Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: A systematic review and meta-analysis

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A B S T R A C T

Purpose: We conducted a systematic review and meta-analysis to quantify the pathological complete response (pCR) rate after preoperative (chemo)radiation with doses of ≥60 Gy in patients with locally advanced rectal cancer. Complete response is relevant since this could select a proportion of patients for which organ-preserving strategies might be possible. Furthermore, we investigated correlations between EQD2 dose and pCR-rate, toxicity or resectability, and additionally between pCR-rate and chemotherapy, boost-approach or surgical-interval.

Methods and materials: PubMed, EMBASE and Cochrane libraries were searched with the terms ‘radiotherapy’, ‘boost’ and ‘rectal cancer’ and synonym terms. Studies delivering a preoperative dose of ≥60 Gy were eligible for inclusion. Original English full texts that allowed intention-to-treat pCR-rate calculation were included. Study variables, including pCR, acute grade ≥3 toxicity and resectability-rate, were extracted by two authors independently. Eligibility for meta-analysis was assessed by critical appraisal. Heterogeneity and pooled estimates were calculated for all three outcomes. Pearson correlation coefficients were calculated between the variables mentioned earlier.

Results: The search identified 3377 original articles, of which 18 met our inclusion criteria (1106 patients). Fourteen studies were included for meta-analysis (487 patients treated with ≥60 Gy). pCR-rate ranged between 0.0% and 44.4%. Toxicity ranged between 1.3% and 43.8% and resectability-rate between 34.0% and 100%. Pooled pCR-rate was 20.4% (95% CI 16.8–24.5%), with low heterogeneity (I² 0.0%, 95% CI 0.00–84.0%). Pooled acute grade ≥3 toxicity was 10.3% (95% CI 5.4–18.6%) and pooled resectability-rate was 89.5% (95% CI 78.2–95.3%).

Conclusion: Dose escalation above 60 Gy for locally advanced rectal cancer results in high pCR-rates and acceptable early toxicity. This observation needs to be further investigated within larger randomized controlled phase 3 trials in the future.

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Colorectal cancer is the third most common cancer and often diagnosed in an advanced stage. Treatment of locally advanced rectal cancers (LARC) then consists of neoadjuvant chemoradiation therapy (CRT) followed by total mesorectal excision (TME). The clinical outcome after CRT is largely dependent on tumor response to CRT [1,2]. Overall, ~15% of patients experience a pathological complete response (pCR) at the standard radiation dose (45–50.4 Gy) [1,3]. Complete response is relevant since this could select a proportion of patients for which organ-preserving strategies might be possible, either by local excision [4,5], ISRCTN14422743) or a “wait-and-scan” strategy [6–8]. Since response to radiotherapy is dose dependent in rectal cancer, dose escalation may lead to higher complete response rates [9–11]. A recent mathematical prediction model on pCR-rate indicated that 50% of patients could reach pCR after 92 Gy and that response exponentially increased after 60 Gy [12]. This was in line with a prediction-curve based on a large systematic review on dose response in patients with LARC [3,12]. Nevertheless, dose-escalation trials using ≥60 Gy have not been systematically reviewed yet. Therefore, we conducted a systematic review and meta-analysis to quantify the pCR-rate after preoperative (chemo)radiation with doses of ≥60 Gy in patients with LARC. Furthermore, correlations between pCR-rate, acute grade ≥3 toxicity, chemotherapy, boost technique and surgical interval were studied.
Methods

Search strategy

The PRISMA guidelines for systematic review and meta-analysis were used to conduct this review [13]. We searched the electronic PubMed, EMBASE and Cochrane databases with the last search performed on April 10th 2014. Synonym terms for ‘radiotherapy’, ‘boost’ and ‘rectal cancer’ were used (see Supplement). The search was limited to articles published after 1988, because adjuvant treatment became progressively replaced by neo-adjuvant (chemo)radiation since. Duplicates were removed and additional papers were retrieved through cross referencing.

