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The role of para-aortic nodal irradiation in cervical cancer

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ABSTRACT

The current standard of care for locally advanced cervical cancer is whole pelvis and para-aortic radiation when indicated, delivered concomitantly with chemotherapy and brachytherapy. Para-aortic node involvement is a predictor of survival in locally advanced disease but presence of metastases is difficult to determine because the currently available imaging methods lack enough sensitivity to be able to detect accurately para-aortic metastases when surgical staging is not feasible. The objective of this review is to describe the current status of para-aortic lymph node irradiation in locally advanced cervical cancer. It includes analysis of the diagnostic imaging and surgical approaches for assessment of para-aortic lymph node dissemination, together with indications for radiotherapy and radiotherapeutic techniques.

1. Background

External beam radiotherapy (EBRT) and/or brachytherapy are the two radiation modalities for the treatment of cervical cancer and, combined with chemotherapy, remain the main treatment with curative intent in locally advanced disease. The Fédération Internationale de Gynecologie Obstetrique (FIGO)[1] considers cervical cancer to be locally advanced when a tumour is more than 4 cm in diameter (FIGO stage IB2); when the tumour grows into tissues adjacent to the cervix and uterus (FIGO stage IIB); is present in the lower third of the vagina (FIGO stage IIIA); extends to the pelvic walls or lymph nodes (FIGO stage IIIB) or into the bladder, rectum or outside the pelvis (FIGO stage IVA). Radical hysterectomy is technically challenging once pelvic tissues are affected and therefore not indicated in a locally advanced disease.

The lymphatic system drains in from the cervix towards the pelvic, para-aortic and supraclavicular nodes.[2,3] Para-aortic lymph node involvement has been associated with locally advanced disease and is a prognostic factor for survival.[4] Locally advanced cervical cancers are highly aggressive, with higher rates of metastasis and worse survival outcomes than an organ-confined disease.[4] However, para-aortic lymph node

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involvement is often difficult to confirm because imaging is inconclusive and surgical visual confirmation not feasible.[5] The reported incidence of para-aortic lymph node metastases ranges from 17% to 37% of cases.[6]

Numerous studies[7–11] have shown that concomitant platinum-based chemoradiotherapy significantly improves both overall survival and progression-free survival, represents a major advance in the treatment of locally advanced cervical cancer and continues to be the preferred treatment option.

Extended-field radiation therapy (EFRT), to the level of the renal vessels (or even more cephalad based on involved nodal distribution),[12] is used both prophylactically and therapeutically – depending on the extent of regional pelvic and para-aortic lymph node involvement. The value of combining chemotherapy with EFRT has only been demonstrated in patients with positive para-aortic nodes, whereas prophylactic irradiation of the para-aortic nodes has not been proven to have any significant benefit in patients with locally advanced disease, especially those treated with chemoradiotherapy.[13,14]

The objective of this review is to describe the current status of para-aortic lymph node irradiation in locally advanced cervical cancer. It includes analysis of the diagnostic imaging and surgical approaches for assessment of para-aortic lymph node dissemination, together with indications for radiotherapy and radiotherapeutic techniques.

2. Diagnostic imaging modalities

The FIGO cancer staging system[1] takes into consideration the following parameters: tumour diameter, parametrial invasion, vaginal extension, infiltration of the bladder and rectal mucosa, hydroureter, hydronephrosis, and metastasis. The size of the primary tumour, the extension to parametria or vagina and inguinal lymph nodes can be assessed clinically by physical examination but imaging studies are required to detect metastasis or invasion of the ureter. Pelvic magnetic resonance imaging (MRI) is mandatory for assessment of pelvic tumour extension and to guide management.[15]

The presence of positive para-aortic lymph nodes is a key predictor of survival. However, none of the currently available imaging modalities has proven sufficiently sensitive to detect para-aortic metastases in patients with locally advanced cancer. The para-aortic lymph nodes must always be assessed in locally advanced cervical cancer in patients presenting with positive pelvic nodes, tumour >2 cm, or metastatic lesions in the common iliac nodes. The imaging modalities for this purpose include ultrasound (US), computed tomography (CT), MRI and positron emission tomography-computed tomography (PET-CT).[16,17]

3. Ultrasound

Ultrasound offers many advantages. It is inexpensive, widely available, and does not cause discomfort to the patient. Moreover, ultrasound allows physicians to determine the size and location of the tumour in the cervix, visualise the cervical topography, and identify the presence of parametrial involvement.[16,18,19] However, ultrasound is not considered an appropriate method for assessing the extent of cervical cancer by the American College of Radiology; on a rating scale from 1 to 9 for evaluating the appropriateness of different imaging techniques when assessing cervical cancer, the American College of Radiology assigned a score of 2 to transvaginal ultrasound.[20]

4. Computed tomography

Computed tomography is routinely performed for staging purposes and to evaluate lymph node features. A pelvic node with an axis >8 mm is considered enlarged and potentially metastatic. Para-aortic nodes are considered enlarged if the short axis measures >10 mm, with a sensitivity and specificity of 80% and 92%, respectively.[16] In the study by Liu et al.,[21] the diagnostic performance of CT showed 90% specificity and sensitivity was lower than 60%. Results by Vandeperre et al.[22] from the University Hospitals of Leuven show that 82.6% of involved para-aortic nodes are left-sided, and only 3.9% of para-aortic metastases are not associated with pelvic disease, a finding consistent with previous results.

5. Magnetic resonance imaging

Magnetic resonance imaging uses strong magnets with phased array coils to obtain high contrast resolution images of tissues.[17,23] In particular, the finer soft tissue detail rendered by MRI allows better risk evaluation for the irreversible ureteral stenosis, or vesico-vaginal, recto-vaginal or utero-enteral fistulae that may develop following chemoradiation. Moreover, the ability to detect lymph node morphological features, such as rounded shape, inhomogeneous signal intensity, and spiculated margins increases the sensitivity of MRI in recognising metastases.[23] Laifer-Narin et al.[24] reported that MRI demonstrated greater than 90% specificity with less than 60% sensitivity in the detection of lymph node metastasis. The main imaging criterion used to identify abnormal lymph nodes was a short-axis diameter greater than 1 cm. Additional imaging features suggesting nodal metastasis include a rounded shape, irregular margins, clusters of multiple small lymph nodes, signal intensity similar to the primary tumour, and necrosis.

6. Positron emission tomography with CT

In locally advanced cervical cancer or in early-stage disease with suspicious lymph nodes on conventional imaging, PET-CT or chest/abdomen CT are recommended for assessment of nodal and distant disease. PET-CT is superior to both CT and MRI in detecting lymph node metastases. The National Cancer Comprehensive Network (NCCN) Cervical Cancer guideline[12] recommends PET-CT for assessment of lymph-node involvement and distant metastases in locally advanced cervical cancer before chemoradiation therapy. PET-CT is also useful to optimise radiotherapy treatment planning. Despite the better accuracy of PET-CT versus CT alone, up to 32% of patients with confirmed nodal invasion will be classified as negative on PET-CT.[25] The overall sensitivity of PET-CT in

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detecting metastatic disease is 36%, the overall false-negative rate of para-aortic node involvement is around 12%, mainly attributable to small non-detectable nodes (i.e. when lymph nodes measure <5 mm). When considering patients with positive pelvic node uptake, the rate of false-negative para-aortic involvement is 22%. However, up to 12% of cases may present para-aortic metastases, even when the PET-CT is negative mainly due to a failure in detection of micrometastases.[26] Guoy et al.[27] showed 85% sensitivity for para-aortic node metastasis with a specificity of 95%.

