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ORIGINAL ARTICLE

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Whole-body ^{18}FDG PET plus pelvic MRI in the pre-treatment assessment of cervical cancers: an alternative to the FIGO clinical staging

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Abstract Growing evidence indicates that whole-body ^{18}F-fluorodeoxyglucose positron emission tomography (wb-^{18}FDG PET) plus pelvic magnetic resonance imaging (pMRI) may significantly improve the pre-treatment staging of primary cervical cancers. Such a combined protocol provides complementary insights into primary tumour delineation, loco-regional involvement and distant spread. As such, pMRI appears particularly reliable for the accurate measurement of tumour size, the detection of parametrial invasion and, even more so, for its exclusion. So far, wb-^{18}FDG PET yields unique information about extra-pelvic nodal and visceral tumour status. Of note, however, is the limitation of both imaging techniques for the detection of microscopic pelvic lymph node metastases, especially in early stage disease. Promising data also highlight the prognostic value of ^{18}FDG uptake as a marker of disease aggressiveness and of tumour resistance to treatment. The recent development of combined PET-CT scans as well as the validation of the sentinel node concept in gynaecological malignancies may grant new perspectives for optimal management of cervical cancers in the pre-treatment setting.

Keywords ^{18}FDG PET · MRI · Cervical cancer · Staging

Introduction

Despite an earlier diagnosis of pre-invasive forms of uterine cancers, the appropriate staging of invasive cervical cancers is still a challenging area [1]. In the pre-treatment setting, the International Federation of Gynaecology and Obstetrics (FIGO) clinical staging system is the most often used classification worldwide [2]. Yet, regardless of FIGO staging, major discrepancies exist when compared to surgical staging [3]. For instance, the underestimation of the pathological extent of disease has been shown to reach nearly one-third of patients with FIGO stage IB and half of those with FIGO stages II–IV [4, 5]. Also, nodal involvement, one of the most important prognostic factors, is not taken into account in the FIGO classification [2]. Taken together, these facts have led a number of clinicians to recommend the use of the TNM classification, which refers to the extent of the primary tumour (T), lymph node metastasis (N) and distant metastasis (M), instead of the conventional FIGO clinical staging [6]. On the other hand, critical changes in treatment planning of newly diagnosed cervical cancers have opened promising perspectives in terms of survival, thereby stressing the need for an accurate staging of disease in the process of patient selection [7, 8, 9].

In recent years, many reports demonstrated the clinical usefulness provided by whole-body ^{18}F-fluorodeoxyglucose positron emission tomography (wb-^{18}FDG PET) as well as by pelvic magnetic resonance imaging (pMRI), respectively, in the initial assessment of uterine cancers [4, 5, 10, 11, 12, 13, 14]. The purpose of this paper was to assess the appropriateness of wb^{18}FDG PET plus pMRI in

Table 1 Current and future technology for staging primary cervical cancers. *MRI* magnetic resonance imaging, *^{18}FDG* ^{18}F-fluorodeoxyglucose, *PET* positron emission tomography, *CT* computed tomography, *SNB* sentinel node biopsy, *^{60}Cu-ATSM* ^{60}Cu-diacetyl-bis (N^4-metylthiosemicarbazone), *^{18}F-FMISO* ^{18}F-fluoromisonidazole, *USPIO MRI* ultra small paramagnetic iron oxide-enhanced magnetic resonance imaging

TNM Staging	T staging	N staging	M staging
Recommended	MRI	^{18}FDG PET	^{18}FDG PET
Perspectives	^{18}FDG PET-CT	^{18}FDG PET-CT SNB	^{18}FDG PET-CT
Research	^{60}Cu-ATSM PET ^{18}F-FMISO PET	USPIO MRI	Whole-body MRI

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the pre-treatment staging of primary cervical cancers on the basis of the TNM classification. Beyond this combined protocol, new tracers and emerging high-end technologies are also discussed as research tools that may improve the pre-treatment evaluation of cervical cancers (Table 1).

Staging

T staging

The accurate characterisation of the primary tumour is a key step in the pre-treatment staging of cervical cancers. This includes the detection of the initial tumour site and its precise delineation in a three-dimensional space. Also critical is the assessment of prognostic variables such as the depth and width of stromal invasion, local extension into the vagina or the parametrium, as well as the spread of the tumour into the pelvic wall and beyond into the bladder and/or the rectum [1, 2, 13, 15].

