Review paper

Brachytherapy boost after chemoradiation in anal cancer: a systematic review

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Abstract

Radio-chemotherapy (RCT) is the primary treatment of anal cancer (AC). However, the role and the optimal total dose of a radiation boost is still unclear. No randomized controlled trials nor systematic reviews have been performed to analyze the efficacy of brachytherapy (BRT) as boost in AC. Therefore, we performed this systematic review based on PRISMA methodology to establish the role of BRT boost in AC.

A systematic search of the bibliographic databases: PubMed, Scopus, and Cochrane library from the earliest possible date through January 31, 2018 was performed. At least one of the following outcomes: local control (LC), loco-regional control (LRC), overall survival (OS), disease-free survival (DFS), or colostomy-free survival (CFS) had to be present for inclusion in this systematic review in patients receiving a BRT boost. Data about toxicity and sphincter function were also included.

Ten articles fulfilled the inclusion criteria. All the studies had retrospective study design. All studies were classified to provide a level of evidence graded as 3 according to SIGN classification. Median 5-year LC/LRC, CFS, DFS, and OS were: 78.6% (range, 70.7-92.0%), 76.1% (range, 61.4-86.4%), 75.8% (range, 65.9-85.7%), and 69.4% (63.4-82.0%), respectively. The reported toxicities were acceptable.

RCT is the treatment cornerstone in AC. High-level evidences from studies on BRT boost in AC are lacking. Further studies should investigate: efficacy of BRT boost in comparison to no boost and to external beam boost, patients who can benefit from this treatment intensification, and optimal radiation dose.

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Key words: anal cancer, brachytherapy boost, systematic review.

Purpose

Anal cancer (AC) is uncommon with approximately 4,300 new cases in both genders every year in Europe and representing only 1-2% of gastrointestinal tract tumors [1]. Squamous cell cancer (SCC) is the most frequent histological type, with about 80-85% of cases [1].

Before the 80s, the main treatment was abdominal perineal resection with anal sphincter removal leading to permanent colostomy. Five-year overall survival (OS) was between 40% and 70% with loco-regional relapse rates of approximately 35% [2,3,4]. In 1974, Nigro *et al*. tested low-dose external beam radiotherapy (EBRT) and concomitant chemotherapy (CT) based on 5-fluorouracil (5FU) and mitomycin C (MMC) as neoadjuvant treatment before surgery in AC treatment, reporting 2 out of 2 complete pathological responses [5]. Later, the same author reported on 28 patients with SCC of the AC treated in the same way. Surgery was done 4-6 weeks after radiation treatment and 12 patients underwent abdominal-perineal. Seven out of the 12 had no residual tumor in the surgical specimen, while one patient had microscopic tumor only; 16 patients had complete clinical response. Twenty-two patients were free of tumor and alive 1-8 years after treatment [6].

Although no randomized trials have directly compared radio-chemotherapy (RCT) and surgery, RCT nowadays represents the primary treatment of AC, while abdominal-perineal resection is reserved for patients with local failure after previous irradiation.

EBRT is the standard technique in RCT of AC [7,8]. However, the addition of brachytherapy (BRT) boost has been suggested [8]. In fact, BRT enables the delivery of

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higher radiation doses to small target volumes and limits the risk of radiation-induced damage to normal surrounding tissues and organs at risk. Unfortunately, the evidence supporting the use of BRT boost has never been evaluated in randomized trials or systematic reviews. Therefore, we performed this systematic review to better define the role of BRT boost in AC.

Material and methods

Bibliographic search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and guidelines were consulted during the stages of design and data analyses [9]. We performed a systematic search of the bibliographic databases: PubMed, Scopus, and Cochrane library from the earliest possible date through January 31, 2018 [9,10,11,12]. The PubMed search strategy was: ("anus neoplasms" [MeSH Terms] OR ("anus" [All Fields] AND "neoplasms" [All Fields]) OR "anus neoplasms" [All Fields] OR ("anal" [All Fields] AND "cancer" [All Fields]) OR "anal cancer" [All Fields]) AND "brachytherapy" [MeSH Terms]).

Eligibility criteria

We included studies of any design (randomized, prospective, and retrospective), excluding case reports and trials with less than 40 patients receiving BRT boost. Studies with patients receiving also EBRT boost were considered provided ≥ 40 patients received BRT boost. Commentaries, editorials, and letters were not excluded during screening but were considered only if they reported original data. When multiple articles were found from a single study with an overlap, the study with the longest period of accrual and if necessary, data from previous publications were analyzed. Eligible intervention included BRT as a boost in AC independently of technique, dose, dose rate, and fractionation. No limits were set on CT regimens and EBRT technique. We analyzed only full text articles published in English.

Data extraction and quality assessment

Abstract and full articles from relevant studies were independently reviewed by 2 investigators (RF, SC) and those meeting the inclusion criteria were considered for further evaluation. Disagreements were resolved with involvement of all authors. In addition, we identified relevant trials from the references list of each selected article. We obtained the following information from each study: year of publication, number of centers involved, country, accrual period, patients characteristics (gender, age), tumor characteristics (histological type, tumor size, nodal status), EBRT dose and fractionation, CT schedule, BRT boost technique, delivered dose, gap between EBRT and boost, local control (LC), local-regional control (LRC), OS, colostomy-free survival (CFS), disease-free survival (DFS), toxicity scale, acute and late toxicity rate, and sphincter function.

The Scottish Intercollegiate Guidelines Network (SIGN) criteria was used to classify the quality of evidence. Briefly, SIGN level of evidence 1 is provided by meta-analyses, 2 by case control or cohort studies, 3 by non-analytic studies like case report and case series, and 4 by expert opinion [13].

Outcome assessment

At least one of the following outcomes: LC, LRC, OS, DFS, or CFS had to be present for inclusion in this review in patients receiving a BRT boost. Data about toxicity and sphincter function were included if available.

Results

Search results and quality

The literature search resulted in 428 articles. Following removal of non-pertinent papers and duplicates, 40 abstracts were selected. Following the selection criteria, 24 of the abstracts were excluded leaving 10 studies for analysis. After full-text articles assessment for eligibility, 6 more papers were excluded. Figure 1 shows the flow chart of the systematic search and review process.

Ten articles fulfilled the inclusion criteria and were considered in our review [14,15,16,17,18,19,20,21,22,23]. All studies were conducted in Europe and most reported French experiences [14,17,19,20,21,23]. No randomized controlled trials were found. All studies had retrospective design and were classified to provide a level of evidence graded as 3 according to SIGN classification [13]. Table 1 shows a summary of studies included in this systematic review. Eight studies were single center studies [14,15,16,17,18,21,22,23] and 2 were multicentric studies [19,20].

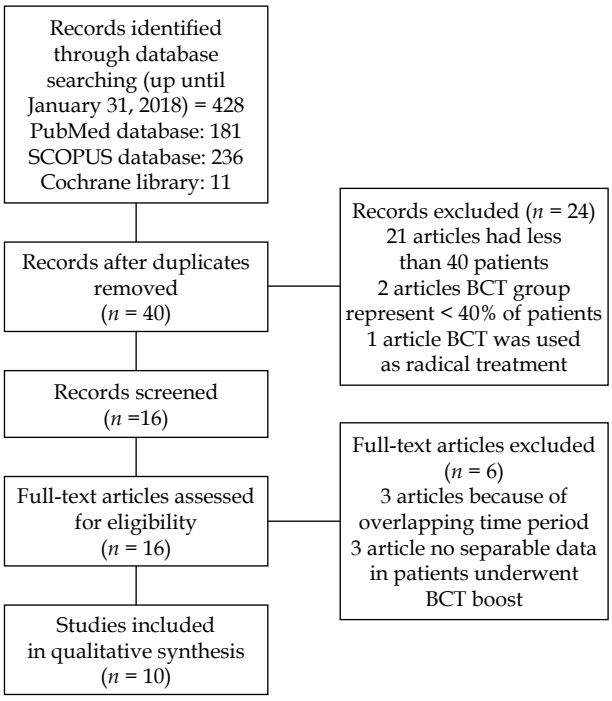

Fig. 1. Flow chart of the systematic search and review process

Table 1. Summary of studies included in this systematic review

Authors, year of publication (reference)	Country	Mono-/ multicentric	Accrual period	Patients' characteristics				Tumor characteristics				Median FU (months)
								Histological type		Stage		
				Number	% female	% male	Median age	% SCC	% other	% T_1-T_2	% N_0	
Papillon *et al.* 1987 [14]	France	Monocentric	1974-1985	221	NR	NR	NR	NR	NR	NR	NR	36-60
Sandhu *et al.* 1998 [15]	Scotland	Monocentric	1984-1994	76	72.0	28.0	70	81.0	19.0	61.0	85.0	37
Weber *et al.* 2001 [16]	Switzerland	Monocentric	1981-1998	49	75.6	24.4	65.5	100	0.0	54.0	63.0	76.2
Chapet *et al.* 2005 [17]	France	Monocentric	1980-1998	218	87.7	12.3	NR	100	0.0	67.0	59.9	58
Doniec *et al.* 2006 [18]	Germany	Monocentric	1993-2001	50	80.0	20.0	64	90.0	10.0	54.0	70.0	34
Bruna *et al.* 2006 [19]	France	Multicentric	1996-2002	71	NR	NR	61.2	83.1	16.9	77.4	73.2	28.5
Hannoun-Levi *et al.* 2011 [20]	France	Multicentric	2000-2004	86	79.0	21.0	65	100	0.0	69.0	85.0*	62
Lestrade *et al.* 2014 [21]	France	Monocentric	1992-2009	209	83.6	16.4	64	94.2	5.8	59.3	72.3	72.8
Gryc *et al.* 2016 [22]	Germany	Monocentric	1980-2014	47	70.2	29.8	60	78.7	21.3	44.7	72.3	60
Cordoba *et al.* 2017 [23]	France	Monocentric	1990-2013	103	85.5	14.5	63.7	95.5	4.5	64.7	81.6	48

*FU – follow up, pts – patients, NR – not reported, SCC – squamous cell carcinoma, % – percentage, * – N_{0-1}*

Patient and tumor characteristics

In this review, 10 studies were included (1,130 patients). Enrollment period of the studies were between 1970 and 2014. Study population and length of follow-up ranged from 47 to 221 patients and from 28.5 to 76.2 months, respectively [14,15,16,17,18,19,20,21,22,23]. Histological types other than SCC classification according to the fourth edition of the World Health Organization [24] were included in 6 studies (range, 4.5-21.3%) [15,18,19,21,22,23].

EBRT and CT characteristics

There was heterogeneity in the EBRT technique, dose, and fractionation, and in the concurrent CT schedules. In the earliest studies, EBRT was delivered by two-dimensional (2D) technique [14,15,16,17,19,20,21,22], while in the most recent series, 3D-conformal EBRT or intensity-modulated radiation therapy techniques were used [18,21]. The most frequent delivered dose was 45 Gy in 25 fractions [19,20,21,23]. The target volume was defined as anal region and pelvic nodes in all studies [13,14,15,16,17,18,19,20,21,22], while inguinal nodes were included in 8 series [15,16,18,19,20,21,22,23]. CT was used either as neoadjuvant in 3 studies [17,20,21] or concomitant treatment in all studies [14,15,16,17,18,19,20,21,22,23]. The concomitant CT schedules were heterogeneous with 1 course [14,16,17,19], 2 courses [15,16,17,18,19,20,21,23], or weekly schedules [18,21] administered in the different studies. At times, even in the same study, different CT protocols were prescribed [17,18,19,21]. MMC and 5-FU combination were the most frequently used agents [14,15,18,21,22,23]. Table 2 shows a summary of treatment features. In all studies, there was a gap between EBRT and BRT boost [14,15,16,17,18,19,20,21,22,23]. The median gap ranged from 27 to 56 days in individual studies. Before BRT boost, tumor response assessment was reported in 6 studies: in 4 studies using a digital rectal examination [17,21,22,23], in one study by ultrasound [18], while in one other study the evaluation modality was not specified [15].

BRT boost characteristics

Interstitial BRT using ^{192}Ir source was the technique performed in all studies [14,15,16,17,18,19,20,2,22,23]. In 2 studies, an anal cylinder was inserted to displace uninvolved anal-rectal mucosa from the high-dose region [18,19]. Different dose rates were used: low-dose-rate (LDR) in 7 studies [14,15,16,17,20,21,23], pulsed-dose-rate (PDR) in three studies [19,21,22], and high-dose-rate (HDR) in one study [18]. The LDR group was the largest with 7 studies (which included 904 patients) [14,15,16,17,20,21,23]. Median prescribed dose ranged from 10 to 40 Gy. In PDR group, 3 studies (176 patients) were included [19,21,22]. Median prescribed dose ranged from 8 to 25 Gy. HDR was used only in 1 study (50 patients) based on ultrasound-guided technique (EUS). In the first 5 patients, 12 Gy in 2 fractions were prescribed but due to toxicity, dose and fractionation were changed to 8 Gy in 2 fractions in the subsequent patients [18].

Table 2. Summary of treatment features

Authors (reference)	EBRT		Chemotherapy		Median gap between EBRT & boost (days)	Brachytherapy boost	
	Median dose (Gy)/ number of fractions, target	EBRT planning technique	% neoadjuvant	% pts concomitant (number of courses)		Dose rate	Total dose median (range) Gy, planning technique
Papillon *et al.* [14]	35/15 AR + PN	2D	–	5-FU + MMC: 40.3	56	LDR	15-20; 2D
Sandhu *et al.* [15]	40-50/20-25 AR + PN + IN	2D/3D	–	5-FU + MMC: 15.7	35	LDR	20-40; 2D
Weber *et al.* [16]	40/22 AR + PN + IN	2D	–	5-FU + MMC: 100 (1/2)	37.5	LDR	18 (17-20); 2D
Chapet *et al.* [17]	30/10 (71.8%) or 39/13 AR + PN	2D	23.9	5-FU + CDDP: 56.3 (1/2)	42-56	LDR	20 (15-25); 2D
Doniec *et al.* [18]	45/25 AR + PN + IN	3D	–	5-FU (weekly) + MMC (1^{st} and 5^{th}): 46.0	28-42	HDR	NR (8-12)/2 fr; 3D
Bruna *et al.* [19]	45.5*/25 AR + PN + IN (24%)	2D/ 3D	–	5-FU + CDDP: 66.1 (1/2)	28	PDR	17.8 (10-25); 2D
Hannoun-Levi *et al.* [20]	45.1/25 (90%) AR + PN + IN (46%)	3D	10.0	FU + CDDP: 72.0 (2)	30	LDR	17.4 (10-25); 2D
Lestrade *et al.* [21]	45*/25 AR + PN + IN (19.0%)	2D/3D/IMRT	8.6	5-FU + CDDP: 49.7 5-FU + MMC: 14.8 (2: 81.5 and 1: 11.9)	32	LDR: (72.2%)/ PDR (27.8%)	18 (10-31.7); 2D
Gryc *et al.* [22]	50.4/28 boost (T1): 5.4; boost (≥ T2): 9, AR + PN + IN	2D/3D	–	5-FU + MMC: 82.9 (2) 5-FU mono, 5-FU + CDDP: 6.3 (NR)	42	PDR	15.5 (8-35.8); 2D, 3D
Cordoba *et al.* [23]	45/NR AR + PN-IN	2D/3D/IMRT	–	5FU + MMC: 15.5 (2) 5-FU + CDDP: 19.5; other: 2.9 (2)	27	LDR	17.2 (10-30); 2D

AR – anal region, BRT – brachytherapy, CDDP – cisplatin, CT – chemotherapy, D – dimensional, EBRT – external beam radiotherapy, fr (s) – fraction (s), HDR – high-dose-rate, IMRT – intensity-modulated radiotherapy, IN – inguinal nodes, LDR – low-dose-rate, MMC – mitomycin C, PDR – pulsed-dose-rate, PN – pelvic nodes, pts – patients, 5-FU – 5-fluorouracil

** – mean dose, % – percentage of patients*

Table 3. Summary of 5-year outcomes

Authors (reference)	LC/LRC	CSF	DFS	OS
Papillon *et al*. [14]	NR	61.4	65.9	NR
Sandhu *et al*. [15]	78.0	NR	NR	NR
Weber *et al*. [16]	70.7	NR	NR	NR
Chapet *et al*. [17]	NR	NR	75.8	63.4
Doniec *et al*. [18]	92.0	NR	74.0	82.0
Bruna *et al*. [19]	NR	NR	NR	NR
Hannoun-Levi *et al*. [20]	88.0	71.0	78.0	NR
Lestrade *et al*. [21]	78.6	79.4	80.9	69.4
Gryc *et al*. [22]	75.0	76.1	75.0	65.0
Cordoba *et al*. [23]	89.1	86.4	85.7	73.0

CFS – colostomy-free survival, DFS – disease-free survival, LC/LRC – local control/loco regional control, NR – not reported, OS – overall survival

The number of implanted planes was 1 in four studies [14,17,21,23], 1-2 in two series [19,22], not clearly specified in 3 analyses [15,16,20], and adapted to the target size (residual tumor after EBRT) in another study [18]. Dose prescription and planning strategies were based on the Paris system [25] in 9 studies [14,15,16,17,19,20,21,22,23]. However, in one series [22], the Paris system was used for dose specification and prescription, while dose calculation was performed using geometrical and manual optimization on Oncentra Brachytherapy Planning System (Nucletron, Veenendal, The Netherlands). On the contrary, the Paris system was not mentioned in the study of Doniec and colleagues [18], where 3D computer generated dosimetry planning was used to adequately cover the target (tumor bed), defined by the surface of visible residual tumor by trans-rectal ultrasound after EBRT.

Outcomes

The median follow-up ranged from 28.5 to 76.2 months in individual studies. LC/LRC was reported in 8 studies [15,16,18,19,20,21,22,23]. One study reported LC at 2 years (89.0%) [19]. Median 5-year LC/LRC was 78.6% (range, 70.7-92.0%) [15,16,18,20,21,22,23]. CFS was reported in 6 studies [14,19,20,21,22,23]. Median 5-year CFS was 76.1% (range, 61.4-86.4%) [14,20,21,22,23].

OS was reported in 9 studies [14,17,18,19,20,21,22,23]. One study reported the crude rate (65.9%) [14] and another study reported 90.0% 2-year OS [19]. In other studies, median 5-year OS was 69.4% (range, 63.4-82.0%), while 5-year DFS ranged from 65.9% to 85.7% (median, 75.8%) [17,18,21,22,23]. In the LDR group [14,15,16,17,20,21,23], median 5-year LC/LRC, CFS, DFS, and OS were: 78.6% (range, 70.7-89.1%), 75.2% (range, 61.4-86.4%), 78.0% (range, 65.9-85.7%), and 69.4% (63.4-73.0%), respectively. In the HDR study, 5-year LC/LRC, OS, and DFS were 92%, 74%, and 82%, respectively [18]. In the PDR group [19,21,22], one study reported the outcome at 2 years (CSF: 89%; OS: 90%) [19], while another study did not differentiate the results based on dose rate (LDR and PDR) [21]. Table 3 shows a summary of outcomes.

Toxicity

Acute toxicity was reported in 5 studies [14,17,18,21,22]. The most frequent toxicities were: cutaneous [17,21,22], hematological [17,21,22], and diarrhea [21,22]. Other reported toxicities were: intermittent anal-rectal bleeding [14], vulvo-vaginal symptoms [21], severe sphincter necrosis [18], urinary toxicity [21], nausea-vomiting [17], and painful necrotic ulcerations [14]. Late toxicity was reported in 8 studies [14,15,17,18,19,21,22,23]. The most frequent were radio-necrosis [14,15,17,19], rectal bleeding [14,17,19,22], proctitis [15,22,23], and incontinence [15,18,19,23]. Some studies reported anal ulceration [17], cystitis [23], and pain [19,23]. Table 4 shows a summary of acute and late toxicity results in more detail.