PET-CT results were verified surgically by laparoscopic extraperitoneal para-aortic lymphadenectomy in a study by Atri et al. where the authors found that PET-CT had a sensitivity of 91.2%.[28] The use of PET-CT to guide treatment was shown to contribute to improved overall survival together with other factors such as age, FIGO stage, histopathology, performance status, body mass index, and concomitant platinum-based chemotherapy in univariate and multivariate analyses in a study by Hansen et al.[26]

Although PET-CT is generally considered superior to CT and MRI in detecting lymph-node metastases, it is still inferior to surgical staging regardless of the stage of cervical cancer. In stage III disease, para-aortic lymph node staging using PET-CT is an alternative to surgery.[29]

Radiation therapy planning can be optimised with fluorodeoxyglucose (FDG) PET-CT imaging by extending the radiation target volume to encompass the para-aortic area, or by modifying the dose to the involved lymph nodes.[30] Pomel et al. recently compared survival outcomes of patients with laparoscopic surgical para-aortic lymphadenectomy and PET-CT. The retrospective analysis showed that overall survival (OS) and disease-free survival (DFS) were improved in patients staged with PET-CT compared to those staged by surgery in both univariate and multivariate analysis.[31]

7. Surgical staging

Surgical staging can be beneficial for detection of occult para-aortic metastases in patients with negative PET-CT. It may also have an impact on the decision between prophylactic or therapeutic radiation in patients with para-aortic lymph nodes <5 mm.[32]

Dissection at least to the level of the inferior mesenteric artery may be considered prior to chemoradiotherapy and/or brachytherapy. Quality of surgery, both parametrectomy and lymph node dissection, is, however, of key importance in the management of large (>4 cm) tumours. Intraoperative assessment of lymph node status (frozen section) is recommended as the first step. If lymph node involvement is detected intraoperatively, including macro- or micro-metastases, further pelvic lymph node dissection and radical hysterectomy should be avoided and patients offered definitive chemoradiotherapy and/or brachytherapy.[33]

If intraoperative lymph node assessment is negative or is not done, systematic pelvic lymph node dissection should be performed and a type C2 radical hysterectomy recommended.

Para-aortic lymphadenectomy is defined by the removal of nodes located in the common iliac nodes up to the left renal vein. There is ongoing debate among surgeons as to whether the removal of nodes should be limited to the inframesenteric artery, to the right gonadal vein, or to the left renal vein. Given the very low rate of skipped metastases above the inferior mesenteric artery, ilio-inframesenteric dissection should be an acceptable pattern of para-aortic lymph node dissection including the removal of all lateroaortic, preaortic, interaortocaval, precaval, and laterocaval nodes as in cervical cancer, nodal metastases spread via the lymphogenous route in an orderly fashion.[34]

Vandeperre et al. found that up to 8% of patients with negative imaging tests were positive on surgical evaluation and that overall survival was significantly reduced in patients with metastatic para-aortic lymph nodes diagnosed with surgery or imaging.[22]

8. External beam radiotherapy

Irradiation of the aortic lymph nodes, known as extended fields, is typically indicated in two distinct clinical scenarios. As prophylaxis when nodal disease is not detected, by imaging studies or lymph node sampling, or as therapeutic when in the presence of risk factors such as lymphovascular invasion or positive pelvic nodes.[35] Regardless of whether the treatment plan is prophylactic or therapeutic, techniques for extension into the para-aortic fields include the anteroposterior–posteroanterior (AP–PA) fields, or a box technique with 4 fields, or intensity modulated radiotherapy (IMRT).

The concept of extended field para-aortic irradiation was first defined in the 1980s based on the RTOG 7920 protocol.[36] The classical limits were determined according to boney reference points, with the upper limit located in the space between T11–T12 or T12–L1 and the lower limit at L4–L5 and 1.5–2 cm to each side of the vertebral body. The para-aortic and pelvic regions were irradiated together under that protocol.

