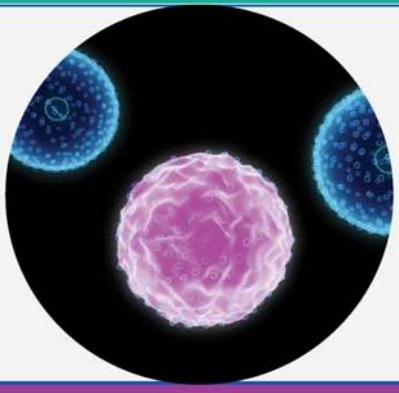
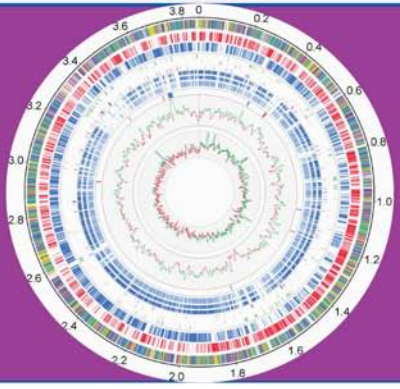
# *Introduction to*

# Stereotactic Hypofractionated Radiotherapy

# Re-Irradiation and





# Cancer Genome Research

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# Introduction to Stereotactic Hypofractionated Radiotherapy, Re-Irradiation, and Cancer Genome Research

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# PREFACE

This eBook was started largely a project of summer 2014 when I worked in New York City [1]. This ebook largely deals with challenging clinical scenarios in clinical oncology using advanced stereotactic radiation treatment machines. It particularly focuses on modern large dose per fraction stereotactic radiotherapy (SBRT), non-invasive stereotactic radiosurgery (SRS), and re-irradiation that has been thought to be very high risk because of normal tissue tolerance has been reached in most cases in these patients. This ebook reviews the relevant techniques that are important to re-irradiation, the outcome and how to select patients for re-irradiation. It also introduces the readers to The Cancer Genome Atlas (TCGA) that is a new public platform allows researchers anywhere in the world to mine the relationship between genomic and clinical data. As my thoughts on what are important in Radiation Oncology changes over time. To catch time like an impressionist, this book treads lightly and deeply in current and emerging topics in Radiation Oncology. As of now, this ebookis meant to be a foundation and will be added and edited from time to time. The content of this ebook only represents my views, not of any association I am associated with.

## Reference

1. Cheung R, Ouyang D, Kang J, Li H, Yeung V. A practical solution to socioeconomic barriers to radiotherapy in New York City. Jacobs Journal of Radiation Oncology. 2014; 1: 1.

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# Stereotactic Radiosurgery (SRS) And Re-SRS Of Brain Tumors

## BACKGROUND

Stereotactic Radiotherapy (SRS) is a well established radiation treatment for brain tumors [1]. The dose fall off of SRS is very steep, the dosing could go from acceptable to exceeding normal tissue tolerance over 1-2 mm. Therefore, SBRT and SRS require very high quality imaging [2]. SRS requires very precise stereotactic radiation treatment machines. For example, CyberKnife is a compact LINAC mounted on a robotic arm [3]. It tracks the skull position using X sight orthogonal x-rays [4]. Then adjust the LINAC to deliver the radiation doses accurately. It usually goes through a large number of positions (nodes) to deliver the radiation dose. This allows for very high conformality index i.e. degree of coverage of the Gross Target Volume (GTV) [4]. The CyberKnife Multiplan radiation treatment planning system allows dedicated SRS MRI [4] to be fused to the treatment CT to contour the GTV and clinical target volume (CTV). The planning target volume (PTV) margin that accounts for positional errors could be as tight as 2 mm because of the tracking [4]. This paper is a part of a series discussing using advanced stereotactic radiation treatment machine to address challenging clinical scenarios [5,6].

## HYPOFRACTIONATED RADIOTHERAPY OF BRAIN TUMORS

In the past, 85% - 95% of metastatic brain lesions are controlled with SRS when the median survival was 4-6 months [7]. But now with better systemic agents, more patients survive longer. Most brain metastatic lesions after SRS are stable or decrease in size. But about one third had a transient increase in size, defined as >120% change in volume [7]. Median survival of 9.5 months for 46% stable/decreased patients, 16.4 months for 9% increased patients, and 14.4 months for 45% mixed response patients. About half of the patients have one lesion increase in size during the follow up. Only 8%patients eventually salvage surgery for focal neurological deficits [7]. It has been proposed that the transient increase in size may be due to vascular damage and the associated immune response [7].

Many patients are found to have new brain metastases from treatment planning MRI. In one study, on the day of treatment, the patients underwent gadolinium enhanced 3-Dimensional 1.5 Tesla MRI with 2 mm slices. The average time between the referral and treatment MRI was 31

days in the study. 41 % of Gamma Knife patients who found to develop additional brain metastasis [8]. Median survival of 6.9 months for the patients with additional metastasis on treatment MRI compared with 12.1 months for patients with no additional metastasis [8].

Radiation resistant clear cell renal cancer brain metastasis has been successfully treated with Linac-based SRS system [9]. In this stusy, patients with 5 or less lesions were treated with SRS. Patients with more than 5 lesions were treated with whole brain radiotherapy followed by SRS boost to the larger lesions. MRI was performed every 2-3 months after the radiotherapy, additional lesions when found were treated with SRS. The doing schedule is as follows: patients with brain metastasis with a maximum diameter < 2 cm, were treated with 20 Gy – 24 Gy; 2 – 3cm, were treated with 18 Gy; and 3 – 4 cm, were treated with 15 Gy. Lesions larger than 4 cm were general not treated with SRS. In the study, there were 84% patients treated with 1 SRS treatment, the rest received 2 treatments. Treatment dose was prescribed to cover 95% of the target volume (range: 80% - 97%). Some of these patients also received immunotherapy (high-dose intravenous interleukin-2, low dose subcutaneous interleukin-2, Interferon-α) and anti-angiogenic (Bevacizumab, Sunitinib, and Sorafenib) [9]. The median survival from diagnosis was 10.1 months. Addition of WBRT and surgery did not improve overall survival but sequential immunotherapy improved survival [9].

Hypofractionated radiotherapy 21 – 30 Gy over 3-5 fractions is also an option for partial brain radiation therapy for large brain metastases from breast, lung, melanoma, and others [10]. When the tumor is larger than 3 cm, there is a 1 cm midline shift, close to critical structures or when the patient was previously irradiated to a high dose, they are at increased risk of toxicities [10]. In this study, the median maximum gross tumor volume/cavity size dimension of 3.9 (13.6 cc), range 0.8 (0.2 cc) – 6.4 (57 cc) cm or cavities not amenable to single fraction radiosurgery [10]. The previous RT and median (range) dose to the hypofractionated treatment site was: whole brain radiotherapy 37.5 (30 – 45) Gy, 18 (5 -21) Gy, 47.5 (10 – 60 Gy) and combination 41.25 (10 – 75) Gy [10]. Median time from previous radiation treatment was 13 (0.3 – 32.4) months [10]. In this study, 0 -10 mm safety margins were used. 10 mm margin was used when there was ambiguity about the target volumes. One year actuarial local control of the study was 61% and progression free survival was 55% [10].Brain metastasis with concurrent Tarceva was used with hypofractionated whole brain radiotherapy 4 Gy x 5 has been found to be safe [11]. There was no difference in toxicity in group using the Tarceva compared with the placebo group [11].

Leukoencephalopathy risk is much lower for SRS with Gamma Knife alone when compared with SRS with whole brain [12]. Based on T2/FLAIR (Fluid Attenuated Image Recovery), 97.3 % of patients (36 out of 37) treated with SRS and whole brain developed leukoencephalopathy, 70.8 % with grade 3 (diffuse white matter changes) on MRI, and 1 out of 31 treated with SRS developed grade 2 (limited periventricular white matter changes) [12].

## RE-IRRADIATION OF RECURRENT BRAIN TUMORS

The major sites of re-treatment are brain metastasis [3], spinal metastasis [13], recurrent head and neck [14], lung[15], liver [16] and colorectal cancers [17]. CyberKnife and other advanced systems with similar capacities have been successfully used in these scenarios [18-20].Tumor control probability (TCP) of recurrent cancers may be different than the original ones [21,22]. Biologic Effective Dose (BED) [23] and EQD2 calculations (Biologic Equivalent Dose at 2 Gy (EQD2) [24]could be calculated. QUANTEC [25] guideline could be used for re-irradiation, but QUANTEC has been tested clinically in re-irradiation.

Standard initial treatment for malignant glioma includes surgery followed by chemoradiation with Temozolomide [26]. Most recur within a year. Stereotactic radiosurgery for recurrent malignant brain glioma is an accepted treatment modality but remain challenging because of the infiltrative nature of the tumor and almost all of these patients had brain irradiation as part of the initial treatment [27]. Advanced imaging is needed to delineate the recurrent brain tumor. It has been shown that adding increased FLAIR (Fluid Attenuated Inversion Recovery) intensity area [28].

Re-irradiation after whole brain has been performed and found to be effective and with acceptable toxicity using 3-Dimensional Conformal Radiotherapy (3D-CRT) [29]. The mean target dose used was 3600 cGy (range 3060-5940 cGy). The mean total cumulative dose ranged from 8060 to 11940 cGy [29]. After retreatment, 8 of 12 patients (67%) had steroid dose decrease and clinical improvement. 1-year survival was 26% [29].

Hypofractionated stereotactic re-irradiation has also been found to be safe and effective [30]. 19 patients with recurrent malignant glioma (Glioblastoma and anaplastic astrocytoma) were treated with linear accelerator, median daily single dose 5 (4-10) Gy, the median total dose 30 (20-30) Gy in 4 – 5 fractions, median planning target volume 15 (4-70) ml. All patients were treated with involved-field radiotherapy with 45 – 61 Gy, and 94% were pretreated with chemotherapy (most often nimustin (ACNU) and teniposide). In this study, 3 mm CT with intravenous contrast was used. The contrast enhancing lesion was contoured as gross tumor volume (GTV). PTV margin used to account for positional errors was 1-3 mm in this study [28]. A large margin has been suggested by others [28]. Patients were maintained on steroid during the radiation treatment, daily dose s ranged from 32 mg of prednisone and 40 mg of dexamethasone [28].

SRS achieves its effects by destroying the tumor vasculature, but it may also stimulate neo-vascularization [26]. SRS with Bevacizumab was found to be effective after failing Bevacizumab. The median SRS dose used for 63 patients was 15 Gy (range, 12.5 – 25 Gy). Twelve patients were treated with 25 Gy in 5 fractions, with NovalisTx system, all others were treated with a single fraction [26]. In this study, 10% patients has radionecrosis. Most of the patients with symptoms were managed successfully with steroids and/or antiepileptic medication [26]. Therefore, salvage

stereotactic radiosurgery could be used safely with adjuvant Bevacizumab for recurrent grade 3 or 4 gliomas [26].

Re-irradiation with SRS has an advantage of delivering high dose with high precision to small volumes in children. In one study, SRS was used to treat recurrent intracranial ependymomas in children that has high recurrence rate [31]. In one study, children with recurrent medulloblastoma of the brain were treated [32]. The median dose for fractionated stereotactic radiotherapy (FSRT) was 24 Gy, and 15 Gy for SRS. The median age was 16 years old, all had cranio-spinal radiotherapy and posterior fossa boost to a total dose of 54 Gy. Chemotherapy was given to all patients [32]. No brain necrosis was seen after a mean follow up of 88.5 months. However, in other studies, it has been reported that brain necrosis occurred beyond an cumulative EQD2 around 100 Gy [33]. There is no definitive data on how histology impact on the re-irradiation outcome for recurrent/progressive brain metastasis [34].

