Original Article

# Fluorodeoxyglucose positron emission tomography–computed tomography in evaluation of pelvic and para-aortic nodal involvement in early stage and operable cervical cancer: Comparison with surgicopathological findings

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ABSTRACT

**Introduction:** Nodal metastases in cervical cancer have prognostic implications. Imaging is used as an adjunct to clinical staging for evaluation of nodal metastases. Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has an advantage of superior resolution of its CT component and detecting nodal disease based on increased glycolytic activity rather than node size. But there are limited studies describing its limitations in early stage cervical cancers. **Objective:** We have done meta-analysis with an objective to evaluate the efficacy of FDG PET/CT and its current clinical role in early stage and operable cervical cancer. **Materials and Methods:** Studies in which FDG PET/CT was performed before surgery in patients with early stage cervical cancers were included for analysis. PET findings were confirmed with histopathological diagnosis rather than clinical follow-up. FDG PET/CT showed lower sensitivity and clinically unacceptable negative predictive value in detecting nodal metastases in early stage cervical cancer and therefore, can not replace surgicopathological staging. False negative results in presence of microscopic disease and sub-centimeter diseased nodes are still the area of concern for metabolic imaging. However, these studies are single institutional and performed in a small group of patients. There is enough available evidence of clinical utility of FDG PET/CT in locally advanced cervical cancer. But these results can not be extrapolated for early stage disease. **Conclusion:** The current data suggest that FDG PET/CT is suboptimal in nodal staging in early stage cervical cancer.

**Keywords:** Early stage cervical cancer, fluorodeoxyglucose positron emission tomography–computed tomography, operable carcinoma cervix, preoperative, surgicopathological

## INTRODUCTION

Cancer of the uterine cervix is the commonest malignancy affecting women in developing countries, including India and its incidence is second to the breast cancer globally accounting for 15% of all new female cancers.[1] Mortality related to the cervical cancer has shown a decline worldwide due to its early detection and treatment of early stage (localized) disease. Therapeutic strategies entirely depend on the clinical stage of the disease. Radical hysterectomy (RH) and pelvic lymphadenectomy is widely used curative surgery for early stage (stage I to IIA) cervical cancer as well as for stage IIB disease in some Asian and European countries.[2] Cervical cancer is staged clinically as per the International Federation of Gynecology and Obstetrics (FIGO) staging system. FIGO system is widely used and acceptable clinical staging in spite of its inherent limitation of underestimation of disease and inability to assess the metastatic involvement of pelvic and para-aortic nodes.[3,4] The frequency of pelvic and para-aortic node metastases increases incrementally with FIGO stage. Lymph node metastases are seen in 12-22% in stage IB, 10-27% in stage IIA and 34-43% in stage II B of cervical cancer.[2] As per historic series based on surgicopathological examination,

Access this article online

Quick Response Code:

Website: www.ijnm.in

DOI: 10.4103/0972-3919.106699

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pelvic and para-aortic nodes may be involved in 12-62% of patients with early stage cervical cancer and regarded as the single most important prognostic determinant. Patients with pelvic and para-aortic nodes metastases have high rate of disease recurrence and poor progression free survival.[5] Therefore, assessment of nodal metastases in the cervical cancer becomes clinically relevant, even if it is not part of routine FIGO staging.

Lymph nodal assessment can be done noninvasively with morphological imaging modalities like contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI). MRI is preferred over CECT for initial staging workup as it accurately evaluates local disease (T stage), involvement of neighboring structures and nodes (N stage). Both CECT and MRI rely on size criteria and have shown modest sensitivity in predicting nodal metastases in the cervical cancer. A node to be regarded/interpreted as pathological/metastatic on CT/MRI, should have dimension of >1 cm in short-axis. Therefore, sub-centimeter to centimeter sized visualized nodes on CT/MRI are not considered metastatic in accordance with size criteria; even though they may or later pathologically proven to harbor micro-metastases (disease *per se*). In this situation, fluorodeoxyglucose (FDG) PET scan is advantageous, as it relies on metabolic criteria rather than the size of a node. Proliferating malignant cells within the metastatic node demonstrate high glycolytic activity and therefore, show focally increased uptake of 18-Fluorine labeled glucose analogue (FDG) on PET scan. PET scan is highly sensitive modality in detecting hypermetabolic foci (positive nodes) in pelvic and para-aortic regions without providing their exact anatomical details.[6,7]

There are many studies published describing FDG PET as an effective imaging technique for nodal staging in the cervical cancer. For diagnosis of para-aortic metastases, sensitivities and specificities of FDG PET have been reported to be between 75-86% and 92-97%, respectively. For diagnosis of pelvic nodal metastases, sensitivity ranges from 80% to 100% and specificity from 92% to 100%.[8] Havrilesky *et al.*,[9] in their meta-analysis incorporating 15 studies on cervical cancer have reported higher pooled sensitivity of PET scan (79%) in comparison to MRI (72%) and CT (47%) in detecting pelvic nodes.

However, there are apparent inconsistencies in these studies inform of patient selection criteria. Majority of these studies have used PET scanners (not PET–CT) and included either patients with locally advanced cervical cancer (stage II to IVA) or heterogeneous patient population incorporating both endometrial and cervical cancers and both recurrent and newly diagnosed cervical cancer.[8] Results of these studies cannot be extrapolated in practice in patients with early stage cervical cancer. There are only few studies published, which have focused on potential clinical utility of FDG PET–CT in early and operable cervical cancer.

### Objective

Advent of dedicated hybrid PET–CT scanners have taken care of the above mentioned limitations of both morphological imaging (size criteria) and metabolic imaging (lack of anatomical information). We have done a meta-analysis of published studies in literature with the objective (1) to evaluate the diagnostic accuracy and explore the current role of FDG PET/CT in detection of nodal metastases in early stage or operable cervical cancer (2) whether FDG PET/CT as pre-operative imaging can obviate or safely replace surgical nodal staging?.

## MATERIALS AND METHODS

We screened MEDLINE (PubMed) database in December 2011 using keywords relevant to the cervical cancer like FDG PET/CT, nodal staging, pre-operative evaluation, early stage cervical cancer. We selected only those published studies from peer reviewed literature, which fulfilled preset strict inclusion criteria of our study (1) Early stage or operable cervical cancer (below stage IIB, Few European countries consider even stage IIB as operable). (2) FDG PET/CT was performed in pre-operative setting. Studies where only PET scanner used (not integrated PET/CT) were excluded. (3) Underwent RH with pelvic and/or para-aortic nodal dissection. (4) Histopathological confirmation of nodal involvement was available, which fulfilled preset strict inclusion criteria of our study.

## RESULTS

There were only six published studies, which could fulfill the criteria for analysis [Table 1]. Sironi *et al.*, performed FDG PET/CT in consecutive 47 patients with FIGO stage IA or IB before RH and pelvic lymph node dissection. Fifteen of their 47 patients (32%) showed nodal metastases on histopathological examination. These authors analyzed patient based sensitivity, specificity, negative predictive value (NPV) and accuracy of FDG PET/CT to be 73%, 97%, 89%, and 89%, respectively.[10] PET/CT showed lower sensitivity (32%) as per Mauro *et al.*,[11] in their study incorporating 159 patients with stage IB1to IIA cervical cancer. Chung *et al.*,[12] also found similar sensitivity (36%) of FDG PET/CT in their series of 34 patients with stage IA2 to IIB. Jacob *et al.*, performed FDG PET/CT pre-operatively in 80 patients with operable cervical cancer (early stage) and diagnosed nodal metastases in 14 of 24 histopathologically proven cases (sensitivity 58%). They could optimally select their patients for surgery based on FDG PET/CT finding and could significantly reduce significant proportion of patients for multimodality treatment (from 30% to 12.5%, $P < 0.01$) associated with its morbidity.[13] Bentivegna *et al.*,[14] missed pelvic and para-aortic nodes in 4 of 16 patients (25%) with cervical cancer stage IB1 evaluated with FDG PET/CT. Sensitivity in this group could not be calculated technically as FDG PET scan was not positive in any of the patients. Boughanim *et al.* performed para-aortic lymphadenectomy in their 38 patients with negative pre-operative MRI and FDG PET/CT. FDG PET/CT found to be false negative in 3 of 38 patients (8%) in histopathologically proven para-aortic node metastases (NPV 92%).[15]

