Commentary

Radiomic models for lymph node metastasis prediction in cervical cancer: can we think beyond sentinel lymph node?

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ABSTRACT

Liu and colleagues performed a retrospective study to validate a computed tomography (CT) scan-based radiomic model to detect lymph node metastasis in cervical cancer. The proposed model incorporating the arterial and venous phase CT-scan features represented a non-invasive method exhibiting high sensitivity in the prediction of lymph node metastasis. It is well established that lymph node metastasis is one of the most significant prognostic factors in cervical cancer. For this reason, management of cervical cancer is strictly related to lymph node status, with international guidelines recommending definitive chemoradiation in case of metastatic lymph node. More and more evidence supports the use of sentinel lymph node in early-stage cervical cancer but its frozen section analysis may result in false negative results; in locally-advanced stages staging para-aortic lymphadenectomy is proposed by many Authors to tailor chemoradiotherapy treatment, with potential intra-and post-operative related complications. The use of a validated radiomic model able to predict lymph node metastases in radiologically normal lymph nodes may represent an essential tool to possibly spare lymphadenectomy related morbidity.

We read with great interest the very recent article by Liu et al [1]. In this retrospective study, the Authors propose and validate a computed tomography (CT) scan-based radiomic model for lymph node metastasis prediction in cervical cancer. With a sensitivity of 0.854 and 0.870 and an area under the receiver operating characteristic curve of 0.912 and 0.859 in the training and internal validation cohorts, respectively, the Authors concluded that the proposed model incorporating the arterial and venous phase CT-scan features represented a non-invasive method exhibiting great ability in the prediction of lymph node metastasis.

It is well established that lymph node metastasis is one of the most significant prognostic factors in cervical cancer [2,3]. Moreover recently, the number of metastatic lymph nodes has recently been shown to have an essential prognostic impact [4]. Therefore, the information on lymph node status becomes of paramount importance.

In case the metastatic lymph node is detected intra-operatively (and possibly confirmed with a staging lymphadenectomy), both the literature evidence and the international guidelines recommend against the continuation of radical surgery in favor of definitive chemoradiotherapy [5,6]. On the other hand, if the lymph node metastasis is diagnosed after radical hysterectomy and lymphadenectomy, adjuvant chemoradiation is indicated [3,5]. For this reason, the frozen section of the pelvic lymph nodes specimen has been proposed [7], but the sensitivity of this technique is not as adequate as the final pathology report.

More recently, the sentinel lymph node (SLN) technique has been proposed with promising results in terms of sensitivity in diagnosing lymph node metastasis [8,9]. Nevertheless, even though the ultrastaging of SLN at final pathology increases its negative predictive value by diagnosing low-volume metastases, different studies questioned the role of frozen section of SLN, with sensitivity ranging from 46.0% to 87.5% [10-12]. For this reason, the use of a frozen section of SLN may not be the best tool to triage patients to radical hysterectomy versus definitive chemoradiation [12]. In this context, the one-step nucleic acid amplification (OSNA) method has been recently proposed to intra-operative detect low-volume metastases in SLN and triage subsequent treatment [13], but this technique is still under evaluation.

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With this background, we could consider that radiomic features of pelvic lymph nodes may represent a promising additional decision-making tool to triage patients to radical surgery versus chemoradiation, even in cases of morphologically normal lymph nodes [1]. Indeed, standard radiology using morphologic and dimensional assessment has been demonstrated to have limitations in sensitivity and specificity [14]. More recently, fluorine18-fluorodeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) has been introduced in clinical practice of cervical cancer staging, with improvement in terms of accuracy in diagnosing lymph node metastases, but still 12-22% of lymph node metastases may be missed [14,15].

More in detail, the advantages of the radiomic-based model in predicting the radiologically normal lymph nodes may be essential in both early and locally advanced stage diseases.

In early-stage cervical cancer, the prediction of the positive lymph node may allow avoiding any lymph nodal dissection, including SLN mapping, with the subsequent risk of performing radical surgery in lymph nodes positive patients [6]. Few studies have already shown that for selected very low-risk patients, the probability of metastasis in SLN is negligible and any kind of lymph node dissection could be avoided [15-16]: radiomics models may broaden the spectrum of patients in whom lymphadenectomy can be spared including also higher risk patients.

In locally advanced stages, it may spare lymphadenectomy-related morbidity and aid in deciding whether para-aortic extended-field radiotherapy is needed [6,17-19].

Multiple studies reported the results of peri-operative morbidity from lymphadenectomy [20,21], significantly reduced by SLN dissection [22,23]: even if low, this complication rate could be potentially further reduced/eliminated by radiomic models.

Different studies analyzed radiomic features to predict lymph node metastasis in cervical cancer [24-26], but the recent study from Liu and colleagues was the first to analyze normal-size lymph nodes [1]. The results in terms of accuracy are promising, and the use of internal and external validation increases the reproducibility of such a method.

This further study appears to be particularly useful as it demonstrates the possibility to extend the radiomics analysis to a mixed multicentric cohort of patients, confirming the applicability of this technique on imaging real world data.

Nevertheless, despite a sound methodology with several tested models merging the information coming from logistic regressions and more advanced machine learning solutions, the Authors do not clarify the possible biological meaning of the involved radiomics features. This confirms the lack of biological correlations as one of the most significant weakness of current radiomics investigations, strongly limiting the translational and personalized medicine applications of this recent and promising analysis technique, especially when not coupled with clinical data, as correctly argued by the Authors [27,28].

Future prospective studies analyzing the accuracy of radiomic models in the prediction of lymph node metastasis and possibly, of low-volume metastasis in SLN, are warranted to increase diagnostic information on lymph node status before surgery, with the perspective of not only reducing but eliminating operative morbidity.

Declaration of Competing Interest

All Authors report no conflict of interest.

Author Contribution Statement

Nicolo Bizzarri, Luca Boldrini, Salvatore Gueli Alletti: Conceptualization, Methodology, Original draft preparation. Maria Gabriella Ferrandina, Giovanni Scambia, Francesco Fanfani: Supervision, Revision. Salvatore Gueli Alletti, Nicolo Bizzarri: Writing - Reviewing and Editing.

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