Radiotherapy and Oncology 171 (2022) 43–52

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review Article

High dose rate brachytherapy in the management of anal cancer: A review

Zakariya S. Ali [a], Eden Solomon [b], Paveen Mann [c], Shun Wong [d,e], Kelvin K.W. Chan [d,e], Amandeep S. Taggar [d,e,*]

[a] Royal College of Surgeons in Ireland, Dublin, Ireland; [b] University of Waterloo, Waterloo, Canada; [c] Switch Health, Toronto, Canada; [d] Sunnybrook Health Sciences Centre, Toronto, Canada; [e] University of Toronto, Toronto, Canada

ARTICLE INFO

Article history:
Received 2 September 2021
Received in revised form 25 March 2022
Accepted 28 March 2022
Available online 4 April 2022

Keywords:
Anal cancer
High dose rate
Brachytherapy
Review

ABSTRACT

Purpose: To conduct a systematic review evaluating the impact of high dose rate (HDR) brachytherapy (BT) on the clinical outcomes and toxicities of patients with anal cancer.

Methods and materials: A search of Medline, Embase, and Cochrane Library databases was performed using search terms: "anal", "anal canal", "squamous", "adenocarcinoma", "cancer", "neoplasm", in combination with "brachytherapy", "high dose rate brachytherapy" or "HDR brachytherapy". Additional studies were identified after scanning references. Studies published in English with ≥10 patients were included.

Results: Ten studies (n = 448) were included in this review. 321 patients were treated with curative intent external beam radiotherapy (EBRT), chemotherapy (CT) and HDRBT; of those, 312 and 9 received interstitial and intraluminal BT, respectively. Mean follow up was 39.9 months (range (R): 24–61 months). Complete response was noted between 80%-93% and local control ranged between 81%-88%. Mean rate of local failure was 12.3% (SD 3.6%, R: 8%-18%). Distant failure rate was reported between 2%-3% and metastasis free survival ranged between 82%-88%. Mean disease free survival and overall survival were 77.3% (SD 6.6%, R: 66%-100%) and 82.5% (SD 13.7%, R: 70%-87.7%). Acute toxicity was mostly grade 1/2 dermatitis, proctitis or cystitis; G3 or higher toxicity was reported only in 4 patients in 2 studies (dermatitis n = 3 and sphincter necrosis n = 1). Most common long term toxicities were incontinence (2.5%-9%) and proctitis (2.5%-19%); G3/4 toxicity ranged between 2.2%-7.1%. Mean sphincter preservation rate and colostomy free survival was 88.0% and 80.4%, respectively.

Conclusion: Pooled analysis in this review suggests excellent response, local control and survival with HDRBT in combination with EBRT and CT, with limited toxicity. Prospective well conducted trials are needed to further establish role of HDRBT management of anal cancer with future focus on development of international consensus on patient selection, dosimetric parameters, treatment sequencing as well as defining uniform outcome and toxicity assessment.

 Radiotherapy and Oncology 171 (2022) 43–52

Anal cancer (AC) is an uncommon disease, yet over the past decade the incidence of anal cancer has increased by 2.2% each year [1]. Development of anal cancer is strongly associated with the presence of human papilloma virus (HPV) infection, with >90% of anal cancers directly attributed to HPV [2].

Historically surgical resection was the curative treatment option for operable anal cancer. However, surgical resection (abdominoperineal resection) does result in less favourable outcomes [3] and the resultant colostomy can have a significant adverse effect on patients' quality of life (QOL) [4,5]. Therefore, radiation plus chemotherapy is the current standard for treatment of anal cancer as it results in good control of primary disease while preserving normal anatomy and function [6]. External beam radiation therapy (EBRT) is the standard approach for delivering radiation in anal cancer; however, it can result in high integral dose. In addition, it has been observed that locally advanced large HPV-related and non-HPV related tumours are more likely to fail locally [7]. Therefore, there is a need to deliver higher dose for these locally advanced tumours. Unfortunately, an attempt to increase EBRT dose would further increase the integral dose and increase the probability of normal tissue complications. IMRT has been shown to reduce the dose to normal tissue and reduce acute toxicity, however, doses have not exceeded 63 Gy due to limited data on late toxicity [8]. Image-guided high-dose rate (HDR)

* Corresponding author.
E-mail addresses: aman.taggar@sunnybrook.ca, aman.taggar@sunnybrook.ca (A. S. Taggar).

https://doi.org/10.1016/j.radonc.2022.03.019
0167-8140/

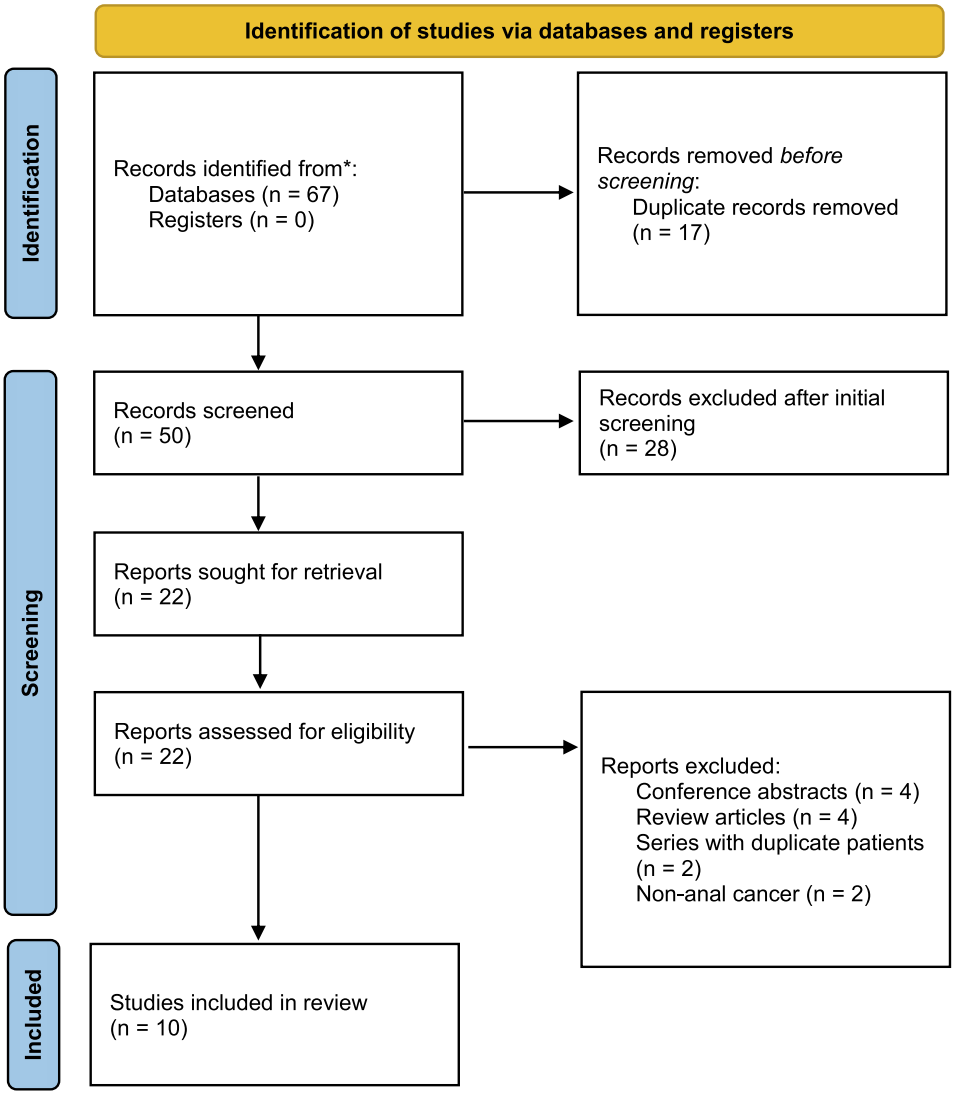

Fig. 1. PRISMA flow diagram.

brachytherapy (BT) is an attractive alternative for dose escalation. With its ability to place the source of radiation directly into the tumour, brachytherapy has an effective therapeutic range of 0.5–2 cm with a steep dose gradient that minimizes the effect on normal tissue while allowing for higher doses to be delivered to the tumour [9]. Furthermore, image guided HDRBT has demonstrated improved tumour control, survival and reduction in toxicity in other pelvic tumours, such as cervix and prostate [10,11].

There are multiple studies published highlighting the benefit of HDRBT in treatment of AC. These studies, however, individually are too small to make a conclusive argument for or against role of brachytherapy in the treatment of this disease. Previously published systematic review by Frakulli *et al.* demonstrated efficacy of BT boost in AC patients [12]. However, 9 out 10 studies in that review performed low dose rate (LDR) and only one did HDRBT [12]. The aim of this review is to systematically review available literature in HDRBT and to synthesize conclusions regarding local control, overall survival, sphincter preservation, and complications.

Methods

An electronic literature search was performed to identify published studies exploring the use of HDRBT in AC patients. Medline, Embase and Cochrane databases were scanned for articles written in English and published in peer-reviewed journals until December 2020. Any combination of following terms: "anal", "anus", or "anal canal", "squamous", "adenocarcinoma", "cancer", or "neoplasm", in combination with "brachytherapy", "high dose rate brachytherapy" or "HDR brachytherapy" was used to detect potentially eligible studies (search strategy attached in supplementary file). Additional publications were identified by scanning references. Studies published in English and reporting outcomes of $\geq$ 10 patients treated with or without external beam radiotherapy (EBRT), chemotherapy, and surgery were included. Studies using LDBRT or studies with repeated data sets were excluded. If two or more publications reported on same series of patients, only data from the largest and/or more recent series were included in the analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed for screening and inclusion of papers in the final analysis and synthesis [13,14]. (Fig. 1).

Two reviewers (E.S. and A.T.) independently screened the titles and abstracts for eligibility. Discrepancies were resolved through consensus. The eligible studies were then independently reviewed by three reviewers (Z.A., E.S., and A.T.). Data were extracted from the studies and tabulated in Excel (Microsoft, Redmond, WA).

The treatment-related data extracted included tumour characteristics, surgical, chemotherapy, EBRT and HDRBT details. The

Table 1
Study Characteristics. NOS – Newcastle-Ottawa Scale for quality assessment of non-randomized studies. Overall survival (OS), local relapse free survival (LRFS), colostomy free survival (CFS), metastasis free survival (MFS), disease free survival (DFS), disease specific survival (DSS), local control (LC), local regional control (LRC), complete remission (CR), partial remission (PR).

Study	Country	Design	Study Period	Patients, *n*	Inclusion Criteria	Study Endpoints	NOS Score
Bertin et al, 2018 [19]	France	Retrospective, Single Institution	2005–2018	46	Squamous Cell Carcinoma Circumference < 2/3 anal canal non-metastatic	Primary: OS Secondary: LRFS, CFS, MFS, DFS	6
Varela Cagetti, et al 2019 [20]	France	Retrospective, Single Institution	2000–2017	100	Biopsy proven anal carcinomaCircumference ≤ 1/2 of anal canal	5-year LC, DFS, OS, and CFS	8
Doniec et al, 2006 [22]	Germany	Retrospective, Single Institution	1993–2001	50	Histology confirmed (squamous, basaloid, or transitional)non-metastatic	5-year DSS	6
Falk et al, 2014 [26]	France	Retrospective, Single Institution	2005–2013	28	Histology confirmed (squamous (*n* = 25), adenocarcinoma (*n* = 3)) Circumference < 2/3 anal canal non-metastatic	2-year LRFS, MFS, DFS, OS	6
Kapoor et al, 2014 [21]	India	Retrospective, Single Institution	2007–2011	16	Biopsy proven anal Carcinoma Circumference < 2/3 anal canal Lesion < 1 cm thick	1- and 2-year LC and OS	6
Kapp et al, 2001 [23]	Austria	Retrospective, Single Institution	1987–1998	39	Biopsy proven epidermoid carcinoma of anal canal Stages T1-4, any N, M0 Performance status ≥ 80 Age ≥ 18	LRC, DSS, Sphincter Preservation	6
Lohnert et al, 1998 [24]	Germany	Prospective, Single Institution	1992–1997	18	Histology proven cancer of the Anal Canal M0	CR	6
Oehler-Janne et al, 2007 [16]	Switzerland	Retrospective, Single Institution	1988–2003	81	Histology proven invasive cancer of the Anal Canal		9
Saarilahti et al, 2008 [17]	Finland	Retrospective, Single Institution	1996–2006	59	Squamous cell carcinoma Patients deemed eligible for brachytherapy: tumors with ≤ 1/2 circumference of anal canal and without any adjacent organ infiltration.	Acute and Late Toxicity, and LRC	8
Tagliaferri et al, 2015 [25]	Italy	Prospective, Single Institution	2012–2014	11	Histology confirmed anal carcinoma Patients with initial T4 or residual disease after EBRT) Tumor circumference ≤ 1/2 of anal canal KPS ≥ 80	Safety, target coverage, acute and late Toxicity	6

clinical outcome measures extracted included complete response (CR)/partial response (PR) rate, sphincter preservation, local control (LC) local failure (LF), regional failure (RF), distant failure (DF), overall survival (OS), procedure related complications and radiation therapy toxicity. For studies that did not report numerical survival value, it was obtained by reading off a survival curve where available. Weighted means were calculated as a summary measure using the following formula: weighted mean = $\Sigma wx/\Sigma w$ where "x" is the outcome and "w" is the sample size [15].

Results

Ten studies with total of 448 patients from seven different countries were included in this review; eight were retrospective and two were prospective cohorts. The overall time period for all included studies ranged from 1987-2018. Eight out of 10 studies indicated the use of HDRBT as a curative modality in conjunction with EBRT and in 2 studies the intent was not specified. Eligibility criteria for individual studies included are listed in Table 1, and most of the studies included patients to be treated with BT if tumour circumference was ≤1/2 of the anal canal.

Treatment, brachytherapy technique, dose and fractionation

Treatment regimens were heterogeneous across the studies, as seen in Table 2. All patients (*n* = 448) received EBRT, while BT boost was administered to 371 (82.8%) patients; 77 (17.2%) patients in 2 studies [16,17] received EBRT boost. Combination of EBRT and chemotherapy was administered across all 10 studies to *n* = 345 (77%) patients. The most common chemotherapy regimen was Fluorouracil (5FU) plus Mitomycin C (MMC), followed by 5FU plus cisplatin. In instances where combination chemotherapy was contraindicated, single agent 5FU, oral Capecitabine or weekly cisplatin was used. Median dose of EBRT was 45 Gy (range: 40–51) in 25 fractions (20–27 fractions), delivered in 1.8–2.0 Gy per fraction as per institutional practices.

Total of 371 patients underwent brachytherapy boost after chemoradiation: nine studies used HDRBT exclusively (*n* = 271) and Varela Cagetti *et al.* used both HDR (*n* = 50) and low dose rate (LDR, *n* = 50). Details for brachytherapy technique, type of anaesthesia, target volumes and image guidance for placement of catheters and treatment planning are highlighted in Table 3. The main criteria for patient selection for BT among all studies was that tumour must be ≤2/3rd the circumference of the anal canal to limit sphincter dysfunction. All 10 studies employed interstitial brachytherapy technique and most prescribed dose based on the Paris system [18]. Kapp *et al.* used both interstitial and intraluminal techniques and delivered 6 Gy boost in single fraction. In most cases, interstitial needles were placed using a custom designed perineal template with a anal/rectal cylinder of 20–25 mm external diameter. Most studies utilized 3D imaging (CT *n* = 5, TRUS *n* = 2, CT + MR *n* = 1) for treatment planning. All, expect one study, performed BT implants under general anaesthesia. The median dose was 6 Gy (range: 4–21) in median of 2 fractions (range: 1–7).

Clinical outcomes

Local control

Eight out of 10 studies reported on LC, CR, PR rates, Table 4. LC reported by 3 studies ranged from 94% at 1 year to 81% at 5 years

Table 2
Treatment Details. EBRT – external beam radiotherapy, BT – brachytherapy, HDR – high dose rate, LDR – low dose rate, CTV – clinical target volume, GTVd – gross tumor volume at diagnosis, GTV_{BT}– gross tumor at BT, TRUS – transrectal ultrasound, 5FU – 5Fluorouracil, APR – abdomino-perineal resection, NR – not reported.

Study	EBRT details median dose (range) (Gy)/fractions (range)	BT details Technique, (*n*) Median dose (range) (Gy)/# fractions (range)	BT prescription & planning details	Surgery, *n*	Chemotherapy, *n*	Chemotherapy Drugs	Overall Treatment Time (Days)
Bertin et al, 2018 [19]	45 (36–50.4)/25 (20–28)	Interstitial, (*n* = 46) 12 Gy (10–18)/3 (2–6)	Implant/planning system: Paris Planning imaging: post-implant CT scan CTV = GTV_d + GTV_{BT}	*n* = 7 colostomies, post RT	33 pts (71.17%) Concomitant	T > 2 or N > 1 1) 5FU + Mitomycin C (*n* = 26) 2) 5FU + Cisplatin (*n* = 6)	44–51
Varela Cagetti et al, 2019 [20]	44.5 (30–46)	Interstitial HDR, (*n* = 50) 12 Gy (12–20)/3–4 fractions Interstitial LDR, (*n* = 50) 18.5 Gy (14–24)/4 wires, treatment time 25.5 hours	Implant/planning system: Paris Needles placed using Papillon's template. Planning imaging: post-implant CT scan CTV = GTV_d + 10 mm	*n* = 8 salvage APR (3 LDR and 5 HDR) *n* = 1 wide local resection	61 pts (61%) Concomitant	1) 5FU + Mitomycin C (*n* = 33) 2) 5FU + Cisplatin (*n* = 18)3) Weekly Cisplatin (*n* = 6)4) Xeloda (*n* = 4)	Median: 55.5 (35–111)
Doniec et al, 2006 [22]	45/25	Interstitial (*n* = 50) 10 Gy (8–12)/2	Implant/planning system: TRUS generated pre-plan 3D dose planning: No CTV = TRUS-guided visual tumor	*n* = 5 (10%) salvage APR; 4 local recurrence, 1 necrosis	50 pts (100%) Concomitant	5FU + Mitomycin C	65–100
Falk et al, 2014 [26]	45 (43.2–52)/25 (23–26)	Interstitial (*n* = 28) 12 Gy (10–15)/3	Implant/planning system: NR 3D dose planning: CT scan images CTV = GTV_d + 10 mm		21 pts (75%) Concomitant	1) 5FU + Mitomycin C (*n* = 17) 2) 5FU + Cisplatin (*n* = 4)	Median: 63 (38–74)
Kapoor et al, 2014 [21]	*n* = 16: 40–45/20–25	Interstitial *n* = 7: 21 Gy/7 *n* = 9: 18 Gy/6	Implant system: Syed-Neblett template 3D dose planning: CT scan images CTV = clinical exam at time BT	*n* = 2 salvage APR due to recurrence	16 pts (100%) Concomitant	1) 5FU + Mitomycin C (*n* = 10) 2) 5FU + Cisplatin (*n* = 6)	Median: 24 (15–38)
Kapp et al, 2001 [23]	50–50.4/25–28	Interstitial (*n* = 35) or Intraluminal (*n* = 4) after initial 30 Gy EBRT 6 Gy/1 2nd interstitial in patients with residual after 50 Gy EBRT (*n* = 7) 6 Gy/1	Implant/planning system: Paris 3D dose planning: No CTV = NR	*n* = 8 salvage APR due to uncontrolled tumor	28 pts (72.0%) Concomitant	5FU + Mitomycin C	Median: 58 (34–120)
Lohnert et al, 1998 [24]	45/25	Interstitial (*n* = 13) or Intraluminal (*n* = 5) 8 Gy (4–28)/2 (1–7)	Implant/planning system: NR 3D dose planning: TRUS CTV = NR	5 pts - prior incomplete Local Excision 1pt. - prior APR 1pt. - prior Colostomy	9 pts (50%), primarily for T3 or T4	5FU + Mitomycin C	77–91
Oehler-Janne et al, 2007 [16]	45/25 EBRT Boost (*n* = 47): 14.4/8	Interstitial, (*n* = 34) 14 Gy/7 (over 3 days given 21 days post EBRT)	Implant/planning system: Paris 3D dose planning: No CTV = NR	5 pts - Radical Surgery w Colostomy, prior to RT11 pts - salvage surgery (7 pts with EBRT and 4 pts with BT Boost)	58 pts (71.6%) Concomitant	5-FU + Mitomycin C (or Cisplatin if MMC contraindicated)	59 +/- 19
Saarilahti et al, 2008 [17]	45/25 EBRT Boost (*n* = 30):8.5 (5.4–18)/3–10	Interstitial (*n* = 29) 5–6 Gy/1–2 fractions	Implant/planning system: Paris 3D dose planning: No CTV = NR	12 pts - APR due to local recurrence	59 pts (100%) Concomitant	5FU + Mitomycin C	43 (31–79)
Tagliaferri et al, 2015 [25]	51 (44–58.5)/35 (22–32)	Interstitial, (*n* = 11) 4 Gy (3.5–7)/1–2 fractions	Implant/planning system: 3D 3D dose planning: Pre-implant MRI and post-implant CT CTV: post EBRT scar seen on MRI	1pt - APR	10 pts (90.9%) Concomitant	1) 5FU + Mitomycin C (*n* = 9) 2) 5FU alone (*n* = 1)	95 (59–165)

Table 3
Brachytherapy details. BT – brachytherapy, CR – complete response, PR – partial response, US – ultrasound, CT – computed tomography, TRUS – transrectal ultrasound, MRI – magnetic resonance imaging, NR – not reported.

Study	Patient Selection	Dosing System	Implant	# Of implants	Anesthesia Type	BT target volume	BT planning	Dose	Safety Margin
Bertin et al, 2018 [19]	Tumors with ≤ 2/3 circumference anal canal were included	Paris System	Custom perineal template with 10 holes (spaced 12 mm apart). Anal cylinder with 20 mm external diameter	1	General	Residual tumor at the time of implantation and pre-treatment tumor volume	CT	CR: 12 Gy in 3 fractions over 2 days, PR: 15 Gy in 3 fractions over 2 days	4–5 mm from needles to anal mucosa
Varela Cagetti, et al 2019 [20]	Tumors with ≤ 1/2 circumference of anal canal were included	Paris System	Papillon template with needles spaced at 1 cm intervals. Anal cylinder with 25 mm external diameter	1	General	Pre-treatment tumor volume	CT	CR: 12 Gy in 3 fractions over 24 hours PR: 16 Gy in 4 fractions over 48 hours	10 mm
Doniec et al, 2006 [22]	NR	US based visible target volume optimized	Custom perineal (RASHA) applicator Anal cylinder with 25 mm external diameter	2 (7–10 days apart)	Spinal or General	Residual tumor based on US as well pre- treatment tumor volume	TRUS	8 or 12 Gy in 2 fractions	5–10 mm
Falk et al, 2014 [26]	Tumours with ≤ 2/3 circumference of anal canal were included Circumferential tumors were excluded	NR	Custom perineal template with 10 holes (spaced 12 mm spart) Anal cylinder with 20 mm external diameter	1	General	Pre- treatment tumor volume	CT	CR: 12 Gy in 3 fractions over 24 hours PR: 15 Gy in 3 fractions over 24 hours	4–5 mm from needles to anal mucosa
Kapoor et al, 2014 [21]	Tumors with ≤ 2/3 circumference of anal canal were included Tumor thickness ≤ 1 cm Patients with > 50% tumor regression after EBRT	Volume-based optimization	Syed Neblett perineal template. Catheter separation of 1 cm	1	General	Combination of clinical exam (clinical residual tumor) and CT scan abnormality	CT	21 Gy in 7 fractions twice daily 18 Gy in 6 fractions twice daily	NR
Kapp et al, 2001 [23]	NR	Intraluminal BT: prescribed to 0.5 cm from applicator surface. Interstitial BT: Paris System	Intraluminal - custom made cylinder of 20 mm diameter	1	General	Pre- treatment tumor volume plus 0.5 cm margin	NR	6 Gy	NR
Lohnert et al, 1998 [24]	NR	US based visible target volume optimized	Custom perineal (RASHA) applicator Anal cylinder with 25 mm external diameter	2	Spinal or General	Residual tumor after EBRT based on endoscopic US	TRUS	2 fractions of 4 or 6 Gy	5–10 mm
Oehler-Janne et al, 2007 [16]	T1-T3 tumors with ≤ 1 cm thickness after EBRT	Paris System	Custom perineal template	1	Local or General	NR	NR	14 Gy in 7 fractions over 3 days	NR
Saarilahti et al, 2008 [17]	Tumors with ≤ 1/2 circumference of anal canal were included No organ infiltration Circumferential tumors were excluded	Paris System	Custom perineal template with rectal cylinder of 22 mm diameter	1–2	NR	Residual tumor at the time of implantation	NR	One or Two weekly 5–6 Gy Fractions	3–5 mm left to skin surface
Tagliaferri et al, 2015 [25]	Patients with local residual disease or T4 at the time of diagnosis Tumors with ≤ 1/2 circumference of anal canal were included	Paris System plus manual volume optimization	Martinez Universal Perineal Interstitial Template (MUPIT) or TPS 081 perineal template	1–2	Spinal	Residual tumor or scar at the time of implantation	MRI and CT	3.5–7 Gy in 1–2 fractions; 2 fractions delivered 1 week apart	NR

Table 4
Clinical Outcomes. BT – brachytherapy, LC – local control, CR – complete response, PR – partial response, LF – local failure, RF – regional failure, DFR – distant failure rate, MFS – metastasis free survival, OS – overall survival, DFS – disease free survival, CFS – colostomy free survival.

Study	*n*	Patients undergoing BT, *n*	Follow-up (months), (range)	LC, CR/PR rate	LF, *n*	RF, *n*	DFR or MFS	OS	DFS	Sphincter Preservation Rate or Sphincter Dysfunction	CFS
Bertin et al, 2018 [19]	46	46	61 (9–145)	LC: 5 yr – 81.2% (SE 6.6%)	15.2% (SE 6.1%)	NR	5 yr MFS: 88.7% (SE 4.8%)	5-yr: 90% (SE 4.7%)	70% (SE 7.6%)	Sphincter Dysfunction: *n* = 2 (4.4%), due to ulceration or severe incontinence	80%
Varela Cagetti, et al 2019 [20]	100	100	42.2	LC: 90%LDR 93% vs HDR 86% (*p* = 0.38)	*n* = 9 (9%)LDR 8% vs HDR 10% (*p* = 0.73)	NR	NR	5-yr: 94% LDR 97% vs HDR 93%	5-yr DFS: 82% LDR 88% vs HDR 72% (*p* = 0.21)	NR	92%LDR 95% vs HDR 86% (*p* = 0.21)
Doniec et al, 2006 [22]	50	50	34 (6–96)	CR: *n* = 47 (92%)	*n* = 4 (8%)	NR	DFR: *n* = 1 (2%)	5-yr: 74% T1/T2: 88% T3/T4: 67%	5-yr: 82%	Sphincter Dysfunction: *n* = 10 (20%); 5 patients (10%) had recurrent/residual disease requiring APR	
Falk et al, 2014 [26]	28	28	27.5	NR	2-yr LRFS: 83% (SE 7.8%)	NR	2 yr MFS: 81.9% (SE 9.5%)	2-yr: 71.8% (SE 10.7%)	2-yr: 87.7% (SE 8.25)	Sphincter Dysfunction: 1pt definitive sphincter amputation	75%
Kapoor et al, 2014 [21]	16	16	41	LC: 1 yr – 93.8% 2 yr – 87.5%	*n* = 2 (16.5%)	NR	*n* = 1 (6%)	NR	NR	Sphincter preservation rate = 87.5%	
Kapp et al, 2001 [23]	39	39	33	CR: *n* = 31 (79.5%) PR: *n* = 8 (20.5%)	*n* = 7 (18%)	Locoregional control: 3-yr: 81% 5-yr: 76%	*n* = 1 (2.5%)	NR	3-yr: 80% 5-yr: 76%	Sphincter preservation: 77% (overall), 97% (in patients with LRC)Full anal continence (28/30, 93%)	78%
Lohnert et al, 1998 [24]	18	18	24	CR: 100%	*n* = 2 (11.1%)	NR	NR	2-yr: 100%	NR	Sphincter preservation rate = 94%	NR
Oehler-Janne et al, 2007 [16]	81	34	EBRT: 45 (+/- 33)BT: 60 (+/- 34)	CR: 93.4% (in patients without prior surgery)	5-yr (NSS) EBRT boost: 15.4% BT boost: 10.3%	5-yr Inguinal Recurrence Rate EBRT: 5.3% BT: 7.2%	EBRT: 6% BT: 3%	5-yr (NSS) EBRT: 66% BT: 66%10-yr (NSS) EBRT: 52% BT: 44%	5-yr (and 10-yr); NSS EBRT: 73% BT: 76%	10-yr sphincter preservation rate EBRT: 82% BT: 85%	NR
Tagliaferri et al, 2015 [25]	11	11	25 (7–36)	CR: 91%	1 patient with persistent disease did not complete EBRT/CT	NR	NR	NR	NR	NR	81%

[19-21]. Rate of CR ranged between 79.5% to 100% in 5 studies and the weighted mean CR was 90.5% in 141 patients from those 5 studies [16,22-25]. Kapp et al reported PR rate of 20.5% and CR rate of 79.5%, indicating overall response in all patients treated with HDRBT [23].

Failure

Local (LF), regional (RF) and distant (DF) failure are detailed in Table 4. Mean rate of LF across 9 studies was 12.3% (SD 3.6%, range: 8% – 18%). [16,19-26] In the study by Varela Cagetti *et al.* rate of LF was similar in patients undergoing HDR or LDR brachytherapy (8% and 10%, respectively, p = 0.73) [20] Oehler-Janne *et al.* did not find a significant difference in 5-year LF among patients who underwent BT boost (10.3%) compared to those who received EBRT (15.4%), even though there were more failures in cohort not receiving BT [16].

RF was reported in 2 out of 10 studies [16,23] The 3-year and 5-year locoregional control in Kapp *et al.* study was 81% and 76% respectively [23] Oehler-Janne *et al.* reported a 5-year inguinal recurrence of 7.2% in patients with BT boost compared to 5.3% in patients with EBRT boost (p > 0.05) [16].

Distant failure rate (DFR) or metastasis free survival (MFS) was reported in 6 studies, Table 4. One study reported a 2-year MFS of 81.9 (SE 9.5%) [26] Another reported 5-year MFS of 88.7 % (SE 4.8%).(19) All other 4 studies reported DFR ranging between 2% and 6% [16,21-23].

Survival

Survival outcomes were reported in six studies with total of 226 patients, Table 4. [16,19,20,22,24,26] The mean of median follow up was 41.5 months (SD 16 months, R 24 – 61 months).

Five studies reported DFS for 219 patients, all treated with brachytherapy in combination with EBRT and chemo [16,19,20,22,23] The weighted mean 5-year DFS was 77.5 % (SD 3.12, R 70% – 82%). Two studies reported 2- and 3-year DFS of 87.7% (SE 8.25%), and 80%, respectively [23,26] None of the studies provided further information regarding additional local or systemic therapies.

Four studies reported 5-year OS ranging from 74% to 93% [16,19,20,22]. Weighed mean 5-year OS among 180 patients included in these 4 studies was 81.9%. Two studies reported 2-year OS and the weighted mean was 82.8% in 46 patients [24,26]. Oehler-Janne *et al.* did not show any difference in 5-year OS between patients treated with BT boost or EBRT boost [16]. Similarly, there was no difference in 5-year OS between patients receiving HDR or LDR BT boost as reported by Varela Cagetti *et al.* [20] Patients with early (T1 or T2) disease had significantly better 5-year OS (88%) compared to those with advanced (T3 or T4) disease (67%) [22].

Sphincter preservation and colostomy free survival

Six studies with 185 patients treated with brachytherapy reported colostomy-free survival, an important surrogate for sphincter preservation [16,21-24,26] With mean follow up of 48.2 months, the weighted mean rate of colostomy free survival was 81.7% (range: 24–120). Based on available data from these studies, there does not appear to be a direct link of organ dysfunction leading to colostomy and brachytherapy treatments. Falk *et al.* had one patient with definitive sphincter amputation, prior to starting any treatment [26] Lohnert *et al.* had one patient who was incontinent due to internal sphincter damage, unrelated to radiation treatment [24] Kapp *et al.* reported 77% sphincter preservation in their entire study population and 97% in those with complete locoregional control. Oehler-Janne *et al.* reported the 10-year sphincter preservation rate of 85% in patients who received BT boost compared to 82% in those that received EBRT boost [16].

Toxicity and complications

Toxicity was reported by all studies, however reporting was not consistent among them, Table 5. Eight studies reported acute toxicity in patients undergoing brachytherapy. Most of the patients suffered from grade 2 or lower toxicity and there were only 9 cases of Grade 3 acute toxicity, which included rectal pain,[19] dermatitis/mucositis [21], and sphincter necrosis [22] Oehler-Janne *et al.* compared rates of grade 3–4 acute toxicity between patients receiving EBRT an BT and found that significantly more patients treated with EBRT suffered toxicity 43% versus 15% with BT (p = 0.008) [16].

Nine studies reported on late toxicity in patients undergoing brachytherapy with a complication rate of 25.7% among 362 patients. There were six studies with 194 patients that graded late toxicity [16,17,19,21,25,26]; across these studies. The most common late toxicity observed was grade 1 or 2 proctitis, and ranged from 2.5% to 20% [16,17,20,23-25]. Incidence of grade 3 or higher proctitis was reported by Varela Cagetti *et al.* in 3 (3%) patients [20] Saarilahti *et al.* demonstrated that rate of proctitis was worse with EBRT compared to BT boost, 37% versus 10%, respectively (p = 0.065) [17] Grade 1 and 2 incontinence was the second most common late toxicity and was observed in 6% to 18% of patients [16,20-25] There was no documented grade 3 or higher incontinence. Ulceration in the perianal skin or within the anal canal was documented in 2 studies: 1 (6%) patient in Lohnert *et al.* [24] and 7 (18%) patients in Kapp *et al.* [23] Three of the 7 patients in Kapp *et al.* series required temporary colostomy due to substantial ulceration at the site of original disease. Rectal bleeding was a rare late complication and was reported in only one study.(20) Anal fibrosis and stenosis was reported in 10% to 25% of the patients [21,25]. Other rare long term toxicities include vaginal stenosis, dyspareunia, and early grade urinary irritable symptoms, listed in Table 4. Bertin *et al.* and Falk *et al.* did not formally reported on individual toxicities, but suggested grade 1–2 GI toxicity occurs in up to 2/3rd of patients, and grade 3 or higher toxicity occurs in 4.4%–7% of patients [19,26].

Discussion

BT has been utilized for the treatment of anal cancer for many decades. A previous systematic review had shown benefit of BT boost in patients undergoing curative intent chemoradiotherapy for anal canal cancer [12]. However, 9 out 10 studies reviewed in that publication performed brachytherapy using LDR or PDR technique and only 1 study performed HDR brachytherapy. BT performed with LDR technique posed significant exposure risk to staff, patient and family members as well as required shielded hospital rooms. While PDR offer advantages of real-time dose-optimization similar to HDR and radiological benefit of longer treatment time similar to LDR, it also requires shielded hospital room, where patients have to admitted for the duration of pulsed treatment. HDRBT can have several advantages over LDR and PDR, and these include: outpatient treatment (same day implant and treatment), real-time dose optimization, ability to perform image-guided treatment (using MRI) and reduce dose to organs at risk, decrease risk to staff and patient's family, as well as reduced recurring cost. The focus of this review is to summarize all available literature on HDRBT in anal cancer with regards to local control, overall survival, sphincter preservation, and complications.

Table 5
Acute and chronic toxicities. GI – gastrointestinal, GU – genitourinary.

Study	Grade 1 (G1) and Grade 2 (G2)	Grade ≥3
Bertin et al, 2018 [19]	AcuteGI: G1 – 33 (71.7%), G2 – 3 (6.5%)GU: G1 – 19 (41.3%) , G2 – 4.3% ChronicGI: G1 – 26 (56.5%), G2 – 4 (8.7%)GU: G1 – 2 (4.3%), G2 – 1 (2.2%)	AcuteGI: G3 – 1 (2.2%) ChronicGI: G3 – 1 (2.2%), G4 – 1 (2.2%)GU: G3 – 1 (2.2%)
Varela Cagetti et al, 2019 [20]	AcuteProctitis: G1 – 10 (10%), G2 – 15 (15%)Rectal bleeding: G1 – 4 (4%), G2 – 3 (3%)Diarrhea: G1 – 1 (1%), G2 – 4 (4%) Chronic **LDR (*n* = 28, 56%) vs HDR (*n* = 17, 34%) (*p* = 0.03)***Proctitis: G1 – 7 (7%), G2 – 13 (13%)Rectal bleeding: G1 – 5 (5%), G2 – 10 (10%)Incontinence: G1 – 2 (2%), G2 – 9 (9%)Diarrhea: G1 – 1 (1%), G2 – 5 (5%)Rectal stenosis: G2 – 1 (1%)GU: G1 – 2 (2%), G2 – 5 (5%)Dyspareunia: G2 – 1 (1%)Vaginal stenosis: G2 – 2 (2%)	Chronic*Proctitis: G3 – 3 (3%)Rectal bleeding: G3 – 1 (1%)Bone fracture: G3 – 1 (1%) **One patient underwent temporary colostomy*
Doniec et al, 2006 [22]	NR	AcuteSphincter Necrosis (*n* = 1, 2%) ChronicIncontinence* (*n* = 3, 6%) **2 patients required colostomy; both were incontinent prior to therapy due to tumor infiltration*
Falk et al, 2014 [26]	Acute GI: G1 – 40.7%, GU: G1 – 37% Cutaneous: G1 – 3.7% Chronic Grade 1–43.1%; Grade 2–22%	ChronicAnal ulceration (*n* = 1, 3.5%)Necrosis (*n* = 1, 3.5%)* **required colostomy*
Kapoor et al, 2014 [21]	AcuteDermatitis: G1 – 7 (44%), G2 – 6 (37%) Proctitis: G1 – 5 (31%), G2 – 2 (12.5%). Mucositis: G2 – 8 (50%) ChronicDermatitis (*n* = 3, 19%)Incontinence (*n* = 1, 6%)Fibrosis (*n* = 4, 25%)	Acute:Dermatitis (*n* = 3, 19%)Mucositis (*n* = 3, 19%)
Kapp et al, 2001 [23]	AcuteDiarrhea (88%)Perineal, vulvar/scrotal dermatitis (75%)Dysuria (19%) ChronicProctitis: (*n* = 1, 2.5%)Sphincter Dysfunction (non-surgical) (*n* = 1, 2.5%),	ChronicUlceration (*n* = 7, 18%) *3 pts required temporary colostomy - occurred at the initial site of primary*
Lohnert et al, 1998 [24]	AcuteHematoma (*n* = 1) due to needle implantation ChronicProctitis (*n* = 1, 6%)Perianal ulcer (*n* = 1, 6%)	ChronicIncontinence (*n* = 1, 6%) *Required Hartmann procedure*
Oehler-Janne et al, 2007 [16]	Chronic:Overall: EBRT 30% vs BT 19% (*p* = 0.5)Proctitis G2: EBRT 32% vs BT 19% (*p* = 0.4)Incontinence G1-2: EBRT 28% vs BT 18% (*p* = 0.5)Qualitative sphincter digital pressure impairment: EBRT 29% vs BT 37% (*p* = 0.6)	AcuteG3/4: EBRT 43% vs BT 15%, (*p* = 0.008) G3/4 dermatitis: EBRT 23% vs BT 8%
Saarilahti et al, 2008 [17]	Acute Proctitis G ≥ 2: EBRT 37% vs BT 10% (*p* = 0.065) Skin toxicity G2-3: EBRT 21% vs BT 0%	NR
Tagliaferri et al, 2015 [25]	AcuteFecal incontinence (*n* = 1, 9%)Hemorrhoids (*n* = 2, 18%) ChronicAnal fibrosis (*n* = 1, 9%)Incontinence (*n* = 1, 9%)Proctitis (*n* = 1, 9%)	NR

The pooled data demonstrated that the use of HDRBT in the treatment of anal cancer has a high rate of sphincter preservation and complete response to treatment as well as acceptable overall survival rate. Across seven studies with 194 patients, there was an 83.5% complete response to treatment [16,22-25]. Across six studies the weighted mean rate of sphincter preservation was 84.8% at a 39.7 month follow-up [16,21-24,26]. This is comparable, if not better than that published by Frakulli *et al.* for patients treated with LDR brachytherapy boost, where they demonstrated local/local–regional control of 78.6% and colostomy-free survival of 76.1% [12]. Most importantly, the biggest benefit of HDR over LDR is increased safety of patient, family members as well as staff monitoring the treatment. The 5-year overall survival and ranges between 74% and 95% and the weighted mean 5-year survival was 81.9%. This is similar to what has been observed after EBRT in randomized RTOG trials (9811 and 0529). [3,27] Gunderson et al reported 5-year OS of 78.% and 70.7% for patients who received mitomycin and cisplatin based chemotherapy, respectively [27].

The overall rate of acute toxicity with HDRBT was acceptable (74.8%) and comparable to RTOG 0529 trial that utilized modern imaging and EBRT (IMRT) techniques. [22] This is not unexpected as all patients included in this review also received EBRT in the first phase of treatment prior to HDRBT boost, suggesting that lower grade of toxicity is perhaps a function of low dose radiation to a larger area. Whereas, Grade 3 acute toxicity was only reported in 9 patients among 2 out of 10 studies analysed in this review [19,21]. This is substantially lower than 21% and 15.7% reported in RTOG 9811 and 0529 trials, respectively [3,27]. There were no documented cases of sphincter necrosis in the acute or late term setting. Furthermore, direct comparison of patients receiving EBRT or BT boost by Oehler-Janne *et al.*, demonstrated significantly lower late toxicity in patients treated with BT [16].

Current evidence suggests high degree of association in development of anal cancer with human papilloma virus (HPV) infection. Dose de-escalation has been suggested for HPV positive cancers [28]. Presently, there are various prospective trials investigating de-escalation in HPV related anal cancers; these trials are assessing loco-regional failure rate (ACT3) or the ability to sufficiently control disease while improving health-related quality of life (QOL) (ACT4) [29]. At our institution we have successfully implemented lower-dose EBRT regimens for HPV-related anal cancers. Preliminary (unpublished) data suggests excellent tumor control and survival for patients treated in this protocol. On the other hand dose escalation may be warranted for large or HPV-negative tumors [7,30,31]. Unfortunately, the studies reviewed in this review did not provide information on HPV status, therefore we cannot draw conclusions about the effect of BT on HPV positive or negative tumors. Nonetheless, the low rates of toxicity illustrated by analysis in this review suggest benefit of BT for all AC patients. Based on the survival and toxicity analysis, BT would be the most effective method to decrease the dose to normal tissue and organs at risk while escalating dose to the gross tumor, as also demonstrated in cervix and prostate cancer patients [32,33]. Thus BT would be an excellent tool improve overall efficacy of radiotherapy treatment for both HPV-positive and negative tumors.

Limitations and future directions

There are several important limitations to this review. Firstly, the ultimate quality of the collection of data is limited by the heterogeneity and flaws of the individual series. The heterogeneity of data may be expected due to the data ranging over 30 years, resulting in variability of both stage and treatment technique over time [34]. Furthermore, it is possible that stage migration might improve outcomes over time and therefore limit the accuracy of interpretation. Next, most of the studies included are retrospective and have a small number of patients and suffer from selection bias. Additionally, lack of large-scale studies or randomized clinical trials in the data means that individually these studies are not adequate to guide management decisions. Therefore, this review provides a pooled analysis of outcomes from multiple small studies and demonstrates effectiveness of HDRBT for tumour control and survival while maintaining sphincter function as well as low toxicity, and generate hypothesis for future prospective studies.

While this review suggests favourable findings towards the use of HDRBT in the treatment of anal cancer in combination with EBRT and chemotherapy in curative setting, its role in salvage setting is yet to be defined. For patients with local recurrence, who are not surgical candidates, BT perhaps provides an alternate to abdomino-perineal resection and provides a chance for sphincter preservation. Therefore, this should also be an area of future studies, where HDRBT is offered on protocol and patients carefully monitored.

Due to the heterogeneity of the data, this review was unable to ascertain a strong conclusion on the impact of overall treatment time (OTT) in the context of brachytherapy. The CORS-03 study in the treatment of squamous cell cancer of the anal canal demonstrated that prolonged OTT resulted in worse clinical outcomes [35]. In cervical cancer, the EMBRACE II study demonstrated similar findings, citing that OTT greater than seven weeks results in a negative impact on local control [36]. With this in mind, it is prudent for future studies to consider the impact of OTT in the context of brachytherapy for anal cancer in their study designs.

While brachytherapy has demonstrated excellent outcomes in retrospective series and in this pooled analysis, but lack of robust level-1 data has impeded it widespread application for anal cancers. Therefore, future studies must be designed by standardizing the optimum HDRBT dose, fractionation and techniques. Quality of life (QOL) is also an important factor to consider for physicians and patients when choosing a treatment option. There is little or no data available on the whether HDRBT has a QOL benefit, and there are no current prospective studies evaluating QOL in AC patients treated with HDRBT. Future prospective studies should consider incorporating validated QOL tools such as EORTC QLQ-C30 and QLQ-ANL27 [37,38].

Conclusion

Anal cancer is an uncommon tumour and has multiple treatment options that include RT, combination of chemotherapy and radiation, surgery and BT. Pooled analysis in this review suggests excellent response, local control and survival outcomes with HDRBT in combination with EBRT and CT, with limited toxicity. Prospective well conducted trials are needed to further establish role of HDRBT management of anal cancer with future focus on development of international consensus on patient selection, dosimetric parameters, treatment sequencing as well as defining uniform outcome and toxicity assessment.

Funding

None.

Author contribution

Concept: AST, SW and KC
Data acquisition: ES, ZSA, PM and AST
Analysis: ZSA, AST
Manuscript writing: ZSA, AST

Manuscript editing and approval: all authors

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.03.019.

References

[1] Anon. National Cancer Institute. SEER Cancer Statistics Review (CSR) 1975-2014. SEER Cancer Stat. Rev. 1975-2014. 2018.
[2] Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst 2015;107.
[3] Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 2013;86:27–33.
[4] Jansen F, van Uden-Kraan CF, Braakman JA, van Keizerswaard PM, Witte BI, Verdonck-de Leeuw IM. A mixed-method study on the generic and ostomy-specific quality of life of cancer and non-cancer ostomy patients. Support care cancer Off J Multinatl Assoc Support Care Cancer 2015;23:1689–97.
[5] Sprangers MAG, Taal BG, Aaronson NK, te Velde A. Quality of life in colorectal cancer. Stoma vs. nonstoma patients. Dis Colon Rectum 1995;38:361–9.
[6] Glynne-Jones R, Nilsson PJ, Aschele C, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Radiother Oncol J Eur Soc Ther Radiol Oncol 2014;111:330–9.
[7] Rusten E, Rekstad BL, Undseth C, et al. Anal cancer chemoradiotherapy outcome prediction using (18)F-fluorodeoxyglucose positron emission tomography and clinicopathological factors. Br J Radiol 2019;92:20181006.
[8] Teoh S, Muirhead R. Rectal Radiotherapy–Intensity-modulated Radiotherapy Delivery, Delineation and Doses. Clin Oncol (R Coll Radiol) 2016;28:93–102.
[9] Sun Myint A, Lee CD, Gerard J-P. Rectal cancer. In: Van Limbergan E, Potter R, Hoskin PJ, editors. *The GEC ESTRO Handbook of Brachytherapy*. p. 3–14.
[10] Pötter R, Tanderup K, Kirisits C, et al. The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. Clin Transl Radiat Oncol 2018;9:48–60.
[11] Rijkmans EC, Nout RA, Rutten IHHM, et al. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. Gynecol Oncol 2014;135:231–8.
[12] Frakulli R, Buwenge M, Cammelli S, Macchia G, Farina E, Arcelli A, et al. Brachytherapy boost after chemoradiation in anal cancer: a systematic review. J Contemp Brachytherapy 2018;10:246–53.
[13] M.J. Page D. Moher P.M. Bossuyt I. Boutron T.C. Hoffmann C.D. Mulrow et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews n160 n160.
[14] M.J. Page J.E. McKenzie P.M. Bossuyt I. Boutron T.C. Hoffmann C.D. Mulrow et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews n71 n71.
[15] Buckley H, Wilson C, Ajithkumar T. High-Dose-Rate Brachytherapy in the Management of Operable Rectal Cancer: A Systematic Review. Int J Radiat Oncol 2017;99:111–27.
[16] Oehler-Jänne C, Seifert B, Lütolf UM, Studer G, Glanzmann C, Ciernik IF. Clinical outcome after treatment with a brachytherapy boost versus external beam boost for anal carcinoma. Brachytherapy 2007;6:218–26.
[17] Saarilahti K, Arponen PP, Vaalavirta L, et al. The effect of intensity-modulated radiotherapy and high dose rate brachytherapy on acute and late radiotherapy-related adverse events following chemoradiotherapy of anal cancer. Radiother Oncol 2008;87:383–90.
[18] Pierquin B, Dutreix A, Paine CH, et al. The Paris system in interstitial radiation therapy. Acta Radiol Oncol Radiat Phys Biol 1978;17:33–48.
[19] Bertin E, Benezery K, Kee DLC, François E, Evesque L, Gautier M, et al. Efficacy and tolerance of high-dose-rate brachytherapy boost after external radiotherapy in the treatment of squamous cell carcinoma of the anal canal. J Contemp Brachytherapy 2018;10:522–31.
[20] Varela Cagetti L, Zemmour C, Salem N, Minsat M, Ferrè M, Mailleux H, et al. High-dose-rate vs. low-dose-rate interstitial brachytherapy boost for anal canal cancers. Brachytherapy 2019;18:814–22.
[21] Kapoor R, Khosla D, Shukla AK, Kumar R, Gupta R, Oinam AS, et al. Dosimetric and clinical outcome in image-based high-dose-rate interstitial brachytherapy for anal cancer. Brachytherapy 2014;13:388–93.
[22] Doniec JM, Schniewind B, Kovács G, et al. Multimodal therapy of anal cancer added by new endosonographic-guided brachytherapy. Surg Endosc Other Interv Tech 2006;20:673–8.
[23] Kapp KS, Geyer E, Gebhart FH, et al. Experience with split-course external beam irradiation +/- chemotherapy and integrated Ir-192 high-dose-rate brachytherapy in the treatment of primary carcinomas of the anal canal. Int J Radiat Oncol Biol Phys 2001;49:997–1005.
[24] Lohnert M, Doniec JM, Kovacs G, et al. New method of radiotherapy for anal cancer with three-dimensional tumor reconstruction based on endoanal ultrasound and ultrasound-guided afterloading therapy. Dis Colon Rectum 1998;41:169–76.
[25] Tagliaferri L, Manfrida S, Barbaro B, Colangione MM, Masiello V, Mattiucci GC, et al. MITHRA - multiparametric MR/CT image adapted brachytherapy (MR/CT-IABT) in anal canal cancer: a feasibility study. J Contemp Brachytherapy 2015;5:336–45.
[26] Falk AT, Claren A, Benezery K, et al. Interstitial high-dose rate brachytherapy as boost for anal canal cancer. Radiat Oncol 2014;9:240.
[27] Gunderson LL, Winter KA, Ajani JA, et al. Long-term update of US GI intergroup RTOG 98–11 Phase III trial for anal carcinoma: Survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol 2012;30:4344–51.
[28] Dietz A, Wichmann G, Wiegand S. Should We De-escalate the Treatment for HPV-Positive Tumors? *Recent results cancer Res. Fortschritte der Krebsforsch. Prog. dans les Rech. sur le cancer*. 2017;206:173–181.
[29] E. Miller J. Bazan De-Escalation of Therapy for Patients with Early-Stage Squamous Cell Carcinoma of the Anus Cancers 13 9 2099.
[30] Joo JiHyeon, Park J-H, Yoon SangMin, Kim JinCheon, Yu ChangSik, Kim TaeWon, et al. Long-term oncologic and complication outcomes in anal cancer patients treated with radiation therapy. J Cancer Res Ther 2020;16:194.
[31] Johnsson A, Leon O, Gunnlaugsson A, et al. Determinants for local tumour control probability after radiotherapy of anal cancer. Radiother Oncol J Eur Soc Ther Radiol Oncol 2018;128:380–6.
[32] Han K, Milosevic M, Fyles A, Pintilie M, Viswanathan AN. Trends in the utilization of brachytherapy in cervical cancer in the United States. Internat J Radiat Oncol Biol Phys 2013;87:111–9.
[33] Morris WJ, Tyldesley S, Rodda S, et al. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT Trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost. Int J Radiat Oncol Biol Phys 2017;98:275–85.
[34] Gunderson LL, Moughan J, Ajani JA, et al. Anal carcinoma: impact of TN category of disease on survival, disease relapse, and colostomy failure in US Gastrointestinal Intergroup RTOG 98–11 phase 3 trial. Int J Radiat Oncol Biol Phys 2013;87:638–45.
[35] Ortholan C, Resbeut M, Hannoun-Levi JM, et al. Anal Canal Cancer: Management of Inguinal Nodes and Benefit of Prophylactic Inguinal Irradiation (CORS-03 Study). Int J Radiat Oncol Biol Phys 2012;82:1988–95.
[36] Potter R, Tanderup K, Kirisits C, et al. The EMBRACE II study: The outcome and prospect of two decades of evolution within GEC-ESTRO GYN working group and the EMBRACE studies. Clin Transl, Radiat Oncol 2018;9:48–60.
[37] Fayers P, Bottomley A. Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. Eur J Cancer 2002;38:S125–33.
[38] Sodergren SC, Johnson CD, Gilbert A, et al. Phase I-III development of the EORTC QLQ-ANL27, a health-related quality of life questionnaire for anal cancer. Radiother Oncol J Eur Soc Ther Radiol Oncol 2018;126:222–8.