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ORIGINAL ARTICLE

Clinical outcomes using a 3D printed tandem-needle-template and the EMBRACE-II planning aims for image guided adaptive brachytherapy in locally advanced cervical cancer

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ABSTRACT

Background: Extensive local disease or narrow vagina may compromise brachytherapy (BT) in patients with cervical cancer. This is the first study to analyze long-term outcomes of using 3D printed vaginal tandem-needle templates (3DP TNT) for transvaginal insertion of needles in parallel (P) or parallel and oblique (P&O) direction to the tandem.

Material and methods: All patients treated with BT using 3DP TNT from 2015-2020 were included. Decision to use a 3DP TNT and preplanning were made after 4-5 weeks of external beam radiotherapy, based on gynecological examination and MRI with a tandem-ring applicator *in situ*. The TNT was 3D-printed in house consisting of a circular template with P&O holes for guidance of plastic needles and a shaft fitting the uterine tandem. Thus, the radioactive source was never in direct contact with the 3DP TNT. The TNT was 3D printed in a standard or personalized configuration. Planning aims were based on the Embrace II protocol.

Results: 101 patients (median age of 63 years) were included: 49 with P needles only and 52 with P&O needles. Personalized TNT was used in 19 patients in the P&O group. Performance status (WHO) was >0 in 48%. $FIGO_{2018}$ stage III-IV was present in 77%. T-score at diagnosis and BT was 9.1 and 6.3 respectively, with a significantly higher T-score in the P&O compared to P group. The mean high-risk CTV D90 was 93 Gy with no significant difference between the two groups. Three-year local control rates were 85%, 95%, 75% for the overall, P- and P&O group respectively and 68%, 80% and 56% for cancer specific survival. Grade $\geq$3 treatment related complications were observed in 10 (10%) patients.

Conclusions: 3DP TNT for BT in cervical cancer provides successful management of very extensive local disease and/or unfavorable anatomy with the possibility for treatment individualization.

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KEYWORDS
Cervical cancer; image guided adaptive brachytherapy; 3d-printing; interstitial; treatment individualization

1. Introduction

Introduction of image guided adaptive brachytherapy [IGABT] for treatment of locally advanced cervical cancer [LACC] has significantly improved local control and decreased the incidence of severe side effects compared to two-dimensional brachytherapy [BT] [1–4]. The GEC-ESTRO and EMBRACE cooperation have provided evidence-based planning aims and dose-volume histogram [DVH] constraints, which are being tested in the EMBRACE II study [5–7]. However, these aims and constraints may be difficult to reach in large tumors and/or in unfavorable anatomy. The use of intracavitary/interstitial brachytherapy [IC/IS] is therefore considered an essential part of IGABT [8,9].

Several solutions have been developed for IC/IS BT [10]. Initially interstitial needles have been implanted through the periphery of the ring/ovoid and in parallel [P] to the intrauterine tandem [9,11–13]. Later, implantation of needles in both parallel and oblique [P&O] angles toward the pelvic wall has been implemented [14]. Recently, commercially produced applicators with different templates for both transvaginal P&O needles as well as perineal implantation have shown promising results with the possibility of more individualized treatments [15–17]. The arrival of three-dimensional printing [3DP] in the clinical setting is an interesting BT alternative due to the inherent possibility for adaptive individualization of implants and treatments [18].

Publications concerning the use of 3D printing for IC/IS based IGABT in LACC have so far been limited to the description of the dose-volume parameters [18–21]. The EMBRACE II planning aims and DVH constraints together with the routine clinical use of 3DP tandem needle templates (TNT) for IC/IS were implemented as standard in the Oncological Department of Aarhus University Hospital in 2015. The aim of this paper is to present long term clinical outcomes from using 3DP TNT IGABT in patients with cervical cancer.

2. Materials and methods

The study was approved as a quality assurance project by the board of directors of Aarhus University Hospital. All

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patients diagnosed with cervical cancer treated with external beam radiotherapy (EBRT) and IGABT using a 3DP TNT between January 2015 and January 2020 were included. The stage of the primary tumor was determined according to $FIGO_{2018}$ [22]. In addition, tumor score [TS] was calculated both at diagnosis [TS_D] and at BT [TS_{BT}], with the intent to report TS change over treatment [23,24].

Contouring and dose planning for external beam radiotherapy (EBRT) and BT were performed according to the EMBRACE II protocol [5]. The treatment consisted of initial whole pelvic (± para-aortic) EBRT, delivering 45 Gy in 25 daily fractions by use of volumetric modulated arc therapy with simultaneous integrated boost to 55.0-57.5 Gy to pathological nodes. Concomitant weekly cisplatin was given whenever possible [CRT]. Two fractions of pulsed dose rate [PDR] IGABT (BT1 and BT2) with around 7 days interval were delivered at the end of EBRT with an intended maximal overall treatment time [OTT] of 50 days.

Preplanning for IGABT (BT0) was performed during the 4-5th week of EBRT, based on gynecological examination and MRI with a standard polyetheretherketone [PEEK] tandem-ring applicator *in situ* (www.varian.com) [25]. The tumor response and the anatomical conditions were evaluated, including gauging the diameter of the vagina and the transvaginal accessibility of the tumor. Full contouring and dose planning were performed on MRI. When optimization of the IC implant was saturated, virtual needles were gradually added using either a ring cap template [12] or 3DP TNT geometry as a virtual platform for needle guidance [18]. Decision to use the TNT instead of the ring cap template geometry was made in cases with unfavorable anatomical- (e.g. narrow vagina) or tumor-characteristics (e.g. large high-risk target volume [CTV_{HR}] or residual tumor in the distal parametrium), and whenever O-needles were required.

