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Systematic review

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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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.

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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,

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).

Author, year	Study design	Total number of study patients (*n*)	Unique boost treated patients (*n*)	Median age (yr) of total study population	Fractions (standard)	Dose (standard) (Gy)	Fractions (boost)	Total dose (Gy)	EQD2 dose (total)	Boost approach	Boost timing	Chemo-therapy in boost treated patients	Chemotherapy dose	Maximal tumor distance from anal verge (cm)	T3 (%)	T4 (%)	N+ (%)	Interval to surgery (planned/ median)	Resect-ability rate (%)	Percentage acute grade ⩾3 toxicity for ⩾60 Gy (sub)group (% grade 3/grade 4)	Number of pCR events (boost patients only)	Percentage pCR (*n*)
Marks et al., 1993	pSA	52	–	57	31 × 1.8/22 × 2.5	45.0	5 x1	60	61–64	EBRT	SIB	–	–	0–3	–	–	–	4–8/–	100.0	– (–/–)	–	–
Meade et al., 1995	NRCT	20	1	68	25 × 1.8	45.0	9 × 1.8	60	60	EBRT	Sequential	5-FU (+Leu)	225 mg/m^2 d.d. (+30 mg/m^2 d.d.)	–	90.0	10.0	30.0	4–8/–	100.0	100 (–/100)	0	0.0
Movsas et al., 1998	I/II	27	7	61	25 × 1.8	45.0	14 × 1.2 BID	62	60	EBRT	Sequential	5-FU	1000 mg/m^2/d for 4 days in weeks 1 and 4	12	78.0	32.0	–	4–6/–	–	85.7 (71.4/ 14.3)	–	–
Mohiuddin et al., 2000*	NRCT	33	9	64	38 × 1.2 BID	50.0	12 × 1.2 BID	60	56	EBRT	Sequential	5-FU	225 mg/m^2 d.d.	–	–	–	–	6–8/–	77.0	33 (33/0)	4	44.4
Rouanet et al., 2002*	pSA	43	36	64	18 × 2.1	37.8	10.5 × 2.1	60	60	EBRT	Sequential	–	–	6	84.0	16.0	30.0	2/–	100.0	– (–/–)	7	16.3
Pfeiffer et al., 2005*	I/II	18	14	65	27 × 2	48.6	3 × 2	60	60	EBRT	SIB + sequential	UFT + Leu	150–300 mg/m^2/ d + 22.5 mg/d	–	–	–	–	6/5.7	78.0	5.6 (5.6/0)	1	7.1
Jakobsen et al., 2006*	pSA	50	50	61	27 × 2	54.0	3 × 2; 5 Br HDR	65	66	Brachy	Sequential	UFT + Leu	100 mg/m^2 3 d.d. + 7.5 mg 3 d.d.	10	100.0	0.0	70.0	–/–	96.0	6.0 (6.0/0)	13	26.0
Mohiuddin et al., 2006*	RCT	106	16	57	38 × 1.2 BID	45.6	12 × 1.2 BID	60	56	EBRT	SIB	5-FU	225 mg/m^2 d.d.	9	71.0	29.0	–	4–10/7	92.0	42.6 (–/–)	5	31.3
Movsas et al., 2006	II	22	21	64	25 × 1.8	45.0	14 × 1.2 BID	62	60	EBRT	Sequential	5-FU	1000 mg/m^2/d for 4 days in weeks 1 and 6	12	9.0	91.0	–	4–6/–	100.0	13.6 (–/–)	0	0.0
Ho-Pun-Cheung et al., 2007	pSA	70	29	64	25 × 1.8	45.0	9 × 1.8	60	60	EBRT	Sequential	–	–	–	–	–	–	10/–	–	– (–/–)	–	–
Sun Myint et al. 2007	pSA	16	16	–	25 × 1.8	45.0	1 × 10 Br HDR	75	61	Brachy	Sequential	5-FU / Cap	750/1000 mg/m^2 for 4 days in weeks 1 and 5 or 825 mg/ m^2/d	–	–	–	–	6–8/–	–	– (–/–)	7	43.8
Jakobsen et al., 2008*	pSA	35	35	65	27 × 2	54.0	3 × 2; 5 Br HDR	65	66	EBRT + Brachy	Sequential	UFT + Leu	100 mg/m^2 3 d.d. + 22.5 mg 3 d.d.	10	77.0	33.0	77.0	8/–	94.2	5.7 (5.7/0)	7	20.0
Vestermark et al., 2008*	II	52	36	60	27 × 2	48.6	3 × 2	60	60	EBRT	SIB + sequential	UFT + Leu	100 mg/m^2 3 d.d. + 22.5 mg 3 d.d.	–	–	–	–	6/7.9	75.0	5.3 (5.3/0)	3	8.3
Lindebjerg et al., 2009*	MA	135	8	65	27 × 2	60.0	3 × 2 + 5 Br HDR	60–65	66	EBRT + Brachy	SIB + sequential	5-FU + Leu	100 mg/m^2 3 d.d. + 22.5 mg d.d.	10	–	–	–	8/–	100.0	– (–/–)	1	12.5
Maluta et al., 2010	II	76	76	60	25 × 2	50.0	5 × 2	60	60	EBRT	Sequential	5-FU + Oxi	200 m/m^2/d + 45 mg/m^2/wk	12	89.0	11.0	54.0	4–6/–	100.0	1.3 (1.3/0)	18	23.7
Jakobsen et al., 2012*	RCT	243	109	63	28 × 1.8	50.4	2 × 5 Br HDR	60	62	Brachy	Sequential	UFT + Leu (Denmark) or 5-FU (Canada)	100 mg/m^2 3 d.d. + 22.5 mg 3 d.d. (Denmark) or 225/mg/ m2/d (Canada)	10	84.0	16.0	89.0	8/–	92.6	10 (10/0)	20	18.3
Vestermark et al., 2012*	I	18	16	62	27 × 2	48.6	3 × 2	60	60	Brachy	SIB + sequential	TEGAFOX (UFT/Leu/Oxi)	*pre-RT* 100 mg/m2 3 d.d. + 7.5 mg 3 d.d. on day 1–14 + Oxi 130 mg/m^2. *Concurrent* 100 mg/m^2 3 d.d. + 22.5 mg 3 d.d. + 30–60 mg/ m^2/wk increasing with 10 mg/m^2/wk	–	–	–	–	⩾6/8.5	–	– (–/–)	5	31.3
Engineer et al., 2013	RCT	90	44	42	25 × 1.8	45.0	11 × 1.8	65	64	EBRT	Sequential	–	–	–	–	–	–	6–8/10	34.0	4.8 (4.8/0)	5	11.4

* Additional data obtained through the corresponding author.

Table 2
Critical appraisal and eligibility assessment for meta-analysis. y = yes, – = no, na = not applicable.

Author, year	Identification of LARC subgroup with ⩾60 Gy (y/n)	Standard chemotherapy protocol (y/n/na)	Surgical interval reported (y/n)	Standardized pathologic response assessment (y/n)	Reasons for drop-out and/or not undergoing surgery (y/n/na)	TNM stage reported (y/n/partly)	Acute grade ⩾3 toxicity for boost patients only (y/n)	pCR recalculation possible (y/n)	Meta-analysis inclusion
Marks et al., 1993	N	na	Y	N	na	N	N	N	–
Meade et al., 1995	Y	N	Y	Y	Y	Y	Y	Y	Yes
Movsas et al., 1998	Y	Y	Y	N	Y	N	Y	N	–
Mohiuddin et al., 2000*	N	N	Y	N	Y	N	Y	Y	Yes
Rouanet et al., 2002*	N	na	Y	N	na	Y	N	Y	Yes
Pfeiffer et al., 2005*	Y	N	Y	N	Y	N	Y	Y	Yes
Jakobsen et al., 2006*	Y	Y	N	Y	na	y	Y	Y	Yes
Mohiuddin et al., 2006*	Y	Y	Y	Y	Y	Partly	Y	Y	Yes
Movsas et al., 2006	Y	Y	Y	Y	Y	N	N	Y	Yes
Ho-Pun-Cheung et al., 2007	N	na	Y	Y	na	N	N	N	–
Sun Myint et al., 2007	N	N	Y	N	na	N	N	Y	–
Jakobsen et al., 2008*	Y	Y	Y	Y	Y	Partly	Y	Y	Yes
Vestermark et al., 2008*	Y	Y	Y	Y	Y	N	Y	Y	Yes
Lindebjerg et al., 2009*	Y	Y	Y	Y	na	Partly	N	Y	Yes
Maluta et al., 2010	Y	Y	Y	Y	na	Y	Y	Y	Yes
Jakobsen et al., 2012*	Y	N	Y	Y	Y	Partly	N	Y	Yes
Vestermark et al., 2012*	Y	N	Y	Y	Y	Partly	Y	Y	Yes
Engineer et al., 2013	Y	na	N	N	Y	N	Y	Y	Yes

* 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 (⩽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

