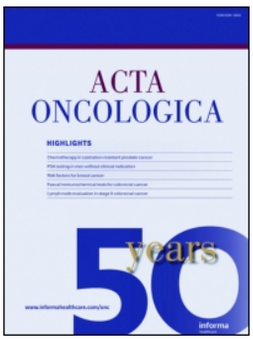

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LETTER TO THE EDITOR

Retrospective validation of coverage probability based simultaneous integrated nodal boost in locally advanced cervical cancer: a mono-institutional analysis

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Introduction

Patients with locally advanced cervical cancer (LACC) treated with concomitant chemo-radiation (CCRT) and image-guided adaptive brachytherapy (IGABT) have outstanding results [1–10]. While local control reaches 86–97% with IGABT [1–10], nodal and distant failures (DF) become the dominant causes of treatment failure, leading to poor overall survival (OS), especially for patients with nodal metastases (N+) [3,7,11].

In the EMBRACE study (IntErnational Magnetic resonance imaging-guided BRAchytherapy in CErvical cancer), the overall nodal failure (NF) was 11%, including 7% and 16% for N- and N + patients [12]. Forty percent of NFs were located inside the elective target volume (39% of which in paraaortic node (PAN)) and 35% inside the nodal boost volume. The actuarial 3- and 5-year nodal control rate was 87% (92% (N−) versus 82% (N+)) and 86%, respectively [12]. The retroEMBRACE study reported a pelvic failure rate of 13% and a pelvic NF rate of 6% [9]. A recent paper showed a 3-year NF rate of 21% with 69% overall survival (OS) with 60 Gy simultaneous integrated nodal boost (SIB-N) without serious morbidity [13].

The EMBRACE II study introduced the Coverage probability (CovP)-based simultaneous integrated nodal boost (SIB-N) concept, which allows for a relaxed planning aim at the edge of the nodal planning target volume (PTV-N, 90% of the prescribed dose), with a full dose with hot spots within nodal gross tumor volume (GTV-N) where regression is expected. Controlled underdosage at the edge of the PTV-N and targeted dose escalation at the center are aimed to reduce high-dose delivery to adjacent organs at risk (OARs) [14–17], while maximizing nodal control. However, these dosimetric advantages come with the potential risk of geographic misses, such as internal nodal movement or positioning errors when PAN-RT is given [14]. Ramlov et al. [14] demonstrated that geographic misses have only mild dosimetric impact for pelvic CovP-SIB-N, but few data were presented with PAN SIB-N. Moreover, published results on clinical outcome and nodal volume changes with CovP SIB-N in LACC patients are very limited [15].

These motives led to this retrospective cohort analysis, which aims to present (1) CBCT verification of nodes hit with CovP SIB-N; (2) their nodal regression during EBRT; and (3) 2-year clinical outcome.

Material and methods

Patients

Between January 2016 and November 2020, 65 biopsy-proven LACC patients were treated with definitive RT ± CT followed by IGABT, including 33 patients with nodal disease. In the absence of voluminous lymph node(s) and/or very close vicinity of primary or mobile organs (bladder, rectum), CovP-SIB-N was the treatment of choice, which was the case in 29 patients. Three patients showed ultra-early (<6 weeks) bizarre distant progression (subcutaneous, peritoneal, hepatic) and were excluded from this study. Analysis was performed using data from 26 LACC patients treated with CovP-SIB-N technique with weekly cisplatin (40 mg/m^2), followed by IGABT.

Staging consisted of gynecological examination according to Fédération Internationale de Gynécologie et d'Obstétrique (FIGO), a thoraco-abdominal scan and 3T abdominal-pelvic magnetic resonance imaging (MRI) (Biograph mMR, Siemens Healthcare GmbH, Erlangen, Germany) for all patients completed by a whole-body 18F-fluorodeoxyglucose positron-emission tomography-computed tomography (18FDG PET-CT, Biograph 64, Siemens Healthcare GmbH, Erlangen, Germany). Cystoscopy or rectoscopy was added if organ infiltration was suspected.

Nodes were considered pathological according to EMBRACE II criteria: FDG-PET positive or short axis >1 cm on CT or MRI and/or short axis between 0.5 and 1.0 cm on MRI with pathological morphology (irregular border, high signal intensity, and/or round shape).

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Supplemental data for this article can be accessed here.

Contouring and planning followed the EMBRACE II protocol [16] for regional irradiation. In summary, CT and MRI scans were obtained with full and empty bladder conditions to assess movement patterns and to create internal target volume (ITV). All scans were co-registered in the Eclipse Treatment Planning System (Eclipse v13, Varian, Palo Alto, CA). Pathological nodes were contoured (GTV-N) on MRI and CTs, then merged to form CTV-N (clinical target volume). The elective target volume (CTV-E) included pelvic lymph-nodes up to the aortic bifurcation. If >2 pathological nodes were identified, or if node(s) were located at the typical iliac vessels or higher, PAN to the level of the renal vessels were systematically included. An ITV for 45 Gy (ITV45) including CTV-E and CTV-N was created using information from co-registered images. PTV45 (PTV for 45 Gy) and PTV-N_x were created using a 5-mm isotropic margin around ITV45 and CTV-N [16].

