available at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.rpor.eu/

Review

Cyberknife: A double edged sword?

Bindhu Joseph[a], *Sanjay S. Supe*[b,*], *Aruna Ramachandra*[a]

[a] *Department of Radiation Oncology, Kidwai Memorial Institute of Oncology, Bangalore, India*
[b] *Department of Radiation Physics, Kidwai Memorial Institute of Oncology, Hosur Road, Bangalore, 560 029 Karnataka, India*

ARTICLE INFO

Article history:
Received 24 February 2010
Received in revised form
23 April 2010
Accepted 9 May 2010

Keywords:
Cyberknife
Stereotactic radiosurgery
Robotics
Image guided radiotherapy
Pros and cons
Greyzone

ABSTRACT

The Cyberknife represents a new, frameless stereotactic radiosurgery system which efficiently incorporates advance robotics with computerized image reconstruction to allow highly conformal image guided radiation delivery. This review focus is on the pros and cons of this new radiotherapy tool, its current indications, safety profile and future directions. A literature search of Medline, Pubmed, Biomed, Medscape and Cancer lit database were referred to retrieve relevant data/information. The authors conclude that the use of this system offers an invaluable solution to the treatment of selective tumours/lesions located close to critical structures, salvage of recurrent and metastatic lesions and potential of treatment of selective early stage malignancies like the carcinoma prostate and lung. However, it is still too premature, with insufficient follow up data to advocate it as the treatment of choice in any set up. There are several radiobiological issues that also remain in the greyzone.

Contents

* *Corresponding author*. Tel.: +91 80 26094043; fax: +91 80 26560723.
E-mail address: sanjayssupe@gmail.com (S.S. Supe).

1507-1367/$ – see front matter © 2010 Wielkopolskie Oncology Centre, Poland. Published by Elsevier Urban & Partner Sp. z.o.o. All rights reserved.
doi:10.1016/j.rpor.2010.05.002

1. Introduction

Stereotactic body radiation therapy (SBRT) utilizes a novel 3D co-ordinate system with advanced image enhancement and fusion to permit a highly conformal and accurate radiotherapy plan. Stereotactic body radiation therapy has the advantage over standard conformal radiotherapy in requiring very minimal margins for setup uncertainty allowing for maximal sparing of normal tissues. The dose volume sparing advantage of SBRT makes it an ideal tool for delivering hypofractionated radiotherapy. With SBRT, discrete lesions are treated with radiobiologically higher doses with the goal of maximizing local control.

In this aspect it has the advantage over surgery in requiring lesser margins than safely required with a surgical resection,[1] the radiobiological benefits of tumour control, as the predicted risk of normal tissue complications is still not understood and more clinical studies with longer follow up would better define these variables.[1–5]

2. Radiobiology of SBRT

2.1. *Double impact*

Potential benefits of hypofractionation: the use of large fraction sizes, greater than 8 Gy, may be more advantageous than conventional fractionation in achieving complete elimination of tumour clonogens with a short continuous schedule, reducing the risks of tumour repopulation.[6,7] However, on the negative side, this aspect of damage also holds true for normal tissue which may not be totally spared in spite of a highly conformal treatment volume. This heightens the concern over late toxicity.[8,9]

2.2. *Mechanism of radiobiological damage*

Evidence has been obtained that large radiation doses induce endothelial cell damage causing microvascular dysfunction enhancing the killing of tumour cells. The instigation of apoptosis for these cells triggers translocation of endothelial cell acid spingomylinase into the plasma membrane where it is hydrolyzed to sphingomyelin.[10] This results in the generation of ceramide, which acts as a second messenger for apoptosis.

The radiobiological effectiveness of a plan is usually predicted by the Linear Quadratic model. The validity of this model to quantify the risk of late effects has been questioned as it has been derived from data acquired through in vitro cell survival assay of cancer cell lines. Therefore, this tool may overestimate the potential for cell kill, and may underestimate the in vivo risk of toxicity. Nonetheless, there is growing evidence that tumours with low alpha/beta value may actually achieve superior biological equivalent dose with hypofractionation and patients are maximally benefitted by this treatment. Carcinoma prostate and other slowly proliferating tumours such as chordomas, chondrosarcomas, meningiomas, acoustic neuroma, etc. all fall into this category. The converse is however also true regarding normal tissues which also have lower alpha/beta ratio and may manifest injury if they receive high dose per fraction.[11,12]

2.3. *Greyzones*

There are a few theoretical downsides that have to be further evaluated. The use of a small number of fractions without a gap prevents the tumour cells from reasserting into more sensitive phases of its cycle.[13,14] The same apply to re-oxygenation, a potential radio sensitizing effect of fractionated treatment.

2.4. *Technical aspects of SBRT*

Stereotactic body radiotherapy uses a 3-dimensional co-ordinate system utilizing internal fiducials or image guidance for tumour tracking and treatment delivery. Cyberknife has the advantage over other SBRT systems in that it is capable of tracking the co-ordinates in real time while the head of the accelerator re-aligns itself to accommodate fluctuations in target position. The delivery of SBRT generally utilizes multiple noncoplanar arcing fields directed at the radiation target. As a result, the dose gradient is much deeper than conventional radiation and irregularly shaped. The dose with SBRT is generally prescribed to the isodose line encompassing the target which allows for an inhomogenous dose delivery in which the core of the target receives a much higher dose. This may be especially advantageous when anticipating a hypoxic core that may harbour resistant clonogens. Stereotactic body radiation fractionation uses doses that may range from 5 to 30 Gy/fraction and often takes into consideration the BED offered by dose escalation.

Stereotactic body radiotherapy is the best tool for sparing parallel normal tissue, abutting planned large volumes. Even several tissues like lung, liver and kidney may benefit when functional subunits are maximally preserved by the deep dose gradients.

3. Practical limitations

A few subgroups of patients with lesions otherwise best benefitted by this treatment may face difficulties associated with stringent immobilization and long delivery times of more than 40 min. In pediatric patients it may often be difficult to reproduce adequate sedation and immobilization for such extended periods. Elderly patients, and others with functional or mechanical bladder instability, or patients with respiratory compromise in the supine position may react with restless movement beyond the machine's correction parameter. Although emergency stops counter the situation, the total treatment times may be overly extended. Some patients with recurrent or metastatic lesions may not meet general conditions amenable to invasive fiducial placement or might be compromised by the time gap usually given to allow for fiducial migration. Fiducial placement is integral to tumour tracking for any extracranial site with anticipated movement with respiration. Therefore, patients with sites not amenable for the same would have to be excluded.

3.1. *Indications for Cyberknife treatment and current clinical scenario*

As of now the majority of Cyberknife treatment has been delivered to adult patients. Only 2 studies have reported its use in children between 5 months and 16 years.[15] The majority of studies are also concentrated on palliative settings, although currently increasing interest is being focused on curative intent for early small volume disease, especially in benign conditions, AV malformations, trigeminal neuralgia, acoustic neuroma, meningiomas and pituitary adenomas.

3.2. *Role of Cyberknife in specific sites – carcinoma lung*

Stereotactic body radiation is commonly used to treat lung cancer, both in a palliative setup of metastatic/recurrent disease and curative treatment of early stage medically inoperable patients or those who refuse surgery.

Fractionation schedules used have varied from 5 Gy/fraction to 33 Gy/fraction. Patients receiving doses greater than 100 Gy BED did significantly better than those receiving less. Local progression was 3 times longer in patients receiving doses of more than 100 Gy BED.[16]

Local control in patients receiving doses of more than 20 Gy/fraction varied from 54 to 73% at 6 months. A dose responsive relation has been observed with local control increasing to 90% with higher doses, however, it is associated with significant toxicity. Radiation associated grade 3/4 toxicity was observed nearly in 40% of patients receiving more than 20 Gy in any series. A significant treatment mortality of 10% can also be expected. Unlike conformal radiation, pneumonitis has not been correlated with V20 and V13 equivalent. Pulmonary tolerance was also dependant on the type of prior treatment received and current condition of the lung.[17]

Rib fractures also constitute a painful complication. No rib fractures were observed when volume of the rib to chest wall receiving more than 30 Gy in 3–5 sessions was less than 35 ml. Bracial plexopathy is another troublesome complication that has been observed in more than 65% cases. Of patients receiving biologically equivalent doses of more than 100 Gy, late changes like consolidation and fibrosis are inevitable at the radiation site often compromising the evaluation of primary lesion on follow up. In spite of various limitations in treating lung lesions, Cyberknife does provide an equally effective management for peripheral, medically inoperable stage 1 lung lesion. Several ongoing Phase II studies focus on its potential in this setup. As of date, the use of SBRT in primary lung cancer treatment is still protocol based and requires validation in a cohort of good surgical risk patients to identify its actual potential.

4. Efficacy in pancreatic tumours

Radiation can play an important role in palliation of pancreatic carcinoma or even prophylactic palliation of local regression, biliary obstruction, and splanchnic nerve pain. Stereotactic body radiotherapy has the advantage of improved local control and is more patient friendly in terms of shorter treatment time, faster palliation and better normal tissue sparing. Two Phase II studies by Aarhus University[18] and Stanford University[19] show conflicting reports regarding toxicity. Surprisingly, the Stanford protocol with single fraction treatment (25 Gy) has lesser toxicity than the Aarhus protocol of 45 Gy in 5 fractions. The disparity only highlights the multitude of variables that may have to be taken into account when designing a stereotactic radiotherapy treatment protocol. Carcinoma Pancreas Phase II studies suggest a dose escalation advantage with doses of 25 Gy achieving 85% local control vs. 66% for 20 Gy and 70% for 15 Gy.[20]

5. Role of Cyberknife in liver

Stereotactic body radiotherapy has been used widely for treatment of limited metastatic diseases and hepatocellular carcinoma, which otherwise do not qualify for alternative modalities. However, the toxicity of radiotherapy at this site is significant. A number of Phase I and II studies have evaluated the role of stereotactic body radiotherapy in liver metastasis. Patients receiving doses in the range of 20–25 Gy per fraction, for 3 fractions did not evidence any considerable toxicity. However, dose escalation to 30 Gy/fraction was associated with significant gastric and duodenal ulceration 3 months after SBRT. At the Princess Margaret Hospital, 41 patients with primary hepatocellular carcinoma or intraphepatic biliary cancer were treated in a Phase I dose escalation study (24–60 Gy) in 6 fractions based on the effective liver volume to be irradiated. Acute (3 months) elevation of enzymes occurred in 24% of patients and acute biliary obstruction was observed in 5% of patients and should be anticipated with stereotactic body radiotherapy at this site. There was one death case following gastrointestinal bleeding subsequent to duodenal ulceration which may be considered as a dose limiting toxicity.

6. Role in treating lesions/tumours of the spine

Nearly 9 studies[21–25] have evaluated the role of Cyberknife in spinal lesions. Conclusions are hard to derive as the subjects are highly hetereogenous in the type of spinal lesions involved (primary metastatic or benign). As a primary treatment Cyberknife can achieve a local control of nearly 90% in patients with a median follow up of 18 months. Radicular pain has been relieved in 25–85% of patients and neurological deficits improved to a lesser degree. Several large studies have analyzed the planning constraints in the treatment of spinal lesions. They have inferred that a constraint of 10 Gy to less than 10% of contoured spinal cord is safe. Currently available data suggest that a higher maximal dose of 20 Gy is also safe and feasible. This makes a very good option for patients with previously irradiated spine and metastatic disease.

7. Other indications

Cyberknife has been tried in the management of intractable trigeminal neuralgia.[26–28] The neuralgia has been relieved in 20–90% of patients reviewed. Doses of 63.3–66 Gy have been

used, however, with these doses failure is likely to occur in 3–29% of treated patients.

Cyberknife has been used in arteriovenous malformation for patients who are not suitable for invasive surgery. Nearly 80% of patients treated will achieve a reduction in the malformation within 3 years.

Currently innovative experimental indications for radiosurgery to treat functional disorders like obsessive compulsive disorder (OCD), depression, parkinsonism, atrial fibrillation, etc. are underway. As benefit in such situations require short term follow up data, we should soon have evidence for a new tool in the management of these usually refractory conditions.

8. Conclusion

8.1. *Future directions*

Cyberknife has already proved its role in effective palliation with superior normal tissue sparing in a number of setups. The next step would be to evaluate curative treatment of small volume malignancies. To this end, larger studies are now underway in carcinoma prostate and non-small cell lung cancer. However, considering a selective nature of indications, limited number and heterogeneity of treatment regimens, Phase III trials/randomized trials are unlikely to materialize. As of now, the best option for gathering such information would be to pool in of multi-institutional data. These have to be analyzed to receive an acceptable standard, of maximum efficacy and minimum toxicity of dose fractionation scheme. Studies need to focus on potential long term expected and unexpected side effects.

Current data, however, have validated that we have a highly efficient radiotherapeutic modality for delivery of hypofractionated radiotherapy in a variety of clinical scenarios and sites.

REFERENCES

1. Kavanagh BD, Mc Garry RC, Timmerman RD. Extracranial radiosurgery (stereotactic body radiation therapy) for oligometastasis. *Semin Radiat Oncol* 2006;**16**:17–84.
2. Timmerman RD, Kavanagh BD, Cho LC, Popicz L, Xing L. Stereotactic body radiation therapy in multiple organ sites. *J Clin Oncol* 2007;**25**:947–52.
3. Baumert BG, Rutten I, Dehing-Oberije C, Twijnstra A, et al. A pathology based substrate for target definition in radiosurgery of brain metastases. *Int J Radiat Oncol Biol Phys* 2006;**66**:187–94.
4. Timmerman R, Bastasch M, Sana D, et al. Optimal dose and fractionation for stereotactic body radiation therapy. Normal tissue and tumour control effects with large dose per fraction. *Front Radiat Ther Oncol* 2007;**40**:352–65.
5. Timmerman RD, Foister KM, Chinsoo Cho L. Extracranial stereotactic radiation delivery. *Semin Radial Oncol* 2005;**15**(3):202–7.
6. Glatstein E. Hypofractionation, long term effects and alpha/beta ratio. *Int J Radial Oncol Biol Phys* 2008;**72**:11–2.
7. Brown JM, Kuang AC. High dose single fraction radiotherapy explaining a new biology? *Int J Radial Oncol Biol Phys* 2008;**71**:324–5.
8. Guerrero M, Lix A. Extending the linear quadratic model for large fraction doses pertinent to stereotactic radiotherapy. *Phys Med Biol* 2004;**49**:4825–35.
9. Jones B, Dale RG, Finst P, et al. Biological equivalent dose assessment of the consequences of hypofractionated radiotherapy. *Int J Radial Oncol Biol Phys* 2007;**47**: 1379–84.
10. Garcia-Banos M, Paris F, Cordon-Cordo C, Lyden D, et al. Tumour response to radiotherapy regulated by endothelial cell apoptosis. *Science* 2003;**300**:1155–9.
11. Brenner PJ, Hall EJ. Fractionation and protraction of radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999;**43**:1095–101.
12. Duchesne GM, Peters LJ. What is the alpha/beta ration for prostate cancer? Rationale for hypofractionated high dose brachytherapy (editorial). *Int J Radiat Oncol Biol Phys* 1999;**44**:747–8.
13. Maciejewski B, Pieuss-Bayer G, Trott KR. The influence of the number of fractional and overall treatment time on local control and late complications in Squamous cell carcinoma of Larynx. *Int J Radiat Oncol Biol Phys* 1983;**9**: 321–8.
14. Maciejewski B, Withers HR, Jaylor JMG, et al. Dose fractionation and regeneration in radiotherapy for cancer of the oral cavity and oropharynx. Part 1. Tumour dose response and repopulation. *Int J Radiat Oncol Biol Phys* 1989;**16**:831–43.
15. Diaz-Santos NC, Blasco Amaro JA, Cordiel GA, et al. The safety and efficacy of robotic image guided radiosurgery treatment system for intra and extracranial lesions. A systematic review of the literature. *Radiother Oncol* 2008;**89**:245–53.
16. Cesaretti JA, Pennathur A, Rosenstein BS, Swanson SJ, Fernando HC. Stereotactic radiotherapy for thoracic malignancies. *Ann Thorac Surg* 2008;**85**:8785–91.
17. Yomoshita H, Natagawa K, Nakamora N, et al. Exceptional high incidence of symptomatic grade 2–5 radiation pneumonitis after stereotactic radiation therapy for lung tumours. *Radiat Oncol* 2007;**2**:21.
18. Hoyer M, Roed H, Roed H, Sengelov L. Phase II study on stereotactic radiotherapy for locally advanced Pancreatic carcinoma. *Radiother Oncol* 2005;**76**:848–53.
19. Kuong AC, Le QT, Ho A, et al. Phase 1 study of stereotactic radiotherapy in patients with locally advanced Pancreatic carcinoma. *Int J Radiat Oncol Biol Phys* 2004;**58**: 1017–21.
20. Kuong AC, Christofferson E, Le QT, et al. Phase II study to access the efficacy of conventional fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced Pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2005;**63**:320–3.
21. Ryu SI, Chang SD, Kim DH, et al. Image guided hypofractionated stereotactic radiosurgery to spinal lesions. *Neurosurgery* 2001;**49**:838–46.
22. Gertzen PC, Ozhasoglu C, Boston SA, et al. Cyberknife frameless stereotactic radiosurgery for tumours of the sacrum. *Neurosurg Focus* 2003;**15** [Article 7].
23. Gertzen PC, Ozhasoglu C, Boston SA, et al. Cyberknife frameless stereotactic radiosurgery for spinal lesions: clinical experience in 125 patients. *Neurosurgery* 2004;**55**:1–11.
24. Bhatnagar AK, Gerszten PC, Ozhasoglu, et al. Cyberknife stereotactic radiosurgery for the treatment of extracranial benign tumours. *Technol Cancer Res Treat* 2005;**4**:571–6.
25. Degen JW, Gagnon GJ, Voyadzis JM, et al. Cyberknife stereotactic radiosurgical treatment of spinal tumours for pain control and quality of life. *J Neurosurg Spine* 2005;**2**:540–9.

26. Romonelli P, Heit G, Chang SD, et al. Cyberknife radiosurgery for Trigeminal neuralgia. *Stereotactic Funct Neurosurg* 2003;**81**:105–9.
27. Lim M, Villavcencio AT, Burneikienes, et al. Cyberknife radiosurgery for idiopathic trigeminal neuralgia. *Neurosurg Focus* 2005;**18**(5):E9.
28. Lim M, Contrutz C, Romonelli P, et al. Stereotactic radiosurgery using CT Cisternography and non isocentric planning for the treatment of Trigeminal neuralgia. *Comput Aided Surg* 2006;**11**:11–20.