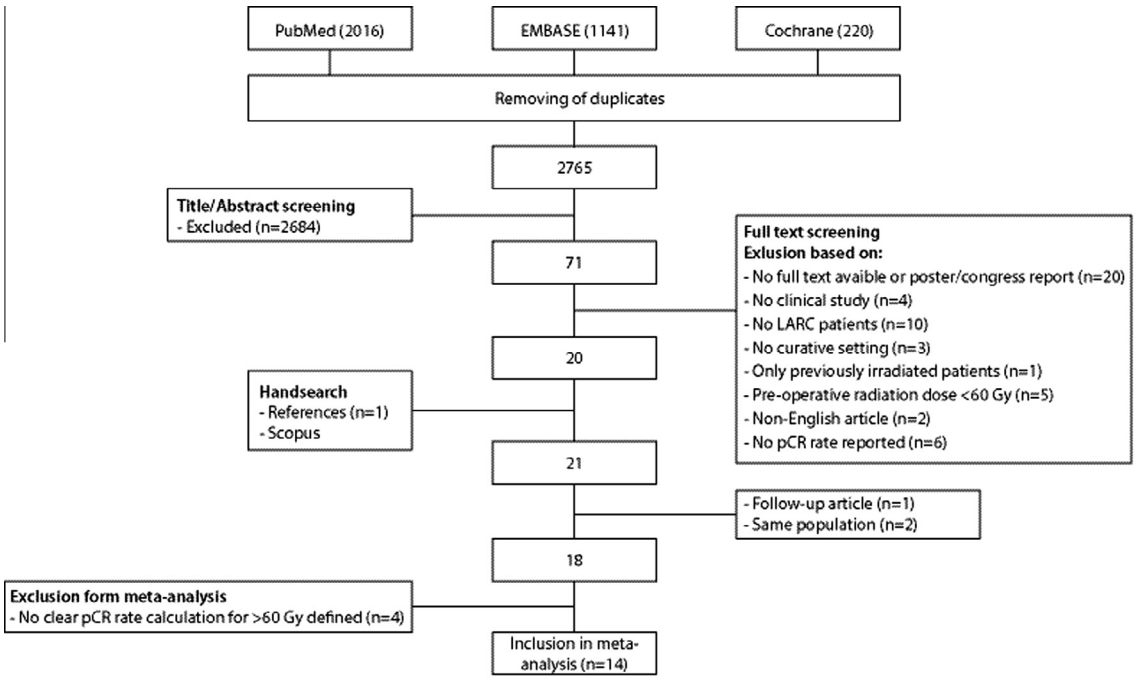

Fig. 1. Flow-chart of the study selection procedure.

60 Gy. This is visualized by their S-shaped dose–response curve [3,12]. We also showed that dose-escalation $\geqslant$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 $\geqslant$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 $\geqslant$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 $\geqslant$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