Study selection

All studies in primary LARC patients (T3-4N(x)M0/fixed tumors) receiving a preoperative physical radiation dose of ≥60 Gy (with at least 45 Gy external beam radiation therapy (EBRT)) to the whole tumor were eligible for inclusion. Original researches, in English, with available full texts were included. Studies without our primary endpoint, palliative intent, or with previously irradiated patients were excluded, as well as studies using contact radiotherapy and/or X-ray treatment (CXR).

Data extraction and quality assessment

The primary outcome was the proportion of patients scheduled for preoperative ≥60 Gy radiation that reached pCR. pCR was defined as absence of residual cancer cells in the resected specimen. This was calculated by intention-to-treat i.e. the number of patients with pCR divided by all patients scheduled for preoperative ≥60 Gy radiation. If not so provided by the authors, pCR-rate was calculated from the data. Corresponding authors were contacted in case of insufficient information.

Secondary outcomes were acute grade ≥3 toxicity, and resectability rate. All toxicity scores were redefined to the National Cancer Institute’s (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.0) [14], and presented as the percentages of patients experiencing acute grade ≥3 toxicity. Resectability rate was defined as the percentage of patients with resectable tumors after (chemo-)radiation divided by all patients scheduled for preoperative ≥60 Gy radiation. Furthermore, we extracted study-design, -size, demographics, the radiation protocol (total dose (EQD2-dose with α/β = 10 [12]), boost dose, radiation approach, margins, chemotherapy regimen (agent(s), administration protocol and doses), and time-to-surgery. Extraction was performed by two authors independently (J.P.M.B. and A.M.dH.). In case of discrepancy consensus was reached between authors.

Critical appraisal

Study quality was assessed by pre-defined criteria (Table 2) based on items listed in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [15]. Also study design, data presentation, and clinical characteristics that may have influenced the primary outcome were used. Quality assessment was also performed independently by two authors (J.P.M.B. and A.M.dH.). Studies were eligible for meta-analysis if at least a valid pCR-rate could be calculated.

Statistical methods

The R statistical environment (version 3.0.2, R Development Core Team, 2011) with ‘metafor’ package (version 1.9-1) was used for statistical analysis [16]. Potential publication bias was checked by funnel plots and rank correlation tests (Kendall’s tau). pCR-rate, grade ≥3 toxicity and resectability rate were logit transformed, pooled, re-transformed and presented as proportions with 95% confidence interval (CI). Heterogeneity was assessed by the I² statistic (i.e. estimated proportion of unexplained inter-study variance) prior to pooling. Random effects models, using a restricted maximum likelihood estimator, were used in case of large inter-study variance (I² > 65%) to calculate a pooled estimate. Otherwise mixed- (25 < I² < 65%) or (≤25%) fixed effects models were used. Robustness of the pooled estimate was addressed by two sensitivity analyses (SA). The first SA excluded studies with pCR-rates lower than the 15% which we took as a reference standard based on large meta-analyses [1,3], i.e. negative outliers. The second SA only included studies with an EQD2-dose of ≥60 Gy. Correlations between EQD2-dose and pCR-rate, toxicity and resectability, as well as between pCR-rate and chemotherapy, boost-approach and surgical-interval were visualized in scatter plots and formally tested by Pearson’s correlation test. P-values were considered significant if the p-value was below 0.05.

Results

In total 3377 articles were identified. After removing duplicates, 2765 articles were screened on title and abstract. Seventy-one remaining articles were screened on full text, of which 54 were excluded for the following reasons: no full text available (n = 20), studies not involving patients (n = 4), not including patients with LARC (n = 10), no curative setting (n = 3), only included previously irradiated patients (n = 1), preoperative dose of <60 Gy (n = 5), already included (non-unique) patient-population (n = 3), non-English articles (n = 2) and studies without our primary endpoint pCR (n = 6). One additional article was identified by cross-referencing. Finally, 18 studies (1106 patients) were included for systematic review, consisting of 7 prospective single/multiple arm studies, 3 RCTs, 2 NRCTs and 6 phase I/II trials (see Table 1 and Fig. 1) [17–34]. Five-hundred-thirty-nine patients (48.7% of identified patients) were scheduled for ≥60 Gy radiation with median of 21 patients per study (range 1–109). Median age ranged between 42 and 68 years. T-stage was reported in 9 studies for 342 of 539 patients (63.5%), with range 9.0–100%. Nodal status was reported in 6 studies for 321 patients (59.6%), with a range of 30.0–89.0%.

Treatment characteristics are summarized in Table 1. Total radiation dose varied between 60 and 75 Gy (EQD2 58.4–66.3 Gy), as an accumulation of standard EBRT (45–54 Gy) and boost dose (6–30 Gy). Twelve studies used EBRT only, 6 studies used brachytherapy only and two combined EBRT and brachytherapy. A simultaneous integrated boost (SIB) approach was used in 2 studies whereas four studies used a combination of SIB and sequential approaches. Target margins were mentioned in all but one study [21]. Most studies used 3–5 field box techniques with almost similar elective fields, predominantly defined by 1–1.5 cm anterior to the sacral wall, 1–2 cm outside the bony pelvis, the L5-S1 border and 3–5 cm caudal of the tumor. No studies used Intensity Modulated Radiotherapy (IMRT).

All but two studies administered 5-Fluorouracil (5-FU) based chemotherapy [21,26], namely 5-FU, Uracil-Tegafur (UFT) or Capecitabine, at varying doses (see Table 1). Leucovorin was added in six studies and OxaLaplatin in two.

One study did not report toxicity at all [30]. In the other studies toxicity was mostly scored according to NCI (10 studies), Radiation Therapy Oncology Group (RTOG, 2 studies), or Response Evaluation Criteria in Solid Tumors list (RECIST, one study) criteria. Four studies did not report specifically which toxicity criteria were used,
Table 1
Characteristics of the included studies (pSA = prospective single arm study, I/II = phase I/II trial, (N)RCT = (non)randomized controlled trial, BID = bis in die (twice daily), Br HDR = brachytherapy high-dose rate, EQD2 = Equivalent 2 Gy dose, 5-FU = Fluorouracil, UFT = Tegafur-uracil, Leu = Leucovorin, Oxi = Oxaliplatin, TEGAFOX = Uracil/ftorafur/leucovorin/Oxaliplatin, Cap = Capecitabine, n d.d. = in n daily doses, /d = per day, /wk = per week, SIB = simultaneous integrated boost, pCR = pathologic complete response).

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design (n)</th>
<th>Total number of study patients (n)</th>
<th>Unique boost treated patients (n)</th>
<th>Median age (yr) of total study population</th>
<th>Fractions (standard)</th>
<th>Fractions (boost)</th>
<th>Total dose (Gy)</th>
<th>EQD2 dose (total)</th>
<th>Boost approach</th>
<th>Chemotherapy dose</th>
<th>Maximal tumor distance from anal verge (cm)</th>
</tr>
</thead>
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<tr>
<td>Marks et al., 1993</td>
<td>pSA</td>
<td>52</td>
<td>57</td>
<td>31 ± 11/22 ± 2.5 45.0</td>
<td>5 x 1</td>
<td>60 61–64 EBRT</td>
<td>SIB</td>
<td>–</td>
<td>0–3</td>
<td>–</td>
<td>225 mg/m²/d d (≥30 mg/m² d)</td>
</tr>
<tr>
<td>Meade et al., 1995</td>
<td>NRCT</td>
<td>20</td>
<td>1</td>
<td>25 ± 1.8 45.0</td>
<td>9 ± 1.8</td>
<td>60 60 EBRT</td>
<td>Sequential</td>
<td>5-FU (+Leu)</td>
<td>1000 mg/m²/d for 4 days in weeks 1 and 4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Movsas et al., 1998</td>
<td>I/II</td>
<td>27</td>
<td>7</td>
<td>25 ± 1.8 45.0</td>
<td>14 ± 1.2</td>
<td>62 60 EBRT</td>
<td>Sequential</td>
<td>5-FU</td>
<td>–</td>
<td>225 mg/m²/d d</td>
<td>100.0 ± 10.0</td>
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<tr>
<td>Mohiuddin et al., 2000</td>
<td>NRCT</td>
<td>33</td>
<td>9</td>
<td>38 ± 1.2 BID 45.0</td>
<td>12 ± 1.2</td>
<td>60 56 EBRT</td>
<td>Sequential</td>
<td>5-FU</td>
<td>–</td>
<td>225 mg/m²/d d</td>
<td>100.0 ± 10.0</td>
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<td>36</td>
<td>18 ± 2.1 45.0</td>
<td>10.5 ± 2.1</td>
<td>60 60 EBRT</td>
<td>Sequential</td>
<td>64.0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pfeiffer et al., 2005</td>
<td>I/II</td>
<td>50</td>
<td>50</td>
<td>27 ± 2 45.0</td>
<td>3 ± 2</td>
<td>65 66 Brachy</td>
<td>Sequential</td>
<td>UFT + Leu</td>
<td>–</td>
<td>1000 mg/m²/d 3 d + 7.5 mg 3 d d d</td>
<td>–</td>
</tr>
<tr>
<td>Mohiuddin et al., 2006</td>
<td>RCT</td>
<td>106</td>
<td>16</td>
<td>38 ± 1.2 BID 45.0</td>
<td>12 ± 1.2</td>
<td>60 56 EBRT</td>
<td>Sequential</td>
<td>UFT + Leu</td>
<td>–</td>
<td>225 mg/m²/d d</td>
<td>100.0 ± 10.0</td>
</tr>
<tr>
<td>Movsas et al., 2006</td>
<td>I/II</td>
<td>22</td>
<td>21</td>
<td>25 ± 1.8 45.0</td>
<td>14 ± 1.2</td>
<td>62 60 EBRT</td>
<td>Sequential</td>
<td>5-FU</td>
<td>–</td>
<td>225 mg/m²/d d</td>
<td>100.0 ± 10.0</td>
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<tr>
<td>Ho-Pun-Cheung et al., 2007</td>
<td>pSA</td>
<td>70</td>
<td>29</td>
<td>25 ± 1.8 45.0</td>
<td>9 ± 1.8</td>
<td>60 60 EBRT</td>
<td>Sequential</td>
<td>5-FU + Cap</td>
<td>–</td>
<td>225 mg/m²/d d</td>
<td>100.0 ± 10.0</td>
</tr>
<tr>
<td>Sun Myint et al. 2007</td>
<td>pSA</td>
<td>16</td>
<td>16</td>
<td>25 ± 1.8 45.0</td>
<td>1 ± 0.2 Br HDR</td>
<td>75 61 Brachy</td>
<td>Sequential</td>
<td>5-FU / Cap</td>
<td>–</td>
<td>750/1000 mg/m² for 4 days in weeks 1 and 5 and 8 ± 25 mg/m² d</td>
<td>–</td>
</tr>
<tr>
<td>Jakobsen et al., 2008</td>
<td>pSA</td>
<td>35</td>
<td>35</td>
<td>27 ± 2 45.0</td>
<td>3 ± 2</td>
<td>65 66 EBRT</td>
<td>Urea + Brachy</td>
<td>Sequential</td>
<td>–</td>
<td>1000 mg/m² d 3 d + 225 mg 3 d d</td>
<td>–</td>
</tr>
<tr>
<td>Vestermark et al., 2008</td>
<td>pSA</td>
<td>52</td>
<td>36</td>
<td>27 ± 2 45.0</td>
<td>3 ± 2</td>
<td>60 60 EBRT</td>
<td>Sequential</td>
<td>Urea + Brachy</td>
<td>–</td>
<td>1000 mg/m² d 3 d + 225 mg 3 d d</td>
<td>–</td>
</tr>
<tr>
<td>Lindebjerg et al., 2009</td>
<td>MA</td>
<td>135</td>
<td>8</td>
<td>27 ± 2 45.0</td>
<td>3 ± 2</td>
<td>65 66 EBRT</td>
<td>Sequential</td>
<td>Brachy + Leu</td>
<td>–</td>
<td>1000 mg/m² d 3 d + 225 mg 3 d d</td>
<td>–</td>
</tr>
<tr>
<td>Malata et al., 2010</td>
<td>II</td>
<td>76</td>
<td>76</td>
<td>25 ± 2 45.0</td>
<td>5 ± 2</td>
<td>60 60 EBRT</td>
<td>Sequential</td>
<td>S-FU + Oxi</td>
<td>–</td>
<td>200 mg/m²/d 45 mg/m² wk</td>
<td>–</td>
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<tr>
<td>Jakobsen et al., 2012</td>
<td>I/II</td>
<td>243</td>
<td>109</td>
<td>28 ± 1.8 45.0</td>
<td>5 ± 2</td>
<td>60 60 EBRT</td>
<td>Sequential</td>
<td>S-FU + Brachy Urea</td>
<td>–</td>
<td>1000 mg/m² d 3 d + 225 mg 3 d d</td>
<td>–</td>
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<tr>
<td>Vestermark et al., 2012</td>
<td>I</td>
<td>18</td>
<td>16</td>
<td>27 ± 2 45.0</td>
<td>3 ± 2</td>
<td>60 60 Brachy</td>
<td>Sequential</td>
<td>S-FU + sequential</td>
<td>–</td>
<td>1000 mg/m² d 3 d + 225 mg 3 d d</td>
<td>–</td>
</tr>
<tr>
<td>Engineer et al., 2013</td>
<td>RCT</td>
<td>90</td>
<td>44</td>
<td>25 ± 1.8 45.0</td>
<td>11 ± 1.8</td>
<td>65 64 EBRT</td>
<td>Sequential</td>
<td>–</td>
<td>–</td>
<td>1000 mg/m² d 3 d + 225 mg 3 d d</td>
<td>–</td>
</tr>
</tbody>
</table>

* Additional data obtained through the corresponding author.
but did report if toxicity demanded treatment. Transformation to NCI criteria was chosen since it was predominant.

Interval to surgery varied between 2 and 10 weeks (median 7) after chemoradiation. Resectability ranged between 34.0 and 100%. Five studies reached 100% resectability [18,21,25,30,31]. Others ranged between 75.0 and 96.0% and one was limited to 34.0% [34]. Three studies did not report resectability rate. Most common reasons to omit surgery were disease progression, distant metastasis or patient refusal. Surgical complication data were scarce for the >60 Gy sub(group) specifically. Six studies reported wound infection, dehiscence or delayed healing problems in 0.0–16.0% [21,23,25,29,31,32], one patient required small bowel resection [18], and two studies reported surgical complications in all patients [18,34]. Eight studies used some form of standardized pathologic response assessment, of which four explicitly used the Mandard tumor regression grade (TRG) [35].

After critical appraisal 14 studies remained eligible for meta-analysis, representing 90.4% (487 of 539) of patients (Table 2). Unexplained inter-study variance ($I^2$) was low for pCR pooling (0.0%, 95% CI 0.0–84.0%) and intermediate for grade $>3$ toxicity and resectability pooling (66.2%, 95% CI 25.5–89.6%, and 80.3%, 95% CI 56.1–92.9%, respectively). Consequently, a fixed effects model was used to calculate the pCR-rate estimate, and a random effects model for the grade $>3$ toxicity and resectability estimates. pCR-rate varied considerably between studies, from 0.0 to 44.4%. The pooled pCR-rate estimate was 20.4% (95% CI 16.8–24.5%) (see Fig. 2). The funnel plot did not show asymmetry (Kendall’s tau = $-0.07$, $p = 0.74$) [36] (see Supplement). Additionally, the first sensitivity analysis, excluding negative outlier pCR-rates below 15%, estimated the pCR-rate at 22.9% (95% CI 18.7–27.6%) and the second sensitivity analysis, using only studies with EQD2 doses of >60 Gy, estimated the pCR-rate at 18.1% (95% CI 13.9–23.2%) (see Fig. 2).

Acute grade $>3$ toxicity for boost patients was reliably reported in 11 of 18 studies. Data on late toxicity specifically for boost patients were scarce and therefore not further discussed in this paper. Acute toxicity consisted mostly of gastro-intestinal complaints, dermatitis, leukopenia/neutropenia and pain. Grade $>3$ toxicity was low ($\leq 10$%) in seven studies, higher in three (13.6, 33.0 and 42.6%) and a single-patient study had 100% (see Table 1) [18]. There was no asymmetry in the funnel plot (Kendall’s tau = $–0.1$, $p = 0.76$) (see Supplement). The acute grade $>3$ toxicity estimate was 10.3% (95% CI 5.4–18.6%) (see Fig. 3). The resectability estimate was 89.5% (95% CI 78.2–95.3%) (see Fig. 3).

Total EQD2 dose did not correlate with acute grade $>3$ toxicity (Pearson $–0.17$, $p > 0.62$) or resectability (Pearson $–0.29$, $p < 0.33$). pCR-rate was not correlated with total EQD2 dose (Pearson 0.44, $p > 0.88$), chemotherapy (5-FU only vs. 5-FU + Oxaliplatin) (Pearson 0.06, $p > 0.83$), boost-approach type (EBRT, Brachy or EBRT/Brachy combination) (Pearson 0.06, $p > 0.85$), nor with length of interval between radiotherapy and surgery (Pearson 0.10, $p > 0.74$).

**Discussion**

This meta-analysis shows a pCR-rate of 20.4% after preoperative >60 Gy radiation in patients with LARC, which was associated with low (10.3%) acute grade $>3$ toxicity and a high resectability rate (89.5%). Furthermore, no correlation between pCR-rate and toxicity, resectability, boost approach, chemotherapy or surgical interval was found.

The calculated pCR-rate estimate of this meta-analysis is in line with the prediction of the previously mentioned mathematical and clinical dose–response prediction models. These models further predict an exponential pCR-rate increase, i.e. degree of tumor cell destruction, which occurs after linear dose-escalation above...
60 Gy. This is visualized by their S-shaped dose–response curve [3,12]. We also showed that dose-escalation ≥60 Gy yielded comparable toxicity-rates as observed in direct and indirect control groups after standard dose [24,32,34,37] or after SIB boost technique of 55.2 Gy [38]. Wiltshire et al. [11] also found a non-linear relation between dose-increase and toxicity, since their 40 Gy, 46 Gy, and 50 Gy dose levels were associated with 13%, 4%, and 14% acute grade 3 toxicity, respectively. Although we looked at a larger dose interval, toxicity remained comparable. None of the studies included in this meta-analysis used IMRT. However, modern radiation and/or planning techniques may further contribute to reduced toxicity due to dose reduction to healthy tissue (especially bowel-dose) [39]. Furthermore, we observed no confounding between type of concurrent chemotherapy (or radio-sensitizer) and pCR-rate. This was also previously illustrated in several studies that found comparable pCR-rates for different sources of 5-FU [40–44], or when Leucovorin was added as a synergistic agent [45]. Neither is there consistent evidence that combination chemotherapy of 5-FU with Oxaliplatin [46–50] or Irinotecan [51–53] significantly improved pCR-rates, since only the German CAO/ARO/AIO-04 trial found 17% vs. 13% pCR (odds ratio 1.40, 95% CI 1.02–1.92; \( p = 0.038 \)) with and without Oxaliplatin respectively [54]. Nevertheless, it is evident that these combined therapies increase acute grade ≥3 toxicity (mostly gastro-intestinal complaints, dermatitis and peripheral neuropathy). Therefore, we are confident that neither chemotherapy type nor its dose influenced the pooled pCR-rate estimate, which restrained us from calculating a biological effective dose for each chemotherapy type and its dose-level. We excluded studies using contact radiotherapy (CXR) since dose distribution is considerably different from other radiation methods. However, this technique could be used to deliver high doses to distal, small (less advanced), well-selected (remaining) lesions. Broad experience shows that CXR can however be safely combined with external-beam radiotherapy [55–59], and could improve ‘good response’ rates and sphincter preservation rates in those tumors [60].

The strength of this study is that it provides a reliable and robust pCR-rate estimate based on a systematic study selection and intention-to-treat analysis. Furthermore, the low heterogeneity between studies allowed to use a fixed-effects model to calculate a robust pCR-rate estimate, since this is a powerful tool to reveal a pattern of the true effects-size among more studies. Also, this could then be compared to a well-based estimate for a ‘control’ population [1,3]. Nevertheless, inter-study pCR variability was present and most likely depends on case-mix. However, such notable spread is not only present in our selected ‘boost population’ but is also present within the identified control populations presented by Maas et al. and Sanghera et al. [1,3]. Furthermore, all doses from different radiation treatments (EBRT-SIB, -sequential or brachytherapy) were recalculated to EQD2 doses to provide an optimal comparison method and dose–response analysis over all approaches together.

The limitations of this study concern study selection, reporting, pathological assessment and timing of surgery. Firstly, our critical appraisal excluded four studies from the meta-analysis because pCR-rates could not be recalculated from the provided data, leading to a smaller number of patients to pool. Nevertheless, we do not expect that those excluded studies would dramatically have influenced the pooled pCR-rate estimate since these studies represented only 9.6% \( (n = 52) \) of the original identified sample of 539 patients. Nor did studies with <60 Gy EQD2-doses influence pCR-rate estimates. This robustness was indicated by the small positive 2.5% and negative 2.3% pCR-rate shift after sensitivity analyses that excluded ‘negative outliers’ or studies with EQD2 doses ≥60 Gy, respectively. However, small numbers are unfortunately inherent to feasibility, dose-finding and early phase (I–II) trials which leaves the opportunity to further strengthen the evidence by conducting larger randomized dose-escalation trials. Secondly, we were not able to study the association between T- or N-stage and pCR-rates since for most studies response rate according to T-/N-stage was not reported. Third, the pCR-rate estimate might still be underestimated since pathologic response could only be obtained from operated patients. Despite our intention-to-treat analysis, and although the resectability rate was high, more patients might have experienced a complete response. However, we conservatively assumed all non-surgical patients to have non-pCR which might be incorrect
### pCR-rate

<table>
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<tr>
<th>Study</th>
<th>Reference line 15%</th>
<th>Study weight</th>
<th>Study estimate</th>
<th>95% Confidence Interval</th>
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<td></td>
<td>0.5%</td>
<td>25.0%</td>
<td>[1.3, 89.1%]</td>
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<td>3.2%</td>
<td>44.0%</td>
<td>[17.7, 74.9%]</td>
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<tr>
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<td></td>
<td>7.2%</td>
<td>16.0%</td>
<td>[7.7, 32.5%]</td>
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#### Pooled pCR-rate estimate

0.0% 20.4% [16.8, 24.5%]

### Sensitivity analysis of studies with \( \geq 15\% \) pCR rate

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<tr>
<th>Study</th>
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<th>Study weight</th>
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#### Pooled pCR-rate estimate

0.0% 22.9% [18.7, 27.6%]

### Sensitivity analysis of studies with \( \geq 60 \text{ Gy} \) EQD2

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#### Pooled pCR-rate estimate

0.0% 18.1% [13.9, 23.2%]

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Fig. 2. Meta-analysis forest plot of pCR-rates and pooled estimate in comparison to a reference line of control group (14.8%) [3] (pCR = pathological complete response).
since in some patients surgery was omitted for other reasons such as a worsened condition, newly diagnosed metastasis or patient’s refusal. Fourth, the pathologic assessment was different between studies, and therefore prone to bias. Ten of 14 included studies standardized assessment, of which 3 explicitly used Mandard’s score [35]. Others only mentioned that one pathologist assessed if there was ‘absence of viable tumor cells’ in the specimen. Fifth, destruction of solitary tumor cells may continue long after termination of radiotherapy, indicating that timing of surgery impacts response assessment. Three studies have shown increased pCR-rates when surgery was postponed from 8 to 11 weeks post-radiation (from 11.5 to 14.0%) [61], and when shorter surgical intervals are compared to intervals of >6–8, or >7, weeks (from 13.7 to 19.5%, and 16 to 28.0% respectively) [62,63]. A relative risk of 1.42 (1.19–1.68) for pCR was reported for intervals longer than 6–8 weeks as compared to intervals shorter than 6–8 weeks. Nevertheless, in our data we did not see an association between interval-length and pCR-rate, presumably because pCR-rate varied largely at each interval length with only a few studies available per interval-length point in the analysis. Such variation is common, and therefore often observed in systematic reviews on pCR-rates following CRT [1,3,64]. To further investigate the impact of prolonged intervals on pCR-rate and sphincter preservation, several randomized clinical trials are currently recruiting (GRECCAR6/ NCT01648894 [65] and NCT01037049). Nonetheless, if such presumed time-effects allow extrapolation to when doses are escalated, pCR-rates and organ-preservation might even further benefit when longer intervals prove to be safe. Sixth, only a single study reported interval between radiotherapy and brachytherapy, which did not allow further meta-analysis. Finally, accelerated treatment (higher dose per fraction, i.e. simultaneous integrated boost) increases the biological effective dose which may benefit response [66,67], especially when tumor-regrowth time is short [68,69]. Nevertheless, some of these accelerated schedules remain challenging because of considerable toxicity [19,24,70–72] and peri/post-operative complications [72,73]. It is likely that such toxicity originates from irradiation of surrounding tissues instead of the tumor, as a result of a previously acquired treatment plan.
not taking into account tumor-shrinkage during the course of radi- 
the most optimal schedule for high doses thus remains to be investigated in the future. 
In the future disease monitoring will become progressively important. 
To discover that some patients do not respond, and will thus not benefit from additional radiation, should not be kept until surgery. 
Response should rather be monitored all along neo-adjuvant treatment to prevent over-treatment and create the opportunity to adjust an ongoing treatment. 
This demands sensitive response-prediction tools employable concurrently to CRT. 
Such a non-invasive method capable of differentiating pathological good (TRG1–2) from bad/none responders (TRG3–5) early during CRT is diffusion-weighted MRI (DWI) \([74,75]\). At the same time, this creates opportunity to identify those tumors likely to benefit from a sequential radiation boost. 
Whereas the oncological outcome benefits for patients that reach pCR seems favorable, contradictory outcomes have been published after reaching a near pCR, ranging from good prognosis (comparable to pCR) \([27,67]\) to poor prognosis (comparable to poor pathological response) \([78–81]\). For these patients, with a proven radiation-sensitivity but near complete response, early response-assessment could form a future tool to select them to undergo additional boost radiation in order to further improve their response toward a cCR, which is in turn associated with better prognosis and anticipated improved quality-of-life if followed by an organ-preservation strategy. 
Dose escalation above 60 Gy for locally advanced rectal cancer results in high pCR-rates and acceptable early toxicity. This observation needs to be further investigated within larger randomized controlled phase 3 trials in the future. 

Conflict of interest statement

There are no actual or potential conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.08.035.

References