In the assessment of primary cervical cancers, the value of MRI is well documented [4, 5, 16, 17]. More recently, increasing amounts of data also have shown that ^{18}FDG PET may detect an intense metabolic signal at the level of the primary site with a high sensitivity (81–100%) [10, 11, 12, 13, 14, 18, 19, 20]. When the performances of both imaging modalities were compared in a prospective series including 22 patients with histologically proven cervical cancers, a similar sensitivity of 91% was found. Microscopic lesions (FIGO IA–T1A), however, were missed by MRI, and by ^{18}FDG PET as well [21]. On the other hand, only pMRI was able to provide precise assessment of the primary tumour size, which correlated well with the pathological findings. Similarly, MRI has yielded valuable information about the extent of the local tumour in the vagina, the parametrium and the pelvic organs, whereas metabolic imaging could not assess such key parameters owing to its limited spatial resolution. Of interest, morphological imaging was even more accurate to rule out a parametrial involvement, thereby giving a high negative predictive value. In a few cases, however, the inflammation surrounding the primary tumour site as well as the acute oedema following a recent biopsy gave a high MRI signal, which was falsely interpreted as a tumour. In summary, even though MRI and ^{18}FDG PET may detect cervical cancers with a high sensitivity, morphological imaging is better indicated for primary tumour characterisation and loco-regional staging. Hence, MRI appears to be the modality of choice for the T staging of cervical cancers.

N staging

In cervical cancers, nodal status is a major independent prognostic variable [1, 4, 15, 17]. In women presenting with nodal involvement (N1), the 5-year overall survival is dramatically reduced by nearly 30–40% in comparison to that of patients classified as N0 [22, 23, 24]. In particular, para-aortic nodal status has been shown to be the most powerful parameter for patient outcomes [25, 26]. On the other hand, the recent introduction of combined therapies including radiation therapy plus sensitising chemotherapy gives rise to rational hopes in terms of prolonged survival [27, 28, 29]. So far, among the available diagnostic tools that are recommended by the FIGO staging system for the assessment of nodal status, neither lymphangiography, computed tomography (CT) nor MRI are sensitive enough for the accurate detection of nodal metastases [2, 4, 5, 30]. In this particular clinical context, ^{18}FDG PET may be the best alternative for highly sensitive whole-body imaging, which allows the localisation of metastases at each level of the natural history of nodal spreading. Indeed, many clinical reports have shown the added value of metabolic imaging for detecting lymph node metastases at the pelvic and extra-pelvic levels [10, 14, 18, 19, 20, 21]. Quiet frequently, ^{18}FDG PET alone was able to detect nodal involvement missed by the CT and/or MRI [18, 19, 20, 21, 31]. More importantly, ^{18}FDG uptake at the para-aortic level was found the most significant factor for disease-free survival [32]. Like other reports, our experience confirms the superiority of metabolic imaging to MRI for the detection of para-aortic, mediastinal and supra-clavicular lymph node metastases [18, 19, 20, 31, 32]. Unlike many series, however, our data highlight the technical limitations of ^{18}FDG PET for the evaluation of pelvic metastases, lymph node sites that most often harbour microscopic involvement and may even escape the intra-operative palpation [21, 33, 34]. Hence, ^{18}FDG PET appears to be the modality of choice for achieving an accurate N staging in patients with cervical cancers. Care should be taken, however, in the assessment of pelvic metastases that are below the spatial resolution of commercially available PET scanners.

M staging

The staging of distant metastases is critical for treatment decision-making. Although lung, liver and bone metastases are the most frequent sites of secondary localisations arising from cervical cancers, results from large surgical series and autopsy studies showed that a large spectrum of organs may be affected with a variable frequency [35]. Also, ^{18}FDG PET appears particularly appropriate for the detection of distant tumour sites through the entire body [13, 14, 32, 36]. Interestingly, cervical cancers exhibit high rates of GLUT-1 (type-1 glucose transporter) and glycolytic enzymes (type-2 hexokinase, phosphofructokinase and pyruvate kinase), which makes the imaging by means of the glucose analogue theoretically and practically valid for such gynaecological malignancies [37, 38, 39, 40, 41]. In addition, metabolic imaging offers the possibility of non-invasive whole-body scanning in a

single session, whereas the FIGO staging system recommends a number of radiological and endoscopic studies, iterative explorations that are not only invasive and expensive, but often clinically fruitless [2, 3, 4, 5]. Our data are in line with the literature results, which highlight the added value of ^{18}FDG PET in detecting visceral metastases missed by morphological imaging (CT/MRI). Of note is the suboptimal specificity of ^{18}FDG for tumour cell uptake [21] so that, in a particular clinical context, inflammatory or infectious diseases may avidly take up the glucose tracer, thereby leading to false-positive results [42, 43]. In the M staging of cervical cancers, growing evidence indicates the usefulness of ^{18}FDG PET for more appropriate treatment planning. In agreement with some authors, we advocate the introduction of metabolic imaging in the initial work-up of women presenting with cervical cancers [13, 14, 21, 32]. So far, more data need to be gleaned in order to refine the correct place of ^{18}FDG PET on a stage-by-stage basis.

Treatment impact

In most papers published, the use of ^{18}FDG PET in the work-up of cervical cancers significantly altered the treatment options [14]. The rates of treatment impact vary from 14 to 60% depending on the stage of disease, the extent of the lesions detected and ultimately the modalities of treatments initially selected [20, 21, 31, 32, 44]. On average, one-third of patients presenting with various stages of cervical cancers may draw a direct benefit from metabolic imaging alone, a treatment adjustment resulting from a more accurate staging. Para-aortic metastases are the most documented ^{18}FDG-avid sites where metabolic imaging best influences the treatment choices [10, 14, 18, 20, 21, 31, 32]. Indeed, in many clinical data, ^{18}FDG PET modified the fields, volumes and doses of irradiation by detecting unsuspected para-aortic nodal involvement. Metabolic imaging was also found to be the best technique for the detection of inpalpable supra-clavicular metastases, thereby reorienting the conventional therapies to a palliative therapy or irradiation plus concurrent chemotherapy [45]. Similarly, the ^{18}FDG findings may guide the treatment by the detection of visceral metastases (lung, liver, skeleton), which are often overlooked by the routine protocols [14, 21, 36]. Results from a combined protocol including wb-^{18}FDG PET plus pMRI are in line with the data in the literature. In approximately 20% of patients (4/22), the aforementioned imaging work-up significantly modified the treatment options from conservative surgery to chemo-radiation, including the para-aortic fields (three patients upstaged from FIGO-N0M0 to PET-N1M0 and PET-N1M1) or to radiation therapy with a bony pelvic boost (one patient upstaged from FIGO-M0 to PET-M1) [21]. Importantly, in all patients, the PET findings were confirmed either by histology or by clinical and CT follow-up; among them, 80% of women had a surgical confrontation with nodal disease. In addition, the agreement scores of ^{18}FDG PET with the final diagnosis were significantly higher than that of FIGO staging, including pMRI ($P<0.01$). On the other hand, although pMRI upstaged the local extent of disease in five patients (three patients from T2a to T2b, one patient from T3a to T3b and one patient from T3a to T4), results from surgical exploration and the final pathological analysis showed that only two of them had parametrial involvement; the other cases were considered to be false-positive results resulting from peri-tumoral inflammatory changes or artefact-related MRI signals. Ultimately, in the four patients with a positive PET study, metabolic imaging directly influenced the treatment decision-making. Conversely, based on the positive MRI results, the therapeutic decision was always defined a posteriori during surgery or following the pathological conclusions. So far, in all patients but one, a negative MRI was accurately predictive of no disease at the level of the parametrium (T2a vs. T2b), the vagina (T3a vs. T3b) and the bladder/rectum (T4). In conclusion, whether the disease is locally confined or already advanced, the appropriate combination of ^{18}FDG PET and MRI in pre-treatment staging of cervical cancers may help make the choice of the best strategy in terms of maximal versus minimal treatments.

Pending issues

Even though a pre-treatment work-up including wb-^{18}FDG PET plus pMRI may significantly improve the staging of primary cervical cancers, some questions are still pending. First, further studies to assess the cost effectiveness of such a combined protocol in comparison to the routine protocols are needed. This is a key point to consider for a large scale implementation, knowing that nearly 80% of cervical cancers occur in developing countries [46]. Second, large controlled trials are still needed in terms of adequate population sampling, defining a robust gold standard and sufficient follow-up. Despite the increasing number of clinical reports, the best methodological and analytical criteria are not always met [14]. In particular, the pathological confirmation of the imaging findings (^{18}FDG PET, MRI) is a prerequisite when assessing the value of both modalities for nodal staging. The accurate determination of the predictive values of ^{18}FDG PET and MRI (presence of disease when the test is positive and absence of disease when the test is negative) is implicit. Otherwise, owing to the suboptimal performances of the conventional clinical and radiological confrontation, no definitive conclusion can be drawn objectively. Third, metabolic imaging is not just a diagnostic modality, but it may also bring prognostic information to bear upon tumour behaviour and patient survival [32, 47]. Also, the inclusion of homogenous groups of patients based on the TNM/FIGO staging systems is critical to a precise stage-by-stage determination of the best indications of wb-^{18}FDG PET plus pMRI along with the merging of new technologies [6]. Last but not least, a multidisciplinary approach to the disease in

terms of clinical demand and technology supply should be preferred to optimise the protocol proposed for the pre-treatment staging of cervical cancers. At this level, the role of international medical societies, which are primarily involved in this area of clinical investigation (i.e. gynaecology, radiology, pathology and nuclear medicine), appears crucial.

Perspectives

The field of molecular imaging is continuously evolving. Combined imaging technologies, more specific tracers, as well as improved histopathological techniques are available nowadays in the clinical setting to optimise the staging of cervical cancers. At the same time, the recent introduction of PET-CT devices have allowed the assessment of the extent of the disease over the entire body [48, 49]. In previous studies, the software fusion of PET and CT images was already found useful for the accurate determination of the target primary tumour volume in patients who were candidates for radiation therapy [50, 51]. The hardware fusion of PET and CT images may significantly improve the diagnostic accuracy of both imaging techniques, thereby giving an anato-metabolic picture of the disease [52]. In gynaecological cancers, besides a more precise detection of disease, ^{18}FDG PET-CT may impact the treatment options in nearly 30% of the patients compared to ^{18}FDG PET alone [53, 54]. Similarly, the development of moving patient platforms with integrated surface-coil technology has recently enabled the performance of whole-body MRI within a single session. In a comparative study performed in 98 patients with various cancers including genitourinary tumours, ^{18}FDG PET-CT was found more accurate for the T and the N staging, whereas whole-body MRI may be the best modality for the M staging, especially for the detection of liver and bone metastases [55]. Also promising is the use of hypoxia tracers in PET imaging [56, 57]. Because hypoxia is an important prognostic factor in cervical cancers, the use of ^{18}F-FMISO (^{18}F-fluoromisonidazole) or ^{60}Cu-ATSM [^{60}Cu-diacetyl-bis (N^4-metylthiosemicarbazone)] as hypoxia tracers may give the clinicians determining information on tumour components [58]. These tracers also may be particularly useful for the initial assessment of tumour responsiveness to treatment, knowing that hypoxic cells are rather resistant to radiotherapy and chemotherapy [59]. On the other hand, the validation of the sentinel node concept in early stage cervical cancers along with the molecular analysis of the sentinel lymph nodes (SLN) may grant new perspectives for the selective evaluation of regional nodal status [60, 61, 62]. Accordingly, most women with early stage disease and negative SLN will be spared the morbidity resulting from unnecessary complete lymph node dissections. Conversely, the detection of SLN with microscopic involvement, especially in unpredictable sites, may radically change the treatment strategy. Similarly, high-resolution MRI using lymphotropic paramagnetic iron oxide nanoparticles instead of conventional gadolinium-enhanced MRI may significantly improve the detection of lymph node metastases without the need of invasive investigations [63, 64, 65]. In other words, in women suffering from cervical cancers, the development of new technologies as well as the improvement of diagnostic tools already available routinely may help overcome the limitations of the current staging systems. Further, clinical studies are still needed to confirm these encouraging preliminary data.

Conclusion

The staging of primary cervical cancers may be significantly improved by combining whole-body ^{18}FDG PET plus pelvic MRI. Accordingly, MRI is the modality of choice for the T staging of disease, whereas ^{18}FDG PET is better indicated for the assessment of nodal involvement (N staging) and distant metastases (M staging). Further controlled trials are still needed to assess the cost-effectiveness of such a protocol, especially to make its clinical added value more precise on a stage-by-stage basis. Similarly, the introduction of new technologies stresses the need for evaluating the best protocol in the pre-treatment setting. These are prerequisite before incorporating a high-end imaging work-up into the international gynaecological classifications.

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