



# Management of Nodal Disease in Advanced Cervical Cancer

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During the last decade the adoption of image-guided adaptive brachytherapy has dramatically improved local control in patients with locally advanced cervical cancer (LACC) treated with radiotherapy and concomitant chemotherapy; however, nodal failure remains an obstacle. Metastatic lymph nodes can be detected by surgical and imaging approaches with different sensitivities and specificities, that improve the definition of relevant targets for macroscopic and microscopic nodal disease, and that influence our understanding of dose levels of external beam radiotherapy. Systematic use of modern radiotherapy techniques including intensity modulated radiotherapy and simultaneously integrated nodal boosts in combination with daily position verification is emerging as increasingly important for obtaining nodal control in LACC. This review summarizes published and ongoing efforts for optimizing nodal disease treatment in LACC, elaborates the state of the art approach for nodal disease detection, radiotherapy planning and delivery, and discusses future investigational efforts needed for precise optimization.

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## Introduction

In the last decade, treatment outcomes for patients with locally advanced cervical cancer (LACC) have improved through modern external beam radiotherapy (EBRT) techniques and image-guided adaptive brachytherapy (IGABT). Local tumor control rates are excellent and result in improved pelvic control and increasing disease free and overall survival.<sup>1</sup> However, nodal failures remain and improving the treatment of nodal disease is paramount. The detection of nodal disease has

evolved through modern imaging (PET-CT, MRI)<sup>2-4</sup> and improved surgico-pathologic assessment.<sup>5</sup> Radiotherapy techniques like intensity modulated radiotherapy (IMRT) and daily position verification by cone beam CT (CBCT) allow for delivery of more conformal dose distributions.<sup>6,7</sup> Nodal spread beyond the pelvis is considered distant disease, both in FIGO and TNM. However, nodal disease extension to the subrenal para-aortic (PAO region) and inguinal nodes may be treated with curative intent.<sup>6,8,9</sup> This review comprehensively discusses the current knowledge regarding the management of nodal disease in cervical cancer patients treated with definitive chemoradiation (CRT). It describes the characteristic patterns of nodal spread, and the detection of nodal disease at diagnosis and at the time of recurrence. The focus is on pelvic and PAO nodal disease and radiotherapy with curative intent including strategies for achieving improved nodal control.

## Assessment of Nodal Disease

For the assessment of nodal disease, imaging and surgical procedures are required. The decision whether a node is metastatic (N+) or not (N-) is based on morphological, biological, and/or pathological criteria.

**CT and MRI:** CT with oral and intravenous contrast is used routinely in the staging of patients with cervical cancer. Nodes

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greater than 1 cm in short-axis diameter are considered affected as are rounded nodes.<sup>2,10</sup> Central necrosis of a node has a positive predictive value of 100%.<sup>10</sup> The accuracy of assessment of enlarged lymph nodes is 83%-85% for CT and 88%-89% for MR, respectively.<sup>2</sup> Most metastatic nodes, however, are not enlarged. In smaller nodes (>5-10 mm) morphologic MRI features (rounded and/or irregular shape, inhomogeneous appearance and borders) are indicative of nodal involvement.<sup>4</sup> Specificity for CT and MR overall is high at 89%-93%. However, sensitivity is lower at 24%-70% since malignant vs reactive nodes cannot be distinguished on both CT or MRI wherein tumor may also be present in normal-sized nodes.<sup>2</sup>

**PET-CT:** The use of 2-(fluorine 18) fluoro-2-deoxy-D-glucose (FDG) PET combined with CT is considered standard in many countries in the initial work-up of patients with cervical cancer.<sup>11,12</sup> The FDG tracer is a glucose analog that is taken up by rapidly metabolizing cells and 91% of cervical tumors.<sup>2</sup> Additionally, lymph nodes as small as 6 mm can show FDG positivity and hence be considered affected rather than the 1 cm size required on traditional axial CT images. The use of FDG PET improved sensitivity in detection of lymph node metastases from 50%-73% with CT or MRI to up to 83%-91% with PET.<sup>2</sup> However, PET is associated with a high rate of false positive lesions and a positive predictive value of around 75%.<sup>13,14</sup> The false negative rate in the PAO region is 8%-12%.<sup>15,16</sup> Overall, in the large multicenter laparoscopic pathologic evaluations from the last decade,<sup>17</sup> the sensitivity and therefore also the overall accuracy of PET-CT is reported to be lower than previously indicated. Despite the advantage of PET over CT alone, early stage-cervical cancer data show that PET-CT is less sensitive compared to lymphadenectomy with respect to detecting very small metastatic nodes especially in the PAO region which would mandate treatment and impact overall treatment strategy.<sup>18</sup>

**Surgical Staging:** Given the sophistication of modern imaging techniques and the efficacy of CRT, including elective and target boost radiotherapy for patients with N+ and N- disease at diagnosis, surgical staging of cervical cancer is no longer considered standard for LACC. In clinically pelvic N- patients, irrespective of stage, the pelvic nodal control rate is 96%.<sup>19</sup> In the setting of a negative PET-CT scan, the risk of N+ at laparoscopic PAO lymphadenectomy is 8%-12%.<sup>15,16</sup> In the case of pelvic N+ on PET-CT, the risk for PAO nodal disease is much higher (24% vs 2.9%).<sup>16</sup> Surgical PAO staging might be preferable for exploring the extent of nodal disease, tailoring the radiation fields and avoiding the morbidity of unnecessary PAO irradiation.<sup>20,21</sup> Should surgical staging be chosen in order to explore PAO disease or to debulk large pelvic or PAO nodes for dose de-escalation, a subrenal and extra-peritoneal rather than a transperitoneal approach is advised to decrease morbidity. This results in a slight delay in the initiation of CRT.<sup>16</sup>

## Nodal Disease at Diagnosis

Nodal involvement at diagnosis increases with increasing stage of disease. The nodes in the parametrium are the first to be involved. From there, there are different lymphatic

pathways of nodal spread: The lateral route is along the external iliac vessels; the hypogastric route is along the internal iliac vessels; the presacral route is along the uterosacral ligaments and there is a direct route through the uterine corpus and along the ovarian vessels to the PAO region. All 3 routes lead to common iliac and PAO nodes.<sup>2,10</sup> Nodal spread beyond the pelvis to PAO, mediastinal, supraclavicular, and inguinal regions is considered distant disease. However, nodal metastases in the inguinal and/or PAO region up to renal veins still allows for treatment with curative intent.

Utilizing MRI or PET-CT, in a series of 198 cervical cancer patients studied, the number of affected nodes ranged from 1 to 11 per patient,<sup>22</sup> with 37% having a minimum of 3 pathologic nodes. The majority (95%) of N+ patients had lymph nodes located in the lower pelvis, whereas 36% had lymph nodes in the common iliac region. Fontanilla et al<sup>23</sup> analyzed PET-CT data for a group of 41 consecutively treated patients. They found PET avidity in 122 lymph nodes with the highest number of affected nodes located in the external iliac region (64%). Node positivity was considerably lower in the common iliac (17%) and PAO regions (7%), respectively. This pattern of distribution is in line with data recently derived for 1338 LACC patients treated within the EMBRACE I study.<sup>19</sup> The analyses reveals 697 N+ patients (52%) based on CT, MRI, PET-CT, or histopathologic information with 37% of them having affected nodes in multiple regions (177 in 2, 71 in 3 and 8 in 4 regions). Almost all N+ patients (99%) had affected lymph nodes located in the pelvis (common iliac (30%), external/internal iliac (92%), and parametrial region (10%)). Affected PAO and inguinal lymph nodes were present in respectively 14% and 3% of the node positive patients.<sup>19</sup>

## Target Volumes and Contouring for Elective and Boost Irradiation

**Target volumes:** The nodal target volumes for cervix cancer can be broadly divided into elective lymphatic regions (CTV-E) and affected nodes (GTV-N). The extent of CTV-E that has been treated is variable but there is emerging consensus as to what should be included routinely. The extent of CTV-E is based on initial stage of disease and nodal involvement seen on PET-CT, CT, or MRI scans or surgical staging. For early stage cervical cancer (IA2, Ib1, and IIA1), with imaging negative for nodal disease, the risk of failure in the common iliac region and above is low and the suggested CTV-E is external iliac, internal iliac, obturator, radiologic presacral, and distal common iliac regions. For LACC (IB2, IIA2, and above), and imaging negative for pelvic and PAO nodes, the suggested CTV-E includes similar nodes but also the entire common iliac and the aortic bifurcation. If disease extends to the distal vagina, the inguinals are included in the CTV-E. Similarly, if there is extensive tumor infiltration of the uterosacral ligaments or if mesorectal nodes are affected, the mesorectal space should be included partially or completely.

