

## Review Article

# The Connection between SRS Apparatus and Outcome in Patients with Brain Metastases from Lung and Renal Cancer

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**Abstract**

**Objective:** Stereotactic radiosurgery (SRS) is an innovative approach for cancer therapy. It is thought to be generally a good choice even to radioresistant brain metastases (BM), taking also into consideration all of the prognostic factors and co-morbidities. But until now, it has not been revealed whether the apparatus is linked to the outcome.

**Methods:** Because of that, the authors searched the published data on the world search engine for the last decades (1947-2017) on the subject of renal and lung cancer brain metastases (BM) and their radiosurgical therapy, in regard to the used apparatus.

**Results:** After processing the published data, the authors revealed that the three kinds of machines are leading to different results, concerning the brain metastases. LINAC and CyberKnife seem to be linked to the outcome, mainly to the local control/local failure, while GK's analysis revealed no actual connection. Overall survival in general could be linked also to the machine, but it depends on many factors and such relation is difficult to be clearly determined.

**Conclusion:** Concluding to this, it becomes clear that GammaKnife, CyberKnife and LINAC are not the same for the therapy of BM from primary lung and renal cancer. And before proceeding with SRS, it should be considered which machine would be used for the therapy, in order for a better outcome to be achieved.

**ABBREVIATIONS**

AVM: Arteriovenous Malformation; OS: Overall Survival; GK: Gammaknife; SRS: Stereotactic Radiosurgery; BM: Brain Metastases; RCC: Renal Cell Carcinoma; CI: Conformity Index; CGI: Wagner's Conformity/Gradient Index; GI: Gradient Index; LINAC: Linear Accelerator; ASTRO: American Society Of Radiation Oncology; WBRT: Whole Brain Radiation Therapy; VMAT: Volumetric Modulated Arc Therapy; NCP-IMRT: Non-Coplanar Multi-Field - Introducing Intensity Modulated Radiotherapy; DCA: Dynamic Conformal Arcs; LC: Local Control; TV<sub>PIV</sub>: Target Volume Covered By Prescription Isodose Volume; TV: Target Volume; PIV: Prescription Isodose Volume; PIV<sub>half</sub>: Prescription Isodose Volume at Half the Prescription Isodose

**INTRODUCTION**

Radiosurgery was first introduced to the neurosurgical scene by Spiegel and Weeks [1] and a few years later by Lars Leksell as a frame-based procedure, who actually developed its philosophy [2]. As a phrase "stereotactic radiosurgery" (SRS) combines two powerful terms: "radiosurgery" and "stereotactic neurosurgery" [3]. In its application, radiosurgery divides into  $\gamma$ -Knife (GK), Cyber Knife and LINAC (stereotactically modified

linear accelerator) and has many indications, such as brain tumors and brain metastases (BM), arteriovenous malformations (AVM), brain lesions and biopsy.

Its basic concept of high radiation of the lesion and protection of the neighbor tissue makes SRS an excellent choice of therapy for patients with small amount of lesions in the cranium and good performing status [4]. This, however, is strongly connected to the properties of the apparatus. Hence, it raises the question, whether the apparatus of the SRS is also linked to the outcome.

**METHODS**

And because of this and the increasing incidence of renal and lung cancer, the authors aim to prove and compare mainly the local control (LC) (and local failure) of radiosurgery, regarding the brain metastases from both types of cancer linked to the machine used to manage them. For this reason, the reviewers investigated the world's literature on the treatment with radiosurgery of brain metastases from renal and lung cancer that is published mainly on Medline, Cochrane, Wiley Library platform with MeSH terms (Radiosurgery, CyberKnife, Lung Cancer, Renal Cancer, Gamma Knife, Brain Metastases and LINAC) between 1947 and 2017, beginning with historical events associated with

SRS. The search has the aim to conclude the efficiency of the SRS, as well as to compare the outcome of the patients, comparing GammaKnife, CyberKnife and LINAC. (Mainly targeting the outcome of local control/local failure, because of its close relation to the apparatus) The final conclusions are strongly based on the involved studies.