Semi-extended field radiation therapy refers to the inclusion of the macroscopic tumour, uterus, parametrium, upper third of the vagina, pelvic nodes (external and common internal iliac), and excludes the upper third of the para-aortic lymph nodes at the level of the renal vessels, with the corresponding margin.[37] Notably, the site at which the renal vessels emerge ranges from T12 to L2.[38]

Recently published guidelines for contouring the para-aortic region describe delineation of the clinical target volume (CTV) for para-aortic lymph nodes.[36,38,39] The inferior vena cava and aorta should be contoured from the level of the left renal vein to the bifurcation of the aorta. The CTV should extend 10 mm circumferentially and 15 mm laterally from the aorta and 8 mm anteromedially and 6 mm postero-laterally from the inferior vena cava. The CTV should be cropped to avoid the vertebral body, muscle and bowel and extended the posterior border to the anterior vertebral body and exclude the RPC region above the L1–L2 interspace. Exclusion of the upper para-aortic region (T12 to L1–L2 interspace) should be considered in node negative patients or where normal tissue toxicity is a concern. The space around the aorta and the medial portion of the inferior vena cava with a margin of 7 mm should be included as the aortocaval and left para-aortic spaces are the areas of greatest risk for nodal disease at this level.

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Intensity modulated radiotherapy significantly reduces the dose to the organs at risk (gastrointestinal, genitourinary, and hematologic) compared to conformal radiotherapy, thus allowing for better and safer management of nodal disease.[40,41]

Renald-Oldrini et al.[42] performed a dosimetric comparison for the para-aortic and pelvic nodes between volumetric modulated arc therapy (VMAT), an advanced form of IMRT that delivers a precisely sculpted 3D dose distribution with a 360° rotation of the gantry in a single- or multi-arc treatment, and tomotherapy, a form of CT-guided IMRT where radiation is delivered slice-by-slice. Tomotherapy delivered lower doses to the kidneys, an important advantage for patients who receive nephrotoxic drugs.

A retrospective analysis conducted at four institutions in France with median follow-up of 15 months evaluated extended-field helical irradiation in locally advanced cervical cancer.[43] The study found low rates of acute genitourinary and gastrointestinal toxicity, short-term outcomes in terms of pelvic and para-aortic control and survival were similar to those achieved with conformal techniques.

In cases with enlarged para-aortic nodes or positive PET-CT, the prescription dose to the para-aortic nodes ranges from 45 to 50.4 Gy. If feasible, an additional 5–10 Gy sequential boost to the lymph nodes is recommended. IMRT is preferable in this scenario to spare normal tissues, since the use of IMRT to treat the para-aortic nodes is associated with low rates of gastrointestinal toxicities and no duodenal-specific toxicity, even in patients receiving concurrent chemotherapy and dose escalation to 65 Gy or more. Dose escalation to the para-aortic nodes has only become possible in recent years with the development of IMRT and provides excellent disease control, with one study reporting nodal disease control rate of 85% at 2 years post-IMRT with a median dose of 63 Gy.[44]

Wakatsuki et al.[45] observed an association between node disease recurrence to radiation dose and to node size after irradiation. In a retrospective analysis 245 patients were treated with external beam radiotherapy with or without a boost plus high-dose rate brachytherapy. The authors found a significant correlation between node size after delivery of 50 Gy and the control rate of metastatic nodes (<10 mm: 96.7%, ≥10 mm: 75.7%; $p < 0.001$), with no nodal recurrence if nodes received >58 Gy ($p = 0.001$).

More recently, the use of IMRT with simultaneous integrated boost (SIB) combined with platinum-based chemotherapy reported 77% complete clinical and imaging response with acceptable toxicity.[46] The use of SIB in the treatment of nodal disease allows for a small but considerable dose reduction (3.8–4.4%) to the organs at risk, which results in a comparable biological dose despite the higher dose fractions delivered by the boost. Furthermore, SIB-IMRT reduces overall treatment time and simplifies the planning process.[47]

Cibula et al. state that three-dimensional (3D) conformal radiotherapy alone or as definitive para-aortic chemoradiotherapy (platinum based) and/or 2D radiography based brachytherapy is recommended if IMRT and/or imaging guided adaptive brachytherapy (IGABT) are not available. The overall treatment time when using 3D conformal radiotherapy and/or 2D radiography based brachytherapy should be respected. A sequential lymph node boost is applied as appropriate after completion of 3D EBRT.[15]

9. Results and toxicity

The risk of any grade (G1–G4) late toxicity at 3 years is 58% with the use of chemotherapy according to Yap et al.[48] Grade 3 toxicity was described in 16% of cases for pelvic EBRT and chemo and in 49% if EFRT was delivered. Hematologic G3 toxicity can reach 76% when para-aortic lymph nodes are included in the treatment fields. Indeed, an important limitation to the use of EFRT is toxicity, especially when it is administered postoperatively or concomitant with chemotherapy.