For LACC patients with imaging positive for pelvic node(s) and negative for PAO node(s), there is significant variation in practice. In any case, it seems advisable to include the

aortic bifurcation. In addition, there is debate about when and to which amount to include the adjacent PAO region. The published data suggest that the negative predictive value of PET-CT for PAO nodes is about 75 %.<sup>13</sup> EMBRACE I data show PAO recurrence rates of about 11% for N1 disease with the risk of failure increasing based on the number of affected nodes and their location.<sup>19</sup> Recently, a large retrospective study suggested an improvement in survival with treatment of the PAO region prophylactically in pelvic node positive patients.<sup>9</sup>

In general, if the common iliac region is affected, then following the principle of extending CTV-E 1 level above the involved region, it is suggested to include the lower PAO region up to the level of the renal veins, as the majority of affected nodes are found in this region. If only the external, internal, or obturator nodes are affected, then there is wider variation in practice and we do not have prospective data to support whether we have to extend the field to the PAO region or not. One approach is to treat the entire common iliac chain, including the aortic bifurcation nodal region, which is 1 level above the affected pelvic nodes. Another approach is to perform a laparoscopic PAO staging with expansion of the field according to the metastatic status of the PAO nodes. The third approach is to treat the subrenal PAO region prophylactically, especially if the common iliac region or more than 2 nodes are involved, as currently explored within the EMBRACE II study.<sup>6,24</sup> For patients with affected lower PAO nodes, CTV-E would include external iliac, internal iliac, obturator, presacral, common iliac, and PAO region up to the left renal vein. If affected nodes are located at or around the renal vein level, then CTV-E should extend 3 cm above the highest node with inclusion of the retrocrural (inferior mediastinal) space.<sup>25</sup>

**Contouring:** The Pelvic CTV-E is contoured by expanding 7-10 mm around the vessels, editing out the muscles and bones and including any visible nodes and clips if a dissection was done. The lateral border should extend to the psoas muscles and pelvic sidewall.<sup>3,24,26</sup> To cover the pre-sacral region, the volumes on each side of the pelvis are connected with a 10 mm strip over the anterior sacrum. The caudal extent of the presacral region usually extends to the S2/S3 interspace or the beginning of the piriform muscles.

Contouring of the PAO CTV-E should not be defined by a fixed circumferential margin around the vessels. The left para-aortic and aorto-caval spaces should be covered adequately because these are common locations for affected PAO nodes. For microscopic disease superiorly, contouring should extend up to the renal veins rather than using a fixed bony landmark. For patients who have nodal involvement at the level of the renal veins, the 3 cm cranial extent should include the retrocrural space.<sup>25</sup> Similarly for inguinal nodes, the most common location is medial or anteromedial to the femoral vessels and thus the inguinal CTV-E should not be defined by a fixed circumferential margin but instead include this vascular compartment.<sup>27</sup>

The boost volume for affected node(s) is the GTV-N (as seen on PET-CT, MRI, or CT scan or combination) with expansions of 5-10 mm for ITV and PTV, depending on the

position verification approach.<sup>8</sup> The full thickness of critical organs such as the small bowel, duodenum, or sigmoid should be avoided in this expanded volume to decrease the risk of complications. Lindegaard et al<sup>8</sup> have shown that with coverage probability planning and daily CBCT, the margin around the GTV-N can be reduced to 5 mm and still maintain adequate coverage of the node and reduce dose to critical organs like the bone and small bowel.

