 fractions based on lesion location vs. surgery for stage I NSCLC. Terminated for poor accrual.
- Grills et al. (2010). Retrospective comparison of 124 patients (95 % medically inoperable) T1-2 N0 NSCLC receiving wedge resection ($n=69$) vs. SBRT ($n=58$), 48–60 Gy in 4–5 fractions. No statistically significant differences in LRR (27 % wedge vs. 9 % SBRT, $p>0.16$) or CSS (94 % wedge vs. 93 % SBRT, $p=0.53$) noted at a median follow-up of 30 months. OS favored wedge resection (87 % wedge vs. 72 % SBRT, $p=0.01$).
- Crabtree et al. (2010). Retrospective comparison of stage I NSCLC patients receiving either surgery ($n=462$) or SBRT ($n=76$) for definitive care. Surgical

candidates had fewer medical comorbidities. Thirty-five percent of surgical patients were upstaged on final pathology. OS 5 years 55 % surgery and OS 3 years 32 % with SBRT. In propensity matched analysis, no statistically significant difference in LC (88 % vs. 90 %) and OS (54 % vs. 38 %) at 3 years in surgery vs. SBRT groups.

- SEER-Medicare analysis (Shirvani et al. 2012). Comparative outcomes of stage I NSCLC patients ≥60 years old, which demonstrated overall ranked outcomes as lobectomy > sublobar resection > SBRT > conventional EBRT > observation. However, as treatment outcomes were likely influenced by patient selection and comorbidities, there was no difference in OS between SBRT and surgical modalities on propensity matched analysis, and EBRT remained inferior to SBRT.
- Shah et al. (2013a, b). Cost-effectiveness comparison of surgical resection vs. SBRT for stage I NSCLC patients >65 years. For marginally operable patients, SBRT was most cost effective with a mean cost and quality-adjusted life expectancy of $42 k/8.0 years vs. lobectomy at $49 k/8.9 years. However, for completely operable candidates, lobectomy was found more cost effective, having an incremental cost-effectiveness ratio of $13 K/quality-adjusted life year.
- Table 7.3 summarizes several multiple primarily retrospective series indicating local control rates of 85–95 % at 3–5 years, and overall survival rates of 50–95 % at 3–5 years for early-stage NSCLC managed with SBRT. Some series include limited numbers of recurrent and metastatic patients.

Role as Boost for Locally Advanced Lung Cancer

- Studies have suggested a role for dose escalation as part of conventional chemoradiation in locally

Table 7.3 Selected studies of SBRT treated NSCLC patients

Study	Patients	Treatment	LC/OS	Notes
Onishi et al. JRS-SBRTSG (IJROBP 2013)	2226 patients stage I NSCLC	32–70 Gy in 3–12 fractions, median BED 107 Gy (range 58–150 Gy)	3 years LC/OS 85 %/72 % 3 years LPFS 87 % T1, 72 % T2 3 years OS 75 % BED ≥ 100 Gy vs. 63 % BED < 100 Gy ($p < 0.01$)	2.9 % grade ≥3
Grills et al. Multi-institutional (JTO 2012)	482 patients (505 tumors) T1-3N0 NSCLC, 87 % medically inoperable	20–64 Gy in 1–15 fractions, median 54 Gy in 3 fractions	2 years LC/OS 94 %/60 %, LC 96 % BED ≥ 105 vs. 85 % BED < 105 ($p < 0.001$)	7 % grade ≥2 pneumonitis 3 % rib fracture
Shibamoto et al. Japan (IJROBP 2013, Cancer 2011)	180 patients stage I NSCLC (120 medically inoperable, 60 operable)	Volume-adapted 44 Gy in 4 fractions <1.5 cm, 48 Gy in 4 fractions 1.5–3.0 cm, 52 Gy in 4 fractions >3.0 cm	3 years LC/OS 83 %/69 %, OS 74 % operable vs. 59 % inoperable, LC 86 % ≤3 cm vs. 73 % >3 cm 5 years LC/OS 82 %/68 %	13 % grade ≥2 pneumonitis
Uematsu et al. Japan (IJROBP 2001)	50 patients T1-T2N0 NSCLC (21 medically inoperable, 29 operable)	50–60 Gy in 5–10 fractions (18 patients received 40–60 Gy in 20–33 fractions prior to SBRT)	3 years LC/OS 94 %/66 % (86 % OS in medically operable subgroup)	4 % rib fracture

Stephans et al. Cleveland Clinic (JTO 2009)	94 patients stage I NSCLC medically inoperable	50 Gy in 5 fractions, 60 Gy in 3 fractions	1 year LC/OS 97 %/83 % 50 Gy in 5 fractions, 100 %/77 % 60 Gy in 3 fractions	2.2 % grade 2 pneumonitis 10 % grade 1–2 chest wall toxicity
Olsen et al. Wash U. (IJRBOP 2011)	130 patients early-stage NSCLC	Peripheral tumors 54 Gy in 3 fractions, central tumors 45–50 Gy in 5 fractions	2 years LC 91 % (54 Gy in 5 fractions) 100 % (50 Gy in 5 fractions) 50 % (45 Gy in 5 fractions) 2 years OS 85 % operable 61 % inoperable	16 % chest wall pain (grade 1–3) 3 % grade 2 pneumonitis
Modh et al. MSKCC (IJROBP 2013)	107 central tumors (83 primary NSCLC, 10 recurrent, 14 metastatic)	45–50 Gy in 4–5 Gx	2 years LC/OS 72 %/56 %	12 % grade ≥ 3
Trakul et al. Stanford (IJROBP 2012a, b)	111 patients (100 primary NSCLC, 11 metastatic)	Volume-adapted iSABR (GTV < 12 ml → BED < 100, GTV ≥ 12 ml → BED ≥ 100) 18–30 Gy in 1 fraction, 50–60 Gy in 4–5 fractions	1 year LC/OS 94 %/90 % in primary NSCLC subgroup, 15 % DM rate, no difference in LC/OS by BED	4.% grade 3
Taremi et al. Canada (IJROBP 2012)	108 patients, stage I NSCLC medically inoperable, 24 % w/o path diagnosis	Peripheral tumors 48 Gy in 4 fractions or 54–60 in 3 fractions, central tumors 50–60 Gy in 8–10 fractions	4 years LC/OS 92 %/30 % 4 years distant DFS 83 %	11 % grade 3

(continued)

TABLE 7.3 (continued)

Study	Patients	Treatment	LC/OS	Notes
Lagerwaard et al. VUMC (IJROBP 2008)	206 patients T1-2N0	Risk-adapted 60 Gy in 3 fractions (T1), 5 fractions (T1 near CW or T2), or 8 fractions (central)	2 years LC/OS 83 %/64 % (LC 92 % T1, 71 % T2) 2 years distant PFS 77 %	3 % grade ≥3 pneumonitis 2 % rib fracture 1 % late CW pain
Badiyan et al. Wash U. (RO 2013)	120 patients (early-stage NSCLC and AIS)	54 Gy in 3 fractions	3 years LC/OS 100 %/35 % AIS, 86 %/47 % NSCLC	Not reported
Bradley et al. Wash U. (IJROBP 2010)	91 patients stage I/ II NSCLC, medically inoperable	Peripheral tumors 54 Gy in 3 fractions, central tumors 45 Gy in 5 fractions	2 years LC/OS 86 %/70 %	3 % grade 2 pneumonitis 4 % rib fracture 1 % brachial plexopathy
Palma et al. VUMC (IJROBP 2012)	176 patients stage I NSCLC, severe COPD	60 Gy in 3–5 fractions	3 years LC/OS 89 %/47 %	3 % grade 3
Chang et al. MDACC (RO 2012)	130 patients stage I NSCLC	50 Gy in 4 fractions	2 years LC/OS 98 %/78 %	12 % grade 2–3 pneumonitis
Griffioen et al. VUMC (RO 2013)	62 patients with multiple synchronous primary early-stage NSCLC	54–60 Gy in 3–8 fractions	2 years LC/OS 84 %/56 %	4.8 % grade 3

advanced lung cancer, with current focus on reduced volume boost, to minimize normal lung toxicity, for which SBRT may be of utility.

- Karam et al. (2013). Retrospective series of 16 primarily stage III NSCLC (38 % IIIA, 56 % IIIB) patients who received conventional chemoradiation to a median dose of 50.4 Gy (range 45–60 Gy) followed by an SBRT boost (20–30 Gy in 5 fractions) to residual disease on interval planning CT. LC and OS at 1 year were 76 % and 78 %, respectively. Grade ≥2 pneumonitis occurred in 25 % of patients.
- Feddock J et al. (2013). Prospective feasibility trial at Univ Kentucky with 35 stage II-III NSCLC patients treated with conventional chemoradiation to 60 Gy followed by an SBRT boost of 20 Gy in 2 fractions or 19.5 Gy in 3 fractions (for central tumors) limited to persistent primary tumor (≤5 cm without additional residual disease) on interval CT ± PET. With a median follow-up of 13 months, LC was 82.9 %. Acute and late grade 2–3 pneumonitis were 17 % and 9 %, respectively. Two patients had large cavitary recurrences associated with likely hemorrhagic death, which may be considered grade 5 toxicities.

Chemotherapy in Early-Stage Lung Cancer

- The role and timing of adjuvant chemotherapy for SBRT-treated NSCLC remains unclear, although several surgical series have shown a survival benefit with adjuvant chemotherapy in early-stage lung cancer.
- CALGB 9633 (Strauss et al. 2008). Phase III trial of 344 pT2N0 patients randomized to observation vs. adjuvant chemotherapy (paclitaxel/carboplatin q3w × 4c) following lobectomy or pneumonectomy. With a median follow-up of 74 months, there was no difference in OS. However, exploratory analysis demonstrated improved OS in patients with tumors ≥4 cm (HR 0.69, $p = 0.043$).

- LACE (Lung Adjuvant Cisplatin Evaluation) meta-analysis (Pignon et al. 2008; JCO). Meta-analysis of five trials of 4584 patients with stage I-III NSCLC receiving cisplatin-based adjuvant chemotherapy after completed surgical resection. At 5 years, absolute OS benefit of 5.4 % with adjuvant chemotherapy. However, subset analysis showed benefit limited to stage II and III patients.
- Preoperative chemotherapy meta-analysis (NSCLC Meta-analysis Collaborative Group, 2014). Analysis of 15 RCT, with a total of 2385 primarily stage IB-IIIA NSCLC patients, demonstrated benefit of preoperative chemotherapy on survival (HR 0.87, $p = 0.007$), with an absolute benefit of 5 % at 5 years across all stages.
- Postoperative chemotherapy meta-analyses (NSCLC Meta-analyses Collaborative Group). Meta-analysis of surgery plus chemotherapy vs. surgery alone based upon 34 trial comparisons with 8447 stage I-III NSCLC patients. Adjuvant chemotherapy associated with OS benefit (HR 0.86, $p < 0.0001$), with 4 % absolute increase in survival at 5 years. Subset analysis showed an absolute benefit of 3 % and 5 % with adjuvant chemotherapy for stages IA and IB, respectively.

Metastatic Lung Cancer

- Multiple studies suggest safety and efficacy of SBRT in management of oligometastatic disease, in populations with modest to poor KPS, many having received prior multimodal therapy. Optimal volume-based and histology-specific dose schemas are under investigation.
- Rusthoven et al. (2009). Multi-institutional phase I/II dose-escalation study of 38 patients with 1–3 lung metastases with cumulative tumor diameter <7 cm. Study consisted of SBRT dose escalation from 48 to 60 Gy in 3 fractions. Grade 3 toxicity was 8 %. With a median follow-up of 15.4 months, actuarial 1 and 2 years LC was 100 % and 96 %, respectively. OS 39 % at 2 years.

Table 7.4 Selected studies of SBRT for metastatic lung lesions

Study	Patients	Treatment	LC/OS	Toxicity
Singh et al. Rochester (J Thorac Dis 2014)	34 patients with 1–5 metastatic lesions	40–60 Gy in 5 fractions	2 years LC/OS 88 %/44 %	No grade ≥2
Johnson et al. UCSF (Oncology 2014)	90 patients with central tumors (72 with metastatic lesions)	50 Gy in 5 fractions	2 years LC/OS 82 %/32 % metastatic subgroup	4 % ≥ grade 3
Baschnagel et al. Wash University (Clin Oncol 2013)	32 patients with 1–3 metastatic lesions	48–60 Gy in 4–5 fractions	2 years LC/OS 92 %/76 %	16 % grade 3 no grade ≥4
Hamamoto et al. Japan (JJCO 2009)	62 patients (10 with metastatic lesions, 52 with stage I NSCLC)	48 Gy in 4 fractions	2 years LC/OS 25 %/86 % in metastatic subgroup (vs. 88 %/96 % in primary NSCLC patients, $p < 0.0001$)	Not reported
Norihisa et al. Japan (IJROBP 2008)	34 patients with 1–2 metastatic lesions	48 Gy in 4 fractions, 60 Gy in 5 fractions	2 years LC/OS 90 %/84 %	12 % grade 2 3 % grade 3
Wulf et al. Germany (IJROBP 2004)	61 patients (41 with metastatic lesions, 20 with stage I-II NSCLC)	30–37.5 Gy in 3 fractions, 26 Gy in 1 fraction	1 year LC/OS 80 %/85 % metastatic subgroup	3 % grade 2 no grade ≥3

(continued)

Table 7.4 (continued)

Study	Patients	Treatment	LC/OS	Toxicity
Lee et al. S. Korea (Lung Cancer 2003)	28 patients (19 with metastatic lesions)	30–40 Gy in 3–4 fractions	2 years LC/OS 88 %/88 % metastatic subgroup	No grade ≥2
Nakagawa et al. Japan (IJROBP 2000)	15 patients (14 with metastatic lesions)	15–24 Gy × 1 fraction	Median LC 8 months Median OS 9.8 months	1 patient with late toxicity

- Le et al. (2006). Single-fraction SBRT phase I dose-escalation study of 32 patients (21 T1-2 N0 NSCLC, 11 with oligometastatic lung tumors). Dose escalation was from 15 to 30 Gy. LC for all tumors at 1 year was 91 % for >20 Gy and 54 % for <20 Gy ($p = 0.03$). For metastatic tumors specifically, LC and OS at 1 year were 25 % and 56 %, respectively. Toxicity included 4 cases of grade 2–3 pneumonitis, 1 pleural effusion, and 3 possible treatment-related deaths.
- Ernst-Stecken et al. (2006). Phase I/II study of SBRT dose escalation in 21 patients (3 primary stage I NSCLC, 18 metastatic). Dose escalation 35–40 Gy in 5 fractions. One instance of grade 3 toxicity reported. Median follow-up was 6.3 months. LC 81 % at 13 months.
- Table 7.4 summarizes multiple retrospective institutional series indicating local control rates of largely 80–90 % at 2 years, and overall survival rates of 30–85 % at 2 years for patients with pulmonary metastases managed with SBRT. Most series include patients having previously received multimodal therapy and with both primary controlled and uncontrolled disease. As noted, several series also include both primary and metastatic disease.

