Author’s response to reviews

Title: Intraoperative Electron Radiation Therapy (IOERT) in the Management of Locally Recurrent Rectal Cancer

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Author’s response to reviews: see over
Dear Editorial Team,

we have read the reviewers comments with interest and have included corresponding changes into the revised manuscript. All comments are addressed by a point-by-point response listed below. The changes have been marked in yellow colour inside the revised manuscript.

Best regards

Dr. F. Roeder

Reviewer 1 (Michael G Haddock):

Major compulsory revisions: none

Minor essential revisions:

1. Change “curative intended therapy” to “curative intent therapy” in multiple locations

   -> We have changed the mentioned terms throughout the manuscript

2. Change “table x” to “Table x” in multiple locations

   -> We have changed the mentioned term throughout the manuscript. We have also changed “figure x” to “Figure x” in the whole manuscript.

3. Given that unirradiated patients are often treated with 50.4 Gy in 28 fractions and the finding that preoperative irradiation was associated with complete resection, what was the reason for limiting the dose to 41.4 Gy?

In the beginning of our IOERT program back in 1991, IOERT was introduced into the treatment of several cancers including recurrent rectal cancer and also locally advanced primary rectal cancer. Assuming, that the biological effect of the large single dose used in IOERT is considered to be equivalent to 1.5-2.5 times the same total dose of fractionated RT, the EBRT dose of 41.4 Gy was chosen at the beginning of our IOERT program with the idea to reach dose escalation in the high risk area by the combination approach, while reducing late effects resulting from EBRT (i.e. small bowel obstruction) and IOERT (i.e. neuropathy) by combining moderate doses of each treatment as described in a previous publication of our group by Eble et al. [8]. This concept emerged over time, especially with the widespread adoption of neoadjuvant RCHT in primary rectal cancer and also the increasing evidence for the association between neoadjuvant EBRT dose and tumor regression. Therefore since 2003 all previously not irradiated patients received EBRT doses of 45-54 Gy. However, because the majority of the patients included in this analysis was treated before 2003, the calculated median of the EBRT dose was 41.4 Gy.

Currently we use 45 to 50.4 Gy in previously not irradiated patients.
4. Neuropathy was observed in 8% of the patients. In other series, the frequency and severity of neuropathy was associated with IOERT dose. Was there any relationship to IOERT dose or overall dose in this series?

We found an increased rate of neuropathy of 11% in patients who received IOERT doses ≥ 15 Gy compared to 6% in patients with < 15 Gy. However, this difference was not statistically significant.

5. A statement regarding the limitations of a retrospective analysis should be added to the discussion.

Comment:

1. How were the patients for IOERT chosen?

Patients were scheduled for this treatment approach, if the risk for close or positive margins seemed high according to the surgeons assessment of preoperative imaging or after multidisciplinary discussion, especially if pelvic side wall or sacral involvement was present, whereas patients with limited, mainly intraluminal recurrences confined to the anastomotic region were usually treated with surgery alone. Currently patients with recurrent rectal cancer are discussed within a multidisciplinary tumor conference on a regular basis before initiation of treatment (which is strongly recommended).

2. Why was the median dose for the neoadjuvant chemoradiation 41.4 Gy and not 50.4. Gy?

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Currently we use 45 to 50.4 Gy in previously not irradiated patients.

-> We have included a corresponding statement explaining the used EBRT doses into the Patients and methods section and also a statement of our currently used dose concept into the conclusion section.

3. Was the IOERT dose determined by intraoperative margin status? Was frozen pathologic assessment performed or available?

Dose prescription was based on surgeons assessment of margin status including increasing but not routine use of intraoperative pathologic assessment of frozen sections during the overall study period. In general, higher IOERT doses were applied in cases suspicious of positive margins or residual disease according to the surgeons assessment.

-> We have included a corresponding statement into the Patients and Methods section

4. For table 2 and Table 3, would specify cutoff used for age and time to FD to rec in univariate and multivariate analysis instead of writing “median”

-> We included the specific cutoff values for age and time from FD to rec into the corresponding tables.
Reviewer 3 (John Plastaras):

Major compulsory revisions:

1. The mix of previously radiated and non-radiated patients, 2 distinct groups that received distinct treatments. They did not include prior EBRT as an independent factor in their analysis. It gets buried in with the grouping (EBRT or not) and (neoadjuvant EBRT or not). If the tumor recurred after prior EBRT, I think that is a significant difference in terms of the expected biology and the expected response from neoadjuvant EBRT or IOERT. This should be separately analyzed.

