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Review Article

Anal cancer brachytherapy: From radon seeds to interstitial Papillon technique in a century. What does the future hold?

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ABSTRACT

Evidence from studies which combined 2D-3D external beam radiotherapy (EBRT) ± chemotherapy with 2D brachytherapy (BT) for anal cancer suggest favorable outcomes when compared with chemo-EBRT alone. Further improvement of results can be expected in the era of intensity modulated EBRT and MRI-guided adaptive BT. Despite this, BT is not discussed as a therapeutic option in the prominent international guidelines and its use remains limited to selected institutions. Special skills, complexity, equipment, cost and reimbursement policies have been highlighted as barriers for its wider implementation. However, these factors are relevant for modern radiotherapy in general. Therefore, it can be argued that the role of BT as a component of chemoradiation should be redefined. We describe the historical evolution and current role of BT boost for anal cancer and outline its potential in the context of combined intensity modulated EBRT, chemotherapy and MRI-guided adaptive BT.

With annual incidence of 0.5 per 100,000, anal cancer accounts for <3% of lower gastrointestinal tract malignancies [1,2]. It is more common in immunocompromised patients and smokers [3]. Rise of incidence over past decades [4] can be attributed to the increased prevalence of HPV infection which is the most important cause [3,5]. Abdominoperineal resection was the main treatment in the past, but resulted in suboptimal locoregional control and high morbidity due to sphincter loss [6]. Following encouraging first experience with chemoradiation [7,8], its effectiveness was confirmed by several retrospective and phase II studies [9–13]. Randomized trials showed superiority of chemoradiation over radiotherapy alone [14,15] with 5-fluorouracil and mitomycin-C as concomitant regimen of choice [16–18]. Pelvic external beam radiotherapy (EBRT) with concurrent chemotherapy and simultaneous integrated EBRT or sequential brachytherapy (BT) boost is nowadays standard treatment [19,20]. Old studies used radiography-based or 3D conformal EBRT [21]. Implementation of intensity modulated and image guided radiotherapy (IMRT/IGRT) enabled tighter treatment margins and adaptive approach, resulting in improved outcomes [22–28]. BT was historically performed according to the Paris system rules [29], without specific guidelines for target volume definition. The pace of progress in EBRT was not paralleled in BT, where the techniques from the 1980s [30] remain conceptually unchanged even nowadays. We describe the evolution and current role of BT boost for anal cancer chemoradiation and outline its potential advancements in the context of image guided adaptive BT (IGABT).

Literature search

We performed a PubMed search from the earliest date through January 31, 2020, using the terms "anal cancer" AND "brachytherapy". Secondary search among the references in the identified reports was done to find publications addressing the topic of this review. We included studies of any design. Case reports, commentaries and editorials were excluded.

The dawn of anal cancer brachytherapy

Beginnings of anal cancer BT date back to the 1920's, when it was suggested as alternative to surgery for operable tumours [31]. Interstitial BT was scheduled 2 weeks after EBRT. Gold-filtered radon seeds with activity of 1–2.5 mCi per seed were inserted with trocar needles under proctoscopic or palpatory guidance to deliver 1000–5000 mCi*h, depending on the tumour size. Alternative technique was based on an intracavitary applicator similar to a proctoscope. After applicator insertion, the obturator was replaced by a holder, containing a tandem of brass-filtered sources. Lead was used to protect the uninvolved side. At a rate of 100–250 mCi/day, a total dose of 2000–5000 mCi*h was deliv-

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ered over 3–6 weeks. In <4 cm tumours, the results were described as promising with "long-standing cures and preservation of anus and rectum in most cases". In more advanced tumors, the outcome was disappointing [31]. In the 1950's, interstitial BT with 226-Ra was introduced [32,33]. In a series from Manchester, 59 patients were treated for moderately advanced and advanced disease. Poor 5-year overall survival (OS) was accompanied by a high radionecrosis rate [32]. In the 1960s, the Lyon group introduced a fractionated technique for carefully selected patients. Interstitial needles were loaded with 2.6 or 4 mg of 226-Ra over 3.2 cm. They were inserted through the skin or mucosa and fixed by sutures or intraanal tube. Most applications were one-plane, but selected cases received volume implants. The dose of first-session was up to 4000 rads over 2–3 days. In incomplete responders at 6 weeks, a second implant was used to deliver 2500 to 3000 rads. In rare cases, a third implant of additional 2000 rads was applied 2 months later. 5-year survival was 68% and necrosis rate 5% [33].

Reneissance by Papillon

Papillon et al. introduced the novel Lyon approach in 1971 and published it in1983 [30]. Radium was replaced by 192-Ir wires, and BT technique refined according to the improved understanding of the natural history of the disease and technical developments. Papillon described 3 protocols, adapted to tumour characteristics. *Protocol 1* was designed for T1-T3 N0 disease, considered to have high probability of tumor control and anal function preservation. It started with Co-60 EBRT, delivering 3000 rad transperineally at 5 cm and 1800 rad presacrally at 8 cm depth. This was followed by a 2-months interval to allow for toxicity resolution and tumor downsizing to a volume, suitable for a single-plane implant. At BT, a crescent-shaped or circular 15 mm thick plastic template with guiding holes was sutured to the skin. The distance between adjacent and opposite holes was 1 and 3.2 cm, respectively. The implant volume corresponded to the quadrant and depth of initial tumour extension, underscoring the importance of tumor assessment at diagnosis. A single row of equidistant and parallel needles was inserted through the template under guidance of palpating finger approximately 5 mm below the mucosa. Needle position was checked with fluoroscopy. 5–7 Ir-192 wires with activity of 1.5–2.5 mCi/cm and 5 cm length were applied to deliver 1500–2000 rad at the 85% isodose over 18–28 hours according to the Paris system [29]. The dose was chosen depending on the findings at diagnosis and BT. To minimize the complications risk, BT was not used upfront or as monotherapy, was limited to single-plane implants and was kept <30 Gy [30,34]. *Protocol 2* included preoperative chemoradiation and surgery. *Protocol 3* was used for fixed lesions and cases with nodal metastases. 18 MV photons and electrons were used to deliver 4000 rad to the inguino-pelvic nodal regions, followed by a 6–7 weeks break and an EBRT or BT boost of up to 5500 rad to the tumor and enlarged nodes [30].

Modern era

Papillon's split-course Protocol 1 evolved in the context of the European BT experience [35]. Built on this tradition, a typical modern conventional regimen starts with EBRT + concomitant chemotherapy to the primary tumour and elective nodal volumes, followed by an EBRT or BT boost [35]. A treatment gap was applied between sequences in most series [36–41].

Reports using conventional radiography-based BT boost are listed in Table 1. EBRT dose in these series ranged from 33 Gy to 50 Gy (biologically equivalent estimates in 2 Gy/fraction; linear-quadratic model; α/β = 10 Gy). Concomitant chemotherapy was used in 10–100% of cases. At BT, around 3–10 parallel and equidistant needles were inserted through a Papillon-type interstitial template to a depth of 3–10 cm, according to the Paris system rules for curved planar implants [29]. Target concepts were not consistently detailed and were generally based on the residual tumour or scar at BT, while taking the initial tumour into account. Radiography was used for dose planning and documentation. Dose was specified at 85% of the mean basal dose [29]. A dose of 10–30 Gy was delivered with low dose rate (LDR) or pulsed dose rate (PDR) technique in most series [34,36–38,40,42–52]. Experience with high dose rate (HDR) BT is emerging [26,40,53]. Single plane implants were used by majority of authors, indicating that residual tumours >10 mm in thickness were typically deemed unsuitable for BT boost. Several authors used a plastic tube or cylinder in the anus to stabilize implant geometry, displace uninvolved tissue from the high-dose and allow flatus and faeces escape [36,49–51]. Studies in Table 2 used ultrasound, CT or MRI for insertion guidance. This "2D to 3D experience" was typically limited to optimization of implant geometry without systematic dose adaptation in the context of standardized target concepts (Table 2).

Patient selection for brachytherapy boost

Patients need to be fit for anaesthesia and tolerate immobilization. Advanced age is not a contraindication for BT. Lestrade et al. reported on 76 patients >70 years treated with a median EBRT dose of 45 Gy (range: 36–56 Gy), concomitant chemotherapy (51%) and BT boost of 18 Gy (range: 10–31.7 Gy). Five-year local control (LC) and OS were 76%. Acute and late Grade 3–4 toxicities were 14% and 7%, respectively. Modified Charlson Comorbidity index [54] had no impact on outcome [55]. Good tolerance among elderly and comparable tumour control with the younger cohorts was confirmed by others [26,56]. In the original Papillon experience, BT was applied in tumours <4 cm, involving <2/3 of circumference and with good response to EBRT [30]. Others have suggested that BT target should extend <5 cm craniocaudally and involve <1/2 of circumference [35]. These criteria correspond to T2 and well-responding T3 tumors, which constitute 75–95% cases from published series [36–39,42,43,45,46]. The proportion of T1 and T4 tumors in the reported cohorts ranges from 5-20% [36–38,38,39,42,43,45,46,53,57]. Evidence on effectiveness of BT as single or upfront therapy in small tumours is limited [20,47,50]. Several authors have demonstrated that node-positive patients benefit from anal BT [43,58]. In oligometastatic disease pelvic chemoradiation, local BT and ablative treatment of metastases can offer a chance of cure. In metastatic disease, BT may be used to palliate or prevent local symptoms.

Local control and survival

In a recent systematic review, median 5-year local/locoregional control (LC/LRC) after EBRT and BT was 79% (range: 71–92%), disease free survival (DFS) 76% (range: 66–86%), OS 69% (range: 63–82%) and colostomy free survival (CFS) 76% (range: 61–86%) [21]. Published series are detailed in Tables 1 and 2. Node-negative status at diagnosis and good response to EBRT are prognostic of superior outcome in most series [21,36,39,40,43,49,52,59]. Stage T3-4 and poor pre-boost regression are negative prognostic factors [43].

Data on comparative effectiveness of BT and EBRT boost come from indirect estimates and retrospective series. Keeping the limitations of such comparisons in mind, the available evidence demonstrates superior or similar effectiveness of BT when compared with EBRT boost. These findings could be attributed to the physical and biological advantages of BT over EBRT (Fig. 1, Table 3). Series in which BT boost was used in majority of patients [21] compare favourably with trials, based predominantly on EBRT alone

Table 1
Series on pelvic chemoradiation and brachytherapy boost which used conventional Papillon technique, Paris system and radiography for brachytherapy optimization. Some reports included non-radiotherapy patients in outcome analysis. Brackets: ranges. Standard deviation specified by ±. Pts–patients; N-number; EBRT-external beam radiotherapy; Fx-Fractions: TL-treatment length (target, active or insertion length). D-Dose; ChT-chemotherapy; BT-Brachytherapy; DR-dose rate; Ref. DR-reference dose rate; Y-years; LC-local control; DFS-disease free survival; OS-overall survival; CFS-colostomy free surivival; Ch–channel; NS-not specified; NA-not applicable; St-stage; L-low; P-pulsed; H-high; [a]Crude rate.

Reference and pt. N	EBRT [Gy/Fx]	ChT [%]	Boost [N]		Brachytherapy details						Outcome [%]				
			BT	EBRT	Planes	Needles	DR	TL [cm]	D [Gy]	Ref. DR [cGy/h]	Y	LC	DFS	OS	CFS
Papillon [34] *N* = 369	48/16	NS	221	0	1	4–8	L	5–7	NS (15–20)	NS	–	–	–	66[a]	61[a]
Peiffert [59] *N* = 118	45–48/21–25	31	101	3	1 – 2	3–8	L	4–8	22 (15–29)	92 (40–138)	5	80[a]	–	60[a]	pre-1989: 75[a] post-1989: 84[a]
Gerard [44] *N* = 95	48/16 39/13	100	85	5	1	3–9	L	4–9	19 (14–28)	110 (59–158)	5	85[a]	–	84	72
Sandhu [49] *N* = 79	30–50/10–25	16	79	0	1	5–10	L	6–10	24 (20–40)	43 (36–57)	3	78 [a]	–	T1-2: 93 T3-4: 65	71[a]
Gerard [51] *N* = 19	44–50/22–25	47	19	0	1 – 2	4–9	P	4–7	15 (10–25)	50 (50–50)	–	–	–	–	–
Weber [38] *N* = 90	median 40/22	100	49	41	NS	NS	L	NS	19 NS)	51.8 (NS)	5	–	–	77	–
Chapet [43] *N* = 252	48/16 39/13	67	218	34	1	5–6	L	5–6	20 ±5	NS	5	83[a]	T1-2: 66 T3-4: 47	T1-2:77 T3-4: 63	61
Ortholan [47] *N* = 69	27–55/9–25 -	11	46	20	1	NS	L	NS	20 (NS)55 (NS)	NS	5	91[a]	89	94	85
Bruna [46] *N* = 71	44–50/25 36/12	66	71	0	1 – 2	3–12	P	4–8	18 (10–25)	70 (50–150)	2	90[a]	81	90	89
Saarilahti [56] *N* = 62	45/25	100	29	30	1	4–7	H	4–7	1–2 × 5–6	NA	5	81	77	–	100
Tournier-R. [45] *N* = 286	30–50/7–25 17–50/10–30	44	233	24	1 – 2	2–16	L, P	4–10	19 (10–37)	NS	5	St I: 89 St II: 77 St IIIA; 96 St IIIB: 77	St I: 82 St II: 67 St IIIA: 54 St IIIB: 49	-	St I: 88 St II: 70 St IIIA: 75 St IIIB: 56
Oehler J. [53] *N* = 81	45/25	72 [h]	34	47	1	3–8	H	4–9	7 × 2	NA	5	BT: 90 EBRT: 85	BT: 76 EBRT: 73	BT: 66 EBRT: 66	BT: 85 EBRT: 82
Widder [40] *N* = 129	46/23	74 [h]	23	106	1	4–7	P, H	4–8	13 (5–26)	NS	5	St I: 94 St II: 86 St III: 80	St I: 70 St II: 57 St III: 27	St I: 76 St II: 64 St III: 32	St I: 76 St II: 58 St III: 25
Hannoun-L. [37] *N* = 162	40–50/20–25	72	86	76	1 – 2	3–6	L	4–6	17 (10–25)	NS (50–70)	5	T1-2: 85 T3-4: 64	–	T1-2: 84 T3-4: 68	T1-2: 72 T3-4: 51
López-G. [50] *N* = 38	32–50/25	58 [i]	32 + 6 BT only	0	1	4–8	L P	3–10	20 (15–35)	68 (50–70) 52 (50–70)	5	87	58	76	84[a]
Lestrade [42] *N* = 219	30–56/10–28	72	209	0	1	4–12	L, P	4–9	18 (10–32)	75 (23–125)	5	T1-2: 80 T3-4: 77	T1-2: 70 T3-4: 68	T1-2: 85 T3-4: 76	T1-2: 81 T3-4: 78
Cordoba [36] *N* = 103	median 45/NS	38	103	0	1	2–12	L	4–10	17 (10–30)	NS	5	89	–	86%	86%
Kent [48] *N* = 52	45/25	100	36	16	1	5	L	NS	NS (15–20)	NS	5	–	BT: 91 EBRT: 78	BT: 75 EBRT: 68	BT: 97 EBRT: 80
Arcelli [52] *N* = 123	45/25	94	102	21	NS	2–7	P	5–8	20 (13–25)	67–80	5	T1-2: 84 T3-4: 79	–	T1-2: 84 T3-4: 64	T1-2: 64 T3-4: 49

Table 2
Series on pelvic chemoradiation and brachytherapy boost which used 2-3D technique and limited dose optimization. Brackets: ranges. Standard deviation specified by +/−. N-number; EBRT-external beam radiotherapy; Fx-Fractions; D-Dose; ChT-chemotherapy; BT-brachytherapy; DR-dose rate; D-dose; Ref. DR-reference dose rate; Y-years; LC-local control; DFS-disease free survival; OS-overall survival; CFS-colostomy free surivival; Clin-clinical; US-ultrasound; TRUS-transrectal ultrasound; MUPIT-Martinez universal perineal template; TV-target volume; P-pulsed; H-high; CT-computed tomography; MRI-magnetic resonance imaging; T-tumor; NS-not specified; NA-not applicable; P-pulsed; H-high.
[a]All patients in this series received EBRT boost; in incomplete responders at 4–6 weeks, BT boost was added. [b]Dose of 6 Gy per fraction was omitted after 5 patients, experiencing proctitis (n = 2) or sphincter necrosis (n = 3). [c]Crude rate.

Reference and pt. N	EBRT [Gy/Fx]	ChT [%]	Boost [N]		Brachytherapy details						Outcome [%]				
			BT	EBRT	Technique	Target concept	Treatment planning	DR	D [Gy]	Ref. DR [cGy/h]	Y	LC	DFS	OS	CFS
Gryc [57] N = 190[a]	50.4–59.4 /28–33	89	47	143	Papillon 80% Free hand 20%	Residual T (Clin., US, CT) +5 mm margin	CT based Paris system Geometric Manual	P	15.5 (8–36)	0.45 (0.25–0.7)	5	BT[a]: 76 EBRT: 81	BT[a]: 64 EBRT: 69	BT[a]: 75 EBRT: 72	BT[a]: 76 EBRT: 83
Doniec [65] N = 50	45/25	NS	50	0	Papillon TRUS guided	Residual T (Clin., US) Or initial T	D specified @TV surface	H	2 x 4–6[b]	NA	5	92	T1-2: 88 T3-4: 67	74	90
Oblak [39] N = 84	45/25	89	49	33	Papillon/MUPIT TRUS guided Anal & vaginal dilator	Residual T (Clin., US, CT)	CT based Paris system Manual	P	NS (15–30)	<70	5	T1-2: 80 T3-4: 55	T1-2: 80 T3-4: 47	T1-2: 75 T3-4: 58	T1-2: 94 T3-4: 46
Tagliaferri [64] N = 11	44–58 /22–29	100	11	0	MUPIT Off-line MRI Anal & vaginal dilator	Residual T (Clin., MRI)	CT based Paris system Manual	H	1–2 × 3.5–7	NA	-	-	-	-	-
Falk [41] N = 28	43.2–50 /24–26	75	28	0	Papillon Anal tube	Initial T (Clin., CT)	CT based Graphical	H	2–6 x 3–5	NA	2	83	72	78	75
Boukhelif [93] N = 21	30–54 /15–30	33	21	0	Papillon Anal dilator	Residual T + 5–10 mm	CT based Paris system	P	20 (10–30)	40 (38–50)	5	86[c]	81[c]	95[c]	-
Kapoor [66] N = 16	40–45 /20–25	100	16	0	Syed Neblett	Residual T (Clin., CT)	CT based	H	6–7 × 3	NA	2	88	-	-	88

[14–18,60–62]. In the CORS-03 study, boost type was one of the prognostic factors for 5-year local recurrence (LR) (BT: 12% vs. EBRT: 33%; p = 0.002) and CFS (BT: 71% vs. EBRT: 56%; p = 0.04). This was in spite of a trend for a lower nominal BT (mean: 17.4 Gy; range: 10–25 Gy) than EBRT dose (mean: 18.3 Gy; range 8–25 Gy; p = 0.07). Importantly, characteristics of patients and tumours were balanced across the two groups of patients in this study. For LR, prognostic significance of boost type was maintained on multivariate analysis (hazard ratio 0.62; 95% CI: 0.41–0.92). Surgery for progression or complications was needed in 26% EBRT and 8% BT boost patients (p = 0.003) [37]. In analysis of node-positive patients from the CORS-03 cohort, BT boost maintained a positive impact with lower 5-year LR when compared with EBRT (4% vs. 31%, p = 0.003; hazard ratio 0.08; p = 0.042) [58]. In a series from Lyon, BT boost was associated with superior OS (75.8% vs. 47.5%; p < 0.0001) and DFS (63.4 % vs. 37.9%; p < 0.001) when compared with EBRT [43]. Similar advantage of BT was published recently by an Italian group demonstrating a 5-year OS of 79% vs. 52%; p = 0.015 and distant metastases free survival (DMFS) of 95% vs. 77%; p = 0.015 [52]. Other reports which used both types of boost offer similar results, but should be interpreted cautiously due to unbalanced samples and bias with large tumours being boosted more often with EBRT [37–39,43,57,63]. Some authors found no impact of boost-type. In one study, 5-year DFS was 86.5% for BT and 71.6% for EBRT boost (p = 0.07), but only 6% of patients received BT boost [63]. Another series with a more balanced cohort found similar results [39]. In a report from Switzerland, a median of 20 Gy EBRT and 18 Gy BT boost was applied in 41 (46%) and 49 (54%) cases, resulting in a 5-year LRC of 70.7% and 75.5%, respectively (p = 0.82) [38]. Kent et al. reported on non-significant differences at 5 years between BT for anal canal (cancer specific survival-CSS: 91%, OS: 75%) and electron boost for anal margin tumors (CSS: 78%, OS: 68%) [48]. In another series, BT (n = 34) and EBRT (n = 47) boost resulted in similar 5-year LR rate (10% vs. 15%; p = 0.5) and OS (66% in both groups) [53].

Toxicity

Radiosensitivity and functional stress make anal region prone to treatment toxicity, but data interpretation is challenging. Majority of studies reported crude rates, different scoring systems were used, and grading criteria were often not specified. Further, approximately 1/4 of patients received EBRT boost, but toxicity was reported jointly with BT, making it difficult to corelate specific endpoints with specific boost technique. Heterogeneity of tumours, RT schedules and sample sizes complicates interpretations further. Notwithstanding all these challenges, the available evidence demonstrates that the toxicity profile after BT compares favorably with EBRT boost, which can be attributed to the sparing of the healthy mucosa, uninvolved sphincter complex and the contralateral nerves and vessels afforded by BT (Fig. 1, Table 3).

Acute local and hematologic toxicity during (chemo)radiation develops in majority of patients. G1-2 dermato-mucositis in the published studies ranged from 30–60% and proctitis from 10–30% [39,43,44,50]. While side effects were limited to G1-2 in some series [41,64], G3-4 acute toxicity was common, ranging from 10-30% and often necessitating un-planned treatment breaks [39,42,47,50]. In a report from Switzerland, Grade 3–4 toxicity was higher in patients after EBRT when compared with BT boost (43% vs. 15%; p = 0.008). This was due to worse hematologic (13% vs 0%) and cutaneous (23% vs. 8%) reactions, while severe diarrhea occurred in 6% in both subgroups [53]. In another study, acute G3-4 toxicity didn't differ between EBRT and BT boost [57].

Collectively, most common late toxicity for EBRT and BT-boost cohorts is sphincter dysfunction with G1-2, G3 and G4 inconti-

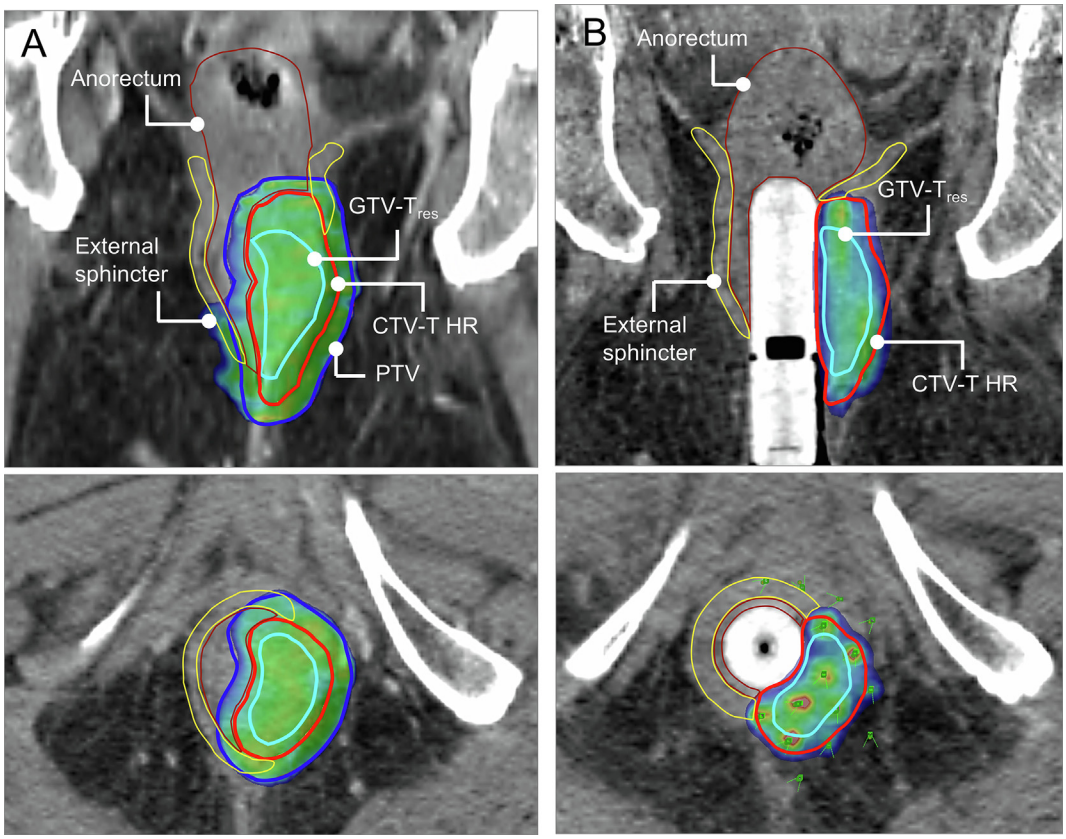

Fig. 1. Comparison of volumetric modulated arc therapy (VMAT) with virtual image guided adaptive brachytherapy (IGABT) boost in a patient with a T3 N0 tumor, who underwent planning CT both for VMAT and IGABT. To compare dose distributions, iso-effective prescriptions were selected and D98 was normalized to 95% of prescribed dose both for the PTV_{EBRT} and CTV-T HR_{BT} (Table 3). (A) VMAT plan, optimized to PTV (CTV-T HR + 5 mm). Color wash: 95% to 105% of prescribed dose. (B) Virtual IGABT with a 2 cm anal dilator. Virtual perineal template was projected on CT to place 15 virtual needles in 3 planes at a median depth of 63 mm (range: 37–88 mm). Paris-system plan, specifying the dose at 85% isodose of basal dose-points was used as the starting point and optimized to meet the planning aims. Color-wash: 95% to 200% of prescribed dose. Absence of CTV to PTV margin, sharp dose fall-off and displacement of healthy tissues result in a lower dose to the sphincter and anorectum when compared with VMAT. Simultaneously, superior coverage and dose escalation inside the GTV-T_{res} is achieved. GTV-T_{res} – residual gross tumor volume; CTV-T HR – high risk clinical target volume of the primary tumor.

nence in up to 25%, 10% and 4%, respectively [15,26,36,39,40,42,44,47,49–51,53,64–66]. Mild to moderate fibrosis ranges from 0–25%, G3 stricture occurs in ≤5%, and complete obstruction is extremely rare [18,26,36,39,40,47,49,51,64,66]. Mild and transient late anorectal bleeding can occur in up to 15–70%, but G3-4 bleeding is uncommon, reported in ≤2% of patients (36,43,44,47,59). G2 and G3-4 necrosis occurrs in <10% and ≤5%, respectively. Peiffert et al., using the Chassagne grading system [67], reported on 13% of G3 necrosis [59]. Other chronic toxicities of any grade include proctitis (0–26%), chronic pain (0–15%), skin toxicity (0–10%) and fistulae (0–1%). Grade 3 genitourinary problems occur in up to approximately 5% [26,36,40,41,47–50,53,57,59,64]. Colostomy or abdominoperineal resection rate due to toxicity is typically ≤5% [26,36,37,39–43,46–48,50–52,65], but was up to 9% in selected series. [34,49,59]. The most frequent cause of treatment-induced colostomy is necrosis, followed by severe incontinence, hemorrhage, pain and fistula [36,40,41,43,44,48,49,65].

In most of the published series offering direct comparisons, BT results in a more favorable profile of late toxicities than the EBRT boost. A group from Finland reported on biologically equivalent doses ($EQD2_{3Gy}$: linear quadratic model, 2 Gy/fraction, α/β = 3 Gy) to the anal canal after pelvic chemoradiation followed by BT (n = 29) or EBRT boost (n = 30). BT boost resulted in a lower mean $EQD2_{3Gy}$ to the uninvolved anus than EBRT (44.8 Gy vs. 50.2 Gy; p < 0.01), and higher $EQD2_{3Gy}$ to the tumor-infiltrated portion (56.5 vs. 50.2 Gy; p < 0.01). Rate of late G2-3 proctitis corelated with the $EQD2_{3Gy}$ to the uninvolved anus and was non-significantly higher after EBRT (12%) than BT boost (3%) (p = 0.065) [26]. Three out of 129 patients from Vienna series (23 BT, 106 EBRT boost) developed post-treatment necrosis, all after EBRT boost [40]. In a series from Ljubljana, late toxicity was lower after BT than EBRT boost [39]. Ortholan et al. treated early stage tumours with EBRT alone, EBRT + BT or BT alone and found overall complication rates of 30%, 26% and 25%, respectively [47]. In the CORS 3 study, abdominoperineal resection due to toxicity was needed in 5% of patients after EBRT and 3% after BT boost [37]. Recent Italian series reported on similar results with a 5% colostomy rate for both boost types [52]. In the report by Gryc et al., there was no significant increase of late G3-4 toxicity in patients who received additional BT boost after EBRT. Most common G3-4 toxicity was proctitis, occurring in 23% after EBRT and 16% after BT boost. Overall rates of severe skin and genitourinary side effects were below 3% and all cases occurred in the non-BT group [57]. Oehler-Jänne et al. found no significant impact of BT (n = 34) and EBRT (n = 47) boost on quality of life, overall late side effects (19% vs. 30%; p = 0.5), G1-2 incontinence (18% vs. 28%; p = 0.5), G3-4 diarrhea (6% vs. 4%; p = NS) and sphincter pressure impairment (37% vs. 29%; p = 0.6) [53].

Table 3
Dose-volume histogram parameters of volumetric modulated arc therapy (VMAT) and image guided adaptive brachytherapy (IGABT) plans, presented in Fig. 1. GTV-T_{res}: residual gross tumor volume; CTV-T HR: high risk clinical target volume of primary tumor; PTV: planning target volume; EQD2: equivalent biological dose in 2 Gy fractions, according to the LQ model and α/β ratio of 10 Gy and 3 Gy for tumor and late-reacting normal tissues, respectively. [a] For IGABT there is no PTV margin and PTV is identical to CTV-T HR. [b] Selected EBRT and BT prescriptions are almost iso-effective in terms of EQD2.

	VMAT	IGABT
Target volume size [cm^3]		
GTV-T_{res}	11	11
CTV-T HR	31	31
PTV	67	[a] 31
[b] PTV dose prescription		
Nominal D / Fractions	16 Gy / 8 Fractions	15 Gy / 25 Pulses
EQD2 [Gy_{10}]	16	15.5
EQD2 [Gy_3]	16	16.2
PTV EQD2 [Gy_{10}]		
D 98%	15.1	14.6
D 90%	15.6	16.6
D mean	16	23
PTV V 100%	59%	95%
GTV-T_{res} EQD2 [Gy_{10}]		
D 98%	16	19.3
D 90%	16	21.8
D mean	16.2	35.4
Ano/Rectum EQD2 [Gy_3]		
D 0.1 cm^3	16.5	20.2
D 2 cm^3	15.8	8.7
D 5 cm^3	15.3	5.2
D mean	12.2	4.9
Ano/Rectum V 50% [cm^3]	12	5
Sphincter EQD2 [Gy_3]		
D 0.1 cm^3	16.5	37.9
D 2 cm^3	15.8	10.8
D 5 cm^3	14.2	5.4
D mean	7.7	5.2
Sphincter V 50% [cm^3]	12	5
Body Volumes [cm^3]		
V 50%	250	112
V 150%	0	6.7
V 200%	0	1.6
Average D to Basal points [Gy]	16	20

In the series of Lestrade et al., severe toxicity correlated with the total dose and was 3% for doses ≤63 Gy and 10% for >63 Gy ($p = 0.02$) [42]. In another study, a homogeneous cohort of patients who received single-plane implants was assessed. Severe complications were curtailed (2% vs. 11%; $p = 0.03$) without compromising the LC by a personalized reduction of the mean number of 192-Ir wires (5 vs. 6), shorter wire length (54 mm vs. 63 mm), lower BT reference dose (20 Gy vs. 23 Gy) and smaller volume of 85% isodose (12 vs. 17 cm^3). In multivariate analysis, total equivalent dose for late responding tissues remained prognostic for late toxicity ($p = 0.01$) [59].

Inter-sequence gap and overall treatment time

Detrimental effect of tumour cell repopulation due to prolonged overall treatment time (OTT) was demonstrated for various tumours, including anal cancer [38–40,63,68–70]. Gaps are difficult to avoid in anal cancer chemoradiation and doses of 60–65 Gy were applied historically to counteract the effect of prolonged OTT [46,51]. Landmark trials on chemoradiation mandated a 6-week gap between pelvic EBRT and tumour boost [14,15]. In the RTOG 92-08 and ECOG E4292 studies, planned break was associated with lower complete response, LRC and CFS, when compared with the no-break cohort [71,72].

OTT comparisons between sequential EBRT and BT boost are scarce. Available evidence indicates advantage of BT which enables dose delivery over a shorter time than sequential EBRT. In CORS-03 study, the mean inter-sequence gap was 36 (range: 0–106) days and OTT 75 (range: 37–143) days. When compared with sequential EBRT boost, BT boost was associated with a shorter gap (39 vs. 30 days; $p = 0.02$) and OTT (82 vs 69 days; $p < 0.001$). Shorter OTT (<80 days vs. ≥80 days) was prognostic of lower 5-year local relapse (LR: 14% vs. 34%; $p = 0.005$), and higher OS (84% vs 67%; $p < 0.001$) and CFS (74% vs. 50%; $p = 0.004$). This was maintained on multivariate analysis with a hazard ratio of 0.47 for LR (95% CI: 0.22–1.0), 0.39 for OS (95% CI: 0.2–0.74) and 0.51 for CFS (95% CI:0.29–0.9) [37]. Short OTT was not the only factor leading to improved outcome: there was a positive impact of BT vs. EBRT boost on LR, which was most pronounced when OTT was <80 days (BT: 9% vs. EBRT: 28%; $p = 0.03$) and non-significant for longer OTTs (BT: 29% vs. EBRT: 38%; $p = 0.21$). In another series, median OTT was 63 (range: 20–143) days. It was shorter for BT-boost when compared with EBRT-only subgroup (55 vs. 63 days; p = NS). Shorter OTT had positive impact on LC in stage T1-2 ($p = 0.021$) [40].

Nowadays, anal cancer chemoradiation is predominantly based on pelvic EBRT with simultaneous integrated EBRT boost to the primary tumor without planned treatment breaks. The results of this approach can therefore not be compared directly with the historical data from the published BT studies which are typically characterized by often long inter-sequence gaps and OTTs. Series which used sequential BT boost report on an average gap of around 1 month [36–38,41] and even up to 3–4 months in individual cases [36,38]. Correspondingly, average OTT in these reports ranged from 60–80 days [37–41]. Cordoba et al. found that the OTT cut-off for superior LC was at ≤58 days ($p = 0.008$) [36]. Another group identified the gap-threshold of ≤38 days as independent prognostic factor for DFS (HR 1.33; 95%CI: 1.04–1.7; $p = 0.0025$) [63]. In another series with a median OTT of 57 (range 30–98) days, an OTT < 73 was associated with superior 5-year LRC (73% vs. 56%; $p = 0.04$) [39]. Weber et al. reported on a median inter-sequence gap of 37.5 days (range: 4–97 days) and OTT of 73.5 days (range: 50–155 days). Factors associated with poorer locoregional control on univariate analysis were age ≤65 years, male gender and inter-sequence gap. Five-year LRC was 84.5% when gap was ≤37.5 days and 61.5% with longer intervals ($p = 0.03$). On multivariate analysis, only age ($p = 0.01$) and gap duration ($p = 0.02$) retained prognostic significance. The authors improved the LRC by limiting the gap to 2 weeks [38].

Therefore, future studies with strategies to minimize or abolish the gap between pelvic EBRT and BT are required to enable comparisons between simultaneous EBRT boost and sequential BT boost. Modern techniques of pelvic EBRT, performed by experienced institutions play a central role in this context. In a recently published population-based analysis including 8948 patients, the use of IMRT, treatment at an academic center and treatment in more recent years were associated with a shorter overall duration of treatment [70]. Pelvic IMRT has been shown to reduce the acute adverse events and un-planned gaps when compared with conventional EBRT [22–25,27,28]. Comparison between RTOG studies demonstrated reduction of acute toxicity in favour of IMRT. Treatment breaks occurred less frequently (49% vs. 62%; $p = 0.09$), were shorter (0–12 days vs. 0–33 days; $p = 0.0047$) and resulted in a shorter median OTT (43 vs. 49 days; $p < 0.01$) with IMRT than with conventional EBRT (27). In a series from Finland, pelvic IMRT ($n = 20$) or 3D conformal radiotherapy (3D CRT) ($n = 39$), was followed by HDR BT boost. There was significantly less grade 3–4 diarrhoea and dermato-mucositis and shorter inter-sequence gap in IMRT than 3D CRT group [56]. In summary, under a premise of equivalent OTTs, it can be reasonable to hypothesize superiority

of BT over EBRT boost due to inherent radiobiological and physical advantages of BT (Fig. 1, Table 3). Well-designed prospective studies are required to address this research question.

Number of brachytherapy channels and planes

Traditionally, it was postulated that multiple-plane implants lead to increased risk of late necrosis and proctitis [20,34] and were avoided in conventional BT cohorts (Table 1). In a French series, late toxicity of any grade was 56% after BT with <6 and 72% with ≥6 interstitial needles (p = 0.014) [42]. In another report, double-plane implant was applied in 4/71 patients due to a large residual tumour. One of these patients required temporary colostomy for G4 necrosis, but was free of disease and toxicity on long-term follow up. None of the remaining 3 developed severe toxicity [46]. Gerard et al. reported on 95 patients, 85 of whom received BT boost. There were 5 cases of severe necrosis, all occurring in T3-4 lesions treated with single-plane implants, one of them following previous bladder cancer EBRT [44]. It is likely that the implants with large number of channels and/or multiple planes are a surrogate for a higher tumour volume. In cases where residual tumour thickness at BT exceeds 10 mm, carefully performed multiple-plane implants according to the rules of the Paris system may be beneficial [35]. This approach has been used safely in a substantial proportion of patients by several authors [37,45,46,51,59].

Radiotherapy dose

In majority of studies, BT was tailored to tumour response after EBRT, with poorly responding tumors receiving higher boost doses [42,43,52]. Therefore, conclusions regarding dose–response relationships are challenging, since pre-boost tumor regression is an important prognostic factor for disease control [42,43,45,51,73]. In a series from Vienna, pelvic chemoradiation was followed by BT or additional EBRT. Total nominal dose was 60 Gy (range: 46–66 Gy) for BT and 60 Gy (range: 30–70 Gy) for EBRT. Radiobiologically equivalent doses were not reported. In T3-4 tumours, 5-year LR was 14% after ≥54 Gy and 70% after <54 Gy (p = 0.007) (40). In T1-2 tumours, no impact of dose was observed. A randomized 4-arm ACCORD 03 trial investigated the impact of chemotherapy prior to pelvic chemoradiation and boost-dose escalation [18]. LDR BT was used to apply 15 Gy in the standard arm and 20 Gy or 25 Gy (depending on response) in experimental arm. The trial didn't demonstrate the benefit of interventions on CFS. However, high LC and low toxicity was observed in the most intensive arm, consisting of induction chemotherapy, chemoradiation and high-dose BT boost [18]. On the contrary, the CORS 3 study in which a mean of 18.3 Gy (range: 8–25 Gy) was applied for EBRT and 17.4 Gy (range: 10–25 Gy) for BT boost, demonstrated no influence of boost dose on 5-year OS, LC and CFS [37]. In the large series from Lyon, a BT boost of 20 ± 5 Gy was applied depending on the degree of tumour regression. No significant impact of dose on the outcome was found [43]. Cordoba et al. applied a similar response-adapted approach, delivering a 10–30 Gy BT boost and found no association between the dose and outcome [36]. A group from Bologna aimed for a BT boost of ≥20 Gy in patients with residual disease after chemoradiation, and ≤16 Gy in complete responders. Five-year OS, LC and DMFS were non-significantly higher in patients, receiving ≤18 Gy when compared with >18 Gy [52]. Similar results were obtained by Lestrade et al., with BT doses of ≥18 Gy associated with significantly inferior 5-year LC, OS, CSS and CFS when compared with lower doses [42]. The apparent lack of impact of BT dose or even the inverse relationship in some studies can be attributed to the selection of poor responders for higher doses [42,43]. This standpoint is supported by the results by Gryc et al. who reported on the outcome of 190 patients treated with pelvic (chemo)radiation to a mean dose of 48.7 Gy and EBRT boost of 15.5 ± 7.5 Gy. At 6 weeks after treatment, 47 (25%) poor responders received an additional BT boost (10.1 ± 9.7 Gy), resulting in a mean total dose of 67.5 ± 7.8 Gy. This dose escalation in poor responders resulted in similar outcome as in good responders treated with EBRT alone [57].

Brachytherapy dose rate

LDR Papillon's interstitial technique and the Paris system remained the cornerstones of anal cancer BT for decades. After the introduction of remote afterloaders, PDR BT has been recognized as an attractive alternative. Based on the linear quadratic formalism, Brenner et al. suggested PDR combinations of pulse-widths and -frequencies that would result in equivalent biological effects on the target volume as LDR BT. The model estimated a 2% increase of late toxicity, showing promise of PDR BT for clinical use with small irradiated volumes [74]. The first report on PDR BT for anal cancer by Roed et al. reported on good LC, but unacceptable necrosis and colostomy rates. This series was characterized by tumor stages similar to other reports, but the volumes receiving ≥25 Gy were exscessive, ranging from 20 to 400 cm^3 and were larger than 200 cm^3 in 47% of cases. Furthermore, the application technique consisted of one or two rows of concentric channels with a large needle spacing from 1.3 to 2 cm. The boost dose converted to the Paris system was excessive, ranging from 23–47 Gy. Toxicity was high: lasting necrosis occurred in 76% of cases and 59% of patients received colostomy [75]. The main advantage of BT over EBRT boost is to deliver a dose of 15–20 Gy to a smaller volume, encompassing only the residual tumor (Tables 1 and 2). The results of Roed et al. should be therefore interpreted critically and the high toxicity has been ascribed to suboptimal implantation technique, deviation from the Paris system and delivery of high doses to large volumes. The potential small increase of risk due to PDR technique as postulated by Brenner [74] was not a toxicity-inducing factor in this series [73].

A study by the French cooperative group has later confirmed feasibility, reliability, safety and good tolerance of PDR technique [51]. Excellent local control rates and toxicity profiles of PDR BT were consequently confirmed by several authors (Tables 1 and 2). Nowadays, PDR BT with nominal doses and hourly pulses corresponding to the historic LDR experience, represents the most common approach with long-term follow up, demonstrating comparable results to LDR BT [39,42,45,46,52,57,76,77]. In this context, the importance of respecting the longstanding experience of the Paris system rules cannot be over-emphasized.

HDR BT offers some practical advantages over the PDR/LDR method and experience with this technique is growing [40,41,53,64–66,78,79]. The published regimens typically consist of initial pelvic EBRT and concurrent chemotherapy, followed by 2–7 HDR fractions of 3–7 Gy (Table 2). LC ranges from 80–90%, OS from 70–80%, and CFS from 75–90%. The reported rates of toxicity compare favorably with the PDR approach. Doniec et al. reported on their HDR experience with 50 patients who received pelvic chemoradiation to 45 Gy in 25 fractions, followed by an HDR boost. First five patients received a boost of 2 × 6 Gy, but two of them developed sphincter necrosis, after which the dose was reduced to 2 × 4 Gy. Local control at 5 years was 92% and sphincter function was completely preserved in 80% [65]. In a series by Falk et al., 25 patients received an HDR boost with 2–6 fractions of 3–5 Gy for a total nominal boost dose of 10–15 Gy. Acute genitourinary, gastrointestinal and cutaneous toxicities were limited to G1 and occurred in 37%, 41%, and 4%, respectively. Late G3 toxicity occurred in 2 (7%), but persisted beyond 5 years only

in one patient. There was no late G4 toxicity. Local control, overall survival and colostomy-free survival at 2 years were 83%, 78% and 75%, respectively. Further research with longer follow up is required to define the optimal fractionation of HDR BT and compare the results with PDR/LDR experience.

What does the future hold?

Available reports consistently show favorable outcomes after anal BT when compared with EBRT boost (Tables 1 and 2). Despite the evidence suggesting an important role of BT in anal cancer chemoradiation, BT is not discussed as therapeutic option in prominent international guidelines [19], it is not part of the ongoing trials on anal cancer, and its use remains limited to selected institutions with long traditions (Tables 1, 2). Operator skills, treatment complexity, special equipment and cost have been considered as barriers for the use of gynecological BT [80] and could be extrapolated to anal cancer. However, these factors are also relevant for adoption of complex EBRT, which remains unimpeded and favoured by the reimbursement policies over BT [80,81]. Furthermore, a cost-utility analysis of MRI-based IAGBT for cervical cancer demonstrated reduced cost and increased effectiveness when compared with CT-based or conventional 2D techniques [82]. It can be hypothesized that similar health-economy effects of IGABT could be observed also for anal cancer. Non-invasiveness of EBRT is a commonly cited argument in its favor over BT boost [80]. However, BT is a minimally invasive treatment with negligible mechanical injury caused by the needle insertion. In fact, the invasiveness of radiotherapy is more appropriately described in terms of radiation damage to uninvolved normal tissues due to exposure to high, moderate and low doses. In this context, anal cancer BT is theoretically superior to EBRT boost at most dose levels (Fig. 1, Table 3). This can be attributed to its intrinsic physical and biological principles, which cannot be matched by even the most complex EBRT techniques:

1. Steep gradients within a BT implant enable dose escalation inside the target volume, high conformity at its periphery, and rapid fall-of in surrounding tissue with small volumes receiving low to moderate doses.
2. Dose-heterogeneity has favourable biological implications due to different sensitivity of the tumour and organs at risk (OAR) to varying time-dose patterns.
3. Since CTV to PTV margin is not used for BT, smaller volumes of healthy tissues are exposed to high doses when compared with EBRT boost.
4. Anal dilatation during BT can further reduce the exposure of uninvolved tissues by displacing them from the high-dose region.
5. BT boost is delivered over a short time, enabling a meaningful reduction of OTT when compared with sequential EBRT boost.
6. BT boost is adapted to the residual tumor, enabling a meaningful reduction of irradiated volume when compared with simultaneous integrated EBRT boost.

In summary, the reasons for BT underutilisation are controversial if not frustrating, underscoring the need for an objective redefinition of its role in anal cancer.

Published experience with anal cancer BT comes mainly from studies which combined 2D EBRT or 3D CRT, inconsistent chemotherapy regimens, and conventional 2D BT after long median inter-sequence gaps (Table 1). Full impact of dose optimization afforded by modern EBRT techniques and IGABT was thus not exploited so far. Pelvic IMRT reduces the acute adverse events and un-planned gaps when compared with conventional EBRT [22–25,27,28,70]. Volumetric modulated arc therapy (VMAT) offers dosimetric and clinical advantage over fixed-beam IMRT [22] and intensity modulated proton therapy (IMPT) can further reduce the volume of bone marrow, bowel and skin receiving low- to moderate doses. Through improved toxicity profile and patient compliance, IMPT can minimize treatment breaks and OTT [81]. Favourable outcomes of anal cancer BT published so far were achieved with techniques which could be considered suboptimal by modern standards (Table 1). Some authors used ultrasound and 3D imaging for insertion guidance and limited dose optimization, but this was done in the absence of standardized target concepts (Table 2). Meanwhile, IGABT led to an unprecedented improvement of clinical outcomes in gynecological tumors [83,84]. Attempts to achieve similar results with sophisticated EBRT in place of BT resulted in decreased survival [85].

It is therefore reasonable to assume that the demonstrated effectiveness of anal cancer BT would be even more pronounced in the era of modern technologies, superseding the results of EBRT-only cohorts. Novel regimens should be investigated in frame of a multicenter study protocol, possibly of randomized design, redefining the role of BT boost in treatment of this rare disease. A combination of pelvic VMAT or IMPT with concurrent chemotherapy +/- immunotherapy, and MRI-based IGABT with a minimal or no inter-sequence gap could provide improved outcomes. In this context, VMAT and IMPT should be regarded as a method for individualized dose de-escalation outside the macroscopic target. Dose to regional lymph-node metastases should be complemented with the simultaneous integrated boost and coverage-probability planning [86]. Finally, the implementation of MRI-based IGABT would enable personalized dose-tailoring to the shrinking primary tumor and establishment of dose-volume-effect relations for the OAR and target volume. Definition and contouring of new OAR (i.e. pudendal nerves, vessels, anal sphincter, healthy anus) implicated in toxicity would become a meaningful task due to the superb ability of IGABT to avoid these structures [87–90]. The definition of concepts and terms regarding the target volumes could benefit from the existent recommendations on gynecological cancer due to some similarities between these tumors [91,92]. Nonetheless, even in the era of IGABT, meticulous attention to application technique based on the Paris system rules remains a precondition for treatment success. In this context, carefully designed perineal templates with appropriate inter-channel distance, reliable needle fixation mechanism, and opening for the palpating finger and ultrasound probe for real-time guidance are of major importance. Adaptive dose optimization should be performed with utmost care, taking the longstanding experience with the Paris system dosimetry into account.

Conclusion

Historically, BT boost generated excellent outcomes and should be considered a component of anal cancer chemoradiation in selected patients in the future. Novel regimens employing VMAT, IMPT, systemic therapy and MRI-based IGABT without treatment gaps are expected to improve the results further and should be tested in frame of a prospective clinical study. In the context of IGABT, the definition of concepts and terms for response-adaptive target volume and organs at risk contouring is required. Adaptive dose-optimization and dosimetry strategies should build on extensive clinical experience from the past, with Paris system representing the cornerstone for future developments.

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