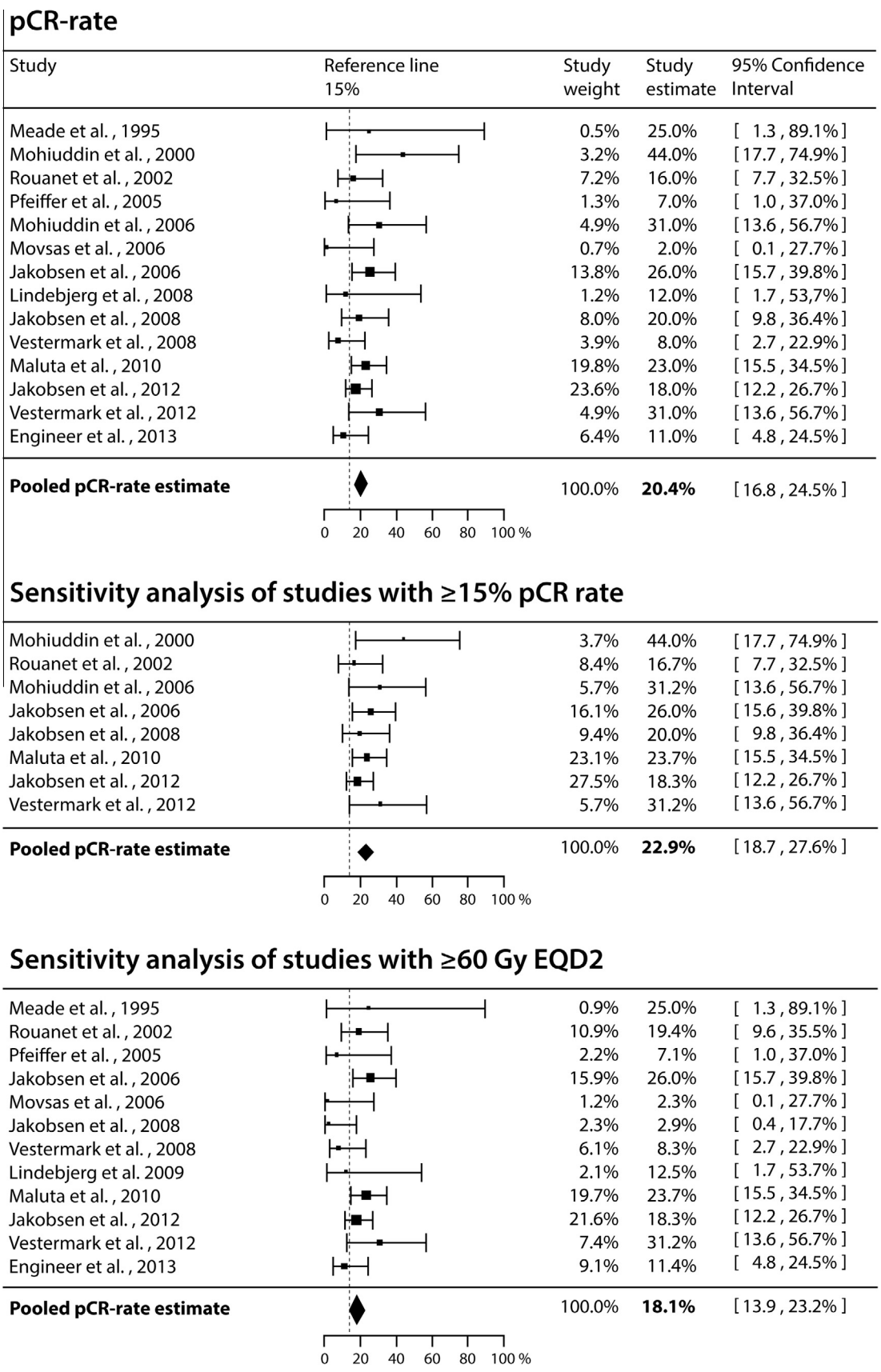

Fig. 2. Meta-analysis forest plot of pCR-rates and pooled estimate in comparison to a reference line of control group (14.8%) [3] (pCR = pathological complete response).

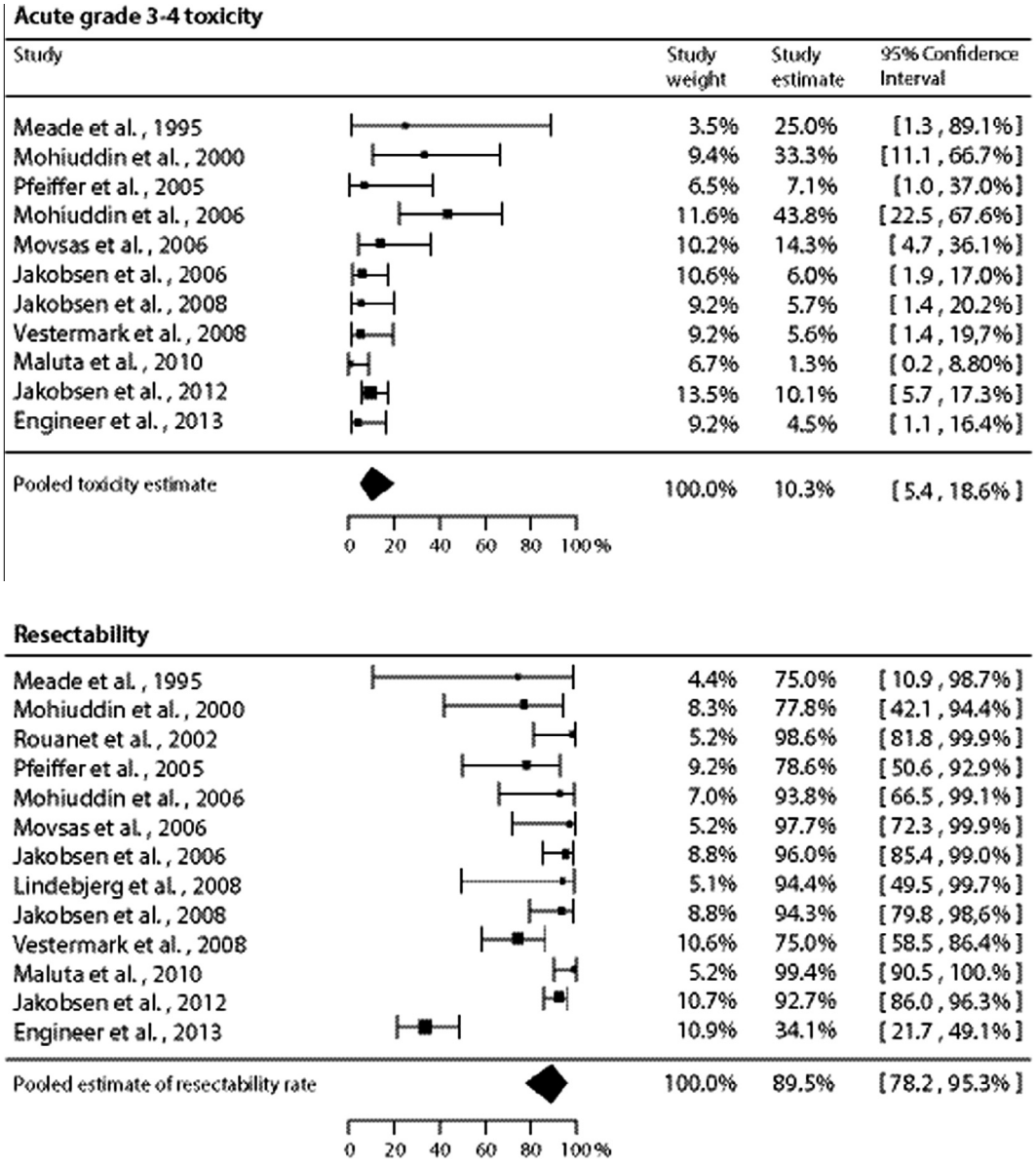

Fig. 3. Forest plot of available acute grade ⩾3 toxicity and resectability with pooled estimate.

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 radiation. 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 benefit for patients that reach pCR seems favorable, contradictory outcomes have been published after reaching a near pCR, ranging from good prognosis (comparable to pCR) [2,76,77] 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

[1] Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol 2010;11:835–44.

[2] Vecchio FM, Valentini V, Minsky BD, Padula GD, Venkatraman ES, Balducci M, et al. The relationship of pathologic tumor regression grade (TRG) and outcomes after preoperative therapy in rectal cancer. Int J Radiat Oncol Biol Phys 2005;62:752–60.

[3] Sanghera P, Wong DW, McConkey CC, Geh JI, Hartley A. Chemoradiotherapy for rectal cancer: an updated analysis of factors affecting pathological response. Clin Oncol 2008;20:176–83.

[4] Bokkerink GM, de Graaf EJ, Punt CJ, Nagtegaal ID, Rutten H, Nuyttens JJ, et al. The CARTS study: chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery. BMC Surg 2011;11:34.

[5] Pucciarelli S, De Paoli A, Guerrieri M, La Torre G, Maretto I, De Marchi F, et al. Local excision after preoperative chemoradiotherapy for rectal cancer: results of a multicenter phase II clinical trial. Dis Colon Rectum 2013;56:1349–56.

[6] Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011;29:4633–40.

[7] Smith JD, Ruby JA, Goodman KA, Saltz LB, Guillem JG, Weiser MR, et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. Ann Surg 2012;256:965–72.

[8] Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Sabbagh C, Lynn PB, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys 2014;88:822–8.

[9] Chan AK, Wong AO, Langevin J, Jenken D, Heine J, Buie D, et al. Preoperative chemotherapy and pelvic radiation for tethered or fixed rectal cancer: a phase II dose escalation study. Int J Radiat Oncol Biol Phys 2000;48:843–56.

[10] Overgaard M, Overgaard J, Sell A. Dose-response relationship for radiation therapy of recurrent, residual, and primarily inoperable colorectal cancer. Radiother Oncol 1984;1:217–25.

[11] Wiltshire KL, Ward IG, Swallow C, Oza AM, Cummings B, Pond GR, et al. Preoperative radiation with concurrent chemotherapy for resectable rectal cancer: effect of dose escalation on pathologic complete response, local recurrence-free survival, disease-free survival, and overall survival. Int J Radiat Oncol Biol Phys 2006;64:709–16.

[12] Appelt AL, Ploen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys 2013;85:74–80.

[13] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W65–94.

[14] Cancer EOfRaTo. Common terminology criteria for adverse events, v1.0–v4.03; 1994.

[15] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370:1453–7.

[16] Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1–48.

[17] Marks G, Mohiuddin M, Masoni L. The reality of radical sphincter preservation surgery for cancer of the distal 3 cm of rectum following high-dose radiation. Int J Radiat Oncol Biol Phys 1993;27:779–83.

[18] Meade PG, Blatchford GJ, Thorson AG, Christensen MA, Ternent CA. Preoperative chemoradiation downstages locally advanced ultrasound-staged rectal cancer. Am J Surgery 1995;170:609–12 (discussion 12–3).

[19] Movsas B, Hanlon AL, Lanciano R, Scher RM, Weiner LM, Sigurdson ER, et al. Phase I dose escalating trial of hyperfractionated pre-operative chemoradiation for locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 1998;42:43–50.

[20] Mohiuddin M, Regine WF, John WJ, Hagihara PF, McGrath PC, Kenady DE, et al. Preoperative chemoradiation in fixed distal rectal cancer: dose time factors for pathological complete response. Int J Radiat Oncol Biol Phys 2000;46:883–8.

[21] Rouanet PS-AB, Lemanski C, Senesse P, Gourgou S, Quenet F, et al. Restorative and nonrestorative surgery for low rectal cancer after high-dose radiation: long-term oncologic and functional results. Dis Colon Rectum 2002;45:305–13.

[22] Pfeiffer P. High-dose radiotherapy and concurrent UFT plus l-leucovorin in locally advanced rectal cancer: a phase I trial. Acta Oncol 2005;44:224–9.

[23] Jakobsen A, Mortensen JP, Bisgaard C, Lindebjerg J, Hansen JW, Rafaelsen SR. Preoperative chemoradiation of locally advanced T3 rectal cancer combined with an endorectal boost. Int J Radiat Oncol Biol Phys 2006;64:461–5.