We do not fully agree with this statement of the reviewer, and would rather think that:

1. Current use of additional EBRT has been included as an independent factor into univariate and multivariate analysis (see results section). As stated in the Patients and Methods section, no external beam reirradiation was performed in previously irradiated patients, and patients without prior irradiation received additional external beam RT (neoadjuvant n=46, adjuvant n=8). Therefore is seemed not useful to integrate prior EBRT as an additional parameter into the analyses as these groups have been already separated by the use or non-use of EBRT in the current situation. Separate rates of LC, DC and OS have been reported (see tables) for EBRT and non-EBRT groups representing previously irradiated and previously not irradiated patients. To our opinion, the differences in outcome between these groups are attributable to the different treatment, (EBRT + IORT vs IORT alone), which has been discussed to be probably improvable in the previously irradiated patients (see discussion section), rather than to different tumor biology.

2. Although theoretically well possible, the clinical data -so far published- do not support the notion of very different tumor biologies in recurrences arising from previously irradiated and previously not irradiated tumors. For example in the series of Dresen et al. 2008, patients who had prior RT were partly treated with IOERT alone and partly with external re-irradiation and IOERT, while previously not irradiated patients were all treated with EBRT and IOERT. There was no significant difference in radicality of resection between re-irradiated patients and first time irradiated patients according to multivariate analysis. There was also no significant difference in metastasis-free survival or in overall survival according to the multivariate model between re-irradiated and first time irradiated patients. Similarly, Haddock et al. found no significant impact of prior EBRT on survival in their multivariate analysis in the largest series ever published (> 600 patients). Therefore the assumption of different tumor biology between these groups seems rather speculative.

3. Many major publications (for example Haddock et al. 2011, Dresen et al. 2008, Lindel et al. 2001) dealing with IOERT in the treatment of recurrent rectal cancer have included previously irradiated and previously not irradiated patients, as we did. In the two largest series ever published, Haddock et al. included 45% previously irradiated and 55% previously
unirradiated patients, and Dresen et al. included 47% patients without and 53% patients with previous irradiation.

In general, different treatment schedules have been used for these patient groups, as we did. In the paper by Haddock et al. 2011, patients without previous irradiation received a median EBRT dose of 50.4 Gy and a median IORT dose of 12.5 Gy, whereas previously irradiated ones received a median EBRT dose of 27 Gy (ranging from 5 to 39.6 Gy) and a median IORT dose of 17.5 Gy. In the paper by Dresen et al. 2008 patients without previous EBRT received EBRT with a median dose of 50.4 Gy, patients with previous IOERT received no at all EBRT or reirradiation with a median dose of 30.6 Gy.

Usually separate rates for both groups in terms of LC and OS have been reported, as we did, but distinct analyses for both groups (e.g. multivariate analysis separately for both groups) were uncommon.

4. The aim of the work was to report our experience with surgery + IOERT in the management of recurrent rectal cancer. Including both previously not irradiated patients and previously irradiated patients represents in our opinion the frequent challenge of daily practice.

In summary we do not feel, that prior RT is a factor justifying separate analysis more than other factors and as it has been done (by separating the groups by use of current EBRT) already in our analysis, to improve the value of the manuscript. Especially separate multivariate analysis of these subgroups may not result in meaningful statistics given the low patient number for each group. In our manuscript we had mentioned, that after correction for current EBRT use, resection status remained the strongest predictive factor for local control and overall survival in univariate analysis (see result section).

-> Nevertheless, to better clarify these findings, we have included another table with separate rates of LC and OS for patients with or without current EBRT according to resection margin.

Minor essential revisions :

2. The use of the term “central control” is confusing. What they are describing is within the IOERT area, which sounds more like what I would call “local control”. They use the term “local control” to describe pelvic control, which I would call “Regional control”. These should be changed to “loco-regional control” and “local control” as a more standard terms. The definitions are only found in the methods, so those regarding only the abstract are likely to have a hard time interpreting the results.

We agree with the reviewer, that different definitions of endpoints are in use, which sometimes make it difficult to interpret and compare the results reported by different groups.

However, the term “central control”, defined as absence of recurrence inside the IOERT area, has been introduced into the IOERT literature by the Mayo
Group two decades ago (see for example Gundersson et al. Dis Col Rectum 1996, Haddock et al. 2001 Int J Radiat Oncol Biol Phys) and is still in use today (Haddock et al. Int J Radiat Oncol Biol Phys 2011). Other groups reporting on IOERT also distinguished between control rates inside and outside the IORT area, for example Nyttens et al. Int J Radiat Oncol Biol Phys 2004, or Pelton et al. J Surg Oncol 1993, who used the term IFF (infield failure) to report the control rate inside the IORT area.

Therefore we feel that the use of the term "central control" is appropriate.

With respect to terms such as “local control”, “regional control” or locoregional control”, also a variety of definitions have been used in the literature: for example the Mayo Group (Gundersson et al. 1996, Haddock et al 2001 and 2011) defined local control as absence of tumor growth in the EBRT area. Wiig et al. Radiother Oncol 2002 and Maennerts et al. Dis Col Rectum 2001 defined local control as absence of recurrence inside the true pelvis and Dresen et al. Ann Surg Oncol 2008 defined local control as absence of recurrence inside the pelvis, as we did.

If we further take a look at the definition of local recurrence in major randomized trials dealing with radiotherapy for primary rectal cancer, many of these trials defined local recurrence as absence of tumor regrowth inside the pelvis and perineal scar, which is almost equivalent to our definition for local control (see pre- vs postop RCHT German Rectal Cancer Trial reported by Sauer et al. NEJM 2004, EORTC 22921 trial reported by Bosset et al. NEJM 2006 or FFCD 9203 trial reported by Gerard J Clin Oncol 2006).

Therefore, in our opinion the definition of local control as we have written in our present manuscript is commonly used in the literature and thus seems appropriate.

The reviewer then mentioned that the terms are only defined in the methods section, so those reading only the abstract are likely to have a hard time interpreting the results. Given the above mentioned differences in the definition of terms such as “local control”, it appeared more practical to us to define those terms in the methods section rather than giving lengthy definitions in the abstract. In fact, due to the limited word count for the abstract in journals, it may be technically hard to include those definitions into the abstract on a regular basis.

-> In summary, we felt that the terms and definitions we have used are appropriate. However we did add an explanation of the terms to the abstract to prevent confusion (see abstract).

3. There is at least one important reference that was not included from MDACC (Das P et al IJROBP (2010) 77:60-5). Here, they reported pts who had re-irradiation and surgery had a 3 yr OS of 66%, which is a bit better than the 3 yr OS of 52% (although the number of resected pts was lower in that series). In the decision tree, a patient who has had prior radiation and a potentially resectable cancer, which is the better route ? External beam re-RT and surgery (as described by Das et al.) or the current series of resection IOERT. This type of comparison is missing in the discussion,
despite the authors point that re-irradiation with external beam is probably the best course of action.

We have included and discussed the Das paper in the revised version, although there are some remarkable differences to our analysis: The paper by Das et al reported 50 previously irradiated patients with (mainly) recurrent rectal cancer who have been treated with hyperfractionated EBRT up to 39 Gy. Only 18 of these patients received surgery after RT, while the remaining 32 had no surgery for various reasons. Of the 18 patients with surgery, 9 (50%) received also IOERT with doses of 10-15 Gy. All of the resected patients had no gross disease after surgery (R0/R1 resections only). For this patient group (who had re-irradiation and surgery +/- IORT), the 3-year LC rate was 47% the 3-year OS rates was 66%.

In contrast, in our manuscript, we did not report the LC and OS rates for the combined group of R0 and R1 resected patients, because in our analysis we found the most distinct difference in outcome between R0 and Non-R0 resected patients. Therefore grouping of R0 and R1 resected patients together did not seem to be useful. This was also observed by other research groups in the field: For example Haddock et al. also found the largest difference on 5-y-OS between R0 and R1 resected patients and Dresen et al. observed a large difference in LC and OS between R0 and R1 resected patients but none between R1 and R2.

Because the results reported in the paper by Das et al. (results after resection based only on 18 patients, all resected patients R0/R1) could not be easily compared with our patients group (all patients resected including R2 resections, no grouping of R0/R1 together), we did not feel initially, that this work was an important reference for our discussion.