Treatment of recurrent high grade gliomas has been performed with hypofractionated image-guided helical tomography [35], BrainlabNovalis system [36] and linear accelerator (LINAC) [37].

## BENIGN MENINGIOMA

Meningiomas are tumors arising from the which meninges, extra axial Central Nervous System (CNS) tumor [38]. Most (90%) are begnin, 6% are atypical and 2% are malignant ref. One study compared the tumor and critical organ contours for pituitary and meningioma [39]. Of note, the contours of the optic chiasms may be variable that could lead to an overdose of about 24 Gy beyond the optic chiasm radiation tolerance of 50 Gy in 2 Gy fractions [39]. It is important to obtain a thin cut MRI in treating meningiomas close the optic chiasm.

The high dose per fraction increases the likelihood of cerebral edema. In a study of post-radiation peritumoral edema [40], 173 mostly WHO grade I meningioma patients underwent Gamma Knife of CyberKnife SRS for meningiomas. 62 patients had parasagittal, parafalcine, and convexity locations. The median tumor volume was 4.7 mL (range, 0.1 – 231.8 mL). About 50% had surgery. The median prescribed dose was 15 (range, 9 – 40 Gy) over 1 to 5 patients except in two patients. The median prscribed biologically equivalent dose (BED) was 67 Gy (range, 14 – 116 Gy) [40]. The tumor control rate was 94%. 8% developed symptomatic peritumoral edema with a median onset of 4.5 months (range, 0.2 – 9.5 months). Large tumor volume and using single fraction are risk factors for developing symptomatic peritumoral edema [40]. Parasagital meningioma, when compared with non-midline lesions, has been found to have about 4 times higher risk of developing post-SRS symptomatic peritumoral edema (35.2 % versus 7.8 % at 18 months after SRS [41]. Meningiomas close to large veins are also at higher risk of developing peritumor symptomatic edema [42] using CyberKnife treating to 25-35 Gy over 5 fractions [42].

CyberKnife has been used in benign optic dural sheath meningiomas[43-45]. In one study [46], a threshold meningioma diameter of 2.56 cm and PTC volume of 11 cm3 was found from

31 patients. The median dose was 27.8 Gy (range, 21-36 Gy) over 3 to 5 fractions [46]. At 5 year, the tumor control was 83%. Half of these are WHO grade I intracranial meningiomas by histology from surgical resection, and about half from radiographic diagnosis [46].

CyberKnife has also been used in spinal schwannomas (28) and meningiomas (11, WHO grade I) [47] because of tumor recurrence, remnants after microsurgery, multiple lesions, or refusal of surgery. The median prescription dose was 14 Gy in one fraction to the 70% isodose line. The median target volume was 3.4 cm3 (range, 0.2 – 43.4 cm3). At 18 months, there was no tumor progression [47]. CyberKnife extends SRS to about 30% meningioma patients (tumor larger than 8 mL or close to critical structures) who could not have been treated with single fraction SRS [48]. For WHO II sub totally resected meningioma, SRS covering the tumor only rather than the post-operative bed achieve similar results to conventional radiotherapy covering larger volume. The median marginal dose of 22 Gy (range, 16 – 30 Gy) in over one to four fractions. The median tumor volume of 5.3 cm3 (range, 0.3 – 26.0). Number of recurrences before SRS, waiting until progression are predictors of worse outcome [49]. 36 months local regional control is about 70% [49].

## CONCLUSION

Combined SRS and re-SRS appear to be very effective and safe. SRS should be considered as a standard treatment for brain tumors.

### References


1. Sperduto PW, Wang M, Robins HI, Schell MC, Werner-Wasik M, Komaki R, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. Int J Radiat Oncol Biol Phys. 2013; 85: 1312-1318.
2. Park HK, Chang JC. Review of stereotactic radiosurgery for intramedullary spinal lesions. Korean J Spine. 2013; 10: 1-6.
3. Yang G, Wang Y, Wang Y, Lin S, Sun D. CyberKnife therapy of 24 multiple brain metastases from lung cancer: A case report. Oncol Lett. 2013; 6: 534-536.
4. Thariat J, Li G, Angellier G, Marchal S, Palamini G, Rucka G, et al. [Current indications and ongoing clinical trials with CyberKnife stereotactic radiotherapy in France in 2009]. Bull Cancer. 2009; 96: 853-864.
5. Cheung R. Using a Robotic Stereotactic Radiation Treatment System to Treat Benign Intracranial Tumors and Trigeminal Neuralgia. Austin J Radiat Oncol & Cancer. 2014; 1: 2.
6. Cheung R. The Utility of a Robotic Stereotactic Radiation Treatment System to Treat Primary and Metastatic Liver Tumors. Austin J Cancer Clin Res. 2014; 1: 2.
7. Patel TR, McHugh BJ, Bi WL, Minja FJ, Knisely JP, Chiang VL. A comprehensive review of MR imaging changes following radiosurgery to 500 brain metastases. AJNR Am J Neuroradiol. 2011; 32: 1885-1892.
8. Patel TR, Ozturk AK, Knisely JP, Chiang VL. Implications of Identifying Additional Cerebral Metastases during Gamma Knife Radiosurgery. Int J Surg Oncol. 2012; 2012: 748284.
9. Samlowski WE, Majer M, Boucher KM, Shrieve AF, Dechet C, Jensen RL, et al. Multidisciplinary treatment of brain metastases derived from clear cell renal cancer incorporating stereotactic radiosurgery. Cancer. 2008; 113: 2539-2548.
10. Eaton BR, Gebhardt B, Prabhu R, Shu HK, Curran WJ Jr, Crocker I. Hypofractionated radiosurgery for intact or resected brain metastases: defining the optimal dose and fractionation. Radiat Oncol. 2013; 8: 135.
11. Müller AC, Eckert F, Heinrich V, Bamberg M, Brucker S, Hehr T. Re-surgery and chest wall re-irradiation for recurrent breast cancer: a second curative approach. BMC Cancer. 2011; 11: 197.

12. Monaco EA 3rd, Faraji AH, Berkowitz O, Parry PV, Hadelsberg U, Kano H, et al. Leukoencephalopathy after whole-brain radiation therapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer. Cancer. 2013; 119: 226-232.

13. Castelli J, Thariat J, Benezery K, Courdi A, Chanalet S, Paquis P, et al. [Spinals and paraspinals tumors treated by CyberKnife: feasibility and efficacy]. Cancer Radiother. 2010; 14: 5-10.

14. Yamazaki H, Ogita M, Kodani N, Nakamura S, Inoue H, Himei K, et al. Frequency, outcome and prognostic factors of carotid blowout syndrome after hypofractionated re-irradiation of head and neck cancer using CyberKnife: a multi-institutional study. Radiother Oncol. 2013; 107: 305-309.

15. Trovo M, Minatel E, Durofil E, Polesel J, Avanzo M, Baresic T, et al. Stereotactic body radiation therapy for re-irradiation of persistent or recurrent non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2014; 88: 1114-1119.

16. Yamashita H, Onishi H, Matsumoto Y, Murakami N, Matsuo Y, Nomiya T, et al, Japanese Radiological Society multi-institutional SBRT study group (JRS-SBRTSG). Local effect of stereotactic body radiotherapy for primary and metastatic liver tumors in 130 Japanese patients. Radiat Oncol. 2014; 9: 112.

17. Abusaris H, Hoogeman M, Nuyttens JJ. Re-irradiation: outcome, cumulative dose and toxicity in patients retreated with stereotactic radiotherapy in the abdominal or pelvic region. Technol Cancer Res Treat. 2012; 11: 591-597.

18. Jeong S, Yoo EJ, Kim JY, Han CW, Kim KJ, Kay CS. Re-irradiation of unresectable recurrent head and neck cancer: using Helical Tomotherapy as image-guided intensity-modulated radiotherapy. Radiat Oncol J. 2013; 31: 206-215.

19. Stuschke M, Kaiser A, Abu-Jawad J, Pöttgen C, Levegrün S, Farr J. Re-irradiation of recurrent head and neck carcinomas: comparison of robust intensity modulated proton therapy treatment plans with helical tomotherapy. Radiat Oncol. 2013; 8: 93.

20. Lin YW, Lin KH, Ho HW, Lin HM, Lin LC, Lee SP, et al. Treatment plan comparison between stereotactic body radiation therapy techniques for prostate cancer: non-isocentric CyberKnife versus isocentric RapidArc. Phys Med. 2014; 30: 654-661.

21. Mantel F, Flentje M, Guckenberger M. Stereotactic body radiation therapy in the re-irradiation situation--a review. Radiat Oncol. 2013; 8: 7.

22. Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys. 2010; 37: 4078-4101.

23. Fowler JF. 21 years of biologically effective dose. Br J Radiol. 2010; 83: 554-568.

24. Tharavichtikul E, Meungwong P, Chitapanarux T, Chakrabandhu S, Klunklin P, Onchan W, et al. The association of rectal equivalent dose in 2 Gy fractions (EQD2) to late rectal toxicity in locally advanced cervical cancer patients who were evaluated by rectosigmoidoscopy in Faculty of Medicine, Chiang Mai University. Radiat Oncol J. 2014; 32: 57-62.

25. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010; 76: S10-19.

26. Cuneo KC, Vredenburgh JJ, Sampson JH, Reardon DA, Desjardins A, Peters KB, et al. Safety and efficacy of stereotactic radiosurgery and adjuvant bevacizumab in patients with recurrent malignant gliomas. Int J Radiat Oncol Biol Phys. 2012; 82: 2018-2024.

27. Koga T, Saito N. Efficacy and limitations of stereotactic radiosurgery in the treatment of glioblastoma. Neurol Med Chir (Tokyo). 2012; 52: 548-552.

28. Ogura K, Mizowaki T, Arakawa Y, Sakanaka K, Miyamoto S, Hiraoka M. Efficacy of salvage stereotactic radiotherapy for recurrent glioma: impact of tumor morphology and method of target delineation on local control. Cancer Med. 2013; 2: 942-949.

29. Kim HK, Thornton AF, Greenberg HS, Page MA, Junck L, Sandler HM. Results of re-irradiation of primary intracranial neoplasms with three-dimensional conformal therapy. Am J Clin Oncol. 1997; 20: 358-363.

30. Vordermark D, Kölbl O, Ruprecht K, Vince GH, Bratengeier K, Flentje M. Hypofractionated stereotactic re-irradiation: treatment option in recurrent malignant glioma. BMC Cancer. 2005; 5: 55.

31. Krieger MD, McComb JG. The role of stereotactic radiotherapy in the management of ependymomas. Childs Nerv Syst. 2009; 25: 1269-1273.

32. Milker-Zabel S, Zabel A, Thilmann C, Zuna I, Hoess A, Wannenmacher M, et al. Results of three-dimensional stereotactically-guided radiotherapy in recurrent medulloblastoma. J Neurooncol. 2002; 60: 227-233.

33. Sminia P, Mayer R. External beam radiotherapy of recurrent glioma: radiation tolerance of the human brain. Cancers (Basel). 2012; 4: 379-399.

34. Ammirati M, Cobbs CS, Linskey ME, Paleologos NA, Ryken TC, Burri SH, et al. The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2010; 96: 85-96.

35. Kim B, Soisson E, Duma C, Chen P, Hafer R, Cox C, et al. Treatment of recurrent high grade gliomas with hypofractionated stereotactic image-guided helical tomotherapy. Clin Neurol Neurosurg. 2011; 113: 509-512.

36. Teh BS, Paulino AC, Lu HH, Chiu JK, Richardson S, Chiang S, et al. Versatility of the Novalis system to deliver image-guided stereotactic body radiation therapy (SBRT) for various anatomical sites. Technol Cancer Res Treat. 2007; 6: 347-354.

37. Sirin S, Oysul K, Surenkok S, Sager O, Dincoglan F, Dirican B, et al. Linear accelerator-based stereotactic radiosurgery in recurrent glioblastoma: a single center experience. Vojnosanit Pregl. 2011; 68: 961-966.

38. Rockhill J, Mrugala M, Chamberlain MC. Intracranial meningiomas: an overview of diagnosis and treatment. Neurosurg Focus. 2007; 23: E1.

39. Yamazaki H, Shiomi H, Tsubokura T, Kodani N, Nishimura T, Aibe N, et al. Quantitative assessment of inter-observer variability in target volume delineation on stereotactic radiotherapy treatment for pituitary adenoma and meningioma near optic tract. Radiat Oncol. 2011; 6: 10.

40. Unger KR, Lominska CE, Chanyasulkit J, Randolph-Jackson P, White RL, Aulisi E, et al. Risk factors for posttreatment edema in patients treated with stereotactic radiosurgery for meningiomas. Neurosurgery. 2012; 70: 639-645.

41. Patil CG, Hoang S, Borchers DJ 3rd, Sakamoto G, Soltys SG, Gibbs IC, et al. Predictors of peritumoral edema after stereotactic radiosurgery of supratentorial meningiomas. Neurosurgery. 2008; 63: 435-440.

42. Oermann EK, Bhandari R, Chen VJ, Lebec G, Gurka M, Lei S, et al. Five fraction image-guided radiosurgery for primary and recurrent meningiomas. Front Oncol. 2013; 3: 213.

43. Romanelli P, Wowra B, Muacevic A. Multisession CyberKnife radiosurgery for optic nerve sheath meningiomas. Neurosurg Focus. 2007; 23: E11.

44. Romanelli P, Bianchi L, Muacevic A, Beltramo G. Staged image guided robotic radiosurgery for optic nerve sheath meningiomas. Comput Aided Surg. 2011; 16: 257-266.

45. Marchetti M, Bianchi S, Milanesi I, Bergantin A, Bianchi L, et al. Multisession radiosurgery for optic nerve sheath meningiomas--an effective option: preliminary results of a single-center experience. Neurosurgery. 2011; 69: 1116-1122.

46. Morimoto M, Yoshioka Y, Shiomi H, Isohashi F, Konishi K, Kotsuma T, et al. Significance of tumor volume related to peritumoral edema in intracranial meningioma treated with extreme hypofractionated stereotactic radiation therapy in three to five fractions. Jpn J Clin Oncol. 2011; 41: 609-616.

47. Kufeld M, Wowra B, Muacevic A, Zausinger S, Tonn JC. Radiosurgery of spinal meningiomas and schwannomas. Technol Cancer Res Treat. 2012; 11: 27-34.

48. Colombo F, Casentini L, Cavedon C, Scalchi P, Cora S, Francescon P. Cyberknife radiosurgery for benign meningiomas: short-term results in 199 patients. Neurosurgery. 2009; 64: A7-13.

49. Choi CY, Soltys SG, Gibbs IC, Harsh GR, Jackson PS, Lieberson RE, et al. Cyberknife stereotactic radiosurgery for treatment of atypical (WHO grade II) cranial meningiomas. Neurosurgery. 2010; 67: 1180-1188.

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Chapter - 2

# Stereotactic Radiosurgery (SRS) and re-SRS of Primary and Metastatic Spinal Tumors

## BACKGROUND

Spinal tumors are difficult to treat because of spinal cord is a radiation dose limiting structure [1]. Most spinal tumors are metastases from cancers such as breast cancers, prostate cancers, lung cancers, rectal cancers, and primary spinal cancers such as sarcomas, and gliomas [1]. Traditional radiation radiotherapy in conventional fraction such as 30 Gy over 10 fractions resulted in about 70-80% local control for metastatic spine cancers, with Stereotactic Body Radiotherapy (SBRT), the local control rate of about 90% has been achieved [2]. Both terms SRS and SBRT have been used in the literature of spinal irradiation [3]. Traditionally, SBRT of spine cancers has been limited to previously irradiated, poor prognosis patients, but with the promising treatment outcome the indications for SBRT of spine cancer are expanding [2]. This a part of papers discussing the use of advanced stereotactic radiation treatment machines in challenging clinical scenarios [4,5]. There is steep dose gradient in SBRT and SRS, the dosing could go from acceptable to exceeding normal tissue tolerance over 1-2 mm. Therefore, SBRT and SRS require very high quality imaging [3].

## STEREOTACTIC HYPOFRACTIONATED RADIOTHERAPY OF BENIGN SPINAL CANCERS

Spinal benign intradural, extramedullary tumors have been treated with SBRT [6,7]. Currently, the dosing of spine cancer SBRT closely follows that used in intracranial SRS. In one study [6], thirty schwanomas, nine neurofilbromas, and sixteen meningiomas were treated to 16 to 30 Gy over 1 to 5 fractions on consecutive days. The tumor volumes ranged from 0.136 to 24.6 $cm^3$. Note that the volume of a sphere of 1 cm diameter is 0.52 $cm^3$, for the volume for 3 cm diameter is 14.14 $cm^3$, 65.45 $cm^3$ for 5 cm diameter, and 179.59 cm3 for 7 cm diameter. Radiation induced myelopathy occurred 8 months after SRS in one patients. 3 patients required surgical resection of their tumor because of persistent of worsening symptoms [6]. Others have also found SBRT for benign spinal tumors are safe and effective [7]. Spine SBRT could be could now be done without fiducials using advance stereotactic treatment machines such as Cyberknife [8]. Spine stereotactic body radiotherapy has also been performed with helical tomography [9] and volumetric modulated arc therapy [10].

## STEREOTACTIC HYPOFRACTIONATED RADIOTHERAPY OF METASTATIC SPINAL CANCERS

Spinal metastases occur in about 20% of cancer patients [11]. Tumor sensitivity, extent of epidural component, mechanical stability, and the status of systemic disease may determine the optimal radiation and surgical treatment for spinal metastasis [11]. The goal of SBRT for spinal metastases are palliative, reducing pain and improving spine stability, and quality of life [11]. SBRT has similar or superior outcome in the treatment of spinal metastases when compared with conventional and/or surgery [12,13]. A review of spinal metastases studies with 1400 patients found a cumulative local control rate of 90-95% and a myelopathy risk of less than 1% [12,13].

SBRT for solitary spinal metastases has been performed in inoperable patients [14]. PET and/or MRI may be required to delineate the gross target volume GTV and spinal cord volume [14,15]. Because of the accuracy of the stereotactic targeting, zero mm has been used for the PTV expansion [16]. Some radiation oncologists use an additional 2-3 mm added to the GTV to form the treatment volume [14]. This additional margin may account for the intrafractional motion [9,17]. Some radiation oncologists may treat the entire vertebral body [18]. The treatment volumes and prescription doses may need to be adjusted to meet the spinal cord radiation dose constraints for epidural tumors or tumors close (< 1 mm) to spinal cord [15]. The spinal tumor could be tracked with or without [19] fiducials.

A phase II/III study has demonstrated the feasibility for spine SRS for localized (1-3) spine metastases [20]. The dose used was 16 Gy in a single fraction. The image guidance was found to be accurate to < 2 mm, the spine cord constraints were met (≤ 10 Gy to < 0.35 cc of absolute spinal cord volume, or ≤ 10% of cord 5-6 mm [14] above and below the target volume. Some radiation oncologists would contour the spinal cord to the level of the tumor D10% [15]). Other normal tissue constraints were also met [20]. There were no grades IV or V toxicities [20].

SBRT has been used in treating radiation resistant tumors such as melanomas and sarcomas that are believed to have low alpha/beta ratio [3]. In one study, spine SBRT has been used in radiation resistance renal cell kidney cancer; there was a small risk of spinal compression fraction [21]. In that study, baseline vertebral column fracture and 18-24 Gy in a single fraction are risk factors of vertebral column fracture [21]. Of note, balloon kyphoplasty with cement augmentation in patients with vertebral column fracture from spinal metastasis has been associated with tumor extravasation with subsequent tumor migration into adjacent area [22].

In other studies, radiation resistant primary and metastatic spinal sarcomas have been successfully treated with SRS [23,24]. In one study, 16 – 45 Gy doses were delivered to the tumor margins over one to three sessions [23] and the median single session equivalent dose was 21.8 Gy [23]. Median local progression free survival was 23 months [23]. And pain control was 61.5% at 2 years [23]. Foley catheters placed intraoperatively have been found to prevent injury to the bowels in SBRT of sarcoma of sacrum [25].

## SRS OF SPINAL CANCERS WITH CONCURRENT SYSTEMIC TREATMENT

In one study [15], 16 – 24 Gy peripheral dose was delivered to previously unirradiated spinal metastases. In the study, renal cell histology received higher doses. There were no significant differences in outcomes for different SBRT doses and histology [15]. However to further improve treatment outcome, anti-angiogenic agents sunitinib and sorafinib have been used simultaneously with SRSof spine metastases especially for the radiation resistant renal cell tumor [16]. There was no added toxicity from the anti-angiogenic therapy by adding SRS [16].

## RE-IRRADIATION OF SPINAL CANCERS

SBRT has been used for recurrent epidural spinal metastases after conventional fractionated radiation for spine metastases [26]. In this study [26], 24 Gy over 3 fractions when the tumor did not touch the spinal cord, and 25 – 30 Gy were used over 5 – 6 fractions when the tumor touches the spinal cord [26]. The cord surface received up to the prescription dose and there were no hot spots in the cord. Median progression free survival was 9 months, and there were no significant toxicities other than fatigue [26].

## SBRT OF OTHER SPINAL LESIONS

Intramedullary lesions SRS is still developing [3]. Arteriovenous malformations, ependymomas and hemangioblastoma have been treated effectively with SRS [3]. SBRT has also been used for intraspinal hemangiopricytoma [27] and benign but painful osteoid osteoma [28].

## POST-OP SBRT OF SPINE CANCERS

Postoperative Spine SBRT has been reported [29]. Post-operative SBRT to 18-26 Gy over 1-2 fractions and absence of postoperative epidural disease predict better local control [29]. For treatment planning, 1 mm CT slices, and 1.5 mm thin slice T1 and T2 non-contrast MRI were fused to the treatment CT [29]. Planning CT myelogram was obtained if surgical instrumentation distorted the MRI. In this study, a donut shaped CTV and PTV was used. Spinal tolerance was followed for radiation-naïve and irradiated patients in this study [29]. High dose hypofractionated postoperative SBRT 24-30 Gy over 3 fractions have been found to be better than lower doses 18-36 Gy over 5-6 fractions after decompression surgery [30].

## CONCLUSION

SBRT is safe and effective in treating primary and metastatic spinal cancers. Spine SBRT has also been found to be cost effective [31].

### References


1. Cox JD, Ang KK. Radiation Oncology: Rationale, Technique, Results, 9th edn. 2009.
2. Gill B, Oermann E, Ju A, Suy S, Yu X, Rabin J, et al. Fiducial-free CyberKnife stereotactic body radiation therapy (SBRT) for single vertebral body metastases: acceptable local control and normal tissue tolerance with 5 fraction approach. Front Oncol. 2012; 2: 39.

3. Park HK, Chang JC. Review of stereotactic radiosurgery for intramedullary spinal lesions. Korean J Spine. 2013; 10: 1-6.

4. Cheung R. Using a Robotic Stereotactic Radiation Treatment System to Treat Benign Intracranial Tumors and Trigeminal Neuralgia. Austin J Radiat Oncol & Cancer. 2014; 1: 2.

5. Cheung R. The Utility of a Robotic Stereotactic Radiation Treatment System to Treat Primary and Metastatic Liver Tumors. Austin J Cancer Clin Res. 2014; 1: 2.