Recurrence/Re-irradiation

- Several institutional series reporting SBRT experience for oligometastatic intrathoracic tumors have included patients with recurrent lung cancer or metachronous primary NSCLC.
- Reyngold et al. (2013). Retrospective series of 39 patients at MSKCC treated with SBRT (median BED_{10} 70.4 Gy, range 42.6–180 Gy) for recurrence or new primary cancer after prior conventionally fractionated EBRT (median dose 61 Gy) for chiefly NSCLC or scc. Median RFS was 13.8 months and median survival was 22 months. Grade 2 and 3 pulmonary toxicities were 18 % and 5 % respectively (dyspnea, hypoxia, cough, and pneumonitis). One patient had grade 4 skin ulceration.
- Trakul et al. (2012a, b). Retrospective series of 15 patients treated at Stanford University LC 65 % at 1 year vs. 92 % for 135 patients receiving SBRT in primary setting. OS 80 % at 1 year vs. 92.9 % for primary SBRT group. Shorter interval between treatments was associated with increased risk of recurrence. One instance of chest wall toxicity observed in re-irradiated group.
- Peulen et al. (2011). Retrospective analysis from the Netherlands of SBRT re-irradiation in 32 patients who received prior thoracic SBRT (30–40 Gy in 2–4 fractions), with re-irradiation (30–40 Gy in 2–5 fractions) defined as 50 % PTV overlap. Grade 3–4 toxicity was 25 % and 3 patients suffered grade 5 toxicity, with death from hemorrhage following re-irradiation of the central chest. LC was 52 % at 5 months. OS 59 % at 1 year.
- Kelly et al. (2010). Retrospective study of 36 patients at MDACC receiving SBRT (50 Gy in 4 fractions) for recurrent NSCLC after prior conventionally fractionated EBRT (median dose 62 Gy). Thirty-three percent grade 3 toxicity (pneumonitis, cough, chest wall ulcer, esophagitis). LC and OS at 2 years, 92 % and 59 %, respectively.

- Liu et al. (2012). Updated data for 72 patients at MDACC who received SBRT (50 Gy in 4 fractions) for recurrent or metachronous second primary NSCLC after prior thoracic conventionally fractionated EBRT (median dose 63 Gy). LC and OS at 2 years were 42 % and 74 %, respectively. Grade ≥3 pneumonitis was observed in 21 % of re-irradiated patients. Predictors of pneumonitis included ECOG PS 2–3, pre-SBRT FEV1 ≤ 65 %, V20 ≥ 30 % in composite plan, and prior bilateral mediastinal PTV (all $p < 0.03$).
- Senthi et al. (2013). Retrospective review of 27 patients treated with pneumonectomy for prior NSCLC, with second early-stage primary NSCLC who then received RT for definitive management (including 20 SBRT patients treated with 54–60 Gy in 3–8 fractions). LC 3 years was 8 %. MS 39 months. Grade ≥3 pneumonitis seen in 15 % SBRT-treated patients.

Technique

- Seppenwoodle et al. (2002). Analysis of lung tumor motion via fiducial tracking in 20 patients during radiotherapy. Tumor motion was greatest in cranial-caudal axis for lower lobe lesion (12 ± 2 mm). Time averaged tumor position was closer to the exhale position, and appears more stable in the exhale vs. inhale phases during intrafraction imaging. Hysteresis was observed in ~50 % of tumors.
- Shah et al. (2013a, b). Analysis of intrafraction variation in target position during lung tumor Linac-based SBRT in 409 patients. Mean target position (MTP) was calculated as the difference between the post setup-shift verification CBCT and post-treatment CBCT. MTP vector was 3.1 ± 2.0 mm, influenced by weight and pulmonary function, and varied with differential motion management techniques. PTV margins of ≥6 mm were recommended in the absence of motion management interventions.

- Bouihol et al. (2012). Study of abdominal compression device in 27 early-stage NSCLC patients undergoing lung SBRT. Results indicated significant reduction of tumor amplitude for lower lobe lesions vs. mid/upper lobe lesions (3.5 mm vs. 0.8 mm, $p = 0.026$), associated with a mean ITV reduction of 3.6 cm^3 vs. 0.2 cm^3.
- Xiao et al. (2009). Twenty treatment plans of 60 Gy in 3 fractions SBRT from RTOG 0236, generated without heterogeneity corrections, were recalculated (but not reoptimized) with heterogeneity corrections (superposition/convolution), and demonstrated an average volume reduction of 10.1 ± 2.7 % from the original 95 % PTV receiving 60 Gy per protocol ($p = 0.001$). In addition, the maximal point dose at ≥2 cm from the PTV increased from 35.2 ± 1.7 to 38.5 ± 2.2 Gy.
- Narabayashi et al. (2012). Review of 20 early-stage NSCLC SBRT treatment plans comparing the effect of different heterogeneity calculation methods on dosimetric parameters. Use of Monte Carlo heterogeneity correction with D95 prescription results in increase of 8.8 % and 16.1 % as compared to BPL and RPL methods, respectively.

Follow-Up

- Categorization and quantification of post-SBRT radiographic changes for objective response criteria and relationship between radiographic changes and tumor response and toxicity is an active area of investigation.
- Takeda et al. (2007). Review of post-treatment CXR and CT for 50 patients treated with SBRT (50 Gy in 5 fractions) for early-stage peripheral NSCLC with minimum 1-year follow-up. Twenty patients showed opacities concerning for recurrence, with three patients showing clear evidence clinical and/or pathological of recurrence with a median follow-up of 21 months.
- Dahele et al. (2011). Review of post-treatment CT scans of 61 patients who received SBRT at VUMC for

early-stage NSCLC with no definitive evidence of recurrence. Median follow-up was 2.5 years. Radiologic abnormalities noted in 54 % of scans at 6 months and 99 % at 36 months. Most common changes were acute patchy consolidation (24 %) and late consolidation, volume loss, and bronchiectasis (71 %).

- Trovo et al. (2010). Review of post-treatment CT scans of 68 patients (largely SBRT-treated early-stage NSCLC) from 6 weeks to 18 months. Early radiographic changes included diffuse and patchy consolidation and GGO, increased from 6 weeks (46 %) to 6 months (79 %). Late changes included consolidation, volume loss, and bronchiectasis with mass- and scar-like fibrosis in 88 % of scans at >12 months.
- Diot et al. (2012). Review of CT scans of 62 patients who received SBRT for early-stage primary NSCLC and metastatic pulmonary lesions. CT numbers showed a dose–response relationship to 20–35 Gy over the 3- to 30-month period post-SBRT.
- Bollneni et al. (2012). Review of 132 medically inoperable stage I NSCLC patients treated with 60 Gy in 3–8 fractions. Max SUV on PETCT at 12 weeks ≥5.0 was associated with 2 years LC of 80 % vs. 98 % for max SUV < 5.0 ($p = 0.019$).

Screening and Diagnosis

- National Lung Screening Trial (NLST Team 2011, 2013). Phase III trial of 50 k individuals at high risk of tobacco-related lung malignancy (55–74-year-old with 30+ pack-year smoking history) randomized to baseline and two subsequent annual screening exams with low-dose CT (1.5 mSV) vs. CXR (0.1 mSv). At median follow-up of 6.5 years, there was 20 % reduction in lung cancer mortality and 6.7 % reduction in all cause mortality with low-dose CT screening. Sensitivity >90 %, specificity ~75 %, PPV ~5 %, NPV ~100 %.

Rates of lung cancer detected within 3 years: Stage I (63 %) vs. Stage IIIB/IV (21 %).

- Prostate, Lung, Colon, Ovarian (PLCO) Screening Trial (Hocking et al, 2010;Tammemagi et al. 2011). Phase III trial of 154 k individuals randomized to 1:1 CXR screening (3 years of annual CXR) vs. no screening. Fifty-two percent were current or former smokers. PPV all 2.4 % at 3 years, 5.6 % for current smokers. Early-stage NSCLC was enriched in the screening arm (~60 %) vs. interval arm (~33 %).
- NELSON Study (van Klaveren et al. 2009, Ru Zhao et al. 2011). Phase III randomized trial of 15 k heavy smokers (current and ≤10 year former with 25–30 years use) randomized to interval CT screening (baseline, 1 and 3 years thereafter). Second-round screening had sensitivity of 96 %, specificity 99 %, PPV 42 %, NPV 100 %. Of detected NSCLC, 64 % were stage I.
- Newman et al. (2014). Application of CAPP-seq method to detect presence of NSCLC via mutant allele targeting in ctDNA within peripheral blood specimens. Method was validated in biopsy-proven and screening settings with ctDNA detection rates of 100 % in stage II-IV patients and 50 % in stage I.

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Chapter 8
Digestive System

David R. Raleigh and Albert J. Chang

Pearls

- Although surgery is the primary treatment modality for pancreatic cancer, as well as oligometastases to the liver, abdominal lymph nodes, and adrenal glands, SBRT is feasible and well tolerated and may achieve high rates of LC.
- Response criteria following SBRT for digestive system malignancies may include radiographic characteristics, serum tumor markers (CA 19-9, CEA, etc.), and/or clinical findings.
- Toxicity is increased after SBRT in patients who have previously been irradiated.
- Numerous SBRT dose/fractionation schemes have been investigated; lower doses and higher fractionation may be more appropriate for lesions located near/within critical structures such as the liver hilum, or in patients with poor performance status.

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Workup

- H&P
  - Pancreas cancer: alcohol use, tobacco use, obesity, BRCA, Peutz-Jeghers syndrome, Familial atypical Multiple-Mole Melanoma syndrome, Ataxia Telangiectasia.
  - Hepatocellular carcinoma: Hepatitis B, Hepatitis C, Hereditary Hemochromatosis, alcohol use, aflatoxin exposure, betel nut chewing, nonalcoholic fatty liver disease.
- Review of systems: Weight loss, epigastric pain, jaundice.
- Laboratories
  - General: CBC, LFTs, LDH, chemistries, and coagulation panel.
  - Liver: Serum AFP, Total bilirubin, albumin, INR, Hepatitis B/C panels, and multiphasic liver CT +/– hepatic protocol MRI. Calculate Childs-Pugh score to estimate liver function. Use increased caution in patients with Childs-Pugh B and C.
  - Pancreas: Serum CA 19-9, CEA, amylase, lipase.
- Imaging
  - CT abdomen with contrast; individualization of additional imaging studies depending on suspected tumor location (i.e., ERCP/MRCP/EUS for pancreatic and biliary malignancies, triphasic CT and/or MRI for hepatic malignancies, etc.).
- Pathology
  - If histology is unknown, CT-guided biopsy for hepatic, adrenal and nodal metastases.
  - Endoscopic retrograde cholangiopancreatography with stent placement and/or endoscopic ultrasound (EUS) guided biopsy is preferred for pancreatic masses, although laparoscopic staging and CT-guided biopsy are also feasible.

Treatment Recommendations

Disease site	Presentation	Recommended treatment
Pancreas	Resectable	Surgery +/– adjuvant chemoradiotherapy or chemotherapy
	Borderline resectable (adequate KPS)	Neoadjuvant chemoradiation followed by restaging and resection if feasible
	Borderline resectable (poor KPS) unresectable	Definitive chemoradiation, conventionally fractionated radiation alone, chemotherapy alone, or SBRT
	Metastatic	Palliation with stents, surgical bypass, chemotherapy, RT, and supportive care as indicated; SBRT not indicated except for expedient palliation
Liver	Resectable HCC or oligometastatic disease with controlled primary	Partial hepatectomy
	Unresectable/ medically inoperable HCC or oligometastatic disease with controlled primary	Upfront Liver transplant Restaging and resection if feasible following transarterial chemoembolization, radiofrequency ablation, cryotherapy, alcohol, SBRT, or sorafenib
Abdominal, retroperitoneal, and pelvic lymph nodes	Metastatic disease	Systemic therapy preferred, although surgery and SBRT should be discussed in oligometastatic settings or for palliation of pain
Adrenal glands	Metastatic disease	Systemic therapy preferred, although surgery and SBRT should be discussed in oligometastatic settings or for palliation of pain

Radiosurgical Technique

Simulation and Field Design

- Gold seed marker (GSM) placement by EUS (pancreas) or CT-guidance (liver) 1+ week prior to simulation to allow inflammation to subside.
- Oral contrast 30–60 min prior to simulation, unless MRI used for planning.
- Supine with arms above head and wingboard or alpha cradle to stabilize torso. Consider abdominal compression depending on image guidance modality.
- Pancreas lies at L1-L2, celiac axis at T12, and SMA at L1.
- Treatment planning:
  - Contrast-enhanced CT and/or MRI useful for delineating pancreatic tumor volume; triphasic CT and/or MRI for hepatic malignancies.
- Image guidance:
  - Preferred: 4D-CT to define ITV with daily on-board imaging for set-up and tracking.
  - Acceptable: Active breathing control (ABC), orthogonal MV imaging and kV fluoroscopy.
- Field Design: ITV based on 4D-CT plus 3–5 mm margin.
  - Optimal: ITV based on 4D-CT plus 3–5 mm margin for PTV.
  - Other tracking/immobilization strategies typically require 5–7 mm radial and 1–1.5 cm craniocaudal expansions on GTV for adequate coverage.
  - Caution regarding inclusion of edema surrounding pancreatic tumors due to excessively large field size.
  - Consider reducing PTV to allow for 2 mm margin to critical structures, especially in patients with poor performance status who are unlikely to tolerate exploratory laparotomy for bleeding, perforation, etc.
  - Avoid or minimize elective nodal stations in SBRT field due to toxicity.

Dose Prescription

- Pancreas: 33 Gy in 5 fractions.
- Liver: Based on location and underlying liver function.
  - Peripheral: 23–30 Gy in 1 fraction, 27.5–60 Gy in 3–6 fractions.
  - Central: 40 Gy in 5 fractions.
- Abdominal lymph nodes based on retrospective case series: 45–60 Gy in 3–6 fractions.
- Adrenal metastases based on retrospective case series: 23 Gy in 1 fraction, 36 Gy in 3–5 fractions (Figs. 8.1 and 8.2).

