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Retrospective Analysis of Patients and Treatment Characteristics: Istanbul CyberKnife Coalition Data

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Abstract

Background: To evaluate the patient and treatment characteristics of four radiotherapy centers with robotic systems (CyberKnife) in İstanbul.

Materials and Methods: Five hundred and ninety-three patients treated with CyberKnife (CK) system during 2010 were included in this study. Data regarding their diagnosis, radiosurgery (SRS) indications, total treatment doses, and number of fractions were analyzed.

Results: Patient numbers from each center were as follows: Acibadem University Maslak Hospital (186), Kartal Egitim ve Arastirma Hospital (161), Anadolu Saglik Merkezi (145), and Istanbul University Istanbul Medical Faculty Radiation Oncology Department (101). Median age of the patients (355 males (59.9%), 238 females (40.1%)) was 55 years (range: 8-87). Intracranial tumors (77.2%) were biggest group, according to location of the disease. Distribution in terms of diagnosis were as follows: metastasis to brain (36.6%), spinal and paraspinal tumors (8.8%), primary lung tumors (7.4%), head-neck tumors (6.1%), glial tumors (5.9%), meningioma (5.4%), other brain malignancies (4.6%), lung metastasis (4.2%), acoustic neuroma (3.9%), other intracranial lesions (3.9%), intra-abdominal malignacy and extracranial metastases (2.9%), liver lesions (2.4%), pituitary adenoma (2.2%), adrenal metastases (1.5%), uveal melanoma (1.3%), prostate cancer (1.2%), pancreatic cancer (0.5%), extracranial schwannoma (0.5%), and unclassified other tumors (0.8%). CK was used as primary treatment in 348 patients, for reirradiation in 209 patients, for planned boost in 26 patients, and in 10 patients for recurrence in previous field edge. Total median dose of whole group was 2100 cGy (800-7500 cGy), median dose per fraction was 800 cGy (200-3750), and median total fraction number was three (1-10).

Conclusions: As stereotactic radiotherapy with CK is getting used more widespread in our country, experiences are getting larger. CK is preferred as the curative or palliative modality in the treatment of certain malignant and some benign lesions with appropriate indications.

Categories: Radiation Oncology
Keywords: tumors, srs, metastases, fiducial, tumor tracking, cyberknife©

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Introduction

Improvements in computer and imaging techniques in last two decades caused a major progress in radiotherapy (RT) techniques. Previously, therapeutic capability of RT was limited, especially due to the normal tissue tolerance. Three dimensional conformal RT and intensity-modulated RT (IMRT) are used to give maximum therapeutic dose to tumor and protect normal tissues. Stereotactic radiosurgery (SRS) and RT were developed to achieve further improvement, especially in tumors with critical locations.

Lars Leksel first used the term of SRS originally more than sixty years ago [1]. He had treated a brain lesion without opening cranium with a single fraction high dose RT. In 1967, he had introduced Gamma Knife, SRS equipment with stereotactic rigid metal frame [2]. Use of the Gamma Knife is limited to intracranial lesions. Linac-based and robotic techniques were developed to spread SRS use to the all body parts without need of any invasive method (frame). SRS is generally used for single fraction stereotactic radiotherapy (SRT). Fractionated (two to five fractions) use of SRT in extracranial localization is named stereotactic body radiotherapy (SBRT). This form of treatment includes characteristics of both SRS and conventional RT. High ablative doses are delivered in every fraction to the tumor and fractionation gives the normal tissues around the treated site a chance for healing [3].

CyberKnife (CK) (Accuray, Sunnyvale, CA) is a frameless robotic SRS system, which was introduced two decades ago [4]. Basically, it is a Linac mounted on a robotic arm with six joints. The arm gives us the chance to build non-isocentric, noncoplanar highly conformal planes. Two additional diagnostic X-ray imagers mounted in the room give the ability of image-guided RT.

This robotic technology was introduced in Turkey in 2005. Today, seven cancer centers own the CK system. After 2010, it has been used more intensely because of the world-wide growing interest on SRS. Four centers in Istanbul collaborated together to constitute a coalition to cooperatively improve similar treatment protocols and organize educational meetings. With this mission, we aimed to analyze the demographic and treatment data of all patients treated with CK in year 2010 in these four centers.

Materials And Methods

Five hundred and ninety-three patients who received CK treatment in Acibadem Maslak Hospital, Kartal Egitim Arastirma Hospital, Anadolu Saglik Merkezi Hospital, and Istanbul University Oncology Institute were included in this study. Patients were analyzed according demographic data, diagnosis, SRS or SBRT indications, total therapeutic dose, dose per fraction, and fraction numbers. Statistical analysis was made with SPSS program.

Results

Each of the four centers added more than one hundred cases: Acibadem Maslak Hospital: 186, Kartal Egitim ve Arastirma Hospital: 161, Anadolu Saglik Merkezi Hospital: 145 and Istanbul University Oncology Institute: 101 patients. Two hundred thirty-eight patients (40.1%) were female and 355 were male (59.9%). Median age was 55 (range: 8-87) years. Ten pediatric patients (<16) were treated because of intracranial tumors. The most frequent diagnosis that lead to CK treatment was brain metastasis (217 patients 36.6%). Detailed distribution of patients, according to diagnoses, may be found in Table *1*. CK was chosen as the primary treatment modality in 348 patients, for reirradiation in 209, for planned boost in 26, and marginal recurrence in borders of irradiated area in 10 patients. In the particular group of brain metastasis, CK was used as primary treatment without whole brain radiation in 48.8 % (n:106) and reirradiation in 42.9% (n:93).

Diagnosis	Patient Number	%	Total Dose (Gy): Median (Range)	Fraction Size (Gy): Median (Range)	Fraction: Median (Range)
Brain metastases	217	36.6	20 (10-60)	14 (3-30)	1 (1-6)
Spinal-paraspinal tumors	52	8.8	18 (8-30)	6 (3-18)	3 (1-6)
Primary lung tumors	44	7.4	46.5 (12-72)	15 (4-37.5)	3 (1-8)
Head and neck tumors	36	6.1	30 (13.5-45)	6 (3-9)	5 (3-10)
Glial tumors	35	5.9	24 (18-30)	6 (3.6-12)	4 (2-5)
Meningioma	32	5.4	24 (15-30)	6.5 (3-15)	3.5 (1-5)
Other malignant brain tumors	27	4.6	21 (15-51)	5 (2.7-18)	5 (1-10)
Lung metastases	25	4.2	45 (24-75)	15 (6-25)	3 (3-5)
Acoustic neuroma	23	3.9	18 (13-25)	6 (4-13)	3 (1-5)
Other intracranial tumors	23	3.9	20 (15-30)	13 (5-20)	2 (1-5)
Intra-abdominal tumors	17	2.9	25 (8-35)	6 (5-20)	4 (1-5)
Liver tumors or metastases	14	2.4	30 (24-45)	10 (4-15)	3 (2-6)
Pituitary adenoma	13	2.2	21 (15-25)	7 (4.2-20)	3 (1-5)
Adrenal metastases	9	1.5	24 (10-40)	8 (2-10)	3 (3-5)
Uveal melanoma	8	1.3	50 (21-50)	10 (7-13)	5 (3-5)
Prostate cancer	7	1.2	36.25 (35-36.25)	7.25 (7-7.25)	5
Primary pancreatic cancer	3	0.5	21 (18-21)	7 (6-7)	3
Schwannoma	3	0.5	21 (20-21)	7 (4-7)	3 (3-5)
Other	5	0.8	14 (8-21)	7 (5-14)	2 (1-3)

TABLE 1: Patient and Treatment Characteristics

Median values of total treatment dose in whole group was 2100 cGy (range 800-7500 cGy) and dose per fraction was 800 cGy (range 200-3750 cGy). Median fraction number was three (range: one to 10). In only eleven patients, the fraction number was more than five. Distribution, according to fractionation, was one in 25.6% (n: 152), two in 9.9% (n: 59), three in 35.2% (n: 209), four in 4.4% (n:26), five in 22.8% (n:135). Details are in Figure *1*.

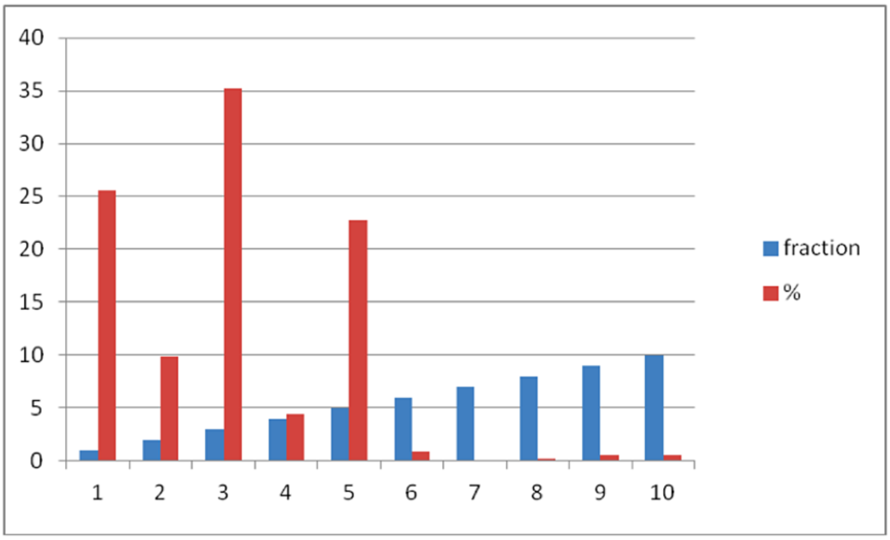

FIGURE 1: Patients distribution according to fraction number

For all intracranial cases, 6-D skull was used for tumor tracking. Other modalities for tumor tracking were as follows: X-Lung in 41, Synchrony in 63, X-spine in 66, and fiducial tracking in 24 patients. Table *2* contains methods for tumor tracking in lung tumors (both primary and metastases). Synchronization with respiratory movement was used in 41 lung tumors and 22 intra-abdominal tumors.

	Primary Lung Cancer		Lung Metastases	
	Number (n)	%	Number (n)	%
X-lung	28	63.6	9	36
Synchrony	28	63.6	14	56
X-spine	5	11.4	4	16
Fiducial	3	6.8	1	4

TABLE 2: Tracking methods for tumors located in the lung.

Discussion

After the introduction in 1992, only 30 patients were treated with the CK in that first year. By 2010, more than 90,000 cases underwent CK treatment worldwide [5]. Seventy-five percent of almost 200 CK systems in the entire world are located in the USA. Seven of 25 systems in Europe are in use in Turkey.

The main advantage of SRT is that it requires the minimal number of fractions. In current literature, it is advised one to five fractions, depending on the tumor size and localization. In our series, 98% of patients received five or less fractions of SRT. More fractions are used because of patient characteristics of clinician preferences.

In July 2012, a Pubmed search with ‘CyberKnife’ revealed 524 articles, including 72 reviews. Reviews mainly agree on the advantages of the system, such as the frameless usage, accuracy in less than 1mm, image fusion capability with multiple modalities, real time tumor tracking, and treatment possibility with linear accelerator [3, 6-7]. The majority of clinical trials using CK are mainly focused on intracranial lesions. The second most frequent group of diagnosis are lung tumors. Our data also showed that the main group of patients (63%) were diagnosed with intracranial tumors. This situation may be explained with long-term Gamma Knife experience. The experience encouraged clinicians for using CK more easily in this part of the body. Also, doses for CK were reflected from Gamma Knife values.

SRS played an effective role in the treatment of brain metastases, arteriovenous malformations, vestibular schwannomas, and meningiomas [8-12]. Brain metastases may be treated with SRS alone or before or after whole brain RT. Retrospective [13-16] and prospective [17-18] studies showed that whole brain RT and SRS had no survival advantages over SRS alone. Phase III randomized trial on patients with one to three brain metastases (RTOG 9508) revealed that adding SRS to whole brain RT had improved functional autonomia and raised overall survival rates in inoperable tumors [19]. Although another randomized study on 132 patients with brain metastases showed that SRS alone caused lower local control and higher local recurrence rates against whole brain radiotherapy and SRS group [20]. An EORTC 22952-26001 study had investigated the effect of adding whole brain radiotherapy to SRS or surgery in patients with one to three brain metastases. They had concluded that intracranial recurrences and neurological deaths decreased but functional independence duration and overall survival did not improve [17]. Authors suggested in patients with good functional capability and stable disease whole brain RT may be postponed under serial imaging control. In our series, almost half (48.8%) of brain metastases received stereotactic RT alone and others with whole brain RT. A new approach is largely accepted to treat resection cavity with SRS after surgical removal of brain metastases. Stanford series has demonstrated similar rates of local control and overall survival when compared with whole brain radiotherapy; however, in our series, no patients were treated with SRS to resection cavity for brain metastases [21-22].

The frameless design of CK enables fractionation especially of tumors located in critical locations. Studies showed good preservation of visual function in perioptic tumors and hearing in acoustic neuromas after stereotactic RT [23-25].

Great care should be given in spinal and paraspinal tumors because of low tolerance of spinal cord, especially in the second series of irradiation. The second most frequent diagnosis in our series is spinal tumor. Good long-term pain palliation was reported in the largest series of patients with spinal tumors treated with CK [26]. With spinal SRS, their rate of overall long-term pain improvement was 86% and clinical improvement was 84%.

Role of SRS in head and neck cancers is encouraging [27-28]. Recurrent cases and planned boosts are the main indications. Six percent of our SRS patients were head and neck tumors.

Medically inoperable early stage lung cancer is another diagnosis, which is suitable for SBRT with CK. The first study about these patients raised hopes with good results [29]. In the study from Japan, authors stated that medically inoperable patients Stage I lung cancer had a five year survival rate of 84% after SBRT. RTOG0236 trial showed comparable results may be reached with SBRT versus surgery in terms of local control and three year survival [30]. The group also designed studies to find safe and effective doses for centrally located tumors (RTOG 0813) and peripheral tumors (RTOG 0915). Tumor tracking in lung cancer is another issue. Most of the studies are designed to track tumors with the gating property of 4DCT. CK is able to track tumors with X-sight spine or X-sight lung systems. In some tumors, gold markers are necessary to be implanted in the body. However, most of the medically inoperable patients also refused fiducial implantation procedure, because of complication risks. Therefore, in our series only four patients were treated with gold markers. In other words, in this series, SBRT with CK in lung tumors, are mainly suitable for the tumors which might be tracked with X-spine or X-lung programs. Dose and fractionation choices of our series are comparable with literature.

Rarely, SBRT of liver, pancreas and prostate cancer are also applicable [31-35]. A prospective study about prostate cancer treatment gave good local control and low toxicity rates after five fractions SBRT [35].

The improvements in the CK system and current-future roles and implications were summarized comprehensively by Dietrich, et al. in a recent review [36]. They have stressed the expanded use of “non-invasive and frameless” system of CK.

Conclusions

Experience with CK is improving in our country. Istanbul CK coalition presents its early experience results. This Coalition is planning to work on different patient groups, according to their frequency, to build collaborative multicentric studies.

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Leksell L: The stereotactic method and radiosurgery of the brain . Acta Chir Scand. 1951, 102:316-319.
2. Heck B, Jess-Hempen A, Kreiner HJ, Schöpgens H, Mack A: Accuracy and stability of positioning in radiosurgery: long-term results of the Gamma Knife system. Med Phys. 2007, 34:1487-1495.
3. Martin A, Gaya A: Stereotactic body radiotherapy: a review . Clin Oncol (R Coll Radiol). 2010, 22:157-172. 10.1016/j.clon.2009.12.003
4. Guthrie BL, Adler JR Jr.: Computer-assisted preoperative planning, interactive surgery, and frameless stereotaxy. Clin Neurosurg. 1992, 38:112-131.
5. Kilby W, Dooley JR, Kuduvalli G, Sayeh S, Maurer CR Jr: The CyberKnife Robotic Radiosurgery System in 2010. Technol Cancer Res Treat. 2010, 9:433-452.
6. Hara W, Soltys SG, Gibbs IC: CyberKnife robotic radiosurgery system for tumor treatment . Expert Rev Anticancer Ther. 2007, 7:1507-1515.
7. Lartigau E, Mirabel X, Prevost B, Lacornerie T, Dubus F, Sarrazin T: Extracranial stereotactic radiotherapy: preliminary results with the CyberKnife. Onkologie. 2009, 32:209-215. 10.1159/000200929
8. Kondziolka D, Niranjan A, Lunsford LD, Flickinger JC: Stereotactic radiosurgery for meningiomas . Neurosurg Clin N Am. 1999, 10:317-325.
9. Lunsford LD, Flickinger J, Lindner G, Maitz A: Stereotactic radiosurgery of the brain using the first United States 201 cobalt-60 source gamma knife. Neurosurgery. 1989, 24:151-159.
10. Lunsford LD, Kondziolka D, Flickinger JC: Stereotactic radiosurgery for benign intracranial tumors . Clin Neurosurg. 1993, 40:475-497.
11. Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lunsford LD: Radiosurgery in patients with renal cell carcinoma metastasis to the brain: long-term outcomes and prognostic factors influencing survival and local tumor control. J Neurosurg. 2003, 98:342–349.
12. Colombo F, Pozza F, Chierego G, Casentini L, De Luca G, Francescon P: Linear accelerator radiosurgery of cerebral arteriovenous malformations: an update. Neurosurgery. 1994, 34:14-21.
13. Chidel MA, Suh JH, Reddy CA, Chao ST, Lundbeck MF, Barnett GH: Application of recursive partitioning analysis and evaluation of the use of whole brain radiation among patients treated with stereotactic radiosurgery for newly diagnosed brain metastases. Int J Radiat Oncol Biol Phys. 2000, 47:993-999.
14. Sneed PK, Lamborn KR, Forstner JM, McDermott MW, Chang S, Park E, et al: Radiosurgery for brain metastases: Is whole brain radiotherapy necessary?. Int J Radiat Oncol Biol Phys. 1999, 43:549-558.
15. Sneed PK, Suh JH, Goetsch SJ, Sanghavi SN, Chappell R, Buatti JM,et al: A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. Int J Radiat Oncol Biol Phys. 2002, 53:519-526.
16. Mehta MP, Tsao MN, Whelan TJ, Morris DE, Hayman JA, Flickinger JC, et al: The American Society for Therapeutic Radiology and Oncology (ASTRO) evidencebased review of the role of radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys. 2005, 63:37-46.
17. Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, et al: Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol. 2011, 29:134-141. 10.1200/JCO.2010.30.1655
18. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH, Meyers CA: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol. 2009, 10:1037-1044. 10.1200/JCO.2010.30.1655
19. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. Lancet. 2004, 363:1665-1672.
20. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. JAMA. 2006, 295:2483-2491.
21. Choi CY, Chang SD, Gibbs IC, Adler JR, Harsh GR 4th, Lieberson RE, Soltys SG: Stereotactic radiosurgery of the postoperative resection cavity for brain metastases: prospective evaluation of target margin on tumor control. Int J Radiat Oncol Biol Phys. 2012, 84:336-42. 10.1016/j.ijrobp.2011.12.009
22. Choi CY, Chang SD, Gibbs IC, Adler JR, Harsh GR 4th, Atalar B, et al: What Is the Optimal Treatment of Large Brain Metastases? An Argument for a Multidisciplinary Approach. Int J Radiat Oncol Biol Phys. 2012, 84:688-693. 10.1016/j.ijrobp.2012.01.028
23. Adler JR Jr, Gibbs IC, Puataweepong P, Chang SD: Visual field preservation after multisession cyberknife radiosurgery for perioptic lesions. Neurosurgery. 2006, 59:244-254.
24. Chopra R, Kondziolka D, Niranjan A, Lunsford LD, Flickinger JC: Long-term follow-up of acoustic schwannoma radiosurgery with marginal tumor doses of 12 to 13 Gy. Int J Radiat Oncol Biol Phys. 2007, 69:845-851.
25. Chang SD, Gibbs IC, Sakamoto GT, Lee E, Oyelese A, Adler JR Jr: Staged stereotactic irradiation for acoustic neuroma. Neurosurgery. 2005, 56:1254-1263.
26. Gerszten PC, Burton SA, Ozhasoglu C, Welch WC: Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. Spine (Phila Pa 1976). 2007, 32:193-199.
27. Voynov G, Heron DE, Burton S, Grandis J, Quinn A, Ferris R, et al: Frameless stereotactic radiosurgery for recurrent head and neck carcinoma. Technol Cancer Res Treat. 2006, 5:529-535.

28. Le QT, Tate D, Koong A, Gibbs IC, Chang SD, Adler JR, et al: Improved local control with stereotactic radiosurgical boost in patients with nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2003, 56:1046-1054.
29. Onishi H, ShiratoH, Nagata Y, Hiraoka M, Fujino M, Gomi K, et al: Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol. 2007, 2:S94–S100.
30. Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, et al: Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010, 303:1070-1076. 10.1001/jama.2010.261
31. Freeman DE, King CR: Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes . Radiat Oncol. 2011, 6:3. 10.1186/1748-717X-6-3
32. Kress MS, Collins BT, Collins SP, Dritschilo A, Gagnon G, Unger K: Stereotactic body radiation therapy for liver metastases from colorectal cancer: analysis of safety, feasibility, and early outcomes. Front Oncol. 2012, 2:8. 10.3389/fonc.2012.00008
33. O'Connor JK, Trotter J, Davis GL, Dempster J, Klintmalm GB, Goldstein RM: Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. Liver Transpl. 2012, 18:949-954. 10.1002/lt.23439
34. Koong AC, Le QT, Ho A, Fong B, Fisher G, Cho C, Ford J, Poen J, Gibbs IC, Mehta VK, Kee S, Trueblood W, Yang G, Bastidas JA: Phase I study of stereotactic radiosurgery in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2004, 58:1017-1021.
35. King CR, Brooks JD, Gill H, Presti JC Jr: Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. Int J Radiat Oncol Biol Phys. 2011, 82:877-82. 10.1016/j.ijrobp.2010.11.054
36. Dieterich S, Gibbs IC: The CyberKnife in clinical use: current roles, future expectations . Front Radiat Ther Oncol. 2011, 43:181-194. 10.1159/000322423