6. Dodd RL, Ryu MR, Kamnerdsupaphon P, Gibbs IC, Chang SD Jr, Adler JR Jr. CyberKnife radiosurgery for benign intradural extramedullary spinal tumors. Neurosurgery. 2006; 58: 674-685.

7. Sahgal A, Chou D, Ames C, Ma L, Lamborn K, Huang K, et al. Image-guided robotic stereotactic body radiotherapy for benign spinal tumors: theUniversity of California San Francisco preliminary experience. Technol Cancer Res Treat. 2007; 6: 595-604.

8. Wowra B, Zausinger S, Drexler C, Kufeld M, Muacevic A, Staehler M, et al. CyberKnife radiosurgery for malignant spinal tumors: characterization of well-suited patients. Spine (Phila Pa 1976). 2008; 33: 2929-2934.

9. Chung Y, Yoon HI, Kim JH, Nam KC, Koom WS. Is helical tomotherapy accurate and safe enough for spine stereotactic body radiotherapy? J Cancer Res Clin Oncol. 2013; 139: 243-248.

10. Marchand EL, Sahgal A, Zhang TJ, Millar BA, Sharpe M, Moseley D, et al. Treatment planning and delivery evaluation of volumetric modulated arc therapy for stereotactic body radiotherapy of spinal tumours: impact of arc discretization in planning system. Technol Cancer Res Treat. 2012; 11: 599-606.

11. Laufer I, Rubin DG, Lis E, Cox BW, Stubblefield MD, Yamada Y, et al. The NOMS framework: approach to the treatment of spinal metastatic tumors. Oncologist. 2013; 18: 744-751.

12. Hall WA, Stapleford LJ, Hadjipanayis CG, Curran WJ, Crocker I, Shu HK. Stereotactic body radiosurgery for spinal metastatic disease: an evidence-based review. Int J Surg Oncol. 2011; 2011: 979214.

13. Wowra B, Muacevic A, Zausinger S, Tonn JC. Radiosurgery for spinal malignant tumors. Dtsch Arztebl Int. 2009; 106: 106-112.

14. Lee S, Chun M, Lee M. Stereotactic body radiotherapy for solitary spine metastasis. Radiat Oncol J. 2013; 31: 260-266.

15. Garg AK, Shiu AS, Yang J, Wang XS, Allen P, Brown BW, et al. Phase 1/2 trial of single-session stereotactic body radiotherapy for previously unirradiated spinal metastases. Cancer. 2012; 118: 5069-5077.

16. Staehler M, Haseke N, Nuhn P, Tüllmann C, Karl A, Siebels M, et al. Simultaneous anti-angiogenic therapy and single-fraction radiosurgery in clinically relevant metastases from renal cell carcinoma. BJU Int. 2011; 108: 673-678.

17. Hyde D, Lochray F, Korol R, Davidson M, Wong CS, et al. Spine stereotactic body radiotherapy utilizing cone-beam CT image-guidance with a robotic couch: intrafraction motion analysis accounting for all six degrees of freedom. Int J Radiat Oncol Biol Phys. 2012; 82: e555-562.

18. Patel VB, Wegner RE, Heron DE, Flickinger JC, Gerszten P, Burton SA. Comparison of whole versus partial vertebral body stereotactic body radiation therapy for spinal metastases. Technol Cancer Res Treat. 2012; 11: 105-115.

19. Bahig H, Campeau MP, Vu T, Doucet R, Béliveau Nadeau D, Fortin B, et al. Predictive parameters of CyberKnife fiducial-less (XSight Lung) applicability for treatment of early non-small cell lung cancer: a single-center experience. Int J Radiat Oncol Biol Phys. 2013; 87: 583-589.

20. Ryu S, Pugh SL, Gerszten PC, Yin FF, Timmerman RD, Hitchcock YJ, et al. RTOG 0631 phase 2/3 study of image guided stereotactic radiosurgery for localized (1-3) spine metastases: phase 2 results. Pract Radiat Oncol. 2014; 4: 76-81.

21. Thibault I, Al-Omair A, Masucci GL, Masson-Côté L, Lochray F, Korol R, et al. Spine stereotactic body radiotherapy for renal cell cancer spinal metastases: analysis of outcomes and risk of vertebral compression fracture. J Neurosurg Spine. 2014; 21: 711-718.

22. Cruz JP, Sahgal A, Whyne C, Fehlings MG, Smith R. Tumor extravasation following a cement augmentation procedure for vertebral compression fracture in metastatic spinal disease. J Neurosurg Spine. 2014; 21: 372-377.

23. Chang UK, Cho WI, Lee DH, Kim MS, Cho CK, Lee SY, et al. Stereotactic radiosurgery for primary and metastatic sarcomas involving the spine. J Neurooncol. 2012; 107: 551-557.

24. Jiang B, Veeravagu A, Feroze AH, Lee M, Harsh GR, Soltys SG, et al. CyberKnife radiosurgery for the management of skull base and spinal chondrosarcomas. J Neurooncol. 2013; 114: 209-218.

25. Maa J, Waterford S, Jahan T, Larson DA, Chou D. A novel use of foley catheters to prevent injury to the pelvic viscera during stereotactic radiosurgery for undifferentiated pleomorphic sarcoma of the sacrum. Perm J. 2014; 18: e146-149.

26. Mahadevan A, Floyd S, Wong E, Jeyapalan S, Groff M, Kasper E. Stereotactic body radiotherapy reirradiation for recurrent epidural spinal metastases. Int J Radiat Oncol Biol Phys. 2011; 81: 1500-1505.

27. Liu HG, Yang AC, Chen N, Yang J, Qiu XG, Zhang JG. Hemangiopericytomas in the spine: clinical features, classification,

treatment, and long-term follow-up in 26 patients. Neurosurgery. 2013; 72: 16-24.

28. Widmann G, Schullian P, Fasser M, Niederwanger C, Bale R. CT-guided stereotactic targeting accuracy of osteoid osteoma. Int J Med Robot. 2013; 9: 274-279.

29. Al-Omair A, Masucci L, Masson-Cote L, Campbell M, Atenafu EG, Parent A, et al. Surgical resection of epidural disease improves local control following postoperative spine stereotactic body radiotherapy. Neuro Oncol. 2013; 15: 1413-1419.

30. Laufer I, Iorgulescu JB, Chapman T, Lis E, Shi W, Zhang Z, et al. Local disease control for spinal metastases following "separation surgery" and adjuvant hypofractionated or high-dose single-fraction stereotactic radiosurgery: outcome analysis in 186 patients. J Neurosurg Spine. 2013; 18: 207-214.

31. Bijlani A, Aguzzi G, Schaal DW, Romanelli P. Stereotactic radiosurgery and stereotactic body radiation therapy cost-effectiveness results. Front Oncol. 2013; 3: 77.

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# Hypofractionated Radiotherapy and Re-Irradiation of Breast Cancers

## BACKGROUND

This paper is a part of a series [1,2] discussing the use stereotactic hypofractionated radiotherapy in challenging clinical scenarios. This paper will discuss the use of advanced radiotherapy techniques including stereotactic radiotherapy using CyberKnife, and Stereotactic Radiosurgery (SRS) in treating early and advanced breast cancer. This paper will also discuss re-irradiation used in the setting recurrent breast cancer.

## HYPOFRACTIONATED RADIATION THERAPY OF EARLY BREAST CANCER

Over the past 30 years, the treatment of early breast cancer has become less radical, from radical mastectomy to the current breast conservation therapy [3]. For early breast cancers, adjuvant radiation therapy after lumpectomy has been shown to decrease local recurrence by about 2/3 and improve overall survival by about 10% [3,4]. The typical dose and fraction for whole breast adjuvant radiotherapy is 45-50 Gy in 1.8 – 2 Gy fractions with or without a boost to the surgical bed [3,4]. Although most radiation oncologists boost the surgical bed even when the margin is negative [3,4]. This schedule may be inconvenient to some breast cancer patients because of co-morbidity and distance from the radiation treatment center. To accelerate the treatment process, whole breast adjuvant hypofractionated radiation therapy to 40.05 Gy in 15 fractions has been used. When boost was used, 9 Gy over 3 fractions was used [4]. The use of boost and diabetes were associated with worse late skin toxicity [4]. However, no grade 3 skin toxicity was found [4].

It has been found that 90% of the breast cancer recurrence has been found within the wide local excision (lumpectomy) site based on NSABP B-6 randomized trial for early stage (stage I and stage II) breast cancers [5]. There are 50 % of multicentric foci located outside the index quadrant but suggesting they mostly do not result in local recurrence [6,7]. Thus currently, radiation treatment focusing on the lumpectomy cavity itself has been used [3,8]. To reduce chronic breast and chest wall pain, cardiac toxicity, and poor cosmesis [9]. Different approaches of partial breast irradiation are being studying against whole breast RT including intraoperative single doses,

hypofractionated accelearated brachy therapy, and LINAC (linear accelerator)-based three dimensional external beam therapy [9]. Dose to whole breast and tumor bed were 40.5 Gy and 48 Gy respectively over 15 fractions over 3 weeks [10] using Rapid Arc is well tolerated.

CyberKnife has been used in partial breast RT [11,12]. In this study [11], the CTV is the surgical bed plus 10-15 mm, PTV expansion is 2mm. The gold fudicials were sutured into the cavity wall during lumpectomy. CyberKnife tracks them with Synchrony. Treatment starts 4-5 weeks after surgery, there was no acute toxicities at median follow up of 7 months (range 4-26), the early and late cosmesis are good or excellent [11]. Electron beam has also been used intraoperatively to deliver 5-20 Gy respectively to 1 cm and 0.2 cm of the tumor bed over about 20 minutes [6,8].

Chemotherapy and targeted therapy are indicated for some early stage breast cancer patients[13]. The risk of recurrence with or without adjuvant chemotherapy could be calculated using tools such as Adjuvant! Online based on factors including patient age, tumor size, nodal status, histologic grade and other factors [13,14].The risk model have been validated with population based data [14]. Genomic profiling on risk of distant metastasis has also been done with Oncotype DX, mammaprint and PAM50 [13]. Integrating systemic treatment and hypofractinated radiation treatment needs to be performed cautiously, and will be reviewed separately.

## SRS OF BRAIN METASTASES OF BREAST CANCER

10-30% of breast cancer patients develop brain metastases, and the second most common cause of brain metastases, and 2-5% developed leptomeningeal disease [15-17]. Brain metastases from breast cancer cause significant morbidity and mortality [15,18,19]. The treatment for breast cancer patients with brain metastases includes surgical resection, whole brain radiotherapy, SRS, and systemic treatments for particular cell types [16]. Single fraction Gamma Knife has be found safe and effective upfront and salvage treatment for these patients [15,20]. The median dose was 22 (range 20 – 25) Gy was used. Overall survival was 48.3% at one year. Local recurrence occurred in 38.6% at a median time of 6 (range, 4, 16) months. Tumor volume larger than 5000 mm3 and poor performance status are associated with poor outcome [18]. SRS has been found to preserve the neurocognitive function better. Trastuzumab has been used in Human Epidermal Growth Factor Receptor 2 (HER2) positive breast cancer patients with repeat brain RT and has been found to be safe and effective [21].

