MINI-REVIEW

Advanced Imaging Applications for Locally Advanced Cervical Cancer

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Abstract

Advanced imaging approaches (computed tomography, CT; magnetic resonance imaging, MRI; ^{18}F-fluorodeoxyglucose positron emission tomography, FDG PET) have increased roles in cervical cancer staging and management. The recent FIGO (International Federation of Gynecology and Obstetrics) recommendations encouraged applications to assess the clinical extension of tumors rather than relying on clinical examinations and traditional non-cross sectional investigations. MRI appears to be better than CT for primary tumors and adjacent soft tissue involvement in the pelvis. FDG-PET/CT has increased in usage with a particular benefit for whole body evaluation of tumor metabolic activity. The potential benefits of advanced imaging are assisting selection of treatment based upon actual disease extent, to adequately treat a tumor with minimal normal tissue complications, and to predict the treatment outcomes. Furthermore, sophisticated external radiation treatment and brachytherapy absolutely require advanced imaging for target localization and radiation dose calculation.

Keywords: Locally advanced cervical cancer - advanced imaging - CT - MRI - PET/CT

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Introduction

Cervical cancer is the second most common female cancer in South-East Asia region (Ferlay et al., 2010). Most of these patients presented with locally advanced disease with dismal prognosis. Advanced imaging, including computed tomography (CT), magnetic resonance imaging (MRI), and ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG PET/CT) has increased in their roles in cervical cancer staging and management. According to the prior International Federation of Gynecology and Obstetrics (FIGO) recommendation, a clinical examination is mandatory for cervical cancer staging. The basic non-crossing sectional radiographs such as chest x-ray (CXR), intravenous pyelography (IVP), procedural imaging (barium enema and lymphangiography) and invasive procedures (cystoscopy and sigmoidoscopy) were also recommended in companion with a pelvic examination (Pecorelli & Odicino, 2003). However, these investigations were less than adequate in attaining further information regarding locoregional extension particularly lymph node status and distant metastasis despite the invasive procedures. In addition, the invasive procedure with cystoscopy and sigmoidoscopy would possibly cause discomfort and be harmful to the patients. The discrepancies among physicians for accurate clinical staging were about 65-90% in locally advanced stage regarding tumor volume, lymph node status, parametrial invasion and uterine involvement (Bipat et al., 2003). The consequences of staging discrepancies are stages migration leading to treatment inadequacy and incomparable outcomes among physicians or institutes. The advanced imaging has been increasingly utilized in the developed countries since 1980s while the invasive imaging (lymphangiography and barium enema) and procedures (cystoscopy and sigmoidoscopy) have declined in their usages. Amendola et al reported the 100% usage of CT in the United States for 197 patients with invasive cervical cancer in 2002 compared to 16%, 54%, and 70% in 1978, 1983 and 1989, respectively (Amendola et al., 2005). However, the advanced imaging is not employed widely in the endemic countries of the cervical cancer. The major reason is lacking of medical resources in these under-developed countries. In addition, lacking of consensus regarding the appropriate imaging modality is problematic (Bipat et al., 2003; Hricak et al., 2005). For these reasons, the recent FIGO 2009 has only encouraged the usage of these advanced imaging techniques rather than strongly requiring those for a complete staging work up (Pecorelli, 2009; Pecorelli et al., 2009). The former mandatory investigations including an examination under anesthesia (EUA), cystoscopy, sigmoidoscopy and IVP are only optional.

Benefits of Advanced Imaging for Accurate Staging and Determination of Disease Extent

For accurate staging, imaging provides more information in addition to physical examination regarding tumor size, adjacent organ invasion and distant metastasis

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according to the FIGO staging (Hricak et al., 2005). Lymph node status and uterine involvement were not addressed in the FIGO although these findings will essentially predict the prognosis of the disease (Pecorelli et al., 2009).

MRI, particularly with T2-weighted images, appears to be better than CT to assess primary tumor and adjacent soft tissue invasion due to its high soft tissue contrast. For primary tumor assessment, MRI showed higher ability than CT to visualize the tumor, especially for endocervical lesion (Hricak et al., 2005). For early parametrial assessment, MRI shows higher sensitivity with similar specificity compared to CT (Bipat et al., 2003; Ozsarlak et al., 2003; Hricak et al., 2007; Balleyguier et al., 2011; Bell & Pannu, 2011) (Figure 1). However, MRI is equal to CT for detecting the gross parametrial invasion in the locally advanced disease. The findings from CT/MRI would change the stage of the disease and adjust the treatment modality from surgery to chemoradiation because of the advance of the disease beyond surgical accessibility (Rose et al., 1999; Whitney et al., 1999; Eifel et al., 2004; Petsuksiri et al., 2008).

Regarding vaginal involvement, CT and MRI did not show benefit over pelvic examination for assesing the vaginal invasion (Koyama et al., 2007). For uterine involvement, MRI showed the highest agreement with the pathology (Mitchell et al., 2006; Bell & Pannu, 2011). CT is nearly comparable to MRI to detect bladder or rectal invasion although the specificity is slightly better with MRI (Bipat et al., 2003; Rockall et al., 2006). These cross sectional imagings are recommended as upfront tools so as not to perform invasive procedures (cystoscopy or sigmoidoscopy) in patients with negative finding on the images (Sharma et al., 2010). For lymph node evaluation, MRI showed higher sensitivity with a similar specificity to CT (Bipat et al., 2003). Notably, these results certainly depended on the criteria of a positive lymph node with its maximal diameter (Figure 2).

MRI appears to be a modality of choice compared to CT to assess the extent of locoregional disease in the pelvis. Also, MRI is preferred in patients with poor renal function or who are allergic to iodine. Nevertheless, CT is acceptable for its quality especially in endemic areas with limited medical resources.

Recently, PET/CT scan has increasingly used for staging work up (Haie-Meder et al., 2010, Yoon et al., 2011). PET/CT scan shows a significant benefit over CT/MRI to assess the metabolic activities of the tumor, especially for distant metastasis, through the whole body cross-sectional images (Figure 3). PET/CT scan demonstrates a benefit to assess the pelvic/ paraaortic lymph node involvement with equivocal size and morphology on CT or MRI (Downey & Desouza, 2011). The PET/CT findings will perhaps change the treatment aims and modalities. The data of CT, MRI and PET/CT is reviewed in Table 1 and 2. (Nicolet et al., 2000; Narayan et al., 2001; Belhocine et al., 2002; Bipat et al., 2003; Ozsarlak et al., 2003; Hricak et al., 2005; Park et al., 2005; Rockall et al., 2006; Koyama et al., 2007; Hancke et al., 2008; Magne et al., 2008; Choi et al., 2010; Haie-Meder et al., 2010; Sharma et al., 2010; Amit et al., 2011; Balleyguier et al., 2011; Bell & Pannu, 2011; Leblanc et al., 2011)

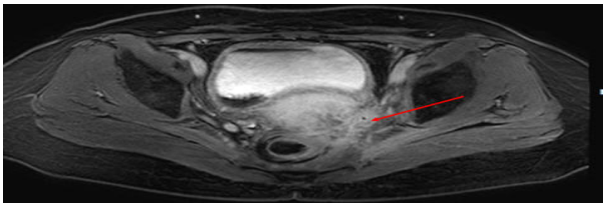

Figure 1. Shows MRI Scan (T1+ Gd) of the Patient with Left Parametrial Invasion

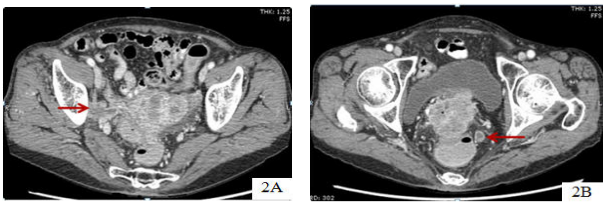

Figure 2. A) Represent the Iliac, B) Perirectal Lymph Nodes Metastases.

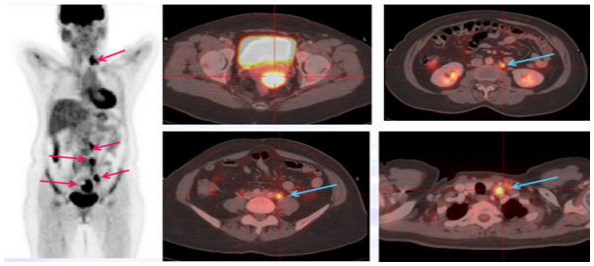

Figure 3. Represented a Female with Metastatic Cervical Cancer to the Pelvic, Paraaortic and Left Supraclavicular Lymph Nodes Detecting on the PET/ CT whole Body Images

Table 1. Comparison of the Available Parameters for CT, MRI and PET/CT for Locoregional Disease Evaluation

	CT					MRI					PET/CT				
	Sens	Spec	PPV	NPV	Acc	Sens	Spec	PPV	NPV	Acc	Sens	Spec	PPV	NPV	Acc
Primary tumor visualization	93%	N/A	N/A	N/A	53%	93%	N/A	N/A	N/A	86-93%	91-100%	N/A	91%	N/A	N/A
Parametrial invasion	43-55%	71%	53%	62%	59-72%	52-80%	63-91%	55-67%	61-95%	58-95%	N/A	N/A	N/A	N/A	N/A
Bladder invasion	64-100%	73-92%	40%	100%	92%	75-100%	88-91%	7%	96-100%	88-99%	N/A	N/A	N/A	N/A	N/A
Rectal invasion	45-100%	88-91%	N/A	100%	100%	71-100%	91%	17%	96-100%	91%	N/A	N/A	N/A	N/A	N/A
Lymph node metastasis	31-50%	84-92%	61%	64%	81-86%	36-89%	78-99%	64-68%	57%	67-86%	10-95%	83-100%	25-90%	84-99%	75-92%

*Sens: Sensitivity, Spec: Specificity, PPV: Positive predictive value, NPV: Negative predictive value, Acc: Accuracy, N/A: No information available.

Table 2. Summarized Usage of Each of the Three Image Modalities for Disease Assessment

	CT	MRI	PET/CT
Primary tumor visualization	Feasible	Recommended	Feasible
Parametrial invasion	Feasible	Recommended	-
Vaginal invasion	-	-	-
Bladder invasion	Feasible	Recommended	-
Rectal invasion	Feasible	Recommended	-
Pelvic lymph node metastasis	Feasible	Feasible	Recommended
Para aortic lymph node metastasis	Feasible	Feasible	Recommended
Distant metastasis	-	-	Recommended
Radiation treatment planning	Use for simulation, radiation field designation and radiation dose calculation	Better for primary tumor delineation	Treatment aim changes in patients with metastatic disease
			Assess the metabolic activity of the equivocal lymph node whether or not to include in the radiation fields
			Adaptive radiation therapy based on the metabolic activity
Tumor response after definitive treatment	Feasible	Feasible	Recommended
Overall advantage	Easily accessible	Better for tumor delineation due to higher soft tissue contrast	Assess the metabolic activity of the tumor
	Acceptable for locoregional disease assessment		Detect distant metastasis
Overall disadvantage	Poor soft tissue contrast	Relatively inaccessible in endemic areas of cervical cancer	High cost and barely accessible in the endemic areas of cervical cancer

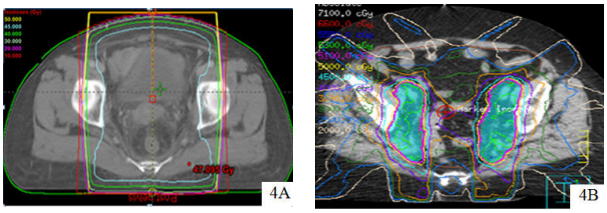

Figure 4. A)Represents CT Based Planning with AP/PA Technique, B) IMRT.

Benefits for Determination of Prognosis

The major factors to determine prognosis of locally advanced disease are tumor size and nodal positivity. Advanced imaging would be better for determining the actual size of the tumor and nodal status than clinical evaluation or non cross sectional imaging.

Tumor size more than 8 cm in diameter or more than 35 cc volumes showed worse survival outcomes (Lee et al., 2010). Tumor size also predicted the risk of lymph node metastasis and ultimately the survival outcomes. Patients with tumor size more than 4 cm in diameter showed evidence of 30-80% chance of pelvic lymph node positivity with 47- 70 % 5 year survival. In contrast, the patients with tumor size less than or equal to 4 cm showed 15-20% chance of pelvic lymph node positivity with 92-95% 5 year survival (Eifel et al., 2009, Lee et al., 2010). Para-aortic metastasis was found in approximately 20% in stage II disease (Follen et al., 2003). Grigsby et al reported inferior 5-yr survival for patients with positive paraaortic metastasis compared to patients with negative paraaortic metastasis (40% vs 80%, p <0.0001) (Grigsby et al., 2004).

The metabolic activity of the PET/CT scan could predict the survival. Schwarz et al reported 5-yr cause specific survival of 82%, 41% and 15% for patients who achieved complete metabolic response, partial metabolic response, and progressive disease, respectively after definitive treatment (Schwarz et al., 2011). Additionally, PET/CT can be used to detect the recurrent disease after definitive treatment with the overall sensitivity and specificity of 48-100% and 57-100%, respectively (Magne et al., 2008).

Benefits for Radiation Treatment Planning

Target delineation and treatment planning

Radiation treatment is composed of external beam radiation therapy and intracavitary brachytherapy. Previously, the conventional radiation treatment fields encompassed the whole pelvis by using bony anatomy on plain radiograph for conventional simulation. Basically, the upper and lateral borders of the AP-PA (antero-posterior) field were routinely placed at about the level of the 5th lumbar vertebral body and 1.5-2 cms beyond the pelvic brim, respectively. The lower border was at

the inferior aspect of the obturator foramen or 2- 3 cms below the lowermost of the tumor. These margins may not adequate especially in patients with high iliac nodal metastasis or bulky nodal disease in the pelvic brim area. Finlay et al reported inadequate margins of the AP fields of about 54% and 20% at the superior and lateral borders, respectively based on the pelvic bony anatomy (Finlay et al., 2006). The inadequate target coverage definitely led to insufficient dose delivery and treatment failure. The most common pattern of regional recurrence (66-97%) was at the margin of the radiation field (Zhang and Yu, 2009; Beadle et al., 2010). Therefore, by using cross sectional images (CT/MRI) radiation oncologists would have more confidence to customize the external radiation treatment fields based on the findings. Nowadays, the CT based simulation has been widely established. The CT simulation would help to entirely encompass the tumor inside the treatment fields either treated with conventional technique (AP/PA), or advanced techniques such as 3 dimensional conformal radiation therapy (3DCRT), or intensity modulated radiation therapy (IMRT) (Figure 4).

Recently, IMRT has increased in its usage for external radiation treatment and confirmed the lower rates of gastrointestinal and genitourinary complications by using the advanced treatment planning system (Chen et al., 2011). Additionally, cervical cancer patients receiving IMRT treatment showed superior cause specific and overall survivals compared to patients who were treated with conventional radiation therapy (Kidd et al., 2010). The advanced techniques definitely require CT simulation images for target localization, radiation fields' designation, and computer based radiation doses calculation. The target delineation is very important for complicated radiation treatments. Radiation doses would be delivered to only the designated targets and avoid the non-designated areas. Likewise, the normal tissues may not be spared if these structures are not assigned. The potential microscopic disease and lymphatic metastasis in the pelvis are also vital and must be properly included in the treatment fields. Lim et al has addressed the guideline for microscopic disease (clinical target volume: CTV) delineation for cervical cancer treatment with IMRT (Lim et al., 2011). Also, lymph node regions contouring guideline has been established (Taylor et al., 2005).

Regarding brachytherapy, it has progressed from two dimensional (2D) planning to three dimensional (3D) planning with CT/MRI based. Conventionally, brachytherapy has utilized the clinical examination in conjunction with orthogonal radiographs to generate the arbitrary 2D prescription points and normal adjacent organs for dose prescription. This 2D method potentially provides the inadequate doses delivered to the tumor while it underestimates the doses to certain volumes of the small bowel, bladder or rectum in individual patients. Recently, 3D brachytherapy planning using CT/MRI images has become a popular tool to visualize the exact tumor and adjacent organs location. This approach would provide adequate dose coverage to the primary tumor and surrounding microscopic diseases while reducing the dose to the adjacent critical structures (Potter et al., 2011, Potter et al., 2006).

PET/CT has increasing influenced the target delineation in cervical cancer treatment. The finding from a PET scan changed about 15% of radiation treatment planning before starting treatment (Belhocine et al., 2002). There was a study escalating the radiation doses based on the nodal diameter and PET positivity with isolated nodal failure of < 2% (Grigsby et al., 2004). On the other hand, negative lymph node may preclude the benefits of concurrent chemoradiation compared to radiation alone in patients with stage IB2-III (Grigsby et al., 2005). However, there were still some discrepancies without clear-cut conclusion between PET and MRI to localize the primary cervical tumor particularly in small tumor volumes (Ma et al., 2011).

Adaptive radiation therapy

Target changes such as tumor shrinkage and internal organ motions during radiation therapy course are of concern. Recently, image guided radiation therapy (IGRT) has been introduced to monitor the tumor changes, either intrafraction or interfraction, during the external radiation courses. On board real time reconstructed cross-sectional images specifically assist to deliver radiation doses to the actual targets. Also, IGRT potentially modifies the radiation treatment planning according to the targets or normal tissues changes during the radiation treatment.

PET scan has been employed to monitor the tumor responses and radiation dose modification. Yoon et al showed that 27% of the radiation plans were modified, including dose escalation or radiation field extension for para-aortic metastases based on the metabolic changes during the radiation course (Yoon et al., 2011). Likewise, adaptive treatment has been applied to the brachytherapy. Lin et al reported the feasibility of using the PET metabolic activity to modify the dose coverage to the tumor and normal tissue avoidance for each brachytherapy session (Lin et al., 2007).

Conclusions

In conclusion, advanced imaging has played a significant role in recent cervical cancer staging and treatment. MRI appears to be better than CT for locoregional disease assessment especially for primary tumor and adjacent soft tissue extension. PET/CT shows benefits of whole body tumor metabolic evaluation in addition to providing locoregional anatomic assessment. Adaptive radiation treatment is increasing in clinical practice by using these images. These approaches aim to improve the treatment precision and ultimately the clinical outcomes.

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