Treatment planning consisted of two 6 MV volumetric arc therapy beams (TrueBeam 2.5, Palo Alto, CA). Planning aims for elective and SIB-N volumes were the following: PTV45: V42.75 Gy >98%, CTV-N and PTV-N: D98 ≥ 90%, CTV-N D98 ≥ 100% and CTV-N D50 ≥ 102% of the prescribed dose, which was 55 Gy/25 fx to nodes in the small pelvis and 57.5 Gy/25 fx to nodes further away. Treatment verification consisted of daily CBCT with bony anatomy match including extended CBCT for PAN SIB-N.

Boosted nodes were contoured on each CBCT (GTV-N_{CBCT}) and were assessed for coverage by PTV-N. Target coverage was evaluated by comparing individual nodal delineations with the relevant PTV-N. In patients with insufficient coverage the dose to 98% (D98%), 50% (D50%) of each GTV-N_{CBCT} was assessed according to the planning CT dose distribution by propagating the individual GTV-N_{CBCT} *via* rigid bony registration to the planning CT. The accumulated D98%, D50% was calculated as the mean of each DVH parameter across all CBCT contours in a given patient.

The high-dose-rate (HDR) BT schedule included 2–4 fractions in one or two applications. Before the introduction of the interstitial needles and in cases with distant parametrial spread where target coverage would have been compromised even with parallel needles, external beam sequential boost was given to the primary tumor up to 60 Gy. These patients were re-planned with empty and full bladder conditions and the target volume was the adapted high-risk CTV. Thus, two fractionation schedules were used for the primary tumor: 60 Gy + 2 × 7 Gy HDRBT ($n = 5$) or 45 Gy + 4 × 7 Gy ($n = 21$). Target and OAR delineation and dose reporting for IGABT were based on the International Commission on Radiation Units and Measurements (ICRU) Report 89 [18].

Patients were followed with gynecological examination every 3 months in the first year, twice a year in the second and the third year, and once a year afterward. Patients also had an MRI at 3 months and PET-CT where it was possible, repeated when relapse was suspected. Both acute hematological (HT)/renal toxicity and late gastrointestinal (GI) and genito-urinary (GU) toxicity were scored using the Common Terminology Criteria for Adverse Events (CTCAE 4.0) and documented in case of ≥ Grade (Gr.) 3 due to the retrospective nature of the study.

Complete clinical remission was defined as no evidence of disease 3 months after completion of treatment. Crude and 2-year actuarial rates of local failure-free (LRFS), distant metastasis-free (DMFS), regional failure-free (RRFS), cancer-specific (CCS), and OS were calculated and described by the Aalen-Johansen competing risk assessment [19]. All follow-up (FUP) were calculated from the end of treatment.

Descriptive statistics were given for clinical variables and dose-volume parameters. Statistical evaluation was performed using scipy (1.6.3) and lifelines (0.26.0) python (3.7) packages (Python Software Foundation, Beaverton, OR).

Results

Patient-, tumor-, and treatment characteristics

Patient cohort characteristics are presented in Table 1. The dominant FIGO stage was IIB (54%), with >50% cases with initial tumor size ≥ 5 cm. Most patients (96%) had squamous cell cancer. The median overall treatment time (OTT) was 49.5 (range: 31–70) days. Eighty-nine percent of patients received ≥ 4 cycles of cisplatin. Eleven patients received PAN irradiation including two cases with elective intention.

Dose constraints for EBRT CTV-N D98 and PTV-N D98 were achieved in 91% and 83% of the nodes, while for OARs, they were fulfilled in ≥96% of the cases (Supplementary Tables 1 and 2). Dose–volume parameters for IGABT are presented in Supplementary Table 3.

In total, 76 nodes (range: 1–6/patients, average volume: 3.20 cm^3, *r*: 0.8–25.3) were boosted, 20% at the PAN region (Table 1).

All lymph nodes showed regression (Figure 1) including 71% with complete or remarkable partial remission during EBRT. There was a trend that smaller lymph nodes achieved diminished volume earlier, than the larger ones (>10 cm^3).

Sixty-one out of 76 nodes were unambiguously detectable on CBCT, the remaining ones were outside the CBCT field of view ($n = 9$) or not clearly identifiable ($n = 6$) (i.e. adjacent nodes, bowel air artefacts). The mean GTV_{CBCT} of PAN and pelvic lymph nodes was not significantly different: 5.4 (SD:6.8) cm^3 versus 4.0 (SD:5.1) cm^3 ($p = 0.427$). In patients with PAN- and pelvic SIB-N the mean reduction in PAN and pelvic nodal size during EBRT was 70% and 75%. During the evaluation of 650 CBCTs, only 3/61 nodes in 5 fractions were

Table 1. Patient, tumor, and treatment characteristics.