Increasing number of these breast cancer patients has been treated with brain RT and repeat RT [21]. Salvage SRS after whole brain for breast cancer patients with good performance status is considered a reasonable option [21-24]. Active extracranial disease and number of brain metastases are predictor of outcome [24]. These patients have a median survival more than 9 months, and for HER2 positive tumors at diagnosis or stable extracranial disease at the time of SRS have median survival > 1 year [22]. MRI of the brain should not be performed routinely, but should be performed at a low threshold because of high incidence of brain metastases among

patients with HER2 positive advanced breast cancer patients [25]. In one study, 1-15 brain lesions were treated with Gamma Knife to a median dose of 20 Gy (range 9-20 Gy). HER2 positive brain metastatic patients have improved survival but increase proportion from neurologic death. And basal subtype has higher risk of distant brain failure [26]. Leptomeningeal failure after radiation therapy, SRS, surgery, chemotherapy and biologic therapy had prolonged survival with systemic bevacizumab and capecitabine[27].

## RE-IRRADIATION OF RECURRENT CHEST WALL BREAST CANCER

Breast cancer patients with chest wall recurrence could be treated with re-surgery and chest wall re-irradiation [28]. In a series for breast cancer chest wall ($2^{nd}$ to the $6^{th}/7^{th}$intercoastal spaces) recurrence from University of Tübingen, 56 Gy was administered, and treated with post-operative 60 (45 – 66) Gy re-irradiation (median field size of 17 x 17 cm) for close (< 0.5 cm) or positive margins, perinodal involvement, multiple recurrences, or other high risk features. The re-irradiation was with concurrent hyperthermia, with sequential chemotherapy (17%) of hormone therapy (19%) [28]. When indicated regional lymphatics (supra-, infraclavicular regions, parasternal or axillary) was treated to 50 Gy in 2 Gy fractions. The total cumulative dose was 110 (85 - 112) Gy. Median time to re-irradiation 53 (12 – 401) months. Late toxicities 3 months after re-irradiation including radiation dermatitis, induration/fibrosis, teleangiectasia, pericarditis, pericardial effusion, and pneumonitis was graded according Common Toxicity Criteria (CTC 3.0). With a median follow up of 41 months, 5 years estimated local control was 62%, overall survival was 59%, no grade 3 or higher toxicity.

## CONCLUSION

Advanced stereotactic radiotherapy techniques are essential to the management of early and advance breast cancer patients. Chest wall re-irradiation is safe and effective in treating chest wall recurrences.

### References


1. Cheung R. Using a Robotic Stereotactic Radiation Treatment System to Treat Benign Intracranial Tumors and Trigeminal Neuralgia. Austin J Radiat Oncol & Cancer. 2014; 1: 2.
2. Cheung R. The Utility of a Robotic Stereotactic Radiation Treatment System to Treat Primary and Metastatic Liver Tumors. Austin J Cancer Clin Res. 2014; 1: 2.
3. Cox JD, Ang KK. Radiation Oncology: Rationale, Technique, Results, $9^{th}$ edn. 2009.
4. Ciammella P, Podgornii A, Galeandro M, Micera R, Ramundo D, Palmieri T, et al. Toxicity and cosmetic outcome of hypofractionated whole-breast radiotherapy: predictive clinical and dosimetric factors. Radiat Oncol. 2014; 9: 97.
5. Fisher ER, Anderson S, Redmond C, Fisher B. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP protocol B-06. Semin Surg Oncol. 1992; 8: 161-166.
6. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet. 2014; 383: 603-613.
7. Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra I. Multicentricity of breast cancer: whole-organ analysis and clinical implications. Br J Cancer. 1996; 74: 820-824.

8. Vaidya JS, Baum M, Tobias JS, D'Souza DP, Naidu SV, Morgan S, et al. Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. Ann Oncol. 2001; 12: 1075-1080.

9. Ross G. Accelerated partial breast irradiation: technically feasible but who will benefit? Breast Cancer Res. 2005; 7: 110-112.

10. Scorsetti M, Alongi F, Fogliata A, Pentimalli S, Navarria P, Lobefalo F, et al. Phase I-II study of hypofractionated simultaneous integrated boost using volumetric modulated arc therapy for adjuvant radiation therapy in breast cancer patients: a report of feasibility and early toxicity results in the first 50 treatments. Radiat Oncol. 2012; 7: 145.

11. Vermeulen S, Cotrutz C, Morris A, Meier R, Buchanan C, Dawson P, et al. Accelerated Partial Breast Irradiation: Using the CyberKnife as the Radiation Delivery Platform in the Treatment of Early Breast Cancer. Front Oncol. 2011; 1: 43.

12. Xu Q, Chen Y, Grimm J, Fan J, An L, Xue J, et al. Dosimetric investigation of accelerated partial breast irradiation (APBI) using CyberKnife. Med Phys. 2012; 39: 6621-6628.

13. Crozier JA, Swaika A, Moreno-Aspitia A. Adjuvant chemotherapy in breast cancer: To use or not to use, the anthracyclines. World J Clin Oncol. 2014; 5: 529-538.

14. Olivotto IA, Bajdik CD, Ravdin PM, Speers CH, Coldman AJ, Norris BD, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. J Clin Oncol. 2005; 23: 2716-2725.

15. Dawood S, Gonzalez-Angulo AM. Progress in the biological understanding and management of breast cancer-associated central nervous system metastases. Oncologist. 2013; 18: 675-684.

16. Gil-Gil MJ, Martinez-Garcia M, Sierra A, Conesa G, Del Barco S, González-Jimenez S, et al. Breast cancer brain metastases: a review of the literature and a current multidisciplinary management guideline. Clin Transl Oncol. 2014; 16: 436-446.

17. Tallet AV, Azria D, Le Rhun E, Barlesi F, Carpentier AF, Gonçalves A, Taillibert S. Rationale for the use of upfront whole brain irradiation in patients with brain metastases from breast cancer. Int J Mol Sci. 2014; 15: 8138-8152.

18. Choi SW, Kwon do H, Kim CJ. Clinical outcome in gamma knife radiosurgery for metastatic brain tumors from the primary breast cancer : prognostic factors in local treatment failure and survival. J Korean Neurosurg Soc. 2013; 54: 329-335.

19. Eksi MS, Hasanov T, Yilmaz B, Akakin A, Bayri Y, Bozkurt SU, et al. Isolated metastasis of breast cancer to the pituitary gland. Neurol India. 2014; 62: 70-71.

20. Jaboin JJ, Ferraro DJ, DeWees TA, Rich KM, Chicoine MR, Dowling JL, et al. Survival following gamma knife radiosurgery for brain metastasis from breast cancer. Radiat Oncol. 2013; 8: 131.

21. Karam I, Nichol A, Woods R, Tyldesley S. Population-based outcomes after whole brain radiotherapy and re-irradiation in patients with metastatic breast cancer in the trastuzumab era. Radiat Oncol. 2011; 6: 181.

22. Kelly PJ, Lin NU, Claus EB, Quant EC, Weiss SE, Alexander BM. Salvage stereotactic radiosurgery for breast cancer brain metastases: outcomes and prognostic factors. Cancer. 2012; 118: 2014-2020.

23. Nieder C. [Radiotherapy and re-irradiation of breast cancer patients with brain metastases: Survival in the trastuzumab era]. Strahlenther Onkol. 2012; 188: 638-639.

24. Yang TJ, Oh JH, Folkert MR, Gupta G, Shi W, Zhang Z, et al. Outcomes and prognostic factors in women with 1 to 3 breast cancer brain metastases treated with definitive stereotactic radiosurgery. Int J Radiat Oncol Biol Phys. 2014; 90: 518-525.

25. Ramakrishna N, Temin S, Chandarlapaty S, Crews JR, Davidson NE, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014; 32: 2100-2108.

26. Vern-Gross TZ, Lawrence JA, Case LD, McMullen KP, Bourland JD, Metheny-Barlow LJ, et al. Breast cancer subtype affects patterns of failure of brain metastases after treatment with stereotactic radiosurgery. J Neurooncol. 2012; 110: 381-388.

27. Vincent A, Lesser G, Brown D, Vern-Gross T, Metheny-Barlow L, Lawrence J, et al. Prolonged regression of metastatic leptomeningeal breast cancer that has failed conventional therapy: a case report and review of the literature. J Breast Cancer. 2013; 16: 122-126.

28. Müller AC, Eckert F, Heinrich V, Bamberg M, Brucker S, Hehr T. Re-surgery and chest wall re-irradiation for recurrent breast cancer: a second curative approach. BMC Cancer. 2011; 11: 197.

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Chapter - 4

# Stereotactic Hypofractionated Radio-Therapy of Primary and Metastatic Lung Cancers

## BACKGROUND

Primary lung cancers and metastatic cancers to the lungs are the leading cancer-related death in men and woman [1]. Main treatments include surgery, Radiofrequency Ablation (RFA), chemotherapy and radiotherapy [2,3]. RFA has successfully been used to treat primary and metastatic liver cancers. Now it is becoming more popular in treating lung cancers [4]. Stereotactic Body Radiotherapy (SBRT) is a method of external beam radiotherapy for extracranial sites in one of few fractions [5]. For treatment of early stage non-small cell lung cancer (NSCLC), SBRT appears to be equivalent to sublobar resection and is an effective alternative to operable patients refusing lobectomy [5,6]. In addition, SBRT for early lung cancers has been found to be cost effective [7]. This paper is part of a series discussing the use of advanced stereotactic radiation treatment machines in challenging clinical scenarios [8,9].

## SBRT OF PRIMARY AND METASTICLUNG CANCERS

The Biologically Equivalent Dose (BED) [10] for primary and metastatic lung cancers has been studies [11]. The BED depends on the alpha/beta ratios, one study has suggested early stage non-small cell lung cancer (NSCLC) has a ratio > 10 Gy [12]. For lung cancers smaller than 3 cm, BED less than 150 Gy has been found to be effective, for lung cancers larger than 3 cm, BED greater than 150 Gy is needed [11].

SBRT for NSCLC covers only the gross lung tumor. However, a study contoured the ipsilateral and contralateral levels, lymph node stations 2 to 7, and ipsilateralhilar lymph node stations, it was found that SBRT also resulted in significant RT dose the draining lymphatics [13]. For CyberKnife tumor tracking, tumor size > 3.5 cm and good tumor radiographic density predicts 80% chance of being adequately tracked by fiducial-less lung tumor tracking with XSight Lung tumor tracking [14]. Helical tomography SBRT [15]. This would greatly reduce the margin needed. For the other patients, the Internal Target Volume (ITV) generated for the early lung cancer primary using 4 phases 4-dimensional Computed Tomography (CT) was found to be most efficient and effective when compared to 10 phases and two phases [16].

The size of Gross Tumor Tumor (GTV) has been associated with grade 5 radiation pneumonitis [15]. In addition, SBRT patient for centrally located lesions with esophagitis during or after SBRT should be monitored closely [17]. Fatal full thickness perforation may occur from this [17]. Chest wall toxicity is acceptable when the dose and fractionation are adjusted to chest wall dosimetry [18]. In one study, patients were treated with 54 Gy in three 18 Gy fractions when chest wall V30 was less than 30 mL or 50-60Gy in five 10-12 Gy fractions. Using these treatment guidelines, 6.9% patients developed rib fractures, Grade 3 chest wall pain was 1.4 %. No grade 4 or 5 chest wall pain [18].

In patients with only limited and controlled oligometastatic lesions (1-5 lesions), SBRT consolidation has been found to be useful [19]. For example, SBRT has been used to treat lung oligometastases from various primaries [20,21]. In one study [20], ≤ 5 lung lesions were treated. Doses used were 48 Gy over 4 fractions for peripheral lesions, 60 Gy over 8 fractions for central lesions, and 60 Gy over 3 fractions for peripheral lesions with diameter ≤ 2 cm [20]. Local control in the study was 89% at 3 years and there were no major pulmonary toxicity, chest wall pain and rib fractions [20]. In another study [21], daily 8-12 Gy x five fractions was used to treat lung oligometastases. The median dose used in that was 50 Gy (range: 40 – 60 Gy) prescribed to 80% isodose line covering the planning target volume (PTV). The PTV was defined as 7 – 11 mm as GTV expansion. In the study, the primary tumors included traditionally considered radiation resistant melanoma, renal cell carcinoma and sarcoma. The overall 3 year local control was 80% [21].