[24] Mohiuddin M, Winter K, Mitchell E, Hanna N, Yuen A, Nichols C, et al. Randomized phase II study of neoadjuvant combined-modality chemoradiation for distal rectal cancer: radiation therapy oncology group trial 0012. J Clin Oncol 2006;24:650–5.

[25] Movsas B, Diratzouian H, Hanlon A, Cooper H, Freedman G, Konski A, et al. Phase II trial of preoperative chemoradiation with a hyperfractionated radiation boost in locally advanced rectal cancer. Am J Clin Oncol 2006;29:435–41.

[26] Ho-Pun-Cheung A, Assenat E, Thezenas S, Bibeau F, Rouanet P, Azria D, et al. Cyclin D1 gene G870A polymorphism predicts response to neoadjuvant radiotherapy and prognosis in rectal cancer. Int J Radiat Oncol Biol Phys 2007;68:1094–101.

[27] Sun Myint A, Lee CD, Snee AJ, Perkins K, Jelley FE, Wong H. High dose rate brachytherapy as a boost after preoperative chemoradiotherapy for more advanced rectal tumours - the clatterbridge experience. Clin Oncol (R Coll Radiol) 2007;19:711–9.

[28] Jakobsen A, Mortensen JP, Bisgaard C, Lindebjerg J, Rafaelsen SR, Bendtsen VO. A COX-2 inhibitor combined with chemoradiation of locally advanced rectal cancer: a phase II trial. Int J Colorectal Dis 2008;23:251–5.

[29] Vestermark LW, Jacobsen A, Qvortrup C, Hansen F, Bisgaard C, Baatrup G, et al. Long-term results of a phase II trial of high-dose radiotherapy (60 Gy) and UFT/l-leucovorin in patients with non-resectable locally advanced rectal cancer (LARC). Acta Oncol 2008;47:428–33.

[30] Lindebjerg J, Spindler KL, Ploen J, Jakobsen A. The prognostic value of lymph node metastases and tumour regression grade in rectal cancer patients treated with long-course preoperative chemoradiotherapy. Colorectal Dis 2009;11:264–9.

[31] Maluta S, Romano M, Dall'oglio S, Genna M, Oliani C, Pioli F, et al. Regional hyperthermia added to intensified preoperative chemo-radiation in locally advanced adenocarcinoma of middle and lower rectum. Int J Hyperthermia 2010;26:108–17.

[32] Jakobsen A, Ploen J, Vuong T, Appelt A, Lindebjerg J, Rafaelsen SR. Dose-effect relationship in chemoradiotherapy for locally advanced rectal cancer: a randomized trial comparing two radiation doses. Int J Radiat Oncol Biol Phys 2012;84:949–54.

[33] Vestermark LW, Jensen HA, Pfeiffer P. High-dose radiotherapy (60 Gy) with oral UFT/folinic acid and escalating doses of oxaliplatin in patients with non-resectable locally advanced rectal cancer (LARC): a phase I trial. Acta Oncol 2012;51:311–7.

[34] Engineer R, Mohandas KM, Shukla PJ, Shrikhande SV, Mahantshetty U, Chopra S, et al. Escalated radiation dose alone vs. concurrent chemoradiation for