The 3DP TNTs were produced in-house in standard configurations, using biocompatible autoclavable material as previously described (Figure 1) [18]. The TNT consisted of a 21 cm long shaft, ending in a circular platform with a thickness of 11 mm and outer diameter of either 32 or 36 mm. This corresponded to the outer diameters of Varian rings without needle cap with the nominal source channel diameters of 26 and 30 mm, respectively. Since the dimensions of the 3DP TNT correspond to the commercially available Varian rings, they could be fitted over the standard Varian tandem applicator. The 3DP TNT did not contain a ring channel and the source would therefore only be in contact with the approved commercially available tandem and needles. Depending on the diameter, the standard TNT allowed for guidance of 8-12 P-needles or 8-10 P- plus 7 O-needles. The diameter of the circle, in which the holes for the P needles were situated, was either 26 mm for the 32 mm TNT platform, or 30 mm for the 36 mm TNT platform. A personalized 3DP TNT with a case-specific design was produced ad hoc in challenging clinical circumstances (Figure 1), for example by adding extra material or needle holes, when the standard 3DP P&O-needle configuration was found inadequate [18]. Since there was no ring channel in the TNT, the dwell positions of the P-needles at the level inside the TNT platform were activated, simulating the loading pattern of a common ring.

BT1 and BT2 were scheduled weekly after BT0. The implant procedure was initiated with placement of the uterine tandem under transabdominal ultrasound guidance. The TNT was then slipped over the tandem rod with its upper surface placed against the portio and fornices. This was followed by insertion of Varian plastic needles (2 mm diameter) through the relevant guiding holes, and to the required depth, according to the preplan from BT0. Needle positions were verified by intraoperative trans-rectal ultrasound. Setting out from a 17.5 Gy point-A standard dose plan, the planning aim was a cumulative CTV_{HR} D90 (minimal dose to 90% of the clinical target volume) of $\geq$ 90 Gy (cumulative EQD2 of EBRT plus BT, LQ model, repair half-time of sub-

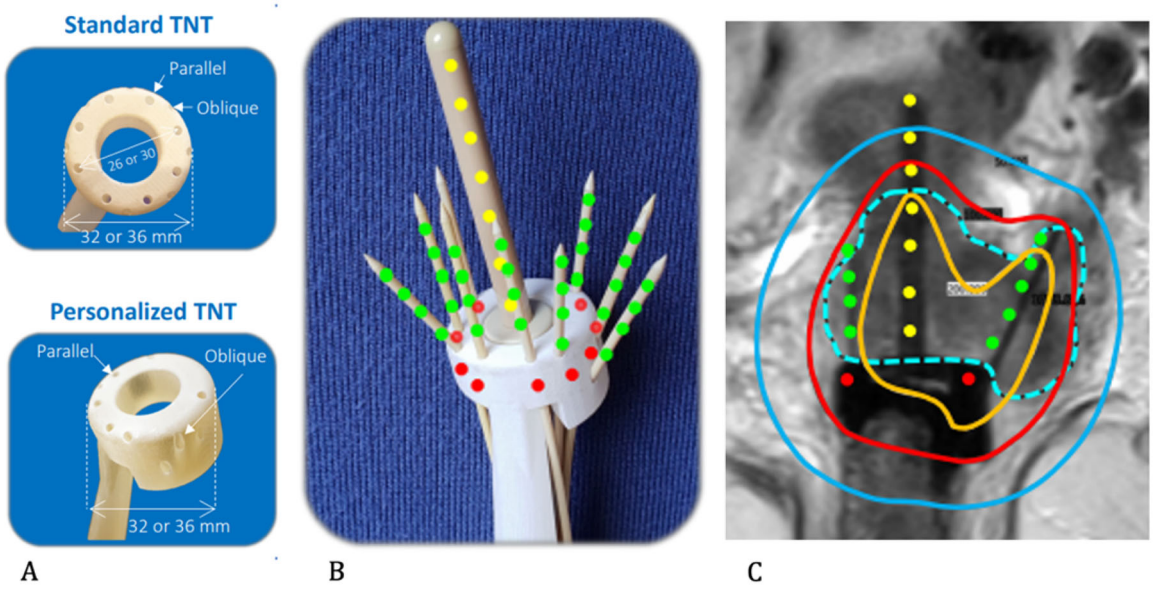

Figure 1. (A) Standard and personalized tandem-needle-template [TNT], with corresponding diameters and needle holes for parallel and oblique needles; (B) Personalized TNT fitted over the Varian tandem with both parallel and oblique needles *in situ*; (C) the tandem and personalized TNT with needles on MRI in coronal view showing oblique and parallel needle position (green dots), stopping positions in the tandem (yellow dots) and at ring level (red dots), CTV_{HR} (blue dashed line) and isodose distribution (yellow 200%, red 90%, blue 50%).

lethal damage of 1.5h, $\alpha/\beta = 10$ Gy). Dose to the organs at risk [OAR] was limited according to EMBRACE II protocol, calculating D2cm^3 (minimal dose to the most exposed 2 cc of the OAR), assuming an α/β of 3 Gy [5]. Each fraction of optimized IGABT was delivered using pulsed dose rate afterloading (GammaMedplus iX), divided in 20 hourly pulses. The 3DP TNT was discarded after single use.

At 3 months after treatment, MRI, PET-CT, and gynecological examination under general anesthesia were performed. MRI was repeated at 12 months. Further, clinical examination including gynecological examination was performed every 3 months during the first year, every 6 months in year 2-3 and annually until year 5. Status beyond follow-up was examined in January 2023 *via* the electronic patient chart and the national civil registry. Absence of persistent or recurrent disease within the BT target was defined as local control [LC]. The event for cancer specific survival [CSS] was active disease at the time of death. LC and CSS were calculated from date of diagnosis until event/censoring. Side effects were scored using the Common Terminology Criteria for Adverse Events [CTCAE v3.0].

Log-rank test was used for comparison of survival outcomes and Kaplan-Meier curves. Logit analysis was used for frequency analysis of binary endpoints. A p-value < 0.05 was considered significant. Patients were divided in two groups: Group P consisted of patients treated with P-needles only. Group P&O included patients receiving P&O-needles in standard or personalized TNT configuration. Patient and treatment characteristics were compared between groups with a paired t-test or a Chi-square test.

3. Results

3.1. Patient and tumor characteristics

Baseline characteristics are outlined in Table 1A. In total, 209 consecutive patients were treated during the studied period.

Table 1. Patient, tumor, and treatment characteristics according to template type: Needle directions in parallel to the tandem (P) or needle directions in parallel and oblique to the tandem (P&0).

A: Patient and tumor characteristics		All	P	P&O	*p*-value
No. of patients	No. (%)	101 (100)	49 (49)	52 (51)	
Age	Mean (SD)	63 (16)	66 (14)	60 (17)	0.073
Performance (WHO)	>0 (%)	48 (48)	19 (39)	29 (56)	0.087
Comorbidity	Present (%)	52 (51)	25 (51)	27 (52)	0.928
Histology	SQ (%)	91 (90)	45 (92.0)	46 (87)	0.570
Tumor score at diagnosis (TS_D)	Mean (SD)	9.1 (4.1)	7.7 (3.6)	10.5 (4.2)	0.000
Tumor score at brachytherapy (TS_{BT})	Mean (SD)	6.3 (3.2)	5.0 (2.0)	7.6 (3.6)	0.000
Tumor score High-High[a]	Present (%)	53 (53)	18 (37)	35 (67)[c]	0.003
DPPW at BT[b]	Present (%)	46 (46)	10 (20)	36 (69)[c]	0.000
Nodal status	Positive (%)	61 (60)	27 (55.0)	34 (65)	0.291
$FIGO_{2018}$ stage	IB (%)	1 (1)	1 (2)	–	0.177[d]
	IIB (%)	22 (22)	13 (27)	9 (17)	
	IIIA (%)	1 (1)	1 (2)	–	
	IIIB (%)	15 (15)	7 (14)	8 (15)	
	IIIC1 (%)	39 (39)	18 (37)	21 (40)	
	IIIC2 (%)	13 (13)	7 (14)	6 (12)	
	IVA (%)	10 (10)[e]	2 (4)	8 (15)	

B: Treatment characteristics		All	P	P&O	*p*-value
Concomitant cisplatin	Initiated (%)	56 (55)	27 (55)	29 (56)	0.946
Overall Treatment Time (days)	Median (IQR)	48 (45-50)	47 (42-50)	49 (46-52)	
	>50 days (%)	23 (23)	7 (14)	16 (31)	0.048
Extended EBRT[f] target	Yes (%)	34 (34)	11 (22)	23 (44)	0.021
TNT[g] diameter "small"	Yes (%)	84 (83)	43 (88)	41 (79)	0.232
Number of needles[h]	Median (IQR)	9 (8-12)	8 (8-9)	12 (9-13)	
Number of active needles[h]	Median (IQR)	8 (8-11)	8 (7-8)	10 (9-12)	
TRAK[i] cGy	Mean (SD)	1.64 (0.49)	1.54 (0.42)	1.73 (0.53)	0.063
CTV_{HR}[j] (volume, cm^3)	Mean (SD)	37.9 (24.0)	33.9 (22.0)	41.5 (25.5)	0.111
CTV_{HR} D_{90} (Gy_{EQD2})	Mean (SD)	93.4 (3.3)	93.9 (3.1)	92.9 (3.4)	0.121
Bladder D_2cm^3 (Gy_{EQD2})	Mean (SD)	73.1 (8.0)	71.0 (7.5)	75.1 (8.0)	0.009
Rectum D_2cm^3 (Gy_{EQD2})	Mean (SD)	60.8 (5.7)	59.1 (4.4)	62.4 (6.3)	0.004
Sigmoid D_2cm^3 (Gy_{EQD2})	Mean (SD)	58.8 (6.0)	58.3 (6.2)	59.2 (5.8)	0.436
Bowel D_2cm^3 (Gy_{EQD2})	Mean (SD)	59.2 (8.4)	59.4 (8.5)	59.0 (8.6)	0.774
Recto-vaginal point (Gy_{EQD2})	Mean (SD)	58.9 (5.2)	58.1 (4.9)	59.6 (5.4)	0.137
CTV_{HR} D90 soft constraint[k]	Fulfilled (%)	93 (92)	47 (96)	46 (89)	0.165
OAR[l] all soft constraints[k]	Fulfilled (%)	60 (59)	35 (71)	25 (48)	0.017

[a]High-High: TS_D AND $TS_{BT} > 5$.
[b]Involvement of distal parametrium or pelvic wall at first brachytherapy.
[c]3 cases with DPPW were High-Low in TS and 3 cases with High-High in TS did not have DPPW involvement.
[d]Comparing stage I-II versus III-IV.
[e]Biopsy confirmed. Additional 21 patients had bladder wall infiltration/bullous edema on MRI/cystoscopy.
[f]External beam radiotherapy.
[g] Tandem needle template.
[h]Maximal number used for first or second bachytherapy implant.
[i]Total reference air kerma.
[j]High risk clinical target volume, (dose to 90% of the CTV_{HR}).
[k]According to the EMBRACE II Study.
[l]Organs at risk.

