



## Review Article

# Para-aortic lymph node involvement in cervical cancer: Implications for staging, outcome & treatment

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**Locally advanced cervical cancer with the involvement of para-aortic lymph nodes (PALN) is a common occurrence in low-income and low-middle-income countries. With the incorporation of PALN in the recent FIGO staging, therapeutic management becomes crucial. There are varied presentations of this group which may range from microscopic involvement to extensive lymphadenopathy. Various imaging modalities have been studied to accurately diagnose PALN metastases without surgical intervention, while some investigators have studied the survival benefit of para-aortic lymph node dissection for accurate staging and guiding extent of radiation. With recent advances in radiation therapy, its application to treat bulky nodal metastases and the role of prophylactic irradiation have been reported. In this review, the available evidence and the scope of further interventions is presented.**

**Key words** Locally advanced cervical cancer - para-aortic lymph nodes - staging - treatment

## Introduction

Cervical cancer is the fourth most common cause of cancer-related mortality in women<sup>1</sup>. The rate of para-aortic lymph node (PALN) metastases was found to be <5 per cent in early cervical cancer with a small lesion, without vaginal or parametrial involvement, while the incidence was 5-45 per cent in locally advanced cervical cancer (LACC)<sup>2</sup>. PALN positivity primarily depends on pelvic lymph nodal involvement. The other key factors increasing the probability of PALN involvement are tumour size, parametrial and/or uterine corpus involvement<sup>3</sup>.

The 2018 FIGO (International Federation of Obstetrics and Gynaecology) staging system has

incorporated lymph nodal involvement; hence, the importance of accurate lymph nodal assessment is compounded and has direct implications on the mode of management<sup>4</sup>. There is no universally accepted diagnostic modality for the detection of PALN metastases. Positron-emission tomography-contrast-enhanced computed tomography (PET-CECT) and surgical staging via open/laparoscopic approach have failed to show a significant survival advantage<sup>5,6</sup>. Similarly, prophylactic irradiation of non-enlarged para-aortic nodes has a doubtful survival benefit<sup>7</sup>.

So, purpose of this review is to present the recent evidence for diagnostic evaluation of PALN and alteration in treatment plan based on PALN involvement.

### Assessment of para-aortic lymph node (PALN)

Para-aortic (PA) lymph nodal involvement has been proven to be a detrimental factor in the overall survival of cervical cancer patients irrespective of primary tumour size<sup>8</sup>. Tumours larger than 3.5 cm, parametrial invasion, metastasized pelvic lymph node (LN) size >1 cm, multiple pelvic LN metastases and common iliac LN metastasis are independent predictors of PALN involvement<sup>3</sup>.

In early cervical cancer (stage IA1 with LVSI through IB2 and IIA1), surgical assessment of radiologically negative LNs is the standard recommendation. The recommendation for PALN dissection for staging purposes is category 2B because of the low risk of nodal disease in the absence of pelvic LN metastases<sup>9</sup>. The ESGO (European Society of Gynaecological Oncology) guideline recommends only pelvic LN dissection in early-stage disease<sup>10</sup>. Sentinel node dissection has been used in early-stage cervical cancer. The most common locations of sentinel nodes are below common iliac bifurcation<sup>11,12</sup>. Hence, it is not useful for the detection of PALN metastases.

Diagnostic assessment of PA nodal disease in LACC is commonly done, using various cross-sectional imaging such as CECT scan, contrast-enhanced magnetic resonance imaging (MRI) and PET-CECT with or without histopathologic proof<sup>4</sup>. CECT and MRI have the advantage of wide availability but have lower sensitivity and specificity compared to PET-CECT. Diffusion-weighted MRI has the highest sensitivity and PET-CECT has the highest specificity of all imaging modalities<sup>13</sup>. Maximum standardized uptake value (SUV Max) of the involved PALN is a significant factor in overall survival with higher SUV Max having detrimental outcomes<sup>14</sup>.

Radiological as well as nuclear imaging modalities have fallacies when differentiating between granulomatous, reactive and malignant nodes<sup>15</sup>. The role of PET-CECT is established but it has lower sensitivity in non-enlarged nodal disease compared to grossly enlarged nodes<sup>16</sup>. In the study by Guoy *et al*<sup>16</sup>, false-negative rates with PET-CT were 9-22 per cent; however, in half of these patients, nodal metastases were <5 mm in size and had no bearing on survival.

Surgico-pathological assessment provides the most precise information about the nodal disease. The safety and feasibility of surgical staging of para-aortic nodes and its accuracy compared to PET-CT is being studied in the PALDISC trial<sup>17</sup> (the results are not mature yet).

Gouy *et al*<sup>16</sup> reported false-negative rates ranging from 4-18 per cent of PET-CT compared to surgical staging. Histologic sample can be obtained with image-guided fine-needle aspiration cytology (FNAC)/biopsy or LN dissection via laparotomy or minimal access approach. Image-guided FNAC/ biopsy of para-aortic nodes is not always feasible because of difficulty in accessing the nodes, while surgical removal is associated with morbidity and might delay primary treatment.

In a large retrospective analysis by Vandepierre *et al*<sup>18</sup>, it was observed that approximately eight per cent of the patients were under-staged with respect to PALN if only radiological investigation was considered<sup>18</sup>. The prospective randomized Uterus-11 trial of imaging versus surgico-pathological staging reported pelvic and PALN metastases in 45 and 20 per cent of IIB patients and 71 and 37 per cent of IIIB patients, respectively. An upstaging of 33 per cent was observed with surgical staging, however, there was no statistically significant difference of overall survival between surgical staging for PALN versus clinico-radiological staging<sup>19</sup>. The matched pair analysis by Yang *et al*<sup>20</sup>, reported that approximately 30 per cent of the patients underwent modifications in the treatment protocol after surgical staging as compared to patients who underwent imaging for nodal burden. However, there was no difference in survival outcomes. A retrospective analysis of 74 patients by Gonzales-Benitez *et al*<sup>21</sup> with PALN metastases were compared for PFS and OS between radiological confirmation and surgical staging. It was observed that 44 per cent of the surgical group required EFRT (Extended Field Radiation Therapy) as compared to 19 per cent in the radiological group. However, there was no difference in two-year overall survival rates among the groups. De Cuyper *et al*<sup>22</sup> reported that 28 per cent of patients needed radiation field modifications after the surgical staging of PALN because of positivity.

Minimal access surgery for retroperitoneal LN dissection (RPLND) (laparoscopic/robotic) has a low surgical morbidity rate compared to laparotomy. Loverix *et al*<sup>23</sup> compared the perioperative morbidity of robotic versus laparoscopic approach in LACC and found that the perioperative morbidity was significantly lesser in the robotic approach; however, the outcomes were similar in both approaches<sup>23</sup>.

The LN ratio is an important prognostic factor in predicting the outcomes of cervical cancer, with patients with higher ratios having poor outcomes<sup>24</sup>.

The number of LNs dissected is crucial to interpret the LN ratio. Bogani *et al*<sup>25</sup> reported the outcomes of stage IIICp patients who underwent lymphadenectomy and concluded that the number of positive LNs is correlated with poorer survival and the need for aggressive management.

The extent of PALN dissection has also been debated due to associated morbidity. Leblanc *et al*<sup>26</sup> reported that the rate of skip metastases was low, and a systematic dissection above the inferior mesenteric artery (IMA) was not warranted. It was concluded from this study that dissection below IMA is sufficient in patients with a high risk of PALN dissemination but with no macroscopic PALN identified on imaging<sup>26</sup>. Locally advanced cervical cancer being more common in low and low-middle-income countries, the cost-effectiveness of an extensive approach should also be considered. Lee *et al*<sup>27</sup> in their study have reported that it is cost-effective to tailor treatment depending on PALN positivity based on PET-CT and surgical staging. The randomized Phase III LiLACS trial<sup>28</sup> aimed to study prophylactic PALN dissection in patients with PET-positive pelvic LNs. The trial was however, stopped due to slow accrual; however, results from already accrued patients may clarify the role of prophylactic treatment of PA nodes in patients at high risk of subclinical involvement<sup>28</sup>.

The NCCN guidelines version 1.2021 recommends staging of para-aortic nodes with PET-CECT in stages IB1 and beyond and surgical staging is a category 2B recommendation, even in LACC. The recommended level of para-aortic lymphadenectomy for staging purposes is up to the IMA according to both ESGO and NCCN guidelines<sup>9,29</sup>.

### Selection of treatment modality

The decision of EFRT in LACC depends on, (i) the involvement of PALN after exclusion of distant metastases or; (ii) the prophylactic setting in the presence of heavy pelvic nodal burden/involvement of common iliac LN.