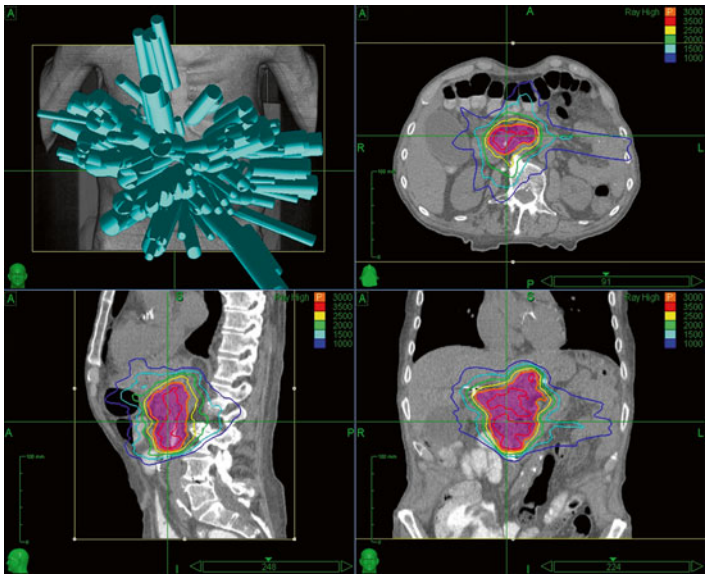

FIG. 8.1. Pancreatic SBRT. 88-year-old male with locally advanced, unresectable pancreatic adenocarcinoma. A 4D CTV with an ITV expansion was used for treatment planning, which was carried out via robotic radiosurgery to a total dose of 3000 cGy in 5 fractions with 6 MV photons prescribed to the 73 % isodose line. Proceeding clockwise from the top left, beam angles, and axial, coronal, and sagittal CT images with isodose lines and the PTV in red color wash are shown

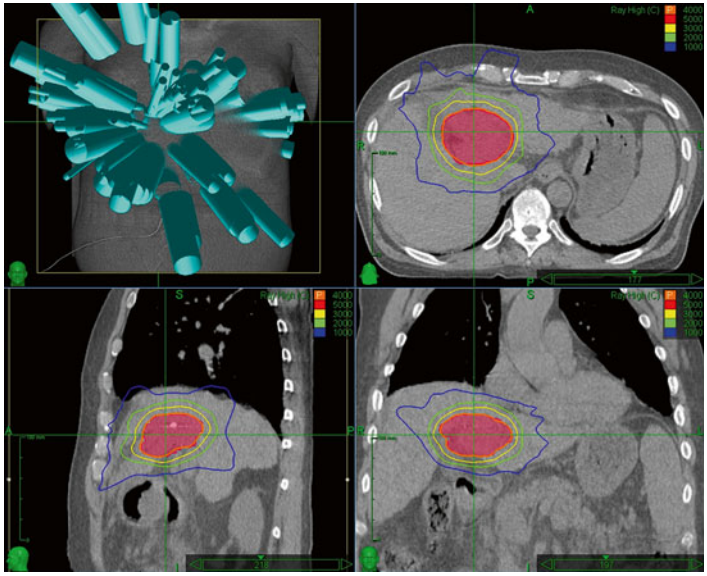

FIG. 8.2. Liver SBRT. 61-year-old male with a history of hepatitis C and recurrent hepatocellular carcinoma of the porta hepatis status post transcatheter arterial chemoembolization on four occasions, and alcohol injection twice. A single intra-lesional fiducial marker was used for tracking during robotic radiosurgery. The tumor was treated to a total dose of 4000 cGy in 5 fractions with 6 MV photons prescribed to the 82 % isodose line. Proceeding clockwise from the *top left*, beam angles, and axial, coronal, and sagittal CT images with isodose lines and the PTV in red color wash are shown

Dose Limitations

Structure	Fractions	Constraints	Dose limiting toxicity	Study
Stomach	1	$V_{22.5\ Gy} < 4\ \%$ Distal lumen wall free from 50 % isodose line	Ulceration, fistula	Chang et al. *Cancer* 2009
	3	$D_{max} < 30$ Gy		Kavanagh et al. *IJROBP* 2010
	6	$D_{max} < 32$ Gy $D_{3\ cc} < 36$ Gy		Bujold et al. *JCO* 2013, Tozzi et al. *Rad Onc* 2013
Small bowel	1	$V_{12.5\ Gy} < 30$ cc	Ulceration, fistula	Kavanagh et al. *IJROBP* 2010
	3	$D_{max} < 30$ Gy		Bujold et al. *JCO* 2013
	6	$D_{max} < 36$ Gy		Kavanagh et al. *IJROBP* 2010
Duodenum	1	$V_{22.5\%} < 5\ \%$ $V_{12.5\ Gy} < 50\ \%$ Distal lumen wall free from 50 % isodose line	Ulceration, fistula	Chang et al. *Cancer* 2009
	6	$D_{max} < 33$ Gy $D_{1\ cc} < 36$ Gy		Bujold et al. *JCO* 2013, Tozzi et al. *Rad Onc* 2013

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Structure	Fractions	Constraints	Dose limiting toxicity	Study
Large bowel	6	$D_{max} < 36$ Gy	Colitis, fistula	Bujold et al. *JCO* 2013
Liver	1	$V_{5\ Gy} < 50$ % $V_{2.5\ Gy} < 70$ %	Liver function, cirrhosis/ hepatitis, biliary stricture, radiation-induced liver disease (RILD)	Chang et al. *Cancer* 2009
	1, 3-5	700 cc < 15 Gy		Rusthoven et al. *JCO* 2009, Pan et al. *IJROBP* 2010, Goodman et al. *IJROBP* 2010
	3-6	HCC: MNLD < 13 Gy (3 fx), <18 Gy (6 fx) Metastases: MNLD < 15 Gy (3 fx), < 20 Gy (6 fx)		Pan et al. *IJROBP* 2010
	5	$V_{30\ Gy} < 60$ % $V_{27\ Gy} < 70$ % for cirrhosis/ hepatitis		Katz et al. *IJROBP* 2007
	6	$V_{tot} - V_{21\ Gy} > 700$ cc		Tozzi et al. *Rad Onc* 2013

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Structure	Fractions	Constraints	Dose limiting toxicity	Study
Kidney	1	$V_{5\ Gy} < 75\ \%$	Kidney function, malignant hypertension	Goodman et al. *IJROBP* 2010
	6	$V_{15\ Gy} < 35\ \%$ Mean dose < 12 Gy		Rusthoven et al. *JCO* 2009, Tozzi et al. *Rad Onc* 2013, Bujold et al. *JCO* 2013
Spinal cord	1	$D_{max} < 12$ Gy	Myelitis	Goodman et al. *IJROBP* 2010
	6	$D_{max} < 18$ Gy		Rusthoven et al. *JCO* 2009, Tozzi et al. *Rad Onc* 2013
Chest wall	3	$V_{30\ Gy} < 10$ mL	Pain or fracture	Rusthoven et al. *JCO* 2009
	6	$D_{max} < 54$ Gy		Dawson et al. *Acta Oncol* 2006
Heart	6	$D_{max} < 40$ Gy	Pericarditis	Dawson et al. *Acta Oncol* 2006

Toxicities and Management

- Acute complications such as nausea and vomiting can occur immediately or within hours of treatment, and may be effectively managed or even prophylaxed with oral medications.
  - Inflammation after GSM placement for tracking of pancreatic/hepatic tumors may lead to biliary system stenosis requiring (re)stenting.
- Long-term complications:
  - Dyspepsia, cramping, and diarrhea from mucosal injury or ulceration, potentially leading to weight loss from malabsorption, as well as fistulae, bleeding, and perforation; difficult to manage beyond best supportive care.
  - Bowel wall fibrosis leading to adhesions and obstruction, potentially requiring laparoscopy/laparotomy for resolution.
  - Chest wall pain and rib fractures, especially with hepatic SBRT.
  - Pancreatic and adrenal insufficiency potentially requiring exogenous supplementation.
  - Radiation-induced liver damage (RILD) typically occurs within 3 months of therapy, and may lead to hepatic failure and death; treatment options are limited to supportive measures.
    - Classic RILD is associated with anicteric hepatomegaly, ascites, and alkaline phosphatase elevation due to occlusion and obliteration of the central veins with secondary hepatocyte necrosis.
    - Nonclassic RILD is associated with transaminitis greater than 5 times the upper limit of normal, or worsening of Child-Pugh score by 2 or more in the absence of classic features.

Recommended Follow-Up

- H&P, laboratories, and abdominal CT (multiphasic vs. pancreatic protocol) every 3 months for 2 years, then every 6 months thereafter to evaluate for disease recurrence/progression.

Evidence

Pancreas

SBRT Boost Following Conventionally Fractionated Chemoradiation

- *Stanford* (Koong et al. 2005): Phase II study of 16 patients with unresectable pancreatic cancer treated with 45 Gy IMRT in 25 fractions plus concurrent 5FU or capecitabine, followed by SBRT boost to 25 Gy in 1 fraction within 1 month of CRT. Median OS 33 weeks, with estimated 6-month survival 80 % and 1-year survival of 15 %; 94 % FFLP (i.e., no evidence of tumor growth within the treatment field) until death. Two incidents of grade 3 toxicity; no grade 4+ events. Treatment strategy abandoned in favor of intensive systemic therapy followed by SBRT boost due to high GI toxicity and necessary recovery period with CRT → SBRT regimen.

Primary SBRT

- *Italy* (Tozzi et al. 2013): Prospective analysis of 30 patients with unresectable (70 %) or recurrent (30 %) pancreatic cancer treated with gemcitabine followed by SBRT to 45 Gy in 6 fractions (reduced to 36 Gy in 6 fractions to meet constraints in 5 patients). CTV defined as gross disease on arterial-phase CT, and expanded 0.5 cm radially and 1 cm craniocaudally with

cropping to achieve 2 mm margin to critical organs for PTV. Median follow-up 11 months. FFLP 85 % (96 % for 45 Gy group); median PFS 8 months. OS 47 % at 1 year; median OS 11 months. No grade 3+ toxicity.

- *Stanford* (Chang et al. 2009): Retrospective analysis of 77 pancreatic cancer patients ineligible for surgery (58 % locally advanced, 14 % medically unfit, 19 % metastatic, and 8 % recurrent) with primary tumors <7.5 cm in diameter. Median follow-up 6 months (12 months in survivors). All received 25 Gy SBRT in 1 fraction with gemcitabine-based chemotherapy in 96 %. 6- and 12-month LC (91 % and 84 %), PFS (26 % and 9 %), and OS (56 % and 21 %) reported. 8 of 9 patients who failed regionally (12 %) also failed distantly. 16 % of patients previously received IMRT, including 3 out of 10 patients who had late grade 3+ toxicity.
- *Denmark* (Hoyer et al. 2005): Phase II study of 22 patients with unresectable pancreatic cancer treated with SBRT to D_{max} 45 Gy in 3 fractions. GTV included both tumor and surrounding edema; PTV defined as CTV plus 0.5 cm transverse and 1 cm longitudinal margins. Median OS 6 months; 1-year OS 5 %. 27 % LF but only 5 % without concurrent regional/distant failure. 66 % improvement in performance status, nausea, pain, and analgesic requirement at 3 months. 22 % of patients experienced severe acute GI toxicity within 14 days of treatment, including mucositis, ulceration, and perforation. Poor outcome and likely due to low BED, but with unacceptable toxicity due to large treatment volume.

Ongoing

- *Pancreatic Cancer Radiotherapy Study Group (Stanford)*: Presently accruing phase III trial of FOLFIRINOX +/− SBRT in locally advanced pancreatic cancer patients. Primary endpoint PFS; secondary endpoints MFS, OS, LPFS, toxicity, FDG-PET response, and QOL. Estimated primary completion 2018.

Liver

Technique

- *Stanford* (Goodman et al. 2010): Phase I dose escalation trial of single-fraction SBRT with motion tracking of 3–5 implanted fiducial markers in 26 patients with 40 hepatic lesions. All lesions ≤5 cm and treated with 18–30 Gy SBRT in 4 Gy increments. 4D-CT used to delineate ITV, which was then expanded 3–5 mm to create a PTV. Median follow-up 17 months; no grade 2+ toxicity. LC 77 %, 2-year actuarial survival 50 %, and median survival 28.6 months.
- *Princess Margaret Hospital* (Dawson et al. 2006): Phase I/II dose escalation trial including 79 patients (45 primary hepatic tumors, 34 metastases) to establish immobilization scheme, radiation planning, PTV margin, image guidance, and prescription dose for liver SBRT. GTV defined on exhale breath-hold triphasic CT and/or MRI; 8 mm margin added for CTV, and PTV margin individualized ≥5 mm based on extent of liver motion. Target motion largest in the craniocaudal dimension (average 29 mm), followed by anterior-posterior (average 9 mm) and lateral (average 8 mm) translocation. Active breathing control and image guidance strategies (orthogonal MV imaging, orthogonal kV fluoroscopy, and kV cone beam CT) resulted in excellent intra-fraction reproducibility (median displacement 1.5 mm), although inter-fraction errors were larger (median displacement 3.4 mm). Dose individualized to maintain 5–20 % risk of RILD; median 36.6 Gy in 6 fractions (range 24–57 Gy).
- *Germany* (Herfarth et al. 2000): Phase I/II study of 24 patients with hepatic metastases treated with single-fraction SBRT; set-up accuracy evaluated under fluoroscopy using abdominal compression. Mean displacements: lateral 1.8 mm, craniocaudal <5 mm, and anterior-posterior 2 mm; diaphragm 7 mm. Concluded high-accuracy set-up of body and target can be achieved with abdominal compression alone.

Dose Response

- *Germany* (Wulf et al. 2006): Prospective trial of "low dose" (10 Gy × 3 or 7 Gy × 4) vs. "high dose" (12–12.5 Gy × 3 or 26 Gy × 1) in 44 patients with 56 hepatic lesions (5 primary liver cancer, 51 metastases). With median follow-up of 15 months, borderline significant correlation ($p = 0.077$) between dose and LC at 1 year (86 % vs. 100 %) and 2 years (58 % vs. 82 %) in favor of the "high dose" cohort that became significant for predicting local control on multivariate analysis ($p = 0.0089$). OS at 1 and 2 years was 72 % and 32 %, respectively. No severe acute or late physician-reported toxicity.

Metastases

- *Colorado* (Rusthoven et al. 2009): Phase I/II trial of SBRT in 47 patients with 1–3 hepatic metastases <6 cm; median follow-up 16 months. Dose escalation in Phase I from 36 to 60 Gy in 3 fractions; phase II dose of 60 Gy in 3 fractions prescribed to the 80–90 % IDL. GTV expanded 5 mm radially and 10 mm craniocaudally when using active breathing control, and 7 mm radially and 15 mm craniocaudally when using abdominal compression. LC at 1 and 2 years 95 % and 92 %, respectively, with 100 % control of lesions <3 cm. Median and 2-year overall survival 20.5 months and 30 %, respectively. One incident of grade 3 toxicity; no hematologic complications in patients who later went on to receive bevacizumab.
- *Rochester* (Katz et al. 2007): Retrospective single-institution experience with hypofractionated RT for hepatic metastases. 69 patients with 174 hepatic lesions (median size 2.7 cm) and >1000 mL normal liver. Median SBRT dose 48 Gy in 2–6 Gy fractions prescribed to the 80 % IDL (50 Gy in 5 fractions over 2 weeks preferred). PTV = GTV + 7 mm radial and 10 mm craniocaudal margins; respiratory gating used

during treatment. With median follow-up of 14.5 months, 20-month LC 57 %, 12-month PFS 24 %, and median OS 14 months; no grade 3+ toxicity. 75 % of initially treated patients developed additional hepatic lesions, 93 % of which were amenable to repeat SBRT.

Hepatocellular Carcinoma (HCC)

- *Princess Margaret Hospital* (Bujold et al. 2013): Sequential phase I (50 patients) and phase II (52 patients) trials of 24–54 Gy SBRT in 6 fractions. All patients had Child-Turcotte-Pugh class A disease, with at least 700 mL of non-malignant liver and ≤5 lesions, although 52 % received prior therapies, 55 % had tumor vascular thrombosis (TVT), 61 % had multiple lesions, and mean tumor size was 7.2 cm. Active breathing control and abdominal compression used to minimize tumor movement; GTV expanded 5–8 mm to create CTV, which was expanded ≥5 mm to create a PTV. 1-year LC 87 % (11 % CR, 43 % PR, and 45 % SD); SBRT dose and enrolment in phase II prognostic for LC on univariate analysis. Mean OS 17 months with TVT and enrolment in phase II significant for survival on multivariate analysis. Extrahepatic disease not predictive likely due to severity of hepatic disease in enrolled patients. Grade 3 toxicity seen in >30 % of patients, including 7 cases of death possibly related to treatment in patients with TVT.

Adjuvant Radiation After Hepatectomy

- *Sweden* (Gunvén et al. 2003): Retrospective, single-institution experience. Four sites of liver-only recurrence after primary hepatectomy treated with frame-based SBRT (20 Gy×2 or 15 Gy×3). 100 % local control after 13–101 months follow-up.

Imaging Follow-Up

- *Germany* (Herfarth et al. 2003): 131 multiphasic CT scans performed on 36 patients before and after single-fraction SBRT (mean dose 22 Gy) for hepatic tumors. At a median time of 1.8 months post-treatment, 74 % of scans revealed interval development of a sharply demarcated hypodense area surrounding the treated region that shrunk over time.

Ongoing

- RTOG 11-12: Sorafenib vs. SBRT (27.5–50 Gy in 5 fractions) followed by sorafenib in patients with hepatocellular carcinoma unsuitable or refractory to radiofrequency ablation or transarterial chemoembolization who are not candidates for liver transplantation. Primary endpoint overall survival; target accrual 368.

Abdominal, Pelvic, and Retroperitoneal Lymph Nodes

- *Korea* (Bae et al. 2012): Retrospective, single-institution review of 41 patients with 50 colorectal cancer metastases (12 lung, 11 liver, and 18 abdominal lymph nodes) treated with 45–60 Gy SBRT in 3 fractions. For LNs, GTV expanded 2–4 mm in all dimensions to create PTV. With median follow-up of 28 months, 3- and 5-year PFS, LC, and OS rates were 40 %, 64 %, and 60 %, and 40 %, 57 %, and 38 %, respectively. Cumulative GTV and SBRT dose statistically prognostic for LC. One grade 3 perforation after pelvic LN SBRT, and one grade 3 obstruction after para-aortic SBRT.
- *Italy* (Bignardi et al. 2011): Retrospective, single-institution review of 19 patients with unresectable abdominal and retroperitoneal LN oligometastases treated with SBRT to 45 Gy in six consecutive daily

fractions prescribed to the 80 % IDL. Dose reduced 10–20 % in 6 cases to meet normal tissue constraints, and chemotherapy held starting 3 weeks before RT until disease progression. PTV expansion of 3 mm radially and 6 mm craniocaudally. Median 12-month follow-up. Actuarial FFLP rate 78 % and OS 93 % at both 12 and 24 months, with PFS 30 % and 20 %, respectively. Number of metastases (solitary vs. nonsolitary) significant for PFS. No RT-associated grade 2+ events.

Adrenal Gland Metastases

- *Florence* (Casamassima et al. 2012): Retrospective, single-institution analysis of 40 patients with solitary adrenal metastases treated with 36 Gy SBRT in 3 fractions prescribed to the 70 % IDL, plus 8 patients treated with 23 Gy SBRT in 1 fraction; median follow-up 16.2 months. 4D-CT used to create an ITV, which was uniformly expanded 3 mm to create a PTV; cone beam CT used for image guidance. Actuarial 1- and 2-year LC 90 % with only 2 local failures (mean time 4.9 months), although all 48 patients failed distantly with OS 39.7 %. One case of grade 2 adrenal insufficiency.
- Arnaud et al. 2011: Retrospective matched pair series of laparoscopic adrenalectomy vs. SBRT (36 Gy in 5 fractions prescribed to the 80 % IDL) for isolated adrenal oligometastases in 62 patients with controlled primary tumors. Mean follow-up 18 months. No difference in OS at 6 and 12 months between SBRT (77 % and 62 %, respectively) and surgery (87 % and 77 %, respectively).

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Chapter 9
Genitourinary Sites

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Pearls

- Prostate adenocarcinoma is considered to have low α[alpha]/β[beta] ratio of approximately 1.5–3, making it conducive to hypofractionated treatment.
- Renal cell carcinoma α[alpha]/β[beta] ratio relatively low (3–6).
- Few studies on SBRT for bladder, renal, or other GU sites.
- Most prostate studies done using CyberKnife, but standard linear accelerator-based SBRT acceptable.
- Prostate SBRT more cost-effective and convenient for patients than IMRT (Sher et al 2012).
- No randomized trials assessing efficacy of SBRT compared to standard treatments.

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Treatment Indications

Disease site	Presentation	Recommended treatment
Prostate	Low risk	Active surveillance, RP, or definitive radiation (IMRT with IGRT, brachytherapy monotherapy, or SBRT monotherapy)
	Intermediate risk	RP or definitive radiation (IMRT with prostate-specific boost using external beam radiation, brachytherapy, or SBRT boost), with short-term ADT (4 months). Consider HDR or SBRT monotherapy in select favorable patients
	High risk	RP or definitive radiation (IMRT with prostate-specific boost using external beam radiation, brachytherapy, or SBRT boost), with long-term ADT (2–3 years)
	Residual disease after RT	RP, salvage HDR, or SBRT
Bladder	Muscle invasive disease (T2-T4), bladder preservation candidate	+/– neoadj chemo → radical cystectomy or concurrent chemo-RT with IMRT to bladder and pelvis; consider SBRT boost to tumor bed (investigational)
Renal cell carcinoma	Unilateral disease, medically operable	Nephrectomy +/– post-op RT
	Unilateral disease, medically inoperable	SBRT to primary lesion
	Bilateral or recurrent contralateral disease	SBRT to lesion in unresected kidney

Work-Up

Prostate

- Work-up performed per standard-of-care depending on risk group.
- H&P, focusing on urinary symptoms, erectile function, bone pain, and DRE.
- Labs: PSA, Testosterone, and LFTs for intermediate- and high-risk patients anticipating androgen deprivation.
- TRUS-guided biopsy with >8 cores, with prostate volume measurement.
- Bone scan or NaF PET/CT for any of the following (per NCCN 2014):
  - PSA > 20.
  - T2 and PSA > 10.
  - GS > 7.
  - T3 or T4.
  - Symptoms.
- Pelvic CT or MRI for T3, T4 or a probability of lymph node involvement >10 % (per NCCN 2014).
- Prostate MRI for treatment planning.

Bladder

- H&P, labs: CBC, BUN, CR, Alk Phos, UA, Urine cytology.
- Cystoscopy with EUA.
- Upper urinary tract imaging (IVP, CT urography, renal U/S, ureteroscopy, or MRI urogram).
- If muscle invasive, Chest XR or CT, Abdominal/pelvic CT.
- TURBT with random bladder biopsies, including prostatic urethra if trigone involved.

Renal Cell Carcinoma

- H&P (hematuria, flank pain, flank mass most common presenting symptoms).
- Labs: CBC, LFTs, BUN, Cr, LDH, UA.
- CT abdomen, or MRI abdomen if concern for IVC involvement.
- CXR or CT Chest.
- Bone scan, brain MRI only if clinically indicated.

Radiosurgical Technique

Simulation and Field Design

Prostate

- TRUS-guided placement of at least 3 gold seed markers (2 at base, 1 at apex) at least 1 week prior to simulation.
- Simulation: Enema day of simulation, full bladder, supine with alpha cradle.
- Fuse prostate MRI with simulation CT.
- Consider enema 2–3 h prior to each treatment (per RTOG 0938).
- Image Guidance
  - CyberKnife:
    Real-time fiducial tracking using orthogonal kV x-ray fluoroscopy for intrafraction motion (preferred).
  - Linac:
    Daily image guidance using fiducials via EPID, conebeam CT or helical tomo CT imaging.
    If treatment time >7 min, repeat IGRT procedure during treatment at least every 7 min.
    Repeat IGRT procedure at end of treatment to document stability during treatment.

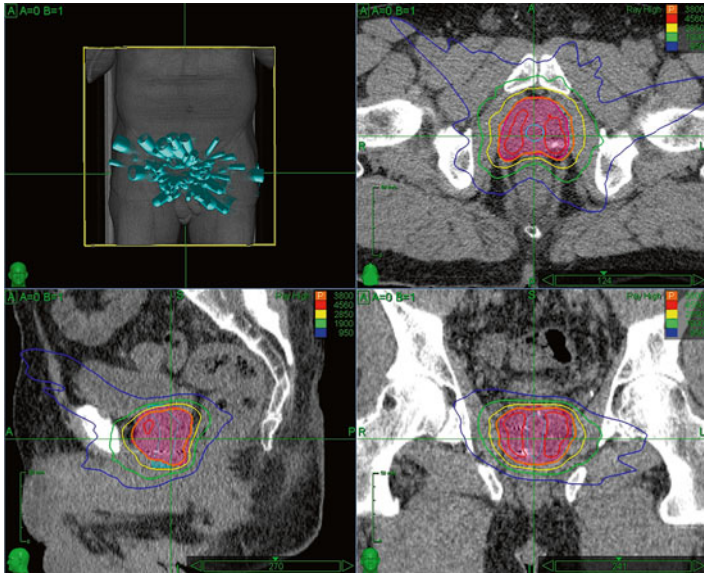

FIG. 9.1 (**b**) Axial, (**c**) sagittal, and (**d**) coronal views of an example prostate SBRT plan. Patient with low risk, cT1c, Gleason 6 prostate cancer with PSA of 3.8 treated with SBRT monotherapy to 38 Gy in 4 fractions. Target volume is shown (*shaded red*), along with urethral avoidance structure (*blue*). Prescription isodose line is shown in *orange*, and 120 % of the prescription dose is shown in *red*. A typical plan uses many (>100) non-coplanar, non-isocentric beams, as shown in (**a**)

- Treatment planning:
  - GTV: any lesion visible on MRI and/or based on biopsy information.
  - CTV: prostate +/− proximal Seminal Vesicles on CT/MRI fusion.
  - PTV: CTV + 3–5 mm expansion, sparing rectum.
  - Contour urethra as avoidance structure.

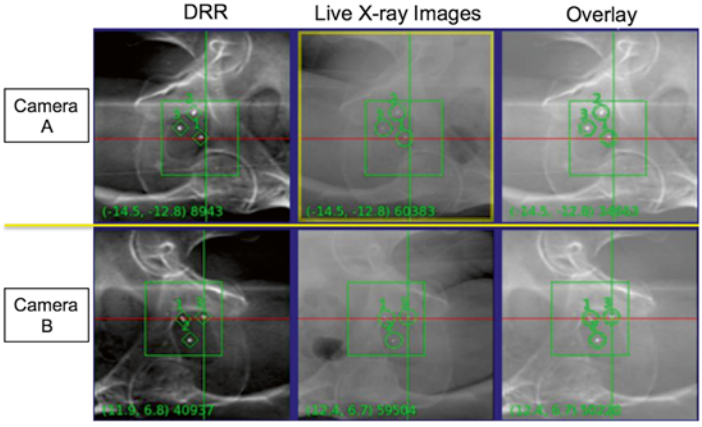

FIG. 9.2 Intrafraction fiducial tracking used for CK prostate treatments. The three gold fiducial markers placed in the prostate are visualized on orthogonal DRRs generated from the planning CT (*left*), and on the live kV X-ray images (*middle*). During treatment delivery, beams are automatically re-targeted based on the registration of fiducials on the two images (*right*) to account for intrafraction motion (within specific translational and rotational bounds)

Bladder

- Placement of 3–4 gold seed markers delineating tumor bed during TUBRT.
- Simulation: Supine with alpha cradle. Full vs. empty bladder controversial: less bowel toxicity with full bladder; more setup reproducibility with empty bladder. At UCSF, we simulate with full bladder.
- Image Guidance
  - CyberKnife: Real-time fiducial tracking for intrafraction motion (preferred).
  - Linac: Daily image guidance with fiducials, with EPID, CBCT, or helical tomo CT.
- Treatment planning:
  - GTV: Macroscopic tumor visible on CT/MRI/Cystoscopy.

- CTV_{boost}: GTV + 0.5 cm + tumor bed as delineated by gold seed markers.
- PTV = CTV + 1.5 cm.

Renal Cell Carcinoma

- Simulation: Supine with alpha cradle, arms above head.
- Obtain 4D-CT to define ITV.
- Image guidance:
  - CyberKnife: Real-time fiducial tracking
  - Daily conebeam CT.
- Field design
  - GTV: Tumor visible on planning CT.
  - ITV: Integrated tumor volume based on movement on 4D-CT.
  - PTV: ITV + 3–5 mm.
  - Contour surrounding normal kidney as avoidance structure.

Dose Prescriptions

- Prostate SBRT monotherapy
  - Acceptable regimens: 7.25 Gy × 5 (most common), 9.5 Gy × 4.
  - QOD treatment given increased toxicity with daily fractionation.
  - Consider simultaneous integrated boost to GTV if dominant lesion visible on MRI.
- Prostate SBRT boost
  - Acceptable regimens: 9.5 Gy × 2, 7 Gy × 3. At UCSF we use 9.5 Gy × 2.
- Prostate post-RT salvage
  - 6 Gy × 5.
  - If focal recurrence demonstrated on biopsy and/or MRI, consider partial volume treatment to dominant intraprostatic lesion.

- Bladder SBRT boost
  - 3.5 Gy × 5 (equivalent to 20 Gy boost in 2 Gy fractions assuming α[alpha]/β[beta] = 10).
- Renal cell carcinoma
  - 10 Gy × 4 (or 10 Gy × 3 if large).

Dose Limitations

Structure	Fractions	Constraints	Source
Rectum	4	V75% < 2 cc	UCSF (Jabbari et al 2012)
	5	Dmax < 105 %	RTOG 0938
Urethra	4	V120% < 10 %	UCSF (Jabbari et al 2012)
	5	Dmax < 107 %	RTOG 0938
Bladder	4	V75% < 3 cc	UCSF (Jabbari et al 2012)
	5	Dmax < 105 %	RTOG 0938
Penile bulb	5	V54% < 3 cc Dmax < 100 %	RTOG 0938
Femoral heads	5	V54% < 10 cc Dmax < 30 Gy	RTOG 0938
Renal cortex	5	V17.5 < 200 cc	TG101 (Benedict et al 2010)
Renal hilum	5	V23 < 66 %	TG101 (Benedict et al 2010)

Toxicities and Management

Complications

- Minimal toxicity data for bladder or renal SBRT.

Prostate

- Acute:
  - GU (~50 %): Most commonly urinary frequency, urgency.

- Management: Tamsulosin, consider routine prescription for 6 weeks after SBRT, longer as needed for symptoms.
- GI (30–40 %): Proctitis, Diarrhea
- Management: Low residue diet, anti-diarrheals, rectal amifostine have been shown to reduce symptoms (Simone et al 2008).

- Long term:
  - Cystitis, urethral stricture, rectal ulcer (<10 %).
  - Erectile dysfunction (20–25 % rate with SBRT, Chen et al 2013, Katz et al 2013).
  - Increased risk of urethral stricture if prior TURP; contraindication to SBRT.

Recommended Follow-Up

Prostate

- H&P with DRE and PSA every 6 months for 5 years, then annually thereafter. DRE may be omitted if undetectable PSA (per NCCN 2014 Guidelines).
- PSA "bounce," previously observed in brachytherapy patients, common in SBRT (10–20 %). Median time to bounce 3 years.
- Phoenix Definition of PSA >2 ng/mL above PSA nadir results in fewer false-positive biochemical failures due to benign PSA bounces.

Evidence

Prostate

Dosimetric Comparison to HDR

- Fuller et al. (2008): Treated 10 patients with CyberKnife SBRT and performed simulated treatment planning for HDR on same patients. Similar prostate coverage

and rectal wall doses for SBRT and HDR; more homogeneity, lower urethral dose and lower bladder maximum point dose for SBRT.

SBRT Monotherapy

- No randomized studies of SBRT vs. other modalities, and no studies with long-term (>4 years) follow-up.
- All studies use Phoenix definition of biochemical failure (PSA nadir +2 ng/dl) unless otherwise specified.
- *Wisconsin* (Madsen et al. 2007): Phase I/II trial of 40 patients with low-risk (GS < 7, PSA < 10, ≤T2a) disease treated with 33.5 Gy in 5 fractions on consecutive days. Conventional linear accelerator with fiducial markers for daily positioning. Median follow-up of 41 months, only 1 acute grade 3 GU toxicity reported with no late grade 3 GI or GU toxicities. 4-year biochemical freedom from relapse of 90 %.
- *Winthrop* (Katz et al. 2010a, b, 2013): Prospective study of 304 patients with low (69 %), intermediate (27 %) and high-risk (4 %) disease treated with 35 Gy in 5 fractions (first 50 patients) and 36.25 in 5 fractions (all subsequent patients) using daily treatment with CyberKnife. Median follow-up 60 months. No acute grade 3 toxicity; 4.3 % and 3.6 % acute grade 2 GU and GI toxicity, respectively. 2 % late grade 3 GU toxicity; 5.8 % and 2.9 % late grade 2 GU and GI toxicity, respectively. 5-year bPFS for low-, intermediate-, and high-risk patients: 97 %, 90.7 %, and 74.1 %.
- *Stanford* (King et al. 2009, 2012): Prospective Phase II trial of 67 patients with low-risk disease treated with 36.25 Gy in 5 fractions using CyberKnife. First 22 patients received daily treatment, subsequent patients received QOD treatment. 33-month median follow-up. 2 patients with late grade 3 GU toxicity, none with grade 3 GI toxicity. Grade 1–2 toxicity significantly worse with daily vs. QOD treatment (GU: 56 % vs. 17 %, GI: 44 % vs. 5 %). 4-year bPFS 94 %.

- Boike et al (2011): Phase I dose escalation study. 45 patients with low- or favorable intermediate-risk disease. First 15 patients treated with 45 Gy in 5 fractions, next 15 with 47.5 Gy in 5 fractions, final 15 with 50 Gy in 5 fractions, with a short median follow-up of 30, 18, and 12 months, respectively. Patients treated on tomotherapy or conventional linear accelerator with fiducials. 2 % Grade 3 GI toxicity, 4 % Grade 3 GU toxicity across all groups. No PSA failures.
- McBride et al. (2012): Prospective multi-institutional Phase I study of 45 patients with low-risk disease treated with 37.5 Gy in 5 fractions (34 patients) or 36.25 Gy in 5 fractions (10 patients) based on institution choice with CyberKnife. Median follow-up of 44.5 months. 19 % acute and 17 % late grade 2 GU toxicities; 7 % acute and 7 % late GI toxicities. One late grade 3 GU toxicity (obstructing requiring TURP) and GI toxicity (proctitis requiring laser ablation). 3-year bPFS was 97.7 % with one death from unrelated cause and no biochemical failures.
- *Netherlands* (Aluwni et al. 2013): Prospective study of 50 low- (60 %) and intermediate-risk (40 %) patients treated with 38 Gy in 4 fractions with CyberKnife. Simultaneous integrated boost to dominant lesion on MRI (if observed) to 44 Gy. Median follow-up of 23 months. Acute grade 2/3 GI toxicity 12 %/2 %, late grade 2/3 GI toxicity 3 %/0 %. Acute grade 2/3 GU toxicity 15 %/8 %, late grade 2/3 GU toxicity 10 %/6 %. No PSA failures.
- *Toronto* (Loblaw et al. 2013): Prospective phase I/II study of 84 low-risk patients treated with 35 Gy in 5 fractions over 28 days using standard linear accelerators using image guidance with EPID. 55 months median follow-up. 0–1 % late GI and GU toxicity. 5-year biochemical control 98 %. Conclusion: prostate SBRT feasible with conventional linear accelerators.
- *Georgetown* (Chen et al. 2013): Retrospective analysis of 100 patients (37 low risk, 55 intermediate, 8 high)

treated with 7 or 7.25 Gy × 5 fractions. 1 % grade 2 or higher GI toxicity, 31 % grade 2 or higher GU toxicity. 2-year bPFS 99 %.

- *Pooled analysis* (King et al. 2013a, b): Combined analysis of all published phase 2 trials from 8 institutions, including most studies listed above. 1100 patients total (58 % low risk, 30 % intermediate, 11 % high) treated with CyberKnife; most received 36.25 Gy in 5 fractions (range 35–40 Gy). Median follow-up 36 months. 5-year bPFS 94 % for all patients (95 %, 83 %, and 78 % for low, intermediate, and high risk, respectively). PSA nadir decreased with increasing dose, but bPFS not dependent on dose.

SBRT Boost After Conventionally Fractionated Radiation

- *Winthrop* (Katz et al. 2010a, b): Retrospective analysis of 73 patients (41 intermediate risk, 32 high risk) treated with SBRT boost after EBRT to 45 Gy. All patients treated with CyberKnife, with doses of 6 Gy × 3, 6.5 Gy × 3, or 7 Gy × 3. 33 month median follow-up; 3-year bPFS of 89.5 % for intermediate-risk and 77.7 % for high-risk patients, with only one local failure. <10 % Grade 2 and above acute or late toxicity, with comparable urinary toxicity and decreased rectal toxicity compared to EBRT and HDR boost historical series. Of note, all patients underwent rectal amifostine prior to each treatment.
- *Barcelona* (Miralbell et al. 2010): Dose escalation study of 50 patients with nonmetastatic prostate cancer (low risk 10 %, intermediate 24 %, high 66 %) treated with EBRT to 64 Gy, then boosted with 10, 12, 14, or 16 Gy in 2 fractions (29/50 patients got 16 Gy) using IMRT with abdominal stereotactic markers. Boost volume consisted of peripheral zone only, +/− SV depending on patient. Median follow-up 63 months.

5-year bPFS 98 %, with toxicity comparable to that seen in dose escalation studies.

- *UCSF* (Jabbari et al. 2012): Retrospective analysis of 38 patients treated with SBRT, 18 of whom underwent SBRT boost to 19 Gy in 2 fractions with CyberKnife after conventional external beam radiation. 72 % of boost patients high risk. 18.3 months median follow-up. No early Grade 3 toxicity; 2 late Grade 3 GU events. 100 % bPFS, PSA nadir of 0.10 comparable to comparison group of 44 patients receiving HDR brachytherapy boost.

Salvage SBRT After Conventionally Fractionated Radiation

- *Milan* (Bolzicco et al. 2013): Case series of 6 patients with PSA failure after EBRT to 70–80 Gy, and choline-PET showing no evidence of metastatic disease. All treated with 30 Gy in 5 daily fractions. Median follow-up of 11.3 months. No severe early or late toxicity, but 4 of 6 experienced biochemical progression, with 3 patients developing regional or metastatic disease.

Toxicity

- *Pooled analysis* (King et al. 2013a, b): 864 patients from pooled analysis described above completed serial questionnaires up to 6 years after treatment. Transient decline in urinary and bowel quality of life within 3 months following SBRT, returning to baseline within 6 months. Decline in sexual function observed, appreciated within 9 months of treatment and persisting thereafter.

Bladder

- Thariat et al. (2010): Case study of a single patient with prior pelvic radiation for rectal cancer, with pT2N0M0 urothelial carcinoma status post TURBT, treated with 24 Gy in 4 Gy fractions to tumor bed. Tolerated well, with NED at 2 years.

Renal Cell Carcinoma

- *Sweden* (Svedman et al. 2008): Case series of 7 patients with RCC with previous nephrectomy with metastatic disease in contralateral kidney. All underwent SBRT to functioning kidney lesion of 10 Gy × 3 or 10 Gy × 4. Local control in 6 of 7 patients, preserved renal function in 5 of 7 patients.

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Chapter 10
Gynecologic Sites

Zachary A. Seymour, Rajni A. Sethi, and I-Chow Joe Hsu

Pearls

- SBRT has been employed in recurrent, oligometastatic, and up-front settings for gynecologic tumors, alone or with EBRT.
- There are no randomized trials to evaluate the efficacy and toxicity of SBRT in these settings.
- Local control rate for SBRT re-irradiation of lymph node or distant metastatic sites is ≥65 %. Local control of small tumors approaches 100 % (Choi et al. 2009; Deodato et al. 2009; Guckenberger et al. 2010).
- Local control rate for SBRT re-irradiation for pelvic sidewall failures is ~50 % (Dewas et al. 2011).
- Distant metastasis is the most common failure pattern after SBRT for recurrent tumors with 45–70 % 2–4-year distant failure rate.

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Treatment Indications

- While early studies have explored SBRT techniques to administer a boost dose in definitive radiotherapy for gynecologic malignancies, brachytherapy remains the gold standard for this purpose.
- SBRT should not be used for salvage of central recurrences within high-dose region of the prior treatment field in patients who have undergone definitive radiation due to high potential toxicity.

Presentation	Treatment recommendations
Isolated lateral pelvic recurrences	Resection, palliative EBRT, SBRT, or systemic therapy
Isolated nodal recurrence	Resection, EBRT ± SBRT, SBRT alone, or systemic therapy
Oligometastatic disease	Resection, SBRT, or systemic therapy

Work-Up and Recommended Imaging

- H&P, including prior radiotherapy, detailed gynecologic history, performance status, pelvic examination.
- Review of systems.
  - Vaginal bleeding.
  - Pelvic or back pain.
  - Neuropathy associated with sidewall recurrences leading to leg pain or weakness.
  - Bowel or bladder symptoms.
- Labs.
  - CBC, metabolic panel, liver function tests.
- Imaging.
  - MRI within 2 weeks of SBRT.
  - PET/CT or CT with contrast as alternatives for recurrent disease.
- Pathology.
  - FNA or CT-guided biopsy of accessible lesions.

Radiosurgical Technique

Simulation and Treatment Planning

- Supine position, arms on chest or overhead.
- Immobilization with body frame and/or fiducial or spine tracking.
- Thin-cut CT (≤2.5 mm thickness) recommended.
- IV and oral contrast to delineate bowel and vessels.
- GTV is contoured using fusion of the MRI or PET/CT scan merged into the area of interest on simulation CT scan.
- PTV = GTV + 3–8 mm (dependent upon site-specific motion considerations).
- Low dose to organs at risk can be achieved using a large number of beam angles and smaller margins.
- Phantom-based QA on all treatment plans prior to delivery of first fraction.

Dose Prescription

- Doses are divided into 1–5 fractions usually over 1–2 weeks.
- SBRT alone in previously un-irradiated sites:
  - 6 Gy × 5 fractions (Deodato et al. 2009; Higginson et al. 2011).
  - 11–15 Gy × 3 fractions (Choi et al. 2009).
- SBRT alone in previously irradiated fields:
  - 8 Gy × 3 fractions (Kunos et al. 2012).
  - 6 Gy × 5–6 fractions (Deodato et al. 2009; Dewas et al. 2011).
  - 5 Gy × 5 fractions (UCSF unpublished).
- SBRT with EBRT 45 Gy for PALN recurrences:
  - 5 Gy × 4–5 fractions (Higginson et al. 2011).
- In series where SBRT has substituted for brachytherapy boost during initial treatment of the primary tumor, dose prescriptions mimic commonly accepted brachytherapy schedules.
- Dose prescribed to 70–80 % IDL.

