Journal of Pharmacoeconomics & Pharmaceutical Management
Journal Homepage: jppm.tums.ac.ir

The Effectiveness of Selected Radiosurgery Devices on Cancer Tumors and Arteriovenous Malformations: A Systematic Review

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Citation Davari M, Afzali M, Sabbagh-Bani-Azad M, Sharif Z, Hadizadeh F, Mirmoghtadaee P, et al. The Effectiveness of Selected Radiosurgery Devices on Cancer Tumors and Arteriovenous Malformations: A Systematic Review. Journal of Pharmacoeconomics and Pharmaceutical Management. 2017; 3(3-4): 54-63.

Running Title A Comparison of the Radiosurgery Devices

Article Type Review Article

Article info:
Received: 08 May 2017
Revised: 15 Sep 2017
Accepted: 10 Oct 2017

Keywords:
CyberKnife, Gamma knife, Linear accelerator, Linac, AVM

ABSTRACT

Background: There are several types of radiotherapy devices available for the treatment of cancer tumors. The present study aimed to evaluate the effectiveness of selected radiosurgery devices on the treatment of cancer tumors and Arteriovenous Malformations (AVM).

Methods: The evaluation was performed in two steps; First, evaluating the effectiveness of CyberKnife, Gamma knife and Linear Accelerator (Linac) on various biological systems. Then, we compered the effectiveness of devices with each other. A systematic review was conducted in MEDLINE, EMBASE, CRD, NHSEED and Cochrane library databases. The search strategy was limited to clinical trials with less than 5 treatment sessions. All searches were conducted on December 21, 2014.

Results: In total, 81 studies have been included to the review. Based on the obtained results of comparison between the reported percentages of local control rate, the safety and accuracy of CyberKnife and linac are higher than Gamma Knife.

Conclusion: Our findings suggested that CyberKnife is not only more effective to cover various types of tumors in the whole body, but also is safer and easier to use for various tumors, as well as AVM treatment.

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1. Introduction

Cancer is one of the most serious and costly conditions in each healthcare system of developing and developed countries. It is the second leading cause of universal deaths and resulted in 208.3 million Disability-Adjusted Life Years (DALYs) globally in 2015 [1]. Lifestyle changes and aging population predict a significant increase in the incidence of cancer and consequently, demands for effective treatments. Radiotherapy is an essential and highly effective method to cure or control most cancer types. Evidence suggests that about 60% of patients with cancer use radiation therapy [2]. In high-income countries, at least one course of radiotherapy is necessary for 52% of newly diagnosed cancer cases. Low- and middle-income countries have a greater need of that; this is because of the advanced diagnostic stage [3]. Therefore, providing access to effective and efficient radiotherapy equipment is among the most important concerns of all healthcare systems.

There are two main types of external beam radiation delivery devices; cobalt units and linear accelerators. There are slight differences in the mechanism, safety, cost, effectiveness, and technical knowledge of each type. The current study evaluated the effectiveness of three popular and broad spectrum devices, including Gamma Knife, CyberKnife and Linear Accelerator (linac) in cancer tumors and Arteriovenous Malformations (AVM) treatment.

2. Methods

Cochrane library, CRD, EMBASE, MEDLINE/PubMed and NHSEED databases were searched for “efficacy or utilization or application or effectiveness or usage”, and “cancer or tumor or neoplasm or arteriovenous malformations or AML” to find all relevant studies. All searches were conducted on December 21, 2014. The Randomized Clinical Trials (RCTs) were scarce. Thus, articles were selected irrespective of the type or year of the publication at the first step. First, the relevant study titles were selected for abstract examination. Then, the full texts of included studies were reviewed and relevant data were extracted. All steps were double-checked with at least two reviewers and one supervisor. The quality of the selected studies was assessed by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

The Population, Intervention, Comparator, and Outcome (PICO) of our study was defined as all patients with cancer or AVM as the population; radiosurgery as the intervention, CyberKnife, Gamma Knife, and linac devices as the comparators and tumor Local Control Rate (LCR) and AVM Obliteration as the outcomes. The additional criteria for including articles were the English language, radiotherapy of <5 sessions, and acceptable quality based on STROBE statement.

3. Results

We selected 49, 37 and 12 full text studies for CyberKnife, Gamma Knife, and linac, respectively. In total, 7 studies which had reported efficacy indicators other than Local Control Rate (LCR) were extracted from the analysis. Likewise, after quality and bias assessments, 10 studies were excluded because of low quality in methodologies or reporting results. The remaining studies were included for comparative analysis. The obtained results are summarized in Table 1.

The effectiveness of CyberKnife on tumors and AVM treatments

Forty-nine manuscripts were identified by title and abstract screening. However, 32 finally matched our inclusion criteria. The LCR of tumors ranged from 40% to 100% for brain tumors [4-15], 37.5% to 100% for spinal tumors [16-21], 65.2% to 100% for lung tumors [22-27], and 57% to 100% for pancreas tumors [28-33]. A single study was reviewed in AVM treatment that indicated a significant obliteration reduction in 80% of studied patients [34]. More details of the studies are presented in Table 2.

The effectiveness of Gamma Knife on tumors and AVM treatments

Thirty-seven studies were identified by title and abstract screening. However, 32 articles eventually matched our inclusion criteria. The application of Gamma Knife was limited to the treatment of brain tumors and AVM. The reported LCRs ranged from 88% to 100% for meningioma [35-39], 93.4% to 100% for pituitary adenomas [40-43], 80% to 97% for vestibular schwannomas [44-47], and 61% to 97% for brain metastases [48-57]. A single study reported 100% of LCR for glomus jugulare tumors [58].

Various uses of Gamma Knife to treat other tumors, including trigeminal schwannoma, intracranial haemangioblastoma, and cavernous sinus hemangiomas revealed an LRC of >83% [59-61]. Four studies were reviewed in AVM treatment that reported a partial and

Table 1. Comparing the effectiveness of radiosurgery devices in the treatment of tumors and AVM

	Brain tumors				Spinal Tumors				Lung Tumors				Pancreas Tumors				AVM			
	Total Articles	Included Articles	LCR%		Total Articles	Included Articles	LCR%		Total Articles	Included Articles	LCR%		Total Articles	Included Articles	LCR%		Total Articles	Included Articles	Obliteration %	
			Mean	Median			Mean	Median			Mean	Median			Mean	Median			Mean	Median
CyberKnife	19	13	73	75.75	13	6	92.4	83	8	6	95	90.7	8	6	87.85	84.28	1	1	SR*	SR*
Gamma Knife	33	28	90	82.64	-	-	-	-	-	-	-	-	-	-	-	-	4	4	84.45	95.65
LINAC	5	5	97	92.92	5	3	96.5	89.5	-	-	-	-	-	-	-	-	4	4	74	72.21

*SR: Significant Reduction without reporting obliteration percentage

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Table 2. The effectiveness of CyberKnife on the local control rate of tumors and AVM

Study	Patients (N) (N° lesions)	Tumor Type and Location	Follow-Up (Mon)	Tumor Local Control Rate (%)/ AVM Obliteration (%)
Kajiwara (2005) [4] Yamagusch, Japan	21	Pituitary adenomas	Mean±SD=35.3±10.7	95.2
Adler et al. (2006) [5] Stanford, USA	49	Pituitary lesions, Meningiomas, pituitary adenomas craniopharyngiomas	Mean=46 [13-100]	94
Phamc et al. (2004) [6] Stanford USA	34	Perioptic lesions, Meningiomas, hemangiopericytoma, pituitary adenomas,metastases	Mean=29 [15-62]	94
Mehta et al. (2002) [7] Stanford, USA	13	Brain metastases	Median=18 [12-54]	100
Nishizaki et al. (2006) [8] Yamaguchi, Japan	71(148)	Brain metastases	Median=10.2	83% at 6 months, 63% at 1 year,
Shimamoto et al. (2001) [9]Osaka, Japan	48(77)	Malignant gliomas, Glioblastomas	Median=6 [0.2-19.5]	54.5
Kajiwara (2005) [4] Yamaguchi, Japan	25(44)	Gliomas andglioblastomas	Mean=5.6	55.05
Chang SD (2003) [10] Stanford, USA	8(9)	Acoustic neurinoma	Mean=11 [2-19]	75
Chang et al. (2005) [11] Stanford, USA	61	Vestibular schwannoma	Mean=12, [9-15.5]	98

Study	Patients (N) (N° lesions)	Tumor Type and Location	Follow-Up (Mon)	Tumor Local Control Rate (%)/ AVM Obliteration (%)
Giller et al. (2005) [13] Dallas, USA	21 Paediatric patients Mean age 7 years SD 5	Primary malignant brain tumors	Mean=18 [1-40]	52.3
Giller et al. (2004) [12] Dallas, USA	5 Pediatric patients Age [0.3-2.5] years	Malignant brain tumors	5-15 months	40
Hirschbein et al. (2008) [14] Stanford university, USA	16	Intraorbital lesions 31% benign 69% malignant	Mean=7	60
Colombo et al. (2009) [15] Vicenza, Italy	199	Benign meningiomas	Median=30	96%
Gwak et al. (2006) [16] Seoul, Korea	9	High cervicospinal, clivus, and petro-clival primary and recurring chordomas and chondrosarcomas	Median=24 [11-30]	88.8
Gerszten et al. (2003) [17] Pittsburgh, USA	18	Benign and malignant primary and metastatic sacral tumors	Mean=6	100
Bhatnagar et al. (2005) [18] Pittsburgh, USA	44(59)	Extracranial and spinal benign tumors, largely of the neck, orbit, the foramen magnum, and the brainstem	Median=8 [1-25]	96
Ryu et al. (2001) [19] Stanford, USA	16	Metastatic and benign tumors, Arterio-venous malformations	Median=3.48	37.5%
Sahgal. (2007) [20] USA, San Francisco	16(19)	Benign		84
Tsai et al. (2009) [21] Taiwan	69	Metastatic spine tumor	Median=10	96.8
Nuyttens et al. (2006) [22] Rotterdam, Netherlands	20(22)	Recurrent lung, tumors metastases	Median=4 [2-11]	100
Le et al. (2006) [23] Stamford, USA	32	Non-small cell lung, Tumors, lungmeta-tases	Median=18 [9-32]	95
Whyte et al. (2003) [24] Stanford, USA	23	Primary lungtumours, lungmetastases	Mean=7 [1-26]	65.2
Brown et al. (2008) [25] Miami	35(69)	Lung metastasis	Median=18	89
Colins et al. (2009) [26] Washington D.C.	20	Stage 1 NSCLC	Median=25	100
Vahdats et al. (2010) [27] Washington, D.C.	20	Stage 1 NSCLC	Median=43	95
Koong et al. (2004) [28] Stanford, USA	15	Inoperable pancreatic adenocarcinoma	-	85.7
Koong et al. (2005) [29] Stanford, USA	16	Pancreatic adenocarcinoma	-	94
Hoyer et al. (2005) [30] Aarhus, Denmark	22	Pancreatic adenocarcinoma	-	57
Mahadevan et al. (2007) [31]Israel	24	Pancreatic adenocarcinoma	-	79
Parikh et al. (2008) [32] Pittsburgh, USA	---	Pancreatic adenocarcinoma	-	100
Shen et al. (2010) [33] China	20	Pancreatic cancer	-	90
Sinclair et al. (2006) [34] California	15	Spinal cord arteriovenous malforma-tions	3-59	80

Table 3. The effectiveness of Gamma Knife on the local control rate of tumors and AVM

Study	Patients (N)	Type and Location	Follow-Up (Mon)	Tumor Local Control Rate (%)/ AVM Obliteration (%)
Kreil et al. (2005) [35]	200	Meningioma of cavernous sinus (69); Petroclival (44); Sphenoid wing (32); Cerebellopontine angle (21); Frontobasis (13); Orbita (10); Craniocervical (7); Sella (4)	60-144 Mean=102	98
Iwai et al. (2003) [53]	42	Cavernous sinus meningioma (42)	18-84 Mean=49.4	90.5
Nicolato et al. (2002) [36]	122	Cavernous sinus meningioma (122)	12.3-99.1 Mean=48.9	97.5
Iwai et al. (2003) [38]	24	Skull Base Meningioma petroclival region: 11 Cavernous sinus: 9 Cerebello pontine angle: 4	6-36 Median=17.1	100
Pamir et al. (2007) [37]	43	Meningiomas that involve superior sagittal sinus (43)	28-86 Median=46	88
Sheehan et al. (2013) [43]	512	nonfunctioning pituitary adenomas 512	36 (1-223)	93.4
Pollock et al. (2008) [40]	62	Pituitary Adenoma (62)	23-161 Median=64	97
Petrovich et al. (2003) [41]	78	Pituitary Adenoma (78)	Median=36	96-100
Liščák et al. (2007) [42]	79	Pituitary Adenoma (79)	36-122 Median=60	100
Pan et al. (2005) [52]	45	Vestibular schwannoma (45)	6-48 Median=25	95.6
Nakamura et al. (2000) [44]	78	Vestibular schwannoma (78)	10-36 Mean=13.3	80
Myrseth et al. (2005) [45]	103	Vestibular schwannoma (103)	Mean=60	89.2
Kim KM et al. (2007) [46]	59	Vestibular schwannoma (59)	Mean=75	97
Mathieu et al. (2007) [48]	175	Malignant Melanoma Brain Metastase (57)	-	82.6
Peterso et al. (1999) [49]	48	Intracranial Metastases (73)	4-125	61
Radbill et al. (2004) [55]	51	Melanoma Brain Metastase (188)	Median=6.2	81
Shuto et al. (2004) [57]	16	Multiple Metastatic (242)	-	97
Iwai et al. (2003) [53]	21	Cavernous sinus metastases (21)	1-36 Median=9	67
Whang et al. (1995) [56]	28	Metastatic Brain Tumors (60)	5-39 Median=12	90
Amendola et al. (2004) [50]	17	Metastatic tumors; quamous cell carcinoma nasopharynx; paranasal sinus; ear soft palate	9-68 Median=45	65
Guseĭnova et al. (2013) [51]	312 3 centers	Renal cell cancer Single metastases were detected in 136 patients (43%); 2–4 metastases, in 149 patients (48%); and multiple metastases (≥5), in 27 patients (9%).	Once per 3–5 months	90
Pan et al. (2005) [52]	191 (total) (49)	Lung cancer (non–small cell carcinoma (171 patients) and small cell carcinoma (20 patients) 88 (single lesion), 39 (two lesions), 64 (more than three)	3-6-9-12	88.9, 80.5, 81, 91%
Muacevic et al. (2008) [54]	64 (total) 31	Cancer lesions at a site outside the central nervous system single tumor	12	96.8%
Eustacchio et al. (1999) [58]	13	Glomus jugulare tumors 13	37.6 (5-68)	100
Sheehan et al. (2007) [60]	25	Trigeminal schwannoma (25)	12-104 Mean=48.05	88

Study	Patients (N)	Type and Location	Follow-Up (Mon)	Tumor Local Control Rate (%)/ AVM Obliteration (%)
Matsung et al. (2007) [59]	22	Intracranial haemangioblastoma (67)	9-146 Mean=63	83
Masaaki Yamamoto et al. (2010) [61]	30	Hemangiomas of the cavernous sinus 30	53 (12-138)	100
Kiran et al. (2009) [63]	120	Arteriovenous malformation	12-96 Mean=28	94
Zhao et al. (2008) [77]	341	Arteriovenous malformation	36-120 Mean=76.8	97.3 Complete=68.6 Partial=28.7
Choe et al. (2008) [64]	100	Arteriovenous malformation	5-63 Mean=37.5	100 Complete: 58 Partial: 42
Javalkar et al. (2009) [62]	37 (total) 15 (follow up)	Arteriovenous malformation	More than 36 months	Total: 46.5 Near total: 20 Moderate three: 20 86.5

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Table 4. The effectiveness of LINAC on the local control rate of tumors and AVM

Study	Patients (N)	Type and Location	Follow-Up (Mon)	Tumor Local Control Rate (%)/ AVM Obliteration (%)
Shafron et al. (1999) [68]	70	Benign meningioma (70 patients with 76 lesions)	23	100
Spiegelman et al. (2002) [69]	42	Meningioma (42)	36	97.5
Noel et al. (2004) [67]	28	Renal Cell Carcinoma (RCC) metastasis (28 patients with 65 brain metastasis)	14	97
El-Khatib et al. (2011) [65]	16	Meningioma (16 patients with 28 meningiomas)	60.3	84% (3 years), 70% (5 yrs), 70% (10 yrs)
Hsu et al. (2010) [66]	75	Acoustic Neuroma (75)	>5 years	92%
Voges et al. (2006) [72]	142	Pituitary macroadenoma (142)	81.9±37.2	96.5
Mabanta et al. (1999) [71]	18	Non-acoustic schwanoma (18)	5 to 75	100
Chua et al. (2003) [70]	18	Recurrent or persistent NPG (18)	11 to 48	72
Nataf et al. (2003) [75]	57	Cerebral arteriovenous malformation (57 children)	7-172 (Median=34 months)	61.2
Esteves et al. (2008) [74]	61	arteriovenous Malformation (61)	>18	72
Friedman et al. (1995) [76]	155	Arteriovenous malformation (155)	33	(1-4 cc) 81 (4-10 cc) 89 (>10 cc) 69
Ding et al. (2013) [73]	565	Arteriovenous malformation (565)	76	62% (cumulative obliteration)

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complete reduction in obliteration rate [62-64]. The details of these studies are listed in Table 3.

The effectiveness of Linac on tumors and AVM treatments

Through initial title and abstract screening, 12 studies were identified. All of them were included and reviewed. The reported LCRs ranged from 70% to 100% for brain tumors [65-69] and 72% to 100% for spinal tumors [70-72]. Four studies were reviewed in AVM treatment that suggested a significant reduction in obliteration rate [73-76]. The obtained results are summarized in Table 4.

4. Discussion

The current study aimed to evaluate the effectiveness of 3 popular and broad spectrum devices, including Gamma Knife, CyberKnife, and linac. Comprehensive evaluation and the comparison of the effectiveness of treatment methods is an important determinant of clinical decision making for implementing evidence-based policymaking.

Various tumors studied in the selected articles were primary or metastatic. There was a significant variation between the severity and characteristics of the tumors from patient to patient in the selected studies. Likewise, the number of patients in each study varied, significantly. Our findings revealed that most studies on brain tumors were performed by Gamma Knife. Additionally, most studies on spinal tumors were performed by CyberKnife. Our findings suggested an acceptable effectiveness for all reviewed devices linac in tumor and AVM treatments. However, there are important differences between radiosurgery domains.

Linac is a very effective device in the management of cerebrospinal tumors. Gamma Knife has a higher rate of success in controlling brain tumors, compared to CyberKnife; however, it was not as effective as linac. Gamma Knife has shown better operation in AVM treatment than the other devices. However, due to the limited evidence in AVM radiosurgery, it is a debating conclusion. CyberKnife is the only effective device on the tumors of different organs such as respiratory or gastrointestinal systems.

This could be a comparative advantage when the epidemiological pattern of cancers is considered. Furthermore, the safety of CyberKnife with linac external-beam radiation delivery is more than radiation delivery devices with cobalt units, like Gamma Knife. Nonetheless, it should be mentioned that linear accelerator devices are technically more complicated and require higher levels of training.

There were three main limits to our literature review. The most important limitation was the lack of RCTs. Part of this limitation is due to the nature of the diseases; thus, all of the selected studies on cancer were limited in RCTs. The second limitation was the difference in selecting effectiveness criteria and reporting methods which make it difficult or even impossible to compare the results of studies.

The final main limitation was assessing the risk of bias. Most of the studies had no declaration of conflicts of interests and financial support. To overcome these constraints, all kinds of studies, including clinical trials or retrospective ones which had reported tumor LCR or AVM obliteration rate were reviewed. Studies reported a variable length of follow up, ranging from one month to more than 5 years. Furthermore, many of the selected studies had significant differences in the follow up duration of the patients. The sample size of the studies ranged from 8 to 565 patients (cohort data) with a wide age range in both males and females.

5. Conclusion

Our findings revealed that linac was the most effective device in controlling cerebrospinal tumors. Moreover, Gamma Knife was the most effective device in AVM treatment. However, CyberKnife was not only more effective to cover different types of tumors in the whole body, but also was safer and easier to use for various tumors, as well as AVM treatment. However, further RCTs are required to achieve more reliable evidence.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Isfahan University of Medical Sciences.

Funding

This project was financially supported by the Ministry of Health and Medical Education of Iran.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

The authors would like to thank Ministry of Health and Medical Education and Isfahan University of Medical Sciences for supporting this project.

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