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Number 6

Stereotactic Body Radiation Therapy

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Stereotactic Body Radiation Therapy

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy or intervention. It provides an overview of key issues related to the intervention—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions, the decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future comparative effectiveness research.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this Technical Brief. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Peer Reviewers

We wish to acknowledge individuals listed below for their review of this report. This report has been reviewed in draft form by individuals chosen for their expertise and diverse perspectives. The purpose of the review was to provide candid, objective, and critical comments for consideration by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

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Stereotactic Body Radiation Therapy

Structured Abstract

Objectives. Conduct a systematic literature scan for published data for the treatment of stereotactic body radiation therapy (SBRT) and provide a broad overview of the current state of SBRT for solid malignant tumors.

Data Sources. Ovid, MEDLINE, EMBASE, the Cochrane Database, and the Health Technology Assessment Database from January 2000 to December 2010. We also searched www.ClinicalTrials.gov, www.fda.gov, and gray literature within *Windhover, Current HC News, Gray Sheet*, The Wall Street Journal, *Clinica*, and the Google search engine.

Review Methods. Clinical studies of any design, published in English that delivered SBRT in 10 or fewer fractions, and enrolled at least three patients with solid malignant tumors in the body (excluding head and spine) were included. Two reviewers abstracted information on study design, patients, and reported outcomes. We synthesized the following variables if reported: cancer type, patient inclusion criteria, type of radiation, instrumentation, and algorithms used, study design and size, comparators, concurrent and/or prior treatments, length of followup, outcomes measured, and adverse events.

Results. Our searches identified a total of 124 relevant prospective and retrospective single group studies. The bulk of the studies examined SBRT for tumors of the lung/thorax (k = 68). We found 27 studies of tumors located in the pancreas, liver, colon, and fewer than 10 studies each for sites within uterus, pelvis, sacrum, kidney, prostate, and thyroid. There were 10 studies that included multiple treatment sites within the study. Study designs for SBRT include prospective and retrospective single group studies. Study size varied from 3 (minimum acceptable for inclusion in this review) to 398 patients. None of the published trials were comparative studies. Reported patient inclusion criteria include inoperable tumors, patients refusing surgery, biopsy proven disease, life expectancy, no prior radiation therapy (RT) or prior RT received in a particular time frame prior to SBRT, and required performance levels on the Karnofsky or World Health Organization/Eastern Cooperative Oncology Group scales. Several studies reported the use of modified linacs (k = 47), CyberKnife (k = 39), Novalis Shaped Beam or Clinac (k = 16), Body GammaKnife (k=1), Tomotherapy Hi-Art (k = 2), FOCAL unit (k = 1), and Synergy systems (k = 6). Typically, inverse treatment planning algorithms; pencil beam algorithms for dose calculation; and tissue maximum ratio calculation algorithms were reported. Prior treatments reported include surgery, radiation therapy (e.g., intensity-modulated radiation therapy (IMRT), brachytherapy), pharmaceuticals (e.g., tamoxifen), and/or chemotherapy. We calculated an overall mean and median for the length of followup for each cancer type. The shortest mean and median followup was within the multiple site category (12.9 and 8.2 months [1-95 months] respectively). Studies of the tumors involving the pelvis, sacrum, and uterus had the longest mean/median followup (31 and 33 months [range 2-77 months]). The reported outcomes include tumor control/response, toxicity, and overall survival. Most studies used four criteria to measure tumor control/tumor response: complete response, partial response, stable disease, and progression of disease. The most frequently reported adverse events include pain, fatigue, nausea, bleeding, and diarrhea.

Conclusions. In brief, SBRT appears to be widely disseminated for treatment of a variety of cancer types, although a majority of studies have only focused on treatment of thoracic tumors. None of the currently available studies include comparison groups. Comparative studies are needed to provide evidence that the theoretical advantages of SBRT over other radiotherapies actually occur in the clinical setting. Currently, there is only one small ongoing trial doing so. Consequently, a full systematic review of the current literature cannot answer questions on the effectiveness and safety of SBRT compared to other radiotherapy interventions.

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Executive Summary

Background

The development of stereotactic body radiation therapy (SBRT) began in the early 1990s at the Karolinska Institute (Stockholm, Sweden) with researchers Ingmar Lax and Henric Blomgren and was derived from the techniques and procedures of stereotactic radiosurgery (SRS). Researchers in Japan and North America helped develop this treatment during this same time in the 1990s. The American College of Radiology (ACR) and the American Society for Radiation Oncology (ASTRO) define SBRT as "an external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions."[1] SBRT combines multiple finely collimated radiation beams and stereotaxy (3D target localization). The multiple radiation beams intersect to deliver an accurate, high dose of radiation to a carefully defined location.

There are several terms that have been used interchangeably for SBRT. These terms include "stereotactic radiotherapy," "fractionated stereotactic radiosurgery," "hypofractionated stereotactic radiosurgery," and "staged radiosurgery." Consensus does not exist for the definition of SBRT with respect to a maximum number of radiation fractions, the minimum radiation dose per fraction, or the maximum number and diameter of lesions to be treated.[2]

SBRT is characterized by patient immobilization, limiting normal tissue exposure to high-dose radiation, preventing or accounting for organ motion (e.g., respiratory motion), the use of stereotaxy, and the subcentimeter[3,4] accuracy of the delivered dose. The key components of a SBRT procedure are target delineation,[5] treatment planning, and treatment delivery. The treatment team includes a radiation oncologist, medical physicist, radiation therapist, and depending on the body site and indication, a diagnostic radiologist, nurse, anesthetist, and dosimetrist as needed.[6] Medical professionals, such as surgeons, may also play a role in the treatment team.

Scope

The goal of this Technical Brief is to provide a broad overview of the current state of SBRT for solid malignant tumors. The first draft included a review of SRS and SBRT treatment for all sites within the body (including spine and head) excluding the brain. However, based on the feedback of external reviewers and current working definitions of SRS and SBRT, the scope of this Technical Brief has been adjusted to focus on SBRT.

The definition of SRS developed by the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the American Society for Radiation Oncology (ASTRO) is as follows:

> Stereotactic radiosurgery is a distinct discipline that utilizes externally generated ionizing radiation in certain cases to inactivate or eradicate (a) defined target (s) in the head or spine without the need to make an incision. The target is defined by high-resolution stereotactic imaging. To assure quality of patient care the procedure involves a multidisciplinary team consisting of a neurosurgeon, radiation oncologist, and medical physicist.

> Stereotactic radiosurgery (SRS) is typically performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or a stereotactic image-guidance system, but can be performed in a limited number of sessions, up to a maximum of five.
>
> Technologies that are used to perform SRS include linear accelerators, particle beam accelerators and multisource Cobalt 60 units. In order to enhance precision, various devices may incorporate robotics and real time imaging.[7]

The American Medical Association (AMA) has common procedural terminology (CPT) codes for SRS and SBRT that are recognized by the Centers for Medicare and Medicaid Services (CMS). According to the CPT codes, SRS treatment is delivered to a cranial lesion or spinal lesion consisting of one session (CPT codes: 77371, 77372, 77432, 63620); while SBRT has two applicable codes (77373 and 77435) with treatment delivery not to exceed five fractions within the body.[8]

This Technical Brief reports on the current technologies available to deliver SBRT; the types and locations of tumors that have been treated with SBRT; the possible advantages and disadvantages of the technology; the extent of diffusion of the technology; and provide information about advances in the technology that are currently in development. This Technical Brief does not assess the quality of the retrieved studies or come to any conclusions about the reported results and adverse events.

Methods

Literature Searches

ECRI Institute's biomedical engineers and medical physicists suggested confining our searches to the past five to eight years given the changes in the technology over time. Consequently, our search strategy for published studies involved Ovid, MEDLINE, EMBASE, the Cochrane Database, and the Health Technology Assessment Database from January 2000 to December 2010. The full search strategy can be found in Appendix A: Literature Search Methods.

We also searched the Internet for gray literature applicable to the Background section, Guiding Question 1 and Guiding Question 2. We performed the Internet searches in the Google search engine, and visited relevant links within the first 10 pages of search results. Gray literature was also searched within *Windhover*, *Current HC News*, *Gray Sheet*, *The Wall Street Journal*, and *Clinica*. We also visited association and organization Web sites (e.g., International RadioSurgery Association), and Web sites posted within each organization's site. Information for instrumentation was captured by a search of the manufacturers' Web sites and a search of the Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) (http://www.fda.gov/cdrh/). Instrumentation information can be found in Appendix F: Currently Marketed Devices for SBRT. Additional information on device specifications and compatible accessories was obtained through interviews with manufacturers (Appendix N).

Study Eligibility

Eligible studies were clinical studies of any design, published in English, with patient population of at least 3 patients, the use of SBRT, and with treatments delivered in 10 or fewer fractions. Studies not eligible for data extraction included treatment planning (e.g., dosing),

treatment delivery (e.g., accuracy), nonmalignant tumors, the use of more than 10 treatment fractions, and fewer than 3 patients.

Guiding Questions and Findings of This Technical Brief

Guiding Question 1.

1a. For which cancers has stereotactic body radiation therapy been used?

Based on our literature search, SBRT has been used for tumors located in the lung/ thorax, thyroid, pancreas, liver, colon, uterus, pelvis, sacrum, kidney, prostate, and thyroid. The bulk of the studies identified in our searches were for tumors of the lung/thorax (k = 68).

1b. What are the theoretical advantages and disadvantages of stereotactic body radiation therapy compared to other radiation therapies that are currently used for cancer treatment?

Theoretically, SBRT's most important features and reported advantages compared to other forms of external beam radiation therapy (EBRT) are the use of high-dose radiation, the delivery of one to five fractions within a few days (e.g., 2–3 days), decreasing the overall length of treatment, and an improved treatment response.[5] Standard fractionated radiotherapy (e.g., 2D-CRT, 3D-CRT, intensity-modulated radiation therapy (IMRT)) are typically delivered in 25–50 fractions, 5 days per week, for approximately 5 to 10 weeks. SBRT can be difficult to administer because of interfraction or intrafraction movements within the body (e.g., respiratory movements) and movements of the body.[5]

1c. What are the potential safety issues and harms of the use of stereotactic body radiation therapy?

As with other radiation treatments, geographic misses of the targeted tumor cause damage to surrounding healthy tissues. However, because each SBRT radiation fraction is a higher dose compared to other forms of EBRT, the potential for radiation injury is also higher.[9] An essential part of SBRT is maintaining the delivery of the prescribed dose by strict quality control of the tumor images and the regular verification of the image sets.

Guiding Question 2.

2a. What specialized instrumentation is needed for stereotactic body radiation therapy and what is the FDA status of this instrumentation?

SBRT can be delivered by dedicated and nondedicated linear accelerators. Advanced patient positioning, patient immobilization, multi-leaf collimators (MLCs) and micro-MLCs, x-ray tracking (stereotactic), advanced control systems, and treatment planning software are requirements for linear accelerator (linac) modification when performing an SBRT treatment. Nondedicated systems are capable of performing conventional radiation therapy, IMRT, along with SBRT, while dedicated systems are geared for SBRT treatments alone. SBRT can be delivered via a step and shoot method or dynamic delivery.[5] Step and shoot delivery turns the radiation beam off when the gantry rotates to the next planned delivery angle. The use of dynamic delivery enables continuous delivery of the radiation beam by adjusting the MLC as the gantry rotates. Advantages of dynamic delivery include a decrease in treatment time, less organ

movement during the treatment session, and an increase in patient throughput.[5,10] SBRT devices are regulated by the FDA under the 510(k) process. To date there are 12 commercially available systems with identifiable features delivering SBRT treatments.

2b. What is an estimate of the number of hospitals that currently have the capability for stereotactic body radiation therapy in the United States?

We identified 384 facilities in the United States capable of performing SBRT in September 2009. An overall listing of these facilities, including specific body sites treated and devices employed can be found in Appendix J: Facilities Performing SBRT for Solid Tumors.

2c. What instrumentation technologies are in development?

The Gyro Knife, manufactured by GammaStar Medical Group Ltd., is commercially available in the European Union having recently received the Conformité Européenne (CE) certification for European Union, medical devices.[11] The device, featuring a Cobalt 60 radioactive source and two vertical rotating gyroscopes, currently awaits clearance by the FDA. It appears that this device has two configurations, linac-based x-rays or Cobalt (gamma) and has the potential to treat any organ in the body.

Guiding Question 3.

Conduct a systematic literature scan for studies on the use and safety of SBRT in cancer, with a synthesis of the following variables:

3a. Type of cancer and patient inclusion criteria

The bulk of the studies examined SBRT for tumors of the lung/thorax (k = 68). We found 27 studies of tumors located in the pancreas, liver, colon, and fewer than 10 studies each for sites within uterus, pelvis, sacrum, kidney, prostate, and thyroid. There were 10 studies that included multiple treatment sites within the study. Patient inclusion criteria commonly used in multiple studies across the different cancer types include inoperable tumors or patients refusing surgery; biopsy proven disease; a particular patient's life expectancy; no prior RT or prior RT received in a particular time frame prior to SBRT; and a required level of performance on the Karnofsky or World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) scales.

3b. Type of radiation and instrumentation and algorithms used

Photon radiation was used in all included studies for SBRT treatment. The instrumentation reported in all studies included modified linacs (k = 47), CyberKnife (k = 39), Novalis Shaped Beam or Clinac (k = 16), Body GammaKnife (k = 1), Tomotherapy Hi-Art (k = 2), FOCAL unit (k = 1), and Synergy systems (k = 6). Algorithms are used to plan and deliver treatment. The studies reported inverse treatment planning algorithms; pencil beam algorithms for dose calculation; and tissue maximum ratio calculation algorithms. Most of the studies described the device and photon energy, radiation beam angles, collimation technique, body immobilization technique, treatment planning imaging, treatment planning system/algorithm, tumor tracking, respiratory tracking/control, and image guidance during treatment. For more information, see Appendix M: Literature Results Device Specifications.

3c. Study design and study size

Study designs for SBRT include prospective and retrospective single group studies. Study size varied from 3 (minimum acceptable for inclusion in this review) to 398 patients.

3d. Comparator used in comparative studies

None of the published trials were comparative studies. We identified 50 ongoing SBRT trials (see Appendix K: Ongoing Clinical Trials). Only one of these trials involved a direct comparison of SBRT to a different form of radiation therapy. This trial commenced in April 2009 in France (NCT00870116), and is a nonrandomized comparison of SBRT delivered by CyberKnife versus SBRT delivered by linac versus conformational RT for treatment of non-small cell lung cancer (NSCLC). There are three other comparative trials which plan to use historical controls, one for metastatic breast cancer (NCT00167414), one in NSCLC (NCT00727350) and one in pancreatic cancer (NCT00350142). A lung cancer trial, based in the Netherlands (ClinicalTrials.gov identifier: NCT00687986), is a randomized trial comparing SBRT with primary resection of the tumor. The primary outcomes are local control, regional control, quality of life, and treatment costs. The enrollment target was 960 patients, and completion was expected in December 2013; however, the trial was terminated in April 2011 because of poor recruitment. Another trial being conducted in China (NCT00840749) will compare SBRT to surgical resection in NSCLC. The enrollment target is 1030 patients, with planned completion in 2013. Another trial (NCT00843726) being conducted in Roswell, NY, will randomize 98 patients to either one or three fractions of SBRT for treatment of NSCLC.

3e. Concurrent and/or prior treatments used

Prior treatments reported include surgery, radiation therapy (e.g., IMRT, brachytherapy), pharmaceuticals (e.g., tamoxifen), and/or chemotherapy. Some studies specified that prior radiation therapy or chemotherapy had to be completed within a certain timeframe before SBRT (e.g., 12 weeks). Chemotherapy was the concurrent treatment most often reported within the studies.

3f. Length of followup

We have calculated an overall mean and median for the length of followup for each cancer type. The shortest mean and median followup was within the multiple site category (12.9 and 8.2 months [1-95 months] respectively). Studies of the tumors involving the pelvis, sacrum, and uterus had the longest mean/median followup (31 and 33 months [range 2-77 months]).

3g. Outcomes measured

The outcomes measured typically included tumor control or tumor response, toxicity, and overall survival. Overall cause-specific survival rates, overall survival, and disease-free survival rates were typically calculated using the Kaplan-Meier method. Most studies used the following four criteria to measure tumor control or tumor response: complete response, partial response, stable disease, and progression of disease.

3h. Adverse events, harms, and safety issues reported

Some of the most frequently reported adverse events include pain, fatigue, nausea, bleeding, and diarrhea. Some of the patients in these studies had prior cancer treatment and received SBRT for recurring cancers, and some patients had comorbidities.

Remaining Issues and Future Research Needs

Based on our literature searches, the studies published after 2000 were single-group prospective or single-group retrospective studies. We found 27 studies for tumors located in the pancreas, liver, colon, and fewer than 10 studies each for sites within the uterus, pelvis, kidney, prostate, and thyroid. These sites of treatment can be difficult to target, as there may be periodic (e.g., respiratory movement) or irregular (e.g., peristalsis) movement, or shrinkage of the tumor between fractionated treatments.

We did not identify any published randomized controlled trials (RCTs). Prospective controlled/comparative trials, preferably RCTs, are essential for establishing the relative safety and efficacy of SBRT in comparison to other methods of treatment. Considerations for selection of appropriate treatment candidates include prior radiation history of the treatment tissues, treatment volume, organ function, capacity for recovery, number of sites of disease, and many other individual cancer-related factors.[9] Future studies may help to determine the optimal number of radiation fractions, the minimum and maximum dose per fraction, the maximum number and diameter of lesions for various locations, and efficacy of SBRT treatment.

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Introduction

According to the American Cancer Society, 1,383,490 new body cancer cases are expected to be diagnosed in the United States in 2009 (This estimate does not include carcinoma in situ of any site except urinary bladder and basal and squamous cell cancers).[12] Approximately 533,990 of these newly diagnosed patients are expected to die from their cancer.[12] Treatments available for cancer include surgery, various forms of radiation therapy, and chemotherapy.

Stereotactic Body Radiation Therapy

In 1951, Dr. Lars Leskell and Borje Larsson introduced the concept of radiosurgery for use in intracranial conditions considered inoperable. Stereotactic radiosurgery (SRS) has been used to treat functional disorders of the brain such as trigeminal neuralgia or arteriovenous malformations, vascular malformations, and intracranial and spinal benign and malignant tumors. The development of stereotactic body radiation therapy (SBRT) began in the early 1990s at the Karolinska Institute (Stockholm, Sweden) and was derived from the techniques and procedures of SRS. Researchers Ingmar Lax and Henric Blomgren at the Karolinska Institute created a body frame to aide in targeting extracranial treatment sites. During this time in Japan, Minoru Uematsu began work on juxtaposing closely a computed tomography (CT) scanner and linear accelerator (linac) into a synthesized "FOCAL" (Fusion Of CT And Linac) unit in lung applications,[13] leading to the development of performing SBRT without a body frame. By the late 1990s, researchers Robert Timmerman, Lech Papiez, and colleagues initiated a phase 1 trial of SBRT for medically inoperable lung cancer at Indiana University in North America.[13]

The American College of Radiology (ACR) and American Society for Radiation Oncology (ASTRO) define SBRT as "an external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions."[1] The similarity between SBRT and SRS is the combining of multiple finely collimated radiation beams and stereotaxy (3D target localization). The multiple radiation beams intersect to deliver an accurate, high dose of radiation to a carefully defined location. The differences between the two radiation treatments include the treatment sites (e.g., SRS involves the head and spine) and the number of fractions utilized (i.e., SBRT one or a small number of fractions, SRS is typically one fraction). SBRT has been used as a treatment for tumors of the abdomen, liver, lung, neck, pancreas, kidney, and prostate. This Technical Brief will focus on SBRT.

Stereotactic Body Radiation Therapy Terms

There are several terms that have been used to describe SBRT. These terms include "stereotactic radiotherapy," "fractionated stereotactic radiosurgery," "hypofractionated stereotactic radiosurgery," and "staged radiosurgery." Within actual practice the differentiation between these various terms is blurred, with terms commonly used interchangeably. Consensus does not exist for the definition of SBRT with respect to the minimum radiation dose per fraction, or the maximum number and diameter of lesions to be treated.[2] However, most define SBRT as the treatment of an extracranial lesion with a single or very few (≤5) high-dose fractions.[14] Based on the current working definitions of ACR, the American Society for Radiation Oncology (ASTRO), and American Medical Association (AMA) common procedural

terminology (CPT) codes, this Technical Brief will use the term stereotactic body radiation therapy (SBRT).

SBRT Treatment Delivery and Treatment Planning

SBRT is characterized by patient immobilization, target localization and tracking software, limiting normal tissue exposure to high-dose radiation, preventing or accounting for organ motion (e.g., respiratory motion), the use of stereotaxy, and the subcentimeter accuracy of the delivered dose.[3,4] Factors used to determine if SBRT is an appropriate procedure include tumor shape and stage, volume (1–35 cm^3),[15] location, histology, invasiveness, and the performance status of the patient. The key components of a SBRT procedure are target delineation,[5] a simulation study, treatment planning, and treatment delivery. The treatment team includes a radiation oncologist, medical physicist, radiation therapist, and, depending on the body site and indication, a diagnostic radiologist, nurse, anesthetist, and dosimetrist as needed.[6] The treatment team may also include specialists such as surgeons.

A simulation study is performed with computed tomography (CT) prior to the treatment planning. The CT table matches the treatment table and the dataset is then imported into the treatment-planning system. Treatment planning includes patient marking (e.g., tattoos, fiducials), preplanning imaging, plan development, and patient positioning. Along with CT simulation images, the treatment-planning system may also import and fuse diagnostic magnetic resonance imaging (MRI), positron emission tomography (PET), combined PET/CT, and/or angiography images with the CT simulation images to add functional data to optimize the treatment plan. The treatment team develops a plan for the procedure using software to select the shape, size, intensity, and entry point of the radiation beam to treat the targeted tumor.

SBRT is particularly challenging because of the added complexities introduced by target motion with natural physiologic processes (e.g., respiration).[16] Techniques used to assist in decreasing organ or body motion include full body immobilization (e.g., vacuum pillows),[5] abdominal compression devices, breath-hold techniques, gating, and tracking methods. The desire to treat lesions outside of the head using the highest precision dose delivery in the setting of fractionated stereotactic radiotherapy has led to the development of image-guided radiotherapy.[10] SBRT devices can use image guidance (kV or MV[5] x-ray imaging, CT, ultrasound) to intermittently monitor the position of the targeted tumor by tracking bony structures or implanted fiducials. Imaging can also visualize soft tissues (e.g., lung, prostate) without referencing bony structures or fiducials.[5] Before treatment begins the patient is positioned on the treatment couch with or without an immobilization device and reoriented to the SBRT system.

In order to deliver treatment accurately in accordance with the treatment plan, it is imperative to accurately position the patient on the treatment system. On-board CT images or x-ray images are acquired with the patient positioned on the treatment couch and these images are compared with the treatment plan images to ensure a match between the planning geometry and the treatment geometry. If the geometries do not match, the treatment table is adjusted so that the treatment geometry then accurately aligns with the planned geometry. If the treatment team determines a change in the tumor morphology from imaging results (e.g., CT), the treatment plan needs the capability to be modified for the new tumor morphology.[5] However, most tumors are not going to change that much between the treatment doses of a SBRT treatment course.[5] The treatment can then begin.

At present, a medical linear accelerator (linac) is used for the delivery of SBRT. A linac emits x-ray photon radiation with typical energies ranging from 6 to 10 MV for SBRT. The angle of the radiation beam can be changed by either the rotation of the linac gantry or by the movement of a linac mounted to a robotic arm. The treatment table can also be adjusted to allow changes in the angle of the delivery beams.[5]

Statement of Work

The Agency for Healthcare Research and Quality requested a Technical Brief on Stereotactic Radiosurgery for Nonbrain Cancer. The following Guiding Questions were provided to the ECRI Institute Evidence-based Practice Center (EPC):

Guiding Question 1

1a. For which cancers (other than brain) has stereotactic radiosurgery been used?

1b. What are the theoretical advantages and disadvantages of stereotactic radiosurgery compared to other radiation and surgical therapies that are currently used for cancer treatment?

1c. What are the potential safety issues and harms of the use of stereotactic radiosurgery?

Guiding Question 2

2a. What specialized instrumentation is needed for stereotactic radiosurgery at sites other than in the brain and what is the FDA status of this instrumentation?

2b. What is an estimate of the number of hospitals that currently have the capability for stereotactic radiosurgery at sites other than the brain in the United States?

2c. What instrumentation technologies are in development?

Guiding Question 3. Systematic literature scans on studies on the use and safety of these therapies in cancers other than in the brain, with a synthesis of the following variables:

3a. Type of cancer/patient inclusion criteria

3b. Type of radiation/instrumentation and algorithms used

3c. Study design/size

3d. Comparator used in comparative studies

3e. Concurrent/prior treatments

3f. Length of followup

3g. Outcomes measured

3h. Adverse events/harms/safety issues reported

The first draft of this Technical Brief included a review of stereotactic radiosurgery (SRS) and SBRT treatment for all sites within the body (including spine and head) excluding the brain. However, based on the feedback of external reviewers and more recent working definitions of SRS and SBRT, the scope of this Technical Brief has been adjusted to focus on SBRT. The definition of SRS developed by the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the American Society for Radiation Oncology is as follows:[7]

> Stereotactic radiosurgery is a distinct discipline that utilizes externally generated ionizing radiation in certain cases to inactivate or eradicate (a) defined target (s) in the head or spine without the need to make an incision. The target is defined by high-resolution stereotactic imaging. To assure quality of patient care the procedure involves a multidisciplinary team consisting of a neurosurgeon, radiation oncologist, and medical physicist.
>
> Stereotactic radiosurgery is typically performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or a stereotactic image-guidance system, but can be performed in a limited number of sessions, up to a maximum of five.
>
> Technologies that are used to perform SRS include linear accelerators, particle beam accelerators and multisource Cobalt 60 units. In order to enhance precision, various devices may incorporate robotics and real time imaging.

The American Medical Association (AMA) has common procedural terminology (CPT) codes for SRS and SBRT that are recognized by the Centers for Medicare and Medicaid Services (CMS). According to the CPT codes, SRS treatment is delivered to a cranial lesion or spinal lesion consisting of one session (CPT codes: 77371, 77372, 77432, 63620); while SBRT has two applicable codes (77373 and 77435) with treatment delivery not to exceed five fractions within the body.[8]

This Brief describes the current technologies available to deliver SBRT; the types and locations of tumors that have been treated with SBRT; the possible advantages and disadvantages of the technology; the extent of diffusion of the technology; and provides information about advances in the technology that are currently in development. This Technical Brief does not assess the quality of the retrieved studies, provide analysis of study outcomes, or come to any conclusions about the reported results and adverse events.

Methods

Literature Searches

Narrative review articles and gray literature searches were used to address Guiding Questions 1 and 2. We searched the Internet for gray literature applicable to the Background section, Guiding Question 1 and Guiding Question 2. We performed the Internet searches in the Google search engine, and visited relevant links within the first 10 pages of search results. Gray literature was also searched within *Windhover*, *Current HC News*," *Gray Sheet*, *The Wall Street Journal*, and *Clinica*. We also visited association and organization Web sites (e.g., International RadioSurgery Association), and Web sites posted within the organization's site. Information regarding instrumentation was captured by a search of the manufacturers' Web sites and a search of the Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) (http://www.fda.gov/cdrh/). Instrumentation information can be found in Appendix F, Currently Marketed Devices for SBRT. Additional information on device specifications and compatible accessories was obtained through interviews with manufacturers (Appendix N).

A systematic scan of the published medical literature was performed to address Guiding Question 3. Our search strategy involved Ovid, MEDLINE, EMBASE, the Cochrane Database, and the Health Technology Assessment Database. ECRI Institute's biomedical engineers and medical physicists suggested confining our searches to the past five to eight years given the technology changes. (There are reports in the literature as far back as 1993 for the use of SRS for ocular melanoma.) Given that this is a Technical Brief, our search range was limited to January 2000 through December 2010. The full search strategy can be found in Appendix A, Literature Search Methods.

Study Eligibility

The titles of the citations identified through the literature searches were screened for relevance to the topic. Articles with titles that seemed potentially relevant were then passed to the abstract- screening level. Abstracts were initially screened in duplicate (first 50 abstracts) by two reviewers to determine relevance for SBRT. Duplicate review was used as a quality control measure to determine inter-rater agreement in regard to the questions asked about the retrieved abstracts. After screening the first 50 abstracts in duplicate, both reviewers understood the questions and proceeded to screen subsequent abstracts individually. All relevant abstracts were ordered as full-text articles for further review. Again, the first 50 full-text articles were screened in duplicate to determine eligibility for data extraction, and subsequent articles were screened individually. Eligible studies were clinical studies of any design, studies in English, patient population of at least three patients, the use of SBRT, and with treatments delivered in 10 or fewer fractions. Studies not eligible for data extraction included treatment planning (e.g., dosing), treatment delivery (e.g., accuracy), nonmalignant tumors, the use of more than 10 treatment fractions, and fewer than three patients.

Data Extraction

SRS 4.0 (Mobius Analytics, Ottawa, Canada) was used for the data extraction process. If reported, the information extracted included: country of study, year of study, authors, study design, type of cancer, patient inclusion/exclusion criteria, comparators, size of patient

population, sex and age of patients, prior or concurrent treatment, instrumentation and type of radiation used (x-ray photons), algorithms, quality assurance and/or training procedures, tumor quantity and tumor size, total radiation dosage, number of fractions and dose of each fraction, length of followup, outcomes measured and how they were measured, and adverse events/harms.

Summary of Items of Interest

For Guiding Question 3, we organized the relevant literature by study design into two tables. Each table is arranged by year of publication (most recent year first) and then alphabetically by author. These tables include the following information: author, year, cancer type, instrumentation/algorithms, study design/study size, prior/concurrent treatment, length of followup, outcomes measured, and adverse events. The tables can be found in Appendix L, Results for Guiding Question 3. The cancer types found within the literature include lung/thorax, colon, liver, pancreas, kidney, pelvic, sacrum, uterus, thyroid, and prostate.

Software

To calculate overall means and medians for patient ages and lengths of followup, we used Microsoft Office Excel 2007 (Microsoft Corporation, Redmond, WA).[17]

Results

Guiding Question 1

1a. For which cancers has stereotactic body radiation therapy been used?

SBRT can be used as a primary therapy for early stage cancer or as a targeted treatment for metastatic disease. In the latter setting, SBRT is intended to be an adjuvant cytoreductive treatment in concert with ongoing systemic therapy.[18] Based on our literature search, SBRT has been used for tumors located in the lung/ thorax, pancreas, liver, colon, uterus, pelvis, sacrum, kidney, prostate, and thyroid. The bulk of the studies identified in our searches were for tumors of the lung/thorax (k = 68).[19-86] Details for these studies can be found in Appendix L, Results for Guiding Question 3.

1b. What are the theoretical advantages and disadvantages of stereotactic body radiation therapy compared to other radiation therapies that are currently used for cancer treatment?

Standard Fractionated Radiotherapy

The goal of external beam radiation therapy (EBRT) is to deliver the prescribed amount of radiation to the targeted tumor and minimize the amount of radiation received by surrounding normal tissues. EBRT can be used as a therapeutic or palliative treatment and is delivered using linacs and various conformal techniques. Technology for the delivery of external radiation therapy includes two-dimensional (2D) conformal radiation therapy (RT), three-dimensional (3D) conformal RT, intensity modulated RT (IMRT), SBRT, proton therapy, carbon ion therapy, and electron therapy[87] (proton, electron, and carbon ion therapy are outside the scope of this Technical Brief.) AHRQ has recently commissioned a Technical Brief on proton therapy.[88]

Two-dimensional radiation therapy (2D-CRT), which uses images from plain x-rays and fluoroscopy for planning purposes, delivers radiation beams of uniform intensity from one to six directions or arcs to the tumor.[89] Anatomical landmarks or fiducials help determine the location of the tumor. Three-dimensional conformal radiation therapy (3D-CRT), on the other hand uses three dimensional images from computed tomography, positron emission tomography or magnetic resonance imaging for treatment planning. 3D-CRT uses computer software and 3D imaging techniques (from a CT simulator) to display the size, shape, and location of the tumor.[90] The treatment planning team can determine the size and shape of the radiation beam to fit the targeted tumor by using a multi-leaf collimator (MLC) or custom fabricated field-shaping blocks.[90] IMRT is a type of therapy in which the leaves of the MLC can be moved while the radiation beam is "on" variably blocking parts of the field to increase the intensity of some of the beamlets and decrease the intensity of others.[91] IMRT involves advanced treatment planning algorithms which allow the physician to input the desired radiation treatment dose constraints for the targeted tumor and the surrounding normal tissue into a computer. The computer software is used to develop a detailed treatment plan of the radiation beams required to deliver the prescribed radiation dose. Multiple iterations may be necessary to optimize the treatment plan. IMRT systems can shape the photon (x-ray) beam through step and shoot and/or dynamic MLCs (computer controlled). As a result, the beam intensity more closely matches the thickness of the

tumor. The EBRT treatment plan is reviewed and agreed upon by members of the treatment team (radiation oncologist, medical physicist, etc.) before the procedure can begin.

Differences Between Standard Fractionated Radiotherapy and SBRT

EBRT is a noninvasive procedure for patients undergoing cancer treatment. Patients are allowed to return to daily activities after the completion of the procedure, and most patients do not require any type of sedation to aid in immobilization during treatment. Patients are advised to complete scheduled follow-up procedures, as results of the treatment may not be visible during first follow-up visits. The importance of imaging techniques, accurate planning techniques, and accurate dose distribution are relevant for all forms of EBRT delivery. Minimizing the exposure of surrounding normal tissues from the radiation dose is also important for all forms of EBRT delivery. However, the ability to shape the radiation beam to the targeted tumor varies among EBRT delivery technologies.

With advances in technology and dose planning, the prescribed dose can be more closely tailored to the tumor volume with greater sparing of surrounding anatomy. The complexity of the treatment plan will depend on the tumor characteristics, surrounding tissue and goal of the treatment (palliative or therapeutic). 2D-CRT and 3D-CRT tend to include larger margins of surrounding normal tissue because of treatment- planning limitations. This may limit the total radiation dose that can be delivered to the target and may decrease the ability to treat the targeted tumor. Treatment planning for IMRT takes into account the dose constraints of the targeted tumor and the surrounding normal tissues with the goal of varying intensities across the treatment field. SBRT uses orthogonal x-ray beams to locate the targeted tumor, and several radiation beams that are finely collimated and that intersect to deliver a conformal, single, high dose of radiation.

When the treatment team determines that a patient is not a candidate for a single high dose treatment based on tumor location and size, tumor motion, and radiosensitivity, fractionated treatment is an option. The number of treatment fractions and overall length of treatment depends on the ability to conform the radiation beam to the shape of the tumor and to protect surrounding normal tissue and organs at risk from the radiation dose. As the number of fractions increase, the dose per fraction decreases. 2D-CRT, 3D-CRT, and IMRT are typically delivered in many more fractions than SBRT. Typical treatment fractions for 2D-CRT, 3D-CRT, and IMRT are 25–50 fractions delivered five days per week for approximately 5–10 weeks. A typical daily dose is approximately 2Gy per fraction. When these small doses are given repeatedly, the cumulative dose may not be as potent as an equivalent single fraction dose, so a higher overall dose is delivered. IMRT can also be used to deliver SBRT (1–5 fractions of a high dose). The two IMRT delivery methods are differentiated by the terms “conventional fraction IMRT” versus “SBRT-based IMRT.” Because SBRT delivers a high dose of radiation (20–60Gy), treatment can be completed in 1–5 fractions delivered in a few days (e.g., 1–5 days).

SBRT’s most important features and theoretical advantages compared to other forms of EBRT are the high degree of dose conformality, the use of high-dose radiation, the delivery of a single or very few fractions (thus decreasing the overall length of treatment), and an improved treatment response.[5] However, SBRT can also be difficult to administer because of the high level of accuracy required, interfraction or intrafraction movements within the body (e.g., respiratory movements) and movements of the body.[5] Similar to other forms of EBRT, SBRT can be used in combination with chemotherapy, and sometimes after other radiation therapy (RT)

interventions.[92] As with other radiation treatments, geographic misses of the targeted tumor causes damage to surrounding healthy tissues. However, because each SBRT radiation fraction is a higher dose compared to other forms of EBRT, there is greater potential for radiation injury.[9]

Table 1. Radiation delivery techniques

	Description
2D-CRT	• Has a routine planning and treatment process • Useful in palliative treatment of metastatic tumors • Treatment can be initiated rapidly[5] • Does not require multi-leaf collimator (MLC)[5] • Typically only 2–4 delivery angles • Treatment is delivered in approximately 25–40 fractions over 5–10 weeks • Tumor is defined in only 2 dimensions • Higher radiation doses delivered to surrounding normal tissue[5] • Does not have the capability to modify treatment if changes in tumor morphology[5]
3D-CRT	• Uses MLCs • Less radiation delivered to adjacent normal tissues than 2D-CRT • Improved target delineation than 2D-CRT[5] • Uses CT planning[5] • Better blocking than 2D-CRT[5] • Typically five to seven treatment angles. As delivery angles increase, treatment times increase.[5] • Treatment delivered in approximately 25–40 fractions over 5–10 weeks • Non-optimal dose distribution in complex cases
IMRT	• Minimum of 5 delivery angles. As delivery angles increase, treatment time increases.[5] • Treatment delivered in approximately 25–40 fractions over 5–10 weeks
SBRT	• High dose delivered in a few fractions (typically 1–5) • Shorter overall treatment time as a result of fewer treatment fractions • Can treat tumors considered inoperable • Tumor size range approx. 1–35 cm^3 [3 15] • Multiple delivery angles • Improved beam shaping • Some systems require stereotactic frames for immobilization • Near or real-time image guidance is necessary to maintain geographic accuracy of treatment

2D-CRT: Conventional radiation therapy
3D-CRT: Three-dimensional conformal radiation therapy
IMRT: Intensity modulated radiation therapy
MLC: Multi-leaf collimator
SBRT: Stereotactic body radiation therapy

1c. What are the potential safety issues and harms of the use of stereotactic body radiation therapy?

Quality Assurance and Quality Control of SBRT Treatment

SBRT is a high-dose radiation treatment. For high-dose radiation treatments, errors in radiation dose and spatial positioning must be minimized.[10] SBRT treatments can be difficult to plan because tumors located within the body may move periodically (e.g., respiratory movement), irregularly (e.g., peristalsis), or with shrinkage of the tumor between fractionated treatments.

The quality assurance (QA) for SBRT must go beyond physical measurements and include a proper review of individual patient data (e.g., results of treatment).[93] An essential part of SBRT is the strict quality control of the tumor images and the regular verification of the image sets to maintain the accurate delivery of the prescribed dose. SBRT requires tight conformity of the prescription dose to the tumor volume, with rapid dose fall off.[16] During treatment the targeted

tumor can be tracked by methods such as respiratory gating or target tracking (monitoring the motion of the tumor). Before a patient is treated, phantoms can be used as part of the QA process to make sure these tracking techniques are measuring the tumor location and movement correctly.[93]

ACR/American Society for Radiation Oncology SBRT Guideline

In 2004, the American College of Radiology (ACR) and the American Society for Radiation Oncology (ASTRO) developed a practice guideline for the performance of SBRT. This guideline was revised in 2009. The purpose of the guideline is to provide guidance to practitioners considering using SBRT and to define quality criteria for the delivery of SBRT.[1] The advanced training of personnel and the careful management of patients are the key aspects for performing SBRT safely. Appendix D lists the qualifications and responsibilities of the personnel, and Appendix E provides a snapshot of the suggestions within the guideline for procedure specifications, quality control of accessories, quality control of images, quality control for the treatment-planning system, simulation and treatment, and followup. This guideline does not specify physician specialties (e.g., surgeons) for SBRT applications. However, specialists (e.g., surgeons) may play an integral role in the treatment process.

Guiding Question 2

2a. What specialized instrumentation is needed for stereotactic body radiation therapy and what is the FDA status of this instrumentation?

Linacs

SBRT can be delivered by dedicated and nondedicated linacs. These systems may require patient immobilization and/or a method to account for any organ motion during treatment. Nondedicated systems are capable of performing conventional radiation therapy, IMRT, along with SBRT, while dedicated systems are for SBRT treatments alone. Advanced patient positioning, patient immobilization, x-ray tracking (stereotactic), advanced control systems, and treatment-planning software are other requirements for linac modification when performing an SBRT treatment. SBRT can be delivered via a step and shoot method or by dynamic delivery.[5] Step and shoot delivery turns the radiation beam off when the gantry rotates to the next planned delivery angle. The use of dynamic delivery enables continuous delivery of the radiation beam by adjusting the MLC as the gantry rotates. Advantages of dynamic delivery include a decrease in treatment time, less organ movement during the treatment session, and an increase in patient throughput.[5,10]

A listing of 12 commercially available systems with identifiable features can be found in Appendix F, Currently Marketed Devices for SBRT. Accessories sold with or incorporated into linacs (nondedicated) include multi-leaf collimators (MLC) and micro-MLCs. MLCs consist of individual leaves usually made of tungsten alloy, which may be mounted to or integrated into the linac. MLC leaf widths typically range from 5 mm to 10 mm. Micro-MLCs have leaf widths ranging in size from 1 mm to 4 mm[94] and generally use smaller treatment fields than MLCs (see listing of available linac-based SBRT accessories including MLC sizes in Appendix G, Linac-based SBRT Accessories. In Appendix M, we provide the details on the energy source, beam angles, collimation techniques, body immobilization systems, imaging used for treatment

planning, treatment planning systems, tumor tracking, respiratory tracking and image guidance during treatment as reported in the studies included for Guiding Question 3. Various manufacturers were contacted to provide further detail on the devices that are capable of performing an SBRT treatment and accessories used with those devices. The information provided included treatment-planning and treatment-delivery techniques and necessary equipment and software. For more information, see Appendix N, Responses from Device Manufacturers on Device Specifications and Compatible Accessories (January 2010).

FDA Status of SBRT Equipment

SBRT devices are regulated by the FDA under the 510(k) process. Most of these devices are generally cleared for marketing for treatment of lesions, tumors, and conditions anywhere in the body. Indications currently approved by the FDA's Center for Devices and Radiological Health (CDRH) as well as marketing clearance information including 510(k) applicant/number, product code, and approval dates are provided in Appendix H, Applicant's FDA 510(k) Information. Devices and accessories used for the administration of SBRT can be accessed by searching the following CDRH codes: IXI, IYE, and MUJ. Information was captured by a search of the manufacturers Web sites (Appendix I, Manufacturer Web sites) and a search of the FDA's CDRH (http://www.fda.gov/cdrh/).

2b. What is an estimate of the number of hospitals that currently have the capability for stereotactic body radiation therapy in the United States?

According to the 2009 Edition of the American Hospital Association (AHA) Guide,[95] approximately 700 facilities claim to administer SRS in the United States. Of these 700, we identified 384 facilities describing capability to perform SBRT. This information was accessed by visiting the Web sites provided in the AHA guide and through manufacturer Web sites (see Appendix I, Manufacturer Web sites). An overall listing of these 384 facilities, including specific body sites treated and devices employed can be found in Appendix J, Facilities Performing SBRT for Solid Tumors. Information from Web sites was updated in September 2009.

2c. What instrumentation technologies are in development?

The Gyro Knife, manufactured by GammaStar Medical Group Ltd.,is commercially available in the European Union having recently received the CE certification for European Union, medical devices.[11] The device, featuring a Cobalt 60 radioactive source and two vertical rotating gyros, currently awaits clearance by FDA.

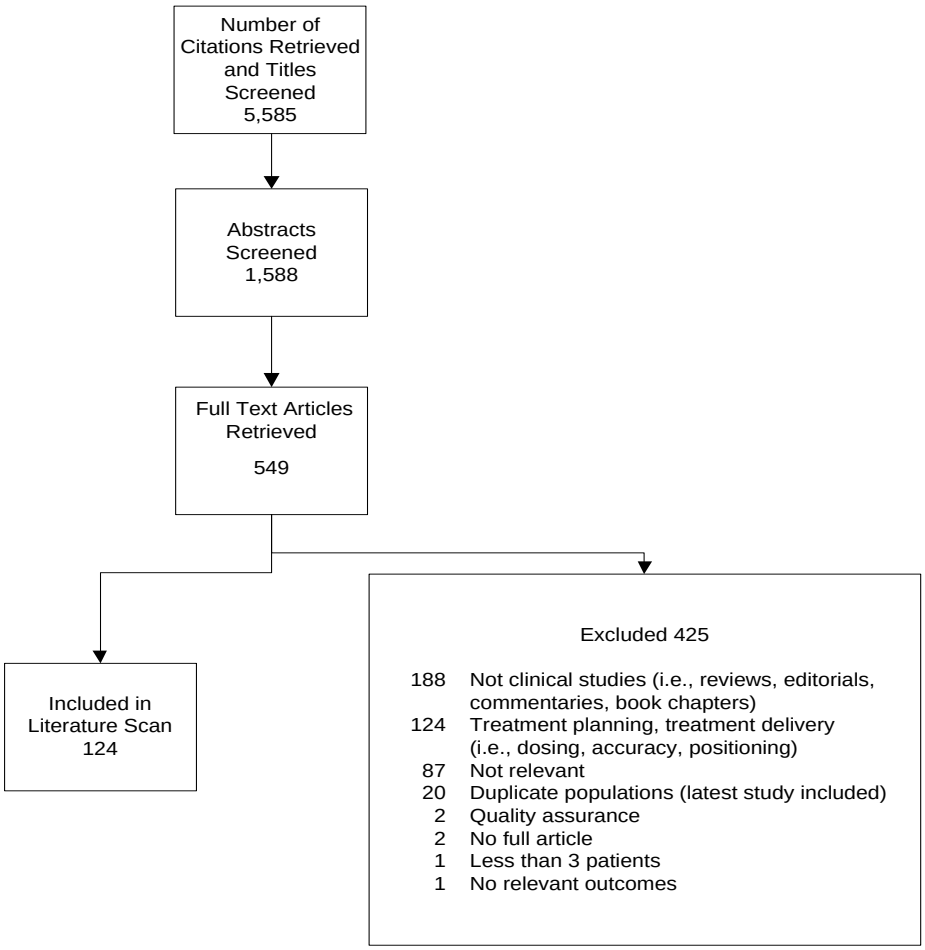
Guiding Question 3

Evidence Base

The goal of this systematic literature scan was to provide an overview of the studies of SBRT, not to evaluate the quality of the studies or to perform analysis of the data reported by the studies. We have screened the titles of 5,585 citations to determine if the abstract should be reviewed. A total of 1,588 abstracts were screened, and 550 full-text articles were ordered for further review. In total, 124 studies were relevant to the topic and data extraction was performed (see Figure 1). The included studies can be found in Appendix B. The excluded studies, along with reason for exclusion, can be found in Appendix C.

The included studies have been organized into two tables by whether they were prospective or retrospective (see Appendix L, Results for Guiding Question 3). These tables are organized by year of publication (most recent year first), and then alphabetically by author. The study details covered within the tables include author; year; cancer type; instrumentation; algorithms; study design; study size; prior and/or concurrent treatment; length of followup in months; outcomes measured; and adverse events. Patient inclusion criteria have not been included in these tables, but are presented in Table 2 in section 3.a.

Figure 1. Study selection process



3a. Type of cancer and patient inclusion criteria

Our search results identified studies of the use of SBRT for tumors located in the lung/thorax, pancreas, liver, colon, uterus, pelvis, sacrum, kidney, prostate, and thyroid. The bulk of the studies were for tumors of the lung/thorax (k = 68).[19-86] We found 27 studies for tumors located in the pancreas, liver, colon,[96-122] and fewer than 10 studies each for sites within uterus, pelvis, sacrum,[123-127] kidney,[128-133] prostate,[134-140] and thyroid.[141] There were 10 studies that included multiple treatment sites within the study.[142-151]

Patient inclusion criteria for SBRT treatment varied based on cancer types and individual studies. Criteria commonly used regardless of cancer type include inoperable tumors or patients refusing surgery; biopsy-proven disease; minimum life expectancy; no prior RT or prior RT received at a minimum length of time before SBRT; and a minimum level of performance on the Karnofsky or World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) scales. The Karnofsky Performance Status (KPS) scoring system measures the cancer patient's abilities to perform ordinary tasks. The scoring system ranges from 0 to 100, with a higher score indicating a better ability to perform tasks.[152] The retrieved studies often reported KPS scores of at least 40. The WHO/ECOG performance status assesses a patient's functional and/or physical performance. There are six codes used to evaluate a patient, and the codes seen within the retrieved studies were between 0 (fully active) and 2 (ambulatory, capable of self-care but unable to carry out work activities).[153] Since the level of detail of patient inclusion criteria varied with each study, we have provided an overview of the criteria frequently reported within the studies for each cancer type. Table 2 below also lists the number of studies retrieved and total number of patients.

Table 2. Patient inclusion criteria summary

Cancer Type	Number of Studies	Total Number of Patients (n)	Summary of Patient Inclusion Criteria
Gastrointestinal (Colon, Liver, and Pancreas)	27	1,281	Histologically proven disease, inoperable, unsuitable for resection, tumor size, no prior radiation therapy, minimum life expectancy, WHO/ECOG performance <2, Karnofsky performance >60
Kidney	6	88	Recurrent disease, inoperable, tumor size, minimum life expectancy, Karnofsky performance >60
Lung/Thorax	68	4,418	Histologically proven disease, inoperable, surgery refusal, tumor size (3–7 cm), lung function, no prior RT or RT received in an adequate time before SBRT, minimum life expectancy, involvement of surrounding tissue or structures, WHO/ECOG performance 0–2, Karnofsky performance <60
Multiple sites (e.g., lung, thyroid, renal, colon, etc. all in one study)	10	610	Inoperable, ≤5 metastases confined to one organ, WHO/ECOG performance <2, Karnofsky ≥70
Pelvis, Sacrum, and Uterus	5	89	Inoperable, tumor size, WHO/ECOG performance 1 or 2
Prostate	7	217	Low risk, favorable prognosis, intermediate prognosis
Thyroid	1	9	Inoperable recurrent lymph node(s), KPS ≥70

RT: Radiation therapy
SBRT: Stereotactic body radiation therapy
WHO/ECOG: World Health Organization/Eastern Cooperative Oncology Group

Based on our search results, the majority of studies (k = 49) performed since 2000 were in the United States for tumors located in the lung/thorax. Germany and Japan have also performed several lung studies in the past 10 years (see Table 3).

Table 3. Country and number of cancer types

Country	Number of Cancer Types	Total Number of Studies
Belgium	1 GI	1[117]
Canada	4 GI	4[99,104,109,154]
Canada & USA	1 GI	1[96]
China	1 GI	1[115]
Denmark	3 GI, 2 Lung,	5[27,61,106,107,112]
Denmark, Norway, & Sweden	1 Lung	1[20]
Germany	3 GI, 6 Lung, 2 Multiple Sites, 1 Pelvis, Sacrum, and Uterus	12[46,50,51,58,69,77,110,118,119,126,144,149]
Germany & Switzerland	1 Lung	1[23]
Italy	5 Lung, 1 Multiple Sites, 1 GI, 1 Prostate	8[34,44,62,63,86,111,139,145]
Italy & Sweden	1 Kidney	1[128]
Japan	14 Lung, 1 Multiple Sites	15[26,31,32,39,41,48,53,55,60,66,70,79,81,82,147]
South Korea	1 Pelvis, Sacrum, and Uterus, 4 Lung, 6 GI, 2 Multiple Sites, 1 Thyroid	13[19,57,71,72,97,98,103,114,116,120,124,141,142,151]
Spain	1 Pelvis, Sacrum, and Uterus	1[155]
Sweden	1 GI, 1 Kidney, 1 Lung	3[42,105,132]
Switzerland	1 Lung, 1 Pelvis, Sacrum, and Uterus	2[47,127]
The Netherlands	1 GI, 4 Lung, 1 Multiple Sites, 1 Prostate	7[24,28,40,59,108,138,146]
USA	6 GI, 2 Pelvis, Sacrum, and Uterus, 4 Kidney, 28 Lung, 3 Multiple Sites, 6 Prostate	49[21,22,25,29,30,33,35-38,43,45,49,52,54,56,64,65,67,73-76,78,80,83-85,100-102,113,121-123,125,129-131,133-137,140,143,148,150,156]
USA & China	1 Lung	1[68]

GI: Gastrointestinal

3b. Type of radiation and instrumentation and algorithms used

Photon radiation was used in all included studies for SBRT treatment. The instrumentation reported in all studies included modified linacs (k = 47), CyberKnife (k = 39), Novalis Shaped Beam or Clinac (k = 16), Body GammaKnife (k = 1), Tomotherapy Hi-Art (k = 2), FOCAL unit (k = 1), and Synergy systems (k = 6). Algorithms are used to plan and deliver treatment. The studies reported inverse treatment planning algorithms, pencil beam algorithms for dose calculation, and tissue maximum ratio calculation algorithms. Most of the studies described the device and photon energy, radiation beam angles, collimation technique, body immobilization technique, treatment planning imaging, treatment planning system/algorithm, tumor tracking, respiratory tracking/control, and image guidance during treatment (Appendix M, Literature Results Device Specifications). The number and type of radiation beams delivered during treatments included 1–12 conformal and/or nonconformal beams. The studies reported various body immobilization techniques including Smithers Medical Alpha Cradle (k = 16) and Elekta's stereotactic body frame (k = 26). CT, MRI, and PET imaging scans were often used to plan treatment. Treatment planning was conducted on software systems typically specific to the device used during treatment. Elekta's Render 3D, Varian's CadPlan and Eclipse, BrainLABs BrainScan systems, CyberKnife planning system, Philips Medical Systems Pinnacle Treatment Planning System (TPS), CMS Focus or Xio, and MDS Nordion Helax were the treatment planning systems most often reported. Studies reported breath-holding, respiratory gating (radiation beam turns on/off during respiratory cycle), and abdominal compression techniques to control respiratory movement. Lastly, the type of image guidance (MV or kV) utilized during treatment (e.g., just before treatment begins) included CT, cone-beam CT, and orthogonal x-rays For more information, see Appendix M, Literature Results Device Specifications.

SBRT doses and fractions varied based on factors such as the type of cancer and location of tumor. According to ACR/ASTRO's SBRT definition[1] and the AMA CPT codes,[8] SBRT is categorized as a treatment delivered in 1–5 fractions. Typically, doses were delivered in one to five fractions. Fourteen studies delivered treatment in more than five fractions, and also considered this to be SBRT. Table 4 lists the 14 studies delivering hypofractionated (more than five fractions) SBRT (also located in Appendix L, Results for Guiding Question 3) alphabetically by author, and details the cancer type, study design, study size (n), instrumentation/algorithms, and total dose (Gy)/number of fractions.

Table 4. Hypofractionated stereotactic body radiation therapy

Study	Country	Cancer Type	Study Design	Study Size (n)	Instrumentation/ Algorithms	Total Dose (Gy)	Number of Fractions
Chawla et al. (2009)[133]	USA	Adrenal metastases	Retrospective single group	n = 30	Novalis/NR	Median: 40 (Range: 16–50)	Median: 10 (Range: 4–16)
Guckenberger et al. (2009)[23]	Germany and Switzerland	Early stage NSCLC and pulmonary metastases	Retrospective single group	n = 40	Linac/Collapsed cone dose calculation algorithm	6–26	1–8
Haasbeek et al. (2009)[24]	The Netherlands	Second lung tumor in the contralateral lung	Prospective single group	n = 15	Linac/NR	60	3–8
Lee et al. (2009)[99]	Canada	Liver metastases	Prospective single group	n = 68	Linac/NR	Median: 41.4 (Range: 27.7–60)	6
Milano et al. (2009)[150]	USA	Oligometastases	Retrospective single group	n = 77: 42 liver,21 lung, 5 thoracic lymph nodes, 9 bone n = 13 lung parenchymal and thoracic lymph nodes	Novalis/NR	Lung and liver: 50	Lung and liver: 10
Stephans et al. (2009)[38]	USA	Stage 1 lung cancer	Retrospective single group	n = 92	Novalis machine/NR	50–60	3–10
Lagerwaard et al. (2008)[28]	The Netherlands	Stage 1 NSCLC	Retrospective single group	n = 206	Linac/NR	60	3–8
Aoki et al. (2007)[41]	Japan	Primary lung and metastases	Prospective single group	n = 19	Mitsubishi EXL-20TP 10-MV standard linac/NR	54	9
Dawson et al. (2006)[104]	Canada	HCC, IHC, liver metastases	Prospective single group	n = 79	Elekta Synergy/NR	24–57 (Median: 36.6)	6
Guckenberger et al. (2007)[47]	Switzerland	NSCLC and pulmonary metastatic lesions	Nonrandomized comparative study (Hypofractionated SBRT (3–8 fractions) vs. 1 fraction SRS)	n = 70	NR/NR	26–56	1–8

Table 4. Hypofractionated stereotactic body radiation therapy (continued)

Study	Country	Cancer Type	Study Design	Study Size (n)	Instrumentation/ Algorithms	Total Dose (Gy)	Number of Fractions
Katoh et al. (2008)[130]	USA	Adrenal tumors	Prospective single group	n = 9	Linac/NR	48 or 30	8
Tse et al. (2008)[109]	Canada	Unresectable HCC and IHC	Prospective single group	n = 41	NR/NR	24–54 (Median: 36)	6
Uematsu et al. (2001)[66]	Japan	Stage 1 NSCLC	Prospective single group	n = 50	FOCAL unit (combination of linac, CT scanner, X-ray simulator, carbon table)/NR	30–60	5–10
Xia et al. (2006)[68]	USA & China	Stage 1 and 2 NSCLC	Prospective single group	n = 43	Gamma-knife (30 rotary conical surface Cobalt 60)/ NR	50–70	10

Gy: Gray
HCC: Hepatocellular carcinoma
IHC: Intrahepatic cholangiocarcinoma
NR: Not reported
NSCLC: Non-small cell lung cancer
SBRT: Stereotactic body radiation therapy
SRS: Stereotactic radiosurgery

3c. Study design and study size

Study designs for SBRT include prospective, single-group studies and retrospective studies. Patient populations were heterogeneous across the cancer types. Study populations included as few as three patients for a prospective, single-group study and as many as 398 for a retrospective study. Table 5, below, lists the smallest and largest patient populations for the studies within each cancer type, and the type of studies conducted for each cancer type. We have also calculated an overall mean and median age for patients in the studies within each cancer type (see Table 6).

Table 5. Study designs and sizes

Cancer Type	Smallest (n)	Largest (n)	Prospective	Retrospective
GI (Colon, Liver, Pancreas)	n = 4	n = 398	18	9
Kidney	n = 3	n = 30	3	3
Lung/Thorax	n = 9	n = 379	35	33
Multiple Sites	n = 14	n = 141	4	6
Pelvis, Sacrum, and Uterus	n = 3	n = 23	1	4
Prostate	n = 10	n = 48	6	1
Thyroid	9	9	0	1
Total Number of Studies			**67**	**57**

GI: Gastrointestinal

Table 6. Overall Mean and Median (Range) for Age

Cancer Type	Mean Age (Years)	Median Age (Years)	Age Range (Years)
GI (Colon, Liver, Pancreas)	62.2	62.8	15–92
Kidney	62.8	64	39–79
Lung/Thorax	71.1	72	9–93
Multiple Sites	60.0	59.5	2–92
Pelvis, Sacrum, and Uterus	63.7	57	27-92
Prostate	69.1	68.5	46–83
Thyroid	46	46	34-81

GI: Gastrointestinal

3d. Comparator used in comparative studies

There were no included studies that compared SBRT to another form of radiation treatment. To date, the largest literature base for SBRT is treatment in the lung/thorax, but these were all single-group studies. We searched www.clinicaltrials.gov and identified 50 ongoing SBRT trials (see Appendix K, Ongoing Clinical Trials). The trials include metastatic breast cancer, biliary tract cancer, kidney cancer, liver cancer, lung cancers (principally non-small cell lung cancer), pancreatic cancer, prostate cancer, and unspecified treatment sites.

Only one of these ongoing trials involves a direct comparison of SBRT to a different form of radiation therapy. This trial commenced in April 2009 in France (NCT00870116), and is a nonrandomized comparison of SBRT delivered by CyberKnife vs. SBRT delivered by linac vs. conformational RT for treatment of NSCLC. The primary outcome measure is local control, and

planned enrollment is 120 patients. There are three other comparative trials which plan to use historical controls, one for metastatic breast cancer (NCT00167414), one in NSCLC (NCT00727350) and one in pancreatic cancer (NCT00350142).One of the lung cancer trials based in the Netherlands (NCT00687986) is a randomized study comparing SBRT to primary resection. The primary outcomes include local control, regional control, quality of life (QoL), and treatment costs. The estimated enrollment is 960 patients and is set for completion in December 2013. Another trial being conducted in China (NCT00840749) will compare SBRT to surgical resection in NSCLC. The enrollment target is 1030 patients, with planned completion in 2013. Another trial (NCT00843726) being conducted in Roswell, NY, will randomize 98 patients to either one or three fractions of SBRT for treatment of NSCLC.

3e. Concurrent and/or prior treatments used

The prior and concurrent treatments used varied with each study based on the population evaluated, and on inclusion and exclusion criteria (see the tables in Appendix L, Results for Guiding Question 3). Some studies included patients with prior and/or concurrent treatment, while other studies excluded patients with prior or concurrent treatment. Prior treatments reported include surgery, radiation therapy (e.g., IMRT, brachytherapy), pharmaceuticals (e.g., tamoxifen), and/or chemotherapy. Some studies specified that prior radiation therapy or chemotherapy had to be completed within a certain timeframe before SBRT (e.g., at least 12 weeks prior to SBRT). Chemotherapy was the concurrent treatment most often reported within the studies.

3f. Length of followup

The individual study length of followup was reported as a mean, median, and/or range. We have calculated an overall mean and median for the length of followup for each cancer type. The shortest mean and median followup was within the multiple site category (12.9 and 8.2 months [1-95 months] respectively). Studies of the tumors involving the pelvis, sacrum, and uterus had the longest mean/median followup (31 and 33 months [range 2-77 months]). Table 7 lists the cancer types and the calculated overall mean, median, and range of followup across studies within each cancer type.

Table 7. Overall mean and median followup

Cancer Type	Mean Followup (months)	Median Followup (months)	Follow-up Range (months)
GI (Colon, Liver, Pancreas)	20.0	16	1–103.2
Kidney	23.5	16	3–70
Lung/Thorax	19.7	17	1–107
Multiple Sites	12.9	8.2	1–95
Pelvis, Sacrum, Uterus	33.3	31	2-77
Prostate	20.1	9.3	2 weeks–74.4 months
Thyroid	23	23	4-63

GI: Gastrointestinal

3g. Outcomes measured

The outcomes measured typically included tumor control or tumor response, toxicity, and overall survival. Overall cause-specific survival rates (chances of death due to cancer at a

defined time point), overall survival rates (chances of death due to cancer and/or other complications at a defined time point), and disease-free survival rates were typically calculated using the Kaplan-Meier method. Most studies used the following four criteria to measure tumor control or tumor response: complete response (disappearance of tumor), partial response (percentage of decrease in tumor size), stable disease (smaller percentage change than with partial response), and progression of disease (increase in tumor size). The percentages of tumor response varied with each study. Table 8 provides a summary of the types of outcomes measured within each cancer type.

Table 8. Summary of outcomes measured

Cancer Type	Summary of Outcomes Measured
GI (Colon, Liver, Pancreas)	Toxicity, tumor response, overall survival, progression-free survival, regional failure, change in liver volume, maximum tolerated study dose, carbohydrate antigen levels (CA 19-9), QoL, late toxicities, deterioration of hepatic function
Kidney	Survival, pain assessment, tumor response, toxicity, kidney function, creatine levels
Lung/Thorax	Tumor response, overall survival, cause-specific survival, toxicity, local control, pulmonary status, disease progression, maximum standardized uptake value, normal tissue changes
Multiple Sites	Morbidity, tumor response, quality of treatment, survival, local failure, local progression, disease-free survival, toxicity, pain relief
Pelvis, Sacrum, Uterus	Pain relief, tumor response, toxicity, local failure
Prostate	PSA response, QoL, acute gastrointestinal toxicities, acute genitourinary toxicities
Thyroid	Tumor response, regional failure

GI: Gastrointestinal
PSA: Prostate specific antigen
QoL: Quality of Life

Evaluating the extent of cell destruction caused by SBRT can be a difficult task, as older calculation methods (e.g., linear quadratic model [LQ]) were developed for use with conventional radiation therapy. The LQ model assumes there are two components of radiation-induced cell destruction—one component proportional to dose and one component proportional to the square of the dose.[16] The application of the LQ model for low dose conventional fractions may not have the same consequences as the use of the model with SBRT. The LQ model possibly overestimates cell destruction, and it may not describe the cell survival curve for the high doses of SBRT properly.[16] Making comparisons between studies for SBRT can also be challenging. Studies may report equivalent prescription doses; however, differences in fractionation schedules can result in a substantial difference in the biologically effective dose (BED).[16] The BED is an index that can serve as a useful parameter for comparing the potency of two different fractionation schedules.[18]

3h. Adverse events, harms, safety issues reported

Radiation Therapy Oncology Group criteria and Common Toxicity Criteria version 2.0 (RTOG/CTC) were typically used to grade acute and late toxicity at each followup. In general, Grade 1 toxicities require no treatment, Grade 2 toxicities require medication or a simple intervention, Grade 3 toxicities have more severe symptoms and require more complex interventions, and Grade 4 toxicities can be life threatening.[135] Some studies reported acute

versus late complications; however, they did not always specify complications related to individual patients. Some of the most frequently reported adverse events include pain, fatigue, nausea, bleeding, and diarrhea. Some of the patients in these studies had prior cancer treatment and received SBRT for recurring cancers, and some patients had comorbid conditions. Toxicities for large radiation doses are predominantly late occurrences which take more time to observe. Therefore, longer followup will be required for wider acceptance of SBRT.[9]

A total of 11 studies did not report any adverse events for tumors located at the following sites: one kidney,[131] six lung,[29,35,52,61,77,157] two multiple sites,[148,150] and two GI (colon, liver, pancreas).[100,103] Also, some studies did not report adverse events using the RTOG/CTC scale, or stated that investigators and/or patients observed or reported no adverse events. One study of SBRT for renal cell cancer stated that there were no adverse effects of treatment.[131] Table 9 summarizes the reported adverse events for the studies within each cancer type.

Table 9. Summary of adverse events

Cancer Type	Summary of Adverse Events
GI (Colon, Liver, Pancreas)	Severe mucositis, epigastric pain, fatigue, deterioration of hepatic function, abdominal pain, bleeding esophageal varices, gastrointestinal bleeding
Kidney	Fatigue, cough, nausea, vomiting, local pain
Lung/Thorax	Grade 1–4 toxicities, rash, pneumonitis, cough, rib fracture, pneumothorax (fiducial placements), chest wall pain, fatigue, nausea, interstitial lung tissue changes, shortness of breath, dermatitis, pleural effusion, fibrosis
Multiple Sites	Grade 1–4 toxicities, pain, nausea, diarrhea, rectal bleeding
Pelvis, Sacrum, Uterus	Abdominal pain, rectal bleeding, nausea
Prostate	Mild rectal toxicity, urinary toxicity, rectal discomfort, diarrhea, occasional blood, constipation, frequency/nocturia
Thyroid	No grade 3 or higher adverse events

GI: Gastrointestinal

Discussion

This Technical Brief provides a broad overview of the current state of SBRT. Aspects of the brief include current technologies available to deliver SBRT; types and locations of tumors that have been treated with SBRT; the possible advantages and disadvantages of the technology; the extent of diffusion of the technology; and information about advances in the technology that are currently in development. We searched the Internet for gray literature to identify information for cancer sites, theoretical advantages and disadvantages of SBRT, and potential safety issues and harms. Specialized instrumentation for SBRT, the FDA status, technologies in development, and an estimate of the number of hospitals performing SBRT in the United States were also explored using the Internet. The information collected for Guiding Questions 1 and 2 may not be inclusive of all resources. For Guiding Question 3, we performed a systematic search of bibliographic databases, including MEDLINE, EMBASE, and Cochrane. If the literature searches for Guiding Question 3 returned relevant information, we also included it in the first two Guiding Questions. We also searched ClinicalTrials.gov to determine if any trials are currently in progress for SBRT. Appendix K lists the condition being studied, the intervention, study design, primary and secondary outcomes to be measured, estimated enrollment, planned duration, and location of ongoing trials.

The available literature addressing SBRT is considerably large. The bulk of the studies were for tumors located in the lung/thorax (k = 68). We found fewer than 10 studies each for tumors of the pancreas, liver, colon, uterus, pelvis, sacrum, kidney, prostate, and thyroid. This literature base also includes many theoretical treatment-planning studies and treatment technique studies. The study designs identified in our literature search for SBRT treatment included prospective and retrospective single-group studies. There were several studies that included duplicate populations.

Our literature search did not identify any published comparison (whether randomized or nonrandomized) studies. Currently (as of September 2010), there is one ongoing nonrandomized trial comparing two methods of delivering SBRT to conformal radiation for management of NSCLC with a planned enrollment of 120 patients. There are also two ongoing randomized clinical trials comparing SBRT vs. primary resection for lung cancer (see Appendix K, Ongoing Clinical Trials). A third randomized trial is comparing SBRT delivered in one vs. three fractions for NSCLC.