**Table 1: Positron emission tomography–computed tomography studies included in meta-analysis (*n*=6)**

| Author | No. of patients (*n*) | Stage of cervical cancer | Surgery | Diagnostic efficacy (%) |
|---|---|---|---|---|
| Sandro *et al.,* Radiology, 2006 | 47 | IA or IB | RH with pelvic lymphadenectomy | Sensitivity – 73<br>Specificity – 92<br>NPV – 89 |
| Mauro *et al*., Gyenecologic Oncology, 2011 | 159 | IB1-IIA | RH with pelvic lymphadenectomy | Sensitivity – 32<br>Specificity – 96.9<br>NPV – 87 |
| Chung *et al*., Gynecol Obstet Invest, 2009 | 34 | IA2-IIB | RH with pelvic lymphadenectomy | Sensitivity– 36%<br>Specificity-98.8%<br>NPV – 88.9% |
| Jacob, J Clin Oncol, 2008 | 80 | Operable | RH with pelvic lymphadenectomy | Sensitivity – 58<br>Specificity – 92.8<br>NPV – 83.8 |
| Bentivegna *et al*., Obstet Fertil, 2011 | 16 | IB1 | RH with pelvic lymphadenectomy | NPV – 87 |
| Boughanim *et al*., J Clin Oncol, 2008 | 38 | IB2/II | Para-aortic lymphadenectomy | NPV – 92 |

NPV: Negative predictive value, RH: Radical hysterectomy

## DISCUSSION

Pelvic and para-aortic lymph node dissection followed by histopathology is the gold standard for diagnoses of regional nodal metastases in cervical cancer. As we know that surgical nodal dissection is associated with its immediate and delayed complications.[7] Therefore, objective of any imaging modality should be the pre-operative accurate diagnosis of pelvic and para-aortic nodal metastases in early stage cervical cancer so that need for surgical nodal staging can be avoided or obviated. Analysis of published six studies [Table 1] incorporating a total 374 patients, have shown low to moderate sensitivity (32-73%) of FDG PET/CT for detection of nodal metastases in early stage cervical cancer.[10-15] It means that pre-operative imaging with FDG PET/CT similar to MRI and CT scan; cannot replace the surgical staging in early cervical cancer due to its moderate and variable sensitivity. Although, these studies have reported a high NPV of FDG PET/CT scan in the range of 83-92% in predicting locoregional nodes. But these figures of NPV are not high enough and not within clinically acceptable limits to allow use FDG PET/CT scan as a screening modality to exclude pelvic and para-aortic nodal involvement noninvasively in early stage cervical cancer. Sironi *et al*.,[10] have shown that FDG PET/CT fails to detect diseased nodes having size <5 mm. Therefore, sub-centimeter sized nodes with micro-metastases (microscopic disease) is still a concern and remain elusive from FDG PET/CT similar to other imaging modalities. Therefore, role of FDG PET/CT in nodal staging in an early and operable cervical cancer is questionable. However, FDG PET/CT has shown promising results in patients with a locally advanced cervical cancer (stage IIB to IVA). FDG PET/CT performed in pre-treatment setting is advantageous for many other reasons. If pre-treatment FDG PET/CT scan shows positive nodes in the para-aortic region then this information is vital for deciding therapeutic strategy and radiation field can be extended to include para-aortic region in such cases. Magnitude of uptake in primary lesion has prognostic significance and is useful for evaluation of treatment response if baseline study is available.[5]

## CONCLUSION

FDG PET/CT is suboptimal in nodal staging for early stage cervical cancer contrary to its impressive performance in locally advanced disease.

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**How to cite this article:** Bansal V, Damania K, Sharma AR. Fluorodeoxyglucose positron emission tomography-computed tomography in evaluation of pelvic and para-aortic nodal involvement in early stage and operable cervical cancer: Comparison with surgicopathological findings. Indian J Nucl Med 2011;26:177-80.

**Source of Support:** Nil. **Conflict of Interest:** None declared.