-> Taken together, we agree with the reviewer, that a closer look to the results of re-irradiation in the discussion section was helpful. Therefore we added a corresponding paragraph into the discussion section. In this paragraph we summarized the results of four major papers focussing on re-irradiation of recurrent rectal cancer patients (including the Das paper) in terms of toxicity, outcome and value of external beam irradiation especially in achieving higher rates of complete resection in order to explain more carefully our already in the first version mentioned conclusion, that IORT alone in previously irradiated patients is probably an improvable treatment especially after incomplete resection based on our results and the findings of other (larger) series.

4. With regard to the statement that doses over 60 Gy result in excessive small bowel toxicity should probably reference direct data. A better reference would be Mohiuddin et al IJROBP 1997 39:643 (which used lower doses for re-irradiation, but did report small bowel toxicity)

We could not fully comprehend these comments by the reviewer. In an effort to discuss the single vs. fractionation effect and doses for local tumor problems we wrote the following paragraph in the initial discussion section of the revised manuscript:
“Because the rate of complete resections in patients undergoing surgery is only in the range of 30-45% [3], additional irradiation has been investigated. Response to neoadjuvant EBRT has been shown to result in increased complete resection rates and decreased local failure rates in primary rectal cancer [1,13]. Similar effects have been also described for recurrent rectal cancer [5,10]. However, the dose of conventionally fractionated EBRT required for control of residual disease is estimated to be ≥60 Gy and therefore exceeds small-bowel tolerance [4]. Further on, an increasing number of patients suffering from recurrent rectal cancer had already been previously irradiated and concerns about toxicity prevented many groups from the use of re-irradiation [4]. Therefore IOERT has been investigated … “

The estimated requirement of total doses of ≥60 Gy for control of (even microscopic) residual disease has been described in several publications (for example Maennerts et al. Dis Col Rectum 2001, Gundersson et al. 1996, which referenced Allee et al. 1989, Lybeert et al. 1992, Overgaard et al. 1984 and Wong et al. 1989) for colorectal cancer in general including the referenced one. There is (to our knowledge) no hard data supporting the notion that different doses were required to control recurrent rectal cancer dependent on their prior irradiation status (irradiated or not). Further on, the usually accepted tolerance dose for small bowel is about 50 Gy in conventional fractionation (see Emami et al. 1991). Therefore it seems reasonable to state that doses of ≥60 Gy exceed small bowel tolerance, as done by us and the author of the referenced paper. This statement referred not specifically to patients who had already been previously irradiated. Therefore the reference Mohiuddin et al., which deals with re-irradiation, has also only limited use in this context.

As a compromise, we agree with the reviewer that referencing direct data might be more useful in general. We therefore added two references (one for the statement the dose of conventionally fractionated EBRT required for control of residual disease is estimated to be ≥60 Gy, and one for the statement that 60 Gy exceeds small bowel tolerance) to the manuscript (see discussion section). We also added some explaining words into the paragraph, in order to prevent misunderstanding of the statements.

5. I fundamentally disagree with the statement that there is a higher biological effectiveness of a large single dose (referenced 15). This is simply not true – fractionation has been shown in fundamental radiobiological experiments to be more effective than single doses. A single fraction is a necessity with IORT, but radiobiological effectiveness is not one of the reasons. This statement should be altered.

Clearly these issues are easy to confuse, and terms such as “higher” or “effectiveness” need definitions of their respective endpoints. Large single doses as used in IOERT are considered to be equivalent to 1.5 to 2.5 times the same total dose of fractionated RT (see for example Calvo et al 2006). Our statement of a higher biological effectiveness of a large single dose referred to the comparison with the same total dose of a fractionated regimen. This statement was included into our manuscript to make clear (especially for readers not specialized in radiation oncology and not familiar with fractionation
issues), that the absolute doses of IORT treatments cannot be directly compared to the doses of external beam treatments.

We agree with the reviewer that the statement, as it was written in our manuscript leads to misinterpretation especially as it was included in the context of the rationale for IORT. We agree of course with the reviewer that in general the biological effectiveness in terms of therapeutic ratio is improved with fractionation. We also agree with the reviewer that the use of a high single dose in IORT is not a major part of the rationale for the use of IORT itself (although it has been described as an advantage compared to fractionated RT in the treatment of other cancers (for example breast cancer) because of the reduction in overall treatment time compared to fractionated RT), but this is obviously not an issue in treating recurrent rectal cancer.

-> We deleted this statement from the manuscript (see introduction section and discussion section)

6. Should more carefully define all abbreviations in tables.

-> We defined the abbreviations more carefully in the tables.