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Original article

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

Johannes Peter Maarten Burbach [a,*,1], Annemarie Maria den Harder [b,1], Martijn Intven [a], Marco van Vulpen [a], Helena Marieke Verkooijen [c], Onne Reerink [a]

[a] Department of Radiation Oncology; [b] Department of Radiology; and [c] Trial Bureau Imaging Division, University Medical Center, Utrecht, The Netherlands

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ABSTRACT

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 (I^2 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.

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.

* Corresponding author at: Department of Radiation Oncology, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands.
E-mail address: j.p.m.burbach-2@umcutrecht.nl (J.P.M. Burbach).

[1] Authors contributed equally.

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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 (T3-4NxM0/fixed tumors) receiving a preoperative physical radiation dose of $\geqslant$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 $\geqslant$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 $\geqslant$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 $\geqslant$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 $\geqslant$3 toxicity. Resectability rate was defined as the percentage of patients with resectable tumors after (chemo-)radiation divided by all patients scheduled for preoperative $\geqslant$60 Gy radiation. Furthermore, we extracted study-design, -size, demographics, the radiation protocol (total dose (EQD2-dose with alfa/beta = 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 $\geqslant$3 toxicity and resectability rate were logit transformed, pooled, re-transformed and presented as proportions with 95% confidence interval (CI). Heterogeneity was assessed by the I^2 statistic (i.e. estimated proportion of unexplained inter-study variance) prior to pooling. Random effects models, using a restricted maximum likelihood estimator, were used in case of large inter-study variance ($I^2 \geqslant 65\%$) to calculate a pooled estimate. Otherwise mixed- ($25 < I^2 < 65\%$) or ($\leqslant$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 $\geqslant$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 $\geqslant$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 two 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 Oxaliplatin 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,

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