External beam radiation treatment has long been a mainstay of cancer treatment. Advances in this technology have allowed smaller and hard-to-target tumors to be treated; reducing the amount of radiation received by adjacent healthy tissue. SBRT requires accuracy in delivery of the high dose of radiation, patient immobilization, target localization, maneuvers to either limit or compensate for target movement (tracking software), and the use of stereotaxy. It can be completed in one to five fractions and may be a treatment option for patients who refuse surgery, for tumors considered inoperable, or when traditional RT is not an option.

One of the most critical aspects of SBRT is ensuring accurate delivery of the intended dose to the intended target, particularly given the higher dose of radiation typically used. This requires rigorous quality control and quality assurance measures for treatment planning and treatment delivery. Tumor sites within the body tend to move (e.g., respiratory movement) between fractionated treatments, causing difficulties immobilizing the targeted tumor. Therefore, tumor tracking techniques will continue to play an integral role in the procedure. Considerations for selection of appropriate treatment candidates include prior radiation history of the treatment

tissues, treatment volume, organ function, capacity for recovery, number of sites of disease, and many other individual cancer-related factors.[9]

Groups such as the American Association of Physicists in Medicine (AAPM) have urged participation in trials sponsored by the National Cancer Institute (NCI), or in trials run by the NCI-sponsored Radiation Therapy Oncology Group, a multi-institutional research cooperative. In a recent guidance document, AAPM pointed out that protocol-driven treatment in the context of such studies would reflect the guidelines produced by experts in the field (Also available: http://www.aapm.org/pubs/reports/RPT_101.pdf.).[158] Future studies may help to determine the optimal number of radiation fractions, the minimum and maximum dose per fraction, the maximum number and diameter of lesions for various locations, and the radiobiological explanations for the efficacy of SBRT treatment.

Conclusion

In brief, there are many publications on SBRT for the treatment of cancer, principally cancer involving the lung. None of the currently available studies include comparison groups. Comparative studies (preferably randomized trials, but at the least, trials with concurrent controls) are needed to provide convincing evidence that the theoretical advantages of SBRT over other radiotherapies actually occur in the clinical setting. At present, there is only one small ongoing trial making such a comparison. Consequently, a full systematic review of the current literature cannot answer questions on the effectiveness and safety of SBRT compared to other radiotherapy interventions. Two large ongoing trials scheduled for completion in 2013 have the potential to answer questions about the effectiveness and safety of SBRT as compared to surgical resection in resectable early-stage lung cancer.

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Glossary

Biologically Effective Dose (BED)
The dose deposited corrected for variation in biological response.

Collimator
Defines the dimensions and direction of a beam of x-ray radiation, usually by eliminating the peripheral, more divergent part of the x-ray beam.

Fiducial
Markers that help to precisely identify the targeted tumor location. They may be located on a headframe, or surgically implanted for tumor locations throughout the body.

Fractionation
Dividing a prescribed treatment dose into smaller amounts.

Gray (Gy)
A measure of the absorbed radiation dose and equal to the absorption of one joule of energy by one kilogram of matter.

Multi-leaf Collimator (MLC)
A device with individual tungsten leaves that are programmed to moved independently in order to shape the prescribed beam profile to the targeted tumor.

Abbreviations

Abbreviation	Description
2D-CRT	Conventional radiation therapy
3D-CRT	Three-dimensional conformal radiation therapy
AAA	Anisotropic analytical algorithm
AAPM	American Association of Physicists in Medicine
ABC	Active breathing control
ACR	The American College of Radiology
AHA	The American Hospital Association
AHRQ	The Agency for Healthcare Research and Quality
ASTRO	American Society for Radiation Oncology
AVM	Arteriovenous malformation
BED	Biologically effective dose
Bq	Becquerel
CDRH	Center for Devices and Radiological Health
cGY/min	Centigray per minute
cm	Centimeter
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRR	Clinical response rate
CT	Computed tomography
CT/MR	Computer tomography/magnetic resonance
CTC	Common toxicity criteria
DF	Distant failure
DFS	Disease-free survival
DMMLC	Dynamic Micro Multileaf Collimator
DOF	Degrees of freedom
DPFS	Disease progression-free survival
DRR	Digitally reconstructed radiographs
DSS	Disease-specific survival
DVH	Dose volume histogram
EBRT	External beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
FDA	United States Food and Drug Administration
Gy	Gray
HCC	Hepatocellular carcinoma
HD	High definition
hFSRT	Hypofractionated stereotactic radiotherapy
HRQoL	Health-related quality of life
HSBRT	Hypofractionated stereotactic body radiotherapy

Abbreviation	Description
IGRT	Image guided radiation therapy
IHC	Intrahepatic cholangiocarcinoma
IMRT	Intensity modulated radiation therapy
IMSRS	Intensity modulated stereotactic radiosurgery
KPS	Karnofsky Performance Status
kV	Kilovolt
kVp	Peak kilovoltage
LC	Local control
LCR	Local control rate
LED	Light emitting diode
LF	Local failure
linac	Linear accelerator
LP	Local progression
LQ	Linear quadratic model
M	Male
MD	Minimum dose
MEV	Million electron volt
MLC	Multi-leaf collimator
mm	Millimeter
mMLC	micro Multi-leaf collimator
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MU/min	Monitor units per minute
MV	Megavolt
MVCT	Megavoltage computed tomography
NCI-CTC	National Cancer Institute-Common Toxicity Criteria
NR	Not reported
NS	Not specified
NSCLC	Non-small cell lung cancer
NTC	Normal tissue changes
OS	Overall survival
PALN	Para-aortic lymph nodes
PET	Positron emission tomography
PFS	Progression-free survival
PSA	Prostate specific antigen
QA	Quality assurance
QALY	Quality-adjusted life years
QC	Quality control
QoL	Quality of Life
RC	Regional control
RECIST	Response evaluation criteria in solid tumors

Abbreviation	Description
RFA	Radiofrequency ablation
RS	Radiosurgery
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SBF	Stereotactic body frame
SBRT	Stereotactic body radiation therapy
SRS	Stereotactic radiosurgery
SRT	Stereotactic radiotherapy
TACE	Transcatheter arterial chemoembolization
TACI	Transarterial chemoinfusion
VMAT	Volumetric modulated arc therapy
WHO	World Health Organization

Appendix A. Literature Search Methods

A variety of approaches were used to identify relevant information for this report, including searches of peer-reviewed literature, gray literature, and federal regulations.

Part I. This portion of the search report includes searches of bibliographic resources. ECRI Institute's search strategies employ combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategies presented below are in OVID syntax; the searches were simultaneously conducted across EMBASE, MEDLINE, and CINAHL. Parallel strategies based on MeSH headings and keywords were used to search the databases comprising the Cochrane Library.

Electronic Database Searches

The following databases have been searched for relevant information:

Name	Date Limits	Platform/Provider
The Cochrane Central Register of Controlled Trials (CENTRAL)	Through 2010, Issue 3	www.thecochranelibrary.com
The Cochrane Database of Methodology Reviews (Methodology Reviews)	Through 2010, Issue 3	www.thecochranelibrary.com
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Through 2010, Issue 3	www.thecochranelibrary.com
Database of Abstracts of Reviews of Effects (DARE)	Through 2010, Issue 3	www.thecochranelibrary.com
EMBASE (Excerpta Medica)	1980 through December 29, 2010	OVID
Health Technology Assessment Database (HTA)	Through 2010, Issue 3	www.thecochranelibrary.com
MEDLINE	1990 through December 29, 2010	OVID
PreMEDLINE	Searched March 18, 2010	National Library of Medicine
U.K. National Health Service Economic Evaluation Database (NHS EED)	Through 2010, Issue 3	www.thecochranelibrary.com
U.S. National Guideline Clearinghouse™ (NGC)	Searched November 7, 2008	www.ngc.gov

Hand Searches of Journal and Nonjournal Literature

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Nonjournal publications and conference proceedings from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

The search strategies employed combinations of freetext keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. The strategy below is presented in OVID syntax; the search was simultaneously conducted across EMBASE and MEDLINE. A parallel strategy was used to search the databases comprising the Cochrane Library.

Medical Subject Headings (MeSH), EMTREE, PsycINFO and Keywords

Conventions

OVID

$ = truncation character (wildcard)
exp = "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy)
.de. = limit controlled vocabulary heading
.fs. = floating subheading
.hw. = limit to heading word
.md. = type of methodology (PsycINFO)
.mp. = combined search fields (default if no fields are specified)
.pt. = publication type
.ti. = limit to title
.tw. = limit to title and abstract fields

PubMed

[mh] = MeSH heading
[majr] = MeSH heading designated as major topic
[pt] = publication type
[sb] = subset of PubMed database (PreMEDLINE, Systematic, OldMEDLINE)
[sh] = MeSH subheading (qualifiers used in conjunction with MeSH headings)
[tiab] = keyword in title or abstract
[tw] = text word

Topic-Specific Search Terms

Many controlled vocabulary terms and keywords were considered for inclusion in the search strategies. The following table contains an alphabetical listing of terms and keywords grouped by broad concepts. These are the terms and keywords that were actually included in the final search strategies.

Concept	Controlled Vocabulary	Keywords
Cancer	exp neoplasm/ exp neoplasms/	acoustic neuroma$ antibody therap$ biops$ brain$ cranial nerve Da Vinci epileps$ farnesyl transferase inhibitor$ glioma$ gliomastosis hemangiocytoma$ hemangiopericytoma$ herpceptin laparoscop$ mdl medulloblastoma$ meningioma$ neurocytoma$ oligodendroglioma$ pinealoma$ pituitary plesiomorphic robot-assisted tumo?r$ xanthoastrocytoma$
Device		American Radiosurgery Brainlab Cyber knife Cyberknife Cyber-knife Elekta Elekta Axesse ExacTrac Gamma ART 6000 Gamma knife Linac Novalis Perfexion Rotating Gamma System Vertex360 Synchrony Synergy Synergy Trilogy XKnife

Concept	Controlled Vocabulary	Keywords
Radiosurgery	Radiosurgery/ Robotics/ Stereotaxic surgery/ Surgery, computer-assisted/is	hypo fractionated hypofractionated radiosurg* radiosurgery radiotherapy real-time tumor tracking robotic single-dose single-fraction stereotactic stereotaxis

English Embase/Medline

English language, human, remove overlap

Set Number	Concept	Search Statement
1	Device	(Gamma knife or Cyber knife or Cyberknife or Cyber-knife or linac or Novalis or Trilogy or XKnife or Synchrony or Synergy or Elekta or Elekta Axesse or Perfexion or Gamma ART 6000 or American Radiosurgery or Rotating Gamma System Vertex360 or Synergy or ExacTrac or BrainLAB).mp.
2	Radiosurgery	Radiosurgery/ or Robotics/ or Surgery, computer-assisted/is or Stereotaxic surgery/ or real-time tumor tracking.mp. or (robotic and (radiotherapy or radiosurgery)).mp. or (radiosurg* and (stereotactic or stereotaxis or hypo fractionated or hypofractionated or single-fraction or single-dose)).mp.
3	Combine sets	1 or 2
4	Cancer	exp neoplasms/ or exp neoplasm/ or (neoplasm$ or cancer$ or carcinoma$ or adenoma$ or sarcoma$ or tumo?r$).mp.
5	Combine sets	3 and 4
6	Cancer of the brain	(Tumo?r$ adj2 (brain$ or pituitary or cranial nerve)).ti.
7		(Glioma$ or gliomastosis or hemangiocytoma$ or hemangiopericytoma$ or medulloblastoma$ or mdl or meningioma$ or neurocytoma$ or oligodendroglioma$ or pinealoma$ or plesiomorphic xanthoastrocytoma$ or acoustic neuroma$ or epileps$ or herpceptin or robot-assisted or laparoscop$ or antibody therap$ ir farnesyl transferase inhibitor$ or Da Vinci or biops$).ti.
8	Combine sets	6 or 7
9		5 not 8
10	Remove overlap	Remove duplicates from 9

Part 2. The following databases have been searched for relevant information for Guiding Questions 1 and 2.

Name	Date Limits	Platform/Provider
ClinicalTrials.gov	Searched 11/13/08, 09/22/2009, and 03/23/10	www.clinicaltrials.gov
ECRI Institute cross-search	Searched 5/28/2009	www.ecri.org
Lexis-Nexis Major Newspapers	Searched 8/20/08	www.lexis.com
U.S. National Guideline Clearinghouse™ (NGC)	Searched 11/7/08	www.ngc.gov

The following Web sites have been mined for information.

Name	Date Limits	URL
Centers for Medicare and Medicaid Services (CMS)	4/30/2009	www.cms.gov

Appendix B. Included Studies

Studies Included To Address Guiding Question 3

Reference
Chang et al. (2009)[1]
Ahn et al. (2009)[2]
Aluwini et al. (2010)[3]
Aoki et al. (2007)[4]
Baumann et al. (2006)[5]
Baumann et al. (2008)[6]
Beitler et al. (2004)[7]
Bolzicco et al. (2010)[8]
Bradley et al. (2010)[9]
Brown et al. (2007)[10]
Cardenes et al. (2010)[11]
Casamassima et al. (2008)[12]
Chang et al. (2008)[13]
Chawla et al. (2009)[14]
Choi et al. (2008)[15]
Choi et al. (2009)[16]
Collins et al. (2009)[17]
Coon et al. (2008)[18]
Crabtree et al. (2010)[19]
Dawson et al. (2006)[20]
Dunlap et al. (2010)[21]
Ernst-Stecken et al. (2006)[22]
Freeman et al. (2011)[23]
Fritz et al. (2008)[24]
Fuller et al. (2008)[25]
Gerszten et al. (2003)[26]
Goodman et al. (2010)[27]
Grills et al. (2010)[28]
Guckenberger et al. (2007)[29]
Guckenberger et al. (2009)[30]
Guckenberger et al. (2010)[31]
Gunven et al. (2003)[32]

Reference
Haasbeek et al. (2009)[33]
Hamamoto et al. (2010)[34]
Harada et al. (2002)[35]
Henderson et al. (2008)[36]
Hodge et al. (2006)[37]
Hof et al. (2007)[38]
Hof et al. (2007)[39]
Hof et al. (2009)[40]
Hoopes et al. (2007)[41]
Hoyer et al. (2005)[42]
Hoyer et al. (2006)[43]
Ishimori et al. (2004)[44]
Jereczek-Fossa et al. (2008)[45]
Jorcano et al. (2010)[46]
Joyner et al. (2006)[47]
Kang et al. (2010)[48]
Katoh et al. (2008)[49]
Kawase et al. (2009)[50]
Kim et al. (2008)[51]
Kim et al. (2009)[52]
Kim et al. (2010)[53]
Kopek et al. (2009)[54]
Kopek et al. (2010)[55]
Koto et al. (2007)[56]
Kunos et al. (2008)[57]
Lagerwaard et al. (2008)[58]
Le et al. (2006)[59]
Lee et al. (2003)[60]
Lee et al. (2009)[61]
Louis et al. (2010)[62]
Madsen et al. (2007)[63]
Mahadevan et al. (2010)[64]
McCammon et al. (2009)[65]
Milano et al. (2009)[66]
Milano et al. (2009)[67]
Milano et al. (2009)[68]

Reference
Muacevic et al. (2007)[69]
Nakagawa et al. (2000)[70]
Norihisa et al. (2008)[71]
Nuyttens et al. (2006)[72]
Nuyttens et al. (2007)[73]
Oermann et al. (2010)[74]
Olsen et al. (2009)[75]
Onimaru et al. (2008)[76]
Onishi et al. (2004)[77]
Paludan et al. (2006)[78]
Pennathur et al. (2009)[79]
Polistina et al. (2010)[80]
Ponsky et al. (2007)[81]
Ricardi et al. (2007)[82]
Ricardi et al. (2009)[83]
Romero et al. (2006)[84]
Rusthoven et al. (2009)[85]
Rusthoven et al. (2009)[86]
Rusthoven et al. (2009)[87]
Salazar et al. (2008)[88]
Schellenberg et al. (2008)[89]
Scorsetti et al. (2007)[90]
Seo et al. (2010)[91]
Seong et al. (2009)[92]
Shin et al. (2010)[93]
Shioyama et al. (2005)[94]
Sinha et al. (2006)[95]
Son et al. (2010)[96]
Song et al. (2005)[97]
Song et al. (2009)[98]
Stephans et al. (2009)[99]
Stephans et al. (2009)[100]
Stintzing et al. (2010)[101]
Stintzing et al. (2010)[102]
Svedman et al. (2006)[103]
Svedman et al. (2008)[104]

Reference
Takeda et al. (2009)[105]
Takeda et al. (2010)[106]
Teh et al. (2007)[107]
Timmerman et al. (2006)[108]
Timmerman et al. (2010)[109]
Townsend et al. (2010)[110]
Trovo et al. (2010)[111]
Tse et al. (2008)[112]
Uematsu et al. (2001)[113]
Unger et al. (2010)[114]
Vahdat et al. (2010)[115]
Van der Voort van Zyp et al. (2009)[116]
Whyte et al. (2003)[117]
Wulf et al. (2001)[118]
Wulf et al. (2006)[119]
Xia et al. (2006)[120]
Yamashita et al. (2010)[121]
Yang et al. (2010)[122]
Yoon et al. (2006)[123]
Zimmermann et al. (2006)[124]

Appendix C. Excluded Studies

Full Article Excluded Studies

Reference	Exclusion Reason
(2001)[125]	Not relevant
(2002)[126]	Not a clinical study
(2002)[127]	Not relevant
(2003)[128]	Not a clinical study
Abbas et al. (2007)[129]	Not a clinical study
Aboulafia et al. (2007)[130]	Not relevant
Ahn et al. (2000)[131]	Not relevant
Anantham et al. (2007)[132]	Not relevant
Andrews (2007)[133]	Not a clinical study
Andrews et al. (2006)[134]	Not a clinical study
Arimura et al. (2009)[135]	Treatment planning
Armstrong (2001)[136]	Not a clinical study
Asamura (2006)[137]	Not a clinical study
Astrahan (2008)[138]	Not a clinical study
Attia et al. (2005)[139]	Not a clinical study
Auberger et al. (2007)[140]	Not relevant
Baisden et al. (2006)[141]	Treatment planning
Bale and Sweeney (2002)[142]	Not a clinical study
Ball and Withers (2007)[143]	Not a clinical study
Ball D (2008)[144]	Not a clinical study
Bance and Guha (2001)[145]	Not a clinical study
Banki et al. (2009)[146]	Not a clinical study
Barnett et al. (2000)[147]	Not a clinical study
Baser et al. (2000)[148]	Not relevant
Bauman et al. (2006)[149]	Not relevant
Bayouth et al. (2007)[150]	Not a clinical study
Benedict et al. (2008)[151]	Not a clinical study
Bernier et al. (2006)[152]	Not relevant
Bese et al. (2006)[153]	Not a clinical study
Bhatnagar et al. (2002)[154]	Not relevant
Bhatnagar et al. (2009)[155]	Not relevant
Bissonnette et al. (2009)[156]	Treatment planning

Reference	Exclusion Reason
Blute ML (2009)[157]	Not a clinical study
Bogart (2004)[158]	Not a clinical study
Bogart (2006)[159]	Not a clinical study
Bogart (2007)[160]	Not a clinical study
Bourland and Shaw (2003)[161]	Not a clinical study
Bradley (2007)[162]	Not a clinical study
Brenner and Schwade (2007)[163]	Not a clinical study
Bridgewater and Spittle (2000)[164]	Not relevant
Brock (2007)[165]	Not a clinical study
Brock et al. (2008)[166]	Not a clinical study
Buatti et al. (2000)[167]	Not a clinical study
Buatti et al. (2000)[168]	Not relevant
Burton et al. (2002)[169]	Not relevant
Buyyounouski et al. (2010)[170]	Not a clinical study
Cadman (2007)[171]	Treatment planning
Calcerrada Diaz-Santos et al. (2008)[172]	Not a clinical study
Casamassima et al. (2006)[173]	Treatment delivery
Cesaretti et al. (2008)[174]	Not a clinical study
Chang and Adler (2001)[175]	Not a clinical study
Chang and Adler (2001)[176]	Not a clinical study
Chang and Lo (2003)[177]	Not relevant
Chang and Roth (2007)[178]	Not a clinical study
Chang and Saif (2008)[179]	Editorial
Chang and Timmerman (2007)[180]	Not a clinical study
Chang et al. (2007)[181]	Not a clinical study
Chang et al. (2007)[182]	Not a clinical study
Chang et al. (2008)[183]	Not a clinical study
Chang et al. (2009)[184]	Treatment planning
Chen et al. (2007)[185]	Not a clinical study
Cheung et al. (2007)[186]	Treatment planning
Chi et al. (2009)[187]	Not a clinical study
Chin et al. (2001)[188]	Not relevant
Cho et al. (2008)[189]	Not relevant
Chou et al. (2001)[190]	Not a clinical study
Christie et al. (2008)[191]	Not a clinical study
Classen et al. (2003)[192]	Not relevant

Reference	Exclusion Reason
Clifford et al. (2009)[193]	Not relevant
Coker (2003)[194]	Not a clinical study
Collins et al. (2007)[195]	Duplicate population
Colombo et al. (2006)[196]	Not a clinical study
Crane and Willett (2009)[197]	Editorial
Curtis and Teh (2006)[198]	Not relevant
Dahele et al. (2008)[199]	Treatment planning
Dawood (2008)[200]	Not a clinical study
Day (2002)[201]	Not a clinical study
De Mey et al. (2005)[202]	Treatment delivery
De Pooter et al. (2007)[203]	Treatment planning
Decker et al. (2006)[204]	Not a clinical study
Demarco et al. (2002)[205]	Not relevant
Derweesh and Novick (2003)[206]	Not a clinical study
Dilling and Hoffe (2008)[207]	Not a clinical study
Ding et al. (2005)[208]	Not a clinical study
Dinka et al. (2005)[209]	Not a clinical study
Dunlap et al. (2009)[21]	No full article
Dunlap et al. (2010)[210]	Duplicate population
Dvorak et al. (2005)[211]	Not a clinical study
Ebert et al. (2001)[212]	Treatment planning
Edler (2007)[213]	Not relevant
El Hamri et al. (2005)[214]	Not a clinical study
El-Sherif et al. (2005)[215]	Not a clinical study
Ewing et al. (2010)[216]	Treatment planning
Fatigante et al. (2005)[217]	Not relevant
Fenwick et al. (2006)[218]	Not a clinical study
FitzGerald et al. (2006)[219]	Not relevant
Flickinger et al. (2003)[220]	Not a clinical study
Flickinger et al. (2007)[221]	Not a clinical study
Foote et al. (2004)[222]	Not relevant
Fowler JF (2009)[223]	Treatment planning
Friedman and Foote (2000)[224]	Not a clinical study
Fritz et al. (2006)[225]	Treatment delivery
Fuller DB (2009)[226]	Editorial
Fuller et al. (2006)[227]	Treatment delivery

Reference	Exclusion Reason
Fuss (2001)[228]	Not a clinical study
Fuss and Thomas (2004)[229]	Not a clinical study
Fuss et al. (2006)[230]	Treatment planning
Fuss et al. (2007)[231]	Not a clinical study
Galvin and Bednarz (2008)[232]	Quality Assurance
Ganslandt et al. (2003)[233]	Not relevant
Ganz (2002)[234]	Not a clinical study
Ganz (2007)[235]	Not a clinical study
Gasent Blesa and Dawson (2008)[236]	Not a clinical study
Gaspar (2007)[237]	Not a clinical study
Gerber and Chan (2008)[238]	Not a clinical study
Gerrard and Franks (2004)[239]	Not relevant
Gerszten et al. (2006)[240]	Not relevant
Gibbons et al. (2003)[241]	Not relevant
Gibbs (2006)[242]	Not a clinical study
Gibbs and Chang (2003)[243]	Not a clinical study
Gottlieb (2001)[244]	Not relevant
Gottlieb (2001)[245]	Not a clinical study
Grills et al. (2007)[246]	Treatment planning
Gross and Engenhart-Cabillic (2002)[247]	Not a clinical study
Gross et al. (2003)[248]	Treatment delivery
Grutters et al. (2010)[249]	Not a clinical study
Guckenberger et al. (2006)[250]	Treatment planning
Guckenberger et al. (2007)[251]	Treatment delivery
Guckenberger et al. (2009)[252]	Treatment planning
Guckenberger et al. (2009)[253]	Treatment planning
Guckenberger et al. (2010)[254]	Treatment planning
Guerrero and Li (2004)[255]	Treatment planning
Hadinger et al. (2002)[256]	Treatment planning
Haedinger et al. (2005)[257]	Treatment planning
Hansen et al. (2006)[258]	Treatment delivery
Hara et al. (2007)[259]	Not a clinical study
Heinzerling et al. (2008)[260]	Treatment delivery
Herbert et al. (2003)[261]	Treatment delivery
Hermann et al. (2004)[262]	Not a clinical study
Heron et al. (2003)[263]	Not a clinical study

Reference	Exclusion Reason
Heron et al. (2009)[264]	Not relevant
Heros (2005)[265]	Not a clinical study
Hevezi (2003)[266]	Not a clinical study
Hevezi et al. (2010)[267]	Not a clinical study
Hinson et al. (2007)[268]	Treatment delivery
Hiraoka et al. (2007)[269]	Not a clinical study
Hocht et al. (2005)[270]	Treatment planning
Hogle (2006)[271]	Not a clinical study
Hoh et al. (2007)[272]	Not a clinical study
Holland (2001)[273]	Not a clinical study
Holmes et al. (2008)[274]	Not a clinical study
Hoogeman et al. (2008)[275]	Treatment delivery
Hoogeman et al. (2009)[276]	Treatment delivery
Horstmann et al. (2000)[277]	Not relevant
Hui et al. (2004)[278]	Not relevant
Huntzinger et al. (2007)[279]	Not a clinical study
Imura et al. (2005)[280]	Treatment delivery
Imura et al. (2008)[281]	Treatment delivery
Inoue et al. (2010)[282]	Not relevant
Isaksson et al. (2005)[283]	Not relevant
Jaffray et al. (2007)[284]	Not a clinical study
Jamal et al. (2008)[285]	Not a clinical study
Jawahar et al. (2004)[286]	Not relevant
Jeremic et al. (2000)[287]	Not relevant
Jin et al. (2005)[288]	Treatment planning
Jin et al. (2009)[289]	Treatment planning
Joensuu et al. (2000)[290]	Not a clinical study
Jozsef et al. (2000)[291]	Treatment planning
Kassaee et al. (2003)[292]	Treatment delivery
Katz et al. (2007)[293]	Duplicate population
Kavanagh and Timmerman (2006)[294]	Not a clinical study
Kavanagh et al. (2003)[295]	Not a clinical study
Kavanagh et al. (2006)[296]	Duplicate population
Kavanagh et al. (2007)[297]	Not a clinical study
Kavanagh et al. (2007)[298]	Not a clinical study
Kavanagh et al. (2008)[299]	Not a clinical study

Reference	Exclusion Reason
Kawaguchi et al. (2004)[300]	Less than 3 patients
Kelly (2000)[301]	Not a clinical study
Kenai et al. (2005)[302]	Treatment planning
King et al. (2003)[303]	Treatment delivery
King et al. (2008)[304]	Duplicate population
King et al. (2009)[305]	Duplicate population
King et al. (2009)[306]	Editorial
Kitamura et al. (2002)[307]	Not relevant
Kitamura et al. (2002)[308]	Not relevant
Kitamura et al. (2003)[309]	Treatment delivery
Koga et al. (2009)[310]	Not relevant
Kommu et al. (2006)[311]	Not relevant
Kondziolka et al. (2000)[312]	Not a clinical study
Kondziolka et al. (2004)[313]	Not a clinical study
Kondziolka et al. (2005)[314]	Not a clinical study
Kondziolka et al. (2007)[315]	Not a clinical study
Kontrisova et al. (2006)[316]	Treatment planning
Koong et al. (2004)[317]	Duplicate population
Koong et al. (2005)[318]	Duplicate population
Kopek et al. (2010)[319]	Duplicate population
Korreman et al. (2006)[320]	Treatment planning
Kresl (2006)[321]	Not a clinical study
Kunieda et al. (2004)[322]	Treatment planning
Kunieda et al. (2008)[323]	Treatment delivery
Kunzler et al. (2007)[324]	Treatment delivery
Kupferman and Hanna (2008)[325]	Not a clinical study
Laigle-Donadey et al. (2005)[326]	Not relevant
Langner et al. (2009[327]	Treatment delivery
Larre et al. (2007)[328]	Not relevant
Lartigau et al. (2009)[329]	Not a clinical study
Lawson et al. (2009)[330]	Treatment planning
Lax et al. (2006)[331]	Treatment planning
Leavitt et al. (2001)[332]	Treatment delivery
Lee et al. (2000)[333]	Treatment planning
Lee WR (2009)[334]	Not a clinical study
Leskell (2007)[335]	Not a clinical study

Reference	Exclusion Reason
Li and Ma (2005)[336]	Treatment planning
Liao et al. (2000)[337]	Treatment planning
Lillard (2008)[338]	Not a clinical study
Lind et al. (2001)[339]	Not relevant
Lindquist and Paddick (2007)[340]	Not relevant
Lindvall et al. (2008)[341]	Not relevant
Linskey and Johnstone (2003)[342]	Not a clinical study
Linthout et al. (2009)[343]	Treatment delivery
Liu et al. (2004)[344]	Treatment planning
Livi et al. (2005)[345]	Not relevant
Lo et al. (2008)[346]	Not a clinical study
Lo et al. (2009)[347]	Not a clinical study
Lomax et al. (2003)[348]	Treatment planning
Lu et al. (2008)[349]	Treatment planning
Ma et al. (2003)[350]	Not relevant
Maarouf et al. (2005)[351]	Not relevant
Macdermed et al. (2008)[352]	Not a clinical study
Martin and Gaya (2010)[353]	Not a clinical study
Matsumoto et al. (2007)[354]	Not relevant
McDermott et al. (2006)[355]	Not relevant
McGarry et al. (2005)[356]	Duplicate population
Meeks et al. (2003)[357]	Treatment delivery
Mell and Mundt (2005)[358]	Not relevant
Meretoja et al. (2008)[359]	Not relevant
Mery et al. (2007)[360]	Not a clinical study
Meyer et al. (2007)[361]	Not a clinical study
Meyer et al. (2007)[362]	Treatment planning
Mignano et al. (2001)[363]	Treatment planning
Minn et al. (2009)[364]	Treatment planning
Molla et al. (2005)[365]	Duplicate population
Morgia and De (2009)[366]	Editorial
Muacevic et al. (2003)[367]	Not relevant
Muacevic et al. (2004)[368]	Not a clinical study
Muller et al. (2004)[369]	Treatment delivery
Murphy (2004)[370]	Not a clinical study
Murphy et al. (2002)[371]	Treatment delivery

Reference	Exclusion Reason
Murphy et al. (2003)[372]	Treatment delivery
Murphy MJ (2009)[373]	Treatment planning
Murray et al. (2007)[374]	Treatment delivery
Naff (2007)[375]	Not relevant
Nagata et al. (2007)[376]	Not a clinical study
Nakagawa et al. (2003)[377]	Treatment planning
Nakaji and Spetzler (2004)[378]	Not relevant
Nakamura et al. (2001)[379]	Treatment planning
Nedzi LA (2008)[380]	Not a clinical study
Nguyen et al. (2008)[381]	Not a clinical study
Nieder et al. (2009)[382]	Not a clinical study
Niranjan and Lunsford (2000)[383]	Not a clinical study
Niranjan et al. (2003)[384]	Not a clinical study
Niranjan et al. (2007)[385]	Not a clinical study
Niranjan et al. (2007)[386]	Not a clinical study
No Authors Listed (2003)[387]	Not relevant
No authors listed (2006)[388]	Not a clinical study
No Authors Listed (2007)[389]	Not relevant
No Authors Listed (2007)[390]	Not relevant
Noda et al. (2009)[391]	Not relevant
Okunieff et al. (2006)[392]	Duplicate population
Onishi et al. (2003)[393]	Treatment delivery
Orecchia (2007)[394]	Not a clinical study
Pan et al. (2007)[395]	Treatment delivery
Pang (2003)[396]	Not a clinical study
Papiez and Timmerman (2008)[397]	Not a clinical study
Papiez et al. (2003)[398]	Not a clinical study
Park et al. (2008)[399]	Treatment planning
Parman (2004)[400]	Not a clinical study
Pass H (2008)[401]	Not a clinical study
Pawlicki et al. (2007)[402]	Not a clinical study
Pennathur et al. (2007)[403]	Duplicate population
Petersch et al. (2004)[404]	Treatment delivery
Petrovich and Yu (2003)[405]	Not relevant
Pishvaian et al. (2006)[406]	Treatment delivery
Polina et al. (2010)[407]	Not a clinical study

Reference	Exclusion Reason
Poll et al. (2008)[408]	Not a clinical study
Pollock (2006)[409]	Not a clinical study
Pott et al. (2005)[410]	Not relevant
Potters et al. (2005)[411]	Not a clinical study
Prabhu and Demonte (2003)[412]	Not relevant
Prevost et al. (2008)[413]	Treatment delivery
Prevost et al. (2008)[414]	Treatment planning
Purdie et al. (2006)[415]	Treatment delivery
Quang et al. (2007)[416]	Not a clinical study
Quinn (2002)[417]	Not a clinical study
Rassiah-Szegedi et al. (2006)[418]	Treatment planning
Ratto et al. (2000)[419]	Not relevant
Regine (2003)[420]	Not a clinical study
Regis et al. (2009)[421]	Not relevant
Riboldi et al. (2006)[422]	Treatment planning
Rock et al. (2004)[423]	Not a clinical study
Rockhill (2007)[424]	Not a clinical study
Romanelli et al. (2003)[425]	Not a clinical study
Romanelli et al. (2006)[426]	Not a clinical study
Romanelli et al. (2006)[427]	Not relevant
Rosahl et al. (2002)[428]	Not a clinical study
Rosenzweig et al. (2003)[429]	Not a clinical study
Rosenzweig et al. (2009)[430]	Not a clinical study
Rousseau and Gibon (2000)[431]	Not a clinical study
Rutten and Deneufbourg (2000)[432]	Not relevant
Ryken et al. (2001)[433]	Treatment delivery
Samper et al. (2006)[434]	Not relevant
Sankaranarayanan et al. (2003)[435]	Treatment planning
Sarfaraz et al. (2007)[436]	Not a clinical study
Sasai et al. (2000)[437]	Treatment planning
Saunders (2007)[438]	Not a clinical study
Savides (2006)[439]	Not a clinical study
Saw et al. (2008)[440]	Not a clinical study
Sawrie et al. (2010)[441]	Not a clinical study
Schefter et al. (2005)[442]	Duplicate population
Scheib et al. (2004)[443]	Not relevant

Reference	Exclusion Reason
Schellenberg et al. (2010)[444]	Duplicate population
Schlaefer et al. (2005)[445]	Treatment planning
Schweikard et al. (2000)[446]	Treatment delivery
Schweikard et al. (2004)[447]	Treatment delivery
Scorsetti and Bignardi (2008)[448]	Not a clinical study
Seki et al. (2007)[449]	Treatment planning
Senan et al. (2007)[450]	Not a clinical study
Seppenwoolde et al. (2002)[451]	Treatment delivery
Sharma et al. (2010)[452]	Not relevant
Shepard et al. (2000)[453]	Treatment planning
Sherwood and Brock (2007)[454]	Not a clinical study
Shibuya and Tsujii (2005)[455]	Not relevant
Shirato et al. (2003)[456]	Not relevant
Shirato et al. (2006)[457]	Not a clinical study
Shirato et al. (2007)[458]	Not a clinical study
Shiu et al. (2003)[459]	Treatment delivery
Shoshan et al. (2005)[460]	Not a clinical study
Shrieve et al. (2004)[461]	Not a clinical study
Siddiqui et al. (2009)[462]	Not relevant
Silvano (2006)[463]	Not a clinical study
Singletary (2001)[464]	Not relevant
Siva et al. (2010)[465]	Not a clinical study
Slotman et al. (2005)[466]	Not relevant
Slotman et al. (2006)[467]	Not a clinical study
Smink and Schneider et al. (2008)[468]	Not a clinical study
Smit (2000)[469]	Not a clinical study
Smith and Chuang (2007)[470]	Not a clinical study
Snell et al. (2006)[471]	Treatment planning
Soete et al. (2006)[472]	Treatment planning
Solberg et al. (2001)[473]	Treatment planning
Solberg et al. (2004)[474]	Not relevant
Solberg et al. (2008)[475]	Quality Assurance
Solberg et al. (2008)[476]	Not a clinical study
Song et al.(no year)[477]	Not a clinical study
Sonke et al. (2009)[478]	Treatment delivery
Sotiropoulou et al. (2009)[479]	Not relevant

Reference	Exclusion Reason
Spadea et al. (2008)[480]	Treatment delivery
St. George et al. (2002)[481]	Not relevant
Stancanello et al. (2005)[482]	Treatment planning
Steinke (2006)[483]	Not relevant
Sterzing et al. (2007)[484]	Not relevant
Sterzing et al. (2008)[485]	Not relevant
Storme et al. (2006)[486]	Not a clinical study
Strassmann et al. (2004)[487]	Treatment planning
Strassmann et al. (2006)[488]	Treatment delivery
Suzuki et al. (2007)[489]	Treatment delivery
Taguchi et al. (2007)[490]	Treatment delivery
Takayama et al. (2005)[491]	Treatment planning
Takeda et al. (2005)[492]	Treatment planning
Takeda et al. (2008)[493]	Duplicate population
Takeda et al. (2009)[494]	Treatment planning
Takeuchi et al. (2003)[495]	Treatment delivery
Teh et al. (2007)[496]	Not a clinical study
Theil and Winfield (2008)[497]	Not a clinical study
Theodorou et al. (2000)[498]	Treatment planning
Theodorou et al. (no year)[499]	Not a clinical study
Thieke et al. (2006)[500]	Treatment planning
Timmerman et al. (2003)[501]	Duplicate population
Timmerman et al. (2003)[502]	Not a clinical study
Timmerman et al. (2006)[503]	Not a clinical study
Timmerman et al. (2007)[504]	Not a clinical study
Timmerman et al. (2007)[505]	Treatment planning
Timmerman et al. (2007)[506]	Not a clinical study
Timmerman et al. (2007)[507]	Not a clinical study
Timmerman et al. (2009)[508]	Not a clinical study
Tobler et al. (2004)[509]	Treatment planning
Tonn (2004)[510]	Not a clinical study
Tsai et al. (2001)[511]	Treatment planning
Uematsu et al. (2000)[512]	No relevant outcomes
Underberg et al. (2005)[513]	Treatment delivery
Underberg et al. (2006)[514]	Treatment delivery
Vaidya et al. (2002)[515]	Not relevant

Reference	Exclusion Reason
Van Houtte (2003)[516]	Not a clinical study
Van Der Voort Van Zyp et al. (2010)[517]	Duplicate population
Varga et al. (2009)[518]	Not a clinical study
Vassiliev et al. (2009)[519]	Treatment planning
Verbakel et al. (2009)[520]	Treatment delivery
Verellen et al. (2006)[521]	Treatment planning
Videtic et al. (2010)[522]	Duplicate population
Voynov et al. (2006)[523]	Not relevant
Vricella et al. (2009)[524]	Not a clinical study
Wagner et al. (2003)[525]	Treatment planning
Wagner et al. (2007)[526]	Not a clinical study
Wakelee et al. (2008)[527]	Not a clinical study
Wakisaka et al. (2000)[528]	Treatment planning
Wallen (2006)[529]	Not a clinical study
Wiegner and King (2010)[530]	No full article
Willoughby et al. (2006)[531]	Not relevant
Wilt et al. (2008)[532]	Not relevant
Wu et al. (2003)[533]	Treatment planning
Wu et al. (2008)[534]	Treatment delivery
Wu et al. (2009)[535]	Treatment planning
Wulf et al. (2004)[536]	Duplicate population
Wunderink et al. (2007)[537]	Treatment planning
Wurm et al. (2006)[538]	Not relevant
Xiao et al. (2009)[539]	Treatment delivery
Yaeger T.E. (2009)[540]	Editorial
Yin et al. (2004)[541]	Treatment delivery
Yin et al. (2008)[542]	Treatment delivery
Yousefi et al. (2007)[543]	Treatment delivery
Yu and Shepard (2003)[544]	Not a clinical study
Zamzuri et al. (2006)[545]	Not relevant
Zimmermann et al. (2010)[546]	Not a clinical study

Appendix D. Personnel Qualifications

Personnel Qualifications for Stereotactic Body Radiation Therapy

	Radiation Oncologist	Medical Physicists	Radiation Therapist
Qualifications	✓ Certified in radiology, radiation oncology, or therapeutic radiology **OR** ✓ Satisfactory completion in an approved residency program ✓ Specific training on extracranial SRS	✓ Certified in therapeutic radiological physics or radiological physics ✓ Should be in accordance with the ACR Practice Guideline for Continuing Medical Education ✓ Specific training in SRS should be obtained prior to performing any SBRT procedures	✓ Fulfill state licensing requirements ✓ Certified in radiation therapy
Responsibilities	✓ Manage overall disease-specific treatment regimen ✓ Recommend most ideal patient-positioning method ✓ Recommend procedure to account for inherent organ motion ✓ Supervise patient simulation; contour the outline of the gross tumor volume (GTV) on the treatment planning computer ✓ Coordinate design for proper planning target volume (PTV) ✓ Convey case-specific expectations for prescribing radiation dose and setting limits on dose to adjacent normal tissues ✓ Attend and direct actual treatment process ✓ Follow patient with attention to disease control ✓ Monitoring and treating potential complications	✓ Acceptance testing and commissioning of SBRT system ✓ Implementing and managing a QC program ✓ Establishing a comprehensive QC checklist ✓ Directly supervising or checking the 3D and/or intensity-modulated treatment planning process ✓ Consulting with radiation oncologist to discuss optimal patient plan ✓ Determine and check appropriate beam-delivery parameters (calculation of radiation beam parameters consistent with beam geometry) ✓ Double-checking beam delivery process to assure accurate fulfillment of prescription	✓ Preparing treatment room ✓ Assisting the treatment team with positioning/immobilization ✓ Operating treatment unit after radiation oncologist & medical physicists approved clinical technical aspects for beam delivery

Information derived from the American College of Radiology Practice Guideline 2006[547]
SBRT: Stereotactic body radiotherapy
SRS: Stereotactic radiosurgery
QC: Quality control

Appendix E. Recommendations

Recommendations for Stereotactic Body Radiation Therapy Procedures

Procedure Specifications	Accessory QC	Images QC	Treatment Planning QC	Simulation and Treatment	Followup
✓ Treatment-delivery unit requires implementation of/adherence to QA program ✓ Mechanical tolerance must assure actual isocenter is within +/- 2 mm of planned isocenter ✓ Precision should be validated each treatment session by QA process ✓ QA: test beam alignment, calculate dose per unit time, measure MLC movement, measure gantry radiation fluence map for intensity modulated)	✓ Routinely monitor to assure proper function	✓ Digital images thoroughly investigated and corrected for significant spatial distortions ✓ Combining MRI with CT image fusion used to minimize geometrical distortions in MR images	✓ Various testing methods used with equal validity ✓ Maintain system log ✓ Check functionality and accuracy of input devices ✓ Assure functionality and accuracy of output devices ✓ Assure integrity of planning system files ✓ Verify transfer of MLC data and other parameters ✓ Assure system integrity of anatomical modeling ✓ Operational test before treating patients	✓ Comfortable position for the patient to "hold still" during treatment ✓ Respiratory motion accounting program ✓ Minimize the volume of surrounding normal tissues exposed to high dose levels ✓ Validate precision QC process with each treatment session and throughout the treatment process	✓ Maintenance of appropriate records ✓ Determine local control, survival, and normal tissue injury

Information derived from the American College of Radiology Practice Guideline 2006[547]

CT: Computed tomography
MLC: Multi-leaf collimator
MR: Magnetic resonance
MRI: Magnetic resonance imaging
QA: Quality assurance
QC: Quality control

Appendix F. Currently Marketed Devices for SBRT

Devices Currently Marketed for Stereotactic Body Radiation Therapy

Device Name	Manufacturer/ Distributor	Features	Dedicated to SRS	FDA Indication	Extracranial Indications Presented on Company Web site
Axesse™	Elekta	✓ Beam delivery – wide range of noncoplanar angles ✓ Beam energy – multiple energy (photon) ✓ Collimation – MLC ✓ Design – image-guided robotic linac that combines high-conformance beam shaping with 4D Adaptive™ IGRT technology ✓ Dose delivery – multiple energy choices ✓ Imaging – CT/MR imaging with patient in immobilization (no fiducials necessary) ✓ Patient Positioning/Localization – BodyFIX dual vacuum-activated immobilization and fixation system; automatic reposition in up to 6 degrees of freedom ✓ Treatment Sessions – single and fractionated	No	No response from FDA or manufacturer	Spinal metastases, lung, liver, prostate, head, neck

Device Name	Manufacturer/ Distributor	Features	Dedicated to SRS	FDA Indication	Extracranial Indications Presented on Company Web site
CyberKnife® robotic radiosurgery system	Accuray Incorporated	✓ Beam delivery – noncoplanar and nonisocentric; anterior beam delivery ✓ Beam energy – 6 MV nominal (photon) ✓ Collimation – 12 fixed apertures; Xchange™ Robotic Collimator Changer automatically exchanges collimators ✓ Design – a treatment radiation generator, linear accelerator, manipulator (robot) with six degrees of freedom, and a target locating subsystem ✓ Dose delivery – A 6 MV X-band linac ✓ Field size – determined by the use of interchangeable secondary circular cones with diameters ranging from 5.0 to 60.0 mm ✓ Imaging – continuously delivers imaging to ensure target accuracy throughout the entire treatment; InTempo™ Adaptive Imaging System tracks and corrects for intra-fraction prostate motion ✓ Output – available at 800 MU/min at 80 cm, 600 MU/min, and 400 Mu/min ✓ Patient Positioning/Localization – only radiosurgery system to move to and with the patient; room-based stereo x-ray with 2D kV-kV match ✓ Tracking – Fiducial tracking, Xsight™ Spine Tracking, Xsight™ Lung Tracking, and Synchrony™ Respiratory Tracking for dynamic positioning and pointing of the linac ✓ Treatment Sessions – single and fractionated	Yes	Treatment planning and image-guided SRS and precision RT for lesions, tumors and conditions anywhere in the body	Spine, lung, liver, prostate, pancreas, kidney, head, neck

Device Name	Manufacturer/ Distributor	Features	Dedicated to SRS	FDA Indication	Extracranial Indications Presented on Company Web site
Leksell Gamma Knife® Perfexion™	Elekta Inc.	✓ Beam delivery – 192 cobalt-60 sources housed in the central body of the unit produce 192 collimated beams directed to a single focal point (isocenter) ✓ Collimation – 4,8, 16 mm diameter ✓ Design – a radiation unit with patient-positioning system and an operator console ✓ Dose delivery – multiple converging fixed beams of ionizing radiation ✓ Imaging – MRI/CT prior to treatment ✓ Output – >3 Gy/min ✓ Patient Fixation – head fixated in the Leksell® Stereotactic Frame. Awaiting approval on re-locatable frame. ✓ Total cobalt-60 activity at loading (approximate) – <6,300 Curie (2.33 x 10^{14} Bq) ✓ Treatment Sessions – single with availability of fractionated upon approval of Extend™ program	No	Metastatic tumors, and head structure targets (a few millimeters to several centimeters)	Cervical spine, head, neck, larynx tumors
MHI-TM2000 Linear Accelerator System	Mitsubishi Heavy Industries (MHI)	✓ Beam delivery – Gimballed x-ray irradiation offers tilt and pan-rotation functions enabling fine adjustments in any direction ✓ Collimation – MLC ✓ Design – O-ring-shaped mechanical structure provides a high level of rigidity; X-ray generator incorporates a compact accelerator tube ✓ Image Processing System – ExacTrac 3rd Party by BrainLAB (K072046 approved by FDA on 8/07) ✓ Treatment Sessions – single and fractionated	No	Radiation therapy of lesions, tumors and conditions anywhere in the body	NR

Device Name	Manufacturer/ Distributor	Features	Dedicated to SRS	FDA Indication	Extracranial Indications Presented on Company Web site
Novalis TX™	BrainLAB/Varian Medical Systems	✓ Accuracy - millimeter precision utilizing BrainLAB's iPlan and ExacTrac technologies ✓ Beam delivery – fixed beam positions and continuous arc delivery with RapidArc; anterior beam delivery and full 180 degree posterior beams ✓ Beam energy – 6-20 MV/6-20MEV ✓ Collimation –Varian's HD120 MLC 120 interleaved ultra thin collimators provides 2.5 mm collimation at isocenter and 5.0 mm collimations at the periphery. ✓ Design – includes Adaptive Gating and On-Board Imager devices ✓ Field size – 22 x 40 cm maximum ✓ Imaging – ExacTrac and x-ray 6D and Snap Verification ✓ Output – 1,000 MU at 100 cm ✓ Patient positioning/localization – 6D Robotic couch top, Varian Exact® couch ✓ Treatment Sessions – single and fractionated	Yes	The Varian High Energy linear accelerator is intended to provide SRS and precision RT for lesions, tumors and conditions anywhere in the body	Spine, lung, liver, prostate, head, neck

Device Name	Manufacturer/ Distributor	Features	Dedicated to SRS	FDA Indication	Extracranial Indications Presented on Company Web site
Oncor ARTISTE, Impression, Avant-Garde, Expression	Siemens	**Artiste** ✓ Beam energy – 6 MV (photon) ✓ Collimation – 160 leaf MLC ✓ Design – includes an Electronic Portal Imaging Device (EPID), a 160 leaf MLC, and the syngo™ RT Therapist Express Workspace with MVision™ ✓ Imaging – OPTIVUE 1000ART amorphous silicon (a-Si) portal imaging system ✓ Patient-positioning verification – use of the OPTIVUE imaging system, including MVision™ Megavoltage Cone Beam (MVCB) Imaging and/or CTVision ✓ Respiratory Gating – ANZAI breathing belt system **Impression/Avant-Garde/Expression** ✓ Beam energy – 6/10 MV photon/ 6-21 MeV ✓ Collimation – OPTIFOCUS 82 leaf MLC (static and dynamic modes) ✓ Field size – 40 cm x 40 cm fully-conformal ✓ Imaging OPTIVUE 1000/ST electronic portal imaging device (EPID) and MVision™ megavoltage cone beam on-board imaging ✓ Output – 200-500 MU/min, special configuration-1,000 MU/min for maximum 5 x 5 cm field (Avant-Garde); 200-300 MU/min, special configuration-500 MU/min for maximum 5 x 5 field ✓ Patient position localization and setup – Adaptive Targeting™ supports alignment of 3D planning data with newly acquired 3D Cone Beam data ✓ Respiratory Gating – standard on Avant-Garde/ optional on Impression	No	The delivery of x-ray radiation for therapeutic treatment of cancer.	Head, neck, extracranial areas

Device Name	Manufacturer/ Distributor	Features	Dedicated to SRS	FDA Indication	Extracranial Indications Presented on Company Web site
Synergy®S	Elekta Inc.	✓ Beam delivery – a 62 cm treatment head in combination with industry best isocenter clearance allows for a wide variety of treatment approaches including noncoplanar ✓ Beam energy – 4, 6, 10, 15, 18, and 25 MV photon; 6, 9, 12, 15, 18, and 25 MeV ✓ Collimation – Beam Modulator, an integrated high-resolution, multi-leaf collimator designed for extracranial SRS ✓ Dose delivery system – includes an integrated multi-leaf collimator ✓ Field size – 16 cm x 21 cm ✓ Imaging – 4D Adaptive™ IGRT technology ✓ Patient positioning/localization – BodyFix® and HeadFix® immobilization accessories ✓ Treatment Sessions – single and fractionated	No	Radiation therapy treatment of malignant neoplastic diseases	Spine, lung, liver, prostate, pancreas, head, neck
TomoTherapy® Hi-Art®	TomoTherapy Inc.	✓ Accuracy – beam modulating technology that divides a single beam into “beamlets” to better conform to tumors ✓ Beam delivery – 360 degree ✓ Beam energy – 6 MV (photon) ✓ Collimation – 64 leaf MLC ✓ Design – linac mounted to a CT scanner-like ring gantry ✓ Field size – 40 cm x 1.6 meters maximum ✓ Imaging – integrated, 3D daily CTrue™ imaging ✓ Output – 850 cGy/min (photon)* ✓ Patient positioning/localization – AlignRT® (consisting of 2 ceiling-mounted 3D camera units) registers real-time image data and subsequently updates couch coordinates. Complements CTrue™ imaging when tumor is deep-seated or can move internally w/o external evidence ✓ Treatment Sessions – single and fractionated	No	To tumors or other targeted tissues	Lung, liver, prostate, head, neck

Device Name	Manufacturer/ Distributor	Features	Dedicated to SRS	FDA Indication	Extracranial Indications Presented on Company Web site
Trilogy™	Varian Medical Systems	✓ Accuracy – beam modulating technology that divides a single beam into "beamlets" to better conform to tumors ✓ Beam delivery – choice of Intensity modulated radiosurgery (IM-RS) with multi-leaf collimation – for lesions >2.5 cm, irregular shaped and >3 lesions **OR** Cone-based SRS for lesions <2.5 cm, not irregular and 1-3 lesions ✓ Beam energy – 6 MV (photon)/4-22 MeV (6 energies) ✓ Collimation – 120 leaf MLC and conical collimator ✓ Design – external system gating interface, remote couch motion ✓ Field size – 15 cm x 15 cm ✓ Imaging – PortalVision MV imager, On-Board kV Imager (amorphous silicon detector-based radiographic, fluoro and cone-beam CT). ✓ Output – 1,000 MU/min (photon and electron) ✓ Patient position/localization – optional optical imaging-based patient positioning (FrameArray, BodyArray, and SonArray) ✓ Respiratory Gating – Real-time Position Management™ (RPM) System ✓ Treatment Sessions – single and fractionated	No	Lesions, tumors and conditions anywhere in the body	Whole body

*Data derived from[548]

AVM: Arteriovenous malformation
Bq: Becquerel
cGY/min: Centigray per minute
cm: Centimeter
CT/MR: Computed tomography/magnetic resonance
FDA: United States Food and Drug Administration
IGRT: Image guided radiation therapy
kV: Kilovolt
Linac: Linear accelerator
MEV: Million electron volt
MLC: Multi-leaf collimator
mm: Millimeter
MU/min: Monitor units per minute
MV: Megavolt
NR: Not reported
RS: Radiosurgery
RT: Radiotherapy
SRS: Stereotactic radiosurgery
SRT: Stereotactic radiotherapy

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Appendix G. Linac-Based SBRT Accessories

Linac Accessories

Device Name	Manufacturer/ Distributor	Description	Dedicated to SRS	FDA Indications	Indications Presented on Company Web site	Compatibility
AccuChanger	Direx Systems Corporated	A linac-mounted, computer-controlled, fully automated collimator changer for multi arc or step-and-shoot cone based SRS. A unique fixed arrangement of multi-sized taped tungsten cones provides for fast and precise changing and positioning of the collimators. The available 16 circular fields, with diameters in the range of 4 mm to 34 mm in 2 mm steps, enable sharp radiosurgical delivery.	Yes	Collimation of megavoltage photon beams in conjunction with SRS and SRT treatments.	NR	Various linacs
AccuLeaf	Direx Systems Corporated	A computer controlled, video-guided micro multi-leaf collimator (MMLC). A unique two-level perpendicular leaf configuration, with a field size of approximately 100 mm x 110 mm, reduces effective leaf thickness and achieves a higher resolution, low leakage collimator for both conformal shaping and IMRT/IMSRS delivery.	No	Enables irregular field's treatments to be performed with finely shaped patterns; performs the same function as customized beam shaping blocks, and circular or cut blocks collimators.	NR	Various linacs

Device Name	Manufacturer/ Distributor	Description	Dedicated to SRS	FDA Indications	Indications Presented on Company Web site	Compatibility
Beam Modulator™	Elekta Inc.	Integrated multi-leaf collimator with a generous 16 x 21 cm field size. The field comprises 80 individually controlled leaves, each with a travel range of more than 21 cm. Because opposing leaves can pass each other (interdigitate), clinicians can create a range of finely shaped, high-resolution fields simultaneously within one field. This contributes to improved conformal avoidance of critical structures. The integrated design means no compromise in clearance for conventional and noncoplanar beams.	No	X-ray collimator, used with the Elekta range of medical linacs; intended to assist a licensed practitioner in the delivery of radiation in single or multiple fractions to defined target volumes anywhere in the body (e.g., lesions, AVMs, malignant and benign tumors) sparing surrounding normal tissue and critical organs from excess radiation.	NR	Elekta linacs
Dynamic Micro Multileaf Collimator (DMMLC)	Elekta Inc.	3 dynamic micro multileaf add-on collimators: a 3 mm, 5 mm and 7 mm leaf width (at isocenter) and 7x7, 10x12, and 10x17 field size (at isocenter) respectively. All options offer the facility for dynamic treatments and the improved homogeneity in target shaping, including minimizing dose to critical organs. The 3 mm and 5 mm DMMLCs are certified for use up to 18 MV making it an extremely versatile tool for SRT and SRS. To optimize beam shaping provided by the Elekta add on DMMLC, the leaves have been designed to be dual focused, minimizing and homogenizing the penumbra. Leakage and unwanted dose outside the target area is limited by the unique design of the leaves and the 8 cm leaf height.	No	Indicated for use when additional flexibility is required in conforming the radiation beam to the anatomy to be exposed.	NR	Elekta and a range of linacs from other vendors

Device Name	Manufacturer/ Distributor	Description	Dedicated to SRS	FDA Indications	Indications Presented on Company Web site	Compatibility
HD 120 MLC	Varian Medical Systems	HD120 provides 120 interleaved leaves: 64 – 2.5 mm centrally located 56 – 5 mm peripherally with a fixed treatment field of 22 cm x 40 cm and a modulated field of 22 cm x 32 cm., Output – 1,000 MU/min at 100 cm. Options: Gating – Real Time Position Management; Aria.	No	Target volumes during RS and RT		Varian's Trilogy
m3® (micro-Multileaf Collimator)	BrainLAB AG	The m^3 is a therapeutic collimator. It comprises multiple motorized tungsten leafs, which are suited to shaping specific therapeutic X-ray fields, both in a static fashion as well as dynamically via leaf-movement during treatment.	No	In conjunction with Elekta and GE Linacs, the m^3 performs with same function as customized shadow blocks or stereotactic collimators. This standard configuration is suitable for static conformal treatments and "step and shoot IMRT". The advanced m^3 Siemens integration feature available for Siemens Linacs allows additionally to perform "dynamic arc" and automated "step and shoot IMRT" treatments with the m^3. The advanced Varian integration feature available for Varian Linacs allows to perform "dynamic arc" and "dynamic IMRT" treatments with the m^3.	To accommodate a higher-resolution dose delivery, new multileaf collimator designs with 5 mm thick leaves allow the delivery of fractionated SRS, but are not generally acceptable for single-fraction radiosurgery. For radiosurgery, the recommended limit for dose gradient in the beam penumbra (from 80% to 20%) is greater than or equal to 60%/3 mm. The m^3 with its 3 mm-thin leaves has an effective penumbra of less than 3 mm for all SRS field sizes and meets all SRS requirements.	Elekta, GE, Siemens, Varian

Device Name	Manufacturer/ Distributor	Description	Dedicated to SRS	FDA Indications	Indications Presented on Company Web site	Compatibility
micro MLC	Siemens Medical Solutions USA Inc.	The microMLC is a conformal RT and RS device that is mounted to a standard RT linac. The microMLC receives input from planning-system software that determines the collimator aperture shapes at different gantry positions along the arc around the target area. Radiation is delivered at a constant rate.	No	The microMLC is a conformal RT and RS device that delivers a shaped x-ray beam from a RT source. The microMLC is attached to a linac and consists of a series of pairs of tungsten leaves that collimate the radiation delivery to a target based on a treatment plan generated by planning software. The device is used to assist the clinician in the delivery of well-defined target volumes of radiation while sparing the surrounding tissues and organs.		
ModuLeaf™ Mini Multileaf Collimator	Siemens Medical Solutions	Features of the ModuLeaf™ include: 2.5 mm width at the isocenter, 80 leaves, 10 cm x 12 cm maximum field size at isocenter	No	A conformal RT and RS device that delivers a shaped X-ray beam from a RT source. The ModuLeaf is attached to a linac and consists of pairs of tungsten leaves that collimate the radiation delivery to a target based on a treatment plan generated by planning software. The device is used to help the clinician deliver well-defined target volumes of radiation while sparing the surrounding tissues and organs.	Extracranial target volumes where highest precision is required	Major linac systems

Device Name	Manufacturer/ Distributor	Description	Dedicated to SRS	FDA Indications	Indications Presented on Company Web site	Compatibility
XKnife™MMLC™	Radionics	A complete system consisting of an independent device that attaches to a Siemens linac for small field conformal radiosurgery or radiotherapy.		The delivery of radiation to well-defined target volumes while sparing surrounding normal tissue and critical organs from excess radiation. With Radionics' XPlan Conformal Treatment Planning Software or any treatment-planning system, the MMLC enables static conformal treatments to be performed with finely shaped field patterns. In this application, the MMLC performs the same function as customized beam shaping blocks, and circular or cut block collimators.	Spine and other sites	Siemens and a variety of other linacs

AVM: Arteriovenous malformation
cm: Centimeter
DMMLC: Dynamic Micro Multileaf Collimator
FDA: United States Food and Drug Administration
HD: High definition
IMRT: Intensity modulated radiation therapy
IMSRS: Intensity modulated stereotactic radiosurgery
mm: Millimeter
MMLC: Micro multi-leaf collimator
MU/min: Monitor units per minute
MV: Megavolts
NR: Not reported
RS: Radiosurgery
RT: Radiotherapy
SRS: Stereotactic radiosurgery
SRT: Stereotactic radiotherapy

Appendix H. Applicants' FDA 510K Information

Regulatory Status of Devices

Device Name	Manufacturer/ Distributor	510(k) Applicant	Substantial Equivalence	Classification Name	Product Code(s)	510(k) Number	Approval Date
AccuChanger[549]	Direx Systems Corporated	Direx Systems Corp.	AccuLeaf; Cranial stereotactic equipment k010065 Arplay/BrainLAB; Radionics XKnife*	Accelerator, Linear, Medical	IXI	K043409	05/05
AccuLeaf[550]	Direx Systems Corporated	Direx Systems Corp.	BrainLAB MMLC*	Accelerator, Linear, Medical	IXI	K040553	04/04
Axesse™	Elekta Inc.			Approval documentation requested from FDA and manufacturer			
Beam Modulator™ [551]	Elekta Inc.	Elekta Ltd.	Millenium MLC (now Varian's HD 120 MLC); Moduleaf MLC (Siemens)	Radiation therapy beam-shaping block	90 IYE and IXI	K042794	01/05
CyberKnife® Robotic Radiosurgery System[552]	Accuray Incorporated	Accuray Corporation	Predicate device	Medical charged particle radiotherapy device	IYE	K072504	09/07
Dynamic Micro Multileaf Collimator (DMMLC)[553]	Elekta Limited	Elekta Limited	Predicate device	Medical Linear Accessory, IYE	IYE	K082122	08/08
HD 120 MLC[554]	Varian Medical Systems	Varian Medical Systems	Predicate device	Medical Charged Particle Radiation Therapy System	90 IYE	K071992	08/07
Leksell Gamma Knife® Perfexion™ [555]	Elekta Inc.	Elekta Ltd.	Predicate device	Radionuclide radiation therapy system	IWB	K063512	03/07

Device Name	Manufacturer/ Distributor	510(k) Applicant	Substantial Equivalence	Classification Name	Product Code(s)	510(k) Number	Approval Date
m3® (micro-Multileaf Collimator)[556]	BrainLAB AG	BrainLAB AG	Predicate device	Accelerator, Linear, Medical	90 IYE	K020860	06/02
MHI-TM2000[557]	MHI Medical Systems/Hiroshima Machinery Works	Mitsubishi Heavy Industries, Ltd.	Trilogy; Hi-Art System	Accelerator, Linear, Medical	IYE	K072047	08/07
Micro MLC[558]	Siemens Medical Solutions USA, Inc.	Siemens Medical Solutions	Predicate device	Accelerator, Linear, Medical	IXI	K032790	10/03
Moduleaf™ mini Multileaf Collimator[559]	Siemens Medical Solutions	MRC Systems GmbH	Predicate device	Block, Beam Shaping, Radiation Therapy	90 IXI	K030609	03/03
Novalis TX™ [554,560-562]	BrainLAB AG/ Varian Medical Systems	BrainLAB AG/ Varian Medical Systems			Trilogy – 90 IYE HD120-90 IYE ETX™ (Exac-Trac) – IYE OBI – 90 IYE	Trilogy – K081188 HD120-K071992 ETX – K072046 OBI – K042720	07/08 08/07 10/07 10/04
Oncor Artiste, Impression, Avant-Garde, and Expression [563-565]	Siemens Healthcare	Siemens Medical Solutions USA, Inc.	ONCOR linac family	Accelerator, Linear, Medical	IYE	Artiste – K072485 Avant-Garde – K031764 Expression – K060226	12/07 03/06 09/03
Synergy®S [566]	Elekta	Elekta Limited	Predicate device	Medical Linear Accelerator Accessory 90 IYE	90 IYE	K051932	08/05
TomoTherapy® Hi-Art®[567-570]	TomoTherapy, Inc.	TomoTherapy, Inc.	Varian Clinac 600*	Medical charged-particle radiation therapy system	MUJ	K082005 K060912 K042739 K013673	08/08 04/06 11/04 01/02

Device Name	Manufacturer/ Distributor	510(k) Applicant	Substantial Equivalence	Classification Name	Product Code(s)	510(k) Number	Approval Date
Trilogy™[560]	Varian Medical Systems	Varian Medical Systems	BrainLAB Novalis® Shaped Beam Surgery System; Varian Medical Systems' Clinac 2300 C/D	Medical charged-particle radiation therapy system	90 IYE	K081188	07/08
XKnife™ MMLC™ [571] (Miniature multi-leaf collimator)	Radionics	Radionics		Radiotherapy beam shaping block	90 IYE	K993594 Asked Radionics to confirm	12/99

* Purged from CDRH database
CDRH: Center for Devices and Radiological Health
HD: High definition
MLC: Multi-leaf collimator
MMLC: Micro multi-leaf collimator
NR: Not reported

Appendix I. Manufacturer Web Sites

Manufacturers

Company	Web site
Accuray Incorporated[572]	http://www.accuray.com
BrainLAB AG[573]	http://www.brainlab.com http://www.poweringhope.com
Direx Systems Corp.[574]	http://www.direxusa.com
Elekta Inc.[575]	http://www.elekta.com
MHI Medical Systems Inc.[576]	http://www.mhi.co.jp/en/index.html
Radionics[577]	http://www.radionics.com
Siemens USA[578]	http://www.medical.siemens.com
TomoTherapy Incorporated[579]	http://www.tomotherapy.com
Varian Medical Systems[580]	http://www.varian.com

Appendix J. Facilities Performing SBRT for Solid Tumors

Facilities (Information updated September 2009)

Hospital Name	State	City	Device(s)	Treatment Site(s)
St. Vincent's Medical Center	AK	Little Rock	Novalis TX	NS
CyberKnife of Birmingham	AL	Birmingham	CyberKnife	Colon, Kidney, Lung, Ovaries, Pancreas, Prostate, Uterus
Gulf Coast Cancer Centers	AL	Foley	Novalis	Liver mets, Lung
University of Alabama Hospital	AL	Birmingham	Tomotherapy	Prostate
University of Southern Alabama	AL	Mobile	CyberKnife	NS
Banner Good Samaritan Med Center	AZ	Phoenix	Tomotherapy, Novalis TX	NS
Mayo Clinic Hospital	AZ	Phoenix	NR	NS
Scottsdale Healthcare-Osborn	AZ	Scottsdale	Novalis	Breast, Liver, Lung, Pancreas, Prostate, Rectal
Scottsdale Healthcare-Shea	AZ	Scottsdale	Novalis	Breast, Liver, Lung, Pancreas, Prostate, Rectum
St. Joseph's/Carondolette	AZ	Tucson	Novalis TX	NS
St. Joseph's Hospital and Med Center	AZ	Phoenix	CyberKnife	Abdomen, Chest
University Medical Center	AZ	Tucson	Novalis	Liver and other extracranial locations
Cedars-Sinai Medical Center	CA	Los Angeles	NR	Lung
City of Hope National Medical Center	CA	Duarte	Tomotherapy	Lung, Prostate
Community Reg MC/CA Cancer Center	CA	Fresno	CyberKnife	Liver, Lung, Pancreas, Pelvis, Prostate
Comprehensive Blood and Cancer Center	CA	Bakersfield	CyberKnife	NS
CyberKnife Centers of San Diego, Inc. Ruffin	CA	San Diego	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate
CyberKnife Centers of San Diego, Inc., Encinitas	CA	Encinitas	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate
CyberKnife of Southern California at Vista	CA	Vista	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate
Eisenhower Medical Center	CA	Rancho Mirage	Novalis TX	Prostate
El Camino Hospital	CA	Mountain View	Novalis	NS
Hoag Memorial Hospital Presbyterian	CA	Newport Beach	Tomotherapy	Liver Mets, Lung Mets
John Muir Medical Center, Walnut Creek	CA	Walnut Creek	Novalis	Breast, Colon, Liver, Liver Mets, Lung Mets, Prostate

Hospital Name	State	City	Device(s)	Treatment Site(s)
Kaiser Permanente	CA	San Francisco	CyberKnife	NS
Kaiser – Roseville	CA	Roseville	Novalis TX	NS
Long Beach Memorial Medical Center	CA	Long Beach	Tomotherapy	Pelvis, Prostate
Miller Children's Hospital	CA	Long Beach	Tomotherapy	NS
Newport Diagnostic Center	CA	Newport Beach	CyberKnife	Prostate (pending)
Palo Alto Medical Center	CA	Palo Alto	Novalis TX	NS
Palomar Hospital	CA	Escondido	Novalis TX	NS
Pomona Valley Hospital Medical Center	CA	Pomona	Trilogy	Prostate and other extracranial sites
Saint Agnes Medical Center	CA	Fresno	Novalis	NS
Santa Barbara Hospital	CA	Santa Barbara	Novalis TX	NS
Select Healthcare (Orange County Memorial)	CA	Fountain Valley	CyberKnife	Liver, Lung
Sharp Grossmont Hospital	CA	La Mesa	Tomotherapy, Novalis	Prostate and other extracranial sites
Sharp Memorial Hospital	CA	San Diego	Novalis	Prostate and other extracranial sites
St. Bernardine Medical Center	CA	San Bernardino	Tomotherapy	Prostate and other extracranial sites
St. Joseph Hospital	CA	Orange	Trilogy	NS
Stanford Hospital and Clinics	CA	Palo Alto	CyberKnife (2)	Liver, Lung, Pancreas, Prostate
UCLA	CA	Los Angeles	Novalis TX	NS
UCSF Medical Center	CA	San Francisco	CyberKnife	Lung, Pancreas, Prostate
Univ of CA San Diego Medical Center	CA	San Diego	Trilogy	NS
Univ of CA, Davis Medical Center	CA	Sacramento	Novalis	NS
Univ of CA, Irvine Medical Center	CA	Orange	Trilogy	NS
Boulder Community Hospital	CO	Boulder	CyberKnife	NS
Denver CyberKnife Center	CO	Lone Tree	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate
Penrose Hospital	CO	Colorado Springs	CyberKnife	Liver, Lung, Pancreas, Prostate
Poudre Valley Hospital	CO	Fort Collins	NR	NS
Rocky Mountain Cancer Center	CO	Aurora	Novalis TX	NS
Rocky Mountain CyberKnife	CO	Boulder	CyberKnife	Liver, Lung, Musculoskeletal, Pancreas, Prostate
University of CO Hospital/Anschutz Cancer Pavilion	CO	Aurora	Novalis	NS

Hospital Name	State	City	Device(s)	Treatment Site(s)
St. Anthony's Hospital	CO	Denver	Novalis TX	NS
Cyberknife Center at St. Francis	CT	Hartford	CyberKnife	Liver, Lung, Pancreas, Prostate
CyberKnife Center at Stamford Hospital	CT	Stamford	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate
Hartford Hospital	CT	Hartford	Trilogy	NS
Hospital of Central CT	CT	New Britain	Novalis	Lung, Prostate
Yale University	CT	New Haven	Novalis TX	NS
Hospital of Saint Raphael	CT	New Haven	CyberKnife	Liver, Lung, Pancreas, Prostate
Georgetown University Hospital –MedStar Health	DC	Washington	CyberKnife	Kidney, Liver, Lung
Washington Hospital Center	DC	Washington	Trilogy	NS
Christiana Hospital	DE	Newark	CyberKnife	Liver, Lung, Pancreas, Pelvis, Prostate
Baptist Hospital of Miami	FL	Miami	Tomotherapy	Bone, Breast, Lung, Prostate
Baptist Hospital/University of Northern FL	FL	Jacksonville	Novalis TX	NS
Bethesda Memorial Hospital	FL	Boynton Beach	Trilogy	Kidney, Liver, Lung, Pancreas
Blake Medical Center	FL	Bradenton	CyberKnife	Spine
Boca Raton Community Hospital	FL	Boca Raton	Novalis TX	NS
Brandon Regional Hospital HCA	FL	Brandon	CyberKnife	Bile Duct, Bone, Colon/rectum, Kidney, Liver, Lung, Lymph node, Pancreas, Prostate
Broward General Medical Center	FL	Fort Lauderdale	CyberKnife, Trilogy	Liver, Lung, Pancreas
Cancer Care Centers of Brevard	FL	Melbourne	CyberKnife	Kidney, Liver, Lung, Pancreas, Pelvic Organs, Prostate, Skin
Capital Regional Medical Center	FL	Tallahassee	Tomotherapy	Prostate
Coastal CyberKnife and Radiation Oncology	FL	Fort Pierce	CyberKnife	NS
CyberKnife Cancer Center	FL	Jacksonville	CyberKnife	Liver (primary and mets), Pancreas, Prostate
CyberKnife Center of Miami	FL	Miami	CyberKnife	Bladder, Breast, Gynecologic, Liver, Lung, Pancreas, Prostate
CyberKnife Center of Palm Beach	FL	Palm Beach Gardens	CyberKnife	Liver, Lung, Pancreas, Prostate
CyberKnife Center of Tampa Bay	FL	Tampa	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate
Doctors Hospital	FL	Coral Gables	Tomotherapy	Bone, Breast, Lung, Prostate
Florida Hospital	FL	Orlando	Trilogy	NS

Hospital Name	State	City	Device(s)	Treatment Site(s)
H. Lee Moffitt Cancer Center	FL	Tampa	Tomotherapy, Novalis	NS
HCA Central Florida	FL	Sanford	CyberKnife	Kidney, Liver, Lung, Pancreas, Pelvis, Prostate
Jackson Health System	FL	Miami	CyberKnife	Breast
Jupiter Medical Center	FL	Jupiter	CyberKnife, Trilogy	NS
Martin Memorial Hospital	FL	Stuart	Novalis TX	NS
Mayo Clinic Jacksonville	FL	Jacksonville	NR	NS
M.D. Anderson Cancer Center/Orlando	FL	Orlando	Novalis	Lung
Melbourne Internal Medicine Associates	FL	Melbourne	Novalis TX	NS
Memorial Hospital of Jacksonville	FL	Jacksonville	CyberKnife	Liver, Lung, Pancreas, Prostate
Mount Sinai Medical Center	FL	Miami Beach	Trilogy	NS
New Millenium CyberKnife	FL	Brandon	CyberKnife	NS
North Broward Medical Center	FL	Deerfield Beach	CyberKnife, Trilogy	Liver, Lung, Pancreas
North Florida Regional Medical Center	FL	Gainesville	CyberKnife	Liver, Lung, Pancreas, Pelvis, Prostate
Orlando Regional Medical Center	FL	Orlando	Tomotherapy, Novalis	Liver, Lung
Sacred Heart Hospital of Pensacola	FL	Pensacola	Trilogy	NS
Shands at the University of Florida	FL	Gainesville	Trilogy	NS
South Miami Hospital	FL	Miami	Tomotherapy	NS
University of Florida	FL	Gainesville	Triology TX	NS
Wellington Regional Medical Center	FL	Wellington	Novalis	NS
Emory Crawford Long Hospital	GA	Atlanta	Trilogy	NS
Emory University	GA	Atlanta	Trilogy TX	NS
Fannin Regional Hospital	GA	Blue Ridge	NR	NS
Medical College of Georgia Health	GA	Augusta	Trilogy	NS
Memorial Health	GA	Savannah	Trilogy	NS
Piedmont Hospital	GA	Atlanta	Trilogy	NS
South Georgia Medical Center	GA	Valdosta	Synergy	NS
Wellstar Kennestone Hospital	GA	Marietta	CyberKnife	NS
Clarinda Regional Health Center	IA	Clarinda	Novalis	NS
CyberKnife Radiosurgery Center of Iowa	IA	Des Moines	CyberKnife	Liver, Lung

Hospital Name	State	City	Device(s)	Treatment Site(s)
Mercy Medical Center	IA	Cedar Rapids	Tomotherapy	Prostate
Mercy Medical Center-Des Moines	IA	Des Moines	NR	Spine
Saint Alphonsus Regional Medical Center	ID	Boise	Novalis	Liver, Lung, Prostate
Advocate Christ Medical Center	IL	Oak Lawn	CyberKnife	Lung, Pancreas, Prostate
Advocate Good Samaritan Hospital	IL	Downers Grove	CyberKnife	Liver, Lung, Pancreas, Prostate
Advocate Lutheran General Hospital	IL	Park Ridge	Tomotherapy	Bone Mets, Gynecologic, Pancreas, Prostate
CyberKnife Service at Community Cancer Center	IL	Normal	CyberKnife	NS
Edward Hospital	IL	Naperville	Trilogy	Lung, Prostate
Elmhurst Memorial Hospital	IL	Elmhurst	CyberKnife	Liver, Lung, Pancreas, Prostate
Evanston Hospital	IL	Evanston	Novalis	Breast, Liver, Lung, Prostate
Loyola University Medical Center	IL	Maywood	Novalis	NS
Northwest Community Hospital	IL	Arlington Heights	CyberKnife	Liver, Lung, Pancreas, Prostate
OSF Saint Francis Medical Center	IL	Peoria	Trilogy	NS
Provena Saint Joseph Hospital	IL	Elgin	Trilogy	NS
Provena Saint Joseph Medical Center	IL	Joliet	Trilogy	NS
Rush University Medical Center	IL	Chicago	Tomotherapy	Prostate
Saint Joseph Hospital	IL	Chicago	Tomotherapy	NS
Univ of IL Medical Center at Chicago	IL	Chicago	Trilogy	Metastatic treatment
University of Chicago Medical Center	IL	Chicago	Trilogy	Metastatic treatment
Clarian Health Partners	IN	Indianapolis	Novalis	NS
Community Hospital	IN	Munster	CyberKnife, Trilogy	Liver, Lung, Pancreas
CyberKnife Center St. Catherine Hospital	IN	East Chicago	CyberKnife	Liver Mets, Lung, Pancreas
CyberKnife of Indianapolis	IN	Indianapolis	CyberKnife	Liver, Lung, Pancreas, Pelvis, Prostate
Goshen General Hospital	IN	Goshen	Tomotherapy, Trilogy	Breast, Colon, Liver, Lung, Prostate
Memorial Hospital of South Bend	IN	South Bend	Trilogy	NS
Methodist Hospitals	IN	Gary	NR	Lung Mets
Parkview Health	IN	Fort Wayne	CyberKnife	Liver, Lung, Pancreas, Pelvis
St. Mary's Medical Center of Evansville	IN	Evansville	Novalis, Tomotherapy	NS
St. Vincent Indianapolis Hospital	IN	Indianapolis	Novalis	Liver, Lung, and Prostate

Hospital Name	State	City	Device(s)	Treatment Site(s)
St. Vincent Jennings Hospital	IN	North Vernon	Novalis	Liver, Lung, and Prostate
St. Vincent Randolph Hospital	IN	Winchester	Novalis	Liver, Lung, and Prostate
Menorah Medical Center	KS	Overland Park	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate
Providence Medical Center	KS	Kansas City	Trilogy	Liver, Lung, Pancreas
University of Kansas Hospital	KS	Kansas City	Novalis	NS
Via Christi Regional Medical Center	KS	Wichita	CyberKnife	NS
Baptist Hospital East	KY	Louisville	Novalis	Liver, Lung, Prostate
Central Baptist Hospital	KY	Lexington	CyberKnife	NS
CyberKnife Ctr W. Jefferson Med Center	LA	Marrero	CyberKnife	Liver, Lung, Pancreas
CyberKnife of Louisiana	LA	Lafayette	CyberKnife	Liver, Lung, Pancreas, Prostate, Skeletal
East Jefferson Hospital	LA	Metairie	Novalis TX	NS
Mary Bird Perkins Cancer Center	LA	Baton Rouge	Tomotherapy, Novalis	Prostate, Liver
Rapides Regional Medical Center	LA	Alexandria	Trilogy	NS
Slidell Memorial Hospital	LA	Slidell	Trilogy	NS
Baystate Medical center	MA	Springfield	NR	NS
Beth Israel Deaconess Medical Center	MA	Boston	CyberKnife	Liver, Lung, Pancreas, Prostate
Boston Medical Center	MA	Boston	CyberKnife	Liver, Lung, Pancreas, Prostate
Brigham and Women's Hospital	MA	Boston	NR	Lung, Prostate
Brigham and Women's/Harvard	MA	Boston	Novalis TX	NS
Dana Farber Cancer Institute	MA	Boston	Novalis	NS
Children's Hospital Boston	MA	Boston	Novalis	NS
Lahey Clinic Hospital	MA	Burlington	Trilogy	Liver, Lung, Pancreas
Lowell General Hospital	MA	Lowell	Synergy	Prostate
Massachusetts General Hospital	MA	Boston	NR	NS
Mercy Medical Center	MA	Springfield	Synergy	NS
Milford Regional Medical Center	MA	Milford	NR	NS
New England Medical Center	MA	Boston	Axesse	Liver Mets, Lung, Prostate
Northshore Medical Center	MA	Peabody	Novalis TX	NS
St. Ann's Hospital	MA	Fall River	Novalis TX	NS

Hospital Name	State	City	Device(s)	Treatment Site(s)
UMass Memorial Medical Center	MA	Worcester	NR	NS
Anne Arundel Medical Center	MD	Annapolis	Novalis	Liver, Lung, Prostate
Baltimore Washington Medical Center	MD	Glen Burnie	NR	Lung, Nasal, Skeletal Mets
Franklin Square Hospital Center	MD	Baltimore	CyberKnife	Lung
Frederick Memorial Hospital	MD	Frederick	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate, Skeletal Mets
Johns Hopkins Hospital	MD	Baltimore	Tomotherapy	Prostate
Maryland Regional Cancer Care	MD	Rockville	Novalis	Liver, Lung, Prostate
Peninsula Regional Health System	MD	Salisbury	Trilogy	NS
Sinai Hospital of Baltimore	MD	Baltimore	CyberKnife (2)	Liver, Lung, Pancreas, Prostate
St. Agnes HealthCare	MD	Baltimore	Tomotherapy	NS
University of Maryland Medical Center	MD	Baltimore	Trilogy	NS
York Hospital	ME	York	Trilogy	NS
Bay Regional Medical Center	MI	Bay City	Tomotherapy	NS
Beaumont Hospital - Royal Oak	MI	Royal Oak	Synergy	Breast, Lung, Pancreas, Prostate
Henry Ford – Downriver	MI	Trenton	Trilogy TX	NS
Henry Ford Hospital	MI	Detroit	Trilogy TX, Novalis	Adrenal, Liver, Lung, Pancreas
Henry Ford Hospital – WBC	MI	West Bloomfield Campus	Novalis TX	NS
Karmanos Cancer Center	MI	Detroit	Tomotherapy	Lung, Prostate
Lemme Holton Cancer Center	MI	Grand Rapids	Novalis TX	
McLaren Regional Medical Center	MI	Flint	Tomotherapy	NS
MidMichigan Medical Center-Midland	MI	Midland	NR	Kidney, Liver, Lung Mets, Prostate
North Oakland Medical Centers	MI	Pontiac	Tomotherapy	NS
Oakwood Hospital/Med Center	MI	Dearborn	NR	Adrenal, Kidney, Liver, Lung, Pelvis
Saint Mary's Health Care	MI	Grand Rapids	Tomotherapy	NS
Sparrow Health System	MI	Lansing	Tomotherapy	NS
Spectrum Health	MI	Grand Rapids	Novalis	NS
St. Joseph Mercy	MI	Ann Arbor	CyberKnife	Liver, Lung, Pancreas, Prostate
St. Mary's of Michigan	MI	Saginaw	CyberKnife, Tomotherapy	Liver, Lung, Pancreas, Prostate
Abbott Northwestern Hospital	MN	Minneapolis	Trilogy	Pancreas

Hospital Name	State	City	Device(s)	Treatment Site(s)
Park Nicollet Health – Frauenshuh Cancer Ctr	MN	St. Louis Park	Novalis	Liver, Lung, Pancreas
St. Cloud Hospital	MN	Saint Cloud	Synergy	NS
St. Joseph's Hospital	MN	Saint Paul	CyberKnife	Kidney, Liver, Lung, Pancreas, Pelvis, Prostate
St. Luke's Hospital	MN	Duluth	NR	NS
Barnes-Jewish Hospital	MO	Saint Louis	NR	Gynecologic, Lung Mets
Ellis Fischel Cancer Center	MO	Columbia	Trilogy	NS
Lake Saint Louis Oncology/SLU Hospital	MO	Saint Louis	CyberKnife	Liver, Lung, Pancreas, Prostate
Mercy Saint John's Cancer Center	MO	Springfield	CyberKnife	Liver, Lung, Pancreas
Research Medical Center	MO	Kansas City	NR	Liver, Pancreas
Saint Francis Medical Center	MO	Cape Girardeau	NR	NS
Saint Louis University Hospital	MO	Saint Louis	CyberKnife	Liver, Lung, Pancreas, Prostate
Saint Luke's Hospital of Kansas City	MO	Kansas City	Novalis	NS
Southeast Missouri Hospital	MO	Cape Girardeau	Novalis	NS
SSM DePaul Health Center	MO	Bridgeton	Tomotherapy	NS
St. Anthony's Medical Center	MO	Saint Louis	Trilogy	Lung and other extracranial sites
St. Luke's Hospital	MO	Chesterfield	Trilogy	NS
University of Missouri/Ellis Fischel	MO	Columbia	Trilogy TX	NS
Baptist Medical Center	MS	Jackson	CyberKnife	Liver, Lung, Pancreas
Mississippi Baptist Medical Center	MS	Jackson	CyberKnife	Liver, Lung, Pancreas
Benefis Healthcare System	MT	Great Falls	CyberKnife	Lung, Pancreas, Prostate
Kalispell Regional Medical Center	MT	Kalispell	Trilogy	NS
Carloinas Medical Center	NC	Charlotte	Novalis TX	NS
Columbus Reg Healthcare System	NC	Whiteville	NR	NS
Duke University Hospital	NC	Durham	Novalis TX	Liver
East Carloina University CyberKnife Center	NC	Greenville	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate
Grace Hospital	NC	Morganton	Novalis	NS
Mission Hospitals	NC	Asheville	CyberKnife	Kidney, Liver, Lung, Pancreas

Hospital Name	State	City	Device(s)	Treatment Site(s)
North Carloina Baptist Hospital (Wake Forest University Baptist Medical Center)	NC	Winston-Salem	NR	Lung
University of North Carloina Hospitals	NC	Chapel Hill	CyberKnife	Adrenals, Kidney, Liver, Lung, Pancreas, Prostate
Alegent Health Bergan Mercy M Center	NE	Omaha	Tomotherapy	Breast, Lung, Prostate
Alegent Health Lakeside Hospital	NE	Omaha	Tomotherapy	Breast, Lung, Prostate
Columbus Community Hospital	NE	Columbus	NR	NS
Nebraska Medical Center	NE	Omaha	Novalis	Liver, Lung, Prostate
St. Elizabeth CyberKnife Center	NE	Lincoln	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate
Dartmouth-Hitchcock Medical Center	NH	Lebanon	Trilogy	Lung
Elliot Hospital	NH	Manchester	Novalis	Prostate
Huggins Hospital	NH	Wolfeboro	NR	NS
Wentworth-Douglas Medical Center	NH	Dover	Novalis TX, Trilogy TX	NS
Capital Health System at Mercer	NJ	Trenton	CyberKnife	Liver, Lung, Pancreas
CentraState Healthcare System	NJ	Freehold	NR	Liver, Lung
Christ Hospital	NJ	Jersey City	NR	NS
Community Medical Center	NJ	Toms River	Tomotherapy	NS
Cooper CyberKnife Center	NJ	Mount Laurel	CyberKnife	Liver, Lung, Pancreas, Prostate
Cooper Health System	NJ	Camden	CyberKnife	Bone (primary/mets), Liver, Lung, Pancreas, Prostate
Monmouth Medical Center	NJ	Long Branch	Tomotherapy	Lung, Prostate
Morristown Memorial Hospital	NJ	Morristown	CyberKnife	Liver/ Lung/Spine (primary/mets), Pancreas, and Prostate
Newark Beth Israel Medical Center	NJ	Newark	Tomotherapy	NS
Overlook Hospital	NJ	Summit	CyberKnife	Liver, Lung, Pancreas, Prostate
Riverview Medical Center	NJ	Red Bank	CyberKnife	Liver, Lung, Pancreas, Pelvis, Prostate
Robert Wood Johnson Univ Hosp	NJ	Hamilton	NR	NS
Robert Wood Johnson Univ Hospital	NJ	New Brunswick	NR	NS
Saint Barnabas Medical Center	NJ	Livingston	Tomotherapy, CyberKnife	Prostate and other extracranial sites
Somerset Medical Center	NJ	Somerset	Novalis TX	NS

Hospital Name	State	City	Device(s)	Treatment Site(s)
University of Medicine -University Hospital	NJ	Newark	Tomotherapy	NS
Valley Hospital	NJ	Ridgewood	Tomotherapy	NS
Presbyterian Hospital	NM	Albuquerque	NR	Lung
Banner Churchill Community Hospital	NV	Fallon	Tomotherapy	NS
CyberKnife of Reno	NV	Reno	CyberKnife	Liver, Lung, Musculoskeletal, Pancreas, Prostate
Renown Regional Medical Center	NV	Reno	Tomotherapy	Bone, Breast, Colon, Gynecolog., Lymph Nodes, Rectum, Pancreas, Stomach
Columbia University	NY	New York	Trilogy TX	NS
CyberKnife Center of New York	NY	Johnson City	CyberKnife	Liver, Lung, Pancreas, Prostate
Highland Hospital of Rochester	NY	Rochester	Tomotherapy, Trilogy, Novalis	Liver and other extracranial sites
Long Island Jewish Medical Center	NY	New Rochelle	NR	NS
Memorial Sloan-Kettering Cancer Center	NY	New York	Trilogy	Bone Mets, Lung, Pelvis, Prostate, Skin
Mount Sinai Hospital	NY	New York	Novalis	Liver, Lung
New York-Presbyterian Hospital	NY	New York	CyberKnife	NS
North Shore University Hospital	NY	Manhasset	Novalis	Liver, Lung, Prostate
Northern Westchester Hospital	NY	Mount Kisco	Trilogy	NS
Roswell Park Cancer Institute	NY	Buffalo	Trilogy	Breast, Liver, Lung, Pancreas, Prostate
St. Peter's Hospital	NY	Albany	Novalis	Liver, Lung
Stony Brook University Hospital	NY	Stony Brook	NR	NS
Strong Memorial Hospital	NY	Rochester	Novalis, Trilogy	NS
United Health Services Hosp	NY	Binghamton	CyberKnife	Liver, Lung, Pancreas, Prostate
Westchester County Medical Center	NY	Valhalla	Novalis	NS
Winthrop University Hospital	NY	Mineola	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate
Cleveland Clinic Foundation	OH	Cleveland	Novalis	Kidney, Liver, Lung
Doctors Hospital	OH	Columbus	Trilogy	Lung
Flower Hospital	OH	Sylvania	Tomotherapy, Trilogy	NS
Grady Memorial Hospital	OH	Delaware	Trilogy	Lung
Grant Medical Center	OH	Columbus	Trilogy	Lung
James Cancer Hospital	OH	Columbus	NR	NS

Hospital Name	State	City	Device(s)	Treatment Site(s)
Jewish Hospital	OH	Cincinnati	Trilogy	NS
Mercy Medical Center	OH	Canton	Trilogy	NS
Precision Radiotherapy	OH	West Chester	Novalis, Tomotherapy	Breast, Gynecol., Liver, Lung, Pancreas, Prostate, Rectum
Riverside Methodist Hospital	OH	Columbus	Trilogy	Lung
Southern Ohio Medical Center	OH	Portsmouth	Synergy	NS
Southwest General Health Center	OH	Middleburg Heights	CyberKnife, Tomotherapy	Breast, Gynecologic, Kidney, Liver, Lung, Pancreas, Prostate
Summa Health System	OH	Akron	Novalis	NS
Univ Hosp Geauga Regional Hospital	OH	Chardon	CyberKnife, Novalis	Liver, Lung, Pancreas, Prostate
University Hospital	OH	Cincinnati	Lexar	NS
University Hospitals Case Medical Center	OH	Cleveland	CyberKnife, Novalis	Breast, Gynecological, Kidney, Liver, Lung, Pancreas, Prostate
Baptist Medical Center	OK	Oklahoma City	Novalis TX	NS
Deaconess Hospital	OK	Oklahoma City	Tomotherapy	Prostate
Hillcrest Medical Center	OK	Tulsa	CyberKnife	NS
Mercy Health Center	OK	Oklahoma City	CyberKnife	NS
Oklahoma CyberKnife	OK	Tulsa	CyberKnife	Liver, Lung, Pancreas, Prostate
OU Medical Center	OK	Oklahoma City	Trilogy	NS
Saint Anthony Hospital	OK	Oklahoma City	CyberKnife	NS
St. John Medical Center	OK	Tulsa	CyberKnife	Liver, Lung, Pancreas, Prostate
Legacy Emanuel Hospital and Health center	OR	Portland	Novalis	Breast, Liver, Lung, Prostate
OHSU Hospital	OR	Portland	Trilogy, Novalis TX	NS
Providence Portland Medical Center	OR	Portland	CyberKnife	Lung
Abington Memorial Hospital	PA	Abington	NR	NS
Allegheny General Hospital	PA	Pittsburgh	Xknife	Lung
Easton Hospital	PA	Easton	Tomotherapy, Trilogy	NS
Fox Chase Cancer Center	PA	Philadelphia	Trilogy, CyberKnife	Lung mets (Trilogy), NS (CyberKnife)
Frankford Hospital	PA	Philadelphia	Trilogy	Prostate
Geisinger Medical Center	PA	Danville	Trilogy	Lung

Hospital Name	State	City	Device(s)	Treatment Site(s)
Hamot Medical Center	PA	Erie	Trilogy	NS
Hospital of the Univ of PA	PA	Philadelphia	Trilogy, Oncor, Synergy	NS
Lankenau Hospital	PA	Wynnewood	NR	NS
Meadville Medical Center	PA	Meadville	Trilogy	NS
Penn State Milton S. Hershey Medical Center	PA	Hershey	Trilogy	NS
Pennsylvania Hospital	PA	Philadelphia	Trilogy, Oncor	NS
Philadelphia CyberKnife Center	PA	Havertown	CyberKnife	Liver, Lung, Musculoskeletal, Pancreas, Pelvis, Prostate
Pocono Medical Center	PA	East Stroudsburg	NR	NS
Reading Hospital and Medical Center	PA	West Reading	Trilogy	Kidney, Liver, Lung, Pancreas
St. Luke's Hospital - Bethlehem Campus	PA	Bethlehem	Trilogy	Lung
St. Luke's Miner's Memorial Hospital	PA	Coaldale	Trilogy	Lung
Temple University Hospital	PA	Philadelphia	Synergy	NS
Thomas Jefferson University Hospital	PA	Philadelphia	Novalis	NS
UPMC Bedford Memorial	PA	Everett	Trilogy	NS
UPMC Mercy	PA	Pittsburgh	Trilogy, Cyberknife	NS
UPMC Presbyterian	PA	Pittsburgh	Trilogy	NS
UPMC Shadyside Hospital	PA	Pittsburgh	Trilogy, Cyberknife	Abdomen, Lung, Pelvis
Western Pennsylvania Hospital	PA	Pittsburgh	XKnife	Lung
HIMA San Pablo	PR	Caguas	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate
Rhode Island Hospital	RI	Providence	Trilogy, CyberKnife	Breast, Kidney, Liver, Lung, Pancreas, Pelvis, Prostate, Skin
Cancer Centers of the Carloinas and Greenville Hospital System	SC	Greenville	Novalis	Liver, Lung, Prostate
MUSC Medical Center	SC	Charleston	Tomotherapy	Abdomen, Prostate
Roper Hospital	SC	Charleston	CyberKnife	Liver, Lung, Pancreas, Prostate
Sanford Univ of SD Medical Center	SD	Sioux Falls	Novalis	NS
Centennial Medical Center	TN	Nashville	CyberKnife	Liver, Lung, Pancreas, Prostate
University of Tennessee Medical Center	TN	Knoxville	CyberKnife	Liver, Lung, Pancreas, Prostate
Vanderbilt University	TN	Nashville	Novalis TX	NS

Hospital Name	State	City	Device(s)	Treatment Site(s)
Wellmont Bristol Regional Med Center	TN	Bristol	CyberKnife	NS
Baylor Medical Center at Garland	TX	Garland	CyberKnife	NS
Baylor/Sammons Cancer Center	TX	Dallas	Novalis TX	NS
Baylor University Medical Center	TX	Dallas	CyberKnife	NS
Brain and Spine Center/Brackenridge Hospital	TX	Austin	CyberKnife	Liver, Lung, Pancreas, Prostate
East Texas Medical Center Tyler	TX	Tyler	CyberKnife	Lung, Pancreas, Prostate
Harris Methodist Hospital	TX	Fort Worth	Novalis TX	NS
Memorial Herman Hospital SW	TX	Houston	Trilogy TX	NS
Methodist Hospital	TX	San Antonio	CyberKnife, Novalis, Tomotherapy	Liver, Lung, Prostate
North Cypress Medical Center	TX	Cypress	NR	Kidney, Liver/Lung Mets, Lung, Pancreas, Pelvis, Prostate
Richardson Regional Medical Center	TX	Richardson	Novalis	Liver, Lung, Prostate
South Texas Oncology and Hematology at the START Center	TX	San Antonio	CyberKnife, Tomotherapy	NS
Spring Branch Medical Center	TX	Houston	NR	Adrenals, Liver, Lung, Pancreas, Pelvis, Prostate
St. Luke's Episcopal Health System Corp.	TX	Houston	CyberKnife	Kidney, Liver, Lung, Pancreas, Prostate
Tyler Cancer Center	TX	Tyler	Novalis TX	NS
Texas Health Harris Methodist Fort Worth	TX	Fort Worth	CyberKnife	NS
Texas Health Presbyterian Hosp	TX	Dallas	CyberKnife	NS
The Methodist Hospital	TX	Houston	NR	Liver, Lung
Univ of TX (CTRC)	TX	San Antonio	Novalis TX	NS
Univ of TX M. D. Anderson Cancer Center	TX	Houston	NR	Lung
Univ of TX Medical Branch	TX	Galveston	Novalis	Abdomen, Liver, Lung
Univ of TX Southwestern Medical Center	TX	Dallas	CyberKnife	Prostate and other extracranial sites
Walls Regional Hospital	TX	Cleburne	CyberKnife	Liver, Lung, Pancreas, Prostate
Primary Children's Medical Center	UT	Salt Lake City	Trilogy	NS
Salt Lake CyberKnife	UT	Salt Lake City	CyberKnife	Liver, Lung, Musculoskeletal, Pancreas, Prostate
University of Utah	UT	Salt Lake City	Novalis	NS

Hospital Name	State	City	Device(s)	Treatment Site(s)
Carilion Health	VA	Roanoke	CyberKnife	Kidney, Lung, Pancreas, Prostate
Carilion New river Valley Medical Center	VA	Christiansburg	CyberKnife	NS
Centra Health	VA	Lynchburg	Trilogy	NS
CJW Medical Center	VA	Richmond	Trilogy	NS
Inova Fairfax Hospital	VA	Falls Church	NR	Skeletal
Riverside Regional Medical Center	VA	Newport News	Synergy	NS
Sentara Advanced Radiosurgery Center	VA	Norfolk	CyberKnife	Liver, Lung, Pancreas
University of Virginia Medical Center	VA	Charlottesville	Tomotherapy	Liver, Lung
VCU Health System	VA	Richmond	Tomotherapy	NS
Virginia Hospital Center	VA	Arlington	CyberKnife	Lung, Prostate
Harborview Medical Center	WA	Seattle	NR	NS
Multicare Health System	WA	Tacoma	Trilogy	NS
Southwest Washington Medical Center	WA	Vancouver	CyberKnife	Kidney, Liver, Lung, Pancreas, Pelvis
St. Joseph Hospital	WA	Bellingham	Tomotherapy	Gastrointestinal, Gynecologic, Prostate
Swedish Health Services	WA	Seattle	CyberKnife, Synergy	NS
Swedish Medical Center	WA	Seattle	CyberKnife, Synergy	Prostate
University of Washington Med Center	WA	Seattle	Tomotherapy	NS
Virginia Mason Medical Center	WA	Seattle	NR	Prostate
Appleton Medical Center	WI	Appleton	CyberKnife, Tomotherapy, Trilogy	NS
Aurora Medical Center	WI	Kenosha	CyberKnife	Lung, Pancreas
Aurora Memorial Hospital of Burlington	WI	Burlington	CyberKnife	Lung, Pancreas
Aurora St. Luke's Medical Center	WI	Milwaukee	CyberKnife	Lung, Pancreas
Columbia St. Mary's - Columbia Campus	WI	Milwaukee	Trilogy	Breast, Kidney, Liver, Lung, Pancreas, Pelvis, Prostate, Skin
Saint Joseph's Hospital	WI	Marshfield	Trilogy	NS
St. Vincent Hospital	WI	Green Bay	Trilogy	NS
Theda Clark Medical Center	WI	Neenah	CyberKnife, Tomotherapy	NS
University of Wisconsin Hosp	WI	Madison	Tomotherapy	NS
Waukesha Memorial Hospital	WI	Waukesha	CyberKnife	Liver, Lung, Pancreas, Prostate

Hospital Name	State	City	Device(s)	Treatment Site(s)
Wheaton Franciscan Cancer Care – St. Joseph	WI	Glendale	Novalis	NS
St. Mary's CyberKnife Center	WV	Huntington	CyberKnife	Kidney, Liver, Lung, Pancreas, Pelvis

NR: Not reported
NS: Not specified

Appendix K. Ongoing Clinical Trials

Ongoing Clinical Trials

Condition	ClinicalTrials.gov Identifier	Study Design	Intervention	Primary Outcome Measures	Secondary Outcome Measures	Estimated Enrollment	Planned Duration	Location
Breast Cancer, Metastatic	NCT00167414	Nonrandomized; historical control	HSBRT	OS, DFS	CRR, chemical and radiobiological response, QoL	80	December 2000–Ongoing	Rochester, NY
Cholangiocarcinoma Klatskin Tumor Biliary Tract Cancer	NCT00630890	Single group	External beam radiation and CyberKnife radiosurgery boost and capecitabine	Acute toxicities, MTD	LC, radiographic response, delayed and long-term toxicities, DSS, OS	11	October 2007–October 2011	San Francisco, CA
Cholangiocarcinoma	NCT00983541	Single group	SBRT, brachytherapy, fluorouracil (5-FU), gemcitabine	Toxicity	OS, PFS, tumor response, LC, rate of distant mets	12	September 2009–September 2011	Salt Lake City, UT
Colorectal Cancer (fewer than 5 metastases)	NCT00807313	Single group	SBRT	Metabolic complete remission rate	Toxicity, PFS, LC, OS	81	December 2008–Ongoing	Brussels, Belgium
Hepatocellular Carcinoma	NCT00746655	Single group	SBRT with TACE	Feasibility and toxicity	LC, RC, HRQoL	12	July 2009–Ongoing	University of Pittsburgh, Pittsburgh, PA
Hepatocellular Carcinoma	NCT00914355	Single group	SBRT	Local PFS	PFS, OS, QoL, toxicity, cytokine response	47	August 2007–August 2010	Toronto, Canada
Hepatocellular Carcinoma	NCT00243841	Nonrandomized	SBRT	6 month LC	Not specified	60	May 2004–December 2015	Indianapolis, IN
Hepatocellular Carcinoma	NCT01020812	Single group	SBRT with TACE	Efficacy, toxicity	PFS, OS, correlate tumor marker alpha-fetoprotein (AFP) with tumor response and survival	24	September 2009–September 2013	Stanford, CA

Condition	ClinicalTrials.gov Identifier	Study Design	Intervention	Primary Outcome Measures	Secondary Outcome Measures	Estimated Enrollment	Planned Duration	Location
Kidney Cancer	NCT00445757	Single group	Conventional surgery; neoadjuvant therapy; SRS	MTD, toxicity	DFS, LP, DF, DSS	20	January 2007–January 2012	Cleveland, OH
Kidney Cancer	NCT00458484	Single group	SRS	MTD	OS, DFS, LP, DF	32	February 2007–February 2012	Cleveland, OH
Liver Cancer	NCT01030757	Single group	SBRT with Tomotherapy	Tumor response	Toxicity, PFS, OS	43	June 2009–January 2014	Albuquerque, NM
Liver Cancer	NCT00607828	Single group	SBRT	Toxicity, MTD	Not specified	28	November 2007–October 2009	Omaha, NE
Liver Cancer	NCT00777894	Single group	SBRT; Three-dimensional RT; IMRT	Dose limiting toxicity; objective response	Adverse events, tumor response, PFS, OS, Child-Pugh Score	73	November 2008–March 2012	Haifa, Israel; Jerusalem, Israel; Masstricht, Netherlands; Aarau, Switzerland; Zurich, Switzerland; Bellinzona; Switzerland; Bern, Switzerland; St. Gallen, Switzerland; Basel, Switzerland
Liver Cancer	NCT00607828[1]	Single group	SBRT	Toxicity, MTD	NS	28	November 2007–October 2009	Omaha, NE
Liver Metastases	NCT00914615	Single group	SBRT	Local PFS	PFS, OS, QoL, toxicity, cytokine response	17	August 2007–August 2010	Toronto, Canada
Liver Metastases	NCT00938457	Single group	SBRT	MTD, minimum effective dose	Adverse events, toxicity, tumor response, LC, time to progression, blood chemistry and hepatic function	60	July 2009–November 2017	Rochester, MN
Primary and Metastatic Liver Tumors	NCT00691691	Single group	SBRT	CRR	Toxicity	71	November 2007–November 2008	Calgary, Alberta, Canada

Condition	ClinicalTrials.gov Identifier	Study Design	Intervention	Primary Outcome Measures	Secondary Outcome Measures	Estimated Enrollment	Planned Duration	Location
Liver Metastases	NCT00567970[1]	Single group	SBRT	MTD	Toxicity; adverse events; QoL; Response; physical exam results	18	April 2007–October 2008	Jacksonville, FL
Liver Metastases	NCT00547677	Single group	SBRT	Toxicity	Tumor response	27	July 2004–December 2007	Dallas, TX; Minneapolis, MN
Lung and Liver Tumors	NCT00178477[1]	Single group	SBRT	NS	NS	48	January 2002–January 2006	Rochester, NY
Lung Tumors	NCT00632281	Single group	SBRT	Disease status	Toxicity	750	January 2006–Ongoing	University of Florida, Gainesville, FL
Lung Tumors	NCT00832780	Single group	SBRT using Tomotherapy	CRR (complete and partial)		45	January 2008–October 2011	University of New Mexico, Albuquerque, NM
Lung Cancer	NCT00238602	Single group	SRS (CyberKnife)	MTD, symptoms and radiographic responses	NR	60	March 2000–Ongoing	Stanford, CA
Lung Cancer	NCT00687986	Randomized	SRT vs. Primary Resection	LC, RC, QoL; treatment costs	OS; QALY; total costs	960	August 2008–December 2013	Amsterdam, Netherlands
Lung Cancer	NCT01051037	Single group	SBRT and radiofrequency ablation	Toxicity	One year LC, PFS, OS	35	January 2010–January 2013	Los Angeles, CA
Non-small Cell Lung Cancer	NCT00643318	Single group	CyberKnife SRS	CRR, LCR, PFS, OS	QoL, procedures related outcomes	156	April 2006–July 2013	Pittsburgh, PA
Non-small Cell Lung Cancer	NCT00870116	3-group comparison (nonrandomized)	SBRT (CyberKnife) vs. SBRT (linac) vs. Conformational RT	LC	Economic, QoL, PFS, OS	120	April 2009–March 2013	Multiple centers, France
Non-small Cell Lung Cancer	NCT00551369	Single group	SBRT followed by surgical resection in patients with progression	LC	Toxicity, LC, RC, DFS, OS	33	December 2007–June 2012	Multicenter, U.S. and Canada
Non-small Cell Lung Cancer	NCT00843726	Randomized	SBRT—one vs. three fractions	Toxicity, OS	NS	98	September 2008–April 2013	Roswell Park Cancer Institute, New York, NY

Condition	ClinicalTrials.gov Identifier	Study Design	Intervention	Primary Outcome Measures	Secondary Outcome Measures	Estimated Enrollment	Planned Duration	Location
Non-small Cell Lung Cancer	NCT00087438[2]	Single group	SBRT	LC	RC, DFS, OS	52	May 2004–March 2009	University of Rochester, Rochester, NY
Non-small Cell Lung Cancer	NCT00547105	Single group	Erlotinib hydrochloride and SBRT	PFS	Disease progression, Toxicity, OS	24	June 2007–June 2010	University of Texas, Dallas, TX
Non-small Cell Lung Cancer	NCT00238875	Single group	SBRT	OS at 3 years	RFS, Toxicity, PFS, OS	167	July 2004–November 2011	Multiple sites, Japan
Non-small Cell Lung Cancer	NCT00591838	Single group	SBRT	Toxicity	LC, RC, DFS, OS	45	August 2006–August 2016	Washington University Hospital, St. Louis, MO
Non-small Cell Lung Cancer	NCT00727350	Single group, historical control	SBRT	Toxicity	LC, OS, DFS, PFS, QoL	44	March 2007–December 2012	Brussels, Belgium
Non-small Cell Lung Cancer (Stage I, Stage II, or peripheral lung recurrence)	NCT00489008	Three uncontrolled groups	SBRT	DFS, OS	Not reported	138	November 2005–September 2012	M.D. Anderson Cancer Center, Houston, TX
Non-small Cell Lung Cancer	NCT00750269	Single group	SBRT	Toxicity	LC, PFS, OS	94	February 2009–May 2012	Multiple sites, U.S. and Canada
Non-small Cell Lung Cancer	NCT00840749	Randomized, open label	SBRT vs. surgical resection	OS	DSS, PFS, Toxicity	1,030	December 2008–December 2013	Multiple sites, U.S. and China
Non-small Cell Lung Cancer	NCT00246181[1]	Single group	SBRT	Dosage	Efficacy	117	December 1999–December 2009	Indianapolis, IN
Pancreatic Neoplasms	NCT00833859	Single group	SBRT and Gemcitabine, Docetaxel and Capecitabine	Rate of surgical resection with negative margins	Toxicity, OS	24	March 2009–March 2012	Tampa, FL
Pancreatic Cancer	NCT00350142[1]	Single group, historical control	SBRT	OS, QoL	NS	40	December 2004–October 2008 (completed)	Stanford University, Stanford, CA

Condition	ClinicalTrials.gov Identifier	Study Design	Intervention	Primary Outcome Measures	Secondary Outcome Measures	Estimated Enrollment	Planned Duration	Location
Pancreatic Cancer	NCT00425841	Single group	Gemcitabine hydrochloride, oxaliplatin, adjuvant therapy, hypofractionated radiation therapy, neoadjuvant therapy, SRS	CRR	Toxicity, time to progression, time to death, tumor response	29	May 2006–NS[1]	Munich, Germany
Pancreatic Cancer	NCT01068327	Single group	SBRT, gemcitabine hydrochloride, leucovorin calcium, fluorouracil, nelfinavir mesylate; conventional surgery	Dose limiting toxicity, MTD	Tumor response;	24	November 2007–December 2012	Omaha, NE
Pancreatic Cancer	NCT01025882	Single group	SBRT, gemcitabine hydrochloride, pancreato-duodenectomy	Toxicity, morbidity, tumor response, length of hospital stay	NS	30	October 2009–October 2014	Dallas, TX
Prostate Cancer	NCT00643617	Single group	CyberKnife SRS	Biochemical DFS, rates of acute and late gastro-intestinal and genitourinary toxicities	LF, DF, DFS, DSS, OS, QoL	253	November 2007–January 2014	San Diego, CA; Fresno, CA; Great Falls, MT; Oklahoma City, OK; Tyler, TX
Prostate Cancer	NCT00619515	Single group	SRS	Rate of acute toxicities	Rate of late grade 3–5 toxicities, DFS, OS, LF, DF, QoL	102	December 2007–December 2009	Cleveland, OH; Chardnor, OH; Mentor, OH; Canton, OH; South Euclid, OH; Orange Village, OH; Westlake, OH; Middleburgh Heights; OH

Condition	ClinicalTrials.gov Identifier	Study Design	Intervention	Primary Outcome Measures	Secondary Outcome Measures	Estimated Enrollment	Planned Duration	Location
Prostate Cancer	NCT00643994	Single group	CyberKnife SRS	Rates of acute and late grade 3–5 gastro-intestinal and genitourinary toxicities, rate of biochemical DFS	LF, DF, DFS, DSS, OS, QoL	298	December 2007–January 2014	Jupiter, FL; Arlington Heights, IL; Lexington, KY; Boston, MA; Ann Arbor, MI; Trenton, NJ; Seattle, WA
Prostate Cancer	NCT00941915	Single group	SBRT with continuous real-time evaluation of prostate motion and IMRT for plan reoptimization based on "anatomy of the day"	Toxicity	DFS, QoL	60	September 2009–December 2012	Duke University, Durham, NC
Prostate Cancer	NCT00547339	Single group	SBRT	Toxicity	OS, LC, RC, DSS	97	July 2006–October 2010	University of Texas, Dallas, TX
Prostate Cancer	NCT01059513	Single group	SBRT	Long term toxicities; tumor control	Not specified	60	January 2010–January 2017	Los Angeles, CA
Unspecified Adult Solid Tumor	NCT00311597	Single group	SRS	MTD, MD	Radiographic response rate, median time to progression, toxicity, cause of death	48	June 2002–Ongoing	Winston-Salem, NC
Extracranial Recurrent, Metastatic Cancer or Primary Tumors	NCT00006456[1]	Single group	SRS	NR	NR	10–25 within 2–3 years	February 1999–Ongoing	Richmond, VA

[1] Although the estimated completion date has expired, the trial is still ongoing and "active" according to ClinicalTrials.gov at the time of this report.
[2] This study has been completed and results have been published. See Appendix L. Literature Results.[109]

CRR: Clinical response rate
DF: Distant failure
DFS: Disease-free survival
DSS: Disease-specific survival
HRQoL: Health-related quality of life
HSBRT: Hypofractionated stereotactic body radiotherapy
IMRT: Intensity modulated radiation therapy
LC: Local control
LCR: Local control rate
LF: Local failure
LP: Local progression
M: Male
MD: Minimum dose
MTD: Maximum tolerated dose

NS: Not specified
OS: Overall survival
PFS: Progression-free survival
QALY: Quality-adjusted life years
QoL: Quality of life
RC: Regional control
RT: Radiation therapy
SBRT: Stereotactic body radiation therapy
SRS: Stereotactic radiosurgery
TACE: Transcatheter arterial chemoembolization

.

Appendix L. Results for Guiding Question 3

Prospective Single Group Studies

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Freeman et al. (2011)[23]	USA	Low-risk prostate cancer	Cyberknife/NR	n = 41	None	Median: 60 (Range: 50.4–74.4)	PSA levels; toxicity; QoL	Acute: dysuria, urinary urgency, frequency, nocturia, tenesmus Late: grade 1N3 urinary, grade 1N2 rectal
Aluwini et al. (2010)[3]	The Netherlands	Low to intermediate risk prostate cancer	Cyberknife/NR	n = 10	NR	Median: 5.1 (Range: 2–13)	Early and intermediatiat toxicity scores; early PSA response	Acute grade 1N2: rectal bleeding; urinary toxicity
Bolzicco et al. (2010)[8]	Italy	Prostate cancer	Cyberknife/NR	n = 22 low risk n = 23 intermediate risk	Prior: hormone therapy; transurethral resection n = 17 concurrent androgen deprivation	Median: 20 (Range: 6–42)	Toxicity; PSA response	Grade 1-3: urgency, urinary frequency, rectal urgency or stool frequency Late: occasional rectal bleeding
Bradley et al. (2010)[9]	Italy	Stage I NSCLC	NR/NR	n = 91	None	Median: 18 (Range: 6–42)	Local control; nodal failures; distant failures	Skin reaction; grade 2 radiation pneumonitis; painful subcutaneous inflammatory reaction adjacent to treated chest wall; rib fracture; chest wall pain at site of treatment; brachial plexopathy
Cardenes et al. (2010)[11]	USA	Primary HCC	Linac/NR	n = 17 with 25 lesions	None	Median: 24 (Range: 10–42) n = 10 patients alive without progression	Toxicity; tumor response; maximum tolerated dose; survival	Grade 3 and higher: elevation of bilirubin, hypokalaemia, hyperbilirubinaemia, radiation induced liver disease

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Goodman et al. (2010)[27]	USA	Primary and metastatic liver tumors	Cyberknife/NR	n = 19 hepatic mets n = 5 IHCC n = 2 recurrent HCC	None	Median: 17.3 (Range: 2–55)	Local control; survival; overall survival,	Grade 1: nausea, abdominal pain, fever, fatigue Grade 2: duodenal ulcer, gastrointestinal bleeding, musculoskeletal toxicity
Kopek et al. (2010)[55]	Denmark	Cholangiocarcinoma	Siemens Primus/NR	n = 27	None	Median: 64.8 (Range: 27.6–103.2 entire cohort)	Local control; progression-free survival; overall survival; acute and late radiation induced toxicities	Grade ≥3 nausea, vomiting, pain, analgesia, ulceration, duodenal stenosis, hepatic failure
Oermann et al. (2010)[74]	USA	Prostate cancer	Cyberknife/Inverse treatment plan	N = 13 intermediate risk N = 11 high risk	Concurrent: IMRT given immediately after SBRT	Median: 9.3 (Range: 6.6–16.9)	Toxicity; QoL; PSA response	Grade 2: urinary symptoms requiring alpha blockers; bowel frequency/spasms requiring antidiarrheals
Polistina et al. (2010)[80]	Italy	Locally advanced pancreatic adenocarcinoma	CyberKnife/NR	n = 23	None	Mean: 11 +3.95 Median: 9	Gastrointestinal toxicity; tumor response; local control; pain; QoL; overall survival time	n = 5 grade 1 vomiting/nausea; n = 3 enteric bleedings diagnosed endoscopically as bleeding from duodenal wall cancer invasion
Shin et al. (2010)[93]	Korea	HCC	Cyberknife/Pencil beam	n = 6	n = 6 prior TACE	Three alive patients: Median: 25.9 (Range: 8.1–56)	Tumor response; local failure; acute and late toxicities; radiation induced liver disease; dose limiting toxicity; survival	Alkaline phosphatase and liver enzymes increased due to disease progression During treatment: mild nausea, transient asymptomatic, right-sided pleural effusion

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Stintzing et al. (2010)[101]	Germany	Metastatic liver tumors of colorectal cancer	Cyberknife/NR	n = 14	n = 6 prior chemo; n = 9 prior surgery; n = 1 prior chemo-embolization	Median: 16.8	Local control; toxicity; progressional-free survival; overall survival	No patients reported side-effects of RT; bleeding, ulcers, or strictures have not been detected
Stintzing et al. (2010)[102]	Germany	Liver tumors	Cyberknife/NR	n = 36 with 54 mets	Prior: chemo; surgery; RFA; chemoembolization; selective internal radiotherapy; laser-induced thermal therapy	Median: 21.3 (Range: 2.8–44)	Local tumor control; survival; toxicity	Grade 1 fatigue and nausea
Timmerman et al. (2010)[109]	USA	Early stage inoperable NSCLC	Linac/NR	n = 55	None	Median: 34.4 (Range: 4.8–49.9 all evaluable) Median: 38.7 (Range: 30.2–49.9 still living)	Tumor response; 3 year primary tumor control rate; local and regional failures; 3 year rates disseminated recurrence; disease-free survival; overall survival	Grade 1–5 toxicities; n = 6 events related to SBRT (n = 3 complications of skin or ribs)
Vahdat et al. (2010)[115]	USA	Inoperable stage IA NSCLC	CyberKnife/NR	n = 20	None	Median: 43	Disease spread; survival; serial change in maximum standardized uptake value (SUV[max]); local control	Radiation induced pneumonitis and infiltrating lung fibrosis
Collins et al. (2009)[17]	USA	Stage 1 NSCLC	CyberKnife/ Inverse-planning algorithm	n = 20	n = 1 concurrent gefitinib treatment	Median: 25 (Range: 6–36 for survivors)	Pulmonary status; tumor response; disease progression; survival	Pneumothorax requiring tube thoracotomy (after fiducial placement); mild transient fatigue; chest wall discomfort; acute grade III radiation pneumonitis and infiltrate; hypoxia

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Haasbeek et al. (2009)[33]	The Netherlands	Second lung tumor in the contralateral lung	Linac/NR	n = 15	Prior pneumonectomy for an earlier lung tumor; radiation therapy	Median: 16.5 (Range: 4–55)	Overall survival; distant metastasis free survival; local control; regional failure free survival; disease-free survival; toxicity	Mild fatigue, grade 3 late toxicity; grade 3 radiation pneumonitis; grade 3 complication
Kim et al. (2009)[52]	Korea	Pulmonary metastatic colorectal cancer	CyberKnife/NR	n = 13	Prior chemo; surgery	Median: 28 (Range: 15–57)	Overall survival; local control; progression-free survival	Grade 1–2 toxicities: musculoskeletal discomfort and asymptomatic radiation pneumonitis
Kopek et al. (2009)[54]	Denmark	Early stage NSCLC	Linac/NR	n = 88	None	Median: 44 (Range: 1.6–96.5)	Tumor response; actuarial local control; freedom from failure; median cancer-specific survival; overall survival	Deterioration in performance status by >3 grade points, >3 grade point worsening in analgesia use, 3 grade point deterioration in dyspnea; rib facture

Lee et al. (2009)[61]	Canada	Liver metastases	Linac/NR	n = 68	n = 7 prior surgery;
					n = 8 prior RFA;
					prior lines of chemo: n = 9 (0), n = 15 (1), n = 29 (2), n = 15 (>3);
					n = 1 prior Whipple operation and prior radiotherapy to celiac axis lymph nodes
						Median: 10.8	Maximum tolerated study dose (MSD); tumor response; local control; progression-free survival; overall survival	Grade 3 or higher acute toxicity; thrombocytopenia; grade 3 liver enzymes; subacute liver pain; transient gastritis/esophagitis; grade 2 colitis
								Late: grade 4 duodenal bleed; grade 5 malignant small bowel obstruction; grade 4 small bowel obstruction through an abdominal hernia; grade 2 nontraumatic rib fractures; transient grade 2 chest wall pain; grade 2 dyspepsia

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events

Milano et al. (2009)[67]	USA	Oligometastases	Novalis linac/NR	n = 32	n = 10 prior curative intent local therapy;
					n = 9 prior resection;
					n = 1 prior radio-frequency ablation (RFA);
					n = 1 prior radiation therapy (RT)
						Median (deceased): 8 (Range: 3–20);
						Median (survivors): 7 (Range: 2–32)
							Overall survival; progression-free survival; local failure	NR

Olsen et al. (2009)[75]	USA	Liver metastases	Linac/NR	n = 15	None	NR	Change in normal liver volume	NR
Rusthoven et al. (2009)[86]	USA	Liver metastases	Linac/NR	n = 47	Mean 1.7 (Range: 0–7) prior systemic treatment regimens; n = 7 prior local therapy for liver metastases	Median: 16 (Range: 6–54)	Local control, toxicity; progression-free survival; distant progression-free survival; overall survival	Grade 3 soft tissue toxicity: skin erythema, pain
Rusthoven et al. (2009)[87]	USA	Lung metastases	Linac/NR	n = 38	Mean 1.2 (Range: 0–5) prior systemic therapy regimens for metastatic disease	Median: 15.4 (Range: 6–48)	In-field local control; overall survival; toxicity; distant progression; local progression; distant progression-free survival	Grade 3 toxicity rib fracture; grade 2 radiation dermatitis; grade 1 pneumonitis; symptomatic radiation pneumonitis

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
van der Voort van Zyp et al. (2009)[116]	The Netherlands	NSCLC	CyberKnife/NR	n = 70	None	Median: 15	Local control; overall survival; cause-specific survival	Fiducial placement: grade 3 toxicity (pneumothorax requiring a chest drain and cardiac arrhythmia required a pacemaker); grade 2 toxicity pneumothorax but required no chest drain; grade 1 toxicity: minor dyspnea, pneumothorax without clinical symptoms, and self-limiting pulmonary hemorrhage After treatment: acute grades 1–2 toxicity (fatigue, dyspnea, cough); acute grade 3 toxicity requiring morphine, late grade 3 toxicity, radiation pneumonitis, thoracic pain, rib fracture
Chang et al. (2008)[13]	USA	Centrally and superiorly located stage 1 NSCLC or isolated lung parenchymal recurrent NSCLC	Linac/NR	n = 27	None	Median: 17 (Range: 6–40)	Local control; tumor response	Grade 2 pneumonitis; grade 2–3 dermatitis and chest wall pain; brachial plexus neuropathy; partial arm paralysis
Fuller et al. (2008)[25]	USA	Prostate cancer	CyberKnife/NR	n = 10	Concurrent distribution of high dose rate brachytherapy	2 week, 4 week, 8 week, and 4 month follow-up done	Early PSA response	No urinary obstruction observed to date, mild and transient rectal toxicity; no acute rectal bleeding observed
Henderson et al. (2008)[36]	USA	Inoperable stage 1 NSCLC	Linac/NR	n = 70	None	Median: 2.17 years (Range: 0.12–3.62 years)	Survival; pulmonary function	Grade 2 or higher pulmonary toxicity: pneumonitis, pneumonia, and other pulmonary toxicity
Katoh et al. (2008)[49]	USA	Adrenal tumors	Linac/NR	n = 9	None	Median: 16 (Range: 5–21)	Disease progression; local failure	No decline in hormone level, tumor-related flank pain

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Salazar et al. (2008)[88]	USA	Primary and metastatic lung cancer	Linac/NR	n = 104	n = 29 concurrent external beam radiation therapy (EBRT)	Median: 38 (Range: 2–84)	Local tumor response; local tumor control; failure analysis	Grade 1 and 2 acute toxicity: shortness of breath, fatigue, cough, esophagitis, nausea and vomiting, nonmalignant symptomatic pleural effusion, skin reaction; Grade 2 symptomatic subacute or chronic toxicities: symptomatic RT-induced pneumonitis, severe symptomatic fibrosis with sustained shortness of breath; asymptomatic fibrosis of varying degrees
Schellenberg et al. (2008)[89]	USA	Adenocarcinoma of the pancreas	CyberKnife/NR	n = 16	Gemcitabine infusion chemo dose of 1,000 mg/m^2 weekly	Median: 9.1 for all patients; Median: 22.3 for living patients	Local control, toxicities, time to progression, overall survival, carbohydrate antigen (CA 19–9) levels	Pain and gastritis (n = 3); 1 patient required J-tube placement 6 weeks after treatment which was attributed to the SBRT Late toxicities: n = 5 treated medically for ulcer formation (grade 2), 1 required duodenal stent for a non-neoplastic stricture (grade 3), and 1 required surgery after duodenal perforation (grade 4)
Tse et al. (2008)[112]	Canada	Unresectable hepatocellular carcinoma (HCC) and intrahepatic cholangio-carcinoma (IHC)	NR/NR	n = 41	NR	Median: 17.6 (Range: 10.8–39.2)	Survival; local control rate; overall RECIST response rate (complete response, partial response, stable disease)	Transient biliary obstruction; death result of a pulmonary embolus; grade 3 liver enzymes; grade 3 thrombocytopenia; transient asymptomatic right-sided pleural effusion; progression from Child-Pugh A classification to B; late toxicity

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Aoki et al. (2007)[4]	Japan	Primary lung or metastases	Mitsubishi EXL-20TP 10-MV standard linac/NR	n = 19	n = 10 repeat SRT; n = 1 prior RT	Median: 17.7 (Range: 9.4–39.5)	Tumor response; crude local tumor control rate; overall survival rate (Kaplan-Meier)	Grade 1 radiation pneumonia; grade 1 radiation fibrosis
Hof et al. (2007)[38]	Germany	Pulmonary metastases	NR/Pencil beam algorithm for dose calculation	n = 61	None	Median: 14 (Range: 1.5–82)	Local control	Grade 1, 2, 3 toxicities
Hof et al. (2007)[39]	Germany	Early stage lung cancer	Siemens Mevatron Linac/ Pencil beam algorithm for dose calculation	n = 42	None	Median: 15 (Range: 1.5–72)	Actuarial overall survival rates & local tumor control rates (Kaplan-Meier)	Minor cough; slightly increased dyspnea
Hoopes et al. (2007)[41]	USA	NSCLC	NR/NR	n = 58	None	Median: 42.5 (Range: 27–61)	Local failure; regional progression; metastatic dissemination	NR
Koto et al. (2007)[56]	Japan	Stage 1 NSCLC	Varian Clinac 23EX/NR	n = 31	None	Median: 32 (Range: 4–87)	3-year overall survival rate; cause specific survival after 3 years	Grade 1 acute pneumonitis; grade 2 acute pneumonitis; grade 3 acute pneumonitis
Madsen et al. (2007)[63]	USA	Localized prostate cancer	NR/NR	n = 40	None	Median: 41 (Range: 12–60)	PSA levels	Acute: rectal discomfort, constipation, diarrhea, tenesmus Late: proctitis, occasional blood, rectal discomfort, frequent stools, constipation, diarrhea
Muacevic et al. (2007)[69]	Germany	Lung tumors	CyberKnife/ Nonisocentric inverse planning algorithm	n = 15	None	2 month intervals	NR	Pneumothorax; nausea; pneumonitis

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Nuyttens et al. (2007)[73]	The Netherlands	Metastases (para-aortic or pelvic lymph nodes, abdominal wall, muscle tissue, rib, retroperitoneal fat, local recurrences in pelvis, neck)	CyberKnife/NR	n = 14	n = 3 prior chemo; n = 3 prior surgery; n = 4 prior irradiation	Median: 18 (Range: 6–26)	Local failure; local regional progression; tumor progression at a distance or new metastasis; local control and disease-free survival calculated Kaplan-Meier method; toxicity	Acute: transient grade 1 lymphedema in leg, grade 1 abdominal pain, nausea, and diarrhea; grade 1 dermatitis; Late: grade 1 rectal bleeding, chronically painful grade 2 subcutaneous fibrosis, grade 1 diarrhea, grade 2 pain in surgical scar on belly
Ponsky et al. (2007)[81]	USA	Renal	NR/NR	n = 3	Partial or radical nephrectomy 8 weeks after RS	Mean: 12.8 (Range: 12–14)	Tumor response	None reported
Ricardi et al. (2007)[82]	Italy	NSCLC	NR/NR	n = 43	None	Median: 14.7 (Range: 3–44)	Tumor control, complications	Temporary erythema; radiation pneumonitis (grade 1); acute pneumonitis; rib fracture; thoracic pain
Scorsetti et al. (2007)[90]	Italy	NSCLC	Linac/NR	n = 43	NR	Median: 14 (Range: 6–36)	Actuarial survival; morbidity	Acute and late grade I or grade II
Dawson et al. (2006)[20]	Canada	Hepatocellular carcinoma, intrahepatic cholangio-carcinoma, liver metastases	Elekta Synergy/ NR	n = 79	NR	Maximum: 34	Primary end point: rate of radiation-induced liver toxicity or severe toxicity occurring within three months of treatment	None observed
Ernst-Stecken et al. (2006)[22]	Germany	Lung cancer, thyroid cancer	Novalis/Dose calculation done by pencil beam algorithm	n = 21	None	Median: 6.3 (Range: 1-21)	Quality of hFSRT; local tumor control; survival	Grade 1 and 3 toxicity

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Hodge et al. (2006)[37]	USA	NSCLC	Tomotherapy Hi-Art/NR	n = 9	n = 2 single IMRT	Median: 2.1 (Range: 1.8–13.3)	Tumor response	No reports of grade 2 or higher acute toxicity
Hoyer et al. (2006)[43]	Denmark	Colorectal metastases	Siemens Primus or Varian Clinac 2100/2300/NR	n = 65	n = 16 surgery; n = 4 RFA or other treatment; n = 33 neoadjuvant chemo	Median: 51.6 (Range: 2.4–75.6)	Survival (Kaplan-Meier); tumor response (local control, local or distant progression); survival; toxicity	Death related to hepatic failure; perforation of colonic ulceration; duodenal ulceration; abdominal pain , increased consumption of analgesics; grade 2 or higher pain score; WHO performance status deterioration; moderate nausea; moderate diarrhea; skin toxicity
Le et al. (2006)[59]	USA	NSCLC or metastases	CyberKnife/NR	n = 32	n = 10 prior lung resection; n = 6 prior thoracic RT; n = 10 prior systemic therapy	Median: 18 (Range: 9–32)	Treatment response - partial response; minor response; stable disease	Pneumothorax; mild COPD; grade 2 to 3 pneumonitis
Nuyttens et al. (2006)[72]	The Netherlands	Early stage lung cancer	CyberKnife/NR	n = 20	None	Median: 4 (Range: 2–11)	Tumor response	Intrathoracic pain
Romero et al. (2006)[84]	The Netherlands	Primary liver tumors and metastases	Siemens Primus linac/NR	n = 25	None	Median: 12.9 (Range: 0.5–31)	Local control and survival (Kaplan-Meier)	Decompensated portal hypertension; bleeding from esophageal varices; ascites grade 2; elevation of gamma glutamyl transferase (GGT) grade 3; asthenia grade 3
Svedman et al. (2006)[103]	Sweden	Primary and metastatic renal cell carcinoma	Linac 6MV/NR	n = 30	n = 26 nephrectomy; n = 2 interferon alpha; n = 2 tamoxifen	Median: 52 (Range: 11–66)	Local tumor response (primary); toxicity, pain, and survival (secondary endpoint)	Cough, fatigue, skin rash, focal pain, one patient died—cannot be ruled out may have been treatment-related

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Timmerman et al. (2006)[108]	USA	Early stage NSCLC	Linac/NR	n = 70	None	Median: 17.5 (Range: 0.6–44.2)	Tumor response, disease control, survival	Grade 5 toxicities resulting in 6 deaths due to lung cancer treatment: 4 associated with bacterial pneumonia, 1 as a result of complications from pericardial effusion, 1 associated with massive hemoptysis; grade 3-4: decline in pulmonary function tests, pneumonitis, pleural effusions, apnea, skin reaction; grade 1-2: fatigue, musculoskeletal discomfort, radiation pneumonitis
Wulf et al. (2006)[119]	Germany	Primary liver cancer and hepatic metastases	NR/Dose distribution calculated based on a pencil beam algorithm	n = 56	None	Median: 15 (Range: 2–48)	Local tumor control; local failure; Secondary: treatment-related acute and late toxicity; freedom from systemic progression; overall survival	Pain; fever; chills; liver fibrosis; portal hypertension; ascites; bleeding from esophageal varices
Yoon et al. (2006)[123]	South Korea	Thoracic (38 primary or 53 metastatic)	NR/NR	n = 91	NR	Median: 14 (Range: 4–56)	Overall response	None greater than RTOG toxicity criteria grade 2 were observed
Xia et al. (2006)[120]	USA & China	Stage 1 or Stage 2 NSCLC	Gamma-knife (30 rotary conical surface Cobalt 60); NR	n = 43	None	Median: 27 (Range: 24–54)	Local tumor control – complete response; partial response; progressive disease	Acute radiation induced esophagitis; acute radiation induced pneumonitis; mild radiation induced acute whole body reactions (anorexia, nausea, and vomiting); grade 1 neutropenia; late radiation induced local fibrosis

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Zimmermann et al. (2006)[124]	Germany	Stage 1 NSCLC	NR/NR	n = 68	None	Median and Mean: 17 (Range: 3–44)	Tumor response—complete remission; partial remission; local progression; distant progression; overall and cancer-specific survival; acute and late toxicity	Pneumonitis; late lung fibrosis; fatigue; shivering; nausea; dermatitis; benign pleural effusion; rib fracture; fibrosis of soft tissue
Hoyer et al. (2005)[42]	Denmark	Pancreatic cancer	Siemens Primus or Varian Clinac/NR	n = 22	None	2–34	Toxicity; tumor response; overall survival; progression-free survival	Severe mucositis or ulceration of stomach or duodenum; perforation of stomach due to ulcer
Shioyama et al. (2005)[94]	Japan	Lung and liver tumors	Varian Clinac 21 Ex/NR	n = 20	None	1–15	Accuracy of fixation; local tumor response; survival and local rates calculated by Kaplan-Meier method; toxicities	NCI-CTC grade 2 complications
Song et al. (2005)[97]	USA	Lung tumors	NR/Tissue maximum ratio calculation algorithm	n = 17	None	Median: 14	Tumor response; toxicity	Fatigue; mild rib pain & tenderness; rib fracture; nonproductive cough; dyspnea; bronchial stenosis; collapse
Ishimori et al. (2004)[44]	Japan	Solitary lung cancer	Varian Clinac 2300 C/D/NR	n = 9	None	Range: 2–17	Local response – complete response; partial response; no change; progressive disease	Radiation induced pneumonitis

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Onishi et al. (2004)[77]	Japan	Stage 1 NSCLC	Linac/NR	n = 35	None	Range: 6–27	Locally progression; tumor response	Acute interstitial pneumonitis
Gerszten et al. (2003)[26]	USA	Sacrum	CyberKnife/NR	n = 18	n = 15 prior EBRT	NR	Pain improvement	No acute radiation toxicity or new neurological deficits occurred
Lee et al. (2003)[60]	South Korea	Primary and metastatic lung tumors	NR/NR	n = 28	NR	Median: 18 (Range: 7–35)	Survival time (Kaplan-Meier method); acute toxicity; late complications; response to radiation; patterns of treatment failure	All patients developed grade 1 radiation pneumonitis within 3 months; none had symptomatic complications after SRS treatment.
Whyte et al. (2003)[117]	USA	Primary lung cancer and metastases	CyberKnife/ Nonisocentric inverse-planning algorithm	n = 23	n = 1 right lower lobectomy	Mean: 7 (Range: 1–26)	Complete tumor response; Partial tumor response; Stable; Progressive; Death of nontreatment related causes	Pneumothoraces; exacerbation of underlying chronic obstructive pulmonary disease
Harada et al. (2002)[35]	Japan	Lung tumors	NR/NR	n = 18	n = 1 prior RT	Median: 9 (Range: 5–15)	Overall response rate	Pneumonitis
Uematsu et al. (2001)[113]	Japan	Stage 1 NSCLC	FOCAL unit (combination of linac, CT scanner, X-ray simulator, carbon table)/NR	n = 50	n = 18 prior conventional treatment (40-60 Gy in 20-33 fractions, 4-6 weeks)	Median: 36 (Range: 22–66)	Overall cause specific survival rates (Kaplan-Meier Method); local control	Rib fracture; vertebral compression fracture; mild and temporary pleural pain; lung fibroses and/or atelectasis

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Wulf et al. (2001)[118]	Germany	Lung and liver	NR/NR	n = 51	n = 18 chemo	Median lung: 8 (Range: 2–33); Median liver: 9 (Range: 2–28)	Crude local control; actuarial local control; actuarial overall patient survival	Grade 1/2; grade 3; grade 4; grade 5
Nakagawa et al. (2000)[70]	Japan	Thoracic neoplasms	Megavoltage computed tomography assisted SRS/NR	n = 15	n = 1 prior Gamma Knife SRS to a solitary brain metastasis; n = 8 conventional fractionated RT following SRS	Median: 10 (Range: 2–82)	Tumor response; survival	No patient reported adverse acute symptoms; all patients who survived for over 3 months showed some interstitial change in the local lung tissue.

COPD: Chronic obstructive pulmonary disease
CT: Computed tomography
EBRT: External beam radiation therapy
HCC: Hepatocellular carcinoma
hFSRT: Hypofractionated stereotactic radiotherapy
IHCC: Intrahepatic cholangiocarcinoma
IMRT: Intensity modulated radiation therapy
NCI-CTC: National Cancer Institute-Common Toxicity Criteria
NSCLC: Non-small cell lung cancer
NR: Not reported
PSA: Prostate specific antigen
QoL: Quality of life
RECIST: Response evaluation criteria in solid tumors
RFA: Radiofrequency ablation
RS: Radiosurgery
RT: Radiation therapy
RTOG: Radiation Therapy Oncology Group
SBRT: Stereotactic body radiation therapy
SRS: Stereotactic radiosurgery
TACE: Transcatheter arterial embolization
WHO: World Health Organization

Retrospective Studies

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Crabtree et al. (2010)[19 *]	USA	Stage I NSCLC	Trilogy/NR	n = 76 treated with SBRT n = 462 treated with surgical resection	None	SBRT Median: 19 Surgical Median: 31	Local recurrence; disease-specific survival; overall survival	SBRT: grade 1–2 pneumonitis; grade 3 pnuemonitis; rib fractures; pleural effusions; lung collapse; hemoptysis; bacterial pneumonia Surgery: arrhythmias; pneumonia / respiratory

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Dunlap et al. (2010)[21]	USA	Primary NSCLC	Hi-Art Helical TomoTherapy/Inverse planning software	n = 60	None	Median: 12.5 (Range: 2–35) Median: 11.1 (Range: 3–35)	Tumor response; local recurrence; regional nodal recurrence, distant systemic metastases; survival; local control	Chest wall pain; rib fracture; symptomatic pulmonary complications (>grade 1); grade 3-4 pneumonitis
Grills et al. (2010)[28 †]	USA	Stage I NSCLC	NR/NR	n = 55 treated with SBRT n = 69 treated with wedge resection	None	Median: 30	Regional recurrence; locoregional recurrence; distant metastasis; freedom from any failure; overall survival; cause-specific survival	Grade 2–3 radiation pneumonitis; rib fractures; grade 1 skin toxicities; acute or chronic myositis
Guckenberger et al. (2010)[31]	Germany	Locally recurrent gynecological cancer	Linac/NR	n = 12 cervical cancer n = 7 endometrial cancer	n = 12 prior surgery n = 6 prior surgery and adjuvant RT n = 1 prior RT n = 6 concurrent EBRT followed by SBRT boost	Median: 22	Survival; systemic control; local control	Acute: grade 2 diarrhea, nausea, proctitis, dysuria, dermatitis; grade 3 pollakisuria Late: grade 2 proctitis, nausea, stenosis of yereter, neuralgic pain; grade 4 small bowel ileus, intestine vaginal fistula
Hamamoto et al. (2009)[34]	Japan	Primary lung cancer and metastatic lung tumors	Linac/Pencil beam	n = 52 primary lung cancer n = 10 metastatic lung tumors	n = 2 prior intravenous systemic chemo	All tumors Median: 14 (Range: 3–34) Primary Median: 14 (Range: 3–34) Metatastic Median: 19 (Range: 9–31)	Overall survival; local control	None reported

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Jorcano et al. (2010)[46]	Switzerland	Gynecologic tumors	Novalis/NR	n = 9 cervical cancer n = 17 endometrial cancer	Prior: hysterectomy, pelvic lymphadenectomy, chemo, para-aortic irradiation, WPRT Concurrent: traditional RT followed by SBRT boost	Median: 47 (Range: 4–77)	Toxicity; local disease control; distant failures; overall survival; failure-free survival rate	Acute: grade 0–2 sexual, grade 0–3 urinary, grade 0–3 rectal Late: grade 0–3 sexual, grade 0–2 urinary, grade 0–3 rectum
Kang et al. (2010)[48]	Korea	Oligometastases confined to one organ from colorectal cancer	Cyberknife/NR	n = 55 with 78 lesions (lung, liver, pelvic aortic lymph nodes, mediastinal lymph nodes, bone)	n = 21 prior curative intent local therapy (resection, RFA) n = 49 prior chemo	Median: 32 (Range: 9–80)	Tumor response; toxicity; local control; overall survival	Acute: grade 1–2 - nausea, vomiting, musculoskeletal discomfort; grade 4 intestinal perforation, obstruction
Kim et al. (2010)[53]	Korea	Nonanaplastic thyroid cancer	Cyberknife/NR	n = 9	n = 3 prior neck RT, neck surgery, radioisotope	Median: 23 (Range: 4–63)	Tumor response; regional failure	No grade 3 or higher Adverse events
Louis et al. (2010)[62]	Belgium	HCC	Cyberknife/NR	n = 25	n = 3 prior chemoembolization n = 1 prior sorafenib n=3 prior surgery n = 2 prior radiofrequency ablation	Median: 12.7 (Range: 1–24)	Local control; tumor response; toxicity; survival; overall survival; disease free survival	Acute: grade 3 liver pain; grade 3 hepatic toxicity; grade 2 digestive in nature Late: grade 2-3 duodenal ulcers
Mahadevan et al. (2010)[64]	USA	Nonmetastatic locally advanced unresectable pancreatic cancer	CyberKnife/NR	n = 36	None	Median: 24 (Range: 12–33)	Local control; acute toxicity; local and distant progression; overall survival	Fatigue; nausea; persistent nausea; cramping, vomiting, dehydration; worsening inferior vena cava thrombosis that developed at exploratory laparotomy; gastrointestinal bleeding requiring transfusion (late toxicity)

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Seok Seo et al. (2010)[91]	Korea	Inoperable HCC	Cyberknife /NR	n = 38	n = 38 prior TACE	Median: 15 (Range: 3–47) at this time 17 patients had died	Local progression-free survival; disease progression-free survival; overall survival	Grade 1–2: decline in liver function; acute radiation dermatitis with wet desquamation Grade 3: soft tissue toxicity
Son et al. (2010)[96]	South Korea	Small unresectable primary hepatocellular carcinoma	CyberKnife	n = 36	None	NS	Radiation induced hepatic toxicity; deterioration of hepatic function	Grade 2–4 toxicities
Takeda et al. (2010)[106]	Japan	Primary lung cancer and metastatic lung tumors	NR/superposition algorithm	n = 111 primary lung cancer n = 22 lung metastasis	None	Median: 12 (Range: 5–45)	Toxicity	Grade 0–3 radiation pneumonitis
Townsend et al. (2010)[110]	USA	Prostate cancer	CyberKnife/NR	n = 48	n = 11 IMRT, Tomotherapy followed by SBRT boost	Mean: 2.76 Median: 2.64	Acute gastro-intestinal and genitourinary toxicities	Mild increase in frequency/nocturia; acute grade 1–3 gastrointestinal and genitourinary
Trovo et al. (2010)[111]	USA	Lung cancer	Trilogy/superposition convolution algorithm	n = 68 with 70 tumors	None	Four follow-up periods: 6 weeks; 2–6 months; 7–12 months; 13–18 months after SBRT	Radiographical changes; toxicity; local control	Pleural thickening; pleural effusion; bronchiectasis; radiation fibrosis Late radiographical injuries; grade 2 lung toxicity; grade 2 pulmonary toxicity; grade 2–4 emphysema
Unger et al. (2010)[114]	USA	Primary hilar lung cancer or hilar lung metastases	Cyberknife/Non-isocentric, inverse-planning algorithm	n = 20	None	Median: 10	Local tumor recurrence; toxicity; overall survival	Acute grade 2 esophagitis; dyspnea and infiltrate; mainstem bronchus fistula; mild fatigue

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Yamashita et al. (2010)[121]	Japan	Primary lung cancer and metastatic or recurrent lung cancer	Synergy/Collapsed cone convolution	n = 74 primary lung cancer n = 43 metastatic or recurrent lung tumors	None	Median: 14.7 (Range: 0.3–76.2)	Toxicity	Grade 0–5 radiation pneumonitis
Yang et al. (2010)[122]	China	HCC	Body Gamma Knife treatment system/NR	n = 40	Prior and Concurrent: n = 17 prior and concurrent rAd-p53 (recombinant adenovirus-mediated wild-type p53 gene – rAd-p53)	Median: 35 (Range: 11–44)	Response; toxicity; survival	Grade 1–2: Fever; gastrointestinal toxicity; abnormal liver function; thrombocytopenia; leukopenia
Hof et al. (2009)[40]	Germany	Lung tumors	Linac/NR	n = 49	None	Median: 19.3 (Range: 6.44–51.1 with NTC) Median: 12.9 (Range: 4.6–31.3 without NTC)	Normal tissue changes (NTC)	None reported
Ahn et al. (2009)[2]	Korea	Stage 1 NSCLC	CyberKnife/NR	n = 8	None	Range: 5–49	Tumor response; local control	Mild malaise; mild asymptomatic radiation pneumonitis
Chang et al. (2009)[1]	Canada and USA	Unresected pancreatic adenocarcinoma	CyberKnife/NR	n = 77	Prior: n = 9 RT, n = 15 chemo Concurrent: n = 16 IMRT, n = 59 chemo	Median: 6 (Range: 3–31) Median (Survivors): 12 (Range: 3–31)	Local progression; progression-free survival; overall survival; local control	Grade 2–4 toxicities

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Chawla et al. (2009)[14]	USA	Adrenal metastases	Novalis/NR	n = 30 3 of 30 also had metastases in the lungs and/or thoracic lymph nodes, liver, or abdominal and/or pelvic lymph nodes	n = 17 prior chemo; n = 9 SBRT	Median: 9.8 (Range: 3.2–28.3)	Overall survival, survival, distant control, local control, tumor response, pain	Grade 1 nausea, mild fatigue
Choi et al. (2009)[16]	Korea	Para-aortic lymph node (PALN) metastases from uterine cervical and corpus cancer	CyberKnife/SBRT planning algorithm	n = 30	n = 2 prior chemo; n = 9 concurrent chemo	Median: 15 months, Range: 2–65	Tumor response; overall survival; disease progression-free survival (DPFS); local control; toxicity	Grade 3 or higher toxicity Acute hematologic toxicities of grade 3 or higher during chemo Late toxicity: ureteral stricture
Guckenberger et al. (2009)[30]	Germany and Switzerland	Early stage NSCLC and pulmonary metastases	Linac/Collapsed cone dose calculation algorithm	n = 40	None	Mean: 21, Median: 14, Maximum: 91 - early stage NSCLC Mean: 17, Median: 14, Maximum: 80 - pulmonary metastases	Local control; regional and systemic control for early-stage NSCLC; survival	Pneumonitis grade 2; pneumonitis grade 3; pneumothorax grade 2; pleural effusion grade 2; dyspnea grade 2; esophageal ulceration grade 3

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Kawase et al. (2009)[50]	Japan	Isolated T1-T2N0M0 primary or metastatic lung tumors	Linac/Collapsed-cone algorithm of Pinnacle3 or the multigrid superposition algorithm of XiO with a density heterogeneity correction	n = 379	None	Median 29 (Range: 1–72)	Development of extra-pulmonary soft-tissue mass	Co-existing swelling; chest pain; thumb numbness: arm edema
McCammon et al. (2009)[65]	USA	Lung and liver tumors	Linac/Pencil-beam algorithm for tissue inhomogeneity correction	n = 141	None	Median (All): 8.2 (Range: 1.4–44.4) Median (Survivors): 18.3 Median (Deceased): 5.9	Tumor response; local control	Grade 2, 3, and 4 events: grade 2, 3, 4 pneumonitis, grade 2 or 3 dermatitis, grade 2 or higher soft tissue/muscle inflammation, fibrosis, vertebral fractions
Milano et al. (2009)[66]	USA	Central thoracic lesions	Linac/NR	n = 53	n = 6 concurrent SBRT boost; n = 9 multiple courses of SBRT (2–3 courses)	Median 10 (Range: <1–78)	Survival; distant progression; local control	Acute grade 1, 2 esophageal toxicity; grade 2 radiation pneumonitis; grades 1–2 hemoptysis; grade 2 pneumonia; grade 3 pneumonia; grade 2 pneumothorax; fatal hemoptysis; grade 3 pericarditis
Milano et al. (2009)[68]	USA	Oligometastases	Novalis/NR	n = 77: 42 liver, 21 lung, 5 thoracic lymph nodes, 9 bone n = 13 lung parenchymal and thoracic lymph nodes	62 of 77: systemic therapy for metastatic disease prior to SBRT 11 of 13 systemic therapy before SBRT	n = 77 Overall Median (n = 77): 23 (Range: 5–85) Living Median (n = 77): 45 (Range: 14–95) Overall Median (n = 13): 21 (Range: 6–66) Living Median (n = 13): 54 (Range: 42–66)	Patterns of recurrence after curative-intent SBRT	NR

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Pennathur et al. (2009)[79]	USA	Stage NSCLC	Linac/NR	n = 21	None	Mean: 24	Tumor response; survival; local progression	Pneumothorax (after fiducial placement)
Ricardi et al. (2009)[83]	Italy	Stage 1 NSCLC	Elekta Precise linac/NR	n = 60	None	Median: 30.9 (Range: 6.7–56.7)	Radiation-induced lung injury scoring; mean lung dose; normal tissue complication probability	Grade 0–3 pulmonary toxicity
Rusthoven et al. (2009)[85]	USA	Metastatic lung cancer	Linac/NR	n = 64	Prior first-line systemic therapy (cytotoxic chemo and/or molecular targeted therapies)	NR	Progression	NR
Seong et al. (2009)[92]	Korea	Hepatocellular carcinoma	CyberKnife/NR	n = 398	Prior: n = 312 TACE, n = 54 transarterial chemoinfusion (TACI), n = 10 systemic chemotherapy, n = 35 RFA, n = 34 iA-chemotherapy, n = 25 surgery, n = 8 percutaneous ethanol injection, n = 7 holmium	Median: 12 (Range: 0.4–42)	Survival	NR
Stephans et al. (2009)[99]	USA	Stage 1 lung cancer	Novalis/NR	n = 92	None	Median: 18.4 (Range: 1.7–48)	Pulmonary function test; overall survival, local control	Grade 2 radiation pneumonitis

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Stephans et al. (2009)[100]	USA	Stage 1 NSCLC	Novalis/NR	n = 86 receiving 50 Gy or 60 Gy	None	Overall median: 15.3 (Range: 1.9–47.6) 50 Gy Median: 19.8 (Range: 1.9–47.6) 60 Gy Median: 9.5 (Range: 2.1–19.5)	Local control, nodal failure, distant metastasis, overall survival	Grade 2 radiation pneumonitis; grade 1 or 2 chest wall toxicity
Song et al. (2009)[98]	Korea	Stage 1 NSCLC	Linac/NR	n = 32	None	Median: 26.5 (Range: 5.2–92)	Local tumor control, survival, patterns of failure	Grade 3 severe pulmonary toxicities; 1 death due to bleeding aspiration and pneumonia from SBRT-induced complete bronchial stricture; stricture of lobar bronchus and secondary lung collapse
Takeda et al. (2009)[105]	Japan	Primary lung cancer Stage 1A and 1B	Linac/MG-superposition algorithm with heterogeneity correction	n = 63	None	Median of inoperable patients (n = 49) 31 months (Range: 1–72 months)	Local control; disease-free survival; overall survival; regional recurrence-free; distant metastasis-free; cause-specific survival	Grade 2 or higher radiation pneumonitis; fatal bacterial pneumonia (authors considered SBRT to have possibly contributed to the events leading to death)

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Baumann et al. (2008)[6]	Sweden, Denmark, Norway	Stage 1 NSCLC	Linac/Pencil beam algorithms with heterogeneity correction	n = 57	None	Median: 23 (Range: 3–42)	Tumor control; toxicity; lung function and performance status	Overall: grade 1, 2, and 3 toxicity Lung-related toxicity: grade 1–2 cough, grade 3 cough, grade 1–2 dyspnea, grade 3 dyspnea, grade 1–2 pneumonia, grade 3 pneumonia, grade 1–2 pneumonitis, grade 1–2 fibrosis, grade 3 fibrosis, grade 1–2 atelectasis, grade 3 atelectasis, grade 1–2 pleural effusion, grade 3 pleural effusion, grade 1–2 heart disorder, grade 3 heart disorder, grade 1–2 esophagitis General toxicity: grade 1–2 skin, grade 1–2 pain, grade 3 pain, grade 1–2 rib fracture, grade 3 rib fracture, grade 1–2 upper airway infection, grade 1-2 fever, grade 1–2 nausea, grade 1–2 emesis, grade 1–2 fatigue, grade 3 fatigue
Casamassima et al. (2008)[12]	Italy	NSCLC or metastases	Elekta Synergy/ Pencil beam algorithm for dose calculation	n = 104	Metastases prior chemo	Median: 13.88 (Range: 1.37–49.4)	Overall survival (Kaplan-Meier method); tumor response	Acute lung toxicity; dysphagia

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Choi et al. (2008)[15]	South Korea	Hepatocellular carcinoma	CyberKnife/NR	n = 31	Prior: n = 17 (TACE, n = 3) percutaneous ethanol injection (PEI, n = 6 RFA)	Median 10.5 (Range: 2–18.5)	Tumor response; survival	Treatment-related toxicity: liver enzymes grade 0, 1, 3; bilirubin grade 0–1; albumin grade 0–1; leukocytes grade 0–2; platelets grade 0, 1, 3; nausea grade 0–1; progression of Child-Pugh classification from A to B
Coon et al. (2008)[18]	USA	NSCLC, recurrent disease, or solitary lung metastases	CyberKnife/NR	n = 51	NR	Median primary and recurrent cancer: 11 (Range: 2–24); Median metastases: 12 (Range: 2–24)	Complete response; partial response; stable disease; disease progre ssion	Grade 2 radiation pneumonitis; exacerbation of preexisting COPD
Fritz et al. (2008)[24]	Germany	Stage 1 NSCLC	Elekta Precise Sli/NR	n = 40	NR	Median: 20 (Range: 6–61.5)	Tumor response as categorized by WHO	Grade 1 radiation dermatitis; grade 1 subcutaneous fibrosis; grade 4 rib fracture

Jereczek-Fossa et al. (2008)[45]	Italy	Breast, lung, head and neck, urologic, gynecologic, gastrointestinal, CNS, other primaries	Linac (6–18 MV, used for 3D-CRT and SRT)/NR	n = 108	Prior radiation doses ranged from 8 to 74.4 Gy (Mean: 37 Gy);
					n = 95 conventional or 3D-CRT;
					n = 13 SRT;
					n = 55 chemo;
					n = 3 concurrent brachytherapy
						Median: 7 (Range: 1–50)	Overall survival; tumor response	No severe toxicity was reported

Kim et al. (2008)[51]	South Korea	Pelvic recurrence from rectal carcinoma	CyberKnife/NR	n = 23	Prior lower anterior resection, abdomino-perineal resection; adjuvant chemo; concurrent chemo-radiotherapy; all salvage chemo before SBRT	Median: 31 (Range: 7–65)	Tumor response; local failure	Nausea, vomiting, pain (Grade 1 & 2; grade 3 & 4 reported; rectal perforation

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Kunos et al. (2008)[57]	USA	Squamous cell carcinoma of the vulva	CyberKnife/NR	n = 3	n = 3 prior pelvic radiation for vulvar cancer	At least 2	Tumor response	No skin, urinary, or gastrointestinal toxicities were observed during course
Lagerwaard et al. (2008)[58]	The Netherlands	Stage 1 NSCLC	Linac/NR	n = 206	Prior: n = 7 pneumonectomy, n = 2 bilobectomy, n = 17 lobectomy, n = 2 wedge resection, n = 3 chemoradio-therapy, n = 5 radiotherapy, n = 1 endobronchial therapy	Median 12 (Range: 3–44)	Overall survival; disease-free progression; local failure; regional failure; distance progression-free survival	Fatal cerebrovascular accident during treatment; fatigue, local chest wall pain; nausea; dyspnea; cough; grade 3 or greater pneumonitis; rib fractures; chronic thoracic pain syndromes
Norihisa et al. (2008)[71]	Japan	Oligometastatic lung tumors	Linac/NR	n = 34	Most prior surgical resection and chemo for primary cancer	Median 27 (Range: 10–80)	Overall survival rate; local relapse free rate; progression-free rate; disease free interval; local response	Pulmonary toxicity (grade 1 and 2): cough, hemoptysis, dyspnea, pleural effusion, radiographic changes, bacterial pneumonia, grade 3 pulmonary toxicity, grade 1 skin toxicity with faint erythema or pigmentation, skin ulcer Musculoskeletal: bone fracture of the rib, chest wall pain, mild pain, grade pericardial effusion, temporal liver dysfunction
Onimaru et al. (2008)[76]	Japan	NSCLC	NR/treatment planning made with Focus or Xio calculation algorithm: 31 Clarkson, 10 Superposition	n = 41	None	Median: 27 (Range: 9–62)	Overall actuarial survival and cause-specific survival (Kaplan-Meier); deaths from causes other than lung cancer; local control rate	Radiation pneumonitis; pleural effusion; chest wall pain from radiation pleuritis

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Svedman et al. (2008)[104]	Sweden and Italy	Primary or metastatic renal disease	Linac/Pencil beam algorithm (dose planning)	n = 7	n = 1 prior metastatic surgery; n = 1 prior interferon-alpha	Maximum 70	Creatinine levels; local control; kidney function	Grade 1–2: nausea, fatigue, local pain
Brown et al. (2007)[10]	USA	Stage 1 NSCLC and lung metastases	CyberKnife/NR	n = 88	n = 7 prior conventional fractionated external radiotherapy	Range: 1-36	Complete response; partial response; stable disease; progression of disease	Lung and esophagus toxicity, radiation pneumonitis; esophagitis; mild fatigue
Guckenberger et al. (2007)[29]	Switzerland	NSCLC or pulmonary metastatic lesions	NR/NR	n = 70	NR	Median: 16 (Range: 1.5–85)	Actuarial local tumor control; complete response	Symptomatic pneumonitis; mild cough or dyspnea not requiring steroids; grade 2 pneumonitis; pleural effusion
Teh et al. (2007)[107]	USA	Spine, bone, soft tissue/organ, and lymph node	Novalis/NR	n = 80	Prior RT; n = 1 prior surgery for sacral nerve neuroma	NR	Pain relief; symptom control; tumor response	NR
Baumann et al. (2006)[5]	Sweden	Stage 1 NSCLC	Linac/NR	n = 141	None	Median: 33 (Range: 1–107)	Tumor response - complete response; partial response; stable disease; local failure	Mild toxicity; skin rash; costal fracture; cough; radiological pneumonitis/ fibrosis; atelectasis; grade 3-4 toxicity
Joyner et al. (2006)[47]	USA	Metastases or Recurrence NSCLC	Linac/NR	n = 9	None	Median: 10.6 (Range: 2.5–42.5)	Overall survival; local tumor control; normal tissue imaging changes	Transient pneumonitis; fibrotic reactions; some degree of wall thickening; lobe atelectasis; narrowing of lobe bronchus
Paludan et al. (2006)[78]	Denmark	Stage 1 NSCLC	NR/DVH parameters calculated by use of a pencil beam algorithm	n = 28	None	Median: 6.7 (Range: 2.1–7.5)	Dyspnea development	NR

Study	Country	Cancer Type	Instrumentation/ Algorithms	Study Size	Prior or Concurrent Treatment	Length of Followup (Months)	Outcomes Measured	Adverse Events
Sinha et al. (2006)[95]	USA	Bilateral primary lung cancer	NR/NR	n = 10	n = 1 prior resection of lesion	Mean: 20.7, Median: 18.5 (Range: 7–42)	Tumor response	Grade 1 and 2 complications
Beitler et al. (2004)[7]	USA	Renal cell carcinoma	NR/NR	n = 9	n = 1 prior nephrectomy	Median: 26.7	Survival calculated by Kaplan-Meier method	Nausea, vomiting, glandular atypia in the stomach
Gunven et al. (2003)[32]	Sweden	Recurring liver metastases of colorectal cancer	Linac/NR	n = 4	Prior surgical resection	10–101	Tumor sizes and evolution; tumor regressi on	Epigastric pain; slight diffuse mucosal redness

* Author's retrospectively reviewed two case series: patients treated with SBRT (February 2004 – May 2007) and patients treated with surgery (January 2000 – December 2006)

† Author's retrospectively reviewed two case series: patients treated with SBRT or wedge resection (February 2003 – February 2009)

3D-CRT: Three-dimensional conformal radiation therapy
CNS: Central nervous system
COPD: Chronic obstructive pulmonary disease
DPFS: Disease progression-free survival
DVH: Dose volume histogram
Gy: Gray
IMRT: Intensity modulated radiation therapy
NSCLC: Non-small cell lung cancer
NR: Not reported
NTC: Normal tissue changes
PALN: Para-aortic lymph nodes
PSA: Prostate specific antigen
RFA: Radiofrequency ablation
RT: Radiation therapy
SBRT: Stereotactic body radiation therapy
SRT: Stereotactic radiotherapy
TACE: Transcatheter arterial chemoembolization
TACI: Transarterial chemoinfusion
WHO: World Health Organization
WPRT: Whole pelvic radiation therapy

Appendix M. Literature Results Device Specifications

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Freeman et al. (2011)[23]	Cyberknife 6 MV	150-200 noncoplanar beams	NS	NS	CT, MRI	NS	Fiducial markers (3–4)	NS	Orthogonal x-ray images
Aluwini et al. (2010)[3]	Cyberknife	NS	NS	NS	CT, MRI	NS	NS	NS	NS
Bolzicco et al. (2010)[8]	Cyberknife 6 MV	Noncoplanar	NS	NS	CT	Non-isocentric inverse treatment planning	4 Fiducials	NS	Orthogonal x-ray images
Bradley et al. (2010)[9]	NS	8-11 beams	NS	SBF, BodyFix, Alpha Cradle	4D CT	Tissue heterogeneity corrections	NS	NS	NS
Cardenes et al. (2010)[11]	Linac 6MV	7-12 non-opposing, noncoplanar fields	NS	SBF	CT	NS	NS	NS	Cone-beam computed tomography
Crabtree et al. (2010)[19]	Trilogy	10-12 noncoplanar beams	NS	NS	NS	NS	Fiducials	NS	NS
Dunlap et al. (2010)[21]	Hi-Art Tomotherapy	NS	NS	Stereotactic frame	CT	Inverse planning software (Tomotherapy) and BrainScan planning software (BrainLab)	Fiducial markers	NS	NS
Goodman et al. (2010)[27]	Cyberknife	NS	NS	Alpha Cradle	CT, PET	Multiplan (Accuray)	Fiducials (3–5) 5mm x 1mm	Synchrony	NS
Grills et al. (2010)[28]	NS	6–9 coplanar and noncoplanar beams	NS	SBF or Alpha cradle	4D CT, PET	Pinnacle	NS	NS	Cone-beam computed tomography
Guckenberger et al. (2010)[31]	NS	NS	NS	SBF or BodyFix system	CT, cone-beam CT	NS	NS	NS	Verification imaging
Hamamoto et al. (2010)[34]	Linac 4 MV	8–11 noncoplanar static beams	mMLC	BodyFix	CT	3D treatment planning (BrainSCAN)/pencil beam algorithm	NS	NS	NS
Jorcano et al. (2010)[46]	Novalis 6 MV	NS	mMLC	Customized vacuum body cast	CT, MRI	NS	Infrared (IR) reflecting metallic markers	NS	Infrared cameras

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Kang et al. (2010)[48]	Cyberknife	NS	NS	Alpha cradle	CT, MRI, PET	NS	NS	4 belts to compress abdomen	NS
Kim et al. (2010)[53]	Cyberknife	NS	NS	Customized thermoplastic mask and vacuum cushion	Contrast-enhanced CT	On-target Planning System	NS	NS	Orthogonal x-ray images
Kopek et al. (2010)[55]	Seimens Primus	5–8 static coplanar or noncoplanar beams	MLC with leaf width 5 or 10 mm at isocenter	Customized vacuum pillow fixed in SBF (Elekta)	CT	Helax-TMS (MDS-Nordion, Freiburg, Germany) treatment planning system	NS	Abdominal compression	CT scan first treatment day; portal imaging with matching to vertebral column
Louis et al. (2010)[62]	Cyberknife	NS	NS	Vacuum mattress or self-expanding foam mattress	CT	Multiplan (Accuray)	Fiducials (2–6) 0.88 mm x 5 mm	Synchrony	NS
Mahadevan et al. (2010)[64]	CyberKnife 6MV	NS	NS	Memory foam placed over customized Vac-Lok (CIVCO Medical Solutions) immobilization cradle	CT	MultiPlan workstation (Accuray)	Fiducials (3–5) 5 mm x 0.8 mm	Synchrony	NS
Oermann et al. (2010)[74]	Cyberknife	NS	NS	NS	CT, MRI	Multiplan (Accuray)	At least 4 gold fiducials	NS	NS
Polistina et al. (2010)[80]	CyberKnife 6MV	Noncoplanar	NS	Alpha cradle immobilization device; vacuum preconformed bed	CT	NS	Fiducial markers 3 or more	Synchrony	NS
Seo et al. (2010)[91]	Cyberknife	NS	NS	Alpha Cradle	CT, MRI, PET	NS	Fiducials (6) 4 mm x 0.8 mm	4 belts to compress abdomen	Orthogonal x-ray images
Shin et al. (2010)[93]	Cyberknife	NS	20, 25, 30, 35, 40 mm diameter circular collimator	Alpha cradle	CT, MRI, PET	Pencil beams	Fiducials (6) 4 mm x 0.8 mm	4 belts to compress abdomen	NS

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Son et al. (2010)[96]	CyberKnife 6MV	NS	NS	NS	NS	NS	Skin markers	Abdominal compression, breath hold	NS
Stintzing et al. (2010)[102]	Cyberknife 6 MV	NS	NS	NS	CT, MRI	NS	Gold fiducials 5 mm x 0.5 mm	NS	Orthogonal x-ray images
Stintzing et al. (2010)[101]	Cyberknife 6 MV	NS	NS	NS	CT, MRI	NS	Fiducials (1–2) 5 mm x 0.5 mm	NS	Orthogonal x-ray images
Takeda et al. (2010)[106]	NS	NS	NS	NS	CT	Superposition algorithm	NS	NS	NS
Timmerman et al. (2010)[109]	Linac	NS	NS	NS	CT	No tissue density heterogeneity correction was allowed	NS	Abdominal compression, gating, breath hold	4D CT scans, fluoroscopy
Townsend et al. (2010)[110]	CyberKnife 6MV	NS	NS	Custom-fit body mold	CT	Inverse planning technique	Fiducial markers	NS	NS
Trovo et al. (2010)[111]	Trilogy 6 MV	Multiple coplanar and noncoplanar beams	NS	SBF or BodyFix	CT	Superposition/convolution algorithm	NS	NS	NS
Unger et al. (2010)[114]	Cyberknife	NS	NS	NS	CT	Nonisocentric, inverse-planning algorithm with tissue density heterogeneity	Fiducials (3–5) 0.8–1 mm x 3–7 mm	Form fitting vest with 3 red light emitting surface markers	Orthogonal x-ray images
Vahdat et al. (2010)[115]	CyberKnife 6MV	Hundreds of beams	Single collimator 20-30 mm in diameter	NS	CT	Nonisocentric inverse planning algorithm with tissue heterogeneity corrections	Fiducials; 3 LEDs placed on patients anterior torso	NS	Orthogonal x-ray images; live camera array signal and correlation model
Yamashita et al. (2010)[121]	Synergy	At least 8 beams	NS	Body frame	CT	3D treatment planning machine (Pinnacle3)	NS	Abdominal pressure board	NS
Yang et al. (2010)[122]	Body GammaKnife	NS	NS	Vacuum cushion	CT	3D treatment planning system	NS	NS	NS

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Hof et al. (2009)[40]	Linac 6 MeV	6–7 isocentric portals	NS	Vacuum pillow inside stereotactic frame	CT	3D treatment planning VIR-TUOS software (German Cancer research center)/pencil beam algorithm dose calculation	NS	NS	NS
Ahn et al. (2009)[2]	CyberKnife 6MV	NS	NS	NS	NS	NS	NS	NS	NS
Chawla et al. (2009)[14]	Novalis	Conformal arcs	NS	NS	CT, PET	BrainLAB 3D Brain SCAN system	NS	Breath hold technique	ExacTrac
Choi et al. (2009)[16]	CyberKnife 6MV	NS	NS	Alpha Cradle and four belts to restrict respiratory motion (Smithers Medical)	CT	CyberKnife planning system	Six 4 mm length x 0.8 mm diameter fiducials	NS	NS
Collins et al. (2009)[17]	CyberKnife 6MV	NS	NS	NS	CT	Nonisocentric inverse plan	3–5 gold fiducials 0.8–1 mm (diameter) x 3–7 mm (length)	NS	Light emitting diodes (LEDs) on patients anterior torso; Orthogonal x-ray imagers
Guckenberger et al. (2009)[30]	Linac	NS	NS	SBF (Elekta); BodyFix system (Medical Intelligence)	CT	NS	NS	Abdominal compression	Out of room CT scanner, in-room single slice CT scanner; integrated cone-beam CT (Elekta)
Haasbeek et al. (2009)[33]	Linac	8–11 radiation beams	NS	NS	4D CT	BrainLAB BrainScan version 5.31 treatment planning software and Philips medical Systems Pinnacle Treatment Planning System	NS	NS	Orthogonal x-ray images or conebeam CT

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Kopek et al. (2009)[54]	Siemens Primus or Varian Clinac 2100/2300 6 or 8MV	5–8 static coplanar or noncoplanar beams	MLC leaf width 5–1 mm at isocenter	SBF (Elekta)	CT	MDS Nordion Helax TMS or Varian CadPlan Plus/Eclipse treatment-planning systems / pencil beam algorithm dose calculation with heterogeneity correction	NS	Diaphragmatic compression	Portal field imaging and CT scan
Kawase et al. (2009)[50]	Linac	NS	NS	NS	CT	Koninklijke Philips Electronics Pinnacle^3 planning system or CMS Xio	NS	NS	NS
Kim et al. (2009)[52]	CyberKnife 6 MV	NS	Single 20, 25, or 30 mm diameter collimator	Alpha Cradle (Smithers Medical)	CT	CyberKnife planning system/pencil beam	6 gold fiducials 4 mm (long) x 0.8 mm (diameter)	4 belts to compress the abdomen	NS
King et al. (2009)[305]	CyberKnife 6 MV	NS	NS	Alpha cradle	CT	NS	3 gold fiducials	NS	Image guidance
Milano et al. (2009)[68]	Novalis	NS	NS	NS	NS	BrainScan system	NS	Breath hold technique or shallow breathing	ExacTrac
Milano et al. (2009)[66]	Linac	Conformal arcs	NS		CT, PET	BrainLAB BrainScan treatment planning system	NS	NS	ExacTrac
Milano et al. (2009)[67]	Novalis	Conformal arcs or multiple fixed coplanar beams	NS	Vacuum bag	CT	BrainLAB BrainScan treatment planning system	NS	NS	ExacTrac
Lee et al. (2009)[61]	Linac	NS	NS	Customized body mold	CT, MRI	NS	NS	Elekta ABC or abdominal compression	2D orthogonal MV image guidance; 3D kV cone beam CT combined with 2D kV fluoroscopy

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Olsen et al. (2009)[75]	Linac	NS	NS	NS	NS	NS	NS	Assisted breathing device or abdominal compression plate	NS
Pennathur et al. (2009)[79]	Linac	NS	NS	Alpha Cradle (Smithers Medical)	CT	NS	1–4 fiducials implanted	Breath hold, Synchrony	Rea- time image guidance
Ricardi et al. (2009)[83]	Elekta Precise linac 6 and 10 MV	6–8 static nonopposing, noncoplanar	NS	Vacuum pillow and SBF (Elekta)	CT	OTP version 1.5 software for treatment planning Nucletron/collapsed cone algorithm dose calculation	NS	Abdominal compression devices	Orthogonal electronic portal images, DRRs
Seong et al. (2009)[92]	CyberKnife 6 MV	NS	NS	NS	NS	NS	NS	NS	NS
Rusthoven et al. (2009)[85]	Linac	NS	NS	NS	NS	NS	NS	NS	NS
Rusthoven et al. (2009)[86]	Linac 6-15 MV	Dynamic conformal arcs or multiple noncoplanar static beams >7 noncoplanar fields	NS	External vacuum type or synthetic body mold	CT	NS	Fiducial markers on body immobiliza-tion or infrared markers on patients surface	ABC or abdominal compression	Orthogonal x-rays or onboard CT imaging
Rusthoven et al. (2009)[87]	Linac 6-15 MV	Dynamic conformal arcs or multiple noncoplanar static beams	NS	External vacuum type; synthetic body mold; or abdominal compression	CT	NS	NS	Facilitated breath hold or abdominal compression	Orthogonal x-rays or onboard CT imaging
Song et al. (2009)[98]	Linac	Median: 6 (Range: 4–8) coplanar or noncoplanar beams	NS	SBF, vacuum fitted (Elekta)	CT	Elekta Render 3D planning system or Varian Eclipse planning system	NS	ABC, abdominal compression, or respiratory gated therapy (Varian and GE Lightspeed)	Cone-beam or CT simulation; on-board imager with cone beam CT

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Stephans et al. (2009)[100]	Novalis 6MV	7 field noncoplanar IMRT with heterogeneity corrections or 3 or more dynamic arcs without heterogeneity corrections	NS	BodyFix vacuum bag	CT	BrainScan 5.31 planning software	NS	Abdominal compression	Orthogonal films and Exactrac
Stephans et al. (2009)[99]	Novalis	NS	NS	BodyFix (Elekta)	CT	BrainLAB BrainScan 5.31 planning software	NS	Abdominal compression device	ExacTrac, Orthogonal films
van der Voort van Zyp et al. (2009)[116]	CyberKnife 6MV	130 noncoplanar beams	1 or 2 circular collimator cone sizes 20–60 mm	NS	CT	Accuray version 3.4.1 on target treatment-planning system	Minimum of 3 implanted markers	Synchrony	Orthogonal X-ray images
Baumann et al. (2008)[6]	Linac 6MV	5-9 noncoplanar or coplanar beams	MLC	SBF (Elekta)	CT	Helax TMS or Eclipse systems/ pencil beam algorithms with heterogeneity correction	NS	Abdominal compression	CT scan before treatment
Casamassima et al. (2008)[12]	Elekta Synergy 6 MV	Dynamic arc technique; arc interval in the transverse plane minimum of 180 to 270, subarcs of 30; non coplanar arcs were used in some patients	MLC	SBF	CT	Treatment planning system ERGO 3D line/pencil beam algorithm dose calculation	NS	NS	Cone-beam CT for online setup corrections
Chang et al. (2008)[1]	CyberKnife 6MV	6 degrees of freedom	NS	Alpha Cradle (Smithers Medical)	CT, PET	NS	3–5 implanted fiducials	Synchrony	Orthogonal x-ray sources & amorphous silicon detectors
Chang et al. (2008)[13]	Linac 6MV	6–9 noncoplanar beams	NS	NS	CT	NS	NS	NS	CT on-rail simulation during each treatment fraction; orthogonal films
Choi et al. (2008)[15]	CyberKnife 6MV	NS	NS	NS	CT	NS	4 gold markers	Breath hold	NS

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Coon et al. (2008)[18]	CyberKnife 6MV	6 axis robotic arm	NS	NS	PET, CT	Non isocentric inverse planning algorithm	1–4 gold fiducial markers	Synchrony	Orthogonal x-rays
Fritz et al. (2008)[24]	Elekta Precise Sli linac	5–8 coplanar fields planned	MLC leaf width 10 mm	SBF (Elekta)	4D CT	Eclipse 3D planning system version 7.3.10/ pencil beam algorithm dose planning with heterogeneity correction	NS	NS	CT immediately before treatment
Fuller et al. (2008)[25]	CyberKnife 6MV	NS	NS	NS	CT, MRI	NS	Implanted gold fiducial markers	NS	NS
Henderson et al. (2008)[36]	Linac 6 and 15MV	7–10 noncoplanar compensated beams	NS	SBF and vacuum pillow (Elekta)	CT	NS	Prepatellar and sterna positioning marks	Abdominal pressure device	NS
Jereczek-Fossa et al. (2008)[45]	Linac 6-18 MV	1–3 noncoplanar conformal dynamic arc	mMLC	Vacuum pillow fixed on a carbon fiber tray	CT, PET, MRI	BrainLAB BrainScan treatment planning v 5.31	NS	NS	ExacTrac
Katoh et al. (2008)[49]	Linac	NS	MLC	No immobilization	CT	NS	Implanted 2 mm gold marker	Synchrony	4 fluoroscopy image processor units
Kim et al. (2008)[51]	CyberKnife 6MV	NS	NS	Alpha Cradle (Smithers Medical)	CT, PET	CyberKnife planning system	6 gold fiducials 4 mm (long) x 0.8 mm (diameter)	NS	NS
Kunos et al. (2008)[57]	CyberKnife 6MV	NS	NS	Vacuum bag pelvic	CT	Accuray inverse treatment planning system	6 single 1.6 x 3 mm gold soft tissue markers	NS	Cross plane radiographic imaging
Lagerwaard et al. (2008)[58]	Linac	8–12 noncoplanar static beams	mMLC	NS	4D CT	BrainLAB BrainScan v 5.2	NS	NS	Varian real-time position management system

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
McCammon et al. (2008)[65]	Conventional linac and Novalis dedicated linac 6MV	Single or multiple dynamic conformal arcs or multiple noncoplanar static beams	MLC	Vac-Lok, MedTec OR Alpha Cradle (Smithers Medical)	CT, PET, MRI	BrainLAB BrainScan software/ pencil-beam algorithm for tissue inhomogeneity correction	Fiducial skin markers	Elekta ABC, abdominal compression	ExacTrac, CT scan, or stereoscopic image guidance
Onimaru et al. (2008)[76]	Linac 4, 6, and 10MV	NS	NS	NS	CT	CMS Focus or Xio planning systems	Gold markers	Breath hold	NS
Norihisa et al. (2008)[71]	Linac 6MV	5–7 noncoplanar static beams	MLC	SBF (Elekta)	CT	Varian CADPLAN version 3.1 and Eclipse version 7.1	NS	NS	NS
Salazar et al. (2008)[88]	Linac	3–9 fields	MLC	SBF	CT, PET	NS	External fiducial markers on immobilization device	ABC mask	NS
Schellenberg et al. (2008)[89]	CyberKnife 6MV	NS	NS	Alpha cradle	CT, PET	CyberKnife planning system	Implanted gold fiducial seeds	Respiratory gating, Synchrony	NS
Svedman et al. (2008)[104]	Linac 6 MV	5–8 coplanar or noncoplanar static beams	MLC	SBF	CT	Helix TMS planning system/ pencil beam algorithm dose calculation	NS	Abdominal pressure device	NS
Takeda et al. (2008)[105]	Linac	10 dynamic conformal arcs with or without additional static conformal ports	NS	NS	CT	CMS XiO version 4.2 or 4.3 3D treatment-planning system/ MG-superposition algorithm dose calculation with heterogeneity correction	NS	Long scan time CT to account for breathing motion	NS
Tse et al. (2008)[112]	Linac 6-18 MV	3–10 coplanar or noncoplanar beams	NS	Abdominal compression	CT, MRI	Conformal planning	NS	Elekta ABC or abdominal compression	Orthogonal MV image guidance or kV cone beam CT imaging and kV orthogonal fluoroscopy

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Aoki et al. (2007)[4]	Linac EXL-20TP Mitsubishi 10 MV	4–6 fixed multiple noncoplanar conformal beams; 3 noncoplanar oblique anterior beams plus 2 coplanar oblique posterior beams plus 1 coplanar lateral beam	NS	Thermo-shell and custom made MoldCare head rest (Alcare)	CT	XiO version 4.1.1 CMS 3D radiotherapy treatment-planning machine/ dose calculation with Clarkson method by 3D-RTP corrected for inhomogeneity	NS	NS	Electronic portal imaging device for tumor localization before each treatment
Brown et al. (2007)[10]	CyberKnife 6MV	Noncoplanar beams	NS	NS	CT	Inverse planning module	Xsight Lung, fiducial markers	Breath hold, Synchrony	NS
Guckenberger et al. (2007)[29]	NS	5–7 coplanar and noncoplanar beams	NS	SBF (Elekta)	CT	NS	NS	Abdominal compression	CT simulation prior to treatment fractions
Hof et al. (2007)[38]	Siemens linac 6MV	At least 6 different coplanar or noncoplanar isocentric beam directions	MLC leaf width at isocenter 1 cm	SBF with and vacuum pillow	CT	Voxelplan 3D treatment planning/ pencil beam algorithm dose calculation	NS	Abdominal compression	NS
Hof et al. (2007)[39]	Siemens Mevatron linac 6MV	6–8 different coplanar or noncoplanar isocentric beam directions	MLC leaf width at isocenter 1 cm	SBF with vacuum pillow	CT	Voxelplan software DKFZ 3D treatment planning with/pencil beam algorithm dose calculation	Bony landmarks	Abdominal compression device	Orthogonal portal images compared to DRR
Hoopes et al. (2007)[41]	NS	7–10 noncoplanar compensated beams	NS	SBF (Elekta)	CT	3D treatment planning	Prepatellar and sterna positioning marks permanently applied	Abdominal clamping pressure	NS
Koto et al. (2007)[56]	Clinac 23Ex, Varian 6MV	Noncoplanar multi-dynamic arcs and/or multi-static beams	NS	Half body vacuum cast	CT	CadPlan and Eclipse 3D radiotherapy treatment-planning system/modified Batho power law tissue heterogeneity correction algorithm	Gold markers 3.0 x 0.8 mm	Respiratory gating and ABC	X-ray tubes mounted directly to gantry and 2 sets of amorphous silicon flat panel x-ray sensors

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Muacevic et al. (2007)[69]	CyberKnife 6MV	NS	NS	NS	NS	Inverse planning algorithm	Gold fiducials, Xsight	X-ray system	Orthogonally position x-ray cameras
Nuyttens et al. (2007)[73]	CyberKnife 6MV	NS	NS	NS	NS	NS	NS	Synchrony	NS
Ponsky et al. (2007)[81]	NS	NS	NS	Plastic mold	CT	Treatment-planning software	Gold fiducials, Xsight	NS	NS
Ricardi et al. (2007)[82]	NS	6–8 noncoplanar static multiple fields	NS	SBF	CT, PET	NS	NS	Diaphragm control device	NS
Scorsetti et al. (2007)[90]	Linac	4 or more dynamic arcs	3D Line mMLC	Immobilization system with vacuum lock and/or thermoplastic mask	NS	3D Line Medical Systems Ergo treatment-planning system	NS	NS	NS
Teh et al. (2007)[107]	Novalis	NS	NS	Body cast	PET, CT, MRI	NS	Bony lesions or radio-opaque markers	Abdominal compression, gating, or ABC	Stereoscopic x-rays
Baumann et al. (2006)[5]	Linac 6MV	5–9 noncoplanar or coplanar beams	MLC	SBF(Elekta)	CT	3D dose planning	NS	Diaphragm control device	CT scans for image guidance for verification
Dawson et al. (2006)[20]	Elekta Synergy	1–2 segments per beam when required to obtain optimal plans	NS	NS	4D CT	Forward planning	NS	Breath hold using ABC	MV images and orthogonal kV fluoroscopic images
Ernst-Stecken et al. (2006)[22]	Novalis	1–6 either dynamic conformal arc or static conformal beams	NS	Self-constructed abdominal press	CT	Novalis BrainScan version 5.31 - Brain Lab/ pencil beam algorithm dose calculation	NS	NS	ExacTrac
Hodge et al. (2006)[37]	Tomotherapy Hi-Art	NS	NS	Custom made double vacuum	CT	Tomotherapy treatment-planning system	NS	Abdominal pressure pillow	MVCT scan and fused with planning CT

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Hoyer et al. (2006)[43]	Siemens Primus or Varian Clinac 2100/2300 6-8 MV	5–8 static coplanar or noncoplanar beams	MLC leaf width 5–10 mm at isocenter	SBF (Elekta), vacuum pillow	CT	Helax-TMS or Varian CadPlan/Eclipse	Invasive skin marks	NS	Portal imaging
Joyner et al. (2006)[47]	Linac	NS	NS	BodyFix (Medical Intelligence)	CT, PET	Nomos Corp Corvus treatment planning station 5.0/6.0	NS	NS	CT imaging control
Le et al. (2006)[59]	CyberKnife 6 MV	NS	NS	Vac Bag, MedTech	CT	NS	Fiducial markers on body immobiliza-tion or infrared markers on patients surface	Synchrony, Breath hold technique	Orthogonal x-ray image pairs
Madsen et al. (2006)[63]	Linac	6 stationary noncoplanar fields	Custom blocking	NS	CT, MRI	NS	3 fiducial markers	NS	Isoloc Northwest Medical Physics Equipment for daily treatment position; orthogonal images
Nuyttens et al. (2006)[72]	CyberKnife 6 MV	NS	NS	NR	CT	NS	Fiducial markers	Synchrony	2 diagnostic x-ray sources with amorphous silicon detectors to acquire live digital radiographic images
Paludan et al. (2006)[78]	Siemens Primus or Varian Clinac 2100/2300	5–8 static coplanar or noncoplanar beams	MLC	SBF (Elekta), vacuum pillow	CT	Helax TMS treatment-planning system / pencil beam algorithm tissue density inhomogeneity correction	Laser guided skin marks	NS	CT scan verification image
Romero et al. (2006)[84]	Siemens Primus linac	4–10 coplanar and noncoplanar beams	NS	SBF (Elekta)	CT	Varian CadPlan treatment planning system	Implanted gold fiducials	Abdominal compression	CT scan, electronic portal images
Sinha et al. (2006)[95]	Linac 6 MV and 15 MV	7–10 noncoplanar, nonopposing beams	NS	SBF (Elekta)	CT	3D treatment planning	NS	Abdominal clamping pressure	NS

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Svedman et al. (2006)[103]	Linac 6MV	5–8 coplanar or noncoplanar static beams	MLC	SBF (Elekta), vacuum pillow	CT	Helax TMS/pencil beam algorithm dose calculation	NS	NS	CT scan
Timmerman et al. (2006)[108]	Linac	10–12 noncoplanar, nonopposing beams	NS	SBF (Elekta), vacuum pillow	CT	Elekta Render 3D planning system	NS	Abdominal compression	NS
Wulf et al. (2006)[119]	Elekta Synergy S 6–18 MV	Noncoplanar beams	NS	SBF (Elekta)	CT	Helax TMS version 4.01A, 4.01B, 5.1 and 6.1A Theranostic B.V 3D treatment planning system/ pencil beam algorithm dose calculation	Fiducial markers in frame	NS	CT verification
Xia et al. (2006)[120]	Body gammaknife 30 Co(60)	NS	3, 12, 18 aperture diameter collimators	Vacuum bag	CT	NS	NS	NS	NS
Yoon et al. (2006)[123]	NS	Coplanar and/or noncoplanar beams	NS	SBF (Elekta)	NS	Elekta 3D treatment-planning system Render plan	NS	ABC; diaphragm controller	NS
Zimmermann et al. (2006)[124]	NS	Multiple static beams and/or dynamic arcs	MLC leaf width at isocenter 1 cm	Vacuum couch (Medical Intelligence)	CT	Siemens Helax TMS system/pencil beam algorithms	NS	NS	CT scans superimposed with ExacTrac
Hoyer et al. (2005)[42]	Siemens Primus or Varian Clinac 2100/2300	5–8 static coplanar or noncoplanar beams	MLC leaf width 5–10 mm at isocenter	Vacuum pillow, SBF (Elekta)	CT	Helax-TMS or Varian CadPlan Plus/Eclipse	Skin marks	NS	Portal film or electronic portal imaging
Molla et al. (2005)[365]	Novalis linac 6 MV	Dynamic arc treatments	mMLC	Customized vacuum body cast	CT	BrainLAB BrainScan TPS	NS	5–7 infrared metallic markers asymmetrically fixed to skin of abdomen before treatment planning	ExacTrac, Infrared cameras mounted to the ceiling

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Shioyama et al. (2005)[94]	Clinac 12 Ex Varian 6 or 10MV	5–8 noncoplanar static ports	MLC	Thermoplastic body cast with vacuum pillow and arm & leg holding devices (Ximatron Varian)	CT	Varian Eclipse version 6.5 3D RT treatment planning machine	X-ray simulator for tumor	Respiratory gating	CT verification
Song et al. (2005)[97]	NS	4–8 coplanar beams or single plane dynamic arcs	NS	Custom fitted immobilization	CT	BrainLAB version 5.2/tissue maximum ratio calculation algorithm; Philips Pinnacle^3 monitor units confirmed/ inhomogeneity corrections	6–7 infrared reflective skin markers and lateral isocenter tattoos	NS	Infrared marker system, orthogonal films, CT verification
Beitler et al. (2004)[7]	NS	Coplanar and noncoplanar arrangements	NS	SBF	CT	NS	Fiducial markers on the box	NS	NS
Ishimori et al. (2004)[44]	Clinac 2300 6MV Varian	6–10 field noncoplanar	NS	SBF (Elekta)	NS	Varian 3D treatment-planning system CadPlan R.6.0.8	NS	NS	NS
Onishi et al. (2004)[77]	EXL-15DP Mitsubishi	10 different noncoplanar dynamic arcs	NS	NS	CT	CMS 3D treatment-planning computer FOCUS version 3.2.1	Skin marker	Self breath hold	Electronic portal imaging
Gerszten et al. (2003)[26]	CyberKnife 6MV	NS	NS	NS	CT	Inverse treatment plan	Fiducial placement	NS	Two diagnostic x-ray cameras orthogonal to acquire real time images
Gunven et al. (2003)[32]	Linac 6MV	NS	NS	Stereotactic frame	CT	NS	NS	External abdominal pressure	NS
Lee, et al. (2003)[60]	NS	4–8 field coplanar and/or noncoplanar beams	MLC with 1 cm thick leaves	SBF with vacuum pillow	CT	Elekta 3D planning system Render Plan	NS	Diaphragm controller	CT scan and verification films before each treatment

Study	Device and Photon Energy	Beam Angles	Collimation Technique	Body Immobilization Technique	Treatment Planning Imaging	Treatment Planning System/Algorithm	Tumor Tracking	Respiratory Tracking/ Control	Imaging Guidance During Treatment
Whyte et al. (2003)[117]	CyberKnife 6MV	NS	NS	Alpha cradle (Smithers Medical)	CT	CyberKnife inverse planning system and nonisocentric radiation delivery	Implanted metal fiducial markers	Breath hold technique or tracking LEDs placed on the patient's skin	Real-time image processing
Harada et al. (2002)[35]	Linac	NS	NS	NS	NS	3D radiotherapy planning system	Gold marker	NS	X-ray system in floor and on ceiling
Uematsu (2001)[113]	Fusion of CT and linac (FOCAL)	NS	NS	NR	NS	NS	NS	Abdominal pressure belt and/or shallow respirations with oxygen mask	NS
Wulf et al. (2001)[118]	Linac 5-18 MV	Symmetric 5 beam arrangement individualized by addition of rotational beams or opposing beams	NS	SBF, vacuum pillow	CT	Helax TMS version 4.01A and 4.01B MDS Nordion 3D treatment planning system	NS	Diaphragm control device	CT verification
Nakagawa et al. (2000)[70]	NS	NS	Dynamic MLC	NS	CT	NS	NS	NS	MV CT-assisted verification

2D: Two-dimensional
3D: Three-dimensional
4D: Four-dimensional
ABC: Active breathing control
CT: Computed tomography
DRR: Digitally reconstructed radiographs
IMRT: Intensity modulated radiation therapy
kV: Kilovolt
LED: Light emitting diode
MEV: Million electron volt
mm: Millimeter
MRI: Magnetic resonance imaging
MV: Megavolt
mMLC: micro-Multileaf collimator
MLC: Multileaf collimator
NS: Not specified
PET: Positron emission tomography
SBF: Stereotactic body frame

Appendix N. Responses From Device Manufacturers on Device Specifications and Compatible Accessories (January 2010)

	Elekta Axesse[581]	**Elekta Synergy-S**[581]	**Elekta Synergy**[581]	**Elekta Infinity**[581]	**Tomo-Therapy-HiArt**[582]	**Accuray CyberKnife® Robotic Radiosurgery System**[583]	**Varian Clinac iX**[584]	**Varian Trilogy**[584]	**Varian/BrainLAB Novalis Tx**[584]
Device Type (e.g., robot, ring gantry, standard linac)	Standard linac and robotic table	Standard linac and robotic table	Standard linac and robotic table	Standard linac and optional robotic table	Ring gantry	Robotic mounted linac	C-Arm Linac	C-Arm Linac	C-Arm Linac
Photon Energy, MV	6, 10, 12, or 15 MV	6, 10, 12, or 15 MV	6, 10, 12, 15, or 18 MV	6, 10, 12, 15, or 18 MV	6 MV	6 MV	6 MV plus one of 10,15,18,20 HighX	6 MV plus one of 10,15,18,20 HighX	6 MV plus one of 10, 15, 18, 20 HighX
Maximum Dose Rate (MU/min)	600 MU/min	600 MU/min	600 MU/min	600 MU/min	850 cGy/min	1,000 MU/min	600 MU/min[1]	1,000 MU/min[1]	1,000 MU/min[1]
Number of Independent Beam Angles	Infinite[2]	Infinite[2]	Infinite[2]	Infinite[2]	51 per rotation, continuous delivery modeled by treatment (7 degree arcs)	>1,200 noncoplanar, independent beam angles	Continuously variable along gantry, collimator & couch rotational axes plus couch & collimator translational axes[3]	Continuously variable along gantry, collimator & couch rotational axes plus couch & collimator translational axes[3]	Continuously variable along gantry, collimator & couch rotational axes plus couch & collimator translational axes[3]
Collimation Technique (e.g., MLC, etc.)	MLC or cones	MLC or cones	Add-on MLC or cones	Add-on MLC or cones	MLC	Variable aperture collimator and fixed circular collimator[4]	MLC[5]	MLC[5]	MLC and SRS cones[6]
Smallest Collimation Resolution	4 mm throughout or cones[7]	4 mm throughout or cones[7]	3 mm or 2.5 mm throughout or cones[7]	3 mm or 2.5 mm throughout or cones[7]	6.25 mm x 10 mm	Field sizes of 5 mm[8]	5.0 mm	5.0 mm	2.5 mm
Minimum Treatment Size	MLC: 4 mm	MLC: 4 mm	MLC: 3 mm or 2.5 mm	MLC: 3 mm or 2.5 mm	Not limited by collimator	5 mm[8]	MLC: 5 mm x 5 mm SRS cone: 4 mm	MLC: 5 mm x 5 mm SRS cone: 4 mm	MLC: 2.5 mm x 2.5 mm SRS cone: 4 mm

	Elekta Axesse[581]	**Elekta Synergy-S**[581]	**Elekta Synergy**[581]	**Elekta Infinity**[581]	**Tomo-Therapy-HiArt**[582]	**Accuray CyberKnife® Robotic Radiosurgery System**[583]	**Varian Clinac iX**[584]	**Varian Trilogy**[584]	**Varian/BrainLAB Novalis Tx**[584]
Maximum Treatment Size	MLC: 16 cm x 21 cm	MLC: 16 cm x 21 cm	MLC: 7 cm x 7 cm or 12 cm x 12 cm	MLC: 7 cm x 7 cm or 12 cm x 12 cm	NR	Conformal beam targeting allows treatment of tumors >maximum field size of 60 mm	Fixed field: 40 cm x 40 cm Modulated field: 40 cm x 32 cm	Fixed field: 40 cm x 40 cm Modulated field: 40 cm x 32 cm	Fixed field: 22 cm x 40 cm Modulated field: 22 cm x 32 cm
Body Immobilization Technique (e.g., third party)	BodyFIX or HeadFIX	BodyFIX or HeadFIX	BodyFIX or HeadFIX	BodyFIX or HeadFIX	BodyFIX[9]	Not required, optional "vac-bags"[9]	Medical Intelligence CIVCO; Q-Fix; Aktina[9]	Medical Intelligence CIVCO; Q-Fix; Aktina[9]	Medical Intelligence; CIVCO; Q-Fix; Aktina[9]
Treatment Planning Imaging (e.g., CT, PET-CT, MRI, etc.)	CT and/or MRI and/or PET	CT and/or MRI and/or PET	CT and/or MRI and/or PET	CT and/or MRI and/or PET	CT on HiArt planning station, multi-modality on third party fusion/ contouring station	CT, 4D CT, MR, PET, and XA (3DRA)	CT, MR, PET, CT/PET	CT, MR, PET, CT/PET	CT, MR, PET, CT/PET
Treatment Planning Options (e.g., software)	ERGO++ and/or Pinnacle3[9]	ERGO++ and/or Pinnacle3[9]	ERGO++ and/or Pinnacle3[9]	ERGO++ and/or Pinnacle3[9]	Tomo-Helical and Tomo-Direct delivery mode, each with IMRT and 3D options	The MultiPlan® Treatment Planning System	Varian Eclipse recommended	Varian Eclipse recommended	BrainLAB iPlan Standard; Varian Eclipse recommended in addition
Treatment Planning Algorithm (e.g., Monte Carlo, forward, inverse)	Inverse and/or Monte Carlo	Inverse and/or Monte Carlo	Inverse and/or Monte Carlo	Inverse and/or Monte Carlo	Convolu-tion/super-position	Inverse planning with Monte Carlo or ray-tracing methods	Eclipse: AAA and Pencil Beam	Eclipse: AAA and Pencil Beam	Varian Eclipse: AAA and Pencil Beam, BrainLAB iPlan: Pencil Beam and Monte Carlo
Patient Positioning Accuracy (mm)	<1 mm	<1 mm	<1 mm	<1 mm	Approx 0.5 mm	During set-up: 1 mm	Follows AAPM and ASTRO recommen-dations[10]	Follows AAPM and ASTRO recommen-dations[10]	Follows AAPM and ASTRO recommendations[10]

	Elekta Axesse[581]	Elekta Synergy-S[581]	Elekta Synergy[581]	Elekta Infinity[581]	Tomo-Therapy-HiArt[582]	Accuray CyberKnife® Robotic Radiosurgery System[583]	Varian Clinac iX[584]	Varian Trilogy[584]	Varian/BrainLAB Novalis Tx[584]
Patient Position Correction (degrees of freedom)	6D standard	3D standard, optional 6D	3D standard, optional 6D	3D standard, optional 6D	Translation plus roll	RoboCouch® System provides 6-DOF motion capabilities	4	4	6
Image Guided Technology (during treatment)	2D or 3D cone-beam CT	2D or 3D cone-beam CT	2D or 3D cone-beam CT	2D or 3D cone-beam CT	MVCT prior to delivery	Orthogonal X-ray (kV), registers to DRRs	Varian Cone-Beam CT; MV Portal Imaging; Fluoro kV, MV/kV	Varian Cone-Beam CT; MV Portal Imaging; Fluoro kV, MV/kV	Varian Cone-Beam CT; MV Portal Imaging; Fluoro kV, MV/kV, BrainLAB, ExacTrac Stereo X-Ray, ExacTrac Optical (IR), SNAP (kV image w/beam on)
Tumor Tracking (e.g., fiducials, third party, manufacturer)	Active Breathing Coordinator (ABC) and/or Elekta Symmetry 4D cone-beam CT	ABC and/or Elekta Symmetry 4D cone-beam CT	ABC and/or Elekta Symmetry 4D cone-beam CT	ABC and/or Elekta Symmetry 4D cone-beam CT	No tracking during treatment	Xsight Lung Tracking System and fiducial-based tracking	Varian Fluoro kV and via Calypso or VisionRT[9]	Varian Fluoro kV and via Calypso or VisionRT[9]	Varian Fluoro kV and via BrainLAB SNAP (kV image w/ beam on) and Calypso or VisionRT[9]
Respiratory Gating (Yes/No)	Yes, ABC	Yes, ABC	Yes, ABC	Yes, ABC	No	No—Uses Synchrony® Respiratory Tracking System	Varian RPM: Respiratory Position Management	Varian RPM: Respiratory Position Management	Varian RPM: Respiratory Position Management BrainLAB: Adaptive Gating
Standard Treatment Time Per Fraction[11]	2–45 mins (lower with VMAT, higher with SRS)	2–45 mins (lower with VMAT, higher with SRS)	2–45 mins (lower with VMAT, higher with SRS)	2–45 mins (lower with VMAT, higher with SRS)	Typically beam on 20 minutes and time in room 45 minutes	Avg. 30–60 min per fraction imaging interval and tracking method used	5–35[12]	3–20[12]	3–20[12]

[1] Varian states the dose rate is at 100 centimeters (cm).

[2] Based on rotation of linac and control of patient table.

[3] Varian states: linacs rotate continuously + 185 degrees (370 degrees total) about the isocenter from vertical; the couch can yaw + 100 degrees; rotate the multileaf collimator + 165 (+ 0.5 degrees); the leaf positions are continuously variable with a + 0.01 mm leaf position resolution; Exact Couch has a lateral travel of + 25 cm and a longitudinal travel of 145.8 cm; BrainLAB's robotic couch top, standard on the Novalis Tx (and optional on the Trilogy and Clinac iX), can roll and pitch + 2.7 degrees and + 4 degrees respectively.

[4] 5–60 mm diameter.

[5] Millennium 120 MLC: 80 -5 mm leafs bounded by 40 (2 x 20) 10 mm leafs.
[6] HD120 MLC: 64 2.5 mm leafs bounded by 56 (2 x 28) 5 mm leafs.
[7] 2.5 mm to 50 mm.
[8] This represents the smallest collimator size; Accuray states collimator resolution is not applicable for the CyberKnife system.
[9] Third party device or software.
[10] Varian states they follow recommendations of AAPM and ASTRO[585]
[11] Standard treatment time may vary with each patient depending on factors such as tumor size, etc.
[12] Varian based the treatment time on a treatment dose range of 8-20 Gy and delivery using RapidArc or Fixed Gantry.

4D CT: Four-dimensional computed tomography
AAA: Anisotropic analytical algorithm
AAPM: American Association of Physicists in Medicine
ABC: Active Breathing Coordinator
ASTRO: American Society for Radiation Oncology
cGY/min: Centigray per minute
cm: Centimeter
CT: Computed tomography
DOF: Degrees of freedom
DRR: Digitally reconstructed radiograph
IMRT: Intensity modulated radiation therapy
kV: Kilovolt
MLC: Multi-leaf collimator
mm: Millimeter
MRI: Magnetic resonance imaging
MU/min: Monitor units per minute
MV: Megavolt
MVCT: Megavoltage computed tomography
PET: Positron emission tomography
SRS: Stereotactic radiosurgery
VMAT: Volumetric modulated arc therapy

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