locally advanced and unresectable rectal cancers: results from phase II randomized study. Int J Colorectal Dis 2013;28:959–66.
[35] Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer 1994;73:2680–6.
[36] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[37] Swellengrebel HA, Marijnen CA, Verwaal VJ, Vincent A, Heuff G, Gerhards MF, et al. Toxicity and complications of preoperative chemoradiotherapy for locally advanced rectal cancer. Br J Surg 2011;98:418–26.
[38] Engels B, Platteaux N, Van den Begin R, Gevaert T, Sermeus A, Storme G, et al. Preoperative intensity-modulated and image-guided radiotherapy with a simultaneous integrated boost in locally advanced rectal cancer: report on late toxicity and outcome. Radiother Oncol 2014;110:155–9.
[39] Parekh A, Truong MT, Pashtan I, Qureshi MM, Martin NE, Nawaz O, et al. Acute gastrointestinal toxicity and tumor response with preoperative intensity modulated radiation therapy for rectal cancer. Gastrointest Cancer Res 2013;6:137–43.
[40] Hofheinz RD, Wenz F, Post S, Matzdorff A, Laechelt S, Hartmann JT, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012;13:579–88.
[41] Chan AK, Wong AO, Jenken DA. Preoperative capecitabine and pelvic radiation in locally advanced rectal cancer–is it equivalent to 5-FU infusion plus leucovorin and radiotherapy? Int J Radiat Oncol Biol Phys 2010;76:1413–9.
[42] Yerushalmi R, Idelevich E, Dror Y, Stemmer SM, Figer A, Sulkes A, et al. Preoperative chemoradiation in rectal cancer: retrospective comparison between capecitabine and continuous infusion of 5-fluorouracil. J Surg Oncol 2006;93:529–33.
[43] Das P, Lin EH, Bhatia S, Skibber JM, Rodriguez-Bigas MA, Feig BW, et al. Preoperative chemoradiotherapy with capecitabine versus protracted infusion 5-fluorouracil for rectal cancer: a matched-pair analysis. Int J Radiat Oncol Biol Phys 2006;66:1378–83.
[44] Saif MW, Hashmi S, Zelterman D, Almhanna K, Kim R. Capecitabine vs continuous infusion 5-FU in neoadjuvant treatment of rectal cancer. A retrospective review. Int J Colorectal Dis 2008;23:139–45.
[45] Bin Q, Li J, Liao C, Cao Y, Gao F. Oral uracil-tegafur plus leucovorin vs fluorouracil bolus plus leucovorin for advanced colorectal cancer: a meta-analysis of five randomized controlled trials. Colorectal Dis 2011;13:837–45.
[46] Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol 2010;28:1638–44.
[47] Arbea L, Martinez-Monge R, Diaz-Gonzalez JA, Moreno M, Rodriguez J, Hernandez JL, et al. Four-week neoadjuvant intensity-modulated radiation therapy with concurrent capecitabine and oxaliplatin in locally advanced rectal cancer patients: a validation phase II trial. Int J Radiat Oncol Biol Phys 2012;83:587–93.
[48] Dipetrillo T, Pricolo V, Lagares-Garcia J, Vrees M, Klipfel A, Cataldo T, et al. Neoadjuvant bevacizumab, oxaliplatin, 5-fluorouracil, and radiation for rectal cancer. Int J Radiat Oncol Biol Phys 2012;82:124–9.
[49] Martin LK, Bekaii-Saab T. Optimizing neoadjuvant therapy for rectal cancer with oxaliplatin. J Natl Compr Can Netw 2013;11:298–307 (quiz).
[50] O'Connell MJ, Colangelo LH, Beart RW, Petrelli NJ, Allegra CJ, Sharif S, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from national surgical adjuvant breast and bowel project trial R-04. J Clin Oncol 2014;32:1927–34.
[51] Hofheinz RD, von Gerstenberg-Helldorf B, Wenz F, Gnad U, Kraus-Tiefenbacher U, Muldner A, et al. Phase I trial of capecitabine and weekly irinotecan in combination with radiotherapy for neoadjuvant therapy of rectal cancer. J Clin Oncol 2005;23:1350–7.
[52] Klautke G, Kuchenmeister U, Foitzik T, Ludwig K, Prall F, Klar E, et al. Concurrent chemoradiation with capecitabine and weekly irinotecan as preoperative treatment for rectal cancer: results from a phase I/II study. Br J Cancer 2006;94:976–81.
[53] Willeke F, Horisberger K, Kraus-Tiefenbacher U, Wenz F, Leitner A, Hochhaus A, et al. A phase II study of capecitabine and irinotecan in combination with concurrent pelvic radiotherapy (CapIri-RT) as neoadjuvant treatment of locally advanced rectal cancer. Br J Cancer 2007;96:912–7.
[54] Rodel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012;13:679–87.
[55] Gerard JP, Chapet O, Ramaioli A, Romestaing P. Long-term control of T2–T3 rectal adenocarcinoma with radiotherapy alone. Int J Radiat Oncol Biol Phys 2002;54:142–9.
[56] Gerard JP, Ortholan C, Benezery K, Ginot A, Hannoun-Levi JM, Chamorey E, et al. Contact X-ray therapy for rectal cancer: experience in Centre Antoine-Lacassagne, Nice, 2002–2006. Int J Radiat Oncol Biol Phys 2008;72:665–70.
[57] Maingon P, Guerif S, Darsouni R, Salas S, Barillot I, d'Hombres A, et al. Conservative management of rectal adenocarcinoma by radiotherapy. Int J Radiat Oncol Biol Phys 1998;40:1077–85.
[58] Sun Myint A, Grieve RJ, McDonald AC, Levine EL, Ramani S, Perkins K, et al. Combined modality treatment of early rectal cancer: the UK experience. Clini Oncol 2007;19:674–81.
[59] Gerard JP, Romestaing P, Chapet O. Radiotherapy alone in the curative treatment of rectal carcinoma. Lancet Oncol 2003;4:158–66.
[60] Gerard JP, Chapet O, Nemoz C, Hartweig J, Romestaing P, Coquard R, et al. Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: the lyon R96–02 randomized trial. J Clin Oncol 2004;22:2404–9.
[61] Sloothaak DA, Geijsen DE, van Leersum NJ, Punt CJ, Buskens CJ, Bemelman WA, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. Br J Surg 2013;100:933–9.
[62] Petrelli F, Sgroi G, Sarti E, Barni S. Increasing the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer: a meta-analysis of published studies. Ann Surg 2013;19:2833.
[63] Wolthuis AM, Penninckx F, Haustermans K, De Hertogh G, Fieuws S, Van Cutsem E, et al. Impact of interval between neoadjuvant chemoradiotherapy and TME for locally advanced rectal cancer on pathologic response and oncologic outcome. Ann Surg Oncol 2012;19:2833–41.
[64] Foster JD, Jones EL, Falk S, Cooper EJ, Francis NK. Timing of surgery after long-course neoadjuvant chemoradiotherapy for rectal cancer: a systematic review of the literature. Dis Colon Rectum 2013;56:921–30.
[65] Lefevre JH, Rousseau A, Svrcek M, Parc Y, Simon T, Tiret E, et al. A multicentric randomized controlled trial on the impact of lengthening the interval between neoadjuvant radiochemotherapy and surgery on complete pathological response in rectal cancer (GRECCAR-6 trial): rationale and design. BMC cancer 2013;13:417.
[66] Thames Jr HD, Peters LJ, Withers HR, Fletcher GH. Accelerated fractionation vs. hyperfractionation: rationales for several treatments per day. Int J Radiat Oncol Biol Phys 1983;9:127–38.
[67] Withers HR. Biologic basis for altered fractionation schemes. Cancer 1985;55:2086–95.
[68] Ang KK, Peters LJ, Weber RS, Maor MH, Morrison WH, Wendt CD, et al. Concomitant boost radiotherapy schedules in the treatment of carcinoma of the oropharynx and nasopharynx. Int J Radiat Oncol Biol Phys 1990;19:1339–45.
[69] Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988;27:131–46.
[70] Freedman GM, Meropol NJ, Sigurdson ER, Hoffman J, Callahan E, Price R, et al. Phase I trial of preoperative hypofractionated intensity-modulated radiotherapy with incorporated boost and oral capecitabine in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2007;67:1389–93.
[71] Kim DY, Kim TH, Jung KH, Chang HJ, Lim SB, Choi HS, et al. Preoperative chemoradiotherapy with concomitant small field boost irradiation for locally advanced rectal cancer: a multi-institutional phase II study (KROG 04–01). Dis Colon Rectum 2006;49:1684–91.
[72] Myerson RJ, Valentini V, Birnbaum EH, Cellini N, Coco C, Fleshman JW, et al. A phase I/II trial of three-dimensionally planned concurrent boost radiotherapy and protracted venous infusion of 5-FU chemotherapy for locally advanced rectal carcinoma. Int J Radiat Oncol Biol Phys 2001;50:1299–308.
[73] Janjan NA, Crane CN, Feig BW, Cleary K, Dubrow R, Curley SA, et al. Prospective trial of preoperative concomitant boost radiotherapy with continuous infusion 5-fluorouracil for locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2000;47:713–8.
[74] Intven M, Reerink O, Philippens ME. Diffusion-weighted MRI in locally advanced rectal cancer: pathological response prediction after neo-adjuvant radiochemotherapy. Strahlenther Onkol 2013;189:117–22.
[75] Lambrecht M, Vandecaveye V, De Keyzer F, Roels S, Penninckx F, Van Cutsem E, et al. Value of diffusion-weighted magnetic resonance imaging for prediction and early assessment of response to neoadjuvant radiochemotherapy in rectal cancer: preliminary results. Int J Radiat Oncol Biol Phys 2012;82:863–70.
[76] Beddy D, Hyland JM, Winter DC, Lim C, White A, Moriarty M, et al. A simplified tumor regression grade correlates with survival in locally advanced rectal carcinoma treated with neoadjuvant chemoradiotherapy. Ann Surg Oncol 2008;15:3471–7.
[77] Agarwal A, Chang GJ, Hu CY, Taggart M, Rashid A, Park IJ, et al. Quantified pathologic response assessed as residual tumor burden is a predictor of recurrence-free survival in patients with rectal cancer who undergo resection after neoadjuvant chemoradiotherapy. Cancer 2013;119:4231–41.
[78] Swellengrebel HA, Bosch SL, Cats A, Vincent AD, Dewit LG, Verwaal VJ, et al. Tumour regression grading after chemoradiotherapy for locally advanced rectal cancer: a near pathologic complete response does not translate into good clinical outcome. Radiother Oncol 2014.
[79] Gosens MJ, Klaassen RA, Tan-Go I, Rutten HJ, Martijn H, van den Brule AJ, et al. Circumferential margin involvement is the crucial prognostic factor after multimodality treatment in patients with locally advanced rectal carcinoma. Clin Cancer Res 2007;13:6617–23.
[80] Rodel C, Martus P, Papadoupolos T, Fuzesi L, Klimpfinger M, Fietkau R, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005;23:8688–96.
[81] Gavioli M, Luppi G, Losi L, Bertolini F, Santantonio M, Falchi AM, et al. Incidence and clinical impact of sterilized disease and minimal residual disease after preoperative radiochemotherapy for rectal cancer. Dis Colon Rectum 2005;48:1851–7.