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Original Article

Nodal failure after chemo-radiation and MRI guided brachytherapy in cervical cancer: Patterns of failure in the EMBRACE study cohort

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ABSTRACT

Purpose/Objective(s): To investigate the patterns of nodal failure in patients enrolled in the international multicentre EMBRACE study.

Materials/Methods: Nodal disease at diagnosis (N−, N+) and nodal failure were analysed per region (NF) (pelvic (parametrial, common iliac, internal/external iliac), inguinal and para-aortic (PAO)) in 1338 patients. Treatment consisted of chemo-radiation and MRI guided brachytherapy. PAO radiotherapy and/or nodal boost was left to the treating centre. At time of diagnosis 52% of patients had pathologic nodes. Frequency analyses were performed in relation to patient, primary tumour and nodal disease characteristics, and treatment related factors.

Results: Median follow up was 34 months and 83% of NF occurred within 24 months. At diagnosis 99% of the N+ patients had pathologic nodes in the pelvis and 14% in the PAO. NF_{pelvic} and NF_{PAO} were reported in 55% and 68% of patients with NF, respectively. Overall NF was reported in 152 patients (11%); 7 and 16% for N- and N+ patients. Of the patients with NF, 41% were located outside the elective target (39% PAO), 40% inside and 35% inside the nodal boost target. Twelve percent of N+ patients that received a nodal boost had a NF inside the nodal boost target.

Conclusion: Within the EMBRACE study cohort the overall number of patients developing nodal failure is low, significantly lower for N− compared to N+ patients. Pathological nodes at diagnosis are mainly located in the pelvis, whereas nodal failures are more often reported in the PAO region. About 40% of all nodal failures were reported outside the treatment targets.

Single institution reports [1–11] and more recent outcomes of the international multicentre RetroEMBRACE study [12] show excellent treatment outcome for patients with locally advanced cervical cancer (LACC) treated with concomitant chemo-radiation (CCRT) and image guided brachytherapy (IGBT). Advances in IGBT resulted in 3 year local/pelvic control and overall survival of 86–97% [1–7,9,10] and 65–87% [1–6,9,10], respectively. Nodal failure has been rarely reported separately in the literature so far and the range of regional pelvic recurrence rate is considerable (2–17%). Historical data by Beadle et al. [13] (patient inclusion year 1980–2000) show total loco-regional (pelvic failure) and regional recurrence (regional nodal recurrence) rates of 24% and 17% after (C)RT and conventional brachytherapy, respectively. Lower loco-regional and regional failure rates of 13% (2001–2003) and 2% (1998–2003) were described after (C)RT and (MR-)IGBT in a mono-institutional report [14]. Two recently published retrospective mono-institutional studies report regional recurrence rates

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after CCRT and (MR-)IGBT of 9% and 11% [6,10]. The multicentre RetroEMBRACE study reported for 12 centres a pelvic failure rate of 13% [12] and nodal pelvic failure rate of 6% [15] after (C)RT and (MR-)IGBT. The rate of PAO recurrence seems to lie in the upper range of the rate reported for pelvic nodal recurrence in the recent studies [6,10,14]. A poor overall survival has been reported after nodal failure historically [13] and also in a more recent study after CCRT and IGBT [2].

In the setting of excellent local control now achievable with (MR-)IGBT [1–12] nodal and distant failures are the dominant causes of treatment failure. The international multicentre observational EMBRACE study (IntErnational MRI-guided BRAchytherapy in CErvical cancer) has prospectively investigated the outcome of CCRT and MR-IGBT in a large patient cohort with respect to local control, survival and morbidity [16]. Purpose of this study was to investigate the incidence and pattern of nodal failure in LACC patients treated within the EMBRACE study and to relate this to the pattern of nodal disease at diagnosis and (pre-)treatment characteristics.

Materials and methods

A total of 1416 patients treated from 2008 to 2015 in 24 centres were registered. CCRT and MR-IGBT were given to patients with FIGO stage IB-IVA biopsy-proven squamous cell carcinoma (SCC), adenocarcinoma (AC) or adeno-squamous carcinoma (AdSq) of the uterine cervix. Gynaecologic examination, MRI of the pelvis, abdominal CT or MRI, haemoglobin (Hb), white blood cell counts (WBC) and blood chemistry were mandatory. Further clinical investigations were performed according to institutional protocols.

Lymph node involvement at time of diagnosis (N+) was diagnosed using ultrasound, CT, PET-CT, MRI and histology or cytopathology. Lymph node involvement was defined up to the level of the second lumbar vertebra (L2) and allocated to pelvic (parametrial, common iliac, internal/external iliac), inguinal and/or para-aortic (PAO) region (Fig. 1); it was not recorded for individual nodes. Lymphadenectomy or nodal debulking was allowed prior to CCRT according to institutional policy. EBRT was delivered using conformal techniques (3D RT) or intensity modulated radiotherapy (IMRT). Elective regions were to be treated with doses of 45–50 Gy (1.5–2.0 Gy fractions). Lymph nodes could be additionally boosted up to 60–65 Gy (2.0–2.2 Gy/fraction). Nodal treatment was left to each centre, allowing for pre-CCRT nodal surgery and/or sequential or simultaneous RT boost strategies. Dose to lymph nodes was only globally reported as elective or nodal boost dose. Chemotherapy was 5–6 cycles of weekly concomitant cisplatin (40 mg/m^2) and tailored according to patient status. Brachytherapy (BT) was delivered as either pulsed dose rate (PDR) or high dose rate (HDR). MRI guidance was mandatory for at least the first BT implant. Overall treatment was 50 days. For detailed information see the EMBRACE protocol (www.embracestudy.dk) and a recent publication [17].

Follow up (FU) was performed every 3 months (year 1), every 6 months (year 2,3), and annually (year 4,5). MRI was required at 3 and 12 months. Time of FU was calculated from last radiotherapy fraction to event or until last FU.

The aim of this sub-study was to analyse the pattern of nodal regional failure (NF) after treatment. NF was reported for the different nodal regions' analogue to how nodal disease was classified at diagnosis (see above). Nodal regions with recurrent disease beyond the PAO region (e.g. mediastinal, supraclavicular) were not addressed. NF was defined as either nodal recurrence (NR) or persistent nodal disease (PND) at ≥6 months after treatment. NR is NF in case of either no lymph node involvement at diagnosis in the corresponding NR region, or pathologic lymph node(s) at

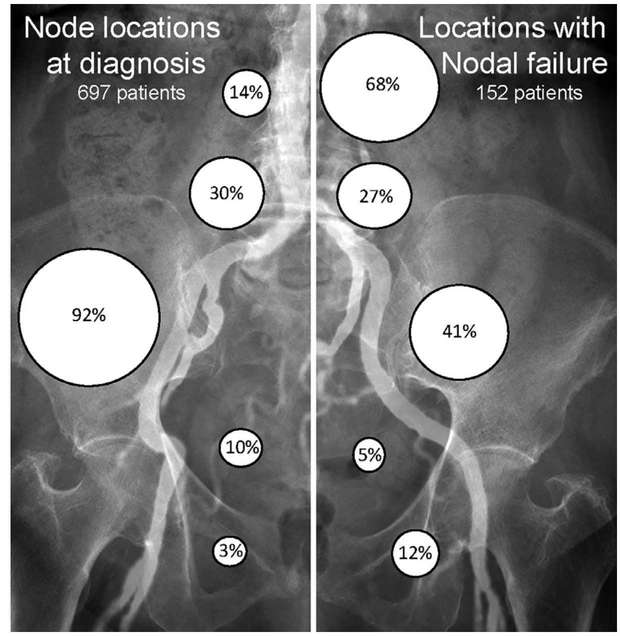

Fig. 1. The percentage of patients having pathological nodes at time of diagnosis (left) or nodal failure (right) for (top to bottom) the para-aortic, common iliac, internal/external iliac, parametrial and inguinal regions.

diagnosis in the particular region with complete remission after treatment. PND was defined as never having reached the state of complete remission after treatment. NF detected within 6 months was scored as NF if 1) additional FU data were missing (worst case assumption), or 2) patient had died within 6 month after treatment. Nodal control was defined as freedom from any NF (NR or PND).

Out of the 1416 patients registered in the EMBRACE study, 78 were excluded from this sub-study for different reasons: not fulfilling inclusion criteria, no patient information, missing tumour and treatment characteristics, death during treatment, radiotherapy not delivered as planned and missing FU. A total of 1338 patients were available for this analysis with a median FU time of 34 (1–98) months. Frequency analyses were performed for factors relating to patient, primary tumour and nodal disease, and treatment. This was done for the whole group and seven subgroups: N− and N+, with and without NF, with PAO failure (NF_{PAO}), with pelvic failure (NF_{pelvic}) and a subgroup with PAO failure but without pelvic failure (NF_{pelvic} (excluding NF_{PAO})). The time to event was calculated from the end of radiotherapy until the date of detection of NF. Statistical analyses were performed with IBM SPSS version 23 and p-values <0.05 were considered significant.

Results

Patient, disease and treatment characteristics

Patient, primary tumour and nodal disease characteristics and treatment related factors are summarized in Table 1 and S1. Median age was 50 years (range 22–92). Volumetric imaging was performed in all and nodal surgery in 386 patients (29%). Lymph node involvement at diagnosis was present in 697 patients (52%), in 335 based on PET-CT; 256 patients had nodes in multiple regions (177 in two, 71 in three, and 8 in four) (Table 1). Almost all N+ patients had nodal involvement in the pelvis covering the common iliac, external/internal iliac and parametrial regions. Pathologic PAO and inguinal lymph nodes were present in 101

Table 1
Disease characteristics for patients with and without nodal disease at diagnosis and patients with overall, pelvic and para-aortic nodal failure.

		All patients		Without NF		With NF		Subgroups of NF					
								With NFpelvic (incl pao)		With NFpelvic (excl pao)		With NFpao	
		n = 1338 (100%)		n = 1186 (89%)		n = 152 (11%)		n = 84 (6%)		n = 36 (3%)		n = 104 (8%)	
Nodal disease characteristics													
Lymph node involvement	Yes	**697**	*(100%)*	588	84%	109	**16%**	61	9%	24	**3%**	78	**11%**
	No	641		598	93%	43	**7%**	23	4%	12	**2%**	26	**4%**
Lymph node multiple regions	Yes	256	*(37%)*	208	81%	48	19%	28	11%	11	4%	32	13%
	No	441	*(63%)*	380	86%	61	14%	33	7%	13	3%	46	10%
Para-aortic nodes	Yes	101	*(14%)*	84	83%	17	17%	11	11%	4	4%	12	12%
Common iliac nodes	Yes	208	*(30%)*	171	82%	37	18%	23	11%	7	3%	27	13%
Lower iliac nodes (ext/int iliac)	Yes	641	*(92%)*	538	84%	103	16%	58	9%	24	4%	72	11%
Other (Parametrial/Inguinal)	Yes	86	*(12%)*	74	86%	12	14%	7	8%	4	5%	6	7%
Nodal involv PET/CT or Hist/Cyt	Yes	433	*(62%)*	357	82%	76	18%	42	10%	17	4%	55	13%
Nodal involv PETCT proven	Yes	335	*(48%)*	281	84%	54	16%	28	8%	12	4%	38	11%
Nodal involv hist/cyt	Yes	120	*(17%)*	95	79%	25	21%	16	13%	5	4%	20	17%

Nodal Surgery = any type of lymph node surgery, NF = nodal failure reported per region, NFpelvic = pelvic nodal failure, NFpao = para-aortic nodal failure, NA = not applicable, Hb = haemoglobin in italic and brackets: percentage of patients with lymph node involvement.

Table 2
Location of nodes at diagnosis and at nodal failure; multiple nodal sites per patient are possible; crude rates.

Patients	All = 1338			All = 1338			N− = 641			N+ = 697		
			N+ = 697 52%			**NF = 152 11%**			NF = 43* **7%**			NF = 109* **16%**
Pelvic	690	*52%*	99%	84	*6%*	55%	23	*4%*	54%	61	*9%*	56%
Common iliac	208	*16%*	30%	41	*3%*	27%	9	*1.4%*	21%	32	*5%*	29%
Int/Ext iliac	641	*48%*	92%	62	*5%*	41%	16	*3%*	37%	46	*7%*	42%
Parametrial	70	*5%*	10%	7	*0.5%*	5%	2	*0.3%*	5%	5	*0.7%*	5%
PAO	101	*8%*	14%	**104**	*8%*	68%	26	*4%*	61%	78	*11%*	72%
Inguinal	20	*2%*	3%	18	*1.3%*	12%	3	*0.5%*	7%	15	*2%*	14%

N− = no nodes at diagnosis, N+ = nodes at diagnosis, NF = patients with nodal failure.
Percentages of patients (respectively All = 1338, All = 1338, N− = 641, N+ = 697) is given in *italic*.
Percentages of (respectively N+ = 697, NF = 152, NF = 43, NF = 109) is given straight.
* For one patient with nodal failure no information on nodal status at diagnosis was available.

and 20 patients, respectively. For detailed information see Table 1, Table 2 and Fig. 1.

Pelvic radiotherapy was delivered in all patients and with additional PAO radiotherapy in 215 patients (16%) (202 N+, 13 N−) (Table S1). Only 35 patients (3%) received inguinal radiotherapy. The median prescribed dose was 45 Gy (range 41–51) given in 25 fractions (range 16–32). Nodal boost was given to 458 of the N+ patients (66%) including 368 patients with solely pelvic, 80 with pelvic/para-aortic, 7 with pelvic/inguinal, and 3 patients with pelvic/inguinal/para-aortic lymph nodes. Of the N+ patients 218 had undergone nodal surgery (31%) and 104 of them received an additional boost. No node-directed treatment (boost or surgery) was given to 125 of the N+ patients (18%). PAO radiotherapy was delivered in 84 of 101 patients with PAO involvement (83%) and 48 of them received a nodal boost. Nodal boost was delivered in 5 of 20 patients with inguinal involvement. Boosted lymph nodes received a total median dose of 59 (range 50–67) Gy. At least 5 cycles of cisplatin were given to 64% of the patients, and at least 1 cycle to 94%.

Nodal failure

Overall, 152 patients (11%) developed nodal failure with 84 patients having pelvic, 104 PAO, and 18 inguinal failure, accounting for 55%, 68%, and 12% of all patients with NF, respectively (Table 2, Fig. 1). The location of NF was not reported for 13 patients. NF was detected in 59% within the first year and 83% within two years of FU.

In the N− and N+ groups 7% ($n = 43$) and 16% ($n = 109$) of the patients developed NF (Table 1). NF_{pelvic} alone occured in 2% and 3% of the patients in the N− and N+ groups, respectively. NF_{PAO} was detected in 4% of the N− group patients and in 11% of the N + group. Overall across FIGO stages (IB-IVB) 8–17% of patients developed NF, without clear tendency of higher NF rates in more locally advanced disease (Tables S2 and S3). Failure in a single nodal region was reported for 27% of patients with $NF_{pelvic,}$ and for 53% of patients with NF_{PAO}. NF in multiple regions was reported in 39% of patients with NF (30 in two, 25 in three, 3 in four and 1 in five regions, respectively). Fig. 2 shows the distribution of absolute numbers of patients with nodal failure per lymph node region.

A total of 215 patients were treated with elective PAO radiotherapy: 84 PAO N+ and 131 PAO N−. PAO failure occurred in 11/84 and 8/131 (13% and 6%) of these patients, respectively. Out of 595 patients with pelvic N+ and PAO N−, 118 received elective PAO radiotherapy and 477 did not. In these groups PAO failure was seen in 8/118 and 58/477 patients (7% and 12%), respectively. Out of 143 patients with common iliac N+ and PAO N−, 78 received elective PAO radiotherapy and 65 did not, with PAO failure in 8/78 and in 12/65 patients (10% and 18%), respectively (Fig. 3).

