Reviewer’s report

Title: Hypofractionated stereotactic radiotherapy of limited brain metastases: A single-centre individualized treatment approach

Version: 1 Date: 8 September 2012

Reviewer: Gert De Meerleer

Reviewer’s report:

The authors report on their experience with frameless hypofractionated cranial radiotherapy. It is a very heterogeneous report with multiple fractionation schemes and different timing of FU. The most interesting part of this paper is the information on local control and EQD2! Although the report is interesting, several important issues should be addressed:

- General remark:
  - The data are too heterogeneous. I would stick to the following patient groups: patient treated with primary hfSRT vs. recurrent treatment after WBRT only. This would make the results easier to interpret and clinically more meaningful. I also do not understand why there are patients in the “recurrent group” who were primary treated with hfSRT. I would put these patients in the analysis of the primary group at time of there first hfSRT and describe their results as such.

- Methods section:
  - Patient characteristics: this part should only describe the patient population inclusion and exclusion criteria and not specific details such as the dose of steroids which could be added to the toxicity data as this may help to interpret these results. Additionally, the 2 last sentences could be put in Table 1 as well.
  - Radiotherapy part:
    - What WBRT dose used in the patients treated with hfSRT for recurrence? What were the constraints used for patients treated with hfSRT after WBRT.
    - Was there a preferred dose schedule for recurrent hfSRT after WBRT or was this left at the discretion of the physician? In the discussion you mention that this is 8-10 x 4 Gy. This information should be in the Methods part.
    - Please mention in how many patients the prescribed dose was used and in how many patients the dose had to be downscaled because of violation of constraints.
  - Table 1: why are the abbreviation mentioned for NSCLC, renal cell and SCLC as they are not repeated in this table. I would remove them. The column of total metastases is only useful for the localization of brain metastases. I would remove this column and simply put the data of the total metastases in the first column with the data of the patients. Additionally, it would be more interesting to put the data of the 2 different patient groups in 2 additional columns: e.g. characteristics of patient with the primary treatment vs. recurrent treatment.
Table 3: the column with all hfSRT could be removed, as it is the simple addition of the 2 other columns.

Why did you use both CBCT and X-Ray images as IGRT measures? Is this useful?

Follow-up: This section should not contain the last 3 sentences on median FU and they should be put in the result section.

Statistics: please mention that the variable “primary vs. recurrent treatment” is also included.

Mention how toxicity was scored and with which scoring system? What is considered acute toxicity and what is late. Also mention in how many patients you scored toxicity as some have died to soon to report on late toxicity and this influences the relative percentage of toxicity.

Result section:

In the OS section, please mention the cause of death of patients; was this due to brain progression or extracranial disease progression?

It should be possible to evaluate response rates as the patients received control MRIs. Please add these data.

Relapse pattern: please mention what the pattern of distant brain relapse was: e.g. how many lesions at relapse?

Salvage treatment: As the distant brain control is low, please mention how many patients received a salvage treatment after distant brain relapse with WBRT or re-hfSRT, surgery,

You mention the significant variables in the result section but you do not mention whether this is a result of uni- or multivariate analysis.

Please add a table with the variables and results of the uni- and multivariate analysis and the corresponding p-values for overall survival.

I would leave out the following sentence: “Median LC was 13.8 months for the 10x4 Gy concept vs. 8.6 months for 7x5 Gy (p=0.58).”

There was a case of radiation necrosis, please mention the cumulative dose to this region as this is informative for the reader and also whether or not it was symptomatic and/or treated?

It would be interesting to see if the toxicity is different according to the dose concept: <35 or >35 Gy, the GTV volume and the V4Gy.

Could you report the median dose for GTV < 2ccm and GTV > 2 ccm.

Discussion:

Please comment on the very low distant brain control. For example in the report of De Potter et al. (Neurol Sci 2012) the different studies using upfront-WBRT and hfSRT boost are summarized in a table. For example they used 5x6 Gy was used as a boost in addition to WBRT with 75% distant brain control at 1 year. You should refer to these papers to put your results in perspective, as this is important information.
You conclude that 10x4Gy is the “best” option considering safety and control, however you were unable to detect a significant difference for control with the other schedules. Based on the results, I believe you should state that doses >35Gy EQ2D are preferable looking at the control rates. From the results I cannot deduct which fractionation option delivering >35Gy EQ2D is best.

As for safety, I cannot deduct from the results that 10x4 is safer compared to 5x6 Gy. I would also use the concept EQ2D > 35 Gy as it might be possible that an EQ2D < 35 Gy is safer. This is important for the discussion part as an EQ2D > 35 Gy might be more optimal it might not be possible to deliver this dose in some patients because of the OAR.

In the discussion you state: “Still, in general the dose concept of 10x4 Gy (EQD2 equivalent 47 Gy) showed a higher 12-months LC with 71% compared to 5x6 Gy (63%, EQD2 equivalent 40 Gy) and 7x5 Gy (21%, EQD2 equivalent 44 Gy), respectively.” This statement should be removed, as the results are not significant.

- Conclusion

I would state in the conclusion that a EQ2D > 35 Gy is most effective for disease control (see above)

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests