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A systematic review comparing radiation toxicity after various endorectal techniques

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ABSTRACT

PURPOSE: A clinical complete response is seen after neoadjuvant chemoradiation for rectal tumors in 15%–20% of patients. These patients can potentially be spared mutilating total mesorectal excision surgery through a watch-and-wait policy. Recent studies show that dose escalation by a radiation boost increases the clinical complete response rate. The boost dose to the tumor can be administered through external beam radiotherapy or through internal radiotherapy using techniques like contact therapy, low-dose-rate or high-dose-rate brachytherapy (BT). However, limited information is available concerning treatment-related toxicity of these techniques. With this systematic review, we aim to summarize and compare published data concerning acute and late toxicity after contact X-ray therapy (CXT) and BT for rectal cancer.

METHODS AND MATERIALS/RESULTS: Thirty-eight studies reporting toxicity after endorectal radiation techniques for rectal cancer were included, resulting in 3682 patients for analysis. Direct comparison of toxicity by the different radiation modes was hampered by various combinations of endorectal techniques, a lack of clear reporting of toxicity scores, dose prescription, technique used, and treated volumes. ≥ Grade 3 rectal toxicity was reported in 2.9% of patients having received only CXT; 6.3% of patients who received only BT had Grade 3 rectal toxicity, and BT also caused Grade 3 urinary toxicity in 1 patient.

CONCLUSION: All techniques reported some ≥ Grade 3 toxicity. Toxicity after CXT was confined to the rectum, whereas after BT, urogenital toxicity and skin toxicity were seen as well. Unfortunately, few specific conclusions could be drawn regarding the dose-related risk of toxicity for the various techniques due to nonuniform reporting strategies and missing information. To enable future comparisons and improvements, the endorectal radiation field urgently needs consensus guidelines on dose reporting, dose prescription, treatment volume specification, and toxicity reporting.

Keywords: Endorectal brachytherapy; HDR; LDR; Contact therapy; Toxicity; Rectal cancer

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Introduction

Colorectal cancer is one of the leading causes of cancer-related deaths in Europe (1). In the Netherlands, approximately one-third of the patients diagnosed with colorectal cancer are diagnosed with rectal cancer (2). The mainstay of rectal cancer treatment is surgery according to the Total Mesorectal Excision (TME) principle. In locally advanced tumors, TME surgery is generally preceded by neoadjuvant radiotherapy or chemoradiation as these have been shown to improve locoregional control (3, 4). Unfortunately, TME surgery may result in significant long-term morbidity. Patients with distally located rectal tumors often face an abdominoperineal resection resulting in a permanent colostomy (5). Moreover, patients who are able to receive a low-anterior resection and retain their anal sphincter, thus avoiding permanent colostomy, still can experience significant comorbidities such as fecal incontinence, painful defecation, as well as sexual and urinary dysfunction (6). Besides, TME surgery is not always possible in the elderly and frail patients, as high postoperative mortality remains a point of concern in this group of patients (7).

For 15%–20% of patients who receive delayed surgery after neoadjuvant chemoradiation, a pathologic complete response is seen, meaning that there is no residual viable tumor at pathology examination of the resection specimen (8). By identifying those with a clinical complete response (cCR) before surgery, some patients could avoid surgery through a "watch-and-wait policy," which has been shown to be safe (3, 7). These findings demonstrate that in selected patients, cure can be achieved while avoiding TME surgery and its associated toxicity, and that, even patients who are inoperable due to comorbidity still have a chance of cure.

Recent studies have shown that dose escalation increases the complete response rate (9). The boost dose to the tumor can be administered through external beam radiotherapy (EBRT) or through internal radiotherapy, the latter using different techniques like contact X-ray therapy (CXT), low-dose-rate (LDR) brachytherapy (BT), or high-dose-rate (HDR) BT. Potential excess toxicity due to the increased dose can be limited through reduction of irradiated volumes (10). This provides, despite recent advances in modern EBRT techniques, at least a theoretical advantage of internal radiotherapy techniques over EBRT, as dose can be delivered more locally. However, internal radiotherapy is only used to a limited extent due to uncertainties and lack of clear target volume definitions and structured toxicity analyses.

In the 1970s, CXT was used and proven effective to treat small rectal tumors due to its ability to give significant dose to a small area using low-energy X-rays while largely sparing the surrounding healthy tissue. This technique was named after its greatest advocate, J. Papillon, who achieved 90% cCR in more than 300 T1N0 rectal tumors (11). Later, CXT was also used in combination with EBRT for larger tumors (11). In 2009, a new contact machine named Papillon 50 was introduced in Europe. The X-ray energy used is 50 kVp, and the source-skin distance is usually 3.8 cm. With these factors, the 50% isodose is seen at 7 mm from the applicator end surface and encompasses 5 cm^3 volume, illustrating a very sharp dose fall-off (11). This allows significant sparing of the surrounding healthy tissue, and the benefit of allowing higher cumulative doses to be delivered, which could potentially provide better tumor control. The rectal applicator diameter can be 3, 2.5, or 2.2 cm, depending on the lesion size. Fraction doses are usually 30 Gy or 20 Gy prescribed on the tumor surface with 2 weeks between fractions, and total doses of CXT can range between 60 Gy and 110 Gy, depending on the size of the lesion and whether the boost is combined with another modality such as interstitial BT. CXT can be given without general anesthesia and is able to be performed on an outpatient basis (11, 12).

BT is usually used under general anesthesia, but less invasive techniques can often be performed under sedation or even local anesthesia. The prescribed dose can be delivered at an LDR or an HDR. To deliver the dose to the treatment volume, often an intraluminal applicator, an interstitial technique or a combination of both is used. With interstitial BT, the rapid dose fall-off can, by optimally placing the interstitial needles, theoretically be as pronounced as for CXT.

LDR BT is often given using an interstitial technique using a ^{192}Iridium implant that delivers LDR radiation, allowing for continuous DNA repair of sublethal damage in normal tissues, potentially leading to better sparing of the healthy tissue. It can be given using two different techniques, depending on the tumor's distance from the anal verge. Tumors within 6 cm of the anal verge can be treated with a perineal template through which needles are placed. More proximal tumors can be treated via the "fork technique" by loading preloaded ^{192}Iridium needles through a rigid proctoscope or a transrectal applicator (13). The method of dose prescription varies among series (14).

HDR BT allows for HDR radiation locally in a short period of time and can be delivered via an intraluminal applicator and/or interstitial needles transrectally or through the perineum. Due to the ability of using flexible catheters, it is possible to reach tumors located at 10 cm from the anal verge. The use of surgical clips can facilitate the localization of the tumor (15). After the applicator/needles has/have been placed, patients may receive a CT scan after which the tumor and all organs at risk can be delineated. After this, a treatment plan is made and approved, followed by giving the treatment itself using a remote afterloading unit with a ^{192}Iridium stepping source. Dose prescription varies among series. Total boost dose can be between 8 and 30 Gy with a fraction dose of 4–7 Gy per session at weekly or biweekly intervals (16, 17). The clinical target volume can be determined depending on gross tumor volume, and the radiation dose can be prescribed at various points, such as 5 mm–2 cm from the applicator

surface or other locations, making it difficult to compare doses.

These radiotherapy boost techniques prove equally effective in increasing the rate of complete response after chemoradiation (9). However, very limited information is available concerning the treatment-related toxicity of these techniques, such as rectal bleeding. Before these boost techniques can be widely advocated, it is important to show that they do not bring unwanted toxicities that could outweigh the benefits of sparing patients from radical surgery. With this systematic review, we aim to summarize and compare the data that have been published concerning acute and late toxicity after CXT and/or different forms of BT for rectal cancer.

Methods

Protocol and registration

This article was written using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Checklist of items to include when reporting a systematic review and meta-analysis 2009 (18).

Search strategy

A combined search was performed in PubMed on February 12th 2017 and was updated on November 25th 2017 by the first two authors. PubMed search terms included rectal cancer, rectal neoplasms [MESH], rectal neoplasms/radiotherapy [MESH], X-ray therapy [MESH], HDR, LDR, toxicity, contact therapy, BT, endorectal BT, and/or endoluminal therapy. Additional articles were selected based on identification from reference lists or included when it was a new important publication after our last search.

Study selection

Published articles were selected and evaluated by the first two authors. Studies were eligible when reporting in English, experimental or observational studies, reporting toxicity of the various techniques, and a publication date between 1985 and 2017. We determined 1985 as the cutoff value, due to differences in standard treatment for rectal cancer and advances in the technical aspects of radiation oncology in the recent decades. Studies clearly only reporting about toxicity or complications after surgery were excluded. Conference abstracts were not included. First, eligibility was determined based on title and abstract screening. Remaining articles were selected based on full-text screening. Articles reporting reirradiation for a locoregional recurrence were also excluded.

Types of endorectal radiation techniques

Techniques included in this systematic review are CXT using 50 kV, HDR BT, and LDR BT. These techniques were eligible when used alone, in combination, or combined with EBRT.

Data extraction and analysis

Data were extracted by full-text screening using a self-made format reporting on (*1*) basic study demographics (country, study design, years of patient inclusion, number of patients, and stage of disease); (*2*) treatment demographics (type of treatment, use of concurrent chemotherapy, median length of followup and primary end points); (*3*) acute and late toxicity reporting (reporting toxicity tool, grade and/or type, number of patients involved, and percentage if available); and (*4*) risk of bias assessment. Acute toxicity was defined as side effects occurring during or within 90 days after the last radiotherapy treatment. Late toxicity was defined as side effects occurring after 90 days receiving the last radiotherapy treatment. Data collection and search were performed by the first two authors. Descriptive analyses of the articles were performed.

Risk of bias in individual studies

Bias reporting of randomized controlled trials (RCTs) was performed using the Cochrane Risk of Bias tool from Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (19). Items reported are random sequence generation; allocation concealment; blinding; incomplete outcome data; and selective reporting. Bias reporting in observational studies was performed using The Newcastle-Ottawa Scale for cohort studies (20).

Results

Study selection

Search of PubMed resulted in 245 records. Based on title and abstract screening, 205 publications were excluded due to various reasons (Fig. 1). After full-text screening, 38 references met the inclusion criteria and were included in this systematic review (9,11,13–17,22–52). The performed search was last updated in November 2017.

Study characteristics

A table of the study demographics can be found in the Supplementary Material (Table S1). A total of 3682 patients from 38 studies are included in this systematic review. Included studies are mainly observational studies (n = 33) of which, 22 retrospective and 11 prospective. This review also includes four RCTs in which the Lyon R 96-02 Randomized Trial is reported twice, once by Gerard *et al.* in 2004 and once by Ortholan *et al.* in 2011, the last article describing the 10-year results (17, 27, 33, 37). Years of patient inclusion range from 1951 to 2014. As the CXT and HDR BT techniques have not changed significantly in

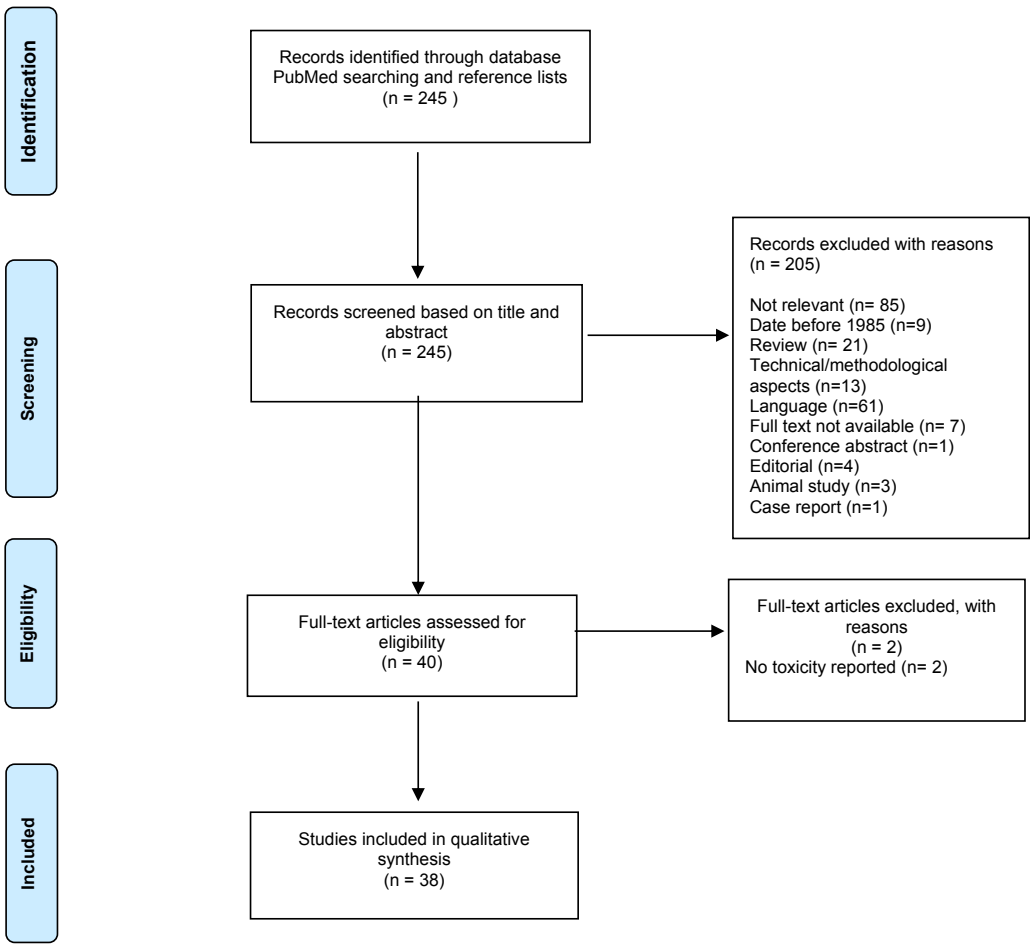

Fig. 1. Study selection process in PRISMA 2009 flow diagram. (21) Adapted from www.prisma-statement.org.

the last decades, this long inclusion period was accepted to prevent the exclusion of important and relevant data. The median of the given median followup lengths was 35 months (range 7–132 months). Seven articles did not report their followup length or used the mean followup instead and were thus excluded from this calculation. Stages of disease include early stages to locally advanced stages of rectal cancer, including some T4 tumors and local recurrences. In some studies, metastasized patients were also included, for which the treatment usually had a palliative purpose. Different Tumor, Node and Metastasis classifications were used, meriting caution when interpreting the stages.

Treatment characteristics

Included treatment options for this review were CXT, HDR BT, and LDR BT for rectal cancer. Various combinations of these and other techniques, as well as various doses, were used in the selected articles. Twenty-four articles including 2562 patients reported rectal surgery in some or all of included patients.

Details on the given treatment can be found in Table 1 (Appendix). In general, CXT was given alone or in addition to EBRT and/or a BT boost (11,13,23–28,34–38,40,48–51). A variety of treatment combinations can be observed in the studies by Gerard *et al.* (11,13,25–28), Frin *et al.* (45), Lavertu *et al.* (34), Maingon *et al.* (36), Ortholan *et al.* (37), and Schild *et al.* (38). They compare various combinations of surgery, CXT, EBRT, and BT. Most often, CXT was preceded or followed by EBRT and/or a BT boost.

BT is used in most of the studies in a more or less prominent role, as it is often given as sole treatment, after previous irradiation, as a boost to EBRT, or along with CXT (9,11,13–17,22,24–34,36–43,46,48,50,51). Of these articles, there were 25 studies using HDR BT and four studies using LDR BT (see Table 1, Appendix). HDR BT was delivered either through an endorectal applicator (multichannel or single channel) or through interstitial needles.

Radiation dose, dose prescription, and the number of fractions per treatment are very heterogeneous and can be found in Table 1 (Appendix). The total dose of radiotherapy delivered with CXT ranges from 20 to 155 Gy. Total dose of BT ranges from 5 to 80 Gy. Used EBRT schemes are mainly 39 Gy/13 fx or 45–50.4 Gy/25–28 fx. Important to note, CXT and BT are two different techniques

Table 1
Treatment characteristics

Reference	Treatment arms	Followed by resection?	Pelvic field radiation?	Endorectal modality used	Type of applicator for brachytherapy	Dose prescription for endorectal modality	RT dose (Gy)	Chemotherapy	Median length of followup (mo)
Appelt, Bentzen *et al*. 2015 (22)	CRT ± boost	Yes	Yes	HDR BT	Endorectal applicator	Not reported	50−60 Gy/28−30 fx ± HDR BT boost (5 Gy or 10 Gy) or EBRT boost (6, 10, or 12 Gy)	Yes	Not reported
Appelt, Ploen *et al*. 2015 (9)	CRT + boost	Some	Yes	HDR BT	Cylinder endorectal applicator	5 Gy at 1 cm from the applicator's surface along the applicator to cover the entire tumor length	60 Gy/30 fx to tumor, 50 Gy/30 fx to pelvic nodes + HDR BT boost (5 Gy)	Yes	23,9
Christoforidis *et al*. 2009 (23)	CXT	No	No	CXT	NA	NA	90 Gy/3 fx (range 60−190 Gy). If no cCR response, 1−2 extra fx	Not reported	69
Coatmeur *et al*. 2004 (24)	CXT ± HDR BT	No	No	CXT, HDR BT	Empty metallic needles inserted submucosally into tumor bed, then filled with 192-Ir wires	10 Gy/day calculated at distance of 0.5 cm from central plane of implant	CXT 95 Gy/3−4 fx, BT 24 Gy	Not reported	Not reported
Corner *et al*. 2010 (15)	Radical: CRT + HDR BT or HDR BT alone Palliative: HDR BT	No	Some	HDR BT	Cylinder endorectal applicator or flexible catheter for high tumors	1 cm from surface of cylinder or from source axis when catheter was used	Radical: CRT 45 Gy/25 fx, HDR BT boost 12 Gy at 1 cm in 2 fx; HDR BT alone up to 36 Gy/6 fx. Palliative: 10 Gy	Some	Not reported
Dhadda *et al*. 2017 (44)	CXT ± CRT	Some	Some	CXT	NA	NA	CXT 110 Gy/4fx or 90 Gy/3 fx + EBRT 45 Gy/25 fx	Some	24
El-Sayed *et al*. 2008 (16)	CRT + HDR BT boost	Yes	Yes	HDR BT	Cylinder endorectal applicator	0.5 cm from applicator surface	CRT 45 Gy/25 fx, HDR BT 8 Gy/2 fx	Yes	14
Frin *et al*. 2017 (45)	(1) T1N0: TLE + CXT ± CRT (2) T2-T3N0: CXT + CRT (3) T3N0-2: CXT + CRT	Some	Some	CXT, HDR BT	Not reported	Not reported	Tumor: CXT 90 Gy/3 fx, normal mucosa 60 Gy/3 fx, 30 Gy when combined with CRT; EBRT 50 Gy/25 fx	Yes	(1) 63 (2) 60 (3) 40
Gerard, Ayzac *et al*. 1996 (26)	CXT ± HDR BT boost	No	No	CXT, HDR BT	Perineal or endoluminal fork implant	85% isodose of basal dose according to Paris System	CXT median dose 92 Gy/5 fx, HDR BT 25 Gy	Not reported	43
Gerard, Roy *et al*. 1996 (25)	CXT + EBRT ± HDR BT boost	No	No	CXT, HDR BT	Perineal or endoluminal fork implant	85% isodose of basal dose according to Paris System	CXT 70 Gy/3 fx, EBRT 43 GY/3fx, HDR BT 20 Gy	None	46

(*Continued*)

Table 1 (*continued*)

Reference	Treatment arms	Followed by resection?	Pelvic field radiation?	Endorectal modality used	Type of applicator for brachytherapy	Dose prescription for endorectal modality	RT dose (Gy)	Chemotherapy	Median length of followup (mo)
Gerard *et al.* 2002 (13)	CXT + EBRT + HDR BT boost	Some	Yes	CXT, HDR BT	Perineal or endoluminal fork implant	85% isodose of basal dose according to Paris System	CXT 80 Gy/3 fx, EBRT 43 Gy/13 fx, HDR BT 20 Gy	None	54
Gerard *et al.* 2004 (27)	EBRT alone VS. EBRT + CXT boost. If cCR, 4 weeks after EBRT, HDR BT I-192 boost	Yes	Yes	CXT, HDR BT	Perineal or endoluminal fork implant	Not reported	EBRT 39 Gy/13 fx, CXT 85 Gy/3 fx, HDR BT 25 Gy	Some	35
Gerard *et al.* 2008 (28)	(1) T1N0: TLE + CXT (2) T2-T3N0−N2M0: CXT + EBRT ± chemo. No surgery. (3) T3 (or low T2) N0−N1M0: CXT + EBRT followed by surgery. (4) Cfr (3) followed by TLE	Some	Some	CXT	Perineal implant	85% isodose of basal dose according to Paris System	(1) CXT 45−50 Gy/3 fx (2) CXT 75−110 Gy/3−5 fx, EBRT 45−50 Gy/25 fx 3 and 4) cfr (2).	Some	25
Gerard *et al.* 2015 (11)	CXT + EBRT ± LDR BT boost	Some	Yes	CXT, LDR BT	Perineal or endoluminal fork implant	According to Paris system	CXT 85 Gy/3 fx ± 4th fraction of 15 Gy; EBRT 39 Gy/3 fx; LDR BT 20 Gy/1 fx	Some	63
Grimard *et al.* 2009 (29)	Local excision + HDR BT	No	No	HDR BT	Single or double plane perineal implant	85% isodose of basal dose according to Paris System	HDR BT 45−50 Gy	Not reported	74,9
Hershman *et al.* 2002 (48)	(1) CXT/EBRT + CXT boost (2) LE + EBRT + CXT boost (3) EBRT/CRT + LE (4) LE alone	Some	Some	CXT	NA	NA	EBRT 39 Gy/13 fx or 45 Gy/20 fx; CXT not reported	Some	33
Hoskin *et al.* 2004 (30)	(1) Radical: CRT + HDR BT boost or HDR BT monotherapy. (2) Palliative: HDR BT	No	Some	HDR BT	Cylinder endorectal applicator or flexible catheter for high tumors	1 cm from surface of cylinder or from source axis when catheter was used	(1) Radical: CRT 45 Gy/25 fx, HDR BT boost 12 Gy, HDR BT monotherapy 36 Gy/6 fx (2) Palliative: HDR BT 10 Gy/1 fx	Not reported	Not reported
Hull *et al.* 1994 (49)	CXT	No	No	CXT	NA	NA	CXT 60−180 Gy/3−6 fx	Not reported	52 (mean)
Ishikawa *et al.* 2004 (31)	EBRT + HDR BT	Yes	Yes	HDR BT	Hand-made applicator	1−2 cm from source	EBRT 30 Gy/15 fx, HDR BT 30−40 Gy	Some	79

(*Continued*)

Table 1 (*continued*)

Reference	Treatment arms	Followed by resection?	Pelvic field radiation?	Endorectal modality used	Type of applicator for brachytherapy	Dose prescription for endorectal modality	RT dose (Gy)	Chemotherapy	Median length of followup (mo)
Jakobsen *et al*. 2006 (32)	CRT + HDR BT boost	Yes	Yes	HDR BT	Rigid cylinder tube	1 cm from surface of cylinder	EBRT 60 Gy/30 fx to CTV1, 48.6 Gy/27 fx to CTV2; HDR BT 5 Gy	Yes	Not reported
Jakobsen *et al*. 2012 (33)	EBRT alone VS. EBRT + HDR BT boost. IF HDR not possible, then EBRT boost.	Yes	Yes	HDR BT	Single-channel cylinder endorectal applicator or central flexible tube with eight catheters	1 cm from the applicator surface	EBRT 50.4 Gy/28 fx, HDR BT 10 Gy/2 fx, EBRT boost 12 Gy/6 fx	Yes	Not reported
Lavertu *et al*. 2003 (34)	(1) CXT (2) CXT + EBRT (3) CXT+ 2 implants LDR BT Ir-192	Some	Some	CXT, LDR BT	Not reported	Not reported	(1) CXT 20−155 Gy/ 1−5 fx (2) CXT 20−155 Gy/ 1−5 fx + EBRT 45−50.4 Gy/25− 28 fx (3) CXT 20−155 Gy/ 1−5 fx + LDR BT 20−25 Gy	Not reported	102
Lavery *et al*. 1987 (35)	CXT	No	No	CXT	NA	NA	80−150 Gy/3−6 fx	Not reported	31
Maingon *et al*. 1998 (36)	(1) CXT (2) CXT + BT (3) EBRT + CXT (4) EBRT + BT	No	Some	CXT, BT	Transrectal or transperineal metallic needles	0.5 cm from central plane of implant	(1) CXT 90−120 Gy 3−4 fx (2) CXT 90−120 Gy/ 3−4 fx + BT 10 Gy (3) EBRT 30 Gy/10 fx + CXT 40− 70 Gy/1−2 fx (4) EBRT 30 Gy/10 fx + BT 15−35 Gy	Not reported	65
Omidvari *et al*. 2015 (14)	(1) LDR BT + CRT (2) CRT	Yes	Yes	LDR BT	Cylinder endorectal applicator	0.5 cm from applicator surface	(1) LDR BT 15 Gy/3 fx + CRT 45− 50.4 Gy/25 fx (2) CRT 45−50.4 Gy/ 25 fx	Yes	Not reported
Ortholan *et al*. 2012 (37)	Preoperative EBRT alone vs EBRT + CXT. If cCR, HDR BT I-192 boost	Yes	Yes	CXT, HDR BT	Perineal or endoluminal fork implant	Not reported	EBRT 39 Gy/13 fx, CXT 85 Gy/3 fx. If cCR, HDR BT boost 25 Gy	Some	132
Papillon *et al*. 1992 (50)	CXT + LDR BT boost	Some	No	CXT, LDR BT	Endoluminal fork implant	Not reported	CXT 100−120 Gy/4 fx; LDR BT 20 Gy	Not reported	>5 y
Rauch *et al*. 2001 (51)	CXT ± HDR BT	No	No	CXT, HDR BT	Endoluminal fork implant	85% reference isodose of the Paris System, allowing to treat a 1-cm thick volume.	CXT 100 Gy/3−5 fx; HDR BT 20 Gy	Not reported	82 (mean)

(*Continued*)

Table 1 (*continued*)

Reference	Treatment arms	Followed by resection?	Pelvic field radiation?	Endorectal modality used	Type of applicator for brachytherapy	Dose prescription for endorectal modality	RT dose (Gy)	Chemotherapy	Median length of followup (mo)
Rijkmans *et al*. 2017 (46)	EBRT + HDR BT at dose levels 5–8 Gy	No	Yes	HDR BT	Flexible OncoSmart applicator, multichannel	CT planning, 100% isodose around CTV	EBRT (39 Gy/13 fx) + HDR BT (5–8 Gy/1 fx)	None	30
Schild *et al*. 1996 (38)	(1) CXT (2) CXT + HDR BT (3) CXT + EBRT	No	No	CXT, HDR BT	Iridium implants, no further specification	Not reported	(1) CXT 20–155 Gy/1–4 fx (2) CXT 40–155 Gy/1–4 fx)+ HDR BT 20–25 Gy (3) CXT 40–155 Gy/1–4 fx + EBRT 45 Gy–50.4 Gy/25–28 fx	Not reported	55
Sischy *et al*. 1985 (47)	(1) CXT (2) CXT + HDR BT (3) EBRT + CXT	No	Some	CXT, HDR BT	Radium needles of forks afterloaded with Cesium wires	At 1 cm	(1) CXT 120 Gy/4 fx (2) CXT 120 Gy/4 fx + HDR BT 15–20 Gy (3) EBRT 40–50 Gy + course of CXT	Not reported	Not reported
Smith *et al*. 2012 (39)	(1) preop HDR BT (2) preop CRT	Yes	Some	HDR BT	Flexible endorectal applicator	Not reported	(1) preop HDR BT (Ir-192 26 Gy/4 fx) (2) preop CRT (50.4 Gy/28 fx) 3D-RT or IMRT	Some	7, 12, 15 (HDR BT, 3DRT, IMRT, respectively)
Sun Myint *et al*. 2010 (40)	(1) preop CRT + preop HDR BT boost ± CXT (2) preop CRT + postop HDR BT boost (3) modified CRT or EBRT	Yes	Yes	HDR BT, CXT	Multichannel endorectal applicator	1 cm from surface of applicator	(1) CRT 45 Gy/25 fx + preop HDR BT 10 Gy ± CXT 30–50 Gy (2) CRT 45 Gy/25 fx + postop HDR BT 10 Gy	Yes	17
Sun Myint *et al*. 2017 (52)	(1) CXT alone (2) EBRT + CXT	some	some	CXT	NA	NA	CXT no more than 90 Gy/3 fx; EBRT 45 Gy/25 fx	some	32
Tunio *et al*. 2010 (17)	(1) CRT + HDR BT boost (2) CRT + EBRT boost	Yes	Yes	HDR BT	Single-channel endorectal applicator	1 cm from surface of applicator	(1) CRT 45 Gy/25 fx + HDR BT boost 11–14 Gy/2 fx (2) CRT 45 Gy/25 fx + EBRT boost 16.2 Gy/3 fx	Yes	18

(*Continued*)

Table 1 (*continued*)

Reference	Treatment arms	Followed by resection?	Pelvic field radiation?	Endorectal modality used	Type of applicator for brachytherapy	Dose prescription for endorectal modality	RT dose (Gy)	Chemotherapy	Median length of followup (mo)
Vuong *et al.* 2002 (41)	Preop HDR BT ± postop CRT EBRT	Yes	Yes	HDR BT	Multichannel endorectal applicator	Tumor radial margins with intramesorectal deposits when seen on MRI	Preop HDR BT 26 Gy/4 fx ± post-op CRT 45 Gy/25 fx	Some	29
Vuong *et al.* 2007 (42)	Preop HDR BT ± postop CRT EBRT	Yes	Some	HDR BT	Multichannel endorectal applicator	PTV	Preop HDR BT 26 Gy/4 fx ± postop CRT 45 Gy/25 fx	Some	60
Yanagi *et al.* 1997 (43)	(1) Preop HDR BT moderate dose (2) Preop HDR BT high dose (3) Surgery	Yes	No	HDR BT	Single-channel endorectal applicator	Not reported	(1) Preop HDR BT 16–40 Gy (2) Preop HDR BT 40–80 Gy (3) Only surgery	Not reported	(1) 49.5 (2) 60 (3) 47.5

BT = brachytherapy; HDR = high-dose-rate; CXT = contact X-ray therapy; EBRT = external beam radiotherapy; cCR = clinical complete response; LDR = low-dose-rate; RT = radiotherapy; IMRT = intensity-modulated radiotherapy; PTV = planning target volume.

regarding, among other factors, radiation delivery. The prescribed total dose of BT is not per definition equal to the same prescribed dose when using CXT. Therefore, the differences in radiation administration and dose prescription make dose comparison between the various endorectal techniques and among the various used BT techniques difficult.

Patients received chemotherapy additionally to their radiation treatment in 19 of 39 articles (Table 1, Appendix), usually in combination with EBRT. Several articles did not report whether or not chemotherapy was given or not. Within these 19 studies with chemotherapy, not all patients received chemotherapy. Most commonly administered chemotherapies were 5-fluorouracil and capecitabine.

Thirty-two studies reported on acute toxicity, and 29 studies reported on late toxicity, as shown in Table 2 (Appendix).

Observed end points of the studies include pathologic and/or cCR, organ/sphincter preservation, evaluation of anorectal function, time to surgical resection, change in carcinoembryonic antigen level after neoadjuvant therapy, overall survival, treatment failure, local recurrence, locoregional/pelvic control, distant recurrence, disease-free survival, progression-free survival, palliation, toxicity, and efficacy and safety.

Acute and late toxicity of CXT and BT

The Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute is the most frequently used toxicity-scoring tool (n = 13), although different versions were used, probably relating to the time period in which the toxicity was reported. Nineteen studies did not report the tool used for toxicity reporting, and six studies used a different scoring system. A summary of the observed treatment-related adverse events per study can be found in Table 2 (Appendix). A detailed description of toxicity per treatment modality can be found in the following sections. As probably the most clinically relevant parameter, a separate description and comparison of late ≥ Grade 3 toxicity of the various treatments and treatment combinations are provided. For the purpose of providing a form of comparison, the CTCAE toxicity-scoring tool is used to compare studies in the analysis.

Contact X-ray therapy

Observed acute toxicities in the studies using CXT include mucositis, proctitis with associated symptoms, rectal pain, diarrhea, rectal stenosis, actinic ulcers, and urgency. The occurrence of acute toxicity ranges from none to more than half of the patients. Some studies, such as the studies by Gerard *et al.* (13,25–27), report that there was no acute toxicity after CXT. Many of the adverse events are reported after treatment completion, making it difficult to determine whether the adverse events occurred from CXT, BT, EBRT, or a combination of these, especially in the studies in which more than one treatment modality

Table 2
Acute and late toxicity

Reference	Reporting toxicity tool	Acute toxicity	Late toxicity	Grade 3 toxicity or higher
Appelt, Bentzen *et al.* 2015 (22)	CTCAE 3.0	12% with ≥ Grade 2 urinary toxicity	Not reported	Grade 3 urinary toxicity (1%), all patients had brachytherapy boost
Appelt, Ploen *et al.* 2015 (9)	CTCAE 4.0	(1) 80% Grade 1-2 (2) 12% Grade 3	78% rectal bleeding of which 7% Grade 3 at 1 y	Grade 3 diarrhea (8%), 7% Grade 3 rectal bleeding
Christoforidis *et al.* 2009 (23)	Not reported	(1) Tenesmus, diarrhea, or rectal pain in 10 patients (13%) (2) Minor rectal bleeding in 9 patients (12%)	Significant morbidity in 7 patients (9%)	(1) Grade 3 9%: 6 patients with rectal bleeding (2) 1 patient with coccygeal fracture
Coatmeur *et al.* 2004 (24)	Not reported	44 patients (35.5%): mucositis proctorrhagia, pain, diarrhea, and rectal stenosis	27 patients (22%) of which rectal bleeding (21 patients, 17%).	(1) Grade 3: rectal bleeding (1 patient), rectal stenosis (1 patient), radionecrosis (1 patient) (2) No relationship between dose and rectal bleeding
Corner *et al.* 2010 (15)	Not reported	Not reported	6 patients (8%): rectal stricture, colovesical fistula, rectal ulcers	None
Dhadda *et al.* 2017 (44)	CTCAE	14 patients (33%) rectal bleeding Grade 1-2	Not reported	1 patient with Grade 3 radiation proctitis
El-Sayed *et al.* 2008 (16)	RTOG	Proctitis Grade 3 in 1 patient (6%), dermatitis Grade 3 in 2 patients (12%)	Not reported	Grade 3 proctitis (6%), dermatitis (12%)
Frin *et al.* 2017 (45)	CTCAE 4	(1) 1 patient with Grade 3 proctitis (3.7%) (2) 4 patients with Grade 3 toxicity (3) 3 patients with fistulas	(1) 7 patients (26%) with rectal bleeding Grade 1–2, (2) 4 patients (9%) with Grade 3 toxicity (3 bleeding, 1 urgency)	Acute: (1) 1 pt with Grade 3 proctitis (3.7%) in patients with CXT + CRT (2) 4 patients with Grade 3 toxicity (constipation, fecal incontinence, diarrhea, proctitis) (3) 3 patients with fistulasLate: Grade 3 bleeding in 4 patients (9%) and 1 patient with urgency and incontinence.
Gerard, Ayzac *et al.* 1996 (26)	Not reported	<15% patients experienced moderate tenesmus, imperiosity, or diarrhea	Ulceration (27 patients) and bleeding (46 patients)	None
Gerard, Roy *et al.* 1996 (25)	EORTC-RTOG	None after CXT or BT. Most patients had acute proctitis after EBRT, half requiring medical therapy	Minor rectal bleeding in most patients. Five patients with rectal necrosis, all had received BT	1 patient with Grade 3 rectal bleeding
Gerard *et al.* 2002 (13)	Not reported	None after CXT or BT. After EBRT: acute proctitis	Intermittent rectal bleeding. In 12 patients (19%), Grade 2 rectal necrosis	1 patient with Grade 3 rectal bleeding
Gerard *et al.* 2004 (27)	MSKCC for anorectal function	No difference in both groups. BT well tolerated	No ≥ Grade 3 late anorectal toxicity	None
Gerard *et al.* 2008 (28)	CTCAE 3.0	(1) None (2) 4 patients with Grade 1 diarrhea or proctitis in CRT group (3) Surgical (4) None	(1) 1 patient with intermittent rectal bleeding (2) Some urgency and intermittent rectal bleeding (3) Most patients had stool fragmentation and urgency (4) None	None
Gerard *et al.* 2015 (11)	EORTC, SOMA LENL and recently CTCAE-NCI	Not reported	Rectal bleeding in up to 70% (84/120) of patients	Not reported
Grimard *et al.* 2009 (29)	Not reported	2 Patients with Grade 2 radionecrosis, 2 patients with Grade 3 radionecrosis	1 Patient with Grade 2 radionecrosis, 2 patients with Grade 3 radionecrosis	2 Patients with Grade 3 radionecrosis

(*Continued*)

Table 2 (*continued*)

Reference	Reporting toxicity tool	Acute toxicity	Late toxicity	Grade 3 toxicity or higher
Hershman *et al.* 2002 (48)	Not reported	Not reported	2 Patients with Grade 2 radiation proctitis	Not reported
Hoskin *et al.* 2004 (30)	Not reported	None	1 Patient with radionecrotic ulcer, 1 patient with stricture	Not reported
Hull *et al.* 1994 (49)	Not reported	100% Actinic ulcers	No significant bleeding	None
Ishikawa *et al.* 2004 (31)	Not reported	Grade 1–2 (61%, 25 patients) diarrhea with anal pain	(1) Perineal dehiscence in 10 (24.3%) with 6 patients (14.4%) having prolonged fistula formation. (2) 9.8% with Grade 3 small bowel obstruction (3) 1 Patient with vesicocutaneous fistula. (4) Chronic cystitis in 2 patients, with 1 Grade 3 (2.4%)	(1) Grade 3 small bowel obstruction (9.8%), cystitis (2.4%) (2) 1 Patient with Grade 4 vesicocutaneous fistula (2.4%)
Jakobsen *et al.* 2006 (32)	CTCAE	3 Patients with Grade 3 diarrhea (6%)	Not reported	3 Patients with Grade 3 diarrhea (6%)
Jakobsen *et al.* 2012 (33)	CTCAE	(1) No differences between the 2 arms (2) Grade 2 or more: diarrhea 23%, skin toxicity 21% vs 24%, dysuria 8% vs 7%, proctitis 18% vs 22%.	Not reported	Not reported
Lavertu *et al.* 2003 (34)	Not reported	77%, most commonly diarrhea or increased stool frequency (54%), and rectal bleeding (37%)	(1) 88%, most commonly rectal bleeding (51%) and diarrhea (40%) (2) 1 patient with Grade 3 radiation proctitis	1 patient with Grade 3 radiation proctitis
Lavery *et al.* 1987 (35)	Not reported	(1) 22 Patients with minor rectal bleeding and 12 patients with urgency (2) 14 Patients with proctitis (3) 47 Patients with actinic ulcers	2 Patients with Grade 3 radiation proctitis	2 Patients with Grade 3 radiation proctitis (7%)
Maingon *et al.* 1998 (36)	Not reported	(1) Intermittent proctitis (34 patients), diarrhea (3 patients), minimal rectal bleeding (3 patients), and pain (1 patient). (2) 3 pts with rectal necrosis	(1) "Late severe damage" in 10 patients (2) Grade 3: stenosis (1 patient), rectal bleeding (1 patient), incontinence (1 patient)	(1) "Late severe damage" in 10 patients (2) Grade 3: stenosis (1 patient), rectal bleeding (1 patient), incontinence (1 patient)
Omidvari *et al.* 2015 (14)	CTCAE 4.0	(1) Most patients with Grade 2 dermatitis, Grade 1 proctitis (2) More frequent proctitis, anemia, and noninfective cystitis in study arm.	Not reported	2 Patients with Grade 3 radiation proctitis in BT arm (6%)
Ortholan *et al.* 2012 (37)	MSKCC for anorectal function	Not reported	Mild rectal bleeding	EBRT alone: 3/34 late definitive colostomies CXT + EBRT: 3/45 late definitive colostomies
Papillon *et al.* 1992 (50)	Not reported	Slight proctitis in 10%; superficial radionecrosis in 5%	Occasional bleeding	Not reported
Rauch *et al.* 2001 (51)	Not reported	Not reported	29 Patients with moderate late hemorrhagic proctitis, 1 patient with severe hemorrhagic proctitis, and 1 patient with radiation-induced ulceration	Not reported

(*Continued*)

Table 2 (*continued*)

Reference	Reporting toxicity tool	Acute toxicity	Late toxicity	Grade 3 toxicity or higher
Rijkmans *et al.* 2017 (46)	CTCAE 3	Grade 3: 4 patients (1 in 5 Gy level, 3 in 8 Gy level)	(1) 9 patients with Grade 3 (33%) (2) 1 patient with Grade 4 (4%)	(1) Acute: 3 patients with Grade 3 proctitis (1 in 5 Gy level and 2 in 8 Gy level); 1 patient with Grade 3 rectal bleeding, 8 Gy level (2) Late: 4 Patients with Grade 3 radiation proctitis, 5 patients with Grade 3 rectal bleeding; 1 patient with Grade 4 rectocutaneous fistula (4%)
Schild *et al.* 1996 (38)	RTOG	Diarrhea (7 patients), bleeding (5 patients), rectal urgency (3 patients), and pain (2 patients)	(1) Grade 1–2 bleeding (10 patients), diarrhea (5 patients), ulcer (5 patients), and pain (3 patients) (2) 1 patient with perforation after ulcer biopsy (Grade 4)	1 patient with Grade 4 perforated ulcer after biopsy (patient with just CXT)
Sischy *et al.* 1985 (47)	Not reported	Minor rectal bleeding	Some patients with asymptomatic superficial necrosis	Not reported
Smith *et al.* 2012 (39)	CTCAE 4.0	(1) Fewer patients with Grade 1–2 toxicity in BT group than in CRT group (2) 1 patient with Grade 3 proctitis in each group	Not reported	3 Patients with Grade 3 radiation proctitis (one from each group)
Sun Myint *et al.* 2010 (40)	Not reported	(1) 1 patient with postoperative mild bleeding (2) 2 patients with delayed wound healing	1 patient with Grade 3 rectal stricture (3.4%)	1 Patient with Grade 3 rectal stricture (3.4%)
Sun Myint *et al.* 2017 (52)	Not reported	Not reported	Grade 1 rectal toxicity in 30%, Grade 1 rectal bleeding in 58%, and Grade 2 rectal bleeding in 28%	None
Tunio *et al.* 2010 (17)	CTCAE 2.0	(1) 12 patients had Grade 3 rectal pain (70.6%); 7 patients with Grade 3 diarrhea (41.2%) (2) less Grade 3 diarrhea and rectal pain than HDR-ILBT arm.	HDR BT group: Grade 1 and 2; no Grade 3	In BT arm: ≥ Grade 3: acute rectal pain (12 patients, 70.6%), diarrhea (7 patients, 42%), cystitis (2 patients, 11%)
Vuong *et al.* 2002 (41)	RTOG	(1) Grade 2 proctitis in all patients (2) 2 Patients with a low lesion developed Grade 3 dermatitis (4%)	Not reported	2 Patients with Grade 3 dermatitis (4%)
Vuong *et al.* 2007 (42)	CTCAE 2.0	Proctitis in all patients, in 99 patients Grade 2 and in 1 patient Grade 3	Not reported	1 patient with Grade 3 radiation proctitis
Yanagi *et al.* 1997 (43)	Not reported	(1) In high-dose BT group, more radiation ileitis and perianal skin troubles (2) 3/19 patients with Grade 3 rectal toxicity	More urgency and incomplete evacuation in Group b	7/19 patients in group A, 36/96 patients in group B with Grade 3 rectal toxicity (statistically significant difference)

BT = brachytherapy; CTCAE = Common Terminology Criteria for Adverse Events; HDR = high-dose-rate; CXT = contact X-ray therapy; EBRT = external beam radiotherapy; RTOG = Radiation Therapy Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; MSKCC = Memorial Sloan Kettering Cancer Center; NCI = National Cancer Institute.

was used. Some studies do report the differences in radiation tolerance between the various endorectal techniques. Gerard *et al.* compared three different treatment groups (EBRT, EBRT with a CXT boost, and EBRT with a BT boost) (27). This study reported no differences in acute toxicity between the groups.

Late adverse events occurred in most studies, ranging from mild to severe. Observed late adverse events include rectal bleeding, ulceration, necrosis, rectal urgency, and diarrhea. There were six studies or arms of studies in which patients only received CXT, there was no surgery performed, and in which it was clearly reported that the

reported toxicity was due to CXT (23, 28, 35, 38, 49, 52). Two studies in which CXT was the only modality used reported Grade 3 rectal toxicity in 8% and in 3% of patients (23, 35). In the study by Schild *et al.*, there was one patient in the CXT-only arm who had a rectal perforation after biopsy of an ulcer, classified as Grade 4 rectal toxicity (38). The study by Christoforidis *et al.* mentions a coccygeal fracture as Grade 3 toxicity, although it is unclear whether there is a causal relationship with the CXT given (23). The studies by Gerard *et al.* in 2008, Sun Myint *et al.* in 2017, and by Hull *et al.* in 1994 reported no ≥ Grade 3 rectal toxicity after CXT (28, 49, 52). After combining these six studies, 9 of 314 patients (2.9%, range 0%–9%) experienced ≥ Grade 3 late rectal toxicity after CXT.

Brachytherapy

Observed acute toxicity occurring from BT includes proctitis, urogenital toxicity, diarrhea, rectal pain, and perianal skin problems. The occurrence of adverse events resulting from BT ranges from 0% to 100%. Toxicity ranges from Grade 1 to Grade 5. Jakobsen *et al*. compared EBRT with EBRT and an additional BT boost (32, 33). They report no differences in the two treatment arms regarding ≥ Grade 2 nonhematological toxicity. In these two studies, and several other studies, all patients received surgery, meaning conclusions cannot be made about potential rectal toxicity. Rijkmans *et al.* reported a Phase 1 dose-escalation study for elderly and/or medically inoperable patients with rectal cancer. EBRT was given (39 Gy/13 fx), followed by an HDR BT boost (46). The HDR BT boost started at 5 Gy per fraction. The dose limiting-toxicity was set at 7 Gy after 3 of 10 patients (30%) experienced acute Grade 3 radiation proctitis (46).

Observed late adverse events include radiation proctitis, in some cases requiring temporary or permanent colostomy, rectal ulcers/radionecrosis, rectal stricture, diarrhea, colovesical fistulae, urinary symptoms, skin ulceration and even cutaneous fistulae, vaginal perforation, and other further unknown Grade 1 to Grade 4 events. The previously described study by Rijkmans *et al.* reported Grade 3 late rectal toxicity in 33% of patients, and 1 patient (4%) experienced Grade 4 toxicity (46).

Notably, there was only 1 article that used BT as only treatment modality, in which patients did not receive subsequent rectum-removing surgery, and it was clearly reported that the toxicity was due to BT. In this study by Grimard *et al.*, 2/32 patients (6.3%) experienced Grade 3 rectal toxicity (29). Caution is required when interpreting this, as many articles using combined modalities including HDR BT reported significant amounts of ≥ Grade 3 toxicity. Table S2 in the Supplementary Material shows EQD2 calculations performed by the first author for articles in which only BT ± EBRT was used, and for articles without rectal surgery after radiotherapy. This resulted in five articles, with a radical dose given ranging from 55 to 68 Gy in EQD2. An alpha-beta ratio of 3 Gy was used for late rectal toxicity.

Grade 3 or higher toxicity in combined modality studies

Seven studies, in which monotherapy or combination of various modalities and a range of different doses were used, reported that there was no ≥ Grade 3 toxicity.

≥ Grade 3 toxicity ranged from 1% to 70%. Grade 4 toxicity included a late rectocutaneous fistula after 39 Gy EBRT +7 Gy HDR BT (34, 38, 46) and a vesicocutaneous fistula after 30 Gy EBRT followed by 30–40 Gy HDR BT (31). Schild *et al.* and Lavertu *et al.* both reported a perforated ulcer after biopsy in 1 patient who had received either CXT as monotherapy or in combination with EBRT and/or HDR BT (34, 38). These two articles possibly refer to the same patient, as the patient inclusion dates overlap and the studies were performed at the same center (34, 38).

Rectal bleeding and radiation proctitis were the most frequently reported Grade 3 toxicities. As ‘‘radiation proctitis’’ was not defined in these studies, it is not clear whether some of these cases of radiation proctitis also entailed rectal bleeding, as this can be a symptom of chronic radiation proctitis. Rectal toxicity is generally less relevant when it is reported in studies in which patients received rectal surgery following radiation. Although after a low-anterior resection a part of the rectum may remain intact, the goal of this review is to analyze rectal toxicity in patients who could potentially be spared surgery after a rectal boost treatment. For this reason, studies in which rectal surgery was given after radiation were excluded in the analysis of rectal toxicity.

Grade 3 rectal bleeding was reported for 20 patients in seven studies (18/531, 3.3%) (13,23–25,36,45,46). For two of these studies, it was clearly reported which treatment modalities and which prescribed dose these specific patients had received (45, 46). In the previously described study by Rijkmans *et al.*, 33% of patients presented with late Grade 3 toxicity, of which 18% experienced Grade 3 rectal bleeding. Sixty percent of these patients had received 7 Gy as HDR BT boost, and 40% had received 8 Gy as HDR BT boost (46). Frin *et al.* report 4 patients (9%), of which all had received CXT (30 Gy) followed by chemoradiation (50 Gy/25 fx), who experienced Grade 3 rectal bleeding (45). In two studies by Gerard *et al.*, in which patients received CXT followed by EBRT and possibly also HDR BT, 1 patient in each study experienced Grade 3 rectal bleeding, although it may concern the same patient due to overlapping inclusion dates (13, 25).

Grade 3 radiation proctitis was reported in five articles in which patients did not receive surgery removing the rectum after their radiation treatment (10/289, 3.4%) (34,35,44–46). For two of these articles, it was clear which treatment modalities and prescribed dose these patients had received (45, 46). Frin *et al.* reported that 2 patients (1.7%)

experienced Grade 3 radiation proctitis. Both of these patients had received CXT 30 Gy followed by EBRT 50 Gy/25 fx (45). In the previously described dose-escalation study by Rijkmans *et al.*, 4 patients (14%) in this study had late Grade 3 radiation proctitis, of which half had received 5 Gy as HDR BT boost and half had received 8 Gy (46).

Other Grade 3 toxicities reported potentially pertaining to internal radiotherapy include sporadic urinary toxicity, nausea, diarrhea, ureteral stricture, coccygeal fracture, rectal stenosis, radionecrosis, incontinence, vaginal perforation, dermatitis/skin ulceration, mucositis, and rectal pain.

Discussion

The objective of this systematic review was to compare treatment-related acute toxicity and late toxicity in rectal cancer patients resulting from various internal radiation techniques. The main question was whether one technique had a more favorable toxicity profile. The two internal radiation techniques compared were 50 kV CXT and BT. It has been suggested in the literature that these techniques have a beneficial role in achieving a complete pathologic response by the delivery of a boost to standard EBRT.

This review describes the adverse events resulting from various internal radiotherapy techniques in 3682 patients included in 38 studies, of which four RCTs.

With caution, it can be concluded from this review that CXT resulted in only acute rectal toxicity and late rectal toxicity, whereas BT also caused urinary and skin toxicity in some studies in addition to rectal toxicity.

As patients are living longer and may more often preserve their rectum due to better treatment modalities and techniques, reducing late toxicity has become increasingly important. However, although it is the general idea that late toxicity is irreversible, literature and experience suggest that this is not always the case, and symptoms of late toxicity may diminish in time (53). There are also several publications that describe helpful ways to treat gastrointestinal radiation toxicity (21, 54). Caution must be advised as some preventable complications can also be induced in areas where toxicity has occurred, as shown in our review when a rectal ulcer was biopsied, causing a perforation.

Limitations of the studies

To formulate a conclusive answer to our research question, the limitations of the studies included must be addressed. Well-executed prospective RCTs provide the highest level of evidence. Unfortunately, this review includes only four RCTs, and all four of these contained a potential risk of bias. Bias control in observational studies led to poor outcome assessment in some studies (shown in Supplementary Information). This is important because acute and/or late toxicity identification is sensitive to subjectivity. A prospective plan for toxicity reporting could diminish differences in interpretation by the clinicians. However, most included studies are retrospective and the accuracy of toxicity reporting can therefore not be confirmed. In 18 studies, the CTCAE tool is used. Furthermore, in 15 studies, the toxicity-scoring tool is not reported and in six studies, a different scoring tool is used. In studies in which the toxicity-reporting tool is not mentioned, there is a higher likelihood that adverse events are not accurately noted. In summary, reporting toxicity is a very delicate process and a potential source of bias. Even when standardized tools are used, there will always be subjective differences in classification by physicians.

Patient-reported outcome measures (PROMs) have recently become increasingly important when scoring toxicity. Aside from the disadvantageous heterogeneity that exists when clinicians report a single same exact symptom, knowing how the patient experiences this symptom can sometimes be seen as more important than how the clinician observes this symptom. Collecting PROMs have been linked to an improved management of symptoms, better quality of life for patients, and even improved survival (55). A radiation proctitis may look mild through a rectoscope but may cause a disproportionately significant decrease in the patient's quality of life. To allow patients to make well-informed decisions regarding their treatments, clinicians need to understand and be able to explain to their patients what they may experience. All studies in this systematic review unfortunately only described physician-reported outcomes. In the future, PROMs should be reported as well.

Another limitation is the overall poor insight in the occurrence of adverse events in the different treatment groups. Some studies simply report ''no differences,'' although others show more details but do not distinguish between the treatment groups. The overall poor toxicity reporting makes it difficult to formulate a conclusive answer whether one technique is more favorable compared to the other. Very few studies reported the dose and/or treatment modality that was given to a patient with a certain type and grade of toxicity. Another important limitation of these studies was the general lack of description of treatment volumes. Having no indication of treatment volumes made any attempt to reconstruct a dose futile, as BT dose distributions are in general very heterogeneous. This combination of missing information on dose as well as on treatment volumes made the correlation of dose to toxicity, which would be highly useful for the purpose of this review, impossible.

The studies delivering BT are very heterogeneous concerning the dose prescription, type of applicator (multichannel or single-channel applicator, interstitial needles), and dose given. Therefore, due to biological differences in dose delivery between the various internal radiation techniques, the total dose delivered to the tumor may be

different from the prescribed dose. The total dose administered to patients by contact therapy and BT thus cannot be directly compared, and it cannot be concluded whether a higher prescribed total dose has an influence on the observed adverse events. Furthermore, inadequate information on dose was often given, making it impossible to reconstruct dose and relate toxicity to these doses. At this moment, there are no guidelines BT for rectal cancer concerning dose reporting, dose prescription, and treatment volume definition, in contrast to other BT fields such as the EMBRACE criteria for cervical cancer (56).

Direct comparison of toxicities resulting from the various internal radiation techniques proved impossible, as these techniques were often combined with each other or with EBRT. Some patients also received extensive or limited rectal surgery following or preceding their radiation treatment, which can have a significant effect on the comorbidities experienced by patients.

Based on the stage of disease, some patients have received additional chemotherapy. Side effects occurring from chemotherapy, such as diarrhea, may interfere with the side effects occurring from radiotherapy. This may bias the observed adverse events occurring in patients with additional chemotherapy.

Limitations of the review

This systematic review has some limitations. The search, important aspects of this review, data extraction, and bias control were done and checked by both authors, but still may contain some flaws. Relevant references may have been missed due to the search strategy and references emerging after November 2017, excepting a few as described in the search strategy, are not included in this review.

Conclusion

In conclusion, this review shows the great heterogeneity in toxicities reported occurring from contact therapy and/or BT. All techniques reported some ≥ Grade 3 toxicity. Furthermore, the theoretical advantage of contact therapy in relation to adverse events is not supported or refuted with the current literature. Toxicity after CXT was confined to the rectum, whereas after BT, urogenital toxicity and skin toxicity were seen as well. Unfortunately, few specific conclusions could be drawn regarding the dose-related risk of toxicity for the various techniques due to nonuniform reporting strategies and missing information. To enable future comparisons and improvements, the endorectal radiation field urgently needs consensus guidelines on dose reporting, dose prescription, treatment volume specification, and toxicity reporting. To compare modalities with the aim of improving treatment of patients, first a common language must be generated.

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Appendix 1. Supplementary Tables

Table S1
Study demographics

Reference	Country	Study design	Years of patient inclusion	Stage of disease	Number of patients	End points
Appelt, Bentzen *et al.* 2015 (22)	Denmark	Observational retrospective	2007–2012	T1-4, N0-2, M0-1	345	Acute toxicity
Appelt, Ploen *et al.* 2015 (9)	Denmark	Observational prospective	2009–2013	T2-T3 within 6 cm anal verge, N0–N1	55	Primary: local recurrence after 1 year
Christoforidis *et al.* 2009 (23)	USA	Observational retrospective	1986–2006	T1-2, N0	77	Treatment failure, DFS, OS
Coatmeur *et al.* 2004 (24)	France	Observational retrospective	1971–2001	T1-3	124	LC, Ultimate LC, DSS, OS
Corner *et al.* 2010 (15)	UK	Observational retrospective	1993–2007	All	79	Local response, median survival, symptom control
Dhadda *et al.* 2017 (44)	UK	Observational retrospective	2011–2015	T1-T3	42	LC, toxicity
El-Sayed *et al.* 2008 (16)	Saudi Arabia	Observational prospective Phase 2	2006–2007	T3-4, M0	17	pCR, toxicity
Frin *et al.* 2017 (45)	France	Observational retrospective	2002–2014	T1-3, N0-2, M0	112	Local response, pathological assessment, rate of organ preservation, local recurrence
Gerard, Ayzac *et al.* 1996 (26)	France	Observational retrospective	1977–1993	T1-2, N0-1, M0	101	OS, DSS, LRRFS
Gerard, Roy *et al.* 1996 (25)	France	Observational retrospective	1986–1992	T1-3, N0-1	29	OS, DSS, LRFS
Gerard *et al.* 2002	France	Observational prospective	1986–1998	T2-3, N0-1, M0	63	LC, pelvic control, OS
Gerard *et al.* 2004 (27)	France	Randomized controlled trial	1996–2001	T2-T3, Nx, M0	88	Sphincter preservation
Gerard *et al.* 2008 (28)	France	Observational retrospective	2002–2006	T1-3, N0-2	44	LC
Gerard *et al.* 2015 (11)	France	Observational retrospective	1986–2012	T1-T3, N0–N1	120	cCR, toxicity, bowel function
Grimard *et al.* 2009 (29)	Canada	Observational prospective	1989–2007	T1-T2	32	Locoregional control, OS, DSS
Hershman *et al.* 2002 (48)	UK	Observational retrospective	1992–2002	T1-T3	100	Local control, cancer-specific survival
Hoskin *et al.* 2004 (30)	UK	Observational retrospective	1992–2001	All	50	Local response, median survival, symptom control
Hull *et al.* 1994 [49]	USA	Observational retrospective	1973–1992	N0, <5 cm diameter	126	Local control, toxicity
Ishikawa *et al.* 2004 (31)	Japan	Observational prospective	1988–1997	T3-4, M0	41	LC, OS, Toxicity
Jakobsen *et al.* 2006 (32)	Denmark	Observational prospective	not reported	T3	50	pCR
Jakobsen *et al.* 2012 (33)	Denmark	Randomized controlled trial	2005–2010	T3-T4	248	pCR
Lavertu *et al.* 2003 (34)	USA	Observational retrospective	1987–2000	T1-3	35	LC, OS, Toxicity
Lavery *et al.* 1987 (35)	USA	Observational retrospective	1973–1984	3 cm or less, cN0	62	LC, OS, Toxicity
Maingon *et al.* 1998 (36)	France	Observational retrospective	1975–1995	T1-3	151	Pelvic control, survival, toxicity
Omidvari *et al.* 2015 (14)	Iran	Observational prospective phase II trial	not reported	cT3–T4, N0–N2, M0	136	efficacy and safety
Ortholan *et al.* 2012 (37)	France	Randomized controlled phase 3 trial	1996–2001	T2-T3	88	Sphincter preservation.
Papillon *et al.* 1992 (50)	France	Observational retrospective	1951–1984	T1-T2	312	Locoregional control, DFS, toxicity
Rauch *et al.* 2001 (51)	France	Observational retrospective	1978–1998	<4 cm diameter	97	cCR, local control, toxicity

(*Continued*)

Table S1 (*continued*)

Reference	Country	Study design	Years of patient inclusion	Stage of disease	Number of patients	End points
Rijkmans *et al.* 2017 (46)	Netherlands	Observational prospective Phase 1 dose escalation	2007–2013	cT2-4, N0-1, M0-1	38	Maximum tolerated dose, toxicity, clinical tumor response, freedom from local progression
Schild *et al.* 1996 (38)	USA	Observational retrospective	1987–1994	T1-T3	25	LC, survival, complications
Sischy *et al.* 1985 (47)	USA	Observational retrospective	1973–1984	5 cm or less	129	LC
Smith *et al.* 2012 (39)	USA	Observational prospective	2010–2012	T2N1 or T3N0-1, M0	17	Time to surgical resection, change in CEA level, acute toxicity, sphincter preservation, and postoperative complications
Sun Myint *et al.* 2010 (40)	UK	Observational retrospective	2004- ?	Locally advanced (T2-T3)	34	Response, recurrence, survival
Sun Myint *et al.* 2017 (52)	UK	Observational retrospective	2003–2012	T1-4, N0-2, M0	200	Tumor regrowth, organ preservation
Tunio *et al.* 2010 (17)	Pakistan	Randomized controlled trial	2008–2009	T3-4, N0-1	36	cCR, pCR, Toxicity
Vuong *et al.* 2002 (41)	Canada	Observational prospective	1998–2001	T2 - early T4, N0–N2	49	pCR, cCR, toxicity
Vuong *et al.* 2007 (42)	Canada	Observational prospective	1998–2002	T2-4, N0-1	100	Toxicity, pCR, OS
Yanagi *et al.* 1997 (43)	Japan	Observational retrospective	1986–1995	T2	230	Radiation effect, local and distant recurrence, and death from cancer

pCR = pathologic complete response; cCR = clinical complete response; DFS = disease-free survival; DSS = disease-specific survival; OS = overall survival; LC = local control; LRRFS = locoregional relapse-free survival.

Table S2
EQD2 calculations

Reference	Treatment arms	RT dose (Gy)	EQD2
Appelt, Ploen *et al.* 2015 (9)	CRT + HDR BT boost	60 Gy/30 fx to tumor, 50 Gy/30 fx to pelvic nodes + HDR BT boost (5 Gy)	60 Gy to tumor (47 Gy to pelvic nodes) + 8 Gy boost = 68 Gy
Corner *et al.* 2010 (15)	Radical: CRT + HDR BT or HDR BT monotherapy. Palliative: HDR BT	Radical: CRT 45 Gy/25 fr, HDR BT as boost 12 Gy in 2 fractions, HDR BT monotherapy up to 36 Gy at 1 cm in 6 fr, 2-3 fr/week. Palliative: 10 Gy at 1 cm single dose.	Radical: 43 Gy + 22 Gy boost = 65 Gy; Palliative = 26 Gy
Grimard *et al.* 2009 (29)	Local excision + HDR BT	HDR BT 45-50 Gy	Unclear in how many fx
Hoskin *et al.* 2004 (30)	Radical: CRT + HDR BT boost or HDR BT monotherapy. Palliative: HDR BT	Radical: CRT 45 Gy/25 fr, HDR BT boost 12 Gy, HDR BT monotherapy 36 Gy/6 fr. Palliative: HDR BT 10 Gy/1 fr	Radical: 43 Gy + 22 Gy boost = 65 Gy; Monotherapy BT = 65 Gy; Palliative BT = 26 Gy
Rijkmans *et al.* 2017 (46)	EBRT + HDR BT at dose levels 5-8 Gy	EBRT (39 Gy/13 fr) + HDR BT (5–8 Gy/1 fr)	47 Gy + {8–18 Gy boost} = 55–65 Gy

HDR = high-dose-rate; BT = brachytherapy; EBRT = external beam radiotherapy.

Table S3
Reporting bias RCTs according to the Cochrane risk of bias tool

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Gerard *et al.* 2004 (27)	+	+	N/A	N/A	+	?	+
Jakobsen *et al.* 2012 (33)	?	?	N/A	N/A	+	+	+
Ortholan *et al.* 2011 (37)	+	+	N/A	N/A	+	?	+
Tunio *et al.* 2010 (17)	-	-	N/A	N/A	?	+	+

+ = low risk of bias; - = high risk of bias; ? = unclear risk of bias; N/A = not applicable; RCT = randomized controlled trial.

Table S4
Reporting bias in observational studies about etiology and harm according to the Newcastle-Ottawa Scale for quality assessment of cohort studies

	Selection				Comparability	Outcome		
	a	b	c	d	a	a	b	c
Appelt, Bentzen *et al.* 2015 (22)	★		★	★		★		★
Appelt, Ploen *et al.* 2015 (9)	★		★	★		★	★	★
Christoforidis *et al.* 2009 (23)	★		★	★			★	★
Coatmeur *et al.* 2004 (24)	★		★	★				
Corner *et al.* 2010 (15)	★		★	★				★
Dhadda *et al*. 2016 (44)	★		★	★		★	★	
El-Sayed *et al.* 2008 (16)	★		★	★		★	★	★
Frin *et al.* 2017 (45)	★		★	★		★	★	★
Gerard, Ayzac *et al.* 1996 (26)	★		★	★			★	★
Gerard, Roy *et al.* 1996 (25)	★		★	★		★	★	★
Gerard *et al.* 2002 (13)	★		★	★			★	★
Gerard *et al.* 2008 (28)	★		★	★		★	★	★
Gerard *et al.* 2015 (11)	★		★	★		★	★	★
Grimard *et al.* 2009 (29)	★		★	★			★	
Hershman *et al*. 2002 (48)	★		★	★			★	
Hoskin *et al.* 2004 (30)	★		★	★				
Hull *et al.* 1993 (49)	★		★	★			★	
Ishikawa *et al.* 2004 (31)	★		★	★			★	
Jakobsen *et al.* 2006 (32)	★		★	★		★		

(*Continued*)

Table S4 (*continued*)

	Selection				Comparability	Outcome		
	a	b	c	d	a	a	b	c
Lavertu *et al.* 2003 (34)	★		★	★			★	
Lavery *et al.* 1987 (35)	★		★	★			★	★
Maingon *et al.* 1998 (36)	★		★	★			★	★
Omidvari *et al.* 2015 (14)	★	★	★	★	★	★		
Papillon *et al.* 1992 (50)	★		★	★			★	★
Rauch *et al.* 2001 (51)	★		★	★			★	★
Rijkmans *et al.* 2017 (46)	★		★	★		★	★	★
Schild *et al.* 1996 (38)	★		★	★		★	★	★
Sischy *et al.* 1985 (47)	★		★	★		★		
Smith *et al.* 2012 (39)	★	★	★	★	★	★	★	
Sun Myint *et al.* 2010 (40)	★		★	★			★	
Sun Myint *et al.* 2017 (52)	★		★	★		★	★	★
Vuong *et al.* 2002 (41)	★		★	★		★	★	
Vuong *et al.* 2007 (42)	★		★	★		★	★	
Yanagi *et al.* 1997 (43)	★		★	★			★	★

Selection a = representativeness of the exposed cohort; Selection b = selection of the nonexposed cohort; Selection c = ascertainment of exposure; Selection d = demonstration that outcome of interest was not present at the start of the study; Comparability a = comparability of cohorts on the basis of the design of analysis; Outcome a = assessment of outcome; Outcome b = was followup long enough for outcome to occur; c = adequacy of followup of cohorts; ★ = criteria present.