For 134 out of 152 patients with NF, information on NF location relative to radiation fields was available. Fifty-five patients developed NF outside the treated volume (PAO $n = 52$). Out of 79 patients with NF inside the treated volume 32 had failures within the elective target volume (PTV-E), (pelvic $n = 29$), and 25 within the nodal boost volume (PTV-N) (pelvic $n = 24$); 22 patients had more than one site of failure, in both PTV-E and PTV-N. Of the

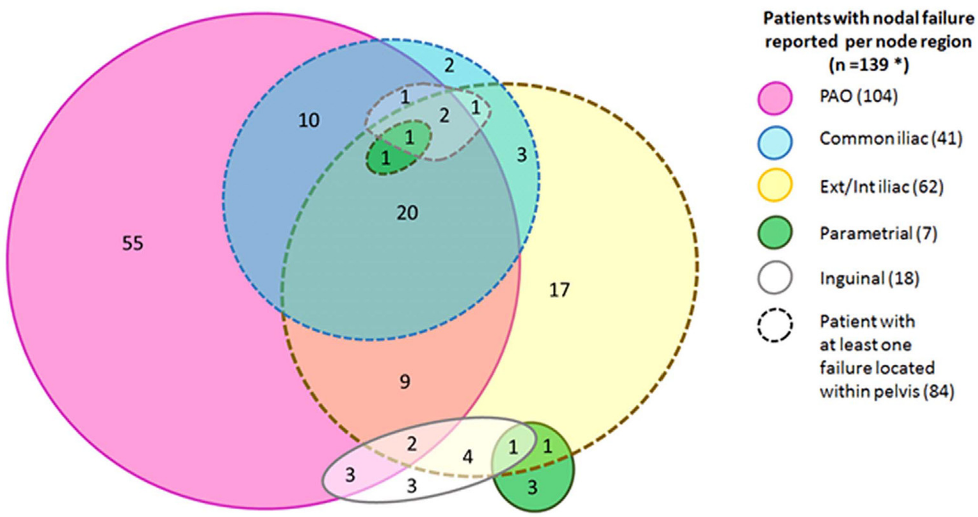

Fig. 2. Venn diagram (not to scale) showing number of patients with failure per lymph node region (*for 139 patients, excluding those with missing location information.

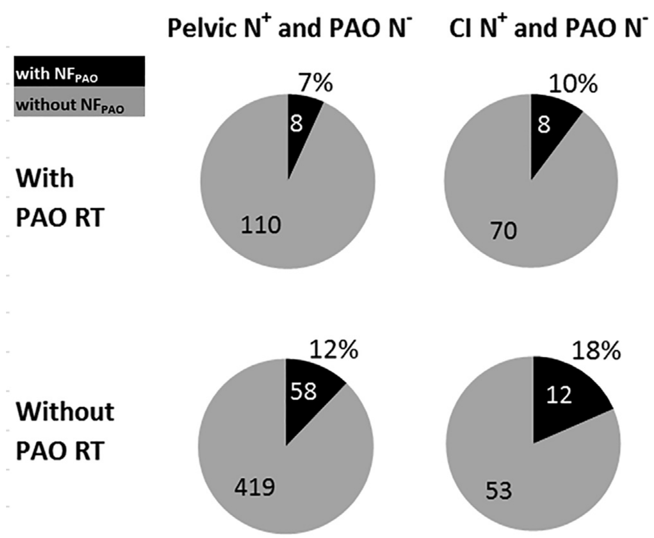

Fig. 3. Paraortic (PAO) Nodal Failure (NF_{PAO}) for patients without PAO pathological nodes at time of diagnosis (PAO N^-). Left: patients with positive pelvic nodes at time of diagnosis ($n = 595$), right: patients with positive common iliac (CI) nodes at time of diagnosis ($n = 143$); upper: patients with PAO radiotherapy (RT), lower: patients without PAO RT. Absolute numbers and percentages are indicated.

104 patients with NF_{PAO}, 46 were observed within PTV-E and/or PTV-N.

Fifty patients were scored with nodal disease within the first 6 months of FU with 18 of them being late responders with nodal disease resolving later in FU. In 32 patients (9 PND and 23 NR) NF occurred within 6 months after treatment.

The actuarial 3 and 5 year nodal control rate was 87% and 86%, respectively, with a median FU of 34 (range 1–98) months. The nodal control rate at 3 years was 92% in the N− group compared to 82% in the N+ group which is an absolute difference of 10% ($p < 0.001$).

One quarter of patients with NF were diagnosed with simultaneous local disease (24%) and more than one third of the patients had simultaneous distant metastases either nodes above PAO (e.g. mediastinal, supraclavicular) or organ metastases. At analysis 110 out of the 152 patients with NF had died (72%).

Discussion

To our knowledge this is the first report to describe the pattern of nodal failure in cervical cancer within a large multicentre prospective cohort. Baseline criteria for our study population are well in line with the literature [12,13]. Other metrics of the EMBRACE study cohort besides NF (e.g. tumour remission and morbidity) are subject of separate analyses [18–25]. Limited data exist on nodal disease at diagnosis and on nodal failure as a separate factor characterizing treatment outcomes for LACC. Nodal failure is often referenced as part of pelvic recurrence or disease free survival, without clarifying information on nodal involvement at diagnosis, node-directed treatment parameters, nor the extent and pattern of nodal failure. Therefore this evaluation provides a benchmark for the effect of chemo-radiation, nodal boost and MR-IGBT on NF in LACC taking into account nodal status at diagnosis.

At diagnosis, overall nodal involvement was reported for 52%: 36% for IIA patients, 45% for IIB, 58% for IIIA, 61% for IIIB and 62% for IVA disease (Table S3). Among stage 1B patients there was 48% node positivity which reflects referral patterns for definitive chemo-radiation when nodal involvement is diagnosed. Improved nodal detection with modern approaches such as PET-CT [26] and laparoscopic histologic assessment may have contributed to a higher nodal involvement in our cohort compared to patients treated a decade ago or longer [14,27]. However, our node positivity rate seems comparable to recent reports 34–57% [1–5,9–12].

At median FU of 34 months there were 152 patients with NF (crude rate 11%). Single institution historical data from Beadle et al. [13], a retrospective analysis of 1894 patients treated with EBRT and BT (concurrent cisplatin chemotherapy in 11%), reported 17% regional recurrence. Ten percent of patients had regional confined recurrences (no local disease). Within EMBRACE 8% NF patients in the pelvic and/or PAO region were without signs for local disease. Sturdza et al. [12] reported on 731 patients treated with CCRT and IGBT in the RetroEMBRACE study with a crude pelvic failure rate of 13%. Tan et al. [15] reported for these RetroEMBRACE patients regional and PAO failure of 6% and 9%, respectively, which is comparable to 6% NF detected in the pelvis and 8% in the PAO region in this study.

Comparing patients with/without pathological lymph nodes at diagnosis revealed significantly different crude rates for overall NF, NF_{pelvic} and NF_{PAO} with 16% versus 7%, 9% versus 4% and 11%

versus 4%, respectively (Table 1). From patients with NF_{pelvic} 57% have additional failures in the PAO region (Fig. 2). For patients with NF_{pelvic} but without NF_{PAO}, nodal status at diagnosis was irrelevant (2% vs. 3% failure rate, for N− vs N+). The overall NF_{pelvic} rate for the whole cohort after pelvic radiotherapy is only 3% when excluding patients with simultaneous NF_{PAO} (Table 1). These rates underline the excellent effect of radiotherapy on pelvic nodal disease.