The use of EFRT is controversial because the available evidence comes mostly from retrospective studies performed in heterogeneous populations using different diagnostic techniques. For example, in some studies the diagnosis was made by laparoscopy whereas others have used imaging methods, such as CT, MRI, or PET-CT with different sensitivities and specificities. For these reasons, it is difficult to objectively assess EFRT. However, Sapienza et al.[49] conducted a meta-analysis to evaluate studies that prophylactically irradiated the para-aortic nodes to eliminate microscopic disease and thus reduce the risk of distant metastasis. The meta-analysis focused on phase III studies carried out in patients who received the same systemic treatment. A total of 1000 patients were included; of these, 506 received pelvic radiotherapy while 494 underwent EFRT. Most of the EFRT patients (87.5%) received prophylactic radiotherapy; aortic imaging studies were not performed in 12.5% of patients. The review reported that para-aortic lymph node treatment failure was lower in the EFRT group compared to the group that received pelvic radiotherapy alone (HR 0.35, 95% CI 0.19–0.64; $p < 0.01$). The incidence of distant metastases was also lower (HR 0.69, 95% CI 0.50–0.96; $p = 0.03$). Both arms received the same treatment to the pelvis without a significant difference in locoregional failure (OR 1.06, 95% CI 0.80–1.42; $p = 0.67$) although there was a trend towards lower mortality in the EFRT group (OR 0.68, 95% CI 0.45–1.01; $p = 0.06$). However, it is worth noting that only two studies reported treatment-related deaths. The authors concluded that prophylactic EFRT decreased systemic failure, but that new studies were needed to examine other chemotherapy regimens and more modern radiotherapy techniques.

Chantalat et al.[6] retrospectively evaluated 155 patients with para-aortic involvement confirmed by pathological examination. Patients received platinum-based chemoradiotherapy at a dose of 45 Gy delivered in 5 weeks followed by intracavitary brachytherapy. Imaging studies were performed at 6 weeks post-treatment. Relapses were observed in 45% of patients. Para-aortic, loco-regional and distant relapses were detected in 25%, 51% and 54%, respectively. Nearly one in ten patients (9.6%) presented an isolated recurrence in the para-aortic region. At 4 years, overall survival was 32.7% and DFS 28.8%. The prognosis of patients with lesions <5 mm was better than those with larger lesions, leading the authors to conclude that clinical stage was the most important prognostic factor.

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Asiri et al.[50] evaluated 102 stage IIB-IVA patients with negative imaging studies, but positive pathological reports, who were treated with EFRT. Patients were randomised to receive either extended field chemoradiotherapy ($n=52$) or pelvic chemoradiotherapy ($n=50$), followed by brachytherapy. At a median follow-up of 60 months, 74 patients had completed the treatment protocol. Outcomes in the two groups (extended field versus pelvic radiotherapy) were, respectively: negative para-aortic nodes: 97% vs. 82%; distant metastasis control: 86.9% vs. 74.7%; DFS: 80.3 vs. 69%; overall survival: 60.4% vs. 60.4%. Grade 3/4 acute toxicity included neutropenia (2.6% in the EFRT group vs. 2.7%), grade 3 diarrhoea (2.6% in the EFRT group), and grade 3 cystitis (2.7% in the pelvic radiotherapy group). Late toxicity in the whole sample included intestinal obstruction (2.6%) and chemotherapy-related hypoacusis (2.8%).