Because of that, inclusion criteria are articles about radio surgical treatment of brain metastases from lung and renal cancer that encompass mainly the technique and outcome, including local control rate, local failure, as well as, the SRS treatment results. Main demographic criterion is the total mean age of the participants to be over 50 years. And after filtering the data, finally included studies are clinical trials, clinical studies and randomized-analyses (on humans). The included studies, afterwards, are processed without any previously written protocol (Figure 1).

On the other hand, the authors excluded articles that: do not provide sufficient information; are not based on humans; describe only the SRS with its doses but do not give sufficient information about the origin of the primary tumor; case reports; comments; letters to editor; studies that combine more than one kind of primary tumor; studies in other than English languages; studies that do not provide sufficient information on the demographical characteristics of the involved patients.

Further analysis of the data was performed with Excel's statistics- F-test and t-test and regression analysis with correlation diagram-statistics.

## RESULTS

After detailed search and excluding some studies (Figure 1 & Table 1 and 2), this systematic review/analysis includes 45 studies, with total number over 4400 patients. We observed male prevalence and we divided the included patients into categories, based on the primary tumor. The studies include mainly brain metastases smaller than 3 centimeters and participants with median age over 50. And because of the importance of the

apparatus to the local control/local failure, the authors studied further these parameters (Tables 1 & 2). We observed also the OS, but it is dependable on many more factors and it is not possible to determine clear association with the machine.

## RENAL CANCER

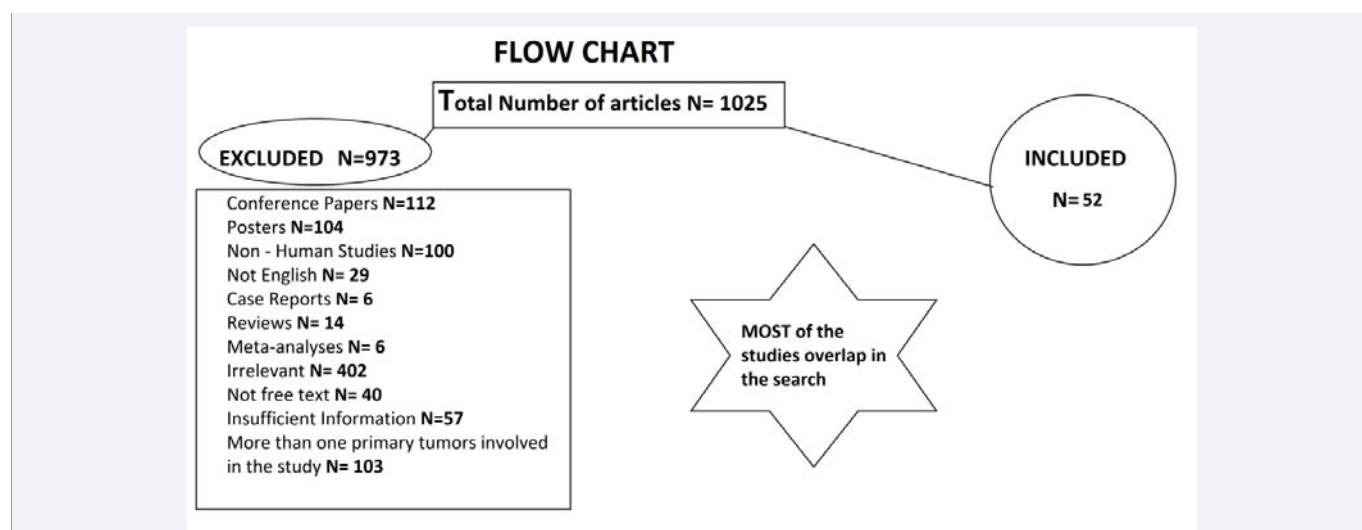
Renal cell carcinoma (RCC), as primary cancer has approximately 2% of incidence and it is thought to be frequent source of brain metastases (4-17% of the RCC patients have BM) [5]. Mori et al. [6], shows that SRS is a good therapeutic choice for RCC's brain metastases, although this type of cancer is considered radioresistent.

When patients present single lesion, SRS alone or SRS, combined with WBRT, seem to be highly favorable [5]. On this subject, Samlowski et al. [8], reports that patients with single brain metastasis have better median survival, which, however, does not represent a predictive feature. Prognostic factor that have a major position is the Motzer classification's stage and the preexisting risk factors.

In addition to the previous statements, the reviewers found that a major role for the outcome (LC, local failure and less OS) is played by the technique that is used for the radiosurgery. After processing the published data, the authors evaluated the possibility of a correlation between GammaKnife, local control and overall survival, shown on diagram 1, and revealed a slight to none negative connection of the local control (LC) ( $R^2 = 0,1071$ ) to the apparatus, and slight to none connection of the median total dose ( $R^2 = 0,1666$ ) and no correlation to the OS ( $R^2 = 0,1653$ ).

On the other hand, LINAC has a medium to strong positive correlation with the local control ( $R^2 = 0,602$ ), low correlation to the median total dose ( $R^2 = 0,2091$ ) and almost no connection to the OS ( $R^2 = 0,0387$ ) (Diagram 2).

And finally, CyberKnife for renal cancer, shows very strong positive correlation with the local control ( $R^2 = 1$ ), and no correlation with the OS and median dose (both  $R^2 = 1$ ) (Diagram 3). From which, could be concluded that CyberKnife, regarding



**Figure 1** List of studies reporting kidney cancer's brain metastases, treated with SRS.

**Table 1:** List of studies reporting kidney cancer's brain metastases, treated with SRS.

| Study                  | Total number of patients | Local failure (%) | Median Overall survival (months) | Local control rate (%) | Technique  |
|------------------------|--------------------------|-------------------|----------------------------------|------------------------|------------|
| Tamari et.al. [25]     | 67                       | 19,4              | 13,1                             | 80,9                   | CyberKnife |
| Yomo et.al. [26]       | 70                       | 13,5              | 7,8                              | 89                     | γ-Knife    |
| Jezierska et.al. [27]  | 83                       | 15                | 7,8                              | 85                     | LINAC      |
| Zabel et.al. [28]      | 86                       | 24,4              | 8,3                              | 76                     | LINAC      |
| Saitoh et.al. [29]     | 49                       | 15,5              | 17,4                             | 84                     | LINAC      |
| Mariya et.al. [30]     | 84                       | 27,38             | 9                                | 73                     | LINAC      |
| Uematsu et.al.[31]     | 45                       | 3,03              | 11                               | 96,97                  | LINAC      |
| Zairi et.al. [32]      | 89                       | 11,24             | 24                               | 88,5                   | γ-Knife    |
| Kuremsky et.al. [33]   | 271                      | 33,77             | 7,13                             | 67,17                  | γ-Knife    |
| Cho et.al. [34]        | 817                      | 17,6              | 13                               | 82,36                  | γ-Knife    |
| Bowden et.al. [35]     | 720                      | 7,03              | 12,6                             | 92,8                   | γ-Knife    |
| Yomo et.al. [36]       | 42                       | 14                | 8,1                              | 85                     | γ-Knife    |
| Rahn et.al. [37]       | 58                       | 8,62              | 9,5                              | 89,58                  | γ-Knife    |
| Kress M-AS et.al. [38] | 88                       | 11                | 10,6                             | 89,1                   | γ-Knife    |
| Golanov et.al. [39]    | 502                      | 22,22             | 8,6                              | 76,89                  | γ-Knife    |
| Aydemir et.al. [40]    | 104                      | 12,5              | 9,5                              | 87,5                   | γ-Knife    |
| Harris et.al. [41]     | 51                       | 54,5              | 5,9                              | 47                     | γ-Knife    |
| Olson et.al. [42]      | 27                       | 22,2              | 3                                | 76,5                   | CyberKnife |
| Lischalk et.al. [43]   | 20                       | 10                | 11,3                             | 90                     | CyberKnife |
| Rades et.al. [44]      | 46                       | 17                | 12                               | 83,5                   | CyberKnife |
| Won et.al. [45]        | 64                       | 10,9              | 14,1                             | 90                     | CyberKnife |

**Table 2:** List of studies reporting stereotactic radiosurgery for brain metastases from primary Lung cancer.

| Study                 | Patients N | Local failure (%) | Median overall survival (months) | Local control rate (%) | Technique  |
|-----------------------|------------|-------------------|----------------------------------|------------------------|------------|
| Ippen et.al. [5]      | 66         | 7,2               | 13,6                             | 84                     | CyberKnife |
| Mori et.al. [6]       | 35         | 8,57              | 11                               | 90                     | γ-Knife    |
| Fokas et.al. [7]      | 88         | 19                | 11                               | 71,3                   | LINAC      |
| Samlowski et.al. [8]  | 32         | 18,75             | 6,7                              | 86                     | LINAC      |
| Wowra et.al [9]       | 75         | 9                 | 11,1                             | 95                     | γ-Knife    |
| Sheehan et.al. [10]   | 69         | 4                 | 9                                | 96                     | γ-Knife    |
| Bates et.al. [11]     | 25         | 31,75             | 6,7                              | 76                     | LINAC      |
| Ikushima et.al. [12]  | 35         | 14                | 18                               | 88                     | LINAC      |
| Shuto et.al. [13]     | 69         | 5,8               | 9,5                              | 82,6                   | γ-Knife    |
| SchoÈggel et.al. [14] | 23         | 4,35              | 11                               | 96                     | γ-Knife    |
| Noel et.al. [15]      | 28         | 14                | 11                               | 97                     | LINAC      |
| Payne et.al. [16]     | 21         | 0                 | 21                               | 100                    | γ-Knife    |
| Seastone et.al. [17]  | 166        | 10                | 12,8                             | 90                     | γ-Knife    |
| Kano et.al. [18]      | 158        | 8                 | 8,2                              | 92                     | γ-Knife    |
| Guseïnova et.al.[19]  | 188        | 10                | 8                                | 89,9                   | γ-Knife    |
| Marko et.al. [20]     | 80         | 5                 | 12,58                            | 95                     | γ-Knife    |
| Cochran et.al. [21]   | 62         | 29                | 9                                | 71                     | γ-Knife    |
| Hoshi et.al. [22]     | 42         | 9                 | 12,5                             | 91                     | γ-Knife    |
| Kawashima et.al. [23] | 15         | 9,4               | 6                                | 93                     | LINAC      |
| Staehler et.al. [24]  | 51         | 0                 | 11,1                             | 100                    | CyberKnife |

the LC, is highly favorable for the outcome of BM from primary renal cancer.

The association with the OS is mainly for comparison and hypothetical possibility, and not actual evidence, because of the multiple factors that play role for the final OS (extracranial disease, number of BM, age, side effects etc).

## LUNG CANCER

Lung cancer is the most common primary tumor at this time and respectively most common source of brain metastases. According to a study by Yano et al. [26], for BM from small cell lung cancer, it is believed that SRS treatment is better for small cell lung cancer patients, because of the low rate of neurological

### Correlation between GK and OS, dose and LC for kidney cancer

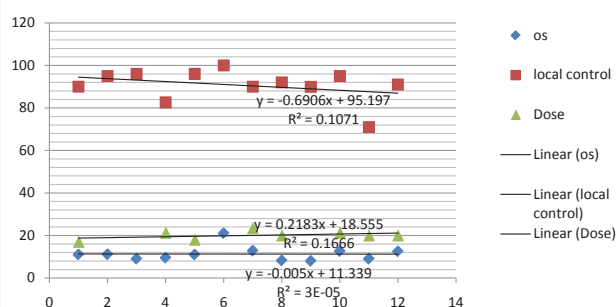


Diagram 1 GK and kidney cancer.

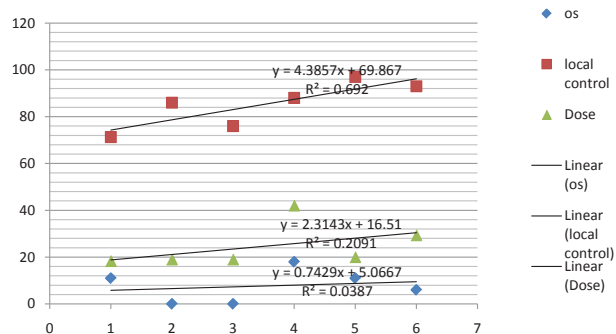


Diagram 2 Linac and renal cancer.

### Correlation between CyberKnife and OS and LC for kidney cancer

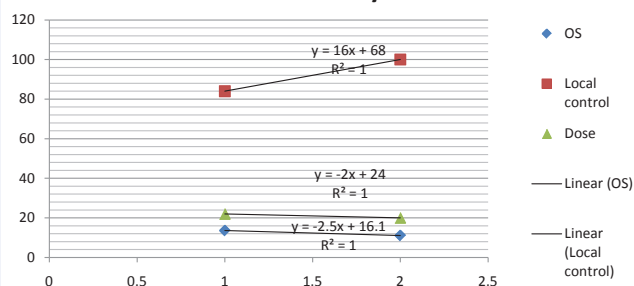


Diagram 3 CyberKnife and renal cancer.

mortality. Last, but not least, the combination of SRS, WBRT, surgery and chemotherapy lead to improvement of the overall survival.

Furthermore, Tamari et al. [25], in a research with 67 patients concludes that overall survival does not depend on local control and distant failure. Pulmonary metastases and higher Brinkman index, on the other hand, are linked to poor overall survival. The small number of patients with radionecrosis is probably due

to the small size of the BM, which suggests that radiosurgery is eligible for patients with small size and number of BM.

Further and final statement, strongly based on the result of this analysis after processing the data, is that the technique used for radiosurgery plays also a role to the outcome for BM from lung cancer. According to our findings on the regression diagrams, GammaKnife has a slight negative correlation with the local control ( $R^2=0.1521$ ), median Dose ( $R^2=0.1587$ ) and OS ( $R^2=0.1878$ ), while LINAC is positively related to the median dose ( $R^2=0.4822$ ), less but positive with the local control ( $R^2=0.1256$ ) and almost none to the OS ( $R^2=0.0813$ ) (Diagrams 4 and 5).

### Correlation between GK, dose and OS for lung cancer

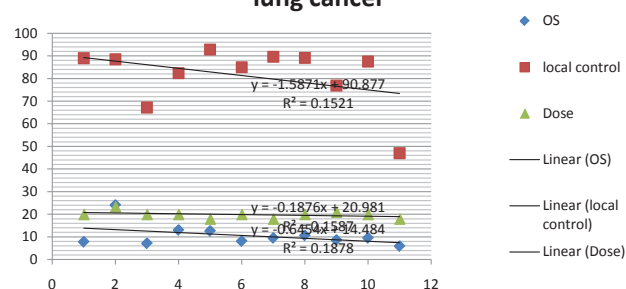


Diagram 4 GK and Lung cancer.

### Correlation between LINAC and LC and OS for lung cancer patients

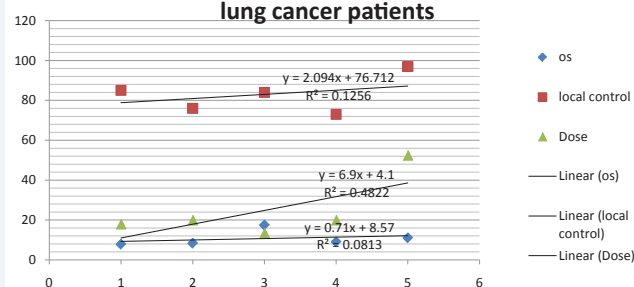


Diagram 5 LINAC and lung cancer.

### Correlation between CyberKnife and OS, dose and LC for lung cancer

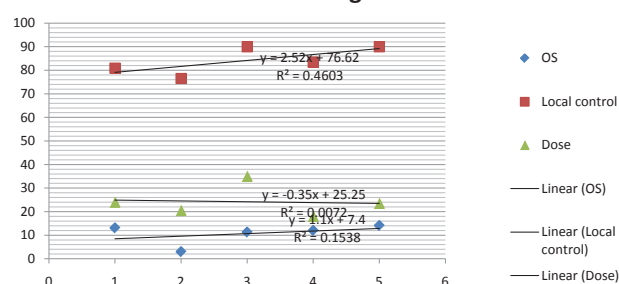


Diagram 6 CyberKnife and lung cancer.

CyberKnife, in this regard, is linked positively to the LC ( $R^2=0,4603$ ), slightly to the OS ( $R^2=0,1538$ ) and negatively to the median dose ( $R^2=0,0072$ ) (Diagram 6).

In order to compare and prove whether the diagrams are correct, we performed a T-test comparing local control of lung and renal LINAC, lung and renal CyberKnife and lung and renal GK. The t-test for LINAC and CyberKnife does not reject the null hypothesis for both groups, suggesting that the apparatus is linked to the local control and local failure (Table 3a, 3b and 3c), while the T-test for GK rejects the null hypothesis, also confirming the results from the diagrams that GK has no significant role for the local control and local failure. The OS is linked also to some extent to the apparatus, but no test could be performed, because of the multifactor origin of this value.

## DISCUSSION

Because of the diversity of the BM, there are plenty of therapies. One of those therapies is SRS with its advantage of less invasiveness and ability of re-irradiation [46].

According to published studies, it is believed that there is a dependence on the number of BM and the therapeutic choice, as well as the radiation dose. In this regard, report by Amsbaugh et al. [46], shows that besides the protocol RTOG, there might be a new suggestion about the dose importance in SRS treatment. There is a link between dose and volume for SRS patients. Latest suggestion is that bigger dose could be delivered to small BM but not to large BM. From which can one retrieve that SRS is likely going to lead to good local control rate in small BM, but in bigger BM - more likely to require adhesive therapy. This theory, however, is refuted by Soliman et al. [47], in his work, suggesting that the newest properties of the radiosurgery allows even bigger than 3 centimeters BM to be treated with SRS, and more precise with fractionated stereotactic radiosurgery. Furthermore, Soliman et al. [47], reports that SRS is much superior to WBRT for the brain metastases, regarding the local control. The addition of WBRT may improve the control temporary, but because of its general toxic effect, the final results are poor quality of life.

| Table 3a: T-test for LINAC and local control |            |            |
|--|------------|------------|
| t-Test: Linac Assuming Unequal Variances     |            |            |
|  | Renal      | Lung       |
| Mean   | 85,72      | 80,13      |
| Variance                                     | 102,52     | 161,85     |
| Observations                                 | 6          | 5          |
| Hypothesized Mean Difference                 | 0          |            |
| Df   | 8          |            |
| t Stat                                       | 0,79       |            |
| P(T<=t) one-tail                             | 0,23       |            |
| t Critical one-tail                          | 1,86       |            |
| P(T<=t) two-tail                             | 0,45       |            |
| t Critical two-tail                          | 2,31       |            |
| Critical Region value                        | 0,29       |            |
| Confidence Interval*                         | 0,18 (82%) | 0,19 (81%) |
| *CI based on one-tail P                      |            |            |

| Table 3b: T-test for GK and local control.     |            |            |
|--|------------|------------|
| t-Test: Gamma knife Assuming Unequal Variances |            |            |
|  | Renal      | Lung       |
| Mean   | 90,46      | 81,45      |
| Variance                                       | 58,30      | 183,78     |
| Observations                                   | 12         | 11         |
| Hypothesized Mean Difference                   | 0          |            |
| Df   | 15         |            |
| t Stat   | 1,94       |            |
| P(T<=t) one-tail                               | 0,04       |            |
| t Critical one-tail                            | 1,75       |            |
| P(T<=t) two-tail                               | 0,07       |            |
| t Critical two-tail                            | 2,13       |            |
| Critical Region value                          | 0,14       |            |
| Confidence interval value*                     | 0,02 (98%) | 0,02 (98%) |
| *CI based on one-tail P                        |            |            |

| Table 3c: T-test for CyberKnife and local control. |            |            |
|--|------------|------------|
| t-Test: Cyber knife Assuming Unequal Variances     |            |            |
|  | Kidney     | Lung       |
| Mean   | 87         | 82,994     |
| Variance   | 18         | 87,29      |
| Observations                                       | 2          | 5          |
| Hypothesized Mean Difference                       | 0          |            |
| Df   | 4          |            |
| t Stat   | 0,78       |            |
| P(T<=t) one-tail                                   | 0,24       |            |
| t Critical one-tail                                | 2,13       |            |
| P(T<=t) two-tail                                   | 0,48       |            |
| t Critical two-tail                                | 2,78       |            |
| Confidence Interval value*                         | 0,33 (67%) | 0,21 (79%) |
| Critical region value                              | 0,7        |            |
| *CI based on one-tail P                            |            |            |

Concluding to this, SRS has treatment level of evidence 1 and represents an excellent choice for brain metastases, while WBRT and chemotherapy have a small to no impact on the local control [21,47].

1. And finally, based on this systematic review/meta-analysis, it could be suggested that the machine is also playing a major role to the outcome of the patients with brain metastases. Regarding the quality of life and the efficacy, it is believed that three main things might have an effect, from which the treatment planning (topographic delineation and dosimetry planning) and delivery method affects greatly the outcome of locoregional tumor control and overall treatment outcome (including side effects). Knowledge and experience of the planner:

Quality of tumor delineation, quality of the dosimetry plan knowledge of planning protocols and recommendations, etc



**Table 4:** Machine's parameters [52,53].

|   | DCA  | NCP-IMRT | VMAT | Cyberknife | GK   | reff. (optimal) |
|---|------|----------|------|------------|------|-----------------|
| Paddick CI  | 0,64 | 0,72     | 0,76 | 0,78       | 0,59 | 1               |
| Paddick GI  | 3,3  | 3,6      | 4,2  | 4,4        | 3,05 | 3               |
| DCA - Dinamic conformal arc (LINAC)                                     |      |          |      |            |      |                 |
| NCP-IMRT - static non-coplanar intensity modulated radiotherapy (LINAC) |      |          |      |            |      |                 |
| VMAT – volumetric modulated arc therapy (LINAC)                         |      |          |      |            |      |                 |
| Cyberknife - robotic radiosurgery                                       |      |          |      |            |      |                 |
| GK - Gamma knife  |      |          |      |            |      |                 |

## 2. Patient positioning during treatment:

It depends mainly on the experience of the therapists and the imaging/positioning options of the machine (does the machine have image guided capabilities and what type are they – Cone beam CT, MV and/or kV imaging, MRI guidance, ultrasound guidance, etc)

## 3. Machine capabilities and delivery methods:

Is it capable of no coplanar treatments, what energy options does it have, how is the beam collimated, etc

The technique is presented through the machine and the delivery method. From all of the previous stated, the only one that could not be optimized are the capabilities of the machine, which is also the basis of the difference in outcome. These differences can be easily shown by using two plan quality indexes in general – Conformity index, that shows how the prescribed isodose line conforms to the shape of the target volume and Gradient index which shows the steepness of dose falloff outside the target volume [48]:

1. Conformity index (CI) – the most common definition of which is the Paddick CI:

$$\text{Paddick CI} = \frac{(TV_{PIV})^2}{TV * PIV} \quad (1)$$

Where,

- $TV_{PIV}$  = Target Volume covered by Prescription Isodose Volume
- TV = Target Volume
- PIV = Prescription Isodose Volume

This is actually two separate ratios multiplied together:

$$\text{Undertreatment ratio: } TV_{PIV} / TV \quad (2)$$

$$\text{Overtreatment ratio: } TV_{PIV} / PIV \quad (3)$$

2. Gradient index/Gradient measurement (GI) – again the most common definition in radiosurgery practice is the Paddick GI:

$$\text{Paddick GI} = \frac{PIV_{Half}}{PIV} \quad (4)$$

- $PIV_{half}$  = Prescription isodose volume, at half the prescription isodose

Although all machines are capable of high accuracy treatment the inherent difference in planning and delivery has its

limitations that inevitably define differences in treatment quality (conformity gradients, inhomogeneity, maximum dose integral dose) of one machine compared to another, as shown in (Table 4).

These parameters could be easily compared in regard to the treatment plan and modalities [49], where could be observed some distinctive differences (Table 4). CyberKnife has the best CI but second worst GI that can be explained by the way the machine operates – dozens of small, low dose beams to cover the target. In this way, one could easily precise with the shape of the isodoses but inevitably there is a big spread of low dose regions that reduce the gradient score.

LINAC, on this point, is encompassed with dynamic conformal arcs (DCA), Volumetric Modulated Arc Therapy (VMAT) and non-coplanar intensity modulated radiotherapy (NCP-IMRT) techniques. DCA has the best GI but the lowest CI because there is no intensity modulation of the dose but with an arc type field so the dose has a steep fall off but no “shape”. NCP-IMRT has good GI and acceptable CI because it combines the treatment delivery method of the CyberKnife (although a lot limited in couch/gentry angle combinations) but with a much more complex multi leaf collimator, and much bigger freedom of choice for field size. VMAT has acceptable GI and good CI. It has a rotational delivery technique (although not helical) but it has a much complex MLC couch and collimator rotation and an option for multiple photon energies – all things that are very beneficial when treating small lesions.

As for GammaKnife, Liu et al. [50], shows that it has better GI but a bit worse CI compared to noncoplanar VMAT, while compared to CyberKnife, the indexes CI, GI and tissue sparing results are similar but with much lower overall integral dose. Generally, it has comparable results concerning the tissue sparing and integral dose (dose to the whole body of the patient). Another study made by Ma et al. [51], suggest that GK is linked to higher dose but with the smallest amount of radiation on the normal tissue, compared with the other machines.

Regarding the treatment planning and delivery method, these are some of the machine differences that affect its maximum capabilities, thus plan quality which directly affects treatment outcome:

## Treatment planning

**Control:** GK treatment is done using a fixed “headframe” put on the same day of the procedure. For LINAC the choice is either head frame or mask, otherwise known as “frameless”.

**Simulation:** The simulation is performed on the same day of the operation for GK, while the patient is wearing this “head frame. For LINAC, the patients will perform this procedure before and will wear a custom mask. LINAC plans need a CT.

**Planning:** For GK, the plan will frequently have many treated isocenters per lesion, called “shots.” LINAC-SRS plans have a single treated isocenter per lesion. Recently, one GammaKnife plan can be shaped even with multiple lesions (each structure potentially will have multiple isocenters).

## Treatment Delivery

**Radiation Source:** LINAC uses mega voltage (MV) x-rays (6MV, 8MV, 10MV) that naturally make a heterogeneous photon beam spectrum of variable energy x-rays which has a different quality of the beam and depth of maximum dose (Dmax) than GK’s Cobalt-60 gamma emitting sources that has only 2 spectral lines 1.17MeV and 1.33MeV and can be represented as a monoenergetic beam with an average of 1.25MeV single spectral line.

**Collimation:** LINAC uses multi-leaf collimators to make the beam. Gamma Knife, on the other hand, has collimators of different sizes (4mm, 8mm and 16mm).

**Fractionation:** Because GK currently has a fixed headframe, most of the procedures are single-fraction. LINAC seems to be easier with mask.

Cyberknife (CK) on the other hand can be counted as a hybrid between standart LINAC and GK – mini LINAC (that uses only 6MV photon energy) with a robotic arm, fixed collimator (as in GK) or micro mlc (similar to standart LINAC), multiple static beams (as in GK), single or multiple isocenters per lesion (as in both other machines)

Despite the fact that the local control is linked to the dose [52], the aforementioned planning and delivery methods inherently limits the performance even with the most capable of teams of specialists and results in different dosimetric plan quality defined by how steep the falloff of the dose is and how much it conforms to the defined treatment volumes which inherently influences clinical outcome as shown by our analysis.

And after comparing the SRS for brain metastases, it could be concluded that LINAC, GammaKnife and CyberKnife, as machines, have some distinguished differences that lead to different results, regarding the local control and local failure of the brain metastases for both groups (renal and lung cancer). For this reason, further investigation would be very important. The OS is dependable on many factors, and because of that we could not conclude whether the machine has some impact on the OS.

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