3DP TNT was used in 101 (48%) patients, who were included in the present analysis: Forty-nine (49%) in group P and 52 (51%) in group P&O. Among the P&O cases, 19 (37%) were treated with a personalized TNT. Mean age was 63 years. Ninety percent of the tumors were squamous cell carcinomas [SCC] and 77% had $FIGO_{2018}$ stage III or IV disease. Patients in the P&O group had a significantly higher TS_D and TS_{BT} compared to the P group ($p < 0.001$). Correspondingly, almost twice as many in the P&O group ($p = 0.003$) had poor response to CRT as evidenced by the high-high pattern of TS [23]. In addition, distal parametrial/pelvic wall involvement [DPPW] at BT was found 3.5 times more frequent in the P&O compared to the P group ($p = 0.003$). Figure 2A displays the total TS points per location for both techniques, showing that quantitatively, the use of O-needles was mainly determined by the parametrial invasion. A detailed description of TS_D and TS_{BT} points from the individual locations can be found in Table 2.

3.2. Treatment characteristics

Treatment characteristics are shown in Table 1B. Concomitant cisplatin was given to 55% of the patients, which was similar in both groups. No other chemotherapy regimens were used. The small 32 mm TNT was used most often (83%), especially in the P-group. A median of 8 and 12 needles were inserted per application in the P and P&O group, respectively. Approximately 90% of the needles were used for treatment (i.e. loaded). The likelihood of implanting O- needles could be described as a function of TS_{BT} by use of logit analysis. A 50% probability for using the O-needles was found at a TS_{BT} of 6 (Figure 2B). Overall, the mean CTV_{HR} volume was 37.9 cm^3 and the CTV_{HR} D90 was 93.4 Gy_{EQD2}, without significant difference between the groups. There was a linear and negative correlation between CTV_{HR} D90 and TS_{BT}, with a slope of −0,30 Gy/TS_{BT} point and an intercept of 95.3 Gy (Figure 2C). The opposite was observed with the rectal

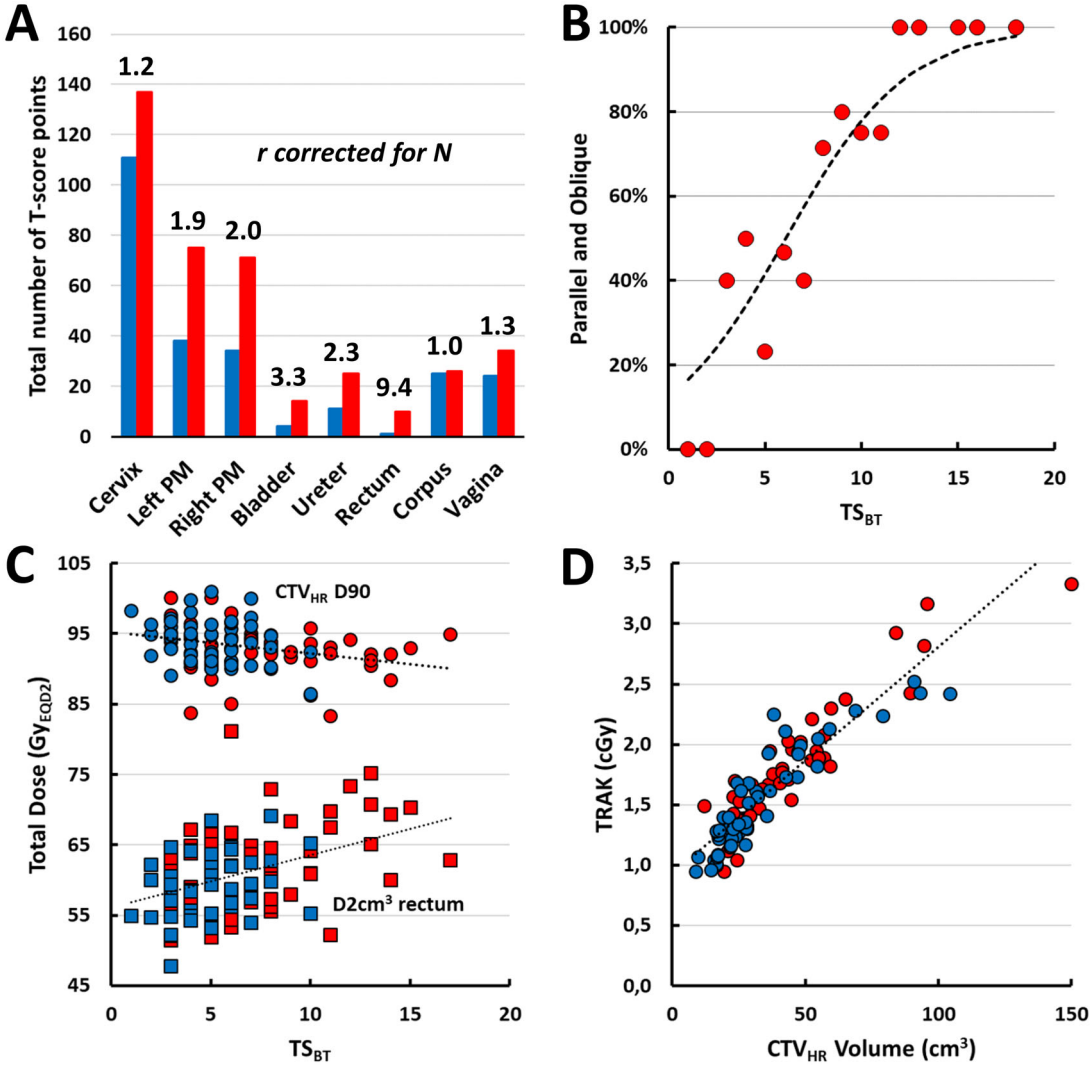

Figure 2. (A) Total number of tumor score [TS] points per location and needle direction: parallel and oblique [P&O] (red) and parallel [P] (blue). above the bars, the ratio [r] is mentioned, corrected for number of patients [N]; (B) Likelihood of using P&O needles as a function of TS at brachytherapy [TS_{BT}] is demonstrated by logit analysis; (C) Total dose of external beam radiotherapy and BT for CTV_{HR} D90 [minimal dose to 90% of the clinical target volume] (circles) and rectal $D2cm^3$ [minimal dose to the most exposed 2 cc of the OAR] (squares) as a function of TS for P&O (red) and P (blue); [D] the mean total reference air kerma [TRAK] as a function of TS for P&O (red) and P (blue).

Table 2. Tumor score at brachytherapy [TS_{BT}] for all patients and the two patient subgroups according to needle direction. The number of patients receiving different number of points according to nominal scale are shown for each anatomical location.

		No. of patients			
Location	Nominal scale	Points	All	P[a]	P&O[b]
Cervix	Not present	0	0	0	0
	≤20 mm	1	2	2	0
	>20, ≤ 40	2	51	32	19
	mm > 40 mm	3	48	15	33
Left	Not involved	0	24	17	7
Parametrium	Proximal	1	50	27	23
	Distal	2	18	4	14
	Pelvic wall	3	9	1	8
Right	Not involved	0	34	22	12
Parametrium	Proximal	1	39	22	17
	Distal	2	18	3	15
	Pelvic wall	3	10	2	8
Vagina	Not involved	0	61	31	30
	Upper 1/3	1	26	13	13
	Middle 1/3	2	10	4	6
	Lower 1/3	3	4	1	3
Uterine	Not involved	0	64	32	33
Corpus	Lower 1/3	1	24	11	13
	Middle 1/3	2	9	4	5
	Upper 1/3	3	3	2	1
Rectum	Not involved	0	90	48	42
	Mesorectum	1	11	1	10
	Rectal wall	2	0	0	0
	Mucosa involved	3	0	0	0
Bladder	Not involved	0	83	45	38
	Bladder wall	1	18	4	14
	Bullous edema	2	0	0	0
	Mucosa involved	3	0	0	0
Ureter	Not involved	0	74	41	33
	Unilateral	1	16	5	11
	Bilateral	2	1	3	8
Total number of patients (%)			101	49	52
TS_{BT}	Median (range)		6(1-17)	5 (1-10)	7 (3-17)
	Mean (SE)		6.3 (0.3)	5.0 (0.3)	7.6 (0.5)

[a]Needle directions implanted in parallel to the tandem.
[b]Needle directions implanted in parallel and oblique to the tandem.

Table 3. Number of events and actuarial 3-year outcome for all patients and the two patient subgroups according to needle direction.

Variable	All[a]	P[b]	P&O[c]	*p*-value[d]
Local failure	13	2	11	
Local control (SE)[e]	85 (4)	95 (3)	75 (7)	0.009
Pelvic failure (local and regional)	22	8	14	
Pelvic control, local and regional (SE)	75 (5)	80 (7)	70 (7)	0.130
Para-aortic failure	10	3	7	
Para-aortic control (SE)	88 (4)	91 (5)	85 (6)	0.140
Systemic failure	21	9	12	
Systemic control (SE)	74 (5)	77 (7)	71 (7)	0.373
Diseased	49	20	29	
Overall Survival	63 (5)	75 (6)	51 (7)	0.058
Cervical cancer deaths	36	13	23	
Cancer Specific survival	68 (5)	80 (6)	56 (7)	0.036
Recurrence or death	52	22	30	
Disease free Survival	51 (5)	56 (7)	47 (7)	0.108
≥ Grade 3 side effect	10	7	3	
≥ Grade 3 side effect (SE)	12 (4)	16 (6)	9 (5)	0.261

[a]One patient in the P&O group died before first follow up leaving 100 patients evaluable for tumor control (local, pelvic, para-aortic, systemic) and 101 evaluable for survival endpoints and grade 3 or worse side effect.
[b]Needles implanted in direction parallel to the tandem.
[c]Needles implanted in directions parallel and oblique to the tandem.
[d]log-rank.
[e]Standard error.

D2cm^3, which was positively and linearly correlated with the TS_{BT} (slope 0.75 Gy/TS_{BT} point, intercept 56.1 Gy) with no crossing of the lines within the TS_{BT} range. The mean total reference air kerma [TRAK] was below 2 cGy in both groups and was positively correlated with CTV_{HR} volume (Figure 2D).

3.3. Local control, survival, and side effects

Oncological outcomes are shown in Table 3 and in Figure 3. The overall median follow-up time was 41 months. Local failure occurred in 13 patients, of whom 11 were from the P&O group, leading to a 20% lower 3-year actuarial LC rate in the P&O group (Figure 3A). Twelve (92%) local failures occurred within the first 12 months, and all 13 within 18 months. Cancer specific survival (pelvic, para-aortic, and systemic control) were also lower in the P&O group by 6-10% with a 24% lower 3-year CSS ($p = 0.036$) compared to the P group (Figure 3B).

Impact of tumor regression during initial CRT as estimated by the change in TS from TS_D to TS_{BT} is demonstrated in Figure 3C for LC and Figure 3D for CSS. A similar pattern was observed for both endpoints, i.e. patients with a TS_D >5 but $TS_{BT} \leq 5$ had a similar outcome as patients with $TS_D \leq 5$. In contrast, patient with TS_{BT} remaining > 5 showed significantly lower rates of LC and CSS, which related to 1/3 and 2/3 of the patients in the P-group and the P&O group, respectively (Table 1A).

No severe bleedings were observed after applicator and needle removal. The few bleedings that occurred, were stopped with compression only and did not need any surgical intervention or embolization. As far as the side effects are concerned, 14 grade ≥3 [$G \geq 3$] adverse events were observed in 10 patients: 6 gastro-intestinal, 3 urological, 2 vaginal and 3 other events (Table 4). There was no significant difference in $G \geq 3$ side effects between the two groups ($p = 0.261$), with a 3-year estimated risk of 12% One patient died of gastro-enteritis after treatment but before first follow-up, with a possible relation to the radiation treatment. Three patients reported more than one event, all with noteworthy comorbidities. Moreover, two of them presented with an infiltrative tumor with a TS_D of 14 and 17, including DPPW involvement, hydronephrosis, and mesorectal involvement. In one patient, the reported G3 event was cisplatin-induced neuropathy.

4. Discussion

This study has shown that 3DP TNT based IC/IS IGABT is able to achieve the ambitious Embrace II planning aims and DVH constraints [5] with favorable oncological outcome even in LACC with prognostically unfavorable infiltrative tumors and in patients with difficult anatomical conditions [2,8,9].

In our experience, there are two major indications to use 3DP TNT, which are reflected by the characteristics of the two groups (P and P&O) of our study. Thus, the main indication for TNT in the P group was narrow vaginal anatomy. This assertion is consistent with the finding that small-diameter TNT was used in 86% of cases in the P-group which also had a higher mean age. This implies a higher proportion

