Is it time to include [^{18}F]FDG-PET/CT in the diagnostic work-up for lymph node staging in cN0 vulvar cancer patients?

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The study from Rufini et al. [1] published in this issue of the *EJNMMI* is the largest series of vulvar cancer patients pre-operatively staged with [^{18}F]FDG-PET/CT. Given the scarcity of this disease and the importance of nodal staging, this study brings important insights to the nuclear medicine and oncology communities.

Current guidelines for the management of vulvar squamous cell cancers describe a limited role for [^{18}F]FDG-PET/CT. The most recent published guidelines from the National Comprehensive Cancer Network (NCCN) [2] recommend only to consider of [^{18}F]FDG-PET/CT (including neck/chest/abdomen/pelvis/groin) at initial diagnosis for T2 or larger tumours or if metastasis is suspected. The European Society of Gynecologic Oncology (ESGO) Vulvar Cancer Guidelines full report from 2017 includes imaging of the groins with ultrasound (US), PET/CT or MRI prior to sentinel lymph node assessment as a Grade C recommendation [3]. According to the ESGO guidelines, sentinel node biopsy (SNB) is recommended in patients with unifocal cancers of less than 4 cm without suspicious groin nodes. If lymph node metastases are diagnosed pre-operatively, inguinofemoral lymphadenectomy should be performed and CT or PET/CT can rule out involvement of pelvic nodes to plan also pelvic nodal debulking. The 2020 American College of Radiology Appropriateness Criteria® for Staging and Follow-up of Vulvar Cancer rates

[^{18}F]FDG-PET/CT as “usually appropriate” for initial staging for patients with a primary tumour greater than 4 cm or tumour of any size with more than minimal involvement of the urethra, vagina or anus [4]. In each of these, and other relevant national guidelines in which there is discussion of [^{18}F]FDG-PET/CT, no studies as large as the cohort reported here by Rufini et al. are referenced. The recent systematic review and meta-analysis by Triumbari et al. included only 10 small-volume studies [5]. Thus, it is likely that the study by Rufini et al. will shape future expert recommendations for management of vulvar cancer in both pre-operative assessment of the groin and pelvis, and for use in treatment planning for patients planned for definitive radiotherapy.

The study from Rufini et al. is a single institution retrospective study involving 160 patients with vulvar cancer (VC) treated within a multidisciplinary standardized approach. PET examinations were acquired on two systems, one of them equipped with point-spread-function (PSF) modelling, which not only improves detectability of small cancer deposits [6] but also leads to a significant increase in SUV metrics compared to conventional algorithms and therefore requires harmonization [7]. In this study, harmonization was achieved by using a post filtering step, though eventually visual analyses overcome SUV-based analysis. Rufini et al. fully covered the information assessable on PET/CT images, namely visual and quantitative (SUV-based) interpretation of PET images as well as CT criteria, i.e. short axis of pelvic nodes. Interestingly, visual analysis overcame SUV-based criteria. Overall, sensitivity (Se) and negative predictive value (NPV) in discriminating metastatic from non-metastatic nodes were 85.6% (95% CI 78.3–92.8) and 91.2% (95% CI 86.7–95.8%), respectively. The authors also concluded that CT criteria were not useful on top of PET interpretation, as the aim of improved interpretation criteria was to reduce the risk of overlooked LN metastases, and PET+CT criteria in fact slightly altered Se and NPV. Hence, simple visual assessment can be safely used for interpretation in busy PET centres.

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Fig. 1 Flowchart of sentinel node biopsy (SNB) in cN0 vulvar cancer, adapted from the EANM experts panel consensus [11]. Situations where pre-operative ^{18}F -FDG-PET/CT could be useful have been highlighted in blue colour

While the study from Rufini et al. included all patients suitable for surgery, one may question which category of patients would most benefit from a pre-operative PET scan, provided sufficient diagnostic performance are demonstrated. Having in mind not only the morbidity of iliofemoral lymphadenectomy (IFL) but also how heavily false-negative results would worsen the prognosis, identification of patients fit instead for SNB would be extremely useful. Current guidelines recommend SNB in cN0 VC with tumour <4 cm, excluding patients with multifocal tumours and complete diagnostic excision.

A perspective for the Oncology and Nuclear Medicine communities would be the use of a combination of PET and SNB, using the latest PET technologies for a better selection of cN0 patients. Indeed, one might assume that new PET technologies [8], such as digital PET with small voxel reconstruction, will allow the PET community to revisit certain indications such as detection of small-volume nodal disease, with hopefully good results in cN0 vulvar cancer patients.

In the study from Rufini, 96 cN0 patients were included and amongst these patients, only 40 of them were candidates for SNB. Focusing on this group, NPV and LR- were 92.2% (95% CI: 87.3–97.1%) and 0.53, respectively. The size of the cancer deposits was not reported but given the short axis of the surgically removed nodes, which ranged from 4 to 8 mm in

false-negative PET examinations, a gain in VPN and LR- thanks to more recent PET systems can surely be expected.

The use of pre-operative PET in cN0 patients not suitable for SNB was investigated by Garganese et al. [9] in a pilot prospective study, seeking whether (i) SNB indication could be extended to cN0 patients currently unfit to SNB and (ii) pre-operative [^{18}F]FDG-PET/CT could improve the selection of cN0 patients for SNB. Their study assessed 73 groins in 23 patients, using a Phillips Gemini system (no PSF modelling, 4mm^3 voxel size) and visual analysis based on the ratio between nodal uptake and the gluteal muscle. They reported a negative predictive value of 93% (95% CI: 84–97). The negative likelihood ratio (LR-) computed from their results, defined as follows: $\text{LR-} = (1 - \text{Se}) / \text{Spe}$, was 0.5. It is noteworthy that the sizes of the metastases in the 4 false-negative results were 1.5, 3, 5 and 6 mm, again clearly within the expected detection capability of modern state-of-the-art PET systems. With regard to the potential combination of SNB with [^{18}F]FDG-PET/CT, large multicentre prospective trials that validated SNB in replacement of lymph node dissection in cN0 VC patients also provide interesting insights regarding the size of cancer deposits: For example, in the GROINSS-V trial, Oonk et al. [10] reported that 49% of the nodes involved at routine pathology had cancer deposits larger than 5 mm.

The small size of metastatic deposits in patients with cN0 disease and false-negative PET is also informative if applied to patients receiving adjuvant radiotherapy. There is little standardization of radiotherapy volumes or doses for these patients, and the high NPV reported in Rufini and colleagues suggest that pre-operative PET/CT could increase confidence in radiation planning for patients with SNB results even in the absence of complete IFL. Elective nodal dose to treat microscopic disease (45–50Gy) would be appropriate in this case. Omission of groin nodal volumes, especially ipsilateral to the primary vulvar tumour, in the absence of negative IFL would require a near-perfect NPV given the risks of undertreatment. Assessment of the GroSNaPET study by Garganese et al. [9] found that all false-negative LNs on pre-operative [^{18}F]FDG-PET were revealed by SLN assessment, and no non-SNs were positive for metastatic disease, suggesting that the combination of PET and SNB could provide near 100% NPV. The current study shows a similarly high NPV of PET (92% for cN0). Validation of these findings on a prospective randomized trial would provide the confidence to omit SLN-negative, PET-negative nodal regions from the adjuvant radiation volumes, thus reducing toxicity of treatment.

Based on the recent consensus of the EANM experts on SLNB in VC [11], one might assume that pre-operative PET could be used in specific situations such as exploration of the contralateral groin in midline tumours unilateral, in case of SLN detected unilaterally, and to expand the use of SLN to patients with larger tumours (Fig. 1).

Declarations

Ethical approval Institutional Review Board approval was not required because the paper is an Editorial.

Informed consent Not applicable.

Conflict of interest The authors declare no competing interests.

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