(For contouring details see: [www.embracestudy.dk/UserUpload/PublicDocuments/Docs/EMBRACE\\_II\\_title\\_page\\_and\\_total\\_protocol\\_v15\\_151015.pdf](http://www.embracestudy.dk/UserUpload/PublicDocuments/Docs/EMBRACE_II_title_page_and_total_protocol_v15_151015.pdf) and [www.nrgoncology.org/contouringatlas](http://www.nrgoncology.org/contouringatlas)).

## Treatment Planning and Dose Volume Parameters

**EBRT planning:** The planning aim for EBRT in cervix cancer is determined by the overall strategy for the combined treatment of EBRT and brachytherapy (BT) and the balance of dose delivered by the 2 modalities. Several dose/fractionation schedules have been reported (ie, 40-50 Gy in 20-28 fx); 45 Gy in 25 fractions is the most common regimen reported. There are currently no data to suggest improved local or regional control with an EBRT dose >45 Gy. However, there are data for reduced vaginal morbidity<sup>28</sup> and pelvic insufficiency fractures<sup>29</sup> when lowering the EBRT dose to the pelvis from 50 to 45 Gy, and the recommended dose of EBRT is therefore 45 Gy/25 fx.

IMRT and VMAT are recommended as these techniques significantly reduce the irradiated volume (V43) and are associated with a reduced risk of acute and late toxicity.<sup>30</sup> It is furthermore recommended to combine IMRT/VMAT with on-board image guided radiotherapy (IGRT) to allow for daily fusion and couch alignment according to bony landmarks.<sup>11</sup> Daily use of CBCT has the additional advantage that organs and targets can be monitored during the EBRT course, and use of MR-Linac guided EBRT and daily plan optimization may further reduce treatment uncertainties and margins. The use of bladder filling protocols with the aim of treating patients with a comfortably full bladder can significantly reduce the exposure of bowel.

Boosting of affected nodes may be carried out either by sequential or simultaneous integrated boost (SIB). Sequential boosting allows for adaptation based on nodal response after 45 Gy, and provides precise calculation of the dose contribution from BT. The dose contribution from BT is about 2-6 Gy at the level of external and internal iliac vessels and negligible at the common iliac vessels and above.<sup>31</sup> SIB is a robust and effective method that use IMRT/VMAT resulting in a shortened overall treatment time.<sup>6-8</sup>

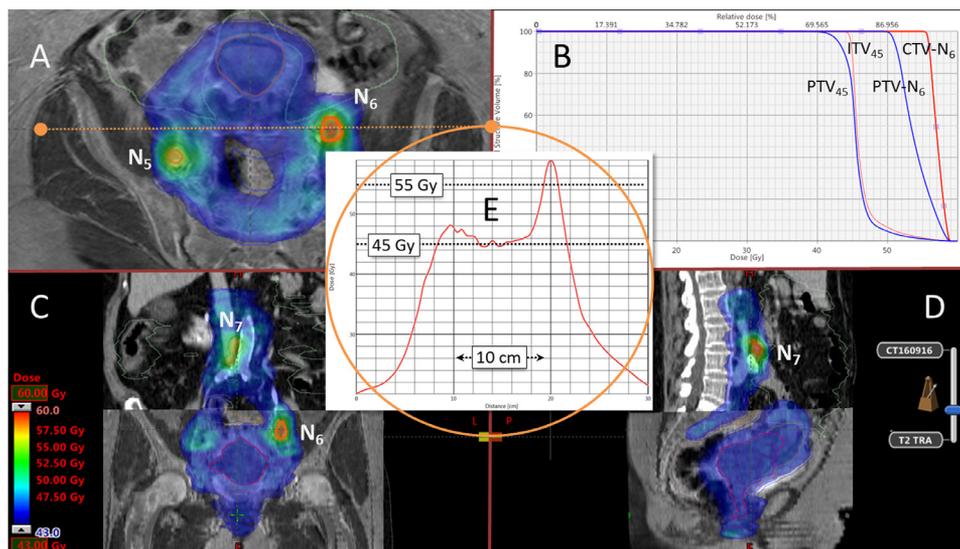
There is little consensus on dose prescription for lymph node boosts, though size, location of the involved node, PET avidity, and regression during treatment may be important factors for the dose needed. Doses of around 60 Gy EQD2 including the contribution from BT has been shown to provide a nodal relapse rates of 2%-12%.<sup>6,32</sup> A recent study indicates that total doses lower than 60 Gy can be related with decreased nodal control, and furthermore large (>

cm) and poorly responding nodes may benefit from more than 60 Gy, irrespective of position.<sup>33</sup> Currently, reported dose levels for nodal boosting using SIB are in a range of 50-55 Gy/25 fx for nodes close to the external and internal iliac vessels and 50-57.5 Gy/25 fx for nodes further away, where little or no dose contribution from BT is expected.<sup>6,24</sup> These dose levels can be achieved with daily SIB doses of 2.0-2.3 Gy, and allow for a somewhat higher radiobiological effect. In the eventual case of very large nodes more dose might be aimed for and an additional sequential boost in 2 Gy fractions might be applied up to 65 Gy<sup>34</sup> on top of a SIB with the above mentioned dose levels. Dose above 60 Gy however might produce increasing morbidity especially when applied in the PAO region irrespective of boost technique.<sup>35</sup> Alternatively, nodes larger than 2 cm might be debulked prior to chemoradiation. There are currently no meaningful data describing the effect of neo-adjuvant chemotherapy on volume reduction in nodal disease. Due to their stable location along the pelvic bones and spine, affected lymph nodes only have minimal position changes during EBRT,<sup>36</sup> and accumulated dose is robust for pelvic lymph nodes treated with SIB.<sup>7</sup>

Dose heterogeneity can occur close to the BT target if pelvic nodes are treated and must be taken into account in the EQD2 calculations at the time of BT. The key approach to avoid small portions of the OAR receiving higher doses per fraction unnecessarily with potentially increasing both acute and late toxicities, is to perform SIB with daily IGRT and limited margins ( $\leq 5$  mm). Furthermore, coverage probability planning can further reduce irradiated volumes<sup>7</sup> (Fig. 1). There are several studies now describing clinical experience

with SIB.<sup>7,8,34,37,38</sup> Overall, these studies suggest that SIB IMRT/VMAT for pelvic nodes is safe, results in reduction of dose outside the CTV-N and has at least comparable outcomes with sequential IMRT boosts. For PAO irradiation it is a specific challenge to align the long target and robust literature on set-up uncertainties for the PAO region is lacking. In addition, care must be taken to define the duodenum, which is a fixed rather than mobile portion of the small bowel, and avoid high doses which could lead to ulceration, bleeding or (fatal) perforation, particularly in patients with large nodal disease adjacent to the duodenum.<sup>35,39</sup>

*DVH parameters and OAR:* Ideally OAR constraints should be based on absolute DVH values for dose effect. However, the ability to reach certain OAR constraints is very much dependent on patient anatomy and on the techniques used for both EBRT and BT, including target selection (pelvic only vs pelvic plus PAO). In addition, the use of neoadjuvant, concomitant, and/or adjuvant chemotherapy as well as surgery has an impact on dose effect and the development of morbidity. In practice, OAR constraints specified in clinical protocols are often based on pragmatic principles such as the ability to respect certain values with certain techniques. Importantly, the adherence to a certain set of DVH constraints does not secure that a high-quality plan has been achieved. A key parameter of plan quality is the plan conformity (eg, 95% and 80% isodoses) that conveys whether irradiation of the normal tissues is as low as possible. New treatment planning approaches such as knowledge-based dose planning and auto-planning takes the individual anatomy into account, and helps achieve high conformity.



**Figure 1** Example for elective and nodal boost dose distributions

Patient with primary cervical cancer and multiple affected nodes in pelvis and PAO region; elective dose of 45 Gy, simultaneous integrated boosts (SIB) to a total dose of 55 Gy for pelvic and 57.5 Gy for common iliac and PAO nodes, respectively; all dose levels delivered in 25 fractions. Colourwash of dose distributions in transversal (Panel A), coronal (Panel C), and sagittal (Panel D) directions on fused planning MRI and CT scans.

Panel B: Dose volume parameter (DVH) curves for elective and SIB dose for one node (N<sub>6</sub>, ITV = internal target volume, PTV = planning target volume).

Panel E: Dose profile across the pelvis at the level of N<sub>6</sub> demonstrating the ability of coverage probability planning to generate a central boost dose with cooling down at the edge and a rapid dose fall off to elective dose levels outside of PTV-N; clinical example from Aarhus University Hospital.

**Table Dose Constraints for EBRT for N+ Patients**

|                                                | <b>Hard Dose Constraints</b>                                                                        | <b>Soft Dose Constraints</b>                                                                                                                                                                                                              |
|------------------------------------------------|-----------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PTV45                                          | V42.75 Gy > 95%                                                                                     | V42.75 Gy = 95%<br>Dmax < 107% for helper structure:<br>PTV45–(PTV-N(#) + 1 cm)                                                                                                                                                           |
| ITV45<br>CTV-HR + 10 mm                        | Dmin > 95%                                                                                          | Dmax < 103%<br>for helper structure:<br>CTV-HR + 10 mm–(PTV-N(#) + 1 cm)                                                                                                                                                                  |
| PTV-N(#)                                       | D98% > 90% of prescribed LN dose<br>Dmax < 107% of prescribed LN dose                               | D98% = 90% of prescribed LN dose                                                                                                                                                                                                          |
| CTV-N(#)<br>Bowel                              | D98% > 100% of prescribed LN dose<br>Dmax < 105%<br>in regions outside 10-15 mm from PTV-N          | D50% > 102% of prescribed LN dose<br>When no para-aortic irradiation:<br>V40Gy < 250 cm <sup>3</sup> *<br>V30Gy < 500 cm <sup>3</sup> *<br>For para-aortic irradiation:<br>V40Gy < 300 cm <sup>3</sup> *<br>V30Gy < 650 cm <sup>3</sup> * |
| Sigmoid                                        | Dmax < 105%<br>in regions outside 10-15 mm from PTV-N                                               |                                                                                                                                                                                                                                           |
| Bladder                                        | Dmax < 105%<br>in regions outside 10-15 mm from PTV-N                                               | V40Gy < 60%*<br>V30Gy < 80%*                                                                                                                                                                                                              |
| Rectum                                         | Dmax < 105%<br>in regions outside 10-15 mm from PTV-N                                               | V40Gy < 75%*<br>V30Gy < 95%*                                                                                                                                                                                                              |
| Spinal cord<br>Femoral heads<br>Kidney<br>Body | Dmax < 48Gy<br>Dmax < 50Gy<br>Dmean < 15Gy<br>Dmax < 107%<br>in regions outside 10-15 mm from PTV-N | Dmean < 10Gy                                                                                                                                                                                                                              |
| Vagina (if not involved)<br>Conformality       |                                                                                                     | D <sub>PIBS-2 cm</sub> < 5Gy<br>1.10 (V43Gy/Volume of PTV)<br>1.55 (V36Gy/Volume of PTV)<br>Dmean < 5 Gy                                                                                                                                  |
| Transposed ovaries<br>Duodenum                 | Dmean < 8 Gy<br>V55 < 15 cm <sup>3</sup>                                                            |                                                                                                                                                                                                                                           |

This Table is part of an update of Table 9.4 of the EMBRACE-II study protocol version 1.0.

Percentages of 45 Gy unless stated otherwise for nodes. Dmax and Dmin for Monte Carlo plans based on D99.9% and D0.1%.

\* Soft constraints which can be used in the treatment planning optimisation. Values are based on DVH parameters of EMBRACE-II patients entered in the study before June 2017. The constraints are not supposed to be fulfilled in all patients, but by ~70%-80% of the patients.

Finally, contouring of the specific organ in question is also important as this has considerable impact on the reported dose and the relevant DVH constraints to use (eg, bowel loops vs bowel bag). The currently employed OAR constraints for the Embrace II protocol are given in Table. Clinical data based on both morbidity assessment and patient reported outcomes increasingly supports the importance of minimizing dose and volume of pelvic organs and the whole body treated to certain dose levels. The results of current clinical protocols are expected to improve our evidence-based dose constraints in the near future. In addition, constraints are sharpened and new OAR measures are being implemented (eg, vagina, bone marrow, duodenum, pancreas, etc). The first data from the Embrace II protocol (also reported in<sup>8</sup>) already shows a significant reduction in V43 from 2400 cm<sup>3</sup> (EMBRACE I) to 1400 cm<sup>3</sup> (EMBRACE II) for elective pelvic target and from 2900 cm<sup>3</sup> (EMBRACE I) to 1900 cm<sup>3</sup> (EMBRACE II) for pelvic plus para-aortic target by employing individualized ITV contouring, bladder filling protocol, IMRT/VMAT, coverage probability planning and daily IGRT.<sup>40</sup>