In the first setting, EFRT is mandatory and has undergone various changes in the techniques in the past two decades. GOG 125 trial<sup>30</sup> reported three-year progression free interval (PFI) and overall survival (OS) of 34 and 39 per cent, respectively, after EFRT with concurrent chemotherapy (45Gy to PALN)<sup>30</sup>. It is important to note that this trial used pathological confirmation for PALN. Approximately 11 per cent of the patients did not complete treatment. The RTOG 0116 trial reported significantly higher grade 3-4 acute

and late gastrointestinal and haematological toxicities with EFRT and concurrent chemotherapy. This may be attributed to the conventional techniques used and the booster doses of up to 60 Gy<sup>31</sup>.

Intensity-modulated radiotherapy (IMRT) improves the therapeutic ratio with independence to escalate dose and give additional booster doses to bulky nodes<sup>32</sup>. Dose escalation of up to 62.5 Gy with simultaneous integrated boost (SIB) has been attempted with acceptable toxicity profiles. However, the EMBRACE group<sup>33</sup> restricted the booster doses to <60 Gy, as long-term outcomes are still awaited. The use of IMRT after surgical staging has been investigated by Marnitz *et al*<sup>34</sup> and reported five-year disease-free survival (DFS) and OS of 34 and 54 per cent, respectively. Chantalat *et al*<sup>35</sup> reported the outcomes of patients who received EFRT after pathological confirmation. It was observed that 25 per cent of the patients had PALN failure. This could be due to the low dose prescription of 45 Gy. Metastatic para-aortic nodes are best treated with IMRT up to doses 45-50.4 Gy and an additional 5-10 Gy simultaneous or sequential boost<sup>36</sup>.

The size of a metastatic LN is another important prognostic factor. Gouy *et al*<sup>16</sup> in their report identified a subset of patients with PALN of size <5 mm (after para-aortic lymphadenectomy). Their outcomes were similar to patients with a pelvic confined disease with CTRT (Cardiotoxicity of Radiation Therapy). It has been reported that lymph nodal size >1 cm irrespective of the station (pelvic or PA region) have higher rates of in-field failures as compared to LN of <1 cm<sup>33</sup>. These patients may be given the option of surgical debulking or IMRT with nodal boost.

In the prophylactic setting, the role of prophylactic EFRT in improving overall survival is not proven yet. The EMBRACE group reported that the most common site of failure in pelvic LN-positive patients was in the PA region<sup>33</sup>. Prophylactic EFRT with concurrent chemotherapy has the potential to reduce PALN failure in patients with common iliac node metastases<sup>36</sup>. The identification of high-risk groups is essential before considering prophylactic EFRT for all because of associated long-term morbidity, which is not justifiable in the absence of survival benefit.

Phase I and II studies have evaluated the safety and feasibility of adjuvant systemic chemotherapy in this group of patients<sup>37</sup>. At present, there is no concrete evidence to support its role in improving survival.

### Future directions

PA nodal metastasis is a strong predictor of poor prognosis. The incorporation of nodal involvement in the FIGO 2018 staging for cervical cancer has brought the need to address PA nodes into a new light. The standardization of surgical technique, route and the extent of LN dissection depends on LN burden. The number of involved nodes, size of the node, as well as stratification based on micro ( $\leq 2$  mm) and macro-metastases ( $>2$  mm) may significantly affect survival. It would be worthwhile to standardize reporting of these parameters in dissected specimens.

In addition, an effort must be made to standardize the dose used for EFRT in patients with proven PALNs. Radiotherapy dose boost to the involved nodes may be given in two ways- either sequentially at the end of standard EBRT (External Beam Radiation Therapy) or as a SIB, with pros and cons associated with each approach. A sequential boost will prolong the overall treatment time, which is a well-established predictor of inferior survival in cervical cancer. The use of SIB has the potential to cause greater normal tissue toxicity due to the associated higher dose per fraction and possibility of inclusion of normal tissue (especially small bowel) within the treatment volume, as nodal regression occurs during RT. Hence, it is worthwhile to investigate the outcomes and toxicities of either approach.

The use of adjuvant chemotherapy in cervical cancer is still under investigation. The OUTBACK trial<sup>38</sup> excluded patients with PA nodal involvement. Adjuvant chemotherapy in patients with PA lymphadenopathy has the potential to address distant metastases, improve overall survival and needs to be studied in a randomized setting.

The incidence of isolated PA nodal recurrences is 2-12 per cent, in radically treated cases of cervical cancer<sup>39</sup>. Treatment options mainly include irradiating the PA chain to 45-50 Gy with or without a boost to the node or treatment of the gross node alone with stereotactic body radiation therapy (SBRT)<sup>40</sup>. Surgery may also be an option for those with previous irradiation to the PA region. Treatment of such patients could be an area of future investigation.

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