Dose Limitations

- Dose limitations to normal structures should meet accepted brachytherapy standards or those as outlined in TG-101 (see Appendix).
- In the setting of re-irradiation, composite planning should be employed, with appropriate BED conversion for dose summation.

Dose Delivery

- Initial verification by kV X-ray or CBCT to visualize the tumor or surrogate markers for positioning.
- Verification imaging should be repeated at least every 5 min for longer treatments.

Toxicities and Management

- Grade 3 or higher acute toxicity or severe late toxicity is rare.
- Common acute toxicities:
  - Fatigue: Usually self-limiting but may last for several weeks to months.
  - Urethritis/cystitis: Treatment with phenazopyridine or topical analgesics at the urethra.
  - Dermatitis: Skin erythema, hyperpigmentation, dry desquamation. Limited by increased number of beam angles to reduce entrance and exit doses. Treated with supportive care, including moisturizers, low-dose steroid creams, topical analgesics, and antimicrobial salves.
  - Diarrhea/proctitis: Managed with low-residue diet and antidiarrheals.
  - Nausea: More common with treatment of retroperitoneal nodes leading to bowel dose. Pretreatment with antiemetic 1 h prior to each fraction can limit acute episodes of nausea after treatment.

- Moderate or severe late toxicities:
  - Vaginal stenosis: Managed with vaginal dilator every other day.
  - Ureteral stricture: Expectant management or dilatation.
  - Vesicovaginal or rectovaginal fistula: Surgical management.
  - Intestinal obstruction: Managed with bowel rest or surgical management.
  - Soft tissue necrosis has been observed particularly in the re-treatment setting.

Recommended Follow-Up

- Pelvic exam every 3 months for 2 years, then every 6 months for 3 years, then annually.
- For cervical cancers, Pap-smear every 6 months for 5 years then annually. Pap-smear surveillance should start 6 months after treatment due to post-radiation changes.
- PET/CT or CT A/P with contrast 3 months after completion of therapy.

Evidence

SBRT as Re-irradiation for Recurrent Tumors

- Kunos et al. (2012): Prospective phase II study, 50 patients with primary gynecologic site, recurrence in ≤4 metastases. Treatment sites were PALN (38 %), pelvis (28 %), other distant sites including abdomen, liver, lung, bone (34 %). Dose was 8 Gy × 3 fractions to 70 % IDL with Cyberknife. CTV = PET-avid lesions. PTV = CTV + 3 mm. Thirty-two percent had treatment in previously irradiated field. Median follow-up for surviving patients 15 months. No SBRT-treated lesion

progressed. Sixty-four percent recurred elsewhere. Three patients (6 %) had grade 3–4 toxicity (one grade 3 diarrhea, one enterovaginal fistula, one grade 4 hyperbilirubinemia).

- Dewas et al. (2011). Retrospective study of 16 previously irradiated patients (45 Gy median dose) with pelvic sidewall recurrences. Primary tumors were cervix ($n=4$), endometrial ($n=1$), bladder ($n=1$), anal ($n=6$), rectal ($n=4$). Treatment was 36 Gy to 80 % IDL in 6 fractions over 3 weeks with Cyberknife. Median maximum tumor diameter 3.5 cm. 10.6 month median follow-up. One year actuarial LC 51 %. Median DFS 8.3 months. Four of 8 patients with sciatic pain had reduction in pain by end of treatment but none were able to discontinue opiates. No grade 3 or higher toxicity.
- Choi et al. (2009): Retrospective study of 28 cervical cancer patients with isolated PALN metastases. Twenty-four had SBRT 33–45 Gy in 3 fractions; 4 had EBRT followed by SBRT boost. PTV = GTV + 2 mm. Rx to 73–87 % IDL. Twenty-five patients received cisplatin-based chemotherapy before ($n=2$), during ($n=9$) or after ($n=14$) SBRT. Four years LC was 68 % overall, 100 % if PTV volume ≤17 mL.
- Higginson et al. (2011): Retrospective study of 16 patients treated with SBRT (9 recurrences, 5 SBRT boost, 2 oligometastatic). SBRT doses were 12–54 Gy in 3–5 fractions. Eleven patients had additional EBRT 30–54 Gy. Eleven months median follow-up. LC 79 %. Distant failure 43 %.
- Guckenberger et al. (2010): Retrospective study of 19 patients with isolated pelvic recurrence after primary surgical treatment (12 cervix, 7 endometrial primaries). 16 previously un-irradiated had 50 Gy EBRT followed by SBRT boost; 3 patients with prior RT had SBRT alone. Patients were selected for SBRT over brachytherapy due to size (>4.5 cm) and/or peripheral location. Dose for SBRT boost was 5 Gy × 3 fractions

to median 65 % IDL; SBRT only 10 Gy × 3 fractions or 7 Gy × 4 fractions to the 65 % IDL. Three years LC 81 %. Median time to systemic progression 16 months. Sixteen percent severe complication rate (2 intestino-vaginal fistulas and one small bowel ileus). Two of the patients with severe complications had prior pelvic RT ± brachytherapy and had bowel maximum point dose of EQD2 >80 Gy.

- Deodato et al. (2009): Retrospective study of 11 patients, dose escalation with 5 daily SBRT fractions up to 6 Gy per fraction, in previously irradiated ($n = 6$) or previously un-irradiated ($n = 5$) patients with recurrent gynecologic tumors. Two years local PFS 82 %. Two years DMFS 54 %. No grade 3–4 toxicity.

SBRT Boost in Initial Definitive Radiotherapy

- Kemmerer et al. (2013): Retrospective study of 11 patients with stage I–III endometrial cancer. Definitive EBRT 45 Gy followed by SBRT boost to the high risk CTV (1 cm around endometrium and any gross disease after EBRT). Dose: 30 Gy/5 fractions in nine patients, 20–24 Gy/4 fractions in two patients, two fractions/week. IMRT-based treatment with daily kV CBCT. Ten-month median follow-up. One year FFP of 68 % for all patients, two years FFP 100 % for Grade 1 or stage IA tumors. Eighty percent of failures were in endometrium. One grade 3 toxicity (diarrhea).
- Molla et al. (2005): Retrospective study of 16 patients with endometrial ($n = 9$) or cervical ($n = 7$) cancer treated with SBRT boost, 7 Gy × 2 (post-op, $n = 12$) or 4 Gy × 5 (no surgery, $n = 4$), two SBRT fractions per week. PTV = CTV + 6–10 mm. Median follow-up 12.6 months. Dynamic arc therapy or IMRT was used. Only 1 failure in a cervix cancer patient. One patient had grade 3 rectal toxicity (persistent rectal bleeding); was treated previously with pelvic RT with HDR boost.

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Chapter 11
Soft Tissue Sarcoma

Steve E. Braunstein and Alexander R. Gottschalk

Pearls

- ~12,000 cases/year and ~4700 deaths/year in the USA.
- Associated with genetic predisposition syndromes: NF-1, Retinoblastoma, Gardner's syndrome, Li-Fraumeni syndrome.
- Most commonly metastatic to lung (extremity primaries) or liver (retroperitoneal primaries).
- Limb salvage surgery combined with pre or post-operative radiotherapy is current standard of care for extremity STS with LC >90 %.
- Several STS histologies have been associated with lower [alpha]/[beta] ratio, suggesting effective response with hypofractionation, and demonstrated in several studies of EBRT and SRS of brain and spinal STS metastases.
- Common adjuvant systemic therapy includes doxorubicin and ifosfamide, as well as imatinib for c-kit GIST.
- Metastatic STS is associated with poor MS <1 year, but treatment of oligometastatic disease is associated with improved survival.

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Work-Up and Recommended Imaging

- H&P, CBC, BUN/Cr, ESR, LDH, plain X-ray films of primary.
- CT/MRI for treatment planning and assessment of peritumoral edema.
- Biopsy for primary (incisional biopsy preferred).
- Biopsy for suspected metastatic disease generally avoided due to concern for further disease seeding.

Treatment Indications

- Preoperative and/or postoperative EBRT and IORT used in primary setting.
- SBRT generally not recommended preoperatively due to historically large margin recommendations for extremity STS (3–5 cm longitudinal and 2 cm circumferential).
- Potential role for SBRT as small-volume postoperative boost following preoperative EBRT and resection with positive margins.
- SBRT may be used in recurrent or metastatic disease, primarily for symptomatic palliation. SBRT should be strongly considered for patients with oligometastatic disease who are poor surgical candidates due to comorbidities or resectability concerns.

Disease site	Presentation	Recommended treatment
Extremity	Early stage (I)	Surgery->EBRT for +/close margin
	Intermediate-advanced stage (II–III)	Surgery->post-op EBRT or pre-op EBRT->surgery, ±chemo for deep/high grade tumors
Retroperitoneal	Resectable	Surgery + IORT->post-op EBRT or pre-op EBRT->Surgery +IORT
GIST	Resectable	Surgery ± imatinib
	Unresectable	Imatinib->re-eval±surgery

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Disease site	Presentation	Recommended treatment
Desmoid	Resectable	Surgery±EBRT for +margin
	Unresectable	EBRT, chemo
Metastatic (stage IV)	Chest, abdominal, or pelvic oligometastases	Surgical metastatectomy, SBRT, systemic therapy
	Spinal metastases	Surgical resection/stabilization, EBRT/SBRT
	Diffuse metastases	Systemic therapy, EBRT/SBRT for palliation of selected involved sites

Radiosurgical Technique

- Dose and fractionation directed by adjacent normal tissue RT toxicity constraints.

Simulation and Treatment Planning

- If biopsy or resection performed, request fiducial marker placement.
- Prefer fine-cut (<5 mm) treatment planning CT ± contrast with 4DCT to define ITV for thoracic or upper abdominal metastases.
- Immobilization with body frame and/or fiducial, lesion, or vertebral element tracking.
- Abdominal compression and/or respiratory gating may be employed to reduce lesion motion associated with diaphragmatic excursion during breathing.
- Image fusion with diagnostic CT, MRI, myelogram, and/or PET for target delineation as appropriate.
- GTV/iGTV = lesion as defined by CT- or MRI-based imaging, with contrast as available. Lung windowing should be used for pulmonary oligometastases.
- CTV/ITV = GTV/iGTV + 0–10 mm (CTV/ITV=GTV/iGTV for pulmonary lesions).

- PTV = CTV/ITV + 3–5 mm (smaller margins with intrafraction image guidance and/or motion management).
- Image guidance with orthogonal kV and/or cone beam CT for daily treatment delivery.

Dose Prescription

- Central lung oligometastases.
  - 10 Gy × 5 fx.
- Peripheral lung oligometastases.
  - 25–34 Gy × 1 fx, 18 Gy × 3 fx, 12 Gy × 4 fx, 10 Gy × 5 fx.
- Abdominal and pelvic oligometastases.
  - 6–8 Gy × 5 fx.
- Vertebral spine metastases.
  - 18–24 Gy × 1 fx, 8 Gy × 3 fx, 6 Gy × 5 fx.

Toxicities and Management

- EBRT late radiation morbidities include decreased range of motion secondary to fibrosis at primary site, lymphedema with circumferential treatment of extremities, and low risk of secondary malignancy.
- SBRT toxicity related to dose and volume of treated adjacent normal tissues.
- Risk of lung injury for pulmonary metastases (see Chap. 7).
- Risk of liver, adrenal, renal, and bowel toxicity for abdominal metastases.
- Nausea most common acute toxicity for abdominal SBRT, often responsive to short-term antiemetic pharmacotherapy.
- Acute pain flare and risk of late myelopathy for spinal metastases.

Recommended Follow-Up

- Exam with functional status, MRI of primary, CT chest every 3 months × 2 years, then every 4 months × 1 year, then every 6 months × 2 years.
- CT imaging of treated oligometastatic site every 3 months × 1 year.
- Consider bone scan, MRI, or PET, if clinically indicated.

Evidence

- There is lack of randomized prospective data on use of SBRT approaches in primary, recurrent, and metastatic disease.

Primary STS

- While there is limited data regarding SBRT in management of primary STS, there is evidence of efficacy of short-course adjuvant hypofractionated RT delivered via brachytherapy, as well as improved outcomes with reduced treatment-volume IGRT and IMRT techniques.
- Itami et al. (2010): Retrospective series of 25 primary STS patients treated postoperatively with HDR monotherapy, 36 Gy in 6 fx in 3 days b.i.d. LC 78.2 % at 5 years, but up to 93.3 % for patients with negative margins and no prior surgical resections. Complication rate of 11.5 % >grade 2.
- Petera et al. (2010): Retrospective series of 45 primary or recurrent STS patients treated post-operatively with HDR monotherapy (30–54 Gy, 3 Gy b.i.d fx) vs. HDR (15–30 Gy, 3 Gy b.i.d. fx)+ EBRT (40–50 Gy at 1.8–2 Gy fx). LC 74 % and OS 70 % at 5 years. LC better for primary tumors (100 %) and for patients treated with combination HDR + EBRT vs. HDR monotherapy (OR 0.2, $p = 0.04$).

- Dickie et al. (2010) and Wang et al. (2011): Two phase II studies of increased conformity of treatment volumes employing image-guided preoperative IMRT suggest improved rates of wound complications and late morbidities including fibrosis, joint stiffness, and edema.
- Alektiar et al. (2008). Retrospective series of 41 STS patients treated with IMRT in pre- and postoperative setting with increased bone sparing as compared with prior 3DCRT techniques. Favorable 5-year LC of 94 %.
- Soyfer et al. (2013): Series of 21 elderly patients with median age 80 underwent post-operative hypofractionated EBRT 39–48 Gy in 13–16 fx. LC 86 % at median follow-up of 26 months. Three patients had LR, all with <3 mm surgical margins. Three patients noted with late grade 2–3 toxicity.
- Levine et al. (2009): Retrospective series of primary and metastatic spinal sarcomas treated with SBRT, including 14 primary, largely STS, spinal sarcomas. Seven patients were treated definitively with SBRT (24–35 Gy in 3–5 fx) with OS 100 % and LR 29 % at mean follow up of 33 months. Seven patients received adjuvant SBRT (3 preoperatively, 4 postoperatively for +margins), treated with 25–30 Gy in 2–5 fx. Two of three preoperatively treated patients died of recurrent disease. OS 100 % for postoperatively treated patients with median follow-up of 43.5 months. There was one instance of severe late toxicity involving rectal tumor cavity fistula in a definitively SBRT-treated patient.

Metastatic STS

Surgical Ablation

- Potential survival benefit for ablative treatment of oligometastatic disease suggested by multiple surgical series.
- Billingsley et al. (1999): MSKCC series of 719 patients with STS pulmonary metastases. MS 33 months for

patients receiving complete metastatectomy vs. 11 months for those receiving non-operative therapy.

- van Geel et al. (1996): Retrospective multi-institutional series of 255 patients with pulmonary STS metastases. OS 42 and 35 % at 3 and 5 years, respectively. Young age (<40), R0 resection, and low/int grade tumors associated with better OS.
- Porter et al. (2004): Comparative effectiveness study of surgical metastatectomy vs. systemic chemotherapy for treatment of pulmonary STS metastases. Despite favorable assumptions of benefit of chemotherapy, surgical ablative therapy was deemed a significantly more cost-effective management approach.
- DeMatteo et al. (2001): 331 patients treated at MSKCC for STS liver metastases. 56 patients underwent R0 or R1 gross resection of hepatic metastases, with MS 39 months vs. 12 months for those who did not undergo complete or any resection independent of adjuvant systemic therapy.
- Marudanayagam et al. (2011): Retrospective series of 36 patients who underwent hepatic resection for oligometastatic STS. OS from metastatectomy was 90.3 % (1 year), 48.0 % (3 years), 31.8 % (5 years). Poor survival associated with high-grade tumors, primary leiomyosarcoma, and positive resection margin of liver metastasis.

Radiotherapy

- Merrell et al. (2014): Retrospective series of 21 patients with metastatic STS receiving SBRT. Median dose 50 Gy in 5 fx (lung), 24 Gy in 1 fx (bone), 42.5 Gy in 5 fx (liver), and 40 Gy in 4 fx (soft tissue). LC was 94 %(12 months), 83 % (24 months), and 83 % (48 months). Most frequent toxicities were of low grade, including acute pain flare and nausea, and late cough.
- Mehta et al. (2013): Retrospective series of 16 patients treated with SBRT to 25 lesions for high-grade STS

lung metastases. Prescription dose ranged from 36 to 54 Gy in 3–4 fx. LC 94 % at 43 months. No ≥grade 2 pneumonitis or esophagitis.

- Stragliotto et al. (2012): Retrospective series of 46 patients with 136 primary sarcoma metastases, including 28 patients with STS metastases (mostly lung, liver, and abdominal/pelvic) treated with SBRT doses of 10–48 Gy in 1–5 fractions. LC 88 % at median follow-up of 21.8 months. Thirty-one percent of patients demonstrated OS >3 years. Sixty-eight percent of those treated experienced some toxicity, largely cough and dyspnea, although there was one incidence of colonic perforation and one incidence of hip contracture following SBRT.
- Dhakal et al. (2012): Retrospective series of 15 patients treated with SBRT to 74 lesions for STS pulmonary metastases with preferred dose of 50 Gy in 5 fx. LC 82 % at 3 years. No grade ≥3 toxicity. MS 2.1 year vs. 0.6 years for 37 patients not receiving SBRT for pulmonary STS metastases ($p = 0.002$).
- Corbin et al. (2007): Retrospective series of 58 patients with STS pulmonary metastases. Sixteen patients received SBRT to median of 4.5 nodules. OS at 2.5 years was 73 % for SBRT patients vs. 25 % for the remaining 42 patients treated with EBRT, surgery, and/or chemotherapy. SBRT found associated with improved outcome on both univariate (HR = 0.43, $p = 0.012$) and multivariate analysis ($p = 0.007$).
- Levine et al. (2009): Retrospective series of primary and metastatic spinal sarcomas treated with SBRT, including 10 patients with 16 sarcoma spinal metastases of various histologies (leiomyosarcoma, chondrosarcoma, angiosarcoma, pleomorphic sarcoma) treated with palliative intent with a median dose 30 Gy in 3 fx. Patients experienced complete pain relief in 50 %, partial relief in 44 %, and no relief in 6 % of treated lesions. MS 11.1 months from time of SBRT.
- Folkert et al. (2014): Retrospective series of 88 patients with 120 sarcoma-related, predominantly STS, spinal

metastases. Patients received hypofractionated (24–36 Gy in 3–6 fx) or single-fraction (18–24 Gy) SBRT. LC 87.9 % and OS 60.6 % at 1 year. Single-fraction was superior to multi-fraction SBRT, with LC rates of 90.8 % vs. 84.1 %, respectively ($p = 0.007$). One percent acute and 4.5 % chronic grade 3 toxicity.

- Chang et al. (2005): Retrospective series of 189 patients treated with SRS for "radioresistant" histologies of brain metastasis, including melanoma (103), RCC (77), and sarcoma (9). Median single-session SRS dose was 18 Gy (10–24 Gy), prescribed by tumor size based upon RTOG 90-05 guidelines. Among patients with sarcoma metastases, MS was 9.1 month at a median follow-up of 9.1 months.

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Chapter 12
Extracranial Oligometastases

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Pearls

- The concept of *oligometastases* was introduced by Hellman and Weichselbaum in 1995 to describe a state in which the extent of metastases is limited in number and location and for which a curative therapeutic strategy may be indicated (Hellman and Weichselbaum 1995).
- Oligometastases are typically defined as 5 or fewer metastases in a limited number of organ systems.
- The incidence of oligometastases is not well known, but the increased use of PET-CT and other advanced imaging modalities are allowing for the earlier and more frequent diagnosis of asymptomatic oligometastases.

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- Given the possibility of long-term survival, oligometastatic lesions can be treated with definitive rather than palliative doses.
- Common primary tumor sites include colorectal cancer, NSCLC (non-small cell lung carcinoma), breast, soft tissue sarcoma, and renal cell carcinoma.
- Common sites of extracranial oligometastasis include lung, liver, bone, adrenals, and lymph nodes.
- Three categories of oligometastatic disease:
  - Present at diagnosis.
  - Remaining disease after treatment.
  - Arising after initial diagnosis/treatment (*oligorecurrence*).
- Tumor biology likely differs for oligometastatic vs. widely metastatic disease, with differing genetic signatures and expression profiles (Wuttig et al. 2009; Lussier et al. 2011).
- Surgical series have demonstrated a 5-year survival of 25–50 % after resection of lung or liver metastases, and 10–20-year survival rates of 15–25 % in selected patients, suggesting that definitive treatment of oligometastases can contribute to long-term survival (Tomlinson et al. 2007, International Registry of Lung Metastases 1997, Fong et al. 1999, Scheele et al. 1995).
- Series of SBRT for oligometastases report 2-year local control rates of approximately 80 %, 2–3-year disease-free survival rates of approximately 20 %, and 2–3 years overall survival rates of 25–40 % (Tree et al. 2013; Corbin et al 2013), which is comparable to surgical series (Tables 12.1 and 12.2).
- The majority of local recurrences occur within the first 2 years.
- Although the majority of patients will have disease progression after ablation of oligometastatic disease, SBRT can serve to delay progression and postpone the need for additional systemic therapy (Table 12.3).

TABLE 12.1 Summary of experience with SBRT for treatment of oligometastatic disease to adrenal glands or lymph nodes

Study	Year	Number of patients	Primary site	Treated site	Dose	Local control	Overall survival	Toxicity
Casamassima	2012	48	Multiple	Adrenal	Most common 36 Gy/3 fractions	90 % (2 years)	40 % (1 year); 15 % (2 years)	No gr3
Scorsetti	2012	34	Multiple (most NSCLC)	Adrenal	Median 40 Gy/5 fractions	32 % (2 years)	MS 22 months	No gr3
Oshiro	2011	19	NSCLC	Adrenal	Median 45 Gy/10 fractions	68 % response rate	33 % (2 years)	No gr3
Holy	2011	18	NSCLC	Adrenal	20–40 Gy/5 fractions	77 % (2 years)	MS 23 months	No gr3
Torok	2011	7	Multiple (most lung)	Adrenal	16 Gy/1 fraction or 27 Gy/3 fractions	63 % (1 year)	MS 8 months	NR

(continued)

TABLE 12.1 (continued)

Study	Year	Number of patients	Primary site	Treated site	Dose	Local control	Overall survival	Toxicity
Chawla	2009	14	Multiple (most lung)	Adrenal	16 Gy/4 fractions to 50 Gy/10 fractions	55 % (1 year); 27 % (2 years)	44 % (1 year); 25 % (2 years)	No gr3
Jereczek-Fossa	2014	69	Multiple	Lymph Node (Single)	Median 24 Gy/3 fractions	81 % (1 year); 64 % (3 years)	50 % (3 years)	3 % acute gr3; 1 % late gr4
Choi	2009	30	Uterus	Lymph Node (single)	33–45 Gy/3fx	67 % (4 years)	50 % (4 years)	3 % late gr 3–4
Kim	2009	7	Gastric	Lymph Node	Median 48 Gy/3 fractions	29 % (3 years PFS)	43 % (3 years)	No gr3

NSCLC non-small-cell lung cancer, *MS* medial survival, *NR* not reported

TABLE 12.2 Summary of experience with SBRT for treatment of oligometastatic disease to lung or liver

Study	Year	Number of patients	Primary site	Treated site	Dose	Local control	Overall survival	Toxicity
Navarria	2014	76	Multiple	Lung	48 Gy/4 fractions (peripheral); 60 Gy/8 fractions (central); 60 Gy/3 fractions (peripheral <2 cm)	89 % (2 years and 3 years)	73 % (2 years); 73 % (3 years)	No gr3
Ricardi	2012	61	Multiple	Lung	26 Gy/1 fraction; 45 Gy/3 fractions; or 36 Gy/4 fractions	89 % (2 years); 83 % (3 years)	66 % (2 years); 52 % (3 years)	2 % gr3 pneumonitis
McCammon	2009	141	Multiple	Lung	Most 60 Gy/3 fractions	100 % (1 year); 89 % (3 years) if ≥60 Gy	NR	5 % gr3; 1 % gr4

(continued)

Table 12.2 (continued)

Rusthoven	2009(a)	38	Multiple	Lung	48–60 Gy/3fx	100 % (1 year); 96 % (2 years)	39 % (2 years)	8 % gr3
Norihisa	2008	34	Multiple	Lung	48 Gy/4 fractions or 60 Gy/5 fractions	84 % (2 years)	90 % (2 years)	3 % gr3
Okunieff	2006	50	Multiple	Lung	50 Gy/10 fractions	85 % (3 years)	71 % (1 year); 255 (3 years)	2 % gr3
Chang	2011	65	Colorectal	Liver	Median 41.7 Gy/6 fractions	67 % (1 year), 55 % 92 years)	72 % (1 year), 38 % (2 years)	3 % acute gr3; 6 % late gr3
Rule	2011	27	Multiple	Liver	30 Gy/3 fractions; 50 Gy/5 fractions; or 60 Gy/5 fractions	100 % (3 years, 60 Gy)	50 %/67 %/56 % (2 years for 30 Gy/50 Gy/60 Gy)	4 % gr3
van der Pool	2010	20	Colorectal	Liver	37.5 Gy/3 fractions	74 % (2 years)	83 % (2 years)	10 % gr3

Goodman	2010	26	Multiple	Liver	18, 22, 26, or 30 Gy/1 fraction	77 % (1 year)	50 % (2 years)	No gr3
Rusthoven	2009	47	Multiple	Liver	Most 60 Gy/3 fractions	95 % 91 years), 92 % (2 years)	30 % (2 years)	2 % gr3
Lee	2009	68	Multiple	Liver	24 Gy/6 fractions	71 % (1 year)	47 % (18 months)	9 % acute gr3, 1 % acute gr4; 1 death from bowel obstruction
Katz	2007	60	Multiple	Liver	50 Gy/5 fractions	76 % (10 months), 57 % (20 months)	MS 14.5 months	No gr3
Kavanagh	2006	36	Multiple	Liver	60 Gy/3 fractions	93 % (18 months)	NR	6 % gr3
Mendez Romero	2006	17	Multiple (most colorectal)	Liver	37.5 Gy/3 fractions	100 % (1 year), 86 % (2 years)	85 % (1 year), 62 % (2 years)	12 % gr3 acute, 4 % gr3 late

MS medial survival, *NR* not reported

TABLE 12.3 Summary of experience with SBRT to mixed oligometastatic sites

Study	Year	Number of patients	Primary site	Treated site	Dose	Local control	Overall survival	Toxicity
Comito	2014	82	Colorectal	Multiple	48–75 Gy/3–4 fractions	80 % (2 years); 75 % (3 years)	65 % (2 years); 43 % (3 years)	No gr3
Jereczek-Fossa	2013	95	Multiple	Multiple	Median 24 Gy/3fx	67 % (3 years)	31 % (3 years)	
Sole	2013	42	Multiple	Multiple	Median 39 Gy/3fx	92 % (1 year), 86 % (2 years)	84 % 91 years), 63 % (2 years)	14 % gr2 or higher
Bae	2012	41	Colorectal	Multiple	Median 48 Gy/3 fractions	64 % (3 years); 57 % (5 years)	60 % (3 years); 38 % (5 years)	No acute gr3; 7 % late gr3
Salama	2012	61	Multiple	Multiple	Increasing 24–48 Gy/3 fractions	67 % (2 years), 88 % if dose ≥30 Gy	81 % (1 year), 57 % (2 years)	3 % acute gr3, 10 % late gr3
Milano	2012	121	Multiple	Multiple	Median 50 Gy/10 fractions	74 %/87 % (2 years non-breast/breast); 65 %/87 % (6 years non-breast/breast)	39 %/74 % (2 years non-breast/breast); 9 %/47 % (6 years non-breast/breast)	1 % gr3
Greco	2011	103	Multiple	Multiple	18–24 Gy/1 fraction	64 % (18 months); 82 % (18 months, dose 24 Gy)	NR	1 % acute gr3, 3 % late gr3

Kang	2011	59	Colorectal	Multiple	36–51 Gy/3 fractions	19 % (5 years)	29 % (5 years)	3 % gr4
Inoue	2010	44	Multiple	Multiple (mostly lung)	48 Gy/8 fractions (adrenal), 35–60 Gy in 4–8 fractions (others)	80 % (3 years)	39 % (3 years)	No gr3
Nuyttens	2007	14	Multiple	Multiple	Median 7 Gy per fraction x Median 6 fractions	100 % (18 months)	NR	No gr3
Svedman	2006	30	Renal cell carcinoma	Multiple	40 Gy/4 fractions most common	98 % (crude, 52 months median follow-up)	MS 32 months	2 % gr3
Hoyer	2006	64	Colorectal	Multiople	45 Gy/3 fractions	63 % (2 years)	67 % (1 year), 38 % (2 years), 13 % (5 years)	30 % gr3, 9 % gr4
Wersall	2005	58	Renal cell carcinoma	Multiple (mostly lung)	30–40 Gy/3 fractions most common	90 % or higher (crude, 37 months follow-up)	MS 37 months (1–3 metastases), 19 months (4+ metastases)	Substantial gr3 toxicity and one death from gastric hemorrhage

MS medial survival, *NR* not reported

- Factors associated with improved outcomes are:
  - Number of metastases: Patients with 1–3 metastases have better PFS than those with 4–5 metastases.
  - Size: Improved local control of smaller lesions <3 cm.
  - Dose: BED >100 Gy (α[alpha]/β[beta] ratio = 10) associated with local control rates of 90 %.
  - Disease-free interval: Improved survival is correlated to disease-free intervals of >12 months after SBRT.

Treatment Indications

- SBRT for oligometastatic sites should be considered when the following criteria are met:
  - Controlled primary lesion.
  - 5 or fewer metastases.
  - ECOG ≤2.
  - Predicted life span at least 3 months.

Work-Up

- H&P, Review of Systems, and Laboratories:
  - These are performed every 3 months in patients with known metastatic disease. Evaluations focus on known sites of involvement, as outlined in the site-specific chapters.
- Imaging.
  - The role and frequency of interval systemic imaging (PET-CT or CT C/A/P ± contrast ± bone scan) to survey for development of metastatic disease in asymptomatic patients is not well defined. High-risk patients may benefit from surveillance imaging every 6 months for early detection of oligometastatic disease.
  - Patients diagnosed with metastatic disease should undergo systemic imaging (PET-CT or CT C/A/P ± contrast ± bone scan, brain MRI) to rule out additional lesions.

- Refer to site-specific chapters for organ-specific imaging recommendations for radiation planning.

- Pathology.
  - The first site of metastasis is usually biopsied to confirm metastatic state. Biopsies of additional lesions may be performed to confirm sites of metastasis if involvement is unclear based on imaging, physical exam, and/or laboratory work-up.

Radiosurgical Technique

- Refer to site-specific chapters for simulation, planning, and dose-delivery recommendations.

Toxicities and Management

- Refer to site-specific chapters for toxicity relevant to different organ systems.

Recommended Follow-Up

- Repeat H&P and PET-CT or CT C/A/P + contrast and bone scan every 3 months starting 2–3 months after treatment to assess for response and progression of disease.

Evidence

Lung Metastases

- Rusthoven et al. (2009a): Multi-institution phase I/II trial with 1–3 lung metastases up to 7 cm total diameter, dose escalation from 48 to 60 Gy in 3 fractions. Thirty-eight patients, 63 lesions, low-burden extrathoracic disease permitted. Grade 3 toxicity in 8 %, symptomatic pneumonitis in 2.6 %. Actuarial local control 100 and 96 % at 1 and 2 years. Median survival 19 months.

- Norihisa et al. (2008): Retrospective analysis of 34 patients with 1–2 lung mets from a controlled primary tumor. Treated with 48 or 60 Gy in 4–5 fractions. Two-year overall survival 84.3 %, local relapse-free 90 %, progression-free 34.8 %. No local progression with 60 Gy. Twelve percent grade 2 toxicity, no grade 3. Longer disease-free interval corresponded to improved overall survival.

Liver Metastases

- Rusthoven et al. (2009b): Phase I/II dose escalation for 47 patients with 1–3 liver mets, each <6 cm. Thirty-six to sixty Gy in 3 fractions. 92 % in-field control at 2 years, 100 % for ≤3 cm lesions. Two percent ≥grade 3 toxicity. Median survival 20.5 months.
- Shefter et al. (2005): Multicenter phase I with 18 patients with 1–3 liver mets, <6 cm max diameter, KPS >60 %, adequate liver function, no other progressive or untreated gross disease. Thirty-six to sixty Gy in 3 fractions. ≥700 cc of normal liver with <15 Gy. No dose-limiting toxicities.
- Chang et al. (2011): Multi-institutional cohort study of 65 patients with 1–4 liver mets from colorectal cancer, treated with 22–60 Gy in 1–6 fractions. Estimated dose of 46–52 Gy in 3 fractions needed for 1-year local control >90 %. Nonactive extrahepatic disease correlated with overall survival.

Adrenal Metastases

- Casamassima et al. (2012): Retrospective single-institution study with 48 patients with adrenal mets (unilateral or bilateral) from various primaries, typically received 36 Gy in 3 fractions (8 patients treated in 1 fraction, mean 24 Gy; 40 patients treated in 3

fractions, mean 35 Gy). Local control 90 % at 2 years. Overall survival 39.7 % at 1 year, 14.5 % at 2 years. No grade 3 toxicity.

Lymph Node Metastases

- Jereczek-Fossa et al. (2014): Retrospective single-institution study with 69 patients (94 lesions) with metastases to a single abdominal lymph node. Primary sites were urological, gastrointestinal, gynecologic, and other. Median follow-up 20 months. Median SBRT dose was 24 Gy in 3 fractions. Three years local control 64 %, PFS 12 %, and OS 50 %. Failures were predominantly out of field. Survival rates were significantly higher (3 years OS 85 %) for prostate or renal cell primaries. There was 3 % acute grade 3 GU toxicity, and one patient had late grade 4 toxicity (hemorrhagic duodenitis).

Studies with Mixed Populations

- Salama et al. (2012): Single-institution prospective dose escalation trial with 61 patients of any histology, 1–5 metastases in varying locations, ≤10 cm or ≤500 mL each, life expectancy >3 months, ECOG ≤2. Dose escalated from 24 to 60 Gy in 3 fractions. Max tolerated dose not reached. One- and two-year progression-free survival 33.3 and 22 %, 1- and 2-year overall survival 81.5 and 56.7 %. Seventy-two percent of patients with progressive disease progressed in 1–3 sites.
- Milano et al. (2012): Prospectively analyzed 121 patients with any primary and 5 or fewer metastases to 1–3 organ sites. For breast primary, 6-year overall survival 47 %, local control 87 %. For non-breast primary, 6-year overall survival 9 %, local control 65 %.

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Appendix

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		One fraction		Three fractions		Five fractions		
Tissue	Max. critical vol. in excess of threshold	Threshold dose (Gy)	Max. point dose (Gy)	Threshold dose (Gy)	Max. point dose (Gy)	Threshold dose (Gy)	Max. point dose (Gy)	Endpoint (≧Grade 3)
Optic pathway	<0.2 cc	8	12	15.3 (5.1 Gy/fx)	17.4 (5.8 Gy/fx)	23 (4.6 Gy/fx)	25 (5 Gy/fx)	Neuritis
Cochlea	–	–	9	–	17.1 (5.7 Gy/fx)	–	25 (5 Gy/fx)	Hearing loss
Brainstem (not medulla)	<0.5 cc	15	18	18 (6 Gy/fx)	23.1 (7.7 Gy/fx)	23 (4.6 Gy/fx)	31 (6.2 Gy/fx)	Cranial neuropathy
Spinal cord+medulla	<0.1 cc	10	14	18 (6 Gy/fx)	21 (7 Gy/fx)	23 (4.6 Gy/fx)	30 (6 Gy/fx)	Myelitis
Cauda equina	<5 cc	14	16	21.9 (7.3 Gy/fx)	24 (8 Gy/fx)	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuritis
Sacral plexus	<5 cc	14.4	16	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Brachial plexus	<3 cc	–	24	–	27 (9 Gy/fx)	27 (5.4 Gy/fx)	30.5 (6.1 Gy/fx)	Neuropathy

Lung (right and left)	1500 cc	7	–	11.6 (3.87 Gy/fx)	–	12.5 Gy (2.5 Gy/fx)	–	Basic lung function
Lung (right and left)	1000 cc	7.4	–	12.4 (4.13 Gy/fx)	–	13.5 Gy (2.7 Gy/fx)	–	Pneumonitis
Bronchi, large (incl. trachea)	<4 cc	10.5	20.2	15 (5 Gy/fx)	30 (10 Gy/fx)	16.5 (3.3 Gy/fx)	40 (8 Gy/fx)	Stenosis/ fistula
Bronchi, small	<0.5 cc	12.4	13.3	18.9 (6.3 Gy/fx)	23.1 (7.7 Gy/fx)	21 (4.2 Gy/fx)	33 (6.6 Gy/fx)	Stenosis w/ atelectasis
Chest wall	<1 cc	22	30	28.8 (9.6 Gy/fx)	36.9 (12.3 Gy/fx)	35 (7 Gy/fx)	43 (8.6 Gy/fx)	Pain or fracture
Chest wall	<30 cc	–	–	30 (10 Gy/fx)	–	–	–	Pain or fracture
Chest wall	<10 cc	–	–	30 [1] (10 Gy/fx)	–	–	–	Pain or fracture
Chest wall	<71 cc to 2 cm chest wall contour	–	–	30 (10 Gy/fx)	–	30 (6 Gy/fx)	–	Pain or fracture

(continued)

(continued)

		One fraction		Three fractions		Five fractions		
Tissue	Max. critical vol. in excess of threshold	Threshold dose (Gy)	Max. point dose (Gy)	Threshold dose (Gy)	Max. point dose (Gy)	Threshold dose (Gy)	Max. point dose (Gy)	Endpoint (≧Grade 3)
Esophagus	<5 cc	11.9	15.4	17.7 (5.9 Gy/fx)	25.2 (8.4 Gy/fx)	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	Stenosis/ fistula
Stomach	<10 cc	11.2	12.4	16.5 (5.5 Gy/fx)	22.2 (7.4 Gy/fx)	18 (3.6 Gy/ fx)	32 (6.4 Gy/fx)	Ulceration/ fistula
Stomach	<4 %	22.5 [2]	–	–	30 [3] (10 Gy/fx)	–	–	Ulceration
Stomach/ bowel	Circumference	–	12	–	–	–	–	Ulceration/ fistula
Small bowel	<30 cc	12.5 [3]	–	–	30 [3] (10 Gy/fx)	–	–	Ulceration/ fistula
Duodenum	<5 cc	11.2	12.4	16.5 (5.5 Gy/fx)	22.2 (7.4 Gy/fx)	18 (3.6 Gy/ fx)	32 (6.4 Gy/fx)	Ulceration

Duodenum	<10 cc	9	–	11.4 (3.8 Gy/fx)	–	12.5 Gy (2.5 Gy/fx)	–	Ulceration
Duodenum	<5 %	22.5 [2]	–	–	–	–	–	Ulceration
Jejunum/ Ileum	<5 cc	11.9	15.4	17.7 (5.9 Gy/fx)	25.2 (8.4 Gy/fx)	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	Enteritis/ obstruction
Colon	<20 cc	14.3	18.4	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Colitis/fistula
Rectum	<20 cc	14.3	16	24 (8 Gy/fx)	28.2 (9.4 Gy/fx)	25 (5 Gy/fx)	38 (7.6 Gy/fx)	Proctitis/ fistula
Rectum	Circumference	–	14	–	–	–	–	Proctitis/ fistula
Rectum	<1 cc	–	–	–	–	36 [4] (12 Gy/fx)	–	Proctitis/ fistula
Bladder	<15 cc	11.4	18.4	16.8 (5.6 Gy/fx)	28.2 (9.4 Gy/fx)	18.3 (3.65 Gy/fx)	38 (7.6 Gy/fx)	Cystitis/ fistula

(continued)

(continued)

		One fraction		Three fractions		Five fractions		
Tissue	Max. critical vol. in excess of threshold	Threshold dose (Gy)	Max. point dose (Gy)	Threshold dose (Gy)	Max. point dose (Gy)	Threshold dose (Gy)	Max. point dose (Gy)	Endpoint (≧Grade 3)
Bladder	–	–	–	–	–	–	54	Cystitis/ fistula
Penile bulb	<3 cc	14	34	21.9 (7.3 Gy/fx)	42 (14 Gy/fx)	30 (6 Gy/fx)	50 (10 Gy/fx)	Impotence
Urethra	<10 %	–	–	–	–	49 [4] (9.8 Gy/fx)	55	Urethral stricture
Femoral heads (right and left)	<10 cc	14	–	21.9 (7.3 Gy/fx)	–	30 (6 Gy/fx)	41.8 (8.36 Gy/fx)	Necrosis
Femoral head	<5 cc	–	–	–	–	25 (5 Gy/fx)	–	Necrosis
Kidney	<2/3 Volume	10.6	–	18.6 (6.2 Gy/fx)	–	23 (4.6 Gy/fx)	–	Malignant hypertension

Kidney (must meet *both* constraints)	<33 % of *spared* kidney volume	10	–	15 (5 Gy/fx)	–	18 (3.6 Gy/fx)	–	Malignant hypertension
	<35 % of *total* kidney volume	10	–	15 (5 Gy/fx)	–	18 (3.6 Gy/fx)	–	
Kidney	<75 % of closest kidney volume	5 [5]	–	–	–	–	–	Not specified
Liver	<700 cc	9.1	–	19.2 (6.4 Gy/fx)	–	21 (4.2 Gy/fx)	–	Basic liver function
Liver	<70 %	–	–	–	–	30 [6] (6 Gy/fx)	–	Cirrhosis/ hepatitis
Liver	<50 %	5 [2]	–	–	–	–	–	Biliary stricture
	<75 %	2.5 [2]						

(continued)

(continued)

		One fraction		Three fractions		Five fractions		
Tissue	Max. critical vol. in excess of threshold	Threshold dose (Gy)	Max. point dose (Gy)	Threshold dose (Gy)	Max. point dose (Gy)	Threshold dose (Gy)	Max. point dose (Gy)	Endpoint (≧Grade 3)
Liver	Mean	–	–	HCC: 13 [7] (4.3 Gy/fx) Mets: 18 [7] (6 Gy/fx)	–	–	–	Radiation-induced liver disease (RILD)
Heart	<15 cc	16	22	24 (8 Gy/fx)	30 (10 Gy/fx)	32 (6.4 Gy/fx)	38 (7.6 Gy/fx)	Pericarditis
Great vessels	<10 cc	31	37	39 (13 Gy/fx)	45 (15 Gy/fx)	47 | (9.4 Gy/fx)	53 (10.6 Gy/fx)	Aneurysm

Source: This table summarizes tolerance doses that are largely based on the AAPM Task Group Report 101 (AAPM TG-101) as well as other sources of primary data, including our own institutional experience. [8-15] Other sources of primary information are cited specifically if based on smaller reports or early data from limited experience. Please note that most of the doses are unvalidated and based either on toxicity observations or on mathematical models, and there is a good measure of subjectivity involved as well. Because of the relative absence of long-term follow-up data for SBRT, it should be recognized that the tolerance data in the table is merely an approximation of normal tissue tolerance. When treating in areas where there is sparse or absent literature support for toxicity and complications, it is strongly recommended that formal institutional guidelines and prospective clinical trials with close oversight are implemented

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