Permanent colostomy related to toxicity was reported in 8 studies [14,15,17,18,19,20,21,23], with 3.7% median rate (range, 2.7-5.3%) [14,15,17,18,19,20,21,23]. The most frequent toxicities leading to colostomy were: radio-necrosis [14,15,17,18,19], incontinence [15,18,23], and bleeding [14].

The sphincter function was evaluated in 2 studies [15,21]. Lestrade and coworkers used Womack's scale [26] and the results were: total continence to gas in 82.0% of patients, incontinence to gas in 15.0%, and incontinence to liquid stools in 3.0% of patients [21]. In the study of Sandhu *et al*., where the used scale was not reported, 71.0% of patients were totally continent with normal anal function [15].

Comparisons

No direct comparison between different dose rates was found in this systematic review, while 4 studies reported patients who also underwent EBRT boost [16,17,20,22] and some comparisons were performed.

In the CORS-03 study, overall treatment time (OTT) was longer in EBRT boost (median, 82 days) compared to BRT group (median, 69 days). BRT boost technique in both univariate and multivariate analysis was associated with lower local recurrence rates (LRR). In the group of patients with OTT < 80 days, 5-year local relapse rate was significantly reduced by BRT boost (BRT: 9.0% vs. EBRT: 28.0%; $p = 0.03$). On the contrary, in the OTT ≥ 80 days group, LRR was not significantly affected by the boost technique (BRT: 29.0% vs. EBRT: 38.0%; $p = 0.21$). Other statistically significant factors associated with lower LRR were T1-2 stage and OTT (OTT < 80 days: 14.0%, OTT ≥ 80 days: 34.0%; $p = 0.005$). In the multivariate analysis, OTT and nodal status were the only prognostic factors for CFS and OS. No correlation was observed between boost technique and OS and CFS [23].

Gryc and colleagues reported no differences in locoregional recurrences (24.0% vs. 19.0%), CFS (76.1% vs. 82.1%), OS (64% vs. 69%), and grade 4 late proctitis (2.0% vs. 1.0%) between BRT boost and EBRT boost, despite higher rate of patients with residual disease at 6 weeks after RCT in the BRT group [22]. Chapet *et al*. in univariate analysis observed an improvement of OS in patients treated with BRT boost, but it was not confirmed at multivariate analysis. Age (≤ 75 years) and tumor response

Table 4. Summary of toxicities and sphincter function

Authors (reference)	Toxicity/sphincter function scale	Acute toxicity %	Late toxicity (%)	Colostomy related to toxicity (%)	Sphincter function (%)
Papillon *et al*. [14]	NR/NR	necrotic ulcerations: 6.0; intermittent AR bleeding: 15.0	radionecrosis/ rectal bleeding: 2.7	radionecrosis/ rectal bleeding: 2.7	
Sandhu *et al*. [15]	NR/NR	NR	Moderate fibrosis: 6.5, stricture: 2.6, proctitis: 5.2, ulceration/ necrosis, incontinence: 3.9	ulceration/ necrosis, incontinence: 3.9	totally continent: 71.0
Weber *et al*. [16]	NR/NR	NR	NR	NR	NR
Chapet *et al*. [17]	RTOG-EORTC/NR	G2-3 nausea-vomiting: 40.0; G3 hematological: 3.0	Anal ulceration: 15.8; G3 rectal bleeding: 8.7; anal necrosis: 5.3	anal necrosis: 5.3	NR
Doniec *et al*. [18]	NR/NR	mild proctitis; severe sphincter necrosis: 2.0	mild continence: 4.0; sever incontinence: 4.0	severe incontinence: 4.0, severe sphincter necrosis: 2.0	NR
Bruna *et al*. [19]	LENT-SOMA/NR	NR	G3 toxicity (pain, bleeding, fecal incontinence or necrosis): 14.0, G4 radionecrosis: 2.8	G4 radionecrosis: 2.8	NR
Hannoun-Levi *et al*. [20]	NR/NR	NR	NR	3.5	NR
Lestrade *et al*. [21]	CTCAE v. 4.0/ Womack scale	G3 toxicity: 13.3 (skin: 5.7, AR: 4.3, vulvo-vaginal: 1.4, diarrhea: 1.4, urinary: 0.4); G3 toxicity related to chemotherapy: 4.6	G3-4 AR toxicity: 6.3	G4 AR toxicity: 2.8	totally continent: 82.0, incontinence to gas: 15.0, incontinence to liquid: 3.0
Gryc *et al*. [22]	NR/NR	G3-4 toxicity: diarrhea; proctitis: 42.0; skin: 26.0; urinary: 2.0; hematological: 50.0	G3-4: proctitis: 16.0; diarrhea: 3.0	NR	NR
Cordoba *et al*. [23]	CTCAE v. 4.0/NR	NR	G2-4 toxicity: proctitis: 26.2, anal incontinence: 10.7, intermittent rectal bleeding: 3.8, cystitis: 2.9, rectal ulcerations: 1.9, lymphedema: 0.9, perineal pain: 0.9	severe incontinence: 3.8	NR

AR – anorectal, BRT – brachytherapy, CTCAE – common terminology criteria for adverse event, EBRT – external beam radiotherapy, EORTC – European Organization for Research and Treatment of Cancer, LENT – late effects normal tissue task force, NR – not reported, RTOG – Radiation Therapy Oncology Group, SOMA – subjective, objective, management, analytic

after the first radiotherapy course significantly correlated with OS at multivariate analysis (p = 0.01). Patients treated with LDR BRT boost technique, concurrent CT, and with better tumor response before boost showed higher DFS at multivariate analysis [17]. In the series of Lestrade and colleagues, the risk of severe late toxicity was increased in patients receiving a total dose higher than the median value, with 2.7% and 10.0% rates after doses of ≤ 63 Gy versus > 63 Gy (p = 0.02), respectively. At multivariate analysis, concomitant CT (p = 0.008) and LC (p < 0.001) had a positive impact on OS [21].

Discussion

RCT is currently the standard treatment of AC with 5-year LC ranging between 68% and 87% [27,28,29,30], while surgery is reserved only for patients with local failure after previous irradiation. We performed this analysis to define the role, optimal dose, and techniques of BRT boost in AC. Ten studies were included in this systematic review [14,15,16,17,18,19,20,21,22,23].

From this review, median 5-year LC/LRC, CFS, and OS were: 78.6% (range, 70.7-92.0%), 76.1% (range, 61.4-86.4%), and 75.8% (range, 65.9-85.7%), respectively.

In the studies with delivered doses lower than 40 Gy, no data about LC/LRC were reported [14,17]. From LDR studies with total EBRT dose > 40 Gy [15,20,21,23], Sandhu *et al*. used the highest BRT boost dose (range, 20-40 Gy) and reported LC crude value of 78.0% [15]. Doniec *et al*. used HDR irradiation modality with a dose of 8-12 Gy given in 2 fractions using endorectal ultrasound (US)-guided technique and reported a LC rate of 92.0% [18]. This positive result might have been related to the optimal identification of the residual disease in real time during the implant. Unfortunately, this cannot be confirmed by other studies due to the different dose-rates used.

The lowest CFS was reported in the earliest study (61.4% crude value) and this result could be related to low EBRT total dose (35 Gy/15 fractions) [14]. The lowest DFS (65.9%) [14] and the lowest OS (63.4%) [17] were recorded in the two earliest series in terms of enrollment. According to the European Society for Medical Oncology-European Society of Surgical Oncology-European Society of Radiotherapy and Oncology AC guidelines 2014, the standard dose recommended for T1-T2 is at least 45-50 Gy, and even higher doses are recommended for more advanced tumors [8].

