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## Response to comment on 'Preoperative nomogram for the identification of lymph node metastasis in early cervical cancer'

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Sir,

We would like to thank Buda *et al*, 2014 for their valuable comments on our study. They make three comments. First, is there really a commitment to offer lymphadenectomy to all women with early-stage cervical cancer? Second, is there an algorithm or nomogram to assess the nodal risk involvement to better select women who can really benefit from retroperitoneal surgical staging? Finally, what is the impact of those tools in the decision making in women desiring to preserve fertility?

So far, pelvic lymphadenectomy is endorsed as a standard surgical procedure in early-stage cervical cancer including stage IA1 disease with lymphovascular space invasion (Koh *et al*, 2013). However, ~80% of early-stage cervical cancer patients are node-negative and the therapeutic effect of lymphadenectomy in these patients is still controversial. Some authors suggested that among node-negative patients survival is improved when a greater number of lymph nodes are removed because of better extraction of micrometastasis (Shah *et al*, 2011). Therefore, lymphadenectomy in early-stage cervical cancer should be offered until clinical trials elucidate the therapeutic value of lymphadenectomy in node-negative disease.

It is clear that patient selection for such trials is the critical issue. The results of our study show accurate identification of the low-risk group of LNM and we believe it could help patients' stratification in designing such trials. Although our nomogram is dependent on the status of lymph node detected by PET/CT, the other two factors (age and tumour size) are incorporated into the model to compensate the false-negative findings of PET/CT. As Buda *et al*, 2014 commented, PET/CT sensitivity and negative predictive values seem to be low in the early-stage cervical cancer patients with tumour size <4 cm (Signorelli *et al*, 2011), although PET/CT is the most accurate imaging tool for assessment of nodal status in cervical cancer currently. After review of our data set comprising a model development cohort with tumour size <4 cm ( $n = 248$ ), PET/CT sensitivity and negative predictive values were 63.9% and 93.5%, respectively. We believe the main reason for the difference in this subgroup could be the different proportions of micrometastasis (defined as metastatic deposits <5 mm). Of the 36 cervical cancer node-positive patients, 14 (39%) patients showed micrometastases in our data set, whereas 56% node-positive patients (34/61) demonstrated micrometastases in previous series of Buda *et al*, 2014 We agree with Buda's opinion that metabolic tumour volume (MTV) correlates with lymph node metastasis. In our recent study of 84 endometrial cancer patients, the group with MTV  $\geq 17.15$  ml was significantly associated with lymph node metastasis (Shim *et al*, 2014). Using this volumetric functional parameter or combining sentinel lymph node (SLN) biopsy could lead to improvement in our model.

To confer the benefits of SLN biopsy to patients who desire to preserve fertility, a careful preoperative evaluation for eligible patients is important. Although SLN biopsy may be useful for avoiding complete lymphadenectomy, its routine clinical use is still limited because of technical difficulties and prerequisites such as a nuclear medicine department, intraoperative frozen sections, and ultrastaging. In addition, SLN detection rate was reported to be associated with tumour size and preoperative conisation; SLN detection rate was statistically lower in patients with tumour sizes >3 cm (Du *et al*, 2011) and those with conisation (Dargent and Enria, 2003; Seong

*et al*, 2007). Thus, SLN biopsy would be useful for detecting nodal metastasis in small-volume tumour, and using imaging modalities such as PET/CT would be useful in other cases. In this regard, the nomogram conjuncted with SLN biopsy would be clinically helpful for selecting appropriate patients who wish to preserve fertility and could be treated with radical trachelectomy.

As suggested by Buda *et al*, 2014, we think that SLN biopsy is of great value in early cervical cancer patients, especially in those with small-size tumor. However, its clinical use is still limited because of technical difficulties and lack of standardisation. Our developed nomogram is a non-invasive, easily applicable, and user-friendly tool. We believe that the nomogram will allow selection of a patient population at low risk for nodal metastasis and thus facilitate the design of clinical trials. Definitely, as suggested by Buda *et al*, 2014, assessment of nodal status solely by PET/CT still represents a challenge and the nomogram requires rigorous validation. Thus, future researches should focus on testing whether the predictive performance can be shown in other independent cohorts and enhanced by incorporating SLN biopsy.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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