Yap et al.[48] evaluated the benefit of elective para-aortic lymph node irradiation in patients with no clinical or radiographic evidence of para-aortic involvement. A total of 228 patients were included; of these, 73 received EFRT and 155 pelvic radiotherapy. Both groups received conventional chemotherapy. Mean follow up was 4.6 years. The primary outcome DFS at 3 years was 49% and 73% in the EFRT and pelvic radiotherapy groups, respectively, with local relapse rates of 31.9% and 17.7%, respectively. Both outcomes were associated with tumour size. The 3 year distant relapse rate was higher in patients receiving EFRT (30.6% vs. 13.5%). Overall grade 3/4 toxicity in the EFRT group at 3 years was 11% (proctitis 3%, urinary urgency 4%, and 1% each for fistula, colitis, and neuropathy). Overall G3-4 toxicity in the pelvic RT group was 8%, including proctitis (4%) and cystitis (3%). These results suggested that EFRT provides no additional benefit.

A review conducted by Hwang et al.[16] concluded that prophylactic EFRT might be useful in stage IB to IVA cervical cancer patients with small (<5 mm) PET-CT negative para-aortic metastases confirmed with laparoscopic lymphadenectomy. According to the authors, the available evidence suggested that administering EFRT decreased the risk of para-aortic recurrence at 8 years from 9% to 4%. Gouy et al.[51] showed disease-free survival in patients with locally advanced cervical cancer with low-volume (<5 mm) para-aortic node disease treated with EFRT chemoradiotherapy, and who were misdiagnosed on PET-CT, was similar to patients without para-aortic node spread and managed with pelvic chemoradiotherapy alone. Conversely, in patients with para-aortic node metastasis exceeding 5 mm, additional treatment modalities should be explored because the survival rate in these patients is poor.

Jung et al.[52] evaluated a group of 45 patients who received 46 Gy radiotherapy to the pelvic and para-aortic regions and 14 Gy-boost to gross nodes, and 30 Gy in six fractions of intracavitary brachytherapy. Overall, 9% of patients developed gastrointestinal toxicity and 2% urinary toxicity. Approximately 80% of patients developed G3 haematological toxicity, but no bone marrow protection was performed in that study.

Toxicity, therefore, varies from study to study and appears to depend largely on technique and dose.

10. Discussion

Metastatic involvement of the para-aortic lymph nodes is a marker of poor prognosis in patients with cervical cancer. However, at present, para-aortic nodal status is not considered in the FIGO staging system. Targeted radiotherapy to these nodes is required together with chemotherapy to improve disease control.[16] In patients with locally advanced cervical cancer at high risk of occult para-aortic metastases, prophylactic irradiation of the para-aortic lymph nodes seems to offer little benefit when administered concomitantly with platinum-based chemotherapy. Rates of local and distant relapse remain high in these patients. The value of para-aortic radiotherapy is also minimal in patients with extensive uncontrolled pelvic disease or distant metastases.[49]

11. Future perspectives

The development of new, more accurate radiotherapy techniques, together with dose escalation and daily soft tissue imaging have led to a decrease in the exposure of healthy organs to radiation. It is clear that better systemic treatments are needed for patients with cervical cancer. Fortunately, new approaches that combine radiotherapy and chemotherapy with modern molecular therapies are emerging.[53] These targeted molecular therapies can treat resistant cell signalling pathways that are likely to cause distant relapses. Another approach involves neoadjuvant chemotherapy followed by radiotherapy in patients with bulky para-aortic nodes who are unlikely to respond to extended field radiation. Anti-angiogenics is another new approach that may provide some benefit in these patients. Stereotactic techniques should be explored to administer limited, focal radiation in association with aggressive immunotherapy or chemotherapy; such an approach could be valuable because it would allow for a shorter course of radiation with fewer adverse effects by protecting the bone marrow and allowing for more intensive chemotherapy. Finally, therapeutic vaccines are being developed that may be useful in locally advanced cervical cancer with para-aortic lymph node involvement.[15,54]

Conflict of interest

None declared.

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