Nodal boost (mean total dose 59 Gy) was given to 66% of N+ patients, resulting in a crude NF rate of 15% compared to 17% for N+ patients treated without nodal boost. Forty-seven of the 134 patients with information on NF location had a failure within PTV-N. Assuming that the distribution of failures in patients with/without information is equal, a total of 53/152 patients would have PTV-N failure. Of the N+ patients treated with a nodal boost 12% developed NF within PTV-N (53/458). A recent paper by Bacorro et al. [28] found in 18.5% of N+ patients failure inside nodes which were pathologic at diagnosis. In this cohort the mean nodal dose including BT was 55 Gy EQD2, and 31% of the patients were not boosted. Ramlov et al. [29] investigated for N+ patients, in a two-institutional cohort, the individual nodal dose and the pattern of nodal failure. Failure in boosted nodes was seen in 6/75 patients (8%). A dose response relationship (median dose of 63 Gy to recurrent nodes) could not be established due to the limited number of events, but their results did not indicate a benefit of a nodal dose beyond 60 Gy EQD2 (EBRT + BT). However, a significant relation between SUV value and risk of failure in boosted nodes was found.

Another important finding of this EMBRACE study is the difference between the pattern of nodal spread at diagnosis and the pattern of NF. Pathologic nodes at time of diagnoses were mainly located in the pelvis (99% of N+ patients). Nodal failures however, were more often reported for the PAO region, crude rate 68% of all patients with NF, compared to 55% in the pelvis (Fig. 1, Table 1). Half of the patients with PAO failure had PAO confined failure.

The role of prophylactic PAO radiotherapy remains a matter of debate. Patients with pelvic nodes at diagnosis treated with prophylactic treatment had less NF_{PAO} compared to those without PAO radiotherapy (7 versus 12%) and this effect was even more pronounced for the subgroup of patients with positive common iliac nodes (10% versus 19%). Beadle et al. [13] reported for 180 patients the relationship between recurrence and radiation field borders. At least a component of marginal recurrence was seen in 119 patients (66%) and these recurrences typically arose immediately adjacent to the superior border of the radiation fields. In the EMBRACE study the upper pelvic field border and PAO radiotherapy was not strictly defined. Allowing for different traditions in EMBRACE the upper field border may have been between L5/S1 and the upper border of L3, if aortic bifurcation was included. Similarly PAO irradiation may have varied considerably. In addition, it remained unclear how to define PAO nodes relative to the aortic bifurcation. PAO region is, however, of particular importance as it is the most common site for nodal recurrence in EMBRACE [13]. Recently centres have included the PAO region systematically in the radiation fields of node positive patients, e.g. the Pittsburgh group through systematic application of IMRT and a concomitant nodal boost of 55 Gy [5]. They report a 0% nodal failure rate in the pelvic and/or PAO region in 128 patients after median 24 months with a 0.9% $\geq$G3 GI and GU morbidity rate. Another more recent publication from Taiwan retrospectively compared the data from patients with nodal involvement at diagnosis (PAO excluded) treated without and with prophylactic PAO radiotherapy with doses of 45–50.4 Gy [30]. For the latter group, positive pelvic lymph nodes were boosted till 59.4 Gy resulting in significant lower PAO nodal failure rate (23.7% versus 1.3%) without increasing severe toxicities. PAO radiotherapy may therefore be regarded as a tool to improve nodal control (Fig. 3) and maybe overall outcome (survival). This topic is addressed in the multicentre EMBRACE II [16,17] by defining risk groups for selection to receive prophylactic extended field irradiation. Comprehensive assessment of risk factors for nodal recurrence in EMBRACE is currently under evaluation by applying a multivariable regression model for nodal control.

Within the EMBRACE study cohort the overall number of patients developing nodal failure is low (11%). Patients without pathological nodes at diagnosis have significantly less failures compared to those with nodal disease (7 versus 16%). Pathologic nodes at diagnosis are mainly located in the lower pelvis. Nodal failures however, are more often seen in the PAO region. About 40% of all failures were reported outside the treatment targets.

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Appendix A

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.02.007.

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