## Disease Outcome Including Pattern of Lymph Node Recurrence and Related Risk Factors

*Overall outcome:* In early and advanced stage cervical cancer, lymph node involvement has a major adverse prognostic impact on survival. For stage IB1, 5 year overall survival (5y overall survival (OS)) in N0 patient is in the range of 95%-100% after surgery or radiotherapy<sup>41</sup> and drops to less than 80% in N+ patients.<sup>42</sup> For stage IB2, 5y OS is about 85% in N– patients after CRT and BT<sup>43</sup> on which adjuvant hysterectomy has no impact. After radical surgery 5y OS is less than 70% in stage IB2 patients.<sup>44,45</sup> Evidence shows CRT combined with IGABT leads to favorable outcome with overall survival over 90% for stage IB2.<sup>1,24,46</sup>

For patients with stage IIB disease and higher, lymph node status also has an essential impact on overall survival with a decrease in 5-year OS of 15%-35% in N1 patients<sup>47</sup> (unpublished material RetroEMBRACE). As FIGO staging lacks information on nodal status but has been the accepted standard for staging, including multicentre phase III CRT

trials, clinical evidence for the impact of nodal disease is mainly based on retrospective and mono-institutional series.<sup>47</sup> Additionally, unpublished data from the RetroEMBRACE study reveals 5y OS rates for stage IB-IVA patients of 49% for N+ vs 82% for N0 patients, respectively.

There is evidence that the risk factors of location of affected nodes,<sup>47</sup> their size,<sup>48</sup> and their number are directly related to survival. Patients with metastatic disease in PAO nodes have the worst prognosis (5y OS about 20%<sup>15</sup>) followed by common iliac/presacral and internal iliac nodes.<sup>47</sup> There seems to be a major difference between microscopic and macroscopic PAO involvement in regard to overall survival after surgery or radiotherapy.<sup>15</sup> There is evolving evidence that prophylactic PAO radiotherapy in the setting of pelvic nodal disease and PAO radiotherapy for microscopic PAO disease, have considerable impact on PAO lymph node recurrence and survival.<sup>6,9,22</sup> With IMRT/VMAT/IGRT and careful small bowel dose constraints (5-15cc <55 Gy).<sup>49</sup> PAO radiotherapy seems to have less impact on the development of morbidity as compared to historical data.<sup>50,51</sup> But also in the era of modern radiotherapy including SIB for PAO nodes and with increasing knowledge on dose volume relations, avoiding treatment related morbidity is not trivial.<sup>35,39</sup>

*Lymph node recurrence:* Complete remission of affected nodes after CRT can be achieved in up to >95% of N1 patients within 3-6 months.<sup>19</sup> Whereas the majority of lymph node involvement at diagnosis is in the pelvis (99%) and only 10%-20% in the PAO region, the pattern of lymph node relapse after pelvic EBRT is balanced between PAO (68%) and pelvic (55%) nodes.<sup>19</sup> The vast majority of lymph node relapses (80%-90%) occur within the first 2-3 years after treatment.<sup>19,52</sup> Overall regional and distant nodal failure may occur in up to 20% of patients including pelvic, PAO, inguinal, and mediastinal/supra-clavicular failure sites.<sup>1,52,53</sup>

In the current EMBRACE and RetroEMBRACE analyses, total lymph node failure after CRT and IGABT is overall 11% and 13%, respectively, including pelvic, PAO and inguinal sites.<sup>19,52</sup> In locally advanced but N- disease, lymph node failure in the pelvis may be as low as 3%-4% after 45-50 Gy pelvic radiotherapy whereas it increases to 8%-9% in pelvic N+ patients.<sup>19,52</sup> Nodal failures can be located within or outside the treatment fields, with 2%-12% being located within PTV-N.<sup>6,19,32</sup> A considerable number of patients develops marginal failures at the field borders, mainly in the PAO regions and groins, after conventional radiotherapy with or without chemotherapy.<sup>53</sup> The overall nodal failure (pelvic, PAO, inguinal) in N+ patients is considerable at 16%.<sup>19</sup>

As nodal failure after definitive treatment leaves very limited possibility for salvage treatment, survival is poor after nodal failure including after CRT and IGABT.<sup>53,54</sup> Effective eradication of metastatic nodes during initial treatment is therefore of utmost importance and about 55-60 Gy (including brachytherapy contribution) are regarded as being sufficient.<sup>7</sup> SIB with daily IGRT, limited margins and coverage probability planning help reduce irradiated volumes. The level of PET-avidity and diameter of affected nodes at the time of diagnosis and their regression during treatment seem to impact nodal control and might also influence the dose

needed to levels above 60 Gy.<sup>32,33,55</sup> Additionally, we are in the process of understanding the prognostic importance of PAO nodes for the development of PAO and distant failures. The impact of diagnostic and therapeutic PAO lymphadenectomy and PAO irradiation based on a defined risk profile and/or the addition of potential systemic treatment is being investigated with promising results published<sup>6,9,21,56</sup> and ongoing investigations.<sup>24</sup>

In addition to lymph node metastases, other tumor and patient-related factors are reported to influence survival in LACC and some of them also seem to impact nodal failure. Among them are FIGO stage, primary tumor diameter, parametrial and uterine infiltration, histopathology, hemoglobin level, leucocytes, chemotherapy, overall treatment time and smoking, with varying degrees of importance. Overall, a robust understanding of the impact of all these factors on nodal disease outcome and their intrinsic relationships is still lacking. Uni- and multivariate analysis of nodal failure after CRT for LACC and related risk factors is currently performed in EMBRACE (1338 patients), and will be repeated in EMBRACE II.

## Summary Including Ongoing and Future Investigational Effort

In the last decade improved outcomes for patients with LACC have been documented, mainly local control and survival. In EMBRACE, the nodal failure rate in the pelvis for patients classified as N- is negligible, indicating that undetected microscopic disease is effectively eradicated by elective radiotherapy. For N+ patients however, considerable pelvic and PAO nodal failure (16%) still necessitates improvement. Efforts for improving nodal control include the diagnostic procedures (surgery and imaging) as well as modern treatment planning and radiation delivery tools. The detection rate of affected nodes has increased through volumetric imaging using morphologic and biologic criteria for disease detection and new PET tracers and MRI developments are promising tools for improvement in the future. Microscopic disease can currently be detected by lymphadenectomy with minimal invasive sentinel node procedures being investigated. The detection of microscopic nodal disease is of special importance in the PAO region for better defining the need for extended field radiotherapy, the risk for further metastatic spread and the eventual need for additional systemic treatments. The impact of either PAO lymphadenectomy or radiotherapy field extension based on individualized risk profiles is currently being investigated.

Future efforts should explore dose effect relationships for affected lymph nodes as well as factors that may influence dose-effect such as size/volume and SUV. Current protocols suggest a dose of about 60 Gy, including the brachytherapy dose contribution for pelvic nodes. Great care should be taken when escalating dose to the para-aortic lymph nodes due to the proximity and immobility of the duodenum. Lymph node boosting might be delivered using a SIB which implies an intensification of treatment due to a reduced

overall treatment time. Daily 3D image guidance such as CBCT or MR-linac is advantageous in conjunction with IMRT/VMAT to reduce treatment margins and uncertainties. The first data from the EMBRACE II protocol including this nodal boost strategy show that a significant reduction of irradiated volumes is possible when employing individualized, highly conformal and adaptive treatment for the primary cervical tumor and the affected nodes. In which way the reduction of radiation volumes will impact dose to the OAR, and morbidity is a matter of ongoing and future investigation. In addition to the improvements in radiotherapy technique, the evolving efforts in translational research for better identifying cervical cancer patients at risk for nodal and distant relapse and for developing more potent and targeted systemic treatments are of utmost importance.

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