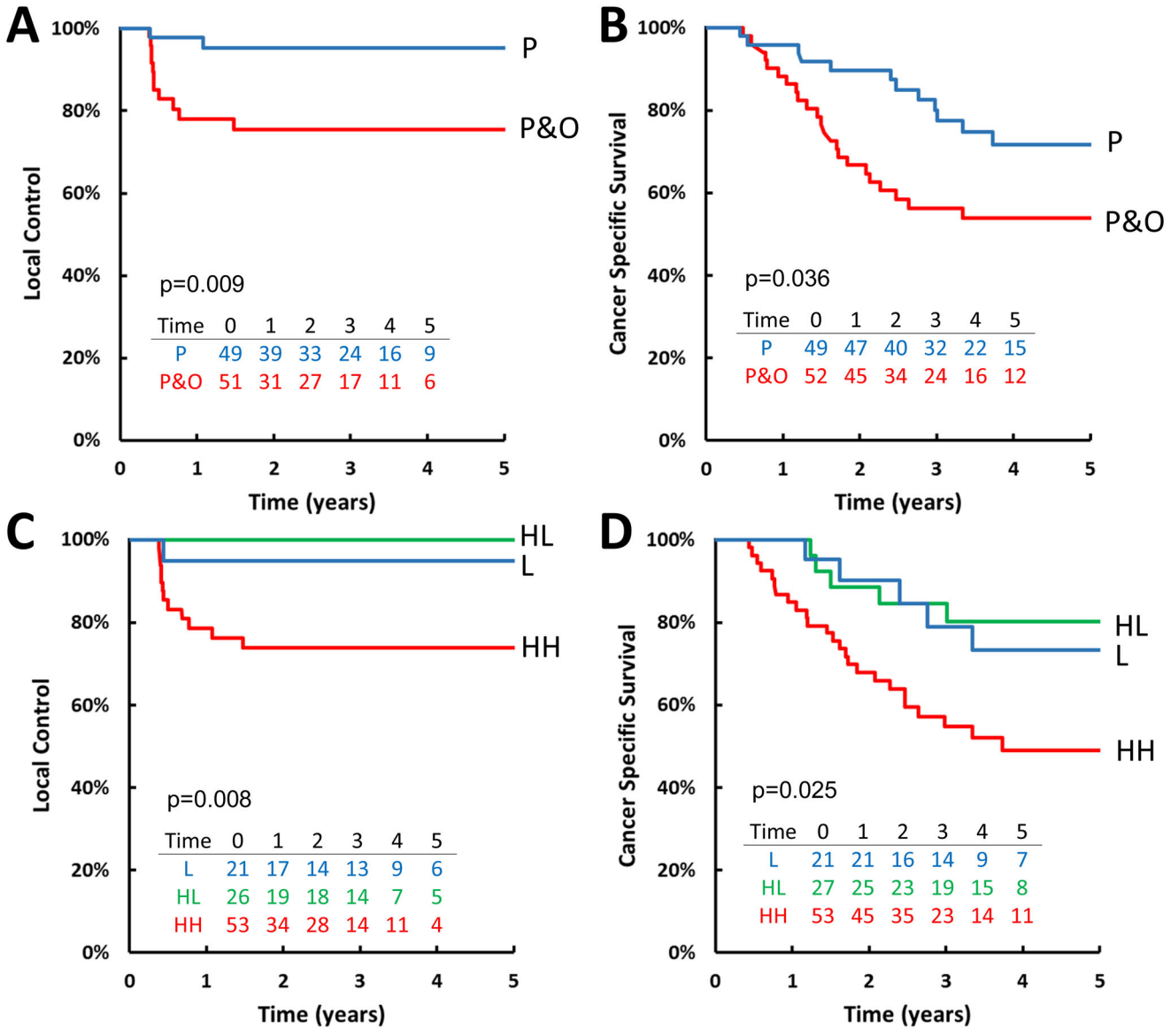

Figure 3. Kaplan-Meier curves for local control (A) and cancer specific survival (B) in group with parallel [P] and parallel and oblique [O] needles; local control (C) and cancer specific survival (D) corresponding with tumor response, based on tumor score at Diagnose [TS_D] and brachytherapy [TS_{BT}]: L (TS_D and $TS_{BT} \leq 5$), HL [$TS_D > 5$ and $TS_{BT} \leq 5$], HH (TS_D and $TS_{BT} > 5$).

of postmenopausal patients with smaller vaginal dimensions, and lower elasticity. In contrast, the dominant features of the P&O group included poor response to EBRT and large CTV_{HR}. In line with our clinical experience, the principal indications for the use of 3DP TNT in the P&O group were therefore unfavorable tumor size, shape, and pattern of infiltration, necessitating the use of oblique needles or even individualization of the TNT geometry. Finally, it can be assumed that some patients from both groups presented with both narrow vaginal anatomy and unfavorable tumor features as combined indication for 3DP TNT.

Despite the relatively unfavorable tumor characteristic, we achieved an excellent mean CTV_{HR} D90 of 93.4 Gy, without exceeding the EMBRACE II OAR dose constraints and keeping mean TRAK $<$ 2 cGy. The relationship between CTV_{HR} D90 and TS_{BT}, was almost flat (Figure 2C), which differs from the CTV_{HR} D90 dose reduction that was seen in the EMBRACE I study with increasingly advanced tumors [24]. In addition, the linear relationship for rectal D2cc and TS_{BT} did not intercept within the observed range of TS_{BT}, indicating the 3DP TNT based IGABT provides an expansion of the therapeutic window compared to conventional IC/IS as evidenced by the results of EMBRACE I [24,26].

Despite the excellent dose reporting of CTV_{HR} D90 in our study cohort, survival outcomes were inferior to the population presented in EMBRACE I and retroEMBRACE [5,8,26]. However, when comparing to the EMBRACE I, our cohort of patients treated with a 3DP TNT were highly selected based on several poor prognostic factors. Our patients were older (63 years compared to 49 years) and only 55% of all patients were able to receive concomitant chemotherapy, compared to 94% in EMBRACE I [26,27]. Moreover, in our cohort, FIGO stage III/IV disease was more common (77% versus 59%) and the mean overall CTV_{HR} volume larger (38 cm^3 versus 28 cm^3) compared to the EMBRACE I study [26]. Finally, the tumor load in our cohort was higher (mean TS_D and TS_{BT} of 9.1 and

Table 4. Patient and tumor characteristics of patients with ≥ grade 3 side effects (CTC-AE version 3.0) including age, WHO performance status (PS), comorbidity, $FIGO_{2018}$ stage, distal pelvic parametrium or pelvic wall involvement at BT (DPPW), tumour score at diagnosis (TS_D) and at BT (TS_{BT}). principal treatment related cause of side effects was assessed to be EBRT in patient A, D, F and I, cisplatin in patient B and BT in patient A, C, E, G, H and J.

Patient	Group	Age	PS	Comorbidity (CM) and late effect (LE)	$FIGO_{2018}$	DPPW	TS_D	TS_{BT}
A	P	72	1	CM: Rheumatoid arthritis LE: Stenosis of ileum	III_{C1}	No	9	6
B	P	71	0	CM: Mammary Cancer LE: Cisplatin induced neuropathy	III_{C1}	No	8	5
C	P	72	1	CM: Apoplexia cerebri LE: Hydronephrosis	III_{C1}	Yes	10	7
D	P	58	1	CM: Mammary cancer, previous actinic castration, Kidney insufficiency, Retroperitoneal fibrosis LE: Gastro-intestinal, urological and vaginal fibrosis	III_{C2}	Yes	14	8
E	P	43	0	CM: None LE: Vaginal necrosis, healed after 3 years	II_B	No	5	4
F	P	65	0	CM: None LE: Mesenteric arterial thrombosis with subsequent sigmoid necrosis	III_{C1}	No	7	7
G	P	50	1	CM: HIV, hepatitis-C LE: Hydronephrosis, intrabdominal abscess	III_{C1}	Yes	8	7
H	P&O	38	2	CM: Post-traumatic stress LE: Recto-vaginal fistula	III_{C1}	Yes	10	10
I	P&O	80	1	CM: Mammary cancer LE: Gastro-enteritis, dead before first follow-up	III_B	No	13	5
J	P&O	39	1	CM: Anorexia LE: Perforation of sigmoid, infection and abscess formation	III_{C1}	Yes	17	12

6.3), than in the EMBRACE I study (5 and 4, respectively). High-high TS pattern was present in 53% in our study, compared to 21% in EMBRACE I. Lindegaard et al. have shown that a $TS_{BT}>5$ corresponds with poorer survival outcomes [24]. The unfavorable TS in our cohort is most evident in the P&O group but is also present in the P group (Table 1). Nonetheless, despite the unfavorable characteristics in the P group, an excellent LC (95%) was achieved, which is comparable to the EMBRACE I (92%) [26]. Patients in the P&O group who had even more advanced tumors, demonstrated an encouraging LC of 75%. It can be argued that many of the patients in this group would otherwise have been treated with an external boost to the tumor/parametria, or even with a palliative intention.

In patients with a $TS_{BT}>5$, our control rates are significantly lower than in those with a $TS_{BT} \leq 5$. In most cases, a TS_D and $TS_{BT}>5$ entails DPPW involvement. The level of tumor infiltration in these patients is comparable with those described by Mahanshetty et al. [14] where patients with residual DPPW at time of BT were treated using a modified applicator (Vienna II) suited for oblique needles. They achieved a promising three and five-year LC of 76% and 72% respectively, which is comparable to our results in this group (75%). Besides patient selection, there are some more differences between our studies. The percentage of non-SCC in our cohort was three times higher; 10% vs. 3%. Non-SCC have a higher risk of local failure and require a higher dose for the same effect as SCC [28]. Therefore, this might have impacted our results negatively. In addition, in the Mahanshetty paper, the mean CTV_{HR} volume was larger (71 cm^3 vs. 37.9 cm^3), and the mean CTV_{HR} D90 was lower than we have achieved (86 Gy vs. 93.4 Gy). However, LC is similar ([14]. The difference in HR CTV D90 but not in outcome may partially be explained by contouring diversities and uncertainties on the basis of different scanning protocols, magnet strengths of the MRI scanner etc.

The recently developed Venezia™ applicator (Elekta©, Stockholm, Sweden) allows for utilization of parallel and oblique needles, vaginal caps for covering the vaginal wall and a perineal template if necessary. It is therefore specifically suitable in patients with invasive tumor growth, such as distal vagina or pelvic wall involvement. Few studies have published promising first results on dose distribution and LC in a small number of patients [15–17,29].

A 3DP TNT can be used for similar patients. However, a 3DP TNT might hold some benefits in comparison to a commercially available applicator. Firstly, 3D printing allows for maximal customization to tumor extension and anatomy, since the operator is not bound to a limited set of accessories delivered with an applicator. This is especially beneficial in patients with a narrow vagina or extensive parametrial and vaginal residual tumor. Secondly, a 3DP TNT can be adapted to a tandem of any vendor and can therefore be used universally. Thirdly, 3D printing is an inexpensive method. Especially for low-income countries, where the incidence of LACC is higher and tumors are often more invasive, this can be a good solution [30]. However, implementing 3D printing in clinical workflow requires time, dedication, and experienced staff. Also, knowledge regarding regulatory processes (FDA approval, CE marking), material biocompatibility and strength, and liability issues in case of equipment failure is necessary. In this context, a development and implementation of a department-specific quality assurance and control process is required. In view of the relative novelty of 3D printing techniques for BT, helpful references and resources to assist this task are difficult to come across. Collaboration with departments with more longstanding experience (i.e. orthopedic and maxillofacial surgery) could be helpful in this context. It is important to keep in mind that our 3DP TNT are only used as a guidance tool for the interstitial needles and do not contain channels that are in direct contact with the iridium source. The 3DP TNT in a standard P&O configuration has recently become commercially available as the "Aarhus Applicator" (www.varian.com), which likely could have been used in 82 (81%) patients of the present cohort.

Since our templates do not have a ring channel, needles must take over this function. Therefore, the median number of needles in our 3DP TNTs was relatively high. However, the implant depth was very shallow (i.e. 1 cm) for needles with a "ring function" only which apparently did not result in more severe complications. No severe bleedings that needed surgical intervention or embolization were observed, nor any symptomatic perforation of hollow organs. Systematic use of transrectal ultrasound for checking needle position may have contributed to both safety and quality of the implants. Furthermore, the individualized loading of needle dwell positions inside the TNT instead of vaginal ring positions may have improved the ratio between dose to the target volume and vagina [31]. Therefore, TNT loading flexibility may enable the reduction of the late vaginal side effects without compromising the LC. Further research is needed to confirm this notion.

Grade 3-5 side effects occurred in 10 patients, corresponding to a 3-year estimated risk of 12%. This incidence is in line with reported late toxicities in retroEMBRACE and EMBRACE I, 11% and 14.6% respectively [2,26]. In fact, since our cohort represents an unfavorable selection of patients with a higher tumor load, less resonse to EBRT and more invasive treatment, higher morbidity rates would have been expected [25]. The fact that the morbidity rate was similar to EMBRACE I, supports the clinical feasibility and safety of 3DP TNTs.

In general, the retrospective nature of a study may be considered as a limitation, due to the risk of missing data and selection bias. However, since our outcome data were collected during prospective follow-up and checked in the national civic registry, there are no missing data in this study. More importantly, regarding the selection bias, the selection is reversed, choosing the difficult cases consecutively for the 3DP technique. Therefore, our confirmation of the effectiveness and safety of the technique should not be discarded as biased.

In conclusion, using 3DP TNT for IGABT in the treatment of cervical cancer has been proven clinically safe, effective and feasible in a cohort of selected patients with unfavorable tumor and/or anatomical characteristics. TNT allows for successful and affordable management of extensive local disease and/or unfavorable anatomy, with the possibility for treatment individualization, without increased side effects.

Disclosure statement

The authors report there are no competing interests to declare.

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Data availability statement

Data cannot be shared

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