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Original Article

Risk factors for nodal failure after radiochemotherapy and image guided brachytherapy in locally advanced cervical cancer: An EMBRACE analysis

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ABSTRACT

Objective: To assess risk factors for nodal failure (NF) after definitive (chemo)radiotherapy and image-guided brachytherapy for locally advanced cervical cancer (LACC) for patients treated in the EMBRACE I study.

Materials and methods: Data for pelvic NF and para-aortic (PAO) NF (NF_{PAO}) were analysed. After multiple imputation, univariable and multivariable Cox-regression was performed for clinical and treatment-related variables. For patients with affected pelvic nodes but no PAO nodes at diagnosis, additional analyses were performed for two subgroups: 1. 'small pelvis' nodes in internal and external iliac, obturator, parametrial, presacral and/or common iliac (CI) region and 2. any CI nodes (subgroup of 1).

Results: 1338 patients with 152 NF and 104 NF_{PAO} events were analysed with a median follow-up of 34.2 months (IQR 16.4–52.7). For the entire group, larger tumour width, nodal risk groups (in particular any CI nodes without PAO nodes), local failure, and lower Hb-nadir increased the risk of NF. Elective PAO-irradiation was independently associated with a decreased risk of NF_{PAO} (HR 0.53, 95%-CI 0.28–1.00, p = 0.05). For subgroup 1, having 'any CI nodes without PAO nodes' and local failure significantly increased NF risk. Additionally, elective PAO-irradiation was associated with less risk of NF_{PAO} (HR 0.38, 95%-CI 0.17–0.86, p = 0.02). For subgroup 2 only local failure was associated with higher risk of NF.

Conclusion: In this patient cohort, nodal disease and tumour width at diagnosis, as well as local failure, are risk factors for NF after definitive treatment. Having either 'any PAO nodes' (with or without pelvic nodes) or 'any CI nodes' (without PAO nodes) are stronger risk factors than involvement of nodes in the small pelvis alone. Elective PAO-irradiation was associated with significantly less NF_{PAO}, particularly in patients with nodal disease in the 'small pelvis' and/or CI region at time of diagnosis.

For patients with locally advanced cervical cancer (LACC) treatment currently consists of concurrent (chemo) radiotherapy (CCRT) and image-guided adaptive 3D brachytherapy (IGABT) resulting in excellent local control and acceptable survival rates [1–4]. However, nodal failure (NF) remains challenging [5].

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Reported estimates of regional pelvic and para-aortic (PAO) NF rates are in the range of 5–17% [1,3,6–8]. For patients with NF salvage options are limited [9] and five-year overall survival is < 10% regardless of in-field or out-of-field recurrence [10]. Lymph node relapses are often located at the upper radiotherapy field borders, but can also occur in the nodal planning target volumes (PTVs) [9]. Additionally, patients with metastatic nodes at diagnosis more often develop NF [1].

Upfront understanding of risk factors can help identify patients at high risk for NF and thereby enable adapted treatment strategies or individualised follow-up protocols to detect relapses when patients might still be eligible for salvage treatment [8,9]. Radiotherapy adaptation such as elective PAO irradiation or nodal boosting potentially reduces the risk of regional relapses in selected patients [11–18].

Therefore, the aim of the current analysis is to assess risk factors for NF using univariable and multivariable analyses in the large multicentre EMBRACE study (IntErnational MRI-guided BRAchytherapy in CErvical cancer).

Materials and methods

Patient, treatment and follow-up details

A 2017 data extraction from the multicentre prospective EMBRACE I cohort was used. Patient selection and treatment details have been described previously (www.embracestudy.dk) [1,19]. In summary, patients from 24 centres with FIGO2009-stage IB-IVA pathology-proven squamous cell carcinoma, adenocarcinoma or adeno-squamous carcinoma of the cervix were treated with CCRT and IGABT. Investigations at time of diagnosis consisted of gynaecological examination, pelvic MRI, abdominal CT/MRI and hematological parameters. For the detection of nodal metastases different diagnostic tools were allowed, including (PET-)CT, ultrasound, MRI as well as histology/cytopathology and/or nodal surgery. External radiotherapy consisted of 3D-conformal or intensity modulated radiotherapy to an elective dose of 45–50 Gy in 1.5–2.0 Gy fractions. Nodal boost(s) were allowed according to the clinical protocol in the treating centres. Elective para-aortic irradiation was advised in case of nodes in the common iliac region or proximal. Concurrent weekly cisplatinum (40 mg/m^2) was recommended, aiming at 5–6 cycles. Brachytherapy was performed using pulsed or high dose rate regimens (PDR/HDR) [20–22].

Follow-up was quarterly in the first year, biannually in the second and third year and yearly thereafter, with pelvic MRI being required at least at 3 and 12 months after treatment. Affected lymph nodes at diagnosis and nodal failures were registered according to regional locations: 'small pelvis' (internal and external iliac, obturator, presacral and parametrial), common iliac (CI) and PAO nodes up to the renal vein (considered M1 in the current TNM-system and stage IIIC2 in FIGO2018), with all combinations being possible. The primary outcome of NF was defined as pelvic and/or PAO nodal recurrence after complete nodal remission, or new occurrence of nodal disease post-treatment, or persistent nodal disease $\geq$ 6 months after treatment.

Variables

Studied clinical variables included age, smoking status, FIGO2009-stage (IIB versus IB-IIA or IIIA-IVA), tumour width on MRI, parametrial involvement, uterine corpus involvement, histopathological type (squamous cell carcinoma versus adeno [squamous] carcinoma), nodal surgery, hemoglobin (Hb) at diagnosis, Hb-nadir, leucocyte count, three nodal risk groups at diagnosis ('small pelvis' only, any CI without PAO nodes, any PAO nodes). Furthermore, we investigated the impact of local failure, chemotherapy cycles ($\geq$5 versus 1–4), overall treatment time (OTT; $\leq$49 versus > 49 days), and EBRT dose (>46 versus $\leq$ 46 Gy).

Statistical analysis

Continuous variables are listed as medians with interquartile ranges (skewed distribution) or mean ± standard deviations (sd; normal distribution). Differences in normally distributed or skewed variables between patients with and without NF were assessed with the Mann-Whitney U test or unpaired t-test, respectively. Categorical variables were tested using the Pearson's X^2 or Fisher's exact test as appropriate. Univariable and multivariable Cox-regression models were used to study associations of studied variables with NF as well as with NF_{PAO}. Follow-up calculation started at the last radiotherapy fraction. For a more detailed analysis regarding NF and NF_{PAO} and contributing risk factors in N1 patients, we defined two subgroups, both excluding patients with affected PAO nodes at diagnosis: 1. patients with 'small pelvis' and/or CI nodes and 2. patients with CI nodes, with or without 'small pelvis' involvement (any CI). We further assessed whether these subgroups within the low and intermediate nodal elective clinical target groups quantitatively differed in a potential benefit from para-aortic irradiation. Hazard ratios (HRs) with 95%-confidence intervals (CIs) were obtained. We applied the rule of testing 1 variable per 10–15 events in the main analyses to prevent overfitting [23]. Variables included in the multivariable analysis were the variables significantly associated with NF in univariable analysis. Additionally, the clinical variables of parametrial involvement and elective PAO-irradiation, both which did not reach univariable statistical significance, were forced in the multivariable model.

Regarding the variables FIGO-stage, tumour width and parametrial involvement, redundancy was considered. Due to the observed effect in univariable analysis, tumour width on MRI was deemed more robust and discriminating in the model than FIGO-stage; the latter of which was therefore discarded for the multivariable analysis. For the supplementary material, we performed a sensitivity analysis including FIGO-stage to assess model fit. Models were compared with Akaike's information criterion (AIC) to assess if the presence of parametrial involvement and OTT resulted in more parsimonious models. Finally, we quantified the absolute NF rates from the multivariable models using the corresponding regression formulas.

Multicollinearity was assessed with correlations between variables upfront and using the variance inflation factor (VIF) in the full model. Factors with correlation > 0.7 or VIF > 5 were excluded, leaving in the clinically most relevant variable. As such, positive nodes at diagnosis and the number of node locations were excluded in all models due to collinearity with the nodal risk groups investigated. Missing data was assumed to be missing at random. Multiple imputation was performed creating 20 datasets in which the multivariable modelling steps were repeated. As sensitivity analyses, complete-case multivariable models were created, as well as competing risk regression models taking into account the competing risk of mortality [24,25]. The proportional hazards assumption was checked. Baseline statistics were performed using SPSS version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). All other analyses were performed using R version 3.6.3 (https://www.R-project.org). The mice package was used for multiple imputation and the rms package for survival analysis. A p-value $\leq$ 0.05 was considered statistically significant.

Results

Descriptive statistics

A total of 1416 patients were available in the database. Due to missing treatment and follow-up information or protocol violation 78 had to be excluded from the analysis. Of the remaining 1338 patients 152 (11.4%) developed NF and 104 (7.8%) NF_{PAO} (descriptive details are listed in Table 1 and Table 2). At diagnosis, 643 patients (48.1%) were node negative (N0), 451 (33.7%) had 'small pelvis' nodes only, 143 (10.7%) had any CI nodes without PAO nodes, and 101 (7.5%) had any PAO nodes. Therefore, 695 patients (51.9%) were node positive (N1). Subgroup 1 consisted of 594 patients with NF in 92 (15.5%) and NF_{PAO} in 66 (11.1%). Subgroup 2 consisted of 143 patients with NF in 26 (18.2%) and NF_{PAO} in 20 (14.0%). Overall median follow-up was 34.2 months (IQR 16.4–52.7).

Cox-regression models for NF and NF_{PAO}

Univariable analyses were performed and demonstrated in Supplementary Tables 2-3. The final multivariable models for NF and NF_{PAO} (n = 1338) are shown in Table 3. Regarding NF, multivariable analysis indicated independent significant associations with tumour width, Hb-nadir, nodal risk groups and local failure. A higher risk of NF was observed for larger tumour width on MRI, for each nodal risk group at diagnosis (in particular 'any CI nodes without PAO nodes' [HR 3.12, 95%-CI 1.79–5.46, p = 0.0001]), for a lower Hb-nadir and for local failure. For NF_{PAO}, multivariable analysis indicated independent significant associations with tumour width on MRI, Hb-nadir, nodal risk groups (specifically 'any CI nodes without PAO nodes'), and local failure. In addition, elective PAO-irradiation had a significant association with NF_{PAO} (HR 0.53, 95%-CI 0.28–1.00, p = 0.05). The model including FIGO risk groups performed slightly better for NF compared to the model

Table 1
Descriptive statistics of factors stratified by nodal failure (NF) after definitive therapy for locally advanced cervical cancer.

	No nodal failure (n = 1186)	Nodal failure (n = 152)	p-value	Missing, n (% of total)
Variable	*n (%), median [IQR], mean ± sd*	*n (%), median (IQR), mean ± sd*		
Age, years	50.6 ± 13.5	48.8 ± 12.1	0.11	40 (3%)
Smoking status (yes vs no)	350 (29.5%)	54 (35.5%)	0.22	60 (4.5%)
FIGO stage in 2 groups			**0.02**	28 (2.1%)
IB-IIB	939 (80.8%)	107 (72.3%)		
IIA-IVA	223 (19.2%)	41 (27.7%)		
FIGO stage in 3 groups			**0.02**	28 (2.1%)
IB-IIA	283 (23.9%)	40 (26.3%)		
IIB	656 (55.3%)	67 (44.1%)		
IIIA-IVA	223 (18.8%)	41 (27.0%)		
Tumour width (on MRI), mm	46.4 ± 14.6	52.2 ± 13.2	**<0.0001**	9 (0.7%)
Parametrial involvement	926 (78.1%)	123 (80.9%)	0.47	1 (0.1%)
Uterine corpus involvement	415 (35.0%)	70 (46.1%)	**0.009**	3 (0.2%)
Histopathological type			0.31	1 (0.1%)
Squamous cell carcinoma	977 (82.4%)	119 (78.3%)		
Adeno(squamous) carcinoma	209 (17.6%)	32 (21.1%)		
Nodal surgery	329 (27.7%)	50 (32.9%)	0.21	2 (0.1%)
Hb at diagnosis, mmol/L	7.8 ± 1.1	7.6 ± 1.1	**0.01**	1 (0.1%)
Hb nadir, mmol/L	6.0 [1–6.8]	5.7 [1.0–6.7]	**0.03**	8 (0.6%)
Leucocytes at diagnosis			0.12	7 (0.5%)
$<10 \times 10^9$/L	854 (72.0%)	99 (65.1%)		
$\geq 10 \times 10^9$/L	327 (27.6%)	51 (33.6%)		
Chemotherapy			1.00	119 (8.9%)
1–4 cycles	326 (27.5%)	42 (27.6%)		
≥5 cycles	752 (63.4%)	99 (65.1%)		
Overall treatment time			**0.008**	4 (0.3%)
<49 days	851 (71.8%)	93 (61.2%)		
≥49 days	331 (27.9%)	59 (38.8%)		
EBRT dose			1.00	3 (0.2%)
≤46 Gy	910 (76.7%)	116 (76.3%)		
>46 Gy	274 (23.1%)	35 (23.0%)		
EBRT dose continuous, Gy	45 [45–46]	45 [45–46]	0.47	3 (0.2%)
Elective para-aortic irradiation	184 (15.5%)	31 (20.4%)	0.13	2 (0.1%)
Affected nodes at diagnosis	588 (49.6%)	109 (71.7%)	<0.0001	0 (0%)
Parametrial nodes at diagnosis	60 (5.1%)	10 (6.6%)	0.44	0 (0%)
Internal/external iliac nodes at diagnosis	538 (45.4%)	103 (67.8%)	**<0.0001**	0 (0%)
Common iliac nodes at diagnosis	171 (14.4%)	37 (24.3%)	**0.003**	3 (0.2%)
Para-aortic nodes at diagnosis	84 (7.1%)	17 (11.2%)	0.07	0 (0%)
Number of node locations			**<0.0001**	0 (0%)
0	598 (50.4%)	43 (28.3%)		
1	380 (32.0%)	61 (40.1%)		
2	141 (11.9%)	36 (23.7%)		
3–4	67 (5.6%)	12 (7.9%)		
Nodal risk group at diagnosis			**<0.0001**	0 (0%)
No nodes	600 (50.6%)	43 (28.3%)		
'Small pelvis'* nodes only	385 (32.5%)	66 (43.4%)		
Any common iliac nodes without para-aortic	117 (9.9%)	26 (17.1%)		
Any para-aortic nodes	84 (7.1%)	17 (11.2%)		
Persistent disease resolving later	50 (4.2%)	5 (3.3%)	0.75	0 (0%)
Local failure	61 (5.1%)	38 (25.0%)	**<0.0001**	0 (0%)

*'Small pelvis'=internal and external iliac, obturator, presacral and/or parametrium.
Abbreviations: IQR = interquartile range, sd = standard deviation, FIGO = Fédération Internationale de Gynécologie et d'Obstétrique, Hb = hemoglobin, EBRT = external beam radiotherapy.

Table 2
Descriptive statistics of factors stratified by para-aortic nodal failure (NF_{PAO}) after definitive therapy for locally advanced cervical cancer.

	No para-aortic failure (n = 1234)	Para-aortic failure (n = 104)	p-value	Missing, n (% of total)
Variable	*n (%), median [IQR], mean ± sd*	*n (%), median [IQR], mean ± sd*		
Age, years	50.4 ± 13.4	50.0 ± 12.8	0.76	40 (3.0%)
Smoking status (yes vs no)	362 (29.3%)	42 (40.4%)	**0.05**	60 (4.5%)
FIGO stage in 2 groups			0.09	28 (2.1%)
1B-2B	973 (80.4%)	73 (73.0%)		
3A-4A	237 (19.6%)	27 (27.0%)		
FIGO stage in 3 groups			0.1	28 (2.1%)
1B-2A	296 (24.0%)	27 (26.0%)		
2B	677 (54.9%)	46 (44.2%)		
3A-4A	237 (19.2%)	27 (26.0%)		
Tumour width (on MRI), mm	46.6 ± 14.6	52.5 ± 12.8	**<0.0001**	9 (0.7%)
Parametrial involvement	964 (78.1%)	85 (81.7%)	0.46	1 (0.1%)
Uterine corpus involvement	433 (35.1%)	52 (50.0%)	**0.004**	3 (0.2%)
Histopathological type			0.89	1 (0.1%)
Squamous cell carcinoma	1012 (82.0%)	84 (80.8%)		
Adeno(squamous) carcinoma	222 (18.0%)	19 (18.3%)		
Nodal surgery	343 (27.8%)	36 (34.6%)	0.14	2 (0.1%)
Hb at diagnosis, mmol/L	7.8 ± 1.1	7.6 ± 1.1	0.054	1 (0.1%)
Hb nadir, mmol/L	6.0 [1.0–8.3]	5.6 [1.0–6.6]	**0.03**	8 (0.6%)
Leucocytes at diagnosis			0.31	7 (0.5%)
$<10 \times 10^9$/L	883 (71.6%)	70 (67.3%)		
$\geq 10 \times 10^9$/L	344 (27.9%)	34 (32.7%)		
Chemotherapy			0.64	119 (8.9%)
1–4 cycles	337 (27.3%)	31 (29.8%)		
≥5 cycles	786 (63.7%)	65 (62.5%)		
Overall treatment time			**0.03**	4 (0.3%)
<49 days	880 (71.3%)	64 (61.5%)		
≥49 days	350 (28.4%)	40 (38.5%)		
EBRT dose			0.90	3 (0.2%)
≤46 Gy	946 (76.6%)	80 (76.9%)		
>46 Gy	286 (23.2%)	23 (22.1%)		
EBRT dose continuous, Gy	45 [45–46]	45 [45–46]	0.34	3 (0.2%)
Elective para-aortic radiotherapy	196 (15.9%)	19 (18.3%)	0.31	2 (0.1%)
Affected nodes at diagnosis	619 (50.2%)	78 (75.0%)	<0.0001	0 (0%)
Parametrial nodes at diagnosis	65 (5.3%)	5 (4.8)	1.00	0 (0%)
Internal/external iliac nodes at diagnosis	569 (46.1%)	72 (69.2%)	**<0.0001**	0 (0%)
Common iliac nodes at diagnosis	181 (14.7%)	27 (26%)	**0.004**	3 (0.2%)
Para-aortic nodes at diagnosis	89 (7.2%)	12 (11.5%)	0.12	0 (0%)
Number of node locations			**<0.0001**	0 (0%)
0	615 (49.8%)	26 (25.0%)		
1	395 (32.0%)	46 (44.2%)		
2	152 (12.3%)	25 (24.0%)		
3–4	72 (5.8%)	7 (6.7%)		
Nodal risk group at diagnosis			**<0.0001**	0 (0%)
No nodes	617 (50.0%)	26 (25.0%)		
'Small pelvis'* nodes only	405 (32.8%)	46 (44.2%)		
Any common iliac nodes without para-aortic	123 (10.0%)	20 (19.2%)		
Any para-aortic nodes	89 (7.2%)	12 (11.5%)		
Persistent disease resolving later	51 (4.1%)	4 (3.8%)	1.00	0 (0%)
Local failure	80 (6.5%)	19 (18.3%)	**<0.0001**	0 (0%)

*'Small pelvis'=internal and external iliac, obturator, presacral and/or parametrium.
Abbreviations: IQR = interquartile range, sd = standard deviation FIGO = Fédération Internationale de Gynécologie et d'Obstétrique, Hb = hemoglobin, EBRT = external beam radiotherapy.

without them. Supplementary Table 4 shows multivariable models for NF and NF_{PAO} with FIGO risk groups included.

Cox-regression subgroup-models for NF and NF_{PAO}

Multivariable models for subgroup 1 (patients with 'small pelvis' and/or CI nodes, n = 594) are presented in Table 4. In subgroup 1 patients with 'any CI without PAO nodes' and local failure had a significantly increased NF risk in multivariable analysis. For NF_{PAO} virtually the same was observed, and in addition elective PAO-irradiation had a significant association (HR 0.38, 95%-CI 0.17–0.86, p = 0.02). Supplementary Table 5 demonstrates the multivariable analyses for subgroup 2 (patients with CI nodes with or without 'small pelvis' nodes, n = 143). In subgroup 2 only local failure was significantly associated with NF. In Supplementary File 6 the regression formulas of the multivariable models are listed that can be used to calculate predicted 5-year NF and NF_{PAO} rates.

Sensitivity analyses and model assumptions

Complete-case and competing risk analysis indicated no differences in the remaining significant clinical variables and direction of associations with NF and NF_{PAO} compared to the primary analyses. Violations of the proportional hazards assumption were observed in none of the generated models.

Kaplan–Meier analysis

Figs. 1a-1d and 2a-2d depict Kaplan–Meier curves and Supplementary Table 1 lists the uncorrected Kaplan–Meier estimates. In the total group of patients, overall nodal control and PAO nodal control at 5 years was 86% (95%-CI 83–88%) and 90% (95%-CI 88–92%), respectively. Patients with tumour width ≤ 40 mm versus >40 mm had both higher nodal control and PAO nodal control. In addition, significant differences were observed in PAO nodal con-

Table 3
Multivariable analysis studying independent associations of clinical variables with overall nodal failure (NF) and para-aortic nodal failure (NF_{PAO}) after definitive therapy for locally advanced cervical cancer (n = 1338 with 152 NF and 104 NF_{PAO}).

NF				
Variable	**HR**	**Lower 95%-CI**	**Upper 95%-CI**	***p*-value**
Tumour width (on MRI), per mm increase	1.02	1.00	1.03	**0.02**
Uterine corpus involvement (yes vs no)	1.01	0.71	1.42	0.98
Hb diagnosis [mmol/L] per point increase	0.92	0.79	1.08	0.30
Hb nadir [mmol/L] per point increase	0.93	0.88	0.99	**0.02**
Elective para-aortic irradiation (yes vs no)	0.76	0.45	1.29	0.31
Reference: no nodes				
'Small pelvis'* nodes only	2.14	1.44	3.18	**0.0002**
Any common iliac nodes without para-aortic	3.12	1.79	5.46	**0.0001**
Any para-aortic nodes	2.90	1.41	5.97	**0.004**
Local failure	7.67	5.15	11.41	**<0.0001**
NF_{PAO}				
Variable	**HR**	**Lower 95%-CI**	**Upper 95%-CI**	***p*-value**
Tumour width (on MRI), per mm increase	1.02	1.00	1.03	**0.05**
Uterine corpus involvement (yes vs no)	1.28	0.85	1.92	0.24
Hb diagnosis [mmol/L] per point increase	0.94	0.77	1.14	0.54
Hb nadir [mmol/L] per point increase	0.93	0.86	1.00	**0.04**
Elective para-aortic irradiation (yes vs no)	0.53	0.28	1.00	**0.05**
Reference: no nodes				
'Small pelvis'* nodes only	2.46	1.50	4.02	**0.0003**
Any common iliac nodes without para-aortic	4.58	2.39	8.81	**<0.0001**
Any para-aortic nodes	4.27	1.83	10.01	**0.0008**
Local failure	4.85	2.85	8.26	**<0.0001**

*'Small pelvis'=internal and external iliac, obturator, presacral and/or parametrium.
Abbreviations: NF = overall nodal failure, NF_{PAO} = para-aortic nodal failure, HR = hazard ratio, CI = confidence interval, Hb = hemoglobin.

Table 4
Multivariable analysis studying independent associations of clinical variables with overall nodal failure (NF) and para-aortic nodal failure (NF_{PAO}) after definitive therapy for locally advanced cervical cancer in patients with small pelvis* and/or common iliac - but no PAO - nodal metastases at diagnosis (subgroup 1) (n = 594 with 92 NF and 66 NF_{PAO}).

NF				
Variable	**HR**	**Lower 95%-CI**	**Upper 95%-CI**	***p*-value**
Tumour width (on MRI), per mm increase	1.01	0.99	1.02	0.38
Uterine corpus involvement (yes vs no)	0.93	0.59	1.45	0.75
Hb diagnosis [mmol/L] per point increase	0.89	0.73	1.09	0.25
Hb nadir [mmol/L] per point increase	0.94	0.87	1.01	0.09
Elective para-aortic irradiation (yes vs no)	0.57	0.30	1.08	0.09
Any common iliac nodes without para-aortic versus 'small pelvis'* nodes only	1.67	1.00	2.78	**0.05**
Local failure (yes vs no)	7.32	4.20	12.74	**<0.0001**
NF_{PAO}				
Variable	**HR**	**Lower 95%-CI**	**Upper 95%-CI**	***p*-value**
Tumour width (on MRI), per mm increase	1.01	0.99	1.03	0.46
Uterine corpus involvement (yes vs no)	1.12	0.66	1.88	0.68
Hb diagnosis [mmol/L] per point increase	0.88	0.69	1.13	0.31
Hb nadir [mmol/L] per point increase	0.92	0.84	1.002	0.06
Elective para-aortic irradiation (yes vs no)	0.38	0.17	0.86	**0.02**
Any common iliac nodes without para-aortic versus 'small pelvis'* nodes only	2.11	1.18	3.77	**0.01**
Local failure (yes vs no)	5.06	2.5	10.24	**<0.0001**

*'Small pelvis'=internal and external iliac, obturator, presacral and/or parametrium.
Abbreviations: NF = overall nodal failure, NF_{PAO} = para-aortic nodal failure, HR = hazard ratio, CI = confidence interval, Hb = hemoglobin.

trol for Hb-nadir categories $\geq$ 7 mmol/L versus 6–7 mmol/L and <6 mmol/L, as well as for the different nodal risk groups at diagnosis.

Corrected Kaplan–Meier estimates after Cox-regression

Corrected (multivariable) Kaplan–Meier estimates from the Cox-regression showed PAO nodal control of 92% versus 87% for elective PAO irradiation (versus 91% in both groups in the uncorrected univariable analysis). These estimates were 85% versus 76% for elective PAO irradiation versus no PAO irradiation in subgroup 1 (compared to 93% and 85% in the uncorrected univariable analysis).

Discussion

The international multicentre EMBRACE I study investigates the impact of MRI-guided brachytherapy for LACC patients after CCRT with primary endpoints local control and survival. Data on nodal disease at diagnosis and NF during follow-up were additionally collected. Nomden et al. [1] published characteristics of EMBRACE I including involvement of pelvic, PAO and inguinal nodal regions and found that 52% of the patients had nodal disease at diagnosis. Overall, 11% (crude rate) developed NF alone or as part of multiple failure sites, with a rate of 7% and 16% in N0 versus N1 patients, respectively. Actuarial 3-year nodal control was 92% in N0 and 82% in N1 patients, which compared favourably to previously pub-

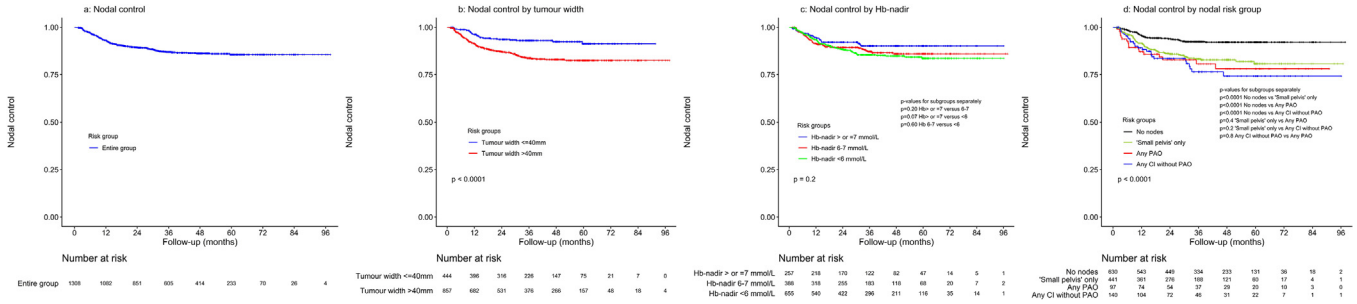

Fig. 1.

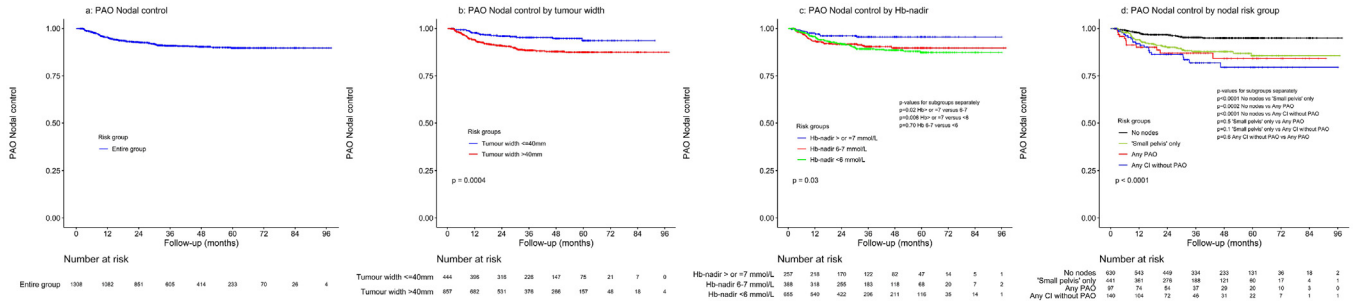

Fig. 2.

lished data [8,10]. Metastatic nodes at diagnosis were mainly located in the pelvis; however, NF was predominantly detected in the PAO region. As the outcomes of patients with NF is known to be poor [1,9,10], we further analysed the EMBRACE I material regarding factors associated with NF to potentially guide nodal treatment decisions in the future.

In the current analysis important differences were observed in nodal control in relation to several risk factors, such as for varying nodal risk groups at diagnosis, tumour width at diagnosis and Hb-nadir. In univariable analysis, FIGO-stage, uterine corpus involvement, OTT, Hb at diagnosis and local failure during follow-up were additional significant risk factors for nodal failure. In multivariable analyses we found nodal risk groups at diagnosis (in particular any CI nodes without PAO nodes), tumour width, Hb-nadir, and local failure to be associated with NF and NF_{PAO}, while after elective PAO-irradiation the NF_{PAO} rate was reduced. We attempted to quantify the effect on nodal control using predictors from these models. However, these models were created with the main goal of exploratively determining clinically relevant predictive factors in a heterogeneous database, and causality between (interventional) variables and NF can therefore not be inferred.

In EMBRACE I the diagnostic strategy for N1 detection was not uniform. Therefore, the current data cannot contribute to the ongoing relevant discussions regarding the optimal diagnostic procedures to detect (PAO) nodal disease [8,10,11,26,27]. However, in all analyses performed on EMBRACE I material, having nodal disease at diagnosis in the investigated risk groups was the most powerful and consistent risk factor for NF, which is in line with literature [8].

Given that NF_{PAO} was more frequent than pelvic NF in EMBRACE I, we analysed risk factors for NF_{PAO} separately, including the effect of elective PAO-irradiation [8,11–13,28]. Elective PAO-irradiation retained its significant association in the subgroup with 'small pelvis' and/or CI nodes without PAO-nodes (Subgroup 1). The effect could not be demonstrated for the subgroup of patients with any CI nodes without PAO nodes at diagnosis (Subgroup 2), which is likely related to the low number of events (n = 20 NF_{PAO} among n = 143). However, the HR of the effect remained around 0.5. Our findings do support the choice for elective PAO-irradiation in case of N1 in the CI region at time of diagnosis in the ongoing EMBRACE II study [19]. The significant association of elective PAO-irradiation seems to be independently retained in the presence of significant NF_{PAO} risk factors. Our findings are in line with literature. The study populations are quite heterogeneous but elective PAO irradiation frequently demonstrated a positive effect for PAO recurrence-free survival, disease-free survival and even overall survival [11–18]. However, not all studies were able to confirm these benefits [29,30]. Increased toxicity from PAO-irradiation is usually $\leq$ grade 2, although increased grade 3 toxicities are also observed [18,31]. Because of these reasons, it is still a matter of debate whether elective PAO-irradiation should be offered to all N1 patients, irrespective of affected nodal regions. The ongoing EMBRACE II study investigates several aspects of nodal disease management including PAO irradiation. Whether the significant association of elective PAO-irradiation on NF_{PAO} is also preventing distal (nodal and organ) failure and positively influencing survival is a matter of ongoing investigations.

Achieving PAO disease control is especially challenging when macroscopic PAO nodes are detected at diagnosis. In this situation, ablative doses are often precluded by the limited tolerance of surrounding organs, especially duodenum and other bowel loops [8,32]. The ongoing EMBRACE II study intends to investigate the value of IMRT/VMAT for elective irradiation and simultaneously integrated nodal boosting [33] with regard to nodal control and organ sparing, including the PAO region. Regarding the best balance between target control and morbidity it is also important that we did not find data suggesting improved regional control with elective dose > 45 Gy; neither in our cohort nor in recently published data [8].

Recent publications show that having multiple affected nodes at diagnosis is associated with a higher risk of development of nodal failure in LACC [34,35]. In the EMBRACE I cohort we found that having affected nodes in multiple nodal regions was a strong risk factor for NF in descriptive analysis. Due to collinearity with nodal risk groups we excluded this factor from uni- and multivariable analysis. However, having affected nodes in multiple regions

(and thus multiple nodes) might be indicative of the metastatic potential, thus warranting adjuvant treatment. We await results of prospective trials combining standard treatment with either adjuvant or neo-adjuvant chemotherapy (RTOG 1174 OUTBACK trial, INTERLACE). The metastatic potential of cervix cancers, based on morphology, pathology and genetic features of the primary tumour and metastatic nodes, should be the focus of future investigations, considering the potential importance in refining roles for newer systemic treatments (immunotherapy, targeted treatment) [36,37]. Interestingly, concurrent weekly cisplatinum did not significantly affect NF in EMBRACE I. A possible explanation is that the majority received $\geq$ 5 cycles cisplatinum and the group of patients with NF that received less or no cisplatinum might be too small to be able to detect any difference. Of course, chemotherapy treatment can be subject to bias such as comorbidity and frailty as well, which could not be taken into account in our analysis.

Among the tumour-related factors, tumour burden expressed as width of the primary tumour at diagnosis was a significant risk factor for NF in the whole cohort and subgroup 1, with higher significance for the development of NF than FIGO2009-stage. Parametrial involvement and histology did not influence NF here, but achieving local control after treatment (defined as no persistent local disease after treatment and no recurrence in follow-up) had highly significant impact on nodal control. This indicates the importance of controlling the primary cervical tumour and preventing metastatic seeding. With regard to improved local control, several studies stress the importance of image guided adaptive brachytherapy including maturing data from Retro-EMBRACE and EMBRACE I [3,38,39].

In multivariable analysis, OTT had no impact on NF, which is different from what we observe in the treatment of primary cervical tumours [40,41]. In EMBRACE I OTT in N1 patients was often longer than in case of N0, due to the additional time needed to deliver sequential boosts. Currently, nodal boosts are usually simultaneously integrated into the elective treatments with promising results [8,11,33].

Among the patient-related factors, Hb-nadir showed a significant relation, with higher values being associated with less NF. Higher Hb might be protective due to better oxygenation impacting radio-sensitivity of tumour cells [42,43]. Factors with possible impact on Hb-nadir might be persisting bleeding from the primary tumour or impact of cisplatinum and/or EBRT on the hematopoietic system. How Hb at diagnosis, Hb-nadir and transfusion interact is complex and not fully understood [44].

In the group of patients without evidence of nodal disease at diagnosis, 43/643 (7%) developed NF [1]. Only tumour width showed any significance (data not shown) and we assume the number of patients with events was too limited for sufficiently powered analyses regarding factors related to NF and NF_{PAO}. Moreover, it could be that in these 43 patients, nodal disease at diagnosis had been undetected.

We realise that this investigation, besides improving our nuanced understanding of nodal disease in LACC, has weaknesses and limitations. As already mentioned, nodal disease outcome was not a primary endpoint in EMBRACE I. Details were not registered for individual affected nodes at diagnosis nor individual nodal events, but rather for entire nodal regions when recurring, and situated quite simplistically relative to elective and nodal boost targets. We aimed for an overall estimation of nodal outcome, to contextualise our findings since earlier published data often included NF among overall pelvic failure rates (and NF was not reported as separate entity). It was not possible, however, to include treatment-related factors (such as nodal boost and dose to individual affected nodes) in this analysis [45]. It was also not possible to relate nodal outcome in this cohort to other potentially impactful factors like SUV-values [46], initial size of affected nodes or regression during CCRT [47]. With regard to descriptive data on the relation of nodal recurrence to treatment targets (PTV-E and PTV-N), and to administered dose, we refer to the paper by Nomden et al. [1]. Furthermore, due to the variability in nodal disease assessment, validation of these findings is necessary to assess whether the found relations hold for a more uniformly diagnosed cohort. In the future, this could be achieved using data from the ongoing EMBRACE II study.

In patients with LACC, nodal disease at time of diagnosis presents a complex clinical situation. Different combinations of microscopic and/or macroscopic involvement at the nodes, and varying numbers of nodes, of different sizes and in different nodal regions, with underlying differences in biology, are possible. How well this can be detected with current diagnostics tools, using different imaging modalities and/or surgical approaches, requires further scrutiny. Nodal recurrence is evenly complex and regularly presents with single or multiple events in one or multiple anatomical regions. Individual failure events may have different anatomic and dosimetric relations to radiation treatment fields, showing varying impacts of dose and other patient-, tumour- and treatment-related factors.

Conclusion

In the EMBRACE I cohort nodal disease at diagnosis, tumour width and local failure represent the strongest risk factors for nodal recurrence after definitive treatment. From the different nodal risk groups having ‘any CI nodes without PAO nodes’ and ‘any PAO nodes’ are stronger risk factors than involvement of ‘small pelvis’ nodes only. Elective PAO-irradiation was associated with significantly less NF_{PAO}, particularly in patients with nodal disease in the ‘small pelvis’ and/or CI region at time of diagnosis. In the ongoing EMBRACE II study, nodal disease outcome is a primary endpoint, with active collection of details for individual metastatic nodes and/or nodal failure events, hopefully improving our understanding of nodal spread and guiding risk-informed treatment decisions in the future.

Conflict of interest

Max Peters: reports research grants from the Dutch Cancer Society, outside the submitted work.

Jacob Lindegaard reports grants from Varian Medical Systems, outside the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.08.020.

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