Ph.D. THESIS

Intraoperative image fusion and linear-quadratic model for Iodine-125 interstitial irradiation of brain tumors

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Summary

Intraoperative image fusion and linear-quadratic model for Iodine-125 interstitial irradiation of brain tumors

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State-of-th-art treatment involves the use of multimodal imaging (CT, MRI, PET) for tumor localization and use of modern 3D radiation treatment planning programs to determine optimal access points and a dose distribution conforming to the tumour. While implanting seeds during a brachytherapy operation, a few millimeter variances from the planning of the operation may cause considerable changes in the radioactive outcome of the tumor volume and the normal tissue. As far as we know, there is no study available investigating both, the accuracy of the stereotactic brachytherapy implantation in brain tumours and the dosimetric consequences of deviations from the planned implantation site. A number of comparisons between different stereotactic radiosurgery treatment techniques have been published, but none of them compared their radiobiological advantages, disadvantages and late radiobiological effect with I-125 interstitial brachytherapy treatment. After the renormalization of LINAC and brachytherapy referential doses, using the dose volume histograms and the linear-quadratic model the brachytherapy doses were compared to the brachytherapy equivalent LINAC radiosurgery doses with respect to late effect of irradiations on normal brain tissue.

It was found, that the application of the intraoperative image fusion and linear quadratic model allows us to increase the quality of stereotactic interstitial irradiation, to choose the optimal stereotactic treatment method and to decrease the radiological exposure of normal tissue surrounding the target volume.
I. Introductions

Shortly after the invention of natural radioactivity in 1896, radioactive isotopes started to be used for therapeutic aims in the early 20th century. One of the types of irradiation is interstitial brachytherapy, when the irradiating isotopes are placed surgically into the target tissue – the tumour. With this local treatment, great doses can be distributed in the proximity of the sources, and there is relatively low radiation exposure of the further normal tissues. This is enabled by the favourable dose relations around the sources, which root in basic physical and geometrical rules. The great doses near to the brachytherapeutic sources reach small volumes, which usually do not cause late complications.

What makes brachytherapy of brain tumours difficult, is the anatomy of the brain. In the way to reach the tumour, there are often life-important brain domains, or the tumour takes place right in the life-important domain. Parallely with the improvement of brachytherapic procedures, also in the first half of the 20th century, interest started to grow intensively towards stereotaxy. This procedure enabled the 3 dimensional orientation in the crane. The fusion of brachytherapy and stereotactic neurosurgery created stereotactic brachytherapy.

The application of the procedure using converging rays meeting in the target point and the stereotactic technique enabled the elaboration of Gamma knife surgery and LINAC.

The integration of modern segmenting imaging techniques and stereotactic instruments made possible the safe placement of the seeds into the target without craniotomy. At the implantation of seeds, even a couple of millimetres’ alteration from the planning makes remarkable difference in the radiation exposure of the target volume and of the normal tissue. There are a few studies comparing the techniques of the stereotactic radiosurgery, but none of them discusses the advantages and disadvantages of the dose distributions of the stereotactic brachytherapy and of the radiosurgical interventions, neither their late radiobiological influence. That is why I have chosen the quantitative analysis of the accuracy of the stereotactic brachtherapy using CT-CT fusion, and the comparison of the dose distributions and late radiobiological influence in the case of brachytherapy and LINAC radiosurgery.

II. Purpose

1. Analysis of the applicability of computer guided intraoperative CT-CT fusion at the Iodine-125 (I-125) brachytherapy.
2. To compare the parameters of dose-volume histograms of plannings and realizations verified using computer guided intraoperative CT-CT fusion, with special regard on the size and the shape of the tumour.

3. Exposure of the inaccuracies and elaboration of corrections to avoid them, using computer guided intraoperative CT-CT fusion.

4. Elaboration of a method enabling the comparison of the parameters of dose-volume in case of I-125 brachytherapy and LINAC stereotactic irradiation, and application of this method to our clinical cases.

5. Comparison of late radiobiological influence of I-125 brachytherapy and LINAC stereotactic radiosurgery on the normal tissue.

1. Summarizing the survival dates of the patients treated with I-125 brachytherapy, and their comparison with the clinical dates found in international sources.

III. Methods and patients

III.1. The parameters of I-125 seeds

Brachytherapy treatment of brain tumours was achieved using I-125 isotope seeds (Iodine – 125 Seeds IMC6702, 6711 Nycomed Amersham, USA). The advantages of I-125 are: lower energy (27-35keV) and the rapid dose fall-off in tissue (within millimetres). This is significant and results in minimal radiological exposure of normal tissue surrounding the target volume. Low energy is also advantageous from the point of view of radiation protection, as it requires merely local radiation protection. The initial value of the seed activity ranged between 5-20 mCi.

III.2. The planning of stereotactic I-125 brachytherapy operations

All patients were immobilized with cranial fixation using a Leibinger/Fischer head ring (Leibinger, GmbH 95., Freiburg, Germany). They were scanned on Elscint Elite 2400 CT (Elscint, Haifa, Israel) with slice thickness and slice increment of 2 mm, from below 2.5 cm of the inferior border of the target to the top of the skull.

Following the import of the images to the computer we drew the contours of the target volume and the eloquent brain structures in each CT slice. With aim of tumor visualization 3D reconstruction of these contours was performed. Depending on the size of the target volume, we determined the number of the catheters required, their location, the activity of the
isotopes within the catheters and their relative position. Our goal was to envelop the shape of the target volume by the isodose surface of the prescribed dose.

IIII.3. The implantation of I-125 seeds
As a result of the planning, the necessary parameters on the localizer frame were established assuring the correct implantation of the catheters. Under local anaesthesia, and using these calculations, we then bur holed a 3.2 mm diameter opening into the skull with the aid of a localizer frame, which had been secured to the base ring. The catheters containing the I-125 radiation sources were then introduced through these holes.

IIII.4. Intraoperative CT-CT image fusion verification
Following the implantation and an additional CT examination, using the stereotactic frame fixed to the patient, the planning and postimplant CT images were fused. The fusion of CT-CT images enabled us to verify the position of the catheters containing the isotopes. If the actual position of the catheter did not correspond to that in the original plan, the position of that catheter was adjusted.

IIII.4.1. Intraoperative CT-CT image fusion verificated cases
The position of the catheters needed to be altered in 14 (20%) of the 70 image fusion cases. As to the catheters, the positions of 16 required adjustment following the control image fusion from the 116 catheters used in the 70 cases.

IIII.5. Comparison of I-125 stereotactic brachytherapy and LINAC radiosurgery modalities based on physical dose distribution and radiobiological efficacy

IIII.5.1. Cases
For irradiation of 24 tumours of 22 patients, treatment plans for low dose rate I-125 interstitial brachytherapy implants and LINAC stereotactic radiosurgery (SRS) were made. Cases 1–12 have been treated with interstitial brachytherapy. For each of these 12 cases an additional radiosurgery plan was prepared retrospectively using the same CT image set as in BT. Cases 13 - 24 have been treated with a LINAC SRS, where the alternative interstitial brachytherapy plans were made retrospectively afterwards. One patient received both brachytherapy (case 5) and LINAC treatments (case 13), and one patient was treated twice with LINAC (case 14 and 15). In 11 of the twenty-four cases the tumor shape was irregular. The tumour was considered
regular when its shape was globoid or ellipsoid, while the tumor was regarded irregular when its surface had large irregularities.

III.5.2. Target volume for stereotactic brachytherapy ans LINAC radiosurgery cases
The brachytherapy planning was performed with the Target 1.19 software module (BrainLab AG, Kirchheim-Heimstetten, Germany), while Target 4.03 software module from the same company was used for the LINAC radiosurgery planning. Target volume and organs at risk were contoured in axial CT slices, and then the same image set with the defined contours was used for both the brachytherapy and radiosurgery treatment planning.

III.5.3. I-125 brachytherapy cases
Depending on the size and the shape of the tumor a median of 1 catheter (range: 1 - 3) and a median of 5 seeds (range:1 - 10) per tumor were used. The median value of the seed activity was 10.3 mCi (range:4.7-19.2 mCi). Based on dose volume histogram (DVH) analysis, the dose was prescribed in such a way that at least 90% of tumor volume received the reference dose (RD). The median prescribed dose was 60 Gy (range: 50-120 Gy), the median average dose rate was 31.3 cGy/hour (range: 12.5-83.3 cGy/hour) and the median treatment time was 192 hours (range: 96-480 hours).

For cases 13 - 24, where a hypothetical interstitial implant was planned, seeds with an activity of 10.3 mCi were considered. This value is the average activity of all I-125 seeds used in the brachytherapy implants performed at our institution over the period 1998-2003.

III.5.4. LINAC radiosurgery cases
In the LINAC radiosurgery cases (Cases 13 – 24) the irradiation was performed on a linear accelerator (Siemens-Mevatron) with 6 MV photon beam at the National Institute of Oncology, Budapest, Hungary.

For treatment we used circular collimators with 7.5-30 mm diameter, 4 standard irradiation arcs, and isocenters between 1 and 4 (median=1). The arcs were as follows: 180° transversal,
100° sagittal and two 100° parasagittal (table rotation +/- 45°). The dose distributions were normalized to the maximum dose, and the dose was prescribed to the 80% isodose line when only one isocenter was used. The 50% isodose line was selected for dose prescription when two or more isocenters were applied.

### III.5.5. Renormalization of referential dose

In order to make the comparison of treatment plans reasonable, all the plans of the twenty-four brachytherapy and LINAC interventions were renormalized in such a way that the reference dose surface enclosed 95% of the target volume. For both treatment modalities the amount of target volume and normal brain tissue, expressed as a percentage of the target volume, receiving at least 90%, 100% and 150% of the reference dose (RD) was calculated.

### III.5.6. Dosimetric considerations

For each of the brachytherapy plans we analyzed the DVH for target volume and implant, and than calculated the amount of normal tissue in relation to the target volume, which received dose between 10-100 Gy. Using the dose-volume histogram (DVH) in the radiosurgery plans we determined the LINAC dose values for the volumes corresponding to the doses between 10-100 Gy in steps of 10 Gy in the DVH of the BT plans. Then, we converted the LINAC doses to brachytherapy doses (equivalent low dose rate BT dose) according to the dose-time formula of the linear quadratic (LQ) model. We used 2 Gy as α/β ratio for the normal tissues, 45 minutes half time for repair and 30 minutes as a treatment time for LINAC irradiations. In the brachytherapy plans we used the actual irradiation time in each plan. With the method described above we assigned two brachytherapy doses (BT dose and BT equivalent LINAC dose) to each volumetric value corresponding to 10-100 Gy in the BT treatments, allowing a comparison of late radiobiological effect of the two treatment modalities on the normal brain tissue.

### IV. Results

#### IV.1. Intraoperative CT-CT image fusion

The CT images used during the planning of the operation were fused with those images prepared following catheter insertion. The position of the catheters needed to be altered in 14
(20%) of the 70 image fusion cases. As to the catheters, the positions of 16 (13.8 %) required adjustment following the control image fusion from the 116 catheters used in the 70 cases.

In each of the 14 patients, we performed the irradiation of one tumor. During the 14 operations, a total of 22 catheters and 72 seeds were utilized. Of the 22 catheters used, the position of 16 catheters required a change.

Using Target 1.19 software, in each of the 14 plans we calculated the percentage of tumour volume covered by the prescribed dose (TV_{PD}). Following this, we determined how much of the normal brain tissue given in percentage of the tumour volume was irradiated by the prescribed dose (NTV_{PD}). Following the “postoperative CT-CT fusion” we calculated once again the tumour dose volume histogram and the normal tissue dose volume histogram for the 14 cases according to the real position of the catheters. We compared the values of TV_{PD} and NTV_{PD} of the planning and of its accomplishment. In reality, the prescribed dose covered an average of 75.8% of the tumour volume (range: 69.1-94%), which meant a 16.6% absence in comparison to the planning (average of 92.4%, range: 87.9-98.3%). The Student t-probe showed a significant difference between the TV_{PD} values of the reality and the plans (p<0.0001). Factually, the average value of the NTV_{PD} was 86.4% (range: 35-195%), which exceeded the 76% average value (range: 32.7-192.3%) determined in the plans by 10.4%. On average, the normal tissue irradiated at least by the prescribed dose was less than the tumour volume.
### Table 1
Dose volume histogram data of the planning and of its accomplishment, and catheter deviations in 14 cases

<table>
<thead>
<tr>
<th>Case</th>
<th>TV (%) Plan</th>
<th>Reality</th>
<th>NTV (%) Plan</th>
<th>Reality</th>
<th>CI Plan</th>
<th>Reality</th>
<th>RPC / deviation (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>89.5</td>
<td>77.1</td>
<td>34.5</td>
<td>45.6</td>
<td>0.65</td>
<td>0.48</td>
<td>D / 2,5</td>
</tr>
<tr>
<td>2.</td>
<td>98.3</td>
<td>94</td>
<td>50.4</td>
<td>50.9</td>
<td>0.65</td>
<td>0.61</td>
<td>D / 4</td>
</tr>
<tr>
<td>3.</td>
<td>90.7</td>
<td>56.7</td>
<td>104.4</td>
<td>125.5</td>
<td>0.42</td>
<td>0.18</td>
<td>D / 5</td>
</tr>
<tr>
<td>4.</td>
<td>93.9</td>
<td>71.2</td>
<td>32.7</td>
<td>35</td>
<td>0.7</td>
<td>0.48</td>
<td>D / 4</td>
</tr>
<tr>
<td>5.</td>
<td>91.7</td>
<td>70.1</td>
<td>58.4</td>
<td>82.5</td>
<td>0.56</td>
<td>0.32</td>
<td>D / 7</td>
</tr>
<tr>
<td>6.</td>
<td>92.9</td>
<td>57.6</td>
<td>32.7</td>
<td>63.2</td>
<td>0.69</td>
<td>0.28</td>
<td>D / 2, P / 3</td>
</tr>
<tr>
<td>7.</td>
<td>89</td>
<td>86.6</td>
<td>116.9</td>
<td>120.8</td>
<td>0.39</td>
<td>0.36</td>
<td>D / 2</td>
</tr>
<tr>
<td>8.</td>
<td>88.7</td>
<td>81</td>
<td>192.3</td>
<td>195</td>
<td>0.28</td>
<td>0.24</td>
<td>D / 2, P / 3</td>
</tr>
<tr>
<td>9.</td>
<td>87.9</td>
<td>84.3</td>
<td>79.3</td>
<td>82</td>
<td>0.46</td>
<td>0.43</td>
<td>D / 2</td>
</tr>
<tr>
<td>10.</td>
<td>92.9</td>
<td>72.1</td>
<td>46.5</td>
<td>67</td>
<td>0.62</td>
<td>0.37</td>
<td>D / 4</td>
</tr>
<tr>
<td>11.</td>
<td>94.8</td>
<td>74.1</td>
<td>112.5</td>
<td>117</td>
<td>0.43</td>
<td>0.29</td>
<td>D / 5</td>
</tr>
<tr>
<td>12.</td>
<td>96.5</td>
<td>80.5</td>
<td>69.6</td>
<td>79.6</td>
<td>0.56</td>
<td>0.41</td>
<td>S / 2</td>
</tr>
<tr>
<td>13.</td>
<td>92.1</td>
<td>86.2</td>
<td>53.6</td>
<td>59.8</td>
<td>0.58</td>
<td>0.51</td>
<td>D / 2; S / 4; P / 2</td>
</tr>
<tr>
<td>14.</td>
<td>94.4</td>
<td>69.1</td>
<td>69.6</td>
<td>101.9</td>
<td>0.54</td>
<td>0.28</td>
<td>D / 4; D / 4</td>
</tr>
<tr>
<td><strong>AV</strong></td>
<td>92.4</td>
<td>75.8</td>
<td>76</td>
<td>86.8</td>
<td>0.54</td>
<td>0.37</td>
<td></td>
</tr>
</tbody>
</table>

p<0.0001  p=0.001  p=0.0001

**Abbreviations:**

**IV.2. Comparison of I-125 stereotactic brachytherapy and LINAC radiosurgery modalities based on physical dose distribution and radiobiological efficacy**

The average volume of the 24 tumors was 5.6 cm³ (range: 0.1 – 19.3 cm³), the average reference dose was 64.3 Gy (range: 50 – 120 Gy) and 16.9 Gy (range: 12 – 20 Gy) for the BT and LINAC treatments, respectively. After renormalizing the dose distributions the mean RD
was 68.4 Gy for BT, while the renormalization has not changed the mean RD of 16.9 Gy for LINAC plans.

IV. 2.1. Dosimetric parameters

The tumor volumes TV90, TV100 and TV150 as well as the normal tissue volumes NT90, NT100 and NT150 irradiated by at least 90 %, 100 % and 150 % of the RD, respectively are shown in Figure 2/A-B. The normal tissue volumes are expressed relative to the corresponding target volume. Figure 2/A shows that the portion of tumor volumes irradiated by at least 90 % of RD were as practically identical for both BT and LINAC SRS treatments (in average 98 % of the target volume). However, there was a significant difference (p=0.0002) between the target volumes irradiated by 150 % of the RD for the two treatments techniques. In the brachytherapy plans, on average, 76 % of the target volume received 1.5 times the RD or more, while in the LINAC plans only 32 %. The TV150 values for the LINAC plans apply only to those plans where two or more isocenters were used, because no high dose volume occurred when only one isocenter was applied and the dose was prescribed to the 80 % isodose line. Normal tissue volumes irradiated by the three selected dose values are shown in Figure 2/B. The statistical analysis showed significant differences between BT and LINAC treatments with a p value of 0.0240 and 0.0001, for the volumes irradiated by 90 % and 150 %, respectively. The BT spared more normal tissue regarding the 90 % and 100 % isodose levels. In the LINAC plans the normal tissue volumes irradiated by at least 90 % and 100 % of RD were on average 27 % and 11 % larger than in the BT plans respectively, while the high dose regions irradiated by at least 150 % of RD were much less in the LINAC than in the BT plans; 8 % compared to 50 % for the BT plans. Figure 3 demonstrates the comparison between the BT and LINAC treatments regarding their radiobiological efficacy with respect to the normal tissue. The low dose rate BT doses between 10-100 Gy are compared with the
biologically equivalent LINAC doses calculated by the LQ model for the normal tissue. At low doses, the calculated radiobiological late effect of normal tissue was equivalent for both treatment modalities. For brachytherapy at doses greater than 30 Gy the calculated equivalent dose to normal tissues was less than for external beam radiosurgery. The difference was statistically significant at doses higher than 40 Gy BT dose.

IV. 2.1. Volumetric parameters

Volumetric parameters calculated in BT and LINAC plans for 24 target volumes are shown in Table 2. Regarding dose conformity the BT plans were better than the LINAC plans, but the difference between their COIN values was not statistically significant (p=0.24). The average COIN was 0.45 (range: 0.22-0.73) for the BT and 0.42 (range: 0.21-0.72) for the LINAC plans. The EI, which represents the unnecessary irradiation of the normal tissues by the reference dose was smaller for BT than for LINAC treatments; 1.28 (range:0.30-3.07) compared to 1.41 (range: 0.3-3.4), that is not significant (p=0.31). Regarding the dose homogeneity, more homogeneous dose distributions were generated in the LINAC plans than in the BT plans. The DHI was significantly higher in LINAC than in brachytherapy plans (0.62 vs. 0.19). This result was anticipated because the high dose gradient surrounding the brachytherapy sources always results in inhomogeneous dose distributions.
V. Discussion

V.1. Intraoperative CT-CT image fusion
During the past few decades brachytherapy has undergone significant technological developments, which have positively influenced the survival rate of patients and their quality of life. The role of image fusion has appeared in a number of publications discussing diagnosis, neuronavigation, and radiotherapy planning.

The application of interstitial irradiation supported by image fusion allows:

- Greater accuracy of establishing the target volume at the time of irradiation planning,
- Control of positioning the catheters and isotopes during the operation,
- Differentiating between necrotic and viable areas of the tumor.

The applied CT-guided (controlled) stereotaxy revealed that nearly twenty percent of the brachytherapy operations required adjustments. Had the adjustments not been made the unnecessary radiation of normal tissues would have been significantly increased in comparison with the planning. At the same time, the irradiation of the tumors with the prescribed dose would have significantly less than the radiation calculations in the plan.

The method of image fusion has proved to be of significant importance in case of irradiation of small, or irregularly shaped tumors. In these cases, the slightest difference from the plan has the potential to alter the dose distribution and data of the dose volume histogram. As a result, this can appear as a decrease of tumor control, of negative outcomes of irradiation and a reduction in the quality of life for the patient. For the smallest tumor volume, the catheter misplacement resulted in the largest differences between the volume parameters. The TV_D decreased by 38 % (90.7 % vs. 56.7 %), and the NT increased by 20 % (104.4 % vs. 125.5 %) due to inaccurate catheter position. Furthermore, the differences between the corresponding volume parameters in the small volume group were much larger than in the large one.

As for the angular offsets near to tangential, the alteration of the position of catheters from the planned position has also been frequently observed. This can be a direct result of slippage of the drill bit on the skull bone. The inaccuracy of the performance can be caused either by the inadequate fixation of the catheter to the lamina externa of the skull bone, or the existence of harder or more solid tumor. When this occurs, the need for modification and realignment becomes necessary.

V.2. Comparison of I-125 stereotactic brachytherapy and LINAC radiosurgery modalities based on physical dose distribution and radiobiological efficacy
While comparing the 24 brachytherapeutical and 24 LINAC dosimetrical plans, we have found the results as follows:

- At higher doses (40-100 Gy brachytherapeutical dose, which equals 11.6 – 19.2 Gy LINAC dose) brachytherapy irradiation is more tolerant, less damaging to the normal tissue than LINAC irradiation. At target volumes with irregular shape the difference can be seen at even smaller doses (20 and 30 Gy brachytherapy dose, which equals 6.3 and 8.9 Gy LINAC dose), but the difference is not significant.

- For target volumes with regular shape (at 8 Gy brachytherapeutical dose, which equals 2.6 Gy LINAC dose), LINAC irradiation is significantly more convenient for the normal tissue, than brachytherapy.

- We achieved better conformality at brachytherapy irradiation than at LINAC plans, but the difference was not significant.

- Concerning dose homogeneity, LINAC irradiation proved to be significantly better than brachytherapy (p = 0,01). At the same time, as a consequence of the greater dose inhomogeneity of brachytherapy, a necrotizing dose can be administered to the central part of the target volume.

VI. Conclusion

1. According to my results, the parallel usage of interstitial irradiation and image fusion enables the more accurate definition of the target volume at the planning of irradiation, the control of the placement of the catheters and isotopes during the operation, and the differentiation of the necrotized and living parts of the tumor at the postoperative period.

2. Our results achieved with Iodine-125 stereotactical interstitial irradiation of brain tumors are not behind the results of LINAC and Gamma knife irradiations as presented in international sources. We showed successfully, that the best tumor control
and the highest measure of tumor shrinkage for meningeomas is effected with interstitial irradiation.

3. The control of interstitial irradiation using CT-CT fusion enables to define and correct the dislocation of the catheter; this makes the procedure more accurate and trustworthy. At the same time, very good conformity has been achieved by low implantation risk. This result also shows that with Iodine-125 interstitial irradiation, which is using a limited number of catheters, dose distribution and conformity is similar than while using Gamma knife and LINAC radiosurgery.

4. According to my calculations using LQ model, at stereotactic irradiation of brain tumors the multiple arc LINAC based radiosurgery is shown to be potentially more damaging to normal tissues than I-125 brachytherapy. This is especially important when the stereotactical radiosurgery is used together with chemotherapy, or follows recurrent, partial or subtotal resection. As in these above mentioned cases normal tissue is more sensitive to radiation, minimization of the dose is of high importance.
VII. List of Publications

VII.1. Articles

1. Julow J, Viola A, Major T: Review of Radiosurgery of Pineal parenchymal Tumors. 125 Iodine Brachytherapy of Pineoblastomas in 2 cases. Min Invas Neurosurg, 2006, 00:00-00. – in press


**VII.2. Abstracts**