## SRS OF METASTATIC LUNG CANCERS TO THE BRAIN AND SYSTEMIC TREATMENT

SRS for metastatic lung cancers to the brain has been found to be less toxic than whole brain radiotherapy [22]. Addition of Temozolomide (75 mg/m2/day x 5 days a month, or erlotonib (150 mg/day) to WBRT (37.5 Gy in 2.5 Gy fractions) and SRS caused a deleterious effects in overall survival [23]. Although this decrement has not been directly linked to the concurrent chemotherapy [23]. In a case report, pathologic vertebral fracture has been reported in a patient with urothelial lung metastasis with 48 Gy in three fractions over 6 days [24]. There is no consensus on re-SRS of brain metastasis. Some have reported it is safe and effective for recurrent metastatic NSCLC to the brain [25]. SBRT has also been used to treat Superior Vena Cava Syndrome (SVCS) effectively [26].

Gamma Knife has been used in treatment lung cancer brain metastases ≥ 4 lesions in a single session [27]. The median tumor volume was 1.2 cc. Tumor volume ≥ 3 cc (about 1.8 cm in diameter), there is worsened survival. The median dose was 21 Gy prescribed to 50% isodose line. The median overall survival was 6.7 months from SRS [27]. SRS for small cell brain metastases is effective, however, 50% of patients required re-irradiation [28].

Systemic treatment is an important part of lung cancer treatment. Tyrosine kinase inhibitors

have been effective in treating brain metastasis from NSCLC [29]. Taking concurrent crizotinib and local ablative therapy, followed by sequential crizotinib in analplastic lymphoma kinase-positive NSCLC was safe and effective [30]. Concurrent erlotinib and SBRT (54 Gy/9 fractions) has been found to be effective in one patient in a case report [31]. More data are clearly needed to establish the efficacy and safety for adding systemic treatment to very large ablative doses of radiotherapy.

## RE-IRRADIATION OF RECURRENT LUNG CANCERS

In one study [19], 44 patients were re-irradiated with external beam radiotherapy for in-field recurrence of primary lung cancer after 50 – 70 Gy initial radiotherapy [19]. This re-irradiation dose ranged from 30 to 60 Gy. The median survival after re-irradiation was 6.5 months. 74% of the patients had improved or complete resolution of symptoms. 3 patients had grade 2 and 3 pulmonary toxicity [19].

SBRT has been used in re-irradiate previously irradiated lung cancers [1]. In a review of re-irradiation studies, 140 patients were included, initial thoracic dose ranged from 50-87.5 Gy and median re-irradiation dose ranged from 40-80 Gy. Local control rates ranged from 65-92%. There were few grade 4 and 5 complications [1].

## CONCLUSION

SBRT and SRS are effective and safe treatment for primary and metastatic lung cancers even in the re-irradiation setting. They should be considered as standard of care treatment options.

### References


1. Amini A, Yeh N, Gaspar LE, Kavanagh B, Karam SD. Stereotactic body radiation therapy (SBRT) for lung cancer patients previously treated with conventional radiotherapy: a review. Radiat Oncol. 2014; 9: 210.
2. Cox JD, Ang KK. Radiation Oncology: Rationale, Technique, Results, 9th edn. 2003.
3. Gomez DR, Chang JY. Accelerated dose escalation with proton beam therapy for non-small cell lung cancer. J Thorac Dis. 2014; 6: 348-355.
4. Hoffmann RT, Jakobs TF, Muacevic A, Trumm C, Helmberger TK, Reiser MF. [Interventional oncology for lung tumors]. Radiologe. 2007; 47: 1109-1116.
5. Guckenberger M, Andratschke N, Alheit H, Holy R, Moustakis C, Nestle U, et al. Deutschen Gesellschaft für Radioonkologie (DEGRO). Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer. Strahlenther Onkol. 2014; 190: 26-33.
6. Soldà F, Lodge M, Ashley S, Whitington A, Goldstraw P, Brada M. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and comparison with a surgical cohort. Radiother Oncol. 2013; 109: 1-7.
7. Mitera G, Swaminath A, Rudoler D, Seereeram C, Giuliani M, Leighl N, et al. Cost-effectiveness analysis comparing conventional versus stereotactic body radiotherapy for surgically ineligible stage I non-small-cell lung cancer. J Oncol Pract. 2014; 10: e130-136.
8. Cheung R. Using a Robotic Stereotactic Radiation Treatment System to Treat Benign Intracranial Tumors and Trigeminal Neuralgia. Austin J Radiat Oncol & Cancer. 2014; 1: 2.
9. Cheung R. The Utility of a Robotic Stereotactic Radiation Treatment System to Treat Primary and Metastatic Liver Tumors. Austin J Cancer Clin Res. 2014; 1: 2.
10. Unger KR, Lominska CE, Chanyasulkit J, Randolph-Jackson P, White RL, Aulisi E, et al. Risk factors for posttreatment edema in patients treated with stereotactic radiosurgery for meningiomas. Neurosurgery. 2012; 70: 639-645.

11. Park S, Urm S, Cho H. Analysis of biologically equivalent dose of stereotactic body radiotherapy for primary and metastatic lung tumors. Cancer Res Treat. 2014; 46: 403-410.

12. Chi A, Wen S, Liao Z, Fowler J, Xu J, Nguyen NP, et al. What would be the most appropriate Î±/Î² ratio in the setting of stereotactic body radiation therapy for early stage non-small cell lung cancer. Biomed Res Int. 2013; 2013: 391021.

13. Parashar B, Singh P, Christos P, Arora S, Desai P, Wernicke AG, et al. Stereotactic body radiation therapy (SBRT) for early stage lung cancer delivers clinically significant radiation to the draining lymph nodes. J Radiosurg SBRT. 2013; 2: 339-340.

14. Bahig H, Campeau MP, Vu T, Doucet R, Béliveau Nadeau D, Fortin B, et al. Predictive parameters of CyberKnife fiducial-less (XSight Lung) applicability for treatment of early non-small cell lung cancer: a single-center experience. Int J Radiat Oncol Biol Phys. 2013; 87: 583-589.

15. Aibe N, Yamazaki H, Nakamura S, Tsubokura T, Kobayashi K, Kodani N, et al. Outcome and toxicity of stereotactic body radiotherapy with helical tomotherapy for inoperable lung tumor: analysis of Grade 5 radiation pneumonitis. J Radiat Res. 2014; 55: 575-582.

16. Yeo SG, Kim ES. Efficient approach for determining four-dimensional computed tomography-based internal target volume in stereotactic radiotherapy of lung cancer. Radiat Oncol J. 2013; 31: 247-251.

17. Sainathan S, Wu LD, Andaz S. Delayed esophageal perforation from stereotactic body radiation therapy for locally recurrent central nonsmall cell lung cancer. Lung India. 2014; 31: 158-160.

18. Coroller TP, Mak RH, Lewis JH, Baldini EH, Chen AB, Colson YL, et al. Low incidence of chest wall pain with a risk-adapted lung stereotactic body radiation therapy approach using three or five fractions based on chest wall dosimetry. PLoS One. 2014; 9: e94859.

19. Ebara T, Tanio N, Etoh T, Shichi I, Honda A, Nakajima N. Palliative re-irradiation for in-field recurrence after definitive radiotherapy in patients with primary lung cancer. Anticancer Res. 2007; 27: 531-534.

20. Navarria P, Ascolese AM, Tomatis S, Cozzi L, De Rose F, Mancosu P, et al. Stereotactic body radiotherapy (sbrt) in lung oligometastatic patients: role of local treatments. Radiat Oncol. 2014; 9: 91.

21. Singh D, Chen Y, Hare MZ, Usuki KY, Zhang H, Lundquist T, et al. Local control rates with five-fraction stereotactic body radiotherapy for oligometastatic cancer to the lung. J Thorac Dis. 2014; 6: 369-374.

22. Monaco EA 3rd, Faraji AH, Berkowitz O, Parry PV, Hadelsberg U, Kano H, et al. Leukoencephalopathy after whole-brain radiation therapy plus radiosurgery versus radiosurgery alone for metastatic lung cancer. Cancer. 2013; 119: 226-232.

23. Sperduto PW, Wang M, Robins HI, Schell MC, Werner-Wasik M, Komaki R, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. Int J Radiat Oncol Biol Phys. 2013; 85: 1312-1318.

24. Rodríguez-Ruiz ME, San Miguel I, Gil-Bazo I, Perez-Gracia JL, Arbea L, Moreno-Jimenez M, Aristu J. Pathological vertebral fracture after stereotactic body radiation therapy for lung metastases. Case report and literature review. Radiat Oncol. 2012; 7: 50.

25. Marvaso G, Barone A, Vaccaro C, Bruzzaniti V, Grespi S, Scotti V, et al. Repeat stereotactic radiosurgery in the management of brain metastases from NSCLC: A case report and review of the literature. Oncol Lett. 2013; 6: 897-900.

26. McKenzie JT, McTyre E, Kunaprayoon D, Redmond KP. Stereotactic body radiotherapy for superior vena cava syndrome. Rep Pract Oncol Radiother. 2013; 18: 179-181.

27. Ojerholm E, Lee JY, Kolker J, Lustig R, Dorsey JF, Alonso-Basanta M. Gamma Knife radiosurgery to four or more brain metastases in patients without prior intracranial radiation or surgery. Cancer Med. 2014; 3: 565-571.

28. Yomo S, Hayashi M. Upfront stereotactic radiosurgery in patients with brain metastases from small cell lung cancer: retrospective analysis of 41 patients. Radiat Oncol. 2014; 9: 152.

29. Jung YH, Han CW, Jung YD, Cho YY, Han DJ. Complete Remission of Brain Metastases in Non-Small Cell Lung Cancer Patients Harboring an EGFR Mutation Treated with Tyrosine Kinase Inhibitor without Radiotherapy: A Report of 3 Cases. Case Rep Oncol. 2014; 7: 149-154.

30. Gan GN, Weickhardt AJ, Scheier B, Doebele RC, Gaspar LE, Kavanagh BD, et al. Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. Int J Radiat Oncol Biol Phys. 2014; 88: 892-898.

31. Hsieh CH, Chang HT, Lin SC, Chen YJ, Wang LY, Hsieh YP, et al. Toxic risk of stereotactic body radiotherapy and concurrent helical tomotherapy followed by erlotinib for non-small-cell lung cancer treatment--case report. BMC Cancer. 2010; 10: 696.

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Chapter - 5

# Stereotactic Body Radiotherapy (SBRT) and re-SBRT of Gastrointestinal Cancers

## BACKGROUND

Gastrointestinal (GI) cancers is a significant cause of death from cancers [1]. The major sites of GI cancers are include the colorectal cancers, esophageal cancers, pancreatic cancers, liver cancers, and biliary cancers [1]. For colorectal cancers, there were 51000 deaths, and 142500 new cases in 2010 [1]. The treatment of GI cancers depends on the primary [2]. Typically, resected tumors are resected, and chemoradiation with or without surgery are used to treat locally advanced GI cancers [2]. Radiotherapy usually spans over 6-7 weeks using conventional dose and fraction (1.8-2 Gy, daily dose and five days a week). To improve outcome, Stereotactic Body Radiotherapy (SBRT) has been used to spare normal tissues with modern stereotaxy and dose escalate with large daily doses leading to higher biologic effective dose [3] in selected sites. This paper is part of a series discussing the use of stereotactic radiotherapy in challenging clinical scenarios [4,5].

