Commentary

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

Nicolò Bizzarri [1], Luca Boldrini [2], Gabriella Ferrandina [1,3], Francesco Fanfani [1,3], Luigi Pedone Anchora [1], Giovanni Scambia [1,3], Salvatore Gueli Alletti [1,3,*]

[1] Fondazione Policlinico Universitario A. Gemelli, IRCCS, UOC Ginecologia Oncologica, Dipartimento per la salute della Donna e del Bambino e della Salute Pubblica, Rome, Italy
[2] Fondazione Policlinico Universitario A. Gemelli, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Rome, Italy
[3] Università Cattolica del Sacro Cuore, Rome, Italy

A B S T R A C T

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 chemo-radiation 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 lympadenectomy 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 chemo-radiotherapy [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.

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 chemo-radiation, 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.

Furthermore, this 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

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

References

[1] Y Liu, H Fan, D Dong, et al., Computed tomography-based radiomic model at node level for the prediction of normal-sized lymph node metastasis in cervical cancer [published online ahead of print, 2021 May 8], Transl Oncol 14 (8) (2021), 101113, https://doi.org/10.1016/j.tranon.2021.101113.

[2] LT Gien, A. Covens, Lymph node assessment in cervical cancer: prognostic and therapeutic implications, J Surg Oncol 99 (4) (2009) 242–247, https://doi.org/10.1002/jso.21199.

[3] WA Peters 3rd, PY Liu, RJ Barrett 2nd, et al., Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix, J Clin Oncol 18 (8) (2000) 1606–1613, https://doi.org/10.1200/JCO.2000.18.8.1606.

[4] L Pedone Anchora, V Carbone, V Gallotta, et al., Should the Number of Metastatic Pelvic Lymph Nodes be Integrated into the 2018 Figo Staging Classification of Early Stage Cervical Cancer? Cancers (Basel) 12 (6) (2020) 1552, https://doi.org/10.3390/cancers12061552. Published 2020 Jun 12.

[5] D Cibula, R Pötter, F Planchamp, et al., The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology Guidelines for the Management of Patients With Cervical Cancer, Int J Gynecol Cancer 28 (4) (2018) 641–655, https://doi.org/10.1097/IGC.0000000000001216.

[6] D Cibula, L Dostalek, P Hillemanns, et al., Completion of radical hysterectomy does not improve survival of patients with cervical cancer and intraoperatively detected lymph node involvement: ABRAX international retrospective cohort study, Eur J Cancer 143 (2021) 88–100, https://doi.org/10.1016/j.ejca.2020.10.037.

[7] HS Scholz, SF Lax, C Benedicic, K Tamussino, R. Winter, Accuracy of frozen section examination of pelvic lymph nodes in patients with FIGO stage IB1 to IIB cervical cancer, Gynecol Oncol 90 (3) (2003) 605–609, https://doi.org/10.1016/s0090-8258(03)00398-6.

[8] F Lécuru, P Mathevet, D Querleu, et al., Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study, J Clin Oncol 29 (13) (2011) 1686–1691, https://doi.org/10.1200/JCO.2010.32.0432.

[9] C Tax, MM Rovers, C de Graaf, PL Zusterzeel, RL. Bekkers, The sentinel node procedure in early stage cervical cancer, taking the next step; a diagnostic review, Gynecol Oncol 139 (3) (2015) 559–567, https://doi.org/10.1016/j.ygyno.2015.09.076.

[10] A Papadia, C Morosi, J Wang, et al., SLN mapping in early-stage cervical cancer as a minimal-invasive triaging tool for multimodal treatment, Eur J Surg Oncol 45 (4) (2019) 679–683, https://doi.org/10.1016/j.ejso.2019.01.184.

[11] A Rychlik, MA Angeles, F Migliorelli, et al., Frozen section examination of sentinel lymph nodes can be used as a decisional tool in the surgical management of early cervical cancer, Int J Gynecol Cancer 30 (3) (2020) 358–363, https://doi.org/10.1136/ijgc-2019-000904.

[12] D Cibula, R Kocian, A Plaikner, et al., Sentinel lymph node mapping and intraoperative assessment in a prospective, international, multicentre, observational trial of patients with cervical cancer: The SENTIX trial, Eur J Cancer 137 (2020) 69–80, https://doi.org/10.1016/j.ejca.2020.06.034.

[13] N Bizzarri, L Pedone Anchora, GF Zannoni, et al., Role of one-step nucleic acid amplification (OSNA) to detect sentinel lymph node low-volume metastasis in early-stage cervical cancer, Int J Gynecol Cancer 30 (3) (2020) 364–371, https://doi.org/10.1136/ijgc-2019-000939.

[14] HJ Choi, W Ju, SK Myung, Y. Kim, 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 101 (6) (2010) 1471–1479, https://doi.org/10.1111/j.1349-7006.2010.01532.x.

[15] A Fagotti, L Pedone Anchora, C Conte, et al., Beyond sentinel node algorithm. Toward a more tailored surgery for cervical cancer patients, Cancer Med 5 (8) (2016) 1725–1730, https://doi.org/10.1002/cam4.722.

[16] G Ferrandina, L Pedone Anchora, V Gallotta, et al., Can We Define the Risk of Lymph Node Metastasis in Early-Stage Cervical Cancer Patients? A Large-Scale, Retrospective Study, Ann Surg Oncol 24 (8) (2017) 2311–2318, https://doi.org/10.1245/s10434-017-5917-0.

[17] S Gouy, P Morice, F Narducci, et al., Nodal-staging surgery for locally advanced cervical cancer in the era of PET, Lancet Oncol 13 (5) (2012) e212–e220, https://doi.org/10.1016/S1470-2045(12)70011-6.

[18] S Gouy, P Morice, F Narducci, et al., Prospective multicenter study evaluating the survival of patients with locally advanced cervical cancer undergoing laparoscopic para-aortic lymphadenectomy before chemo-radiotherapy in the era of positron emission tomography imaging, J Clin Oncol 31 (24) (2013) 3026–3033, https://doi.org/10.1200/JCO.2012.47.3520.

[19] S Marnitz, AT Tsunoda, P Martus, et al., Surgical versus clinical staging prior to primary chemoradiation in patients with cervical cancer FIGO stages IIB-IVA: oncologic results of a prospective randomized international multicenter (Uterus-11) intergroup study, Int J Gynecol Cancer 30 (12) (2020) 1855–1861, https://doi.org/10.1136/ijgc-2020-001973.

[20] M Zikan, D Fischerova, I Pinkavova, et al., A prospective study examining the incidence of asymptomatic and symptomatic lymphoceles following lymphadenectomy in patients with gynecological cancer, Gynecol Oncol 137 (2) (2015) 291–298, https://doi.org/10.1016/j.ygyno.2015.02.016.

[21] H Hareyama, K Hada, K Goto, et al., Prevalence, classification, and risk factors for postoperative lower extremity lymphedema in women with gynecologic malignancies: a retrospective study, Int J Gynecol Cancer 25 (4) (2015) 751–757, https://doi.org/10.1097/IGC.0000000000000405.

[22] P Mathevet, F Lécuru, C Uzan, et al., Sentinel lymph node biopsy and morbidity outcomes in early cervical cancer: Results of a multicentre randomised trial (SENTICOL-2), Eur J Cancer 148 (2021) 307–315, https://doi.org/10.1016/j.ejca.2021.02.009.

[23] D Cibula, M Borčinová, S Marnitz, et al., Lower-Limb Lymphedema after Sentinel Lymph Node Biopsy in Cervical Cancer Patients, Cancers (Basel) 13 (10) (2021) 2360. Published 2021 May 13.

[24] Y Kan, D Dong, Y Zhang, et al., Radiomic signature as a predictive factor for lymph node metastasis in early-stage cervical cancer, J Magn Reson Imaging 49 (1) (2019) 304–310, https://doi.org/10.1002/jmri.26209.

[25] T Wang, T Gao, J Yang, et al., Preoperative prediction of pelvic lymph nodes metastasis in early-stage cervical cancer using radiomics nomogram developed based on T2-weighted MRI and diffusion-weighted imaging, Eur J Radiol 114 (2019) 128–135, https://doi.org/10.1016/j.ejrad.2019.01.003.

[26] J Chen, B He, D Dong, et al., Non-invasive CT radiomic model for preoperative prediction of lymph node metastasis in early cervical carcinoma, Br J Radiol 93 (1108) (2020), 20190558, https://doi.org/10.1259/bjr.20190558.

[27] A Cesario, M D'Oria, F Bove, et al., Personalized Clinical Phenotyping through Systems Medicine and Artificial Intelligence, J Pers Med 11 (4) (2021) 265, https://doi.org/10.3390/jpm11040265. Published 2021 Apr 2.

[28] R De Maria Marchiano, G Di Sante, G Piro, et al., Translational Research in the Era of Precision Medicine: Where We Are and Where We Will Go, J Pers Med 11 (3) (2021) 216, https://doi.org/10.3390/jpm11030216. Published 2021 Mar 18.