Editorial

Extranodal extension of nodal metastasis is the main prognostic moderator in squamous cell carcinoma of the esophagus after neoadjuvant chemoradiotherapy

Claudio Luchini[1], Nicola Veronese[2]

[1]Department of Diagnