The handle http://hdl.handle.net/1887/36461 holds various files of this Leiden University dissertation

Author: Wiggenraad, Ruud  
Title: Stereotactic radiotherapy of intracranial tumors: optimizing treatment and improving outcome  
Issue Date: 2016-02-10
3b: DOSE-EFFECT RELATION IN STEREOTACTIC RADIOTHERAPY FOR BRAIN METASTASES. A SYSTEMATIC REVIEW

RUUD WIGGENRAAD, ANTOINETTE VERBEEK-DE KANTER, HENK B. KAL, MARTIN TAPHOORN, THOMAS VISSERS, HENK STRUIKMANS

Radiotherapy and Oncology
2011 Mar;98(3):292-7
ABSTRACT

Purpose: Stereotactic radiotherapy (SRT) of brain metastases is considered effective when long-term local control is obtained. However, dose–effect data are scarce. We, therefore, performed a systematic literature search to assess the evidence concerning the relation of SRT dose and local control probability.

Methods and materials: A search was performed for papers describing patients treated with SRT for brain metastases, published from 1990 through 2009, in the electronic databases Medline (Pubmed) and Embase. We selected only papers reporting actuarial local control probability, in which a fixed dose had been pre-scribed and in which the size of the metastases was given. Series with SRT as a boost after whole brain irradiation (WBI) or with SRT after surgery were excluded. From the selected papers we extracted data on dose, local control rates and necrosis rates. Biological effective doses of the linear-quadratic-cubic model, using an \( \alpha/\beta \) of 12 Gy (BED\(_{12}\)), were calculated and a dose–response curve was constructed.

Results: Eleven papers fulfilled the selection criteria for further analysis. Six-month local control rates were higher than 80% in almost all the series irrespective of dose. Twelve-month local control rates, however, varied and were higher than 80%, higher than 60% and lower than 50% with single doses of \( \geq 21 \) Gy, \( \geq 18 \) Gy and \( \leq 15 \) Gy, respectively, and 70% or higher with fractionated SRT (FSRT). A BED\(_{12}\) of at least 40 Gy was associated with a twelve-month local control rate of 70% or more.

Conclusion: Local control after single fraction SRT is highly dependent upon dose and is high (>80%) after 21 Gy or more, but low (<50%) after 15 Gy or less. We conclude that SRT for brain metastases should preferably be applied with a BED\(_{12}\) of at least 40 Gy corresponding with a single fraction of 20 Gy, two fractions of 11.6 Gy or three fractions of 8.5 Gy.
Brain metastases occur in 20–40% of patients with cancer [1]. The incidence of symptomatic brain metastases seems to be increasing as more effective systemic treatments have become available [2]. The prognosis of patients with brain metastases remains poor, despite the developments in modern treatment techniques [3]. Patients with brain metastases were originally divided into three prognostic subgroups using the recursive partitioning analysis published by Gaspar et al., but recently it was shown that prognostic factors vary by primary diagnosis [4,5]. Stereotactic radiotherapy (SRT) is one of the accepted treatment modalities for brain metastases, but there is still a debate if and when whole brain irradiation (WBI) should be combined with SRT [6]. SRT plus WBI is associated with improved local tumor control and neurological functioning compared to either treatment alone, but only in subgroups of patients this results in improved survival [3,7–9]. However, patients treated with SRT and WBI are at a greater risk of neurocognitive decline than patients treated with SRT alone [10]. Local control rates are probably higher with the addition of WBI as a result of the higher total radiation dose when both modalities are combined. The primary goal of SRT is a long lasting local control, as most local recurrences are symptomatic and associated with neurological deficits [11]. Local control rates are also reported to improve with higher minimum SRT doses [7,12–16]. Increasing SRT doses may not only lead to higher local control rates, but also to higher rates of radiation necrosis [17]. A correlation has been demonstrated between target size and risk of necrosis [17]. However, the diagnosis of radiation necrosis is difficult and toxicity-risk predictions cannot be made [18,19]. As the radiation necrosis rate is determined by the dose in relation to the size of the tumor, it is a common practice to administer higher SRT doses to smaller tumors and vice versa. However, there is no consensus about the optimal SRT doses. We, therefore, performed a systematic literature review to collect data on local control rates of brain metastases with SRT. The purpose was to summarize the currently available evidence concerning the relation between SRT dose and local control and to define radiation schemes with a twelve-month local control rate of 70% or higher.

MATERIALS AND METHODS

We performed a search for all articles about SRT of brain metastases in the electronic databases Medline (Pubmed) and Embase. We only included papers in English, Dutch, German or French describing patient series published in peer-reviewed journals from 1990 through 2009.

SELECTION OF RELEVANT RESEARCH

We used a selection process in two steps to find the appropriate papers. In the first step we selected only those papers that reported actuarial local control rates of the irradiated brain metastases. A second selection step was done to find the papers in which actuarial local control rates could be related to radiation dose. Therefore, we selected, from the remaining papers, those series in which a fixed dose had been prescribed either to all treated metastases or to clearly defined groups of metastases (with local control data in these groups). Furthermore, at least 10 patients had to be included, who had received SRT as primary treatment or SRT for recurrence after whole brain irradiation (WBI), but not SRT as boost after surgery. Series in which all patients had a planned SRT boost after WBI were excluded in this second step. The papers that remained after the second selection step form the basis of this study.

ANALYSIS OF THE SELECTED PAPERS

From the remaining papers the following data were retrieved: number of patients and number of metastases treated, percentage of patients that received or had received WBI, dose prescription, given minimum dose related to tumor diameter or volume, treatment machine
and technique, six and twelve months local control rates, twelve months survival rate and radiation necrosis rate.

For this analysis we had to use the local control rates as reported in the papers. We could not correct for the relatively small differences in the definition of local control between the papers. Local control was defined as absence of any increase in size, absence of significant increase in size or no increase of at least 25% in size. It was not always clearly stated if increase in size due to suspected radiation necrosis was considered a failure or not.

Table 1. Patients and treatments reported in the 11 selected papers.

<table>
<thead>
<tr>
<th>Author</th>
<th>N patients</th>
<th>N metastases</th>
<th>Diagnoses</th>
<th>Range of diameters/volumes</th>
<th>Dose specification isodose</th>
<th>GTV-PTV margin (mm)</th>
<th>% WBI* (patients)</th>
<th>RTx Machine</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matuso (1999)*</td>
<td>92</td>
<td>162</td>
<td>All histologies</td>
<td>&lt;3 cm/ &lt;10 cm³</td>
<td>1x25 Gy/50%</td>
<td>0</td>
<td>0%</td>
<td>Linear arc</td>
<td>Circular arc</td>
</tr>
<tr>
<td>Cheng (2003)**</td>
<td>185</td>
<td>153</td>
<td>All histologies</td>
<td>&lt;2 cm/ &lt;5 cm³</td>
<td>20-24 Gy/70-100%</td>
<td>0</td>
<td>18%</td>
<td>Linear arc</td>
<td>Circular arc</td>
</tr>
<tr>
<td>Lutterbach (2003)**</td>
<td>101</td>
<td>155</td>
<td>All histologies</td>
<td>&lt;3 cm</td>
<td>18 Gy/80%</td>
<td>0-2</td>
<td>0%</td>
<td>Linear arc</td>
<td>Circular arc</td>
</tr>
<tr>
<td>Chang (2006)**</td>
<td>189</td>
<td>264</td>
<td>Melanoma, sarcoma, renal cell carcinoma</td>
<td>&lt;4 cm/ 2/5 cm³</td>
<td>RTOG/80-100%</td>
<td>0</td>
<td>8%</td>
<td>Linear arc</td>
<td>Circular arc</td>
</tr>
<tr>
<td>Ernst-Steckan (2006)**</td>
<td>51</td>
<td>72</td>
<td>All histologies</td>
<td>1-5 cm/ 0.5-0.6 cm³</td>
<td>5x7 Gy/50% or WBI+ 5x6 Gy/90%</td>
<td>3</td>
<td>5.7%</td>
<td>NovoStar</td>
<td>Conformal beam/ Dynamic arc</td>
</tr>
<tr>
<td>Vogelbaum (2006)**</td>
<td>202</td>
<td>375</td>
<td>All histologies</td>
<td>&lt;4.5 cm</td>
<td>RTOG/50%</td>
<td>0</td>
<td>75%</td>
<td>GK</td>
<td>GK</td>
</tr>
<tr>
<td>Narayana (2007)**</td>
<td>20</td>
<td>20</td>
<td>All histologies</td>
<td>2.5 cm³</td>
<td>5x6 Gy/90%</td>
<td>3</td>
<td>0%</td>
<td>Linear arc</td>
<td>IMRT</td>
</tr>
<tr>
<td>Chen (2008)**</td>
<td>131</td>
<td>17</td>
<td>All histologies</td>
<td>&lt;4 cm</td>
<td>RTOG/F</td>
<td>0</td>
<td>0%</td>
<td>GK</td>
<td>GK</td>
</tr>
<tr>
<td>Higuchi (2009)**</td>
<td>45</td>
<td>45</td>
<td>All histologies</td>
<td>3-4.5 cm/ 10-36 cm³</td>
<td>3x10 Gy/50%</td>
<td>0</td>
<td>0%</td>
<td>GK</td>
<td>GK</td>
</tr>
<tr>
<td>Molinar (2009)**</td>
<td>96</td>
<td>150</td>
<td>All histologies</td>
<td>&lt;4 cm</td>
<td>RTOG/80%</td>
<td>2</td>
<td>15%</td>
<td>NovoStar</td>
<td>Dynamic arc</td>
</tr>
<tr>
<td>Sato (2005)**</td>
<td>49</td>
<td>76</td>
<td>Non small cell lung cancer</td>
<td>&lt;4 cm</td>
<td>3x13 Gy/90% or 3x14.5 Gy/50%</td>
<td>3</td>
<td>0%</td>
<td>Linear arc</td>
<td>Conformal beam</td>
</tr>
</tbody>
</table>

Table 1. Patients and treatments reported in the 11 selected papers.

<table>
<thead>
<tr>
<th>Author</th>
<th>N patients</th>
<th>N metastases</th>
<th>Diagnoses</th>
<th>Range of diameters/volumes</th>
<th>Dose specification isodose</th>
<th>GTV-PTV margin (mm)</th>
<th>% WBI* (patients)</th>
<th>RTx Machine</th>
<th>Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matuso (1999)*</td>
<td>92</td>
<td>162</td>
<td>All histologies</td>
<td>&lt;3 cm/ &lt;10 cm³</td>
<td>1x25 Gy/50%</td>
<td>0</td>
<td>0%</td>
<td>Linear arc</td>
<td>Circular arc</td>
</tr>
<tr>
<td>Cheng (2003)**</td>
<td>185</td>
<td>153</td>
<td>All histologies</td>
<td>&lt;2 cm/ &lt;5 cm³</td>
<td>20-24 Gy/70-100%</td>
<td>0</td>
<td>18%</td>
<td>Linear arc</td>
<td>Circular arc</td>
</tr>
<tr>
<td>Lutterbach (2003)**</td>
<td>101</td>
<td>155</td>
<td>All histologies</td>
<td>&lt;3 cm</td>
<td>18 Gy/80%</td>
<td>0-2</td>
<td>0%</td>
<td>Linear arc</td>
<td>Circular arc</td>
</tr>
<tr>
<td>Chang (2006)**</td>
<td>189</td>
<td>264</td>
<td>Melanoma, sarcoma, renal cell carcinoma</td>
<td>&lt;4 cm/ 2/5 cm³</td>
<td>RTOG/80-100%</td>
<td>0</td>
<td>8%</td>
<td>Linear arc</td>
<td>Circular arc</td>
</tr>
<tr>
<td>Ernst-Steckan (2006)**</td>
<td>51</td>
<td>72</td>
<td>All histologies</td>
<td>1-5 cm/ 0.5-0.6 cm³</td>
<td>5x7 Gy/50% or WBI+ 5x6 Gy/90%</td>
<td>3</td>
<td>5.7%</td>
<td>NovoStar</td>
<td>Conformal beam/ Dynamic arc</td>
</tr>
<tr>
<td>Vogelbaum (2006)**</td>
<td>202</td>
<td>375</td>
<td>All histologies</td>
<td>&lt;4.5 cm</td>
<td>RTOG/50%</td>
<td>0</td>
<td>75%</td>
<td>GK</td>
<td>GK</td>
</tr>
<tr>
<td>Narayana (2007)**</td>
<td>20</td>
<td>20</td>
<td>All histologies</td>
<td>2.5 cm³</td>
<td>5x6 Gy/90%</td>
<td>3</td>
<td>0%</td>
<td>Linear arc</td>
<td>IMRT</td>
</tr>
<tr>
<td>Chen (2008)**</td>
<td>131</td>
<td>17</td>
<td>All histologies</td>
<td>&lt;4 cm</td>
<td>RTOG/F</td>
<td>0</td>
<td>0%</td>
<td>GK</td>
<td>GK</td>
</tr>
<tr>
<td>Higuchi (2009)**</td>
<td>45</td>
<td>45</td>
<td>All histologies</td>
<td>3-4.5 cm/ 10-36 cm³</td>
<td>3x10 Gy/50%</td>
<td>0</td>
<td>0%</td>
<td>GK</td>
<td>GK</td>
</tr>
<tr>
<td>Molinar (2009)**</td>
<td>96</td>
<td>150</td>
<td>All histologies</td>
<td>&lt;4 cm</td>
<td>RTOG/80%</td>
<td>2</td>
<td>15%</td>
<td>NovoStar</td>
<td>Dynamic arc</td>
</tr>
<tr>
<td>Sato (2005)**</td>
<td>49</td>
<td>76</td>
<td>Non small cell lung cancer</td>
<td>&lt;4 cm</td>
<td>3x13 Gy/90% or 3x14.5 Gy/50%</td>
<td>3</td>
<td>0%</td>
<td>Linear arc</td>
<td>Conformal beam</td>
</tr>
</tbody>
</table>

We considered the minimum dose in the planning target volume (PTV) as the given dose. In some papers the PTV was equal to the gross tumor volume (GTV), but in others a GTV-PTV margin was used, usually not more than 2 mm. We did not attempt to correct for these differences, although there is an influence on the actual dose in the GTV.

It was also not possible to correct for differences in dose specification, although the biological effect of these differences may not be negligible. Finally, we also decided not to take into account the timing of WBI, as there was not always sufficient information in the papers, to decide whether the SRT and WBI were a combined treatment, or SRT or WBI was used as salvage treatment.

To compare the different treatment schemes described in the selected articles, biological effective doses (BEDs) were calculated using the adjusted linear-quadratic BED (LQ-BED) concept. In general, the occurrence of a biological effect E depends on the dose in a linear
and quadratic fashion: \( E = n(\alpha d + \beta d^2) \) with \( n \) being the number of fractions, \( d \) being the dose per fraction, and \( \alpha \) and \( \beta \) being parameters that determine the initial slope and curvature of the underlying cell-survival curve. From this equation, the BED can be calculated as: 
\[
\text{BED} = nd \left[ 1 + d/(\alpha/\beta) \right]
\]
[20,21]. However, this model describes the responses to ionizing radiation very well at doses up to about 18 Gy [22]. At higher doses the underlying survival curve is found to more closely resemble a linear relationship between survival and dose. Adjusting the LQ-model to account for the more linear response at higher doses can be done by adding an additional term proportional to the cube of the dose. In this so-called LQC model \( E = n(\alpha d + \beta d^2 - \gamma d^3) \) and 
\[
\text{BED} = nd \left[ 1 + d/(\alpha/\beta) - d^2/(\alpha/\gamma) \right]
\]
[23]. Joiner showed that the survival curve becomes straightened at dose \( D \), by choosing \( \gamma = b/(3D) \), in his example the LQC curve becomes a straight line at a dose of 18 Gy [23].

<table>
<thead>
<tr>
<th>Author</th>
<th>Diameter (cm)</th>
<th>Dose (Gy)</th>
<th>BED (Gy)</th>
<th>6 month local control (%)</th>
<th>12 month local control (%)</th>
<th>12 month survival (%)</th>
<th>Radiation necrosis rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsuo (1999) a</td>
<td>0.3</td>
<td>25</td>
<td>53.0</td>
<td>100</td>
<td>93</td>
<td>40</td>
<td>Na</td>
</tr>
<tr>
<td>Chang (2003) b</td>
<td>0.2</td>
<td>0-20-24</td>
<td>41.0-50.7</td>
<td>Na</td>
<td>69</td>
<td>48</td>
<td>1</td>
</tr>
<tr>
<td>Lutterbach (2003) c</td>
<td>0.3</td>
<td>18</td>
<td>36.0</td>
<td>93</td>
<td>91</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Chang (2006) d</td>
<td>1.3</td>
<td>15-18</td>
<td>28.6-36.0</td>
<td>Na</td>
<td>38</td>
<td>31</td>
<td>3</td>
</tr>
<tr>
<td>Vogelbaum (2006) e</td>
<td>0.2</td>
<td>24</td>
<td>50.7</td>
<td>92</td>
<td>85</td>
<td>50</td>
<td>Na</td>
</tr>
<tr>
<td>2.3</td>
<td>18</td>
<td>36.0</td>
<td>87</td>
<td>49</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.4-5</td>
<td>15</td>
<td>28.6</td>
<td>71</td>
<td>45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choo (2008) f</td>
<td>0.2</td>
<td>0-22-24</td>
<td>45.9-50.7</td>
<td>97</td>
<td>92</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>2.4</td>
<td>15-18</td>
<td>20.6-36.0</td>
<td>83</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molenear (2009) g</td>
<td>0.2</td>
<td>21</td>
<td>43.4</td>
<td>100</td>
<td>82</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>2.1</td>
<td>18</td>
<td>36.0</td>
<td>95</td>
<td>85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.4</td>
<td>15</td>
<td>28.6</td>
<td>93</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Actuarial local control and survival rates and crude radiation necrosis rates from the papers reporting about single fraction SRT.
Na: Not available
a data reported for the entire patient cohort
b data used in Figure 3
It is widely accepted that \( \alpha/\beta \) is about 10–15 Gy for tumors and acutereacting tissues. We used for the brain metastases the value of 12 Gy (BED\(_{12}\)) [24]. Because with SRT high single or high fraction doses were used we applied the LQC model and calculated the BED as nd\([1 + d/(\alpha/\beta) - d^2/(\gamma/\beta)]\). With \( \alpha/\beta = 12 \) Gy and supposing that the survival curve becomes a straight line at \( D_\ell = 18 \) Gy, and with \( \gamma = \beta/(3D) \), \( \alpha/\gamma = \alpha/(\beta/(3D)) = 648 \) Gy\(^2\), the BED\(_{12}\) is calculated as: BED = nd\([1 + d/12 - d^2/648]\).

<table>
<thead>
<tr>
<th>Author</th>
<th>Diameter (cm)</th>
<th>Dose (Gy)</th>
<th>BED(_{12}) (Gy)</th>
<th>6 month local control (%)</th>
<th>12 month local control (%)</th>
<th>12 month survival (%)</th>
<th>Radiation necrosis rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ernst-Stecken</td>
<td>1-5</td>
<td>5x6-7</td>
<td>43.3-52.8</td>
<td>89</td>
<td>76</td>
<td>Na</td>
<td>Na</td>
</tr>
<tr>
<td>(2006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narayaga</td>
<td>2-5</td>
<td>5x6</td>
<td>(^*)43.3</td>
<td>90</td>
<td>70</td>
<td>42</td>
<td>Na</td>
</tr>
<tr>
<td>(2007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higuchi</td>
<td>3-4.5</td>
<td>3x10</td>
<td>(^*)50.4</td>
<td>90</td>
<td>76</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>(2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sato</td>
<td>0.4-3.8</td>
<td>3x13</td>
<td>(^*)71.1</td>
<td>90</td>
<td>89</td>
<td>(^*)61</td>
<td>(^*)12</td>
</tr>
<tr>
<td>(2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sato</td>
<td>3x14</td>
<td>(^*)78.3</td>
<td>100</td>
<td>83</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Actuarial local control and survival rates and crude radiation necrosis rates from the papers reporting about fractionated SRT.

Na: Not available
\(^*\) data reported for the entire patient cohort
\(^b\) data used in Figure 3

RESULTS

Using the search strategy we found 260 potentially relevant articles. Actuarial local control after SRT was reported in 123 of these papers. Finally, eleven papers contained data that could be used to relate dose to local control [16,25–34]. Table 1 shows patient and treatment characteristics of the 11 remaining papers used in this study. From two of these 11 papers only part of the reported results could be used for the final analysis.

Matsuo et al. reported about 162 metastases in 92 patients [31]. In this series a group of 51 patients could not be used for the analysis, because they received a wide range of doses (10–22 Gy) for metastases with a volume up to 33 cm\(^3\). However, the remaining group of 41 patients could be used as they received the fixed dose of 25 Gy for metastases up to 10 cm\(^3\). Chang et al. described a series of 189 patients with 264 “radioresistant” brain metastases, treated using the RTOG 90-05 scheme [26]. Local control rates are only reported for metastases receiving up to 20 Gy, split into groups of more or less than 1 cm diameter. As it was reported that the RTOG scheme was used, we could not determine what doses were given to metastases with a diameter less than 1 cm. Consequently we did not use the data of the metastases with a diameter less than 1 cm.
Tables 2 and 3 show the 6- and 12-month local control rates, the 12-month survival rates and the crude radiation necrosis rates with the corresponding tumor diameters and the given doses from the series reporting about single fraction SRT (Table 2) and fractionated stereotactic radiotherapy (FSRT) (Table 3). Six-month local control rates are higher than 80% for all except one single fraction series and higher than 90% for all FSRT series. Twelve-month local control rates vary considerably in the single-fraction series, depending on the dose. Twelve-month local control rates are higher than 80% with doses above 20 Gy and higher than 60% with a dose of 18 Gy. Reported twelve-month local control rates with a dose of 15 Gy are below 50% in all but one series. FSRT series all report twelve-month local control rates higher than 70%. Radiation necrosis rates are not reported consistently. The highest rate (12%) was found after 3x13Gy or 3x14Gy.

Figure 1. Line plot representing the relation between single fraction SRT, the diameters of the treated metastases and twelve-month local control rates.

We constructed line plots as shown in Figs. 1 and 2 to obtain a better insight into the differences in twelve-month local control rates after all the reported SRT dosage schemes. Fig. 3 shows the relation between BED<sub>12</sub> and twelve-month local control rates. From this we concluded that a BED<sub>12</sub> of at least 40 Gy is needed for a twelve-month local control rate of 70% or more.

DISCUSSION

In this systematic literature search we identified 11 descriptive papers in which actuarial local control rate could be related to applied doses. All studies were characterized by a retrospective design. Six-month local control rates were higher than 80% in almost all series irrespective of dose. Twelve-month local control rates, however, varied substantially and were higher than 80% with a single dose above 20 Gy, higher than 70% with the described FSRT schemes, higher than 60% with a single dose of 18 Gy and almost always below 50% with a single dose of 15 Gy. We found that a BED<sub>12</sub> of at least 40 Gy was necessary to obtain a twelve-month local control rate of 70% or more.
We could relate the volume of the metastases with the given dose in only 11 of the 123 papers that reported actuarial local control rates. Dose prescription in single fraction SRT is often not based on tumor volume, but on estimated late radiation toxicity rates, resulting in a wide range of dose levels in the majority of papers. Some authors use the so-called integrated logistic formula to prescribe doses and estimate complications [35]. In other series dose prescription is based on RTOG 90-05, a prospective study designed to establish the maximum tolerated dose of single fraction radiosurgery in patients with recurrent previously irradiated brain metastases and primary brain tumors [17]. However the relation between dose and local control in RTOG 90-05 was not reported. The 11 descriptive studies we found contain the best available evidence.

Figure 2. Line plot representing the relation between FSRT dose schedules, the diameters of the treated metastases and 12-month local control rates.

Figure 3. Diagram showing the relation between BED$_{12}$ and 12-month local control rates. Data from papers with a range of doses were not used for this diagram, i.e., used BED$_{12}$ values are indicated with $^b$ in Tables 2 and 3. A dose–response curve is constructed by eye fitting.

The definition of local control is not uniform, but in most papers the absence of any tumor growth is considered local control. Enlargement of the tumor after SRT can be a true recurrence or radiation necrosis and modern MRI techniques can be helpful to make the distinction [18]. However, these techniques were probably not available or applied in all 11 studies.
This slight uncertainty about the recurrence rates, combined with the observation that radiation necrosis has in none of the papers been reported as actuarial rate but seven times as crude rate and four times not at all, must be considered a weakness of this study.

In most series 30–50% of patients are still alive after 12 months [16,25–27,29–32,34]. As local control for the rest of the patient’s life is the treatment goal for SRT, the 12-months local control rate can be considered as a measure of the effectiveness of a treatment scheme. To our opinion the 12-month local control rate should be at least 50%, but preferably more than 70% to state that the treatment is sufficiently effective. Higher local control rates should be weighed against the disadvantage of higher radiation necrosis rates. However, only crude necrosis rates are reported and some papers do not report about radiation necrosis at all. We think there is insufficient information about the complication risk for routine use of schemes with a BED\textsubscript{12} higher than 52 Gy (Table 2 and 3).

Whole brain irradiation added to SRT may improve local control rates [36]. As we were interested in local control rates after SRT alone, we omitted the studies that used SRT as a boost in all patients. In some of the 11 studies, however, WBI was added to SRT in selected patients for a variety of reasons, i.e., SRT for recurrence after WBI, SRT as a planned boost after WBI or WBI for recurrence after SRT. The indication for adding WBI to SRT was not always mentioned [34]. In nine of the eleven papers the percentage of the patients that had received WBI was only 0–15% (Table 1). Such a low percentage could not have had a major influence on local control rates. In the two studies that reported higher WBI rates, reported local control rates were low compared to the other studies. This also suggests minor influence of WBI on local control rates in these two studies, probably because in most of their patients SRT was not used as a boost after WBI. Based on this we think that our conclusions about local control effects of SRT doses are still valid, even if some of the patients from the 11 papers received additional WBI.

There is a debate whether the LQ formalism, and consequently the BED formula, can be used to predict the biological effect of the high fraction doses as applied in SRT for brain metastases [22,37]. Those opposing the use of the LQ formalism in this setting argue that tumor control probability after single fraction SRT in fact is much greater than expected based on the LQ model [37]. Brenner discussed that the LQ-model was well validated, experimentally and theoretically, for fraction doses upto 10 Gy, and would be reasonable for use upto about 18 Gy per fraction [22]. We observed that in the reviewed literature here single SRT doses upto 25 Gy were applied. Therefore, we applied the adjusted LQ model. In this limited amount of useful literature we found that with fraction doses in the range of 6–25 Gy, the BED\textsubscript{12} has a relation with 12-month local control rates. We think that the LQC-BED concept is useful to develop treatment protocols for metastases, also for those larger than 3 cm that cannot receive high enough single-fraction doses because of expected toxicity.

Factors other than SRT dose can determine local control rates, such as tumor size, specification isodose, GTV–PTV margins and tumor type. In this literature study it was not possible to take into account the influence on local control of all these factors.

Local control has been reported to be influenced by tumor size [31,38–47]. However, this influence is difficult to quantify, because in many series lower doses are prescribed for larger metastases or prescribed doses vary widely. The effect of the tumor size was quantified in only one study, in which all brain metastases were treated with 20–24 Gy [25]. Twelve-month local control rates were 86% and 56% in metastases of less or more than 1 cm diameter, respectively. This implies that the distribution of tumors within each group of tumors receiving a uniform dose may influence the local control rate in that group.

In gamma knife series dose is often specified on the 50% isodose and in lineac series on the 80–100% isodose (Table 1). Local control may be influenced by the specification isodose. In the final report of RTOG 90-05 the authors state that patients treated on a linear accelerator were more likely to have local progression than those treated on a gamma knife [17]. The
observed difference in local control between the two machine types is probably related to the difference in dose specification. Looking at the results of this literature study we have to bear in mind the influence of dose specification, but we do not have data that enable us to correct for this factor.

A GTV–PTV margin of zero, as used in many SRT series, may lead to a lower dose in the GTV [48]. In one study a significant improvement of local control was reported after GTV–PTV margins were changed from 0 to 1 mm [49]. In the 11 papers we studied the margin was 0 mm in five out of seven single-fraction series and one out of four FSRT series. We cannot exclude that the generally higher local control rates in the FSRT series were not only due to the higher BED, but also due to the used margins, but the data are not sufficient to draw conclusions.

Finally, selection bias cannot be excluded as only 11 studies could be used all with a retrospective design. Presently we conduct a prospective study in our department with fixed doses according to tumor volume and three monthly follow-up including neurocognitive tests and perfusion MRI (personal communication).

Concluding, we found only 11 studies in the literature of the last 20 years that are helpful to study the dose–effect relationship in SRT for brain metastases. Twelve-month local control rates are excellent after single fraction SRT doses above 20 Gy, but disappointing after doses of 15 Gy or less. For brain metastases larger than 3 cm FSRT should be considered. The BED concept can be helpful to develop FSRT treatment protocols. For $\text{BED}_{12}$ values of at least 40 Gy 12-month local-control rates of 70% and higher are found. A $\text{BED}_{12}$ value of 40 Gy translates into a single fraction of 20 Gy, 2 fractions of 11.6 Gy or 3 fractions of 8.5 Gy.

**Conflict of interest notification:** For none of the authors any potential or actual conflict of interest exists.
REFERENCES


[18] Hoefnagels FW, Lagerwaard FJ, Sanchez


[37] Kirkpatrick JP, Meyer JJ, Marks LB. The linear-quadratic model is inappropriate


