Journal of Nuclear Medicine, published on January 28, 2021 as doi:10.2967/jnumed.120.255919

Lymph node staging with a combined protocol of ^{18}F-FDG PET/MRI and sentinel node SPECT/CT: a prospective study in patients with FIGO I/II cervical carcinoma.

Weissinger, Matthias[1]; Taran, Florin-Andrei[2]; Gatidis, Sergios[3]; Kommoss, Stefan[4]; Nikolaou, Konstantin[3,5,6]; Sahbai, Samine[1]; la Fougère, Christian[1,5,6]; Brucker, Sara Yvonne[4*]; Dittmann, Helmut[1*]

[1] Department of Nuclear Medicine and Clinical Molecular Imaging, University Hospital Tuebingen, Germany

[2] Department of Women's Health, University Hospital Zurich, Switzerland

[3] Department of Diagnostic and Interventional Radiology, University Hospital Tuebingen, Germany

[4] Department of Women's Health, University Hospital Tuebingen, Germany

[5] iFIT-Cluster of Excellence, Eberhard Karls University Tuebingen, Germany

[6] German Cancer Consortium (DKTK), Partner Site Tuebingen, Germany

.

* Both authors contributed equally

Word count: 4995 words.

running title:

PET/MR+SLN cervical carcinoma N-staging

First author:

Matthias Weissinger, MD (Resident)
Eberhard-Karls-University Tuebingen
Department of Nuclear Medicine and Clinical Molecular Imaging
Otfried-Mueller-Str. 14, 72076 Tuebingen, Germany
Phone +49-7071-29-86410
Fax +49-7071-29-5869
E-mail: matthias.weissinger@med.uni-tuebingen.de

Corresponding author:

Christian la Fougère, MD
Department of Nuclear Medicine and Clinical Molecular Imaging
University Hospital Tuebingen
Otfried-Mueller-Str. 14, 72076 Tuebingen, Germany
Phone +49 7071 2986553
Fax +49 7071 29 4601
E-mail: christian.lafougere@med.uni-tuebingen.de

ABSTRACT

Lymph node metastases (LNM) are present in a minority of patients with early stages of cervical carcinomas. As conventional imaging including PET/CT has shown limited sensitivity, systematic lymphadenectomies are often conducted for staging purposes. Therefore, the aim of this prospective study was to analyze the impact of ^{18}F-FDG PET/MRI in addition to sentinel node (SLN) biopsy on lymph node status. **Methods:** 42 women with initial diagnosis of FIGO IA-IIB cervical carcinomas were included between 03/2016–04/2019. Each patient received preoperative whole body ^{18}F-FDG PET/MRI (Biograph mMR®, Siemens Healthineers) and SLN imaging with SPECT/CT (Discovery 670 Pro®, GE Healthcare) after intracervical injection of ^{99m}Tc-labeled nanocolloid. Systematic Lymphadenectomy and SLN biopsy served as reference standard. Staging in PET/MRI was performed as a consensus of nuclear medicine and radiology experts. **Results:** One patient was excluded from surgical staging due to newly diagnosed liver metastases in PET/MRI. Overall prevalence of LNM in the remaining 41 patients was 29.3% (12/41). 5/12 patients with LNM solely had small metastases with maximum diameter ≤5mm. Interpretation of PET/MRI as a consensus of experts showed a specificity of 100% (29/29, 95%CI: 88.3-100%) for LNM-staging, but a low sensitivity of 33.3% (4/12, 95%CI: 12.8-60.9%). LN size was the most important factor for the detectability of metastases, since only LNM >5mm could be identified by PET/MRI (sensitivity >5mm: 57.1%; ≤5mm: 0%). Paraaortic LNM were evaluated accurately in 3/4 cases (16 patients with paraaortic LN removal). SLNs were detectable by SPECT/CT in 82.9% of the patients or 69.0% of hemipelvis. In cases with undetectable SLN in SPEC/TCT, malignancy rate was considerably higher (31.2% vs. 19.3%). The combination of PET/MRI and SLN SPECT/CT improved the detection of

pelvic LNM from 33.3% to 75%. **Conclusion:** ^{18}F-FDG PET/MRI is a highly specific N-staging method and improves LNM detection. Due to the limited sensitivity in frequently occurring small LNM, PET/MRI should be combined with sentinel node mapping. The proposed combined protocol helps to decide whether extensive surgical staging is necessary in patients with FIGO I/II cervical cancer.

Key Words: ^{18}F-FDG PET/MRI; ^{99m}Tc-nanocolloid SPECT/CT; sentinel node; cervical carcinoma; combined protocol

INRODUCTION:

Staging of cervical carcinoma is still based on clinical criteria and surgical specimens according to Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) classification (*1*). However clinical staging becomes less accurate with increasing tumor stage, with a reported under- or overstaging in up to 65% of patients (*2-5*).

As the presence of lymph node metastases (LNM) is the most important prognostic factor in early-stages (*4,6-11*), accurate staging is essential. Therefore, imaging methods are increasingly used in addition to clinical staging and are gradually mentioned in current guidelines (*1,4,6,10*).

Unfortunately, LNM can occur in any stage of cervical carcinoma with an increasing prevalence from 15% in early-stage tumors to about 35% in carcinomas >4cm (*10,12,13*). Therefore, pelvic systematic lymphadenectomy –sometimes extended to paraaortic lymph nodes- remains as golden standard for N-staging (*1,4,6,10*). Regrettably, this procedure is often associated with high morbidity and seems to be very invasive for the low prevalence of LNM in early tumor stages (*1,4,6,10,14*).

To minimize overtreatment, sentinel lymph node (SLN) biopsy is increasingly performed in several centers and has been established by guidelines for cervical cancer staging (*4,6*). The minimal invasive SLN biopsy is usually performed after an intracervical injection of fluorescent dye and/or ^{99m}Tc labeled nanocolloid, whereby the combination of both is superior (*10,15*).

Furthermore, a targeted removal of only a few lymph nodes (LN) enables a more intensive histopathological processing, by ultrastaging protocol. By means of ultrastaging, the LN is lamellated finer and, if necessary, processed immunohistochemically so that even single tumor cells can be detected (*16*). This

procedure results in a higher detection rate (upstaging in 5-15% of patients) of micrometastases (*16*), which were shown to have an impact on recurrence probability and overall survival (*17*)

As a noninvasive imaging method MRI, which was first introduced for local tumor staging (*5*), revealed its advantages quickly for pelvic lymph LN with a high pooled specificity of about 95% but low sensitivity of about 55% (*3,6,10,18*).

Moreover, the FDG-PET enables whole-body staging with excellent results in local tumor staging and in the detection of metastases (*19-21*). However, the use of PET/CT is still discussed controversially (*4,10,18*).

According to the National Comprehensive Cancer Network guidelines, PET/CT can be considered for primary staging starting from FIGO IB (*4*), whereas the European ESMO guidelines recommend PET/CT in a locally advanced disease (*10*).

Based on the current data, whole body ^{18}F-FDG PET/MRI has the potential to combine the strength of MRI for loco-regional tumors and LN staging with the capability of whole body PET to exclude distant metastases including lung metastases in a one stop shop (*19*).

We hypothesize that a combined protocol of ^{18}F-FDG PET/MRI and SPECT/CT for SLN detection could be an accurate, minimally invasive whole body staging procedure. In particular, ultrastaging in the SLN enables the detection of micrometastases and isolated tumor cells which can hardly be visualized by any imaging method (*16*). A more precise preoperative staging could save patients with non-respectable N- or M-stage from a possibly unnecessary surgery.

MATERIALS AND METHODS:

42 patients with histopathologically confirmed cervical carcinoma and clinically determined stage FIGO IA to IIB were consecutively enrolled into this prospective study. The study was approved by the institutional review board (registry No.173/2015BO01) and is listed in the German Clinical Trial Register (DRKS-ID: DRKS00014346) (*22*). All patients signed an informed consent.

Each patient underwent a whole body ^{18}F-FDG PET/MRI, preoperative SLN mapping with SPECT/CT and intraoperative SLN detection with a gamma probe as well as a surgical staging between March 2016 and April 2019.

There was one drop out due to newly diagnosed liver metastases in PET/MRI (clinical stage: pT1b1,L1,V0,R1,G1; final stage after PET/MRI: T2b,N1,M1). Two patients respectively three hemipelves were excluded from the evaluations with histological correlation (one patient without pelvic LN extraction, one hemipelvis due to unclear anatomical allocation). Detailed patients characteristics are presented in table 1.

PET/MRI protocol

Acquisition started 65.3±13.9 min after injection of 238.3±14.8 MBq ^{18}F-FDG (Biograph mMR®, Siemens Healthineers). To minimize intestinal movement, all patients received 20mg butylscopolaminium bromide i.v. concomitant with the radiotracer injection except for contraindications. All patients fasted for at least 8 hours and blood sugar level at injection was below 140 mg/dl. Minimum acquisition time per bed position was four minutes. Detailed MR imaging parameters are listed in detail in the supplemental table 1. PET/MRI images were evaluated in consensus by board certified

radiologist and nuclear medicine specialists with at least eight years of experience in PET and MRI imaging.

SLN injection technique

Approximately 200MBq ^{99m}Tc-nanocolloid (Nanocoll®, GE Healthcare) diluted with 0,9% NaCl to a volume of 0.8ml were injected intracervically and evenly distributed to four positions at three, six, nine and twelve o'clock position.

SLN SPECT/CT

Lymph node mapping was performed three to five hours p.i. after ^{99m}Tc-nanocolloid injection. All patients were scanned on a hybrid SPECT/CT device (Discovery 670 Pro®, GE Healthcare) including an area from pelvis to caudal liver with the two camera heads in H-Mode; SPECT acquisition parameters were as follows: energy window 140.5keV±10%, 128×128 matrix, 30 angular steps with 6° interval, acquisition time per step 15'', pixel size 4.42x4.42 mm. SPECT data were reconstructed using an OSEM iterative protocol (2 iterations, 10 subsets).

The technical parameters of the 16-slice-CT- scanner were: gantry rotation speed 0.8s, table feed 20 mm per gantry rotation. CT scans were carried out with a dose modulation system (120 kV, 10-80 mAs, OptiDose®, GE Healthcare). Contrast agent (90ml Ultravist 370®, Bayer Vital GmbH) was injected in case of no contraindication.

The SLN SPECT/CT was analyzed by two nuclear medicine physicians with more than ten years of experience in pelvin SLN imaging. A SLN was defined as focal activity enrichment in SPECT in a plausible anatomical region. SLN mapping was defined as successful, in case of at least one clearly detectable SLN per hemipelvis.

SLN biopsy

Surgical staging was performed laparoscopically the day after ^{99m}Tc-nanocolloid injection. Dye (blue dye or Indocyanine green) was injected intracervically at three and nine o'clock positions (0.2 ml per injection) prior to surgery.

SLNs were localized and identified intraoperatively either by direct visualization or using a laparoscopic gamma probe (Neoprobe®, Models 1017 and 1100, Devicor Medical Products, Inc), resected separately, assigned meticulously and sent to rapid tissue section.

All patients received bilateral systematic lymphadenectomy with resection of SLNs as well as macroscopic suspicious LN. Additional paraaortic LN were removed in case of higher tumor stages or after histopathological proof of LNM by frozen section. Ultrastaging was performed for SLN with complete preparation of the entire LN with 200µm slices.

Statistical analysis

Statistical analysis was performed with SPSS Statistics 25.0 software (IBM Inc.) and MedCalc 19.3 (MedCalc Software Ltd). Test performances were calculated with fourfold tables. Fisher´s exact test (two-tailed) was used to verify significant differences on the prevalence of LNM. A p-value <0.05 was considered as statistically significant.

RESULTS

Tumor histology and prevalence of LNM

Almost every tumor stage from pT1a to pT2b was represented in this cohort (see table 2). Tumor grade was balanced between G1/G2 and G3 (G1: n=4, G2: n=17, G3: n=20). In one case, a peritoneal involvement could not be ruled out histologically (pTx) so that the clinical assessment of the tumor border (cT2b, M1 (peritoneum)) was applied. Prevalence of LNM was 29.3% per patient (12/41) and 22.8% per hemipelvis (18/79). 5/12 patients presented with solely small LNM at a maximum diameter ≤5mm.

The presence of LNM was significantly higher in pT2 (63.6%) than pT1 stages (13.8%, $p<0.05$). No LNM were found with G1 tumors or T1a tumors stages.

Paraaortic LNM were strictly associated with higher tumor stage and grade (3/4 pT2b (1xG1, 2xG2), 1/4 pTx (G3)). All patients with paraaortic LNM presented with LNM in both hemipelves.

^{18}F-FDG PET/MRI

The prospective reading of PET/MRI as an expert consensus demonstrated a very high specificity for pelvic LN staging in both patient (29/29; 100%, 95%CI: 88.1-100%) and hemipelvis (61/61; 100%, 95%CI: 94.1-100%) based analyses.

However, sensitivity for pelvic LNM-detection was considerably limited (patient-based analysis (4/12; 33.3%, 95%CI: 9.9-65.1%); hemipelvis-based analysis (5/18; 27.8%, 95%CI: 9.7-53.5%). Here the size of the LN played a decisive role for LNM detection by PET/MR, as it only enabled the detection of LNM >5mm (4/7; 57%), while no LNM ≤ 5 mm (0/5) was found.

Thus accuracy, PPV and NPV of PET/MRI for LNM detection was 80.5% (33/41, 95%CI: 65.1%-91.2%), 100% (474) and 78.4% (29/37) on patient level respectively 83.5% (66/79, 95%CI: 73.5-90.9), 100% (5/5) and 82% (61/74) on the hemipelvis level.

Tumor grade had no significant impact on detectability in PET/MRI, as the distribution of G3 and G2 status was comparable in detectable (G3: n=2, G2: n=2) and non-detectable LNM (G3: n=4, G2: n=4).

Pelvic lymphadenectomy was extended to a paraaortic LN sampling in 16/41 patients. 4/16 patients presented with paraaortic LNM at histology. These paraaortic LNM were rated correctly by PET/MRI in 3/4 cases, resulting in a sensitivity of 75% (3/4, 95%CI: 19.4.-99.4%), specificity 100% (12/12, 95%CI: 73.5-100%) and accuracy of 94% (15/16, 95%CI: 66.8-99.8%). All detected paraaortic LNM had diameters between 8-45 mm and were related to pT2b, G3 tumors. The single missed LNM was from a G2 tumor and had a maximal diameter of 7 mm.

Sentinel lymph node detection

SPECT/CT detected at least one SLN in 82.9% of all patients (34/41) respectively in 70.7% (58/82) per hemipelvis. SLN in both hemipelves were detectable in 61.0% (25/41). Detection rate of paraaortic SLN was substantially lower (31.7%, 13/41). In one patient, SLNs were solely visualized by dye, increasing the overall detection rate to 85.4% (35/41) on patient based level.

The presence of LNM was higher in patients or hemipelves without detectable SLN in SPECT/CT (50% (3/6) or 31.2% (7/22)) compared to cases with detectable SLN (23.5% (8/34) or 19.3% (11/57)). A representative case is shown in figure 1. However, the difference was not significant on patient and hemipelvis level (p=0.32, respectively

p=0.25). Only 1/4 patients with paraaortic LNM showed corresponding SLNs in SPECT/CT.

To analyze the representativeness of the SLN biopsy for the assessment of N-status on hemipelvis level, we performed an additional subanalysis in SLNs that were clearly assignable in SPECT/CT and gamma probe (44 SLN assignable in 35 hemipelves of 24 patients). Prevalence of malignancy was 22.9% (8/35); sensitivity: 87.5%, 95%CI:47.4-99.7%, (7/8); specificity: 100%,95%CI:87.2-100%, (27/27); accuracy: 97% (34/35, 95%CI:85.1-99.9); PPV: 100% (7/7); NPV: 96.4% (27/28)).

Combined PET/MRI and SLN protocol

Combination of ^{18}F-FDG PET/MRI and SLN imaging improved the detection rate of LNM substantially from 33.3% to 75.0% on patient-based level respectively from 27.8% to 66.7% on hemipelvis level. In return, PET/MRI was superior to SLN imaging for the detection of paraaortic LNM. Further details are shown in table 3.

In a subanalysis of 28 patients with tumor size ≤4cm, no parametrial invasion or enlarged LN, SLN imaging detected LNM in 3/3 patients or 3/4 hemipelves. Implementing additional PET data could not improve LNM detection in this small subgroup (0/3) with metastases of 0.5-4mm.

A representative example of the synergies between the two modalities is presented in figure 2. However, our data implicate, that PET/MRI cannot predict LN status precisely in case of failed SLN detection (demonstrated in figure 3).

DISCUSSION

To our knowledge, this is the first prospective study on a combined protocol of ^{18}F-FDG PET/MRI and SLN SPECT/CT for the purpose of lymph node staging in patients with cervical carcinoma. The data presented here suggest that PET/MRI has a high specificity in LN staging but only a limited sensitivity, because of the presence of small LNM < 5mm, which seem to occur frequently in early stage tumors.

In contrast to i.v. injected tracers and contrast media, the SLN technique provides decisive information about lymphatic drainage of the tumor and identifies LN with the highest risk for metastases independent of its size. Thus, the combination of metabolic and morphological information from PET/MRI with functional information from lymph drainage resulted in a significant improvement of sensitivity and detection rate.

Diagnostic power PET/MRI

Detection of small metastases is known to be a major challenge for PET. However, the sensitivity in our study was lower than reported in earlier PET/CT (44%) and PET/MRI studies (33% vs. 44-88%) (*20,21,23,24*).

This discrepancy might be explained by the high rate of small LNM compared to previous studies (*20,21,23,24*). This might be due to the defined cohort of solely FIGO I-II stage, exhibiting a reported prevalence of micrometastases of more than 40% (*25,26*).

In addition, this is the first PET study on this topic implementing ultrastaging as golden standard, which increases the detection of micrometastases by up to 28% (*16*). In our study, the implementation of ultrastaging enabled the detection of micrometastases down to 0.5 mm. As the partial volume effect increases with

decreasing lesion size, PET has a poor sensitivity in the lower mm range, thus missing smaller metastases (*27,28*).

Consequently, it can be hypothesized that studies without ultrastaging as the gold standard might overrate sensitivity of PET.

Unfortunately, MRI was only able to compensate for the difficulties of PET to a limited extent, especially in small metastases. Due to the limited spatial resolution of diffusion weighted images, only LN >5mm were evaluated sufficiently on ADC images (*29,30*). The described improvement of LNM detection by calculating a ratio of ADC LN/primary tumor (*29*) was not applicable in our cohort, as most of the patients underwent diagnostic conization before PET/MRI.

Contrary to the limited sensitivity, PET/MRI demonstrated a very high specificity in the assessment of LNM. This high specificity does not only refer to pelvic, but also to paraaortic LNM and is comparable to previous PET/CT and (fused) PET/MRI studies with reported specificities of 84-94% (*20,21,23,24*).

As the presence of pelvic or paraaortic LNM results in an upstaging to FIGO IIIB respectively FIGO IVB, PET/MRI can have a major impact on clinical management. For example, the histological confirmation of a PET positive paraaortic LNM via minimal invasive LN biopsy could shift the patient from an unnecessary and stressful hysterectomy to radiochemotherapy.

Furthermore, MRI has the potential to detect infiltration of the pelvic wall, which is important for the differentiation between T3a and T3b or FIGO IIIA and FIGO IIIB stage, with an equal or better accuracy than clinical staging (*5,24,31*).

SLN detection rate

Our study confirms previous work, which stated that the removal of single SLNs is representative of pelvic LN status (*15,32*). Consequently, the presence of pelvic LNM was correctly demonstrated by SLN removal in all our patients with successful SPECT/CT confirmed radioactive SLN labeling.

Our detection rate of SLN in SPECT/CT was slightly lower than described in current literature data (*33,34*). As higher tumor stages and LNM prevalence are associated with a significantly lower SLN detection rate (*33*), the composition of this cohort - with higher tumor stages than in other SLN studies - might be a potential explanation. Current data indicate an up to 50% higher risk for LNM in cases of failed SLN detection in SPECT/CT (*33,34*). Although the significance level was not reached due to the limited number of LN, it might be hypothesized that missed SLN detection in imaging is not necessarily indicative of a non-sufficient injection. Rather, metastatic tissue might inhibit lymph drainage or disrupts the filtering function of involved lymph nodes.

Combination of PET/MRI and SLN

The combination of PET/MRI and SLN resulted in the highest detection rate of LNM, whereas the additional value of PET/MRI increases with advanced tumor stage and parametrial invasion. However, PET/MRI could not improve N-staging in case of small tumors restricted to the cervix, whereby the FNR is described below 0.1% in case of successful SLN mapping and no suspicious LN in MRI (*32*). Thus PET/MRI seems to contribute little in this specific patient group. In clinical practice, however, successful SLN marking and final tumor stage often only become apparent during surgery. If whole-

body imaging would be omitted in case of clinically assumed low T-stage, paraaortic LNM or distant metastases may be missed, as currently demonstrated by a patient with pT1 tumor but liver metastases.

The fact that ^{18}F-FDG PET/MRI contributes to the detection of LNMs might be explained by loss of colloid avidity. In addition, the SLN technique is independent of LN size and thus enables the biopsy based detection of small LNMs beyond the resolution limit of PET and MRI which improves sensitivity considerably.

The detection rate of paraaortic lymph nodes using SPECT/CT was currently higher than in previous studies (*35,36*), but not sufficient as a stand-alone method for a reliable assessment of the paraaortic status.

Our results demonstrate that PET/MRI has the potential to identify paraaortic LNM, however the statistical power is still limited (*23,24*). As imaging with FDG allows an assessment of all organ systems, a full body PET/MRI staging can be performed in 30-40 minutes.

Limitations

The limitation of this study is that the data represent an interim evaluation of an ongoing prospective study. Although the study covers the largest collective to date, the available data tend to indicate trends in some issues. For confirmation of these trends, more data are needed.

So far, the evaluation has only been conducted at a patient and hemipelvis level. However, due to the limited sensitivity of PET/MRI, further evaluation of the multiparametric data at lymph node level is necessary. Thus, a larger study including a

higher number of lymph node metastases is desirable to further evaluate PET/MRI in this entity.

CONCLUSION

^{18}F-FDG PET/MRI is a highly specific method in lymph node staging that improves LNM detection. Due to the limited sensitivity in frequently occurring small LNM, PET/MRI should be combined with sentinel node SPECT/CT. The combined protocol helps to decide whether extensive surgical staging is needed in patients with FIGO I/II cervical cancer.

DISCLOSURE

Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy (EXC 2180 – 390900677)

No other potential conflict of interest relevant to this article was reported.

Figure legend:

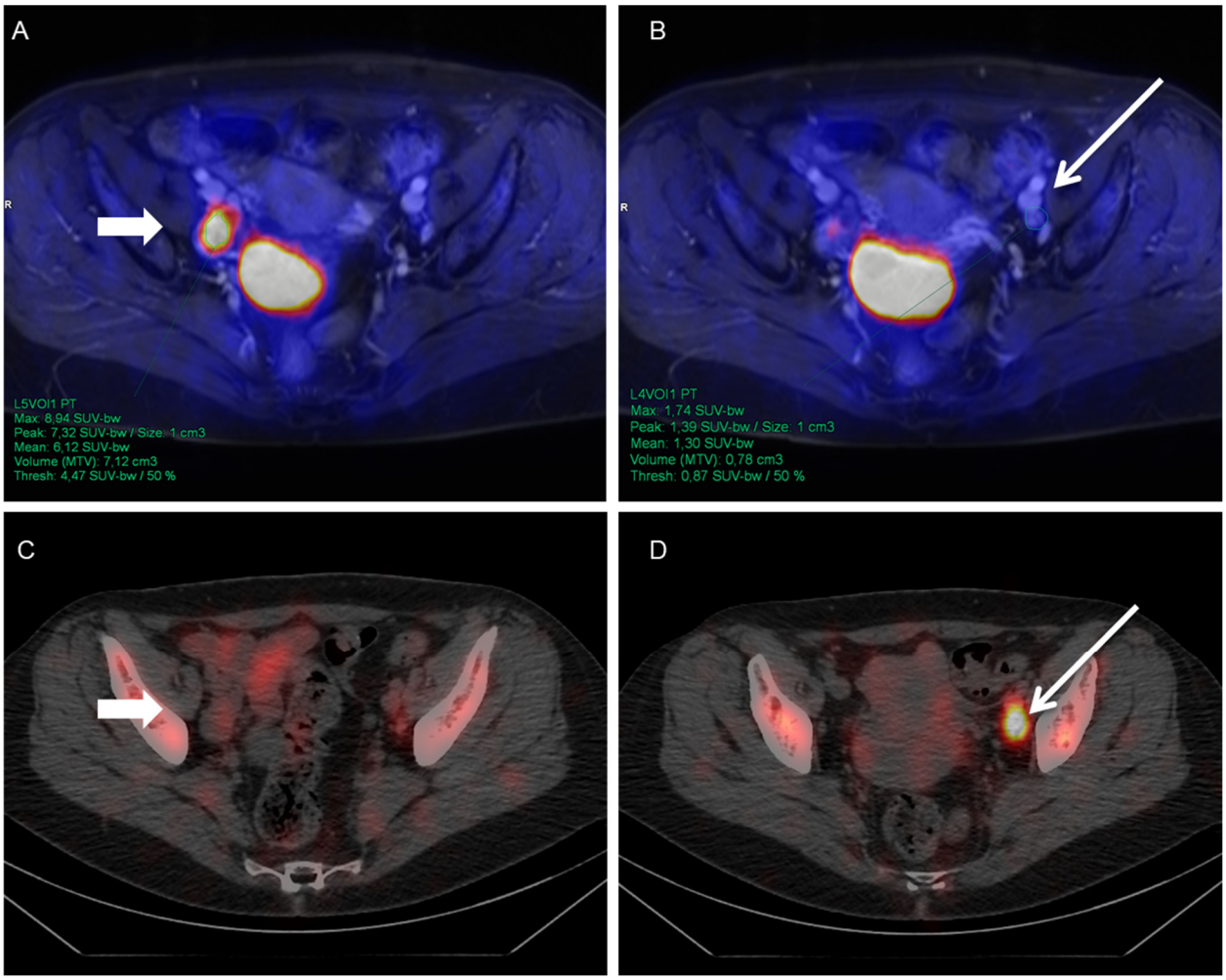


FIGURE 1: 58-year-old woman with new diagnosed T2b G3 cervical carcinoma. PET/MRI (top row) detected an enlarged lymph node in the right hemipelvis (thick arrow) with intense ^{18}F-FDG uptake (A). In contrast, ^{99m}Tc-nanocolloid SPECT/CT showed a clearly definable SLN in the left hemipelvis (D, thin arrow) with benign characteristics in PET/MRI (B). After surgery, the one in the right hemipelvis (A,C) was confirmed as LNM. The SLN on the left (B,D) had benign histology.

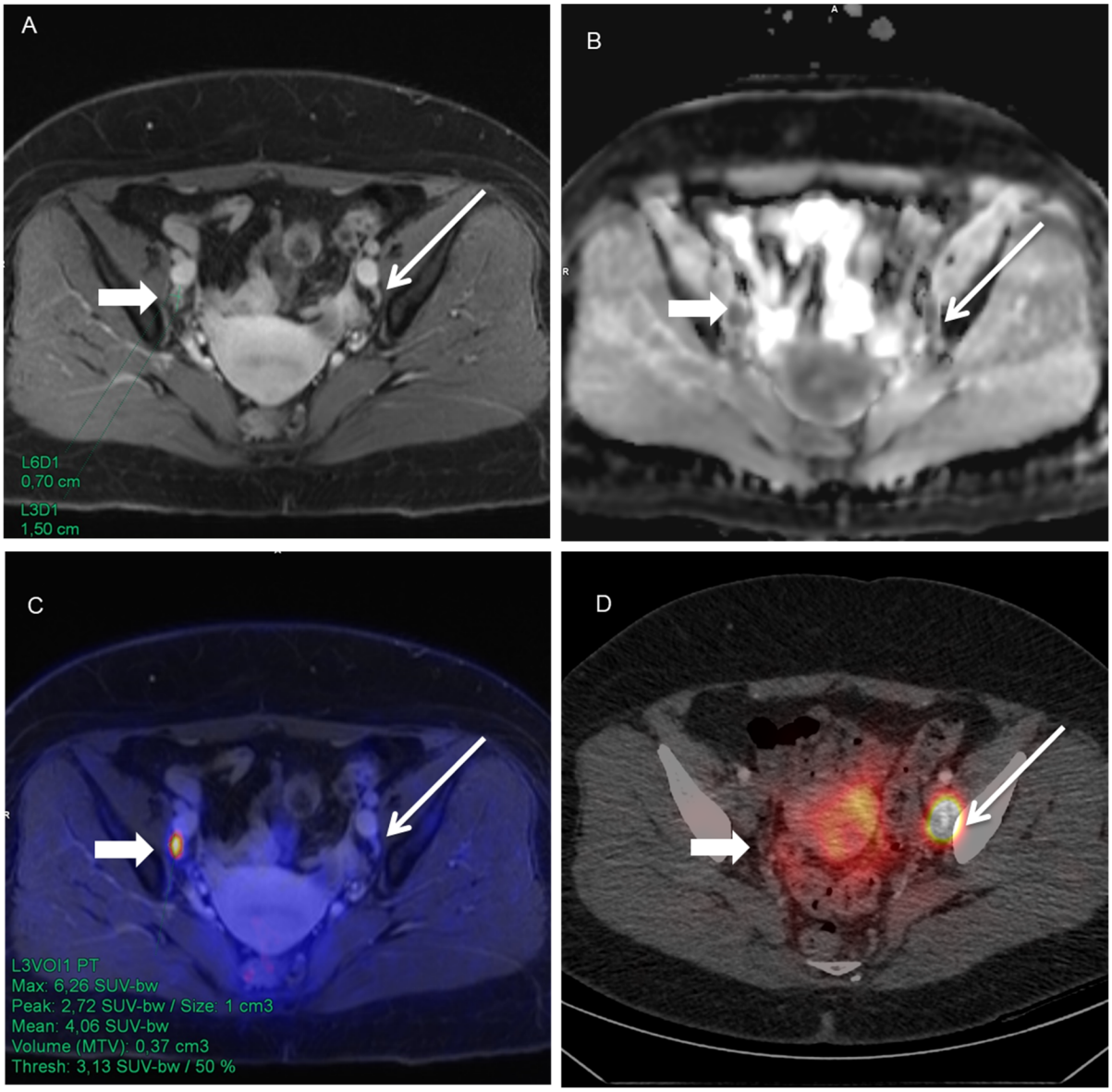


FIGURE 2: 55-year-old patient with initial diagnosis of T1b G2 cervical carcinoma. PET/MRI showed a slightly enlarged contrast enhanced LN in the right hemipelvis (A, thick arrow) with diffusion restriction in the ADC-map (B) and focal ^{18}F-FDG uptake in the PET-fused image (C), but no ^{99m}Tc-nanocolloid uptake in SPECT/CT (D). In contrast, the SLN (C) in the left hemipelvis (thin arrow) was unsuspicious in the PET/MRI images (A,B,C). Both lymph nodes were removed and histologically confirmed as LNMs.

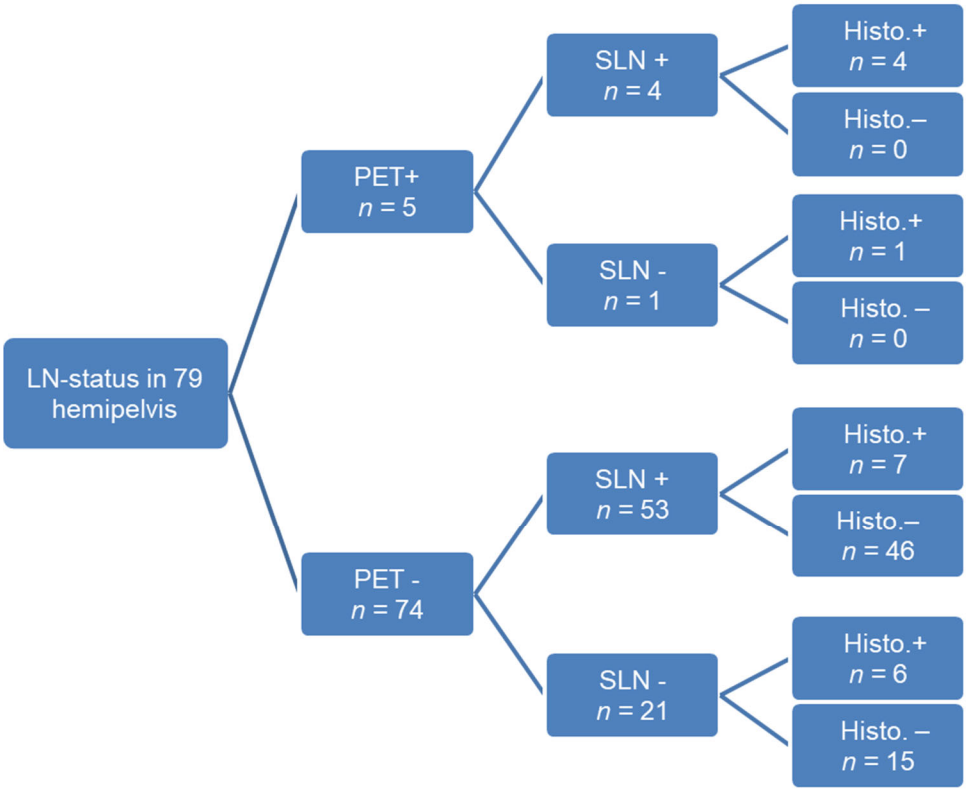


FIGURE 3: Overview of the distribution of lymph node metastases depending on the PET/MRI findings and the detectability of sentinel nodes.

Tables:

Table 1: Patients characteristics (n=41).

	average ±SD	**range**
Age at PET/MRI (years)	48.1±12.2	28.1-80.9
Patient size (cm)	166±6.7	152-187
Patient weight (kg)	70.8±17.0	44.0-117.0
BMI (kg/m²)	25.8±6,0	15.2-40.0
Time between PET/MRI and LN histology (days)	22.4±15.7	1-71

Table 2: Distribution of patients by tumor stage.

Tumor stage		Number of patients (patients with pelvic LNM in brackets)		
		G1	**G2**	**G3**
pT1	pT1a	1(0)	3(0)	1(0)
	pT1b	2(0)	8(2)	14(2)
	pT1c	-	-	-
pT2	pT2a	-	1(0)	-
	pT2b	1(0)	3(3)	6(4)
pTx (cT2b)		-	-	1(1)

Subgroups of tumor stages are summarized

Table 3: Detection rate of lymph node metastases in ^{18}F-FDG PET/MRI, SLN SPECT/CT and combined protocol

	PET/MRI	SLN	PET/MRI + SLN
Per patient	33.3% (4/12)	66.7% (8/12)	75.0% (9/12)
≤ pT2a1 and N0 in MRI	0% (0/3)	100% (3/3)	100% (3/3)
≥ pT2a2	14.3% (1/7)	42.9% (3/7)	42.9% (3/7)
Hemipelvis	27.8% (5/18)	61.1% (11/18)	66.7% (12/18)
≤ pT2a1 and N0 in MRI	0% (0/4)	75.0% (3/4)	75.0% (3/4)
≥ pT2a2	18.2% (2/11)	45.5% (5/11)	54.5% (6/11)
paraaortic LNM	75% (3/4)	25% (1/4)	75% (3/4)

KEY POINTS

QUESTION:

Does the combination of ^{18}F-FDG PET/MRT and SLN SPECT/CT improve the lymph node staging in FIGO I/II cervical carcinoma?

PERTINENT FINDINGS:

In this prospective study PET/MRI exhibited a specificity of 100% but limited sensitivity of 33%. The combination of PET/MRI and SPECT/CT-guided SLN biopsy increased the detection rate of lymph node metastases to 75%.

IMPLICATIONS FOR PATIENT CARE:

^{18}F-FDG PET/MRI can save metastasized patients from unnecessary surgery but should be combined with SLN biopsy because of its limited sensitivity in frequently occurring small metastases.

REFERENCES

1. Bhatla N, Berek JS, Cuello Fredes M, et al. Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynaecol Obstet.* 2019;145:129-135.

2. Lagasse LD, Creasman WT, Shingleton HM, Ford JH, Blessing JA. Results and complications of operative staging in cervical cancer: experience of the Gynecologic Oncology Group. *Gynecol Oncol.* 1980;9:90-98.

3. Selman TJ, Mann C, Zamora J, Appleyard TL, Khan K. Diagnostic accuracy of tests for lymph node status in primary cervical cancer: a systematic review and meta-analysis. *CMAJ.* 2008;178:855-862.

4. Koh WJ, Abu-Rustum NR, Bean S, et al. Cervical Cancer, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2019;17:64-84.

5. Thomeer MG, Gerestein C, Spronk S, van Doorn HC, van der Ham E, Hunink MG. Clinical examination versus magnetic resonance imaging in the pretreatment staging of cervical carcinoma: systematic review and meta-analysis. *Eur Radiol.* 2013;23:2005-2018.

6. *Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe AWMF): S3-Leitlinie Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom, Langversion, 1.0 , AWMF-Registernummer: 032/033OL,* 2014.

7. Tanaka Y, Sawada S, Murata T. Relationship between lymph node metastases and prognosis in patients irradiated postoperatively for carcinoma of the uterine cervix. *Acta Radiol Oncol.* 1984;23:455-459.

8. Fuller AF, Jr., Elliott N, Kosloff C, Hoskins WJ, Lewis JL, Jr. Determinants of increased risk for recurrence in patients undergoing radical hysterectomy for stage IB and IIA carcinoma of the cervix. *Gynecol Oncol.* 1989;33:34-39.

9. Kim SM, Choi HS, Byun JS. Overall 5-year survival rate and prognostic factors in patients with stage IB and IIA cervical cancer treated by radical hysterectomy and pelvic lymph node dissection. *Int J Gynecol Cancer.* 2000;10:305-312.

10. Marth C, Landoni F, Mahner S, et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2018;29:iv262.

11. Pieterse QD, Kenter GG, Gaarenstroom KN, et al. The number of pelvic lymph nodes in the quality control and prognosis of radical hysterectomy for the treatment of cervical cancer. *Eur J Surg Oncol.* 2007;33:216-221.

12. Kadkhodayan S, Hasanzadeh M, Treglia G, et al. Sentinel node biopsy for lymph nodal staging of uterine cervix cancer: a systematic review and meta-analysis of the pertinent literature. *Eur J Surg Oncol.* 2015;41:1-20.

13. SiSaia P, Creasman W, Mannel R, Scott D. *Clinical Gynecologic Oncology* Vol 9: Elsevier; 2017:38-101.

14. Holman LL, Levenback CF, Frumovitz M. Sentinel lymph node evaluation in women with cervical cancer. *J Minim Invasive Gynecol.* 2014;21:540-545.

15. van de Lande J, Torrenga B, Raijmakers PG, et al. Sentinel lymph node detection in early stage uterine cervix carcinoma: a systematic review. *Gynecol Oncol.* 2007;106:604-613.

16. Bats AS, Mathevet P, Buenerd A, et al. The sentinel node technique detects unexpected drainage pathways and allows nodal ultrastaging in early cervical cancer: insights from the multicenter prospective SENTICOL study. *Ann Surg Oncol.* 2013;20:413-422.

17. Marchiole P, Buenerd A, Benchaib M, Nezhat K, Dargent D, Mathevet P. Clinical significance of lympho vascular space involvement and lymph node micrometastases in early-stage cervical cancer: a retrospective case-control surgico-pathological study. *Gynecol Oncol.* 2005;97:727-732.

18. Choi HJ, Ju W, Myung SK, Kim Y. Diagnostic performance of computer tomography, magnetic resonance imaging, and positron emission tomography or positron emission tomography/computer tomography for detection of metastatic lymph nodes in patients with cervical cancer: meta-analysis. *Cancer Sci.* 2010;101:1471-1479.

19. Li K, Sun H, Guo Q. Combinative evaluation of primary tumor and lymph nodes in predicting pelvic lymphatic metastasis in early-stage cervical cancer: a multiparametric PET-CT study. *Eur J Radiol.* 2019;113:153-157.

20. Stecco A, Buemi F, Cassara A, et al. Comparison of retrospective PET and MRI-DWI (PET/MRI-DWI) image fusion with PET/CT and MRI-DWI in detection of cervical and endometrial cancer lymph node metastases. *Radiol Med.* 2016;121:537-545.

21. Kim SK, Choi HJ, Park SY, et al. Additional value of MR/PET fusion compared with PET/CT in the detection of lymph node metastases in cervical cancer patients. *Eur J Cancer.* 2009;45:2103-2109.

22. German Clinical Trials Register. Federal Institute for Drugs and Medical Devices. https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00014346 Updated September 04,2018. Accessed August, 08,2020.

23. Sarabhai T, Schaarschmidt BM, Wetter A, et al. Comparison of (18)F-FDG PET/MRI and MRI for pre-therapeutic tumor staging of patients with primary cancer of the uterine cervix. *Eur J Nucl Med Mol Imaging.* 2018;45:67-76.

24. Grueneisen J, Schaarschmidt BM, Heubner M, et al. Integrated PET/MRI for whole-body staging of patients with primary cervical cancer: preliminary results. *Eur J Nucl Med Mol Imaging.* 2015;42:1814-1824.

25. Lentz SE, Muderspach LI, Felix JC, Ye W, Groshen S, Amezcua CA. Identification of micrometastases in histologically negative lymph nodes of early-stage cervical cancer patients. *Obstet Gynecol.* 2004;103:1204-1210.

26. Juretzka MM, Jensen KC, Longacre TA, Teng NN, Husain A. Detection of pelvic lymph node micrometastasis in stage IA2-IB2 cervical cancer by immunohistochemical analysis. *Gynecol Oncol.* 2004;93:107-111.

27. Bellevre D, Blanc Fournier C, Switsers O, et al. Staging the axilla in breast cancer patients with (1)(8)F-FDG PET: how small are the metastases that we can detect with new generation clinical PET systems? *Eur J Nucl Med Mol Imaging.* 2014;41:1103-1112.

28. Cysouw MCF, Kramer GM, Hoekstra OS, et al. Accuracy and precision of partial-volume correction in oncological PET/CT studies. *J Nucl Med.* 2016;57:1642-1649.

29. Lin G, Ho KC, Wang JJ, et al. Detection of lymph node metastasis in cervical and uterine cancers by diffusion-weighted magnetic resonance imaging at 3T. *J Magn Reson Imaging.* 2008;28:128-135.

30. Roy C, Bierry G, Matau A, Bazille G, Pasquali R. Value of diffusion-weighted imaging to detect small malignant pelvic lymph nodes at 3 T. *Eur Radiol.* 2010;20:1803-1811.

31. Ozsarlak O, Tjalma W, Schepens E, et al. The correlation of preoperative CT, MR imaging, and clinical staging (FIGO) with histopathology findings in primary cervical carcinoma. *Eur Radiol.* 2003;13:2338-2345.

32. Tax C, Rovers MM, de Graaf C, Zusterzeel PL, Bekkers RL. The sentinel node procedure in early stage cervical cancer, taking the next step; a diagnostic review. *Gynecol Oncol.* 2015;139:559-567.

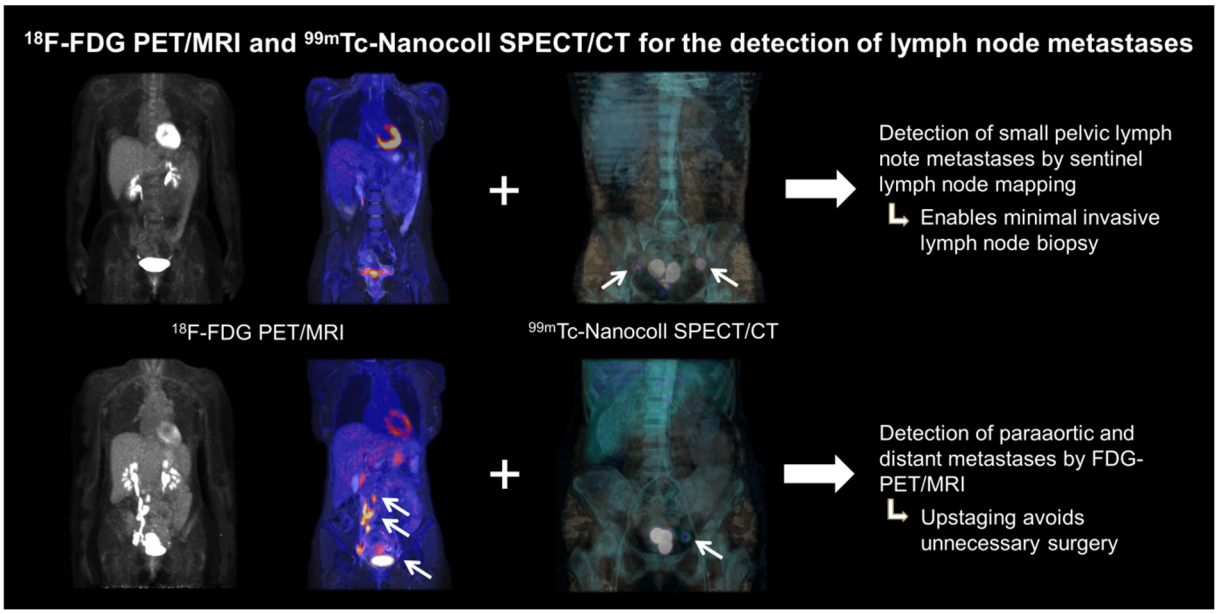
33. Balaya V, Bresset A, Guani B, et al. Risk factors for failure of bilateral sentinel lymph node mapping in early-stage cervical cancer. *Gynecol Oncol.* 2020;156:93-99.

34. Cibula D, Kuzel D, Slama J, et al. Sentinel node (SLN) biopsy in the management of locally advanced cervical cancer. *Gynecol Oncol.* 2009;115:46-50.

35. Diaz-Feijoo B, Perez-Benavente MA, Cabrera-Diaz S, et al. Change in clinical management of sentinel lymph node location in early stage cervical cancer: The role of SPECT/CT. *Gynecol Oncol.* 2011;120:353-357.

36. Ogawa S, Kobayashi H, Amada S, et al. Sentinel node detection with (99m)Tc phytate alone is satisfactory for cervical cancer patients undergoing radical hysterectomy and pelvic lymphadenectomy. *Int J Clin Oncol.* 2010;15:52-58.

Graphical Abstract



Supplemental table 1: MRI parameters.

	Slice thickness	Acquisition matrix	In-plane resolution (mm²)	Repetition time	Echo time	Flip angle	Fat saturation
Wholebody							
T2w HASTE cor	5	320x320	1.5625\ 1.5625	1200	91	160	
T2w HASTE tra	5	256x172	0.785\ 0.78125	1200	95	160	
T1w GRE (VIBE) tra	3	384x234	1.3021\ 1.3021	3.95	1.23	10	Dixon fat saturation
DWI (b50/800)	6	128x104	1.7578\ 1.7578	2500	52	90	Water excitation
Post KM: T1w GRE (VIBE)	3	320x195	1.2813\ 1.2813	3.93	1.24/ 2.48	9	Dixon fat saturation
Pelvis							
T2w TSE tra.	3	320x320	0.78125\ 0.78125	5760	101	160	
T2w TSE cor.	3	320x310	0.78125\ 0.78125	5880	101	160	
T2w TSE sag.	3	320x310	0.625\ 0.625	5760	101	160	

HASTE: **H**alf fourier **A**cquisition single **S**hot **T**urbo spin **E**cho
VIBE: **V**olume **I**nterpolated **B**reath-hold **E**xamination