Characteristics	Value (%)
Number of patients	26 (100)
Median age (year)	61 ± 12 (40–76)
FIGO stage IIA/IIB/IIIA/IIIB/IVA	4/17/1/3/1 (15/65/4/12/4)
No. of nodes per patient 1/2/3/>3	5/4/9/8
No. of nodes per localization total	76 (100)
Para-aortic	15 (20)
Common iliac	7 (9)
Parametrial, mesorectal, presacral	3 (4)
Internal iliac	18 (24)
Ext. iliac and obturator	33 (43)
EBRT target	
Pelvis	15 (58)
Pelvis and para-aortic region	11 (42)

FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; EBRT: external beam radiation therapy.

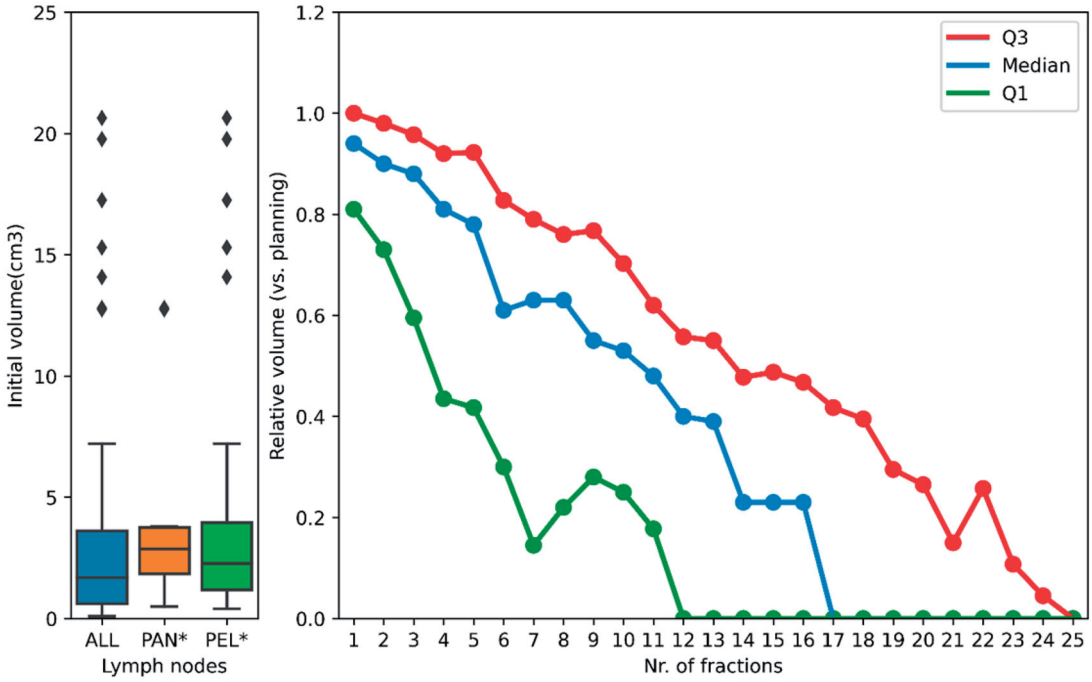

Figure 1. Boxplot representation of initial (planning) volume of all (ALL), CBCT-detected (*) para-aortic (PAN) and pelvic (PEL) positive lymph nodes (left), relative volume changes (regression) in function of the fractions for the Q3 (75%), median (50%), and Q1 (25%) of the cohort.

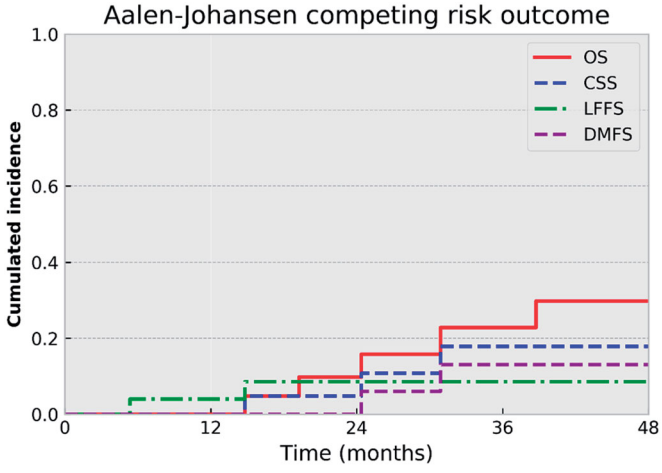

Figure 2. Competing risk analysis for the clinical outcome (OS: overall survival; CSS: cancer-specific survival; LFFS: local failure-free survival; DMFS: distant metastasis-free survival).

not completely covered by the corresponding PTV-N in one patient. All were pelvic nodes. One node had a D98% of 94%, with a D50% of 100%. The volume of this node was 0.8 cm^3 and the node was located close to the round ligament, which with varying uterus position was displaced for 5 fractions. The remaining 2 nodes had D98% >95% with maintained D50%. After a median FUP of 25 months (3–52), there was no NF. There were four recurrences/progressions consisting of two local failures (LF) and 2 DFs. The 2-years actuarial/crude rates of OS/CSS/DMFS/LFFS were 90/80, 95/88, 100/92, and 90/92%, respectively, in alignment with the slightly worse competing risk incidence (Figure 2).

Each failed patient had PAN disease at diagnosis. Twenty-one patients were alive at the last FUP (80.7%), three deaths were cancer-related.

Eleven ≥ Gr.3 hematologic side effects (42%) occurred (4 neutropenia, 2 thrombocytopenia and 5 anemia) in 9 patients from which 7 received PAN irradiation. One patient developed Gr.2 duodenal ulcers after PAN-RT which fully recovered after conservative treatment. One patient had Gr.3 colitis with accompanying stenosis of the sigmoid colon requiring elective surgical removal at 1-year FUP. MRI suggested a relationship with three SIB-N targets. Patient did not receive external beam boost. Full plan revision (including delineation of sigmoid on each CBCT, Supplementary Figure 1) confirmed that dose-limits would have been respected even if the sigmoid colon was in the closest location to SIB-N through 25 fractions (EBRT + HDR-BT, EQD2: D_{2cm3}: 63.8 Gy (ideal:1.8 Gy/fx) versus 67 Gy (median dose based on individual CBCTs: 1.9 Gy/fx) versus 74 Gy ("worst-case scenario": 2.1 Gy/fx).

Discussion

This study aimed to present our experiences with CovP SIB-N in LACC patients referred for CCRT. After a 2-year median FUP, there was no NF either in the boosted or in the elective RT regions. The majority of the nodes were visible on CBCT and 71% of the nodes achieved a diminished volume already during EBRT. Additionally, only one Gr.3 GI event occurred. It should be mentioned that by taking the EMBRACE II guideline into consideration, we have given 10% more elective PAN RT than previously and the average size of boosted nodes was small (3 cm^3).

A positive lymph node both at diagnosis [3,7,11] and as failure is a poor prognostic factor, confirmed by the EMBRACE I study cohort with actuarial 3-year NF of 8% and 18% in the N- and N + group with >70% mortality rate in patients with NF. Even though N + received a median dose

of 59 Gy, 12% developed NF within PTV-N. Moreover, 41% were located outside the elective target, including 39% in the PAO region [12]. EMBRACE II addressed these possible limitations for EBRT [16], including two major improvements for nodal irradiation: expansion of CTV-E to the PAN region and the CoV-SIB-N concept. Published literature with CoV-SIB-N is still limited. Lindegaard et al. [15] were the first to demonstrate a pelvic control of 91%, including only one NF within a boosted 1.1 cm^3 node in the small pelvis boosted with 55 Gy/25 fx and two other NFs in the un-irradiated PAN at 9 months median FUP.

RetroEMBRACE [9] data revealed significant correlation between local control and dosage, volume, and OTT for all primary target volumes. It remains unknown whether involved nodes require much higher doses. Ramlov et al. [20] investigated the pattern of nodal failure for N + patients in function of the individual nodal dose (75 patients, 209 nodal boosts, median dose 62 Gy (EQD2)). Six patients relapsed in boosted area. They did not find correlation between nodal dose and volume [20]. In contrast Bacorro et al. [21] found a nodal dose–volume effect on nodal control probability with increasing benefit of additional doses to higher-volume nodes. These contradictory data should be resolved by a large prospective study.

Investigating lymph node response during treatment on daily CBCTs revealed some additional aspects. First, the image quality of extended CBCT was sufficient to define 80% of SIB-Ns which is in line with the results of Ramlov et al. [14]. Similar to Ramlov [14] and Bacorro et al. [21], we observed a remarkable response of boosted nodes during EBRT which was achieved sooner for the smaller ones (<3 cm^3).

The retrospective nature, small sample size, heterogenous treatment, and follow-up are the main limitations of our study.

Still, CovP-SIB-N with daily image guidance resulted in excellent 2-year nodal control and a low rate of late toxicity, with remarkable nodal response during EBRT. Longer follow-up and larger prospective studies such as EMBRACE II are required to confirm this observation. Our experiences encourage the clinical use of CovP-SIB-N in LACC patients.

Disclosure statement

The authors report no potential conflict of interest.

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