Due to heterogeneity of the scoring systems, in some studies not explicitly reported [14,15,16,18,20,22], comparisons about toxicity are particularly difficult. Most frequently reported severe acute toxicities were: skin (range, 2.0-5.7%) [21,22], bone marrow (range, 0.4-26.0%) [17,21,22], and bowel (range, 1.4-6.0%) [21,22]. The lowest rate of toxicity was reported by Doniec *et al*., who used 3D-EBRT followed by 3D-US-guided HDR-BRT boost with an anal cylinder in place to supersede uninvolved mucosa from the high dose area [18]. Due to the lack of comparison with other studies, it is difficult to define the relative contribution of all these factors. Severe late toxicity requiring permanent colostomy ranged from 2.7% to 5.3% [14,15,17,18,19,20,21,23], in most cases due to incontinence (range, 3.8-4.0%) [15,18,23], and bleeding (2.7%) [14]. Clear correlations between BRT technique and toxicity-induced colostomy rates are lacking.

In this review, only two studies reported the sphincter function and again it is difficult to make any meaningful comparisons [15,21]. Furthermore, none of the analyzed studies included in this review reported quality of life (QoL) of patients undergoing BRT boost with a formal assessment. However, lack of an anal cancer-specific QoL measure is not only limited to patients treated with BRT boost, even to RCT alone [30].

To evaluate more specifically the role of a BRT boost, we compared the results of patients treated with RCT ± boost in randomized trials [27,28,29,31,32] with the ones of the current review. Of course, we report this data being aware of the difficulty and the high-risk of bias in comparing randomized trials with retrospective series. In the randomized trials, 5-year LC/LRC, CFS, and OS with RCT alone were: 74.0% (range, 67.7-83%), 71.5% (range, 46.9-77.1%), and 68.2% (range, 56-80%), respectively. Therefore, the current systematic analysis showed higher outcomes regarding every endpoint hence supporting the addition of BRT boost after RCT in AC. In our analysis, we chose a relatively high threshold of 40 patients in order to analyze only numerically representative series and therefore, with more reliable results due to higher statistical homogeneity. However, some interesting series [33,34,35] with smaller sample size (< 40 patients receiving BRT boost) have been published in the last decades. Saarilahti *et al*. reported a trend towards lower incidence of radiation proctitis in patients receiving the final boost dose by HDR-BRT compared to EBRT (p = 0.065) [33]. In the series of Widder *et al*. the delivery of BRT boost was not significantly related to survival, LC, or time to colostomy at multivariate regression analysis [34]. Falk *et al*. treated 28 patients by split-course EBRT and HDR-BRT with or without CT. Two-year LRC, DFS, and OS were 83%, 71.8%, and 87.7%, respectively [35].

In terms of comparison between the different studies using BRT boost, it should be stressed that the best results in terms of LC and acute toxicity were recorded in the study using 3D-US-guided BRT. This suggests that the use of advanced techniques could improve the results of BRT boost. Further improvements could be produced by more sophisticated planning and delivery techniques. Tagliaferri *et al*. [36] described their advanced BRT technique experience in AC. They evaluated the feasibility of using multiparametric MRI with compatible applicator for image-guided adaptive brachytherapy (IABT). With 11 patients included in the study, the median target volume covered by 200%, 150%, 100%, 90%, and 85% of the prescription dose were 24.6%, 53.4%, 93.5%, 97.6%, and 98.7%, respectively. The median coverage index and median overdose volume index were 0.94 and 0.27, respectively. The authors concluded that multiparametric MR/CT-IABT for AC is feasible and promising based on the planning results [36].

This review is the first to systematically summarize the results of BRT as boost in AC. The level of evidence of the studies was low, 3 according to SIGN criteria. We used this relatively simple system being aware of the lack of prospective studies in literature. Therefore, a proper

assessment of this treatment modality should require prospective trials possibly based on advanced delivery techniques as image-guided adaptive BRT.

Disclosure

The authors report no conflict of interest.

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