## SBRT OF GI CANCERS

SBRT 25 Gy over 5 fractions prescribed to 75-83% isodose line was used with full dose concurrent gemcitabine (1000 gm/m2) and was found to be safe in treating inoperable pancreatic cancer [6]. Duodenal toxicity may be higher with gemcitabine and single 25 Gyfraction SBRT [7]. SBRT tend not to interrupt the gemcitabine-based systemic treatment when compared to the conventional six to seven weeks of conventional chemotherapy [8].Grade 3 and 4 GI toxicities are usually associated with systemic treatments [9].

SBRT for pancreas and liver tumors, organs at risk include stomach, duodenum and liver [10]. For targeting using fiducials in advanced stereotactic radiation machines such as CyberKnife, the fiducials could be place under Endoscopic Ultrasonography (EUS) for pancreatic and liver lesions [11]. Complications include spontaneous fiducial migration and mild pancreatitis [11].

Primary or recurrent cholangiocarcinoma with SBRT has been reported [12-15]. In one study [12], with a median dose of 55 Gy (range 45 – 60 Gy) daily over three or five fractions [12]. Treatment response and toxicities were graded were graded. The sites treated were liver, abdominal lymph nodes, and adrenal gland. With a median follow up of 14 months, local control

was 100%. Toxicities include GI pain, biliary stenosis and liver failure [12]. In another study [13], 27 pateints treated with 45 Gy in 3 fractions was used to treat intrahepatic and Klatskin tumors with linac-based SBRT. Median followup of 5.4 years, 6 patients had severe duodenal/pyloric ulceration and 3 patients had duodenal stenosis [13]. SBRT has been used in treating primary and metastatic liver cancers [5,15-18].

Small bowel injury with SBRT is increased when anti-angiogenic therapy (Bevacizumab, sorafinib, pazopanib, and sunitinib) is used sequentially, Grade 3-5 ulceration or perforation was increased. 6 months estimate of small bowel injury for receiving (Vascular Endothelial Growth Factor Inhibitor (VEGFI) within 3 months of SBRT has a risk of 38% [19]. The median SBRT dose was 50 Gy over 5 fractions [19].

## SBRT AND SRS OF GI CANCERS

Oligometastases from colorectal cancer has been treated with SBRT [20]. In this study, one to three inoperable metastases in lung or liver were treated with SBRT. Dose ranged from 48 to 75 Gy over 3 or 4 consecutive sessions. At median follow up of 2 years, 70 % of lung metastases were controlled, 85% of liver metastases were controlled. 4D CT was obtained for all lung cases and for liver cases with excursion more than 5 mm, ITV enveloped the GTV of all phases. CTV = GTV or ITV when 4D CT was obtained. ITV expanded 5 mm to obtain the PTV. 7-10 mm cranial-caudal axis and 4-6 mm in lateral axes from CTV to obtain PTV when 4D CT was not obtained [20]. Research and Treatment of Cancer Evaluation Criteria in Solid Tumors (RECIST) guideline [21]. Dose higher than 48 Gy over 3 fractions has been suggested to be used to treat liver metastases [22].

Brain metastasis from GI cancers is a late sign [1,23]. Surgery plus WBRT has the best median survival compared with surgery alone, SRS, WBRT alone, an steroid [1]. SRS and re-SRS of brain metastases are discussed separately.

## RE-IRRADIATION OF GI CANCERS

SBRT using Vairan True Beam™ treatment machine using Volumetric Modulated Arc Therapy (RapidArc) has been used in treating abdominal/pelvic recurrence with acceptable tumor control and toxicities [24]. Depending on the area of the GI tract being re-irradiated, there are different critical structures surrounding the re-irradiated area. For esophagus, the critical structures are the lungs, heart, trachea, proximal bronchi and great vessels. For abdominal areas, the critical organs are kidney, liver, small bowel, duodenum and stomach. For pelvic areas, the sensitive organs are the bladder, rectum, small bowel. To determine the dose and fraction for re-irradiation, tumor control probability (TCP) of recurrent cancers may be different than the original ones [25,26]. Biologic Effective Dose (BED) [27] and EQD2 calculations (Biologic Equivalent Dose at 2 Gy (EQD2) [28] could be calculated. QUANTEC [29] guideline could be used for re-irradiation, but QUANTEC has been tested clinically in re-irradiation.

## CONCLUSION

SBRT, SRS with and without chemotherapy are safe and effective treatments in treating selected GI cancers, and should be considered as standard of care treatment options.

## References


1. Go PH, Klaassen Z, Meadows MC, Chamberlain RS. Gastrointestinal cancer and brain metastasis: a rare and ominous sign. Cancer. 2011; 117: 3630-3640.
2. Cox JD, Ang KK. Radiation Oncology: Rationale, Technique, Results, 9th edn. 2009.
3. Unger KR, Lominska CE, Chanyasulkit J, Randolph-Jackson P, White RL, Aulisi E, et al. Risk factors for posttreatment edema in patients treated with stereotactic radiosurgery for meningiomas. Neurosurgery. 2012; 70: 639-645.
4. Cheung R. Using a Robotic Stereotactic Radiation Treatment System to Treat Benign Intracranial Tumors and Trigeminal Neuralgia. Austin J Radiat Oncol & Cancer. 2014; 1: 2.
5. Cheung R. The Utility of a Robotic Stereotactic Radiation Treatment System to Treat Primary and Metastatic Liver Tumors. Austin J Cancer Clin Res. 2014; 1: 2.
6. Gurka MK, Collins SP, Slack R, Tse G, Charabaty A, Ley L, et al. Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: a pilot trial demonstrating safety. Radiat Oncol. 2013; 8: 44.
7. Schellenberg D, Goodman KA, Lee F, Chang S, Kuo T, Ford JM, et al. Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2008; 72: 678-686.
8. Stauder MC, Miller RC. Stereotactic Body Radiation Therapy (SBRT) for Unresectable Pancreatic Carcinoma. Cancers (Basel). 2010; 2: 1565-1575.
9. Thomas TO, Hasan S, Small W Jr, Herman JM, Lock M, Kim EY, et al. The tolerance of gastrointestinal organs to stereotactic body radiation therapy: what do we know so far? J Gastrointest Oncol. 2014; 5: 236-246.
10. Minn AY, Koong AC, Chang DT. Stereotactic body radiation therapy for gastrointestinal malignancies. Front Radiat Ther Oncol. 2011; 43: 412-427.
11. Choi JH, Seo DW, Park do H, Lee SK, Kim MH. Fiducial placement for stereotactic body radiation therapy under only endoscopic ultrasonography guidance in pancreatic and hepatic malignancy: practical feasibility and safety. Gut Liver. 2014; 8: 88-93.
12. Barney BM, Olivier KR, Miller RC, Haddock MG. Clinical outcomes and toxicity using stereotactic body radiotherapy (SBRT) for advanced cholangiocarcinoma. Radiat Oncol. 2012; 7: 67.
13. Kopek N, Holt MI, Hansen AT, Høyer M. Stereotactic body radiotherapy for unresectable cholangiocarcinoma. Radiother Oncol. 2010; 94: 47-52.
14. Polistina FA, Guglielmi R, Baiocchi C, Francescon P, Scalchi P, Febbraro A, et al. Chemoradiation treatment with gemcitabine plus stereotactic body radiotherapy for unresectable, non-metastatic, locally advanced hilar cholangiocarcinoma. Results of a five year experience. Radiother Oncol. 2011; 99: 120-123.
15. Tse RV, Hawkins M, Lockwood G, Kim JJ, Cummings B, Knox J, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol. 2008; 26: 657-664.
16. Boda-Heggemann J, Dinter D, Weiss C, Frauenfeld A, Siebenlist K, Attenberger U, et al. Hypofractionated image-guided breath-hold SABR (stereotactic ablative body radiotherapy) of liver metastases--clinical results. Radiat Oncol. 2012; 7: 92.
17. Jang WI, Kim MS, Bae SH, Cho CK, Yoo HJ, Seo YS, et al. High-dose stereotactic body radiotherapy correlates increased local control and overall survival in patients with inoperable hepatocellular carcinoma. Radiat Oncol. 2013; 8: 250.
18. Scorsetti M, Clerici E, Comito T. Stereotactic body radiation therapy for liver metastases. J Gastrointest Oncol. 2014; 5: 190-197.
19. Barney BM, Markovic SN, Laack NN, Miller RC, Sarkaria JN, Macdonald OK, et al. Increased bowel toxicity in patients treated with a vascular endothelial growth factor inhibitor (VEGFI) after stereotactic body radiation therapy (SBRT). Int J Radiat Oncol Biol Phys. 2013; 87: 73-80.
20. Comito T, Cozzi L, Clerici E, Campisi MC, Liardo RL, Navarria P, et al. Stereotactic Ablative Radiotherapy (SABR) in inoperable oligometastatic disease from colorectal cancer: a safe and effective approach. BMC Cancer. 2014; 14: 619.
21. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45: 228-247.

22. Chang DT, Swaminath A, Kozak M, Weintraub J, Koong AC, Kim J, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. Cancer. 2011; 117: 4060-4069.

23. Takeuchi H, Koike H, Fujita T, Tsujino H, Iwamoto Y. Sunitinib treatment for multiple brain metastases from jejunal gastrointestinal stromal tumor: case report. Neurol Med Chir (Tokyo). 2014; 54: 664-669.

24. Alongi F, Fogliata A, Clerici E, Navarria P, Tozzi A, Comito T, et al. Volumetric modulated arc therapy with flattening filter free beams for isolated abdominal/pelvic lymph nodes: report of dosimetric and early clinical results in oligometastatic patients. Radiat Oncol. 2012; 7: 204.

25. Mantel F, Flentje M, Guckenberger M. Stereotactic body radiation therapy in the re-irradiation situation--a review. Radiat Oncol. 2013; 8: 7.

26. Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys. 2010; 37: 4078-4101.

27. Fowler JF. 21 years of biologically effective dose. Br J Radiol. 2010; 83: 554-568.

28. Tharavichtikul E, Meungwong P, Chitapanarux T, Chakrabandhu S, Klunklin P, Onchan W, et al. The association of rectal equivalent dose in 2 Gy fractions (EQD2) to late rectal toxicity in locally advanced cervical cancer patients who were evaluated by rectosigmoidoscopy in Faculty of Medicine, Chiang Mai University. Radiat Oncol J. 2014; 32: 57-62.

29. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010; 76: S10-19.

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Chapter - 6

# Using Data from the Cancer Genome Atlas (TCGA) to Model Outcome of Cancer Patients to Guide Oncologic Treatment

## INTRODUCTION

With the availability of human cancer genome data, individualized oncology treatment may become a reality in the near future [1-4]. National Cancer Institute (NCI) has made a large amount of cancer genome data available for the research community to mine and study through The Cancer Genome Atlas (TCGA) [1-3,5]. TCGA is funded by NCI and National Human Genome Research Institute (NHGRI). It was started in 2006. It has pooled high quality genome data from individual research teams. TCGA allows the cancer researchers anywhere in the world to use the download, search and provides the tool to analyze the genomic data of more than 20 cancer types (https://tcga-data.nci.nih.gov/) [1-3].This paper summarizes how to use of TCGA largely based on the information provided by the TCGA (http://cancergenome.nih.gov) and discuss the potential of mining these data to build risk models for individual patients as a guide to treatment selection.

## TCGA DATA AND SOFTWARE

After launching the TCGA data portal, TCGA provides the following software to search and download the data: 1. Data Matrix allows users to search and download subsets of currently available data but it does not allow cross-disease search. 2. File Search is similar to Data Matrix but it would allow cross disease type search and download. 3. Bulk Download allows the users to download current and older data. The TCGA data are divided into open access (data are not unique to individuals, no prior permission is required to download data) and controlled access (data are unique to individuals, prior permission is required to download the data). Large scale (more than 100 cases) and global (across platform or across cancer type) analyses using the TCGA data require following publication and presentation guidelines or prior permission from TCGA prior to publication, the specifics are listed and updated by the TCGA.

TCGA provides dashboards that allow users to see the progress of TCGA data acquisition. Currently there are about 1870782 Gigabytes data in TCGA (https://cghub.ucsc.edu via TCGA portal). TCGA provides the following data types: 1. Clinical Data (clinical information, biospecimen data, and pathology reports). 2. Image Data (tissue images, and radiographic pre-surgery staging

images). 3. Microsatellite Instability Data. 4. DNA Sequencing Data (genome, exome, and mutation data). 4. Non-coding microRNAs (except GBM). 5. Protein expression. 6. mRNA Sequencing. 7. Total RNA Sqquencing. 8. Arry-based Expression. 9. DNA Mythylation, and 10. Copy number. TCGA provides information on the platforms used to study the genomic data by the research centers.

TCGA collects and provides the following analytical softwaresfrom participating research centers to analyze the TCGA data and report the analysis: 1. The Cancer Imaging Archive (TCIA) provides access to radiographic imaging data in DICOM format. 2. Cancer Genome Workbench (CGWB) provides whole genome level and heat maps of mutation, deletion and amplification at the sample level. 3. Integrative Genomics Viewer (IGV) is a high performance visualization tool that allows interactive analyses of large and integrated data set. 4. cBioPortal for Cancer Genomics is a web-based tool that allows users to analyze, display and report the genomic analysis and correlation to clinical data. 5. UCSC Cancer Genomics Browser is a browser-based tool that allows analysis of genomic and clinical data. 6. Berkeley Morphometric Visualization and Quantification from H&E sections is a tool allows quantitative analyses of H&E slides and overlay the information on the slides. 7. Broad GDAC Firehoseis a tool to systematize a number of genomic analyses of TCGA data and report the results in a user friendly form.8. MD Anderson GDAC MBatch is a tool for clustering and principal component analyses. 9. Regulome Explorer is an analysis tool correlating clinical and molecular TCGA data and 10. Cancer Slide digital Archive (CSDA) is a browser-based viewing, annotating, and data retrieval tool. The clinical data contain disease specific disease free survival and overall survival data.

## TCGA DATA ANALYSES OF SPECIFIC CANCER TYPES

The cancer types included in TCGA: breast, central nervous system, endocrine, gastrointestinal, gynecologic, head and neck, hematologic, skin, soft tissue, thoracic, and urologic cancers (cancergenome.nih.gov). Major international projects are underway to annotate all the genes related to the initiation and progression of cancers [2,6]. From Genome studies, it has been found that there were only very few genes when mutated could drive tumorigenesis [3]. These genes control 12 signaling pathways and 3 core cellular processes: cell fate, cell survival and genome maintenance [3,7]. “Driver genes” drives oncogenesis. A typical tumor has about 2-6 driver gene mutations [3,7]. The other mutations are “passenger mutations” that do not lead to tumorigenesis [3].

The first tumor characterized using TCGA data was Glioblasto Mamultiforme (GBM) [8]. ERBB2, NF1, TP53, and phosphatidylinositol-3-OH kinase regulatory subunit gene PIK3R1 were found to be important in GBM carcinogenesis [8]. Integrated analyses of the mutations, DNA methylation and clinical treatment data revealed MGMT promoter methylation and hypermutater phenotype consequent to mismatch repair deficiency in treated glioblastomas [8].

The Cancer Cell Line Encyclopedia (CCLE) is an annotation of gene expression of more than

1600 genes, chromosomal copy number from massively parallel DNA sequencing data from 947 human cancer cell lines [9]. Using 24 anticancer drugs across 479 of the cancer cell lines, the CCLE has annotated genetic, lineage, gene-expression-based predictors of drug sensitivity to these drugs [9]. Lineage studies demonstrated that CCLE cell lines were representative of the primary tumors using known datasets including data from Tumorscape (for copy number), expO (expression project for oncology, http://www.intgen.org ), and COSMIC (catalog of somatic mutations in cancers) [5,9]. From this study, plasma cell lineage was found to be sensitive to IGF1 receptor inhibitor [9]. HDAC (histone deacetalase) inhibitor panobinostat showed similar effects across all the cell lines. This study also found BRAF and NRAS mutations were major predictors of MEK inhibitor (PD-032501) efficacy [9]. Expression of MAPK regulator PTEN, PTPN5 and SPRY2 predicted MEK inhibition [9]. EGFR mutations and ERBB2 over-expression predicted for Erlotinib and Lapatinib inhibition, $BRAF^{V600E}$ for RAF inhibitors. EXT2 gene that encoded a glycosyltransferase involved in heparin sulfate synthesis was correlated with Erlotinib sensitivity. NQO1 expression predicted heat shock protein Hsp90 inhibitors sensitivity. SLFN11 expression predicted sensitivity to topoisomerase inhibitors of Topoisomerase I (TOP1) such as irinotecan and topotecan [9]. To identify mutant genes that may be good biomarkers [10], this study tested 130 drugs on several hundred cancer cell lines that represent most of the human cancers. It was found Ewing's sarcoma cells with the EWS-FLI1 gene translocation had increased sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors [10].

Genomic analyses have revealed that prostate cancer could have a chaotic evolution to tumorigenesis consisted of massive non-recurrent singleton genomic translocations and deletions that could cause genomic derangement over a few events [11]. This study analyzed the genomes of hormone naïve, androgen independent and neuroendocrine prostate cancers [11]. Other genomic studies have also found catastrophic chromosomal events in a few percent of other cancers [12].

Endometrial cancers are cancers of the lining of the uterus [13]. Type I endometrioid endometrial cancers are associated with excess estrogen and obesity, type II endometrial cancers are primarily serous type associated with older non-obese patients [14]. An integrated study of genomic, transcription and proteomic data of 373 endometrial carcinomas using array and sequencing technologies have found uterine serous tumors and about 25% of high grade endometrioid tumors similarly had extensive copy number alterations, few DNA methylation changes, low estrogen receptor/progesterone receptor levels and frequent TP53 mutations [14]. On the other hand, most endometrioidendometrial tumors had few copy number alterations or TP53 mutations, but frequent mutations in PTEN, CTNNB1, PIK3CA, ARID1A and KRAS [14] and mutations in the SI/SNF chromatin remodeling complex gene ARID5B, some with mutations in DNA Polymerase Epsilon (POLE) involved in DNA replication and repair [14]. Interestingly, uterine serous carcinomas shared genomic features with ovarian serous and basal-like breast carcinomas [14]. TCGA has also been used to analyze the breast cancer genomes to define the subtypes of breast cancers [15].

Many patients with multiple, large or early colorectal adenomas or cancers have no germline mutations in known oncogenes [16]. Using integrated genome analyses including linkage and association studies, it has been found heterozygous POLE or POLD1 (DNA polymerases delta domain) germline variants were associated with POLE p.Leu424Val and POLD1 p.Ser478Asn, and POLD1 mutations was also associated with endometrial cancer [16]. These mutations were mapped to the exonuclease proofreading domains of DNA polymerases epsilon and delta [16].

A study analyzed DNA from paired tumor and whole blood samples from 92 squamous carcinomas of head and neck (HNSCC) and found about 130 coding mutationsper tumor [17]. Guanosine to thymidine mutations at non-CpG sites characteristic of tobacco exposure were found [17]. The mutation rate of HPV positive tumors was about half of those HPV negative HNSCC tumors [17]. TP53 inactivation by mutation or HPV infection was universal [17]. Squamous differentiation gene NOTCH loss of function mutations were found in about 10% of HNSCC [17]. Patients on gamma secretase inhibitors (inhibitors of NOTCH gene products) should be monitored for skin and HNSCC malignancies because these drugs make patients more susceptible to develop squamous cell carcinomas [17]. A case control integrated study from Thailand studied the relationship between tobacco consumption and genetic susceptibility to Nasopharyngeal Carcinoma (NPC) [18]. Genetic factors included three mutants near the CHRNA3 and TERT genes that were also linked to lung cancer risk in Asian populations [18]. Fermented vegetable, tobacco smoking and a locus on 5p15.33 were associated with NPC risk [18]. These findings may have public health, cancer prevention, and treatment selection implications [19].

## CONCLUSION

With the large amount of genomic, proteomic and survival data available at the TCGA, and the software available to mine the data, it is expected a large amount of information will come out from these data over this decade [2]. These data may help model the individual cancer patients better for personalized cancer treatments. However, clinical trials are required to validate if omics models in addition to the clinical models are superior than the ones that have currently been used in the clinic.

### References


1. Wheeler DA, Wang L. From human genome to cancer genome: the first decade. Genome Res. 2013; 23: 1054-1062.
2. Cancer Genome Atlas Research Network, Weinstein JN, Collisson EA, Mills GB, Shaw KR, Ozenberger BA, Ellrott K. The Cancer Genome Atlas Pan-Cancer analysis project. Nat Genet. 2013; 45: 1113-1120.
3. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. Science. 2013; 339: 1546-1558.
4. McDermott U, Settleman J. Personalized cancer therapy with selective kinase inhibitors: an emerging paradigm in medical oncology. J Clin Oncol. 2009; 27: 5650-5659.
5. Chin L, Hahn WC, Getz G, Meyerson M. Making sense of cancer genomic data. Genes Dev. 2011; 25: 534-555.
6. Lawrence MS, Stojanov P, Polak P, Kryukov GV, Cibulskis K, Sivachenko A, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature. 2013; 499: 214-218.
7. Garraway LA, Lander ES. Lessons from the cancer genome. Cell. 2013; 153: 17-37.

8. Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature. 2008; 455: 1061-1068.

9. Barretina J, Caponigro G, Stransky N, Venkatesan K, Margolin AA, Kim S, et al. The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. Nature. 2012; 483: 603-607.

10. Garnett MJ, Edelman EJ, Heidorn SJ, Greenman CD, Dastur A, Lau KW, et al. Systematic identification of genomic markers of drug sensitivity in cancer cells. Nature. 2012; 483: 570-575.

11. Baca SC, Prandi D, Lawrence MS, Mosquera JM, Romanel A, Drier Y, et al. Punctuated evolution of prostate cancer genomes. Cell. 2013; 153: 666-677.

12. Korbel JO, Campbell PJ. Criteria for inference of chromothripsis in cancer genomes. Cell. 2013; 152: 1226-1236.

13. Cox JD, Ang KK. Radiation Oncology: Rationale, Technique, Results, 9th edn. 2009.

14. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013; 497: 67-73.

15. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012; 490: 61-70.

16. Palles C, Cazier JB, Howarth KM, Domingo E, Jones AM, Broderick P, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet. 2013; 45: 136-144.

17. Stransky N, Egloff AM, Tward AD, Kostic AD, Cibulskis K, Sivachenko A, et al. The mutational landscape of head and neck squamous cell carcinoma. Science. 2011; 333: 1157-1160.

18. Fachiroh J, Sangrajrang S, Johansson M, Renard H, Gaborieau V, Chabrier A, et al. Tobacco consumption and genetic susceptibility to nasopharyngeal carcinoma (NPC) in Thailand. Cancer Causes Control. 2012; 23: 1995-2002.

19. Rothman KJ, Lash TL, Greenland S. Modern Epidemiology. 2012.

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# AFTER THOUGHTS

Besides work and writing, I enjoy hiking, arts, reading, listening to music, photography and painting.Hippocrates was the first person to believe diseases were caused by factors in the environment rather than from God or Evil (http://en.wikipedia.org/wiki/Hippocrates), the first scientific physician. The places where the patients live are also where they could rejuvenate themselves. These are the snapshots of New York City around August 2014: