Stereotactic Body Radiation Therapy As a Derivative of Stereotactic Radiosurgery: Clinically Independent But With Enduring Common Themes

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Cranial stereotactic radiosurgery (SRS) and extracranial stereotactic body radiation therapy (SBRT), despite their modern high-tech incarnations, trace their historical roots to a technique initially explored more than a century ago in the first decade after the discovery of x-rays. In 1902, the Austrian radiotherapy pioneers Holzkecht and Kienböck described the first clinically applied radiation dosimeter and promoted an approach known as “expeditive radiotherapy,” whereby an entire course of treatment would be given in a single large-dose session, as opposed to multiple small exposures given daily over a period of numerous weeks.¹

The indications for radiotherapy in those days included a quaint assortment of non-life-threatening maladies such as alopecia from fungal infection.² However, one impetus for expeditive radiotherapy arose from a serious consideration, namely the significant risk of radiation-induced illness among health care providers administering treatment using unshielded sources with minimal safety features. Awareness of the danger of excess exposure to ionizing radiation emerged quickly. The Law of Bergonie and Tribondeau, published in 1906, is the classic initial observation that mitotically active cells are more sensitive to radiotherapy than quiescent cells; less well remembered is that these authors also stated in their article that “the practice of delivering small and repeated doses, in contradistinction to the technique of few and heavy doses, is more apt to produce [in health care workers] . . . nondestructive irritations with resulting monster cells [ie, carcinogenesis]. Therefore, one should prefer the method of massive doses.”^{3(p588)} Holzkecht himself succumbed to a series of radiation-induced ailments,⁴ and it is important to remember the martyrdom of many early radiation scientists.

Fortunately, radiation treatment delivery technology quickly evolved to eliminate the exposure threat to medical personnel. After a variety of sporadic forays into the realm of high-dose-per-treatment external-beam radiation therapy throughout the 1900s,⁵ by the dawn of the 21st century, advances in technology and clinical knowledge had converged to translate the lessons of SRS into the rapidly burgeoning field of SBRT.

In recent years the American Society for Radiation Oncology (ASTRO) has issued guidelines on SBRT^{6,7} and a white paper on quality and safety in SRS and SBRT.⁸ Apart from providing specifics about personnel and training requirements and quality assurance methodologies, these documents also confirm that multiple radiation delivery systems could be effectively used for SRS and SBRT. While

each has somewhat different means of achieving the same goals, the common end point is to deliver an intense radiation dose conforming to the intended target, with a steep dose gradient away from the target. Typically this goal is achieved by employing multiple nonoverlapping static or dynamically arcing beams that converge on the target so that the normal tissues in the entrance and exit parts of the beam path are relatively spared while the tumor receives a heavy concentration of ionizing energy.

Unmet Medical Need

The signature indication for SBRT that emerged early in the development of the technology and served to distinguish SBRT from SRS clearly is the case of a patient with medically inoperable early-stage lung non-small-cell lung cancer. This patient population dies frequently of cancer if left untreated.⁹ An oft-cited SEER registry analysis suggests that conventionally fractionated radiation therapy (CFRT) offers a modest benefit in this setting,¹⁰ but the results are hardly satisfying. As a leading US pioneer of SBRT, Robert Timmerman, will elaborate in the following contribution in this issue, for various reasons this particular clinical scenario proved to be well suited for the investigation of SBRT and was quickly studied both in single institution pilot trials and larger cooperative group studies.¹¹

Best exemplifying these successes are the Nordic Group study from Europe and the Radiation Therapy Oncology Group (RTOG) study from North America where, in separate trials enrolling contemporaneously, patients with medically inoperable early-stage lung cancer received a dose of 45 to 54 Gy in 3 fractions and enjoyed over 90% local lesion control and a 3-year overall survival of approximately 60%.^{12,13} The survival is roughly twice what was typically achieved historically. Table 1 includes a summary of outcomes from selected major series of CFRT and SBRT for early-stage lung cancer.

Repercussions on the Field of Clinical Radiobiology

“Essentially, all models are wrong, but some are useful.”

George Box¹⁷

Ever since the seminal publication by Puck and Marcus¹⁸ in 1956 graphically representing the surviving fraction of mammalian tumor cells as a function of the dose to which they were exposed, a variety of mathematical models have been used to characterize this nonlinear relationship. In recent years the so-called linear-quadratic (LQ) model

Table 1. Selected Series of Radiation Therapy As Primary Treatment for Medically Inoperable Stage I Non–Small-Cell Lung Cancer

Series	CFRT/ SBRT	No.	Dose to Tumor/ Fractions	3-year LC, Treated Lesion	Median OS (months)	3-year OS (%)
SEER ¹⁰	CFRT	2,374	n/a	n/a	21	30
Mallinckrodt ¹⁴	CFRT	53	63.2 Gy/35	51	21	19
Duke ¹⁵	CFRT	156	64 Gy/32	51*	18	25†
Nordic ¹²	SBRT	57	45 Gy/3	92	41	60
RTOG ¹³	SBRT	55	54 Gy/3	94	48	56
VU ¹⁶	SBRT	676	54-60 Gy/3-8	92†	41	55†

Abbreviations: CFRT, conventionally fractionated radiation therapy; LC, local control; n/a, not available; OS, overall survival; SBRT, stereotactic body radiation therapy; RTOG, Radiation Therapy Oncology Group; VU, Vrije Universiteit.
 *Crude rate.
 †Estimated from graph.

has been most popular. Also dominating the received wisdom concerning radiation-induced tumor and normal tissue effects in the second half of the twentieth century was a canon of literature concerning the importance of DNA damage repair, tumor cell repopulation, postradiation cell-cycle redistribution, and hypoxic cell reoxygenation, collectively known as the 4 Rs of radiobiology.¹⁹ The perturbations introduced by SRS and SBRT into this intellectual framework are noteworthy.

With increasing clinical implementation of high-dose-per-fraction irradiation, numerous groups began to study biologic responses in this setting, and the results have challenged prevailing dogma. First, for the dose range commonly used in SRS and SBRT, namely 6 to 20 Gy or higher per fraction, preclinical and clinical evidence suggests that the LQ model breaks down and fails to maintain accuracy, overestimating the true cytotoxicity in the high-dose range. For example, using H460 cells, the University of Texas–Southwestern group showed that the LQ model overestimated the in vitro cell-killing effect of 15 Gy by roughly two orders of magnitude relative to experimental results.¹⁹ Quantitatively similar observations have been reported for other epithelial cell lines²⁰ as well as for both small-cell lung cancer and prostate cancer cell lines.²¹

For this reason an assortment of alternative models have been proposed, including one that incorporates intrafraction repair kinetics²² and another that segments the radiation dose survival curve into a piecewise function governed by different equations in the low- and high-dose regions.²³ In the latter example, a metric known as the single-fraction equivalent dose (SFED) may be derived as a means of comparing the relative biologic potency of different SBRT-range dose schedules, and SFED has described a clinical dose-local control relationship after SBRT for several tumor types.^{24,25}

As the debate about how best to model radiation responses continues, it is good to remember the words of Dr Box quoted herein and appreciate that all of the formulas currently in vogue are likely at best a first order approximation of a process of extreme complexity at a molecular level. The equation defining the LQ model first appeared in a radiation-related publication in the 1940s, and its initial use was to describe chromosomal translocations in a plant model according to an established understanding of bimolecular reaction kinetics.²⁶ But as other contributions in this special issue demonstrate nicely, the advent of SBRT has coincided with an explosion of knowledge about the

molecular signaling events triggered by ionizing radiation,^{27,28} and it is hard to imagine that a simple two-parameter equation can fully represent the intricacies of all these parallel processes.

A number of investigators believe that SRS and SBRT, with a high-dose-per-fraction radiation exposure, might invoke antiangiogenic mechanisms not present, or at least not prominent, in CFRT—a potential confounding factor not readily accounted for by the traditional 4 R's. As long ago as 1930, James Ewing postulated that an impact on tumor-supplying vasculature might be an important mechanism during radiotherapy.²⁹ However, it was not until many years later that preclinical and clinical data began to accumulate to characterize the antiangiogenic properties of high-dose-per-fraction radiation.

In a rodent model of SRS using a window chamber model that allowed repeated direct visual inspection of the in vivo microcirculation,³⁰ doses of 15 to 30 Gy were administered in a single exposure. Acute reductions in vessel length density and blood flow developed 1 to 30 days after exposure, without a dose-dependence above the 15 Gy level. The pattern of endothelial cell loss after irradiation was consistent with endothelial cell apoptosis. The findings aligned with numerous other reports documenting extensive vascular damage via endothelial apoptosis after doses above a threshold of 13 to 15 Gy in a variety of brain radiation models.³¹⁻³⁴ The observation of radiation-induced endothelial apoptosis after high-dose-per-fraction irradiation has also been observed in extracranial xenograft models, where endothelial apoptosis was triggered above a threshold dose of 8 to 10 Gy.^{35,36}

Refined Perspectives on Normal Tissue Tolerance

From a radiobiological viewpoint, normal tissue structures may be grouped according to whether they have a predominantly so-called parallel or serial architecture. Parallel tissues are comprised of functional subunits organized in a pattern whereby damage to a portion of the structure compromises function in proportion to the percent of the organ injured or removed (eg, liver). Serial structures are organized in a sequential, linked pattern whereby injury to even a small portion of the structure risks major toxicity by disrupting the interdependent sections' function (eg, spinal cord, intestines).

Concern that normal tissue effects after SBRT in parallel organs might not be predicted well by traditional models prompted a conceptually different approach to clinical trial design for the case of liver SBRT. Here, a method known as the critical volume model was applied in early dose-escalation trials. Similarly to the way that a surgeon considers how much normal parenchyma must be preserved to sustain the patient after partial hepatectomy, the implementation of a critical volume model in liver SBRT involves estimating how much liver parenchyma must be spared to retain adequate function after treatment. In one series, an estimate that at least 700 cm³ of normal liver must receive less than 15 Gy was proposed and implemented safely.³⁷

Interestingly, a sharp radiographic demarcation may be observed in normal liver within a few months after SBRT above a dose of approximately 14 Gy in a single fraction.³⁸ The effect may also be seen after 3-fraction SBRT, though at a higher threshold dose, and histopathologically the effect has been characterized as tissue necrosis surrounded by a rim of veno-occlusive disease features.³⁹ Taken together these observations are consistent with a threshold effect largely driven by vascular ablation, though direct injury to hepatocytes is also present

to some extent. Regardless of the underlying mechanisms at work, though, it is possible that the safety of liver SBRT is not a consequence of applying a critical volume model per se but, rather, a result of the fact that the tightly focused beams and steep dose gradients deliver a much lower total dose to uninvolved parenchyma, one that is safely below the level associated with causing radiation-induced liver disease after CFRT.⁴⁰

The QUANTEC (Quantitative Estimates of Normal Tissue Effects in the Clinic) project was sponsored jointly by the American Association of Medical Physicists and ASTRO. Medical physicists, radiobiologists, and radiation oncologists from around the world were charged with cataloguing and analyzing all published literature concerning the quantitative relationship between dose of ionizing radiation and injury to normal tissues. For the case of SRS, the summary conclusion regarding radionecrosis was that the risk of this complication escalates sharply when the volume of normal brain receiving 12 Gy or higher exceeds 5 to 10 cm³.⁴¹ In quantitative SBRT-derived analyses of toxicity to serial organs, a qualitatively similar pattern is emerging. For several different regions of the GI tract (esophagus, duodenum, and rectum), the most significant predictor of post-SBRT late toxicity is a similarly constructed dose-volume metric, whereby toxicity is triggered when the volume of tissue receiving a certain dose exceeds a threshold level.⁴²⁻⁴⁴ One unifying explanation consistent with observed effects of high fractional doses on endothelial cells might be that above a certain volume of tissue, the injury to small vessels might reach a point where local recovery is impossible, and a parenchymal or stromal defect, in this case necrosis or ulceration, develops.

Current Landscape and New Horizons

In addition to its established role in medically inoperable early-stage lung cancer, SBRT has achieved excellent rates of tumor control and survival in a wide variety of indications, notably in ablating oligometastatic tumor deposits in the lung and liver as well as controlling challenging paraspinal tumor deposits. The topic of ablative local therapy for oligometastases is covered in greater depth in another review within this issue.⁴⁵ A few other sites of growing enthusiasm include prostate, pancreas, and hepatocellular cancer.

Many patients with low risk prostate cancer may safely undergo active surveillance for some time after diagnosis. Eventually some progress to a status where active therapy is indicated; furthermore, intermediate risk patients with Gleason 7 cancer are generally advised to receive treatment if there are no comorbid illnesses of near-term threat to longevity. Even at this point, patients enjoy high cure rates with a variety of well-tolerated therapies including radical prostatectomy, seed implant, and conventionally fractionated intensity-modulated radiation therapy. SBRT has now entered the mix of available therapies in this setting with a good track record of safety and efficacy.

A pooled analysis of 1,100 patients enrolled on prospective trials of SBRT demonstrates biochemical relapse-free survival rates and quality-of-life outcomes that compare favorably with other definitive treatments for prostate cancer.^{46,47} After a median dose of 36.25 Gy in 4 to 5 fractions, the 5-year biochemical relapse free survival rate was 93% for all patients; 95%, 83%, and 78% for GS 6, 7 and 8, respectively ($P = .001$), and 95%, 84%, and 81% for low-, intermediate-, and high-risk patients, respectively. Median follow-up was 3 years, and 194 patients remained evaluable at 5 years. A transient decline in the

urinary and bowel domains was observed within the first 3 months after SBRT which returned to baseline status or better within 6 months and remained so beyond 5 years. Sexual quality-of-life decline was observed predominantly within the first 9 months, with no significant impact from androgen deprivation or patient age. An added appeal of SBRT in this setting is cost-effectiveness relative to other forms of radiation therapy of prostate cancer.^{48,49} However, recent retrospective population-based analyses have raised questions about the rate of genitourinary toxicity after SBRT for prostate cancer relative to CFRT,^{50,51} and continued analyses of ongoing prospective studies will be important. As with any new clinical implementation of new technology, there is likely a learning curve toward optimal utilization.

Randomized studies evaluating the role of conventionally fractionated radiotherapy in addition to systemic chemotherapy have had mixed results in adenocarcinoma of the pancreas. SBRT is appealing in this setting given the expediency of the course of treatment and potential for lower toxicity if smaller volumes are targeted, but the lessons of an early Danish study, where a large volume of bowel received a high dose, should be kept in mind.⁵² Fortunately, numerous single-institution studies have documented safe administration of SBRT to tightly focused fields around the primary pancreatic tumor, typically interdigitating the SBRT between cycles of chemotherapy, allowing minimal interruption of the systemic therapy and yielding survival and toxicity rates that compare favorably with series using conventionally fractionated radiotherapy.⁵³⁻⁵⁵

In the primary treatment of hepatocellular cancer, SBRT is a noninvasive therapy that can serve as either primary treatment or as a bridge to liver transplant.⁵⁶ Encouraging prospective North American studies have been published,^{57,58} and a large Japanese retrospective study has been reported.⁵⁹ In the latter experience, patients treated with SBRT had Child-Pugh Classification (CPC) –A or –B status and a single primary or recurrent hepatocellular cancer lesion, ≤ 5 cm. The prescribed dose depended on liver function and total liver dose: 40 Gy for CPC-A and 35 Gy for CPC-B, in 5 fractions, requiring a 5-Gy dose reduction if the proportion of the liver receiving ≥ 20 Gy exceeded 20%. A total of 185 patients ($n = 48$ in the 35-Gy group; $n = 137$ in the 40-Gy group) were followed for a median of 24 months. The 3-year local control and overall survival rates were 91% and 70%, respectively.

In conclusion, SRS and SBRT share certain technological characteristics and clinical rationale. While SBRT is an extracranial departure from SRS with application in many different anatomic sites, there remain opportunities to advance each discipline through thoughtful attention to similarities and differences in their biologic impact on tumors and normal tissues. Both types of therapy have important roles in the anticancer armamentarium.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

REFERENCES

1. Holzknecht G: Das Chromoradiometer. Presentation at Congresse International d'Electrologie, 1902: Cited in Thames HD—Early fractionation methods and the origins of the NSD concept. *Acta Oncol Acta Oncologica* 27:89-103, 1988
2. Kienböck R: On the radiotherapeutic treatment of diseases of the hair. *Archives of the Roentgen ray* 12:12-21, 1908
3. Bergonie J, Tribondeau L: Interpretation of some results of radiotherapy and an attempt at determining a logical technique of treatment. *Radiat Res* 11:587-588, 1959

4. Kogelknik HD: The history and evolution of radiotherapy and radiation oncology in Austria. *Int J Radiat Biol Phys* 35:219-226, 1996
5. Kavanagh BD: Tracing the earliest medical uses of high dose-per-fraction external beam radiation. *J Radiosurgery SBRT* 1:5-11, 2011
6. Potters L, Steinberg M, Rose C, et al: American Society for Therapeutic Radiology and Oncology and American College of Radiology practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 60:1026-1032, 2004
7. Potters L, Kavanagh B, Galvin JM, et al: American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 76:326-332, 2010
8. Solberg TD, Balter JM, Benedict SH, et al: Quality and safety considerations in stereotactic radiosurgery and stereotactic body radiation therapy: Executive summary. *Pract Radiat Oncol* 2:2-9, 2012
9. McGarry RC, Song G, des Rosiers P, et al: Observation-only management of early stage, medically inoperable lung cancer: Poor outcome. *Chest* 121:1155-1158, 2002
10. Wisnivesky JP, Bonomi M, Henschke C, et al: Radiation therapy for the treatment of unresected stage I-II non-small cell lung cancer. *Chest* 128:1461-1467, 2005
11. Timmerman RD, Herman J, Cho LC: Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. *J Clin Oncol* 32:2847-2854, 2014
12. Baumann P, Nyman J, Hoyer M, et al: Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 27:3290-3296, 2009
13. Timmerman R, Paulus R, Galvin J, et al: Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 303:1070-1076, 2010
14. Kaskowitz L, Graham MV, Emami B, et al: Radiation therapy alone for stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 27:517-523, 1993
15. Sibley GS, Jamieson TA, Marks LB, et al: Radiotherapy alone for medically inoperable stage I non-small-cell lung cancer: The Duke experience. *Int J Radiat Oncol Biol Phys* 40:149-154, 1998
16. Senthil S, Lagerwaard FJ, Haasbeek CJ, et al: Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: A retrospective analysis. *Lancet Oncol* 13:802-809, 2012
17. Box GEP, Draper NR: *Empirical Model Building and Response Surfaces*. New York, NY, John Wiley & Sons, 1987
18. Puck TT, Marcus PI: Action of x-rays on mammalian cells. *J Exp Med* 103:653-666, 1956
19. Withers HR: Four R's of radiotherapy. *Adv Radiat Biol* 5:241-247, 1975
20. Wang JZ, Huang Z, Lo SS, et al: A generalized linear-quadratic model for radiosurgery, stereotactic body radiation therapy, and high-dose rate brachytherapy. *Science Trans Med* 2:39ra48-39ra48, 2010
21. Andisheh B, Edgren M, Belkic D, et al: A comparative analysis of radiobiological models for cell surviving fractions at high doses. *Technol Canc Res Treat* 12:183-192, 2012
22. Guerrero M, Li XA: Extending the linear-quadratic model for large fraction doses pertinent to stereotactic radiotherapy. *Phys Med Biol* 49:4825-4835, 2004
23. Park C, Papiez L, Zhang S, et al: Universal survival curve and single fraction equivalent dose: Useful tools in understanding potency of ablative radiotherapy. *Int J Radiat Oncol Biol Phys* 70:847-852, 2008
24. Stinauer MA, Kavanagh BD, Scheffer TE, et al: Stereotactic body radiation therapy for melanoma and renal cell carcinoma: Impact of single fraction equivalent dose on local control. *Radiat Oncol* 6:34, 2011
25. Chang DT, Swaminath A, Kozak M, et al: Stereotactic body radiotherapy for colorectal liver metastases: A pooled analysis. *Cancer* 117:4060-4069, 2011
26. Lea DE, Catcheside DG: The mechanism of the induction by radiation of chromosome aberrations in *Tradescantia*. *J Genet* 44:216-245, 1942
27. Giaccia AJ: Molecular radiobiology: The state of the art. *J Clin Oncol* 32:2871-2878, 2014
28. Morris ZS, Harari PM: Interaction of radiation therapy with molecular targeted agents. *J Clin Oncol* 32:2886-2893, 2014
29. Ewing J: Factors determining radioresistance in tumors. *Radiology* 14:186-191, 1930
30. Acker JC, Marks LB, Spencer DP, et al: Serial in vivo observations of cerebral vasculature after treatment with a large single fraction of radiation. *Radiat Res* 149:350-359, 1998
31. Ljubimova NV, Levitman MK, Plotnikova ED, et al: Endothelial cell population dynamics in rat brain after local irradiation. *Br J Cancer* 1991; 64:934-940, 1991
32. Calvo W, Hopewell JW, Reinhold HS, et al: Dose- dependent and time-dependent changes in the choroid plexus of the irradiated rat brain. *Br J Radiol* 60:1109-1117, 1987
33. Brennan KM, Roos MS, Budinger TF, et al: A study of radiation necrosis and edema in the canine brain using positron emission tomography and magnetic resonance imaging. *Radiat Res* 134:43-53, 1993
34. Burrell K, Hill RP, Zadeh G: High-resolution in-vivo analysis of normal brain response to cranial irradiation. *PLoS one* 2:12:7, e38366
35. Garcia-Barros M, Paris F, Cordon-Cardo C, et al: Tumor response to radiotherapy regulated by endothelial cell apoptosis. *Science* 300:1155-1159, 2003
36. Kolesnick R, Fuks Z: Radiation and ceramide-induced apoptosis. *Oncogene* 22:5897-5906, 2003
37. Rusthoven KE, Kavanagh BD, Cardenas H, et al: Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol* 27:1572-1578, 2009
38. Herfarth KK, Holfer H, Bahner ML, et al: Assessment of focal liver reaction by multiphasic CT after stereotactic single-dose radiotherapy of liver tumors. *Int J Radiat Oncol Biol Phys* 77:444-451, 2003
39. Olsen CC, Welsh J, Kavanagh BD, et al: Microscopic and macroscopic tumor and parenchymal effects of liver stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys* 73:1414-1424, 2009
40. Scheffer TE, Kavanagh BD, Timmerman RD, et al: A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases. *Int J Radiat Oncol Biol Phys* 62:1371-1378, 2005
41. Lawrence YR, Li XA, el Naqa I, et al: Radiation dose-volume effects in the brain. *Int J Radiat Oncol Biol Phys* 76:S20-S27, 2010
42. Murphy JD, Christman-Skieller C, Kim J, et al: A dosimetric model of duodenal toxicity after stereotactic body radiotherapy for pancreatic cancer. *Int J Radiat Oncol Biol Phys* 78:1420-1426, 2012
43. Cox BW, Jackson A, Hunt M, et al: Esophageal toxicity from high-dose, single-fraction paraspinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 83:e661-e667, 2012
44. Kim DW, Cho LC, Straka C, et al: Predictors of rectal tolerance observed in a dose escalated phase I/II trial of SBRT for prostate cancer. *Int J Radiat Oncol Biol Phys* 89:509-517, 2014
45. Salama JK, Milano MT: Radical irradiation of extracranial oligometastases. *J Clin Oncol* 32:2902-2912, 2014
46. King CR, Freeman D, Kaplan I, et al: Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiother Oncol* 109:217-221, 2013
47. King CR, Collins S, Fuller D, et al: Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: Results from a multi-institutional consortium of prospective trials. *Int J Radiat Oncol Biol Phys* 87:939-945, 2013
48. Hodges JC, Lotan Y, Boike TP, et al: Cost-effectiveness analysis of stereotactic body radiation therapy versus intensity-modulated radiation therapy: An emerging initial radiation treatment option for organ-confined prostate cancer. *J Oncol Pract* 8:e31s-37s, 2012 (suppl 3)
49. Parthan A, Pruttivarasin N, Davies D, et al: Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer. *Front Oncol* 2:81, 2012
50. Yu JB, Cramer LD, Herrin J, et al: Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: Comparison of toxicity. *J Clin Oncol* 32:1195-1201, 2014
51. D'Amico AV: Stereotactic body radiation therapy versus intensity-modulated radiation therapy for prostate cancer: Less cost at the expense of more genitourinary toxicity is a concerning but testable hypothesis. *J Clin Oncol* 32:1183-1185, 2014
52. Hoyer M, Roed H, Sengelov L, et al: Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother Oncol* 76:48-53, 2005
53. Gurka MK, Collins SP, Slack R, et al: Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: A pilot trial demonstrating safety. *Radiat Oncol* 8:44, 2013
54. Mahadevan A, Jain S, Goldstein M, et al: Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 78:735-742, 2010
55. Tozzi A, Comito T, Alongi F, et al: SBRT in unresectable advanced pancreatic cancer: Preliminary results of a mono-institutional experience. *Radiat Oncol* 8:148, 2013
56. Klein J, Dawson LA: Hepatocellular carcinoma radiation therapy: Review of evidence and future opportunities. *Int J Radiat Oncol Biol Phys* 87, 22-32, 2013

57. Andolino DL, Johnson CS, Maluccio M, et al: Stereotactic body radiotherapy for primary hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 81:e447-e453, 2011

58. Bujold A, Massey C, Kim JJ, et al: Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol* 31:1631-1639, 2013

59. Sanuki N, Takeda A, Oku Y, et al: Stereotactic body radiotherapy for small hepatocellular carcinoma: A retrospective outcome analysis in 185 patients. *Acta Oncol* 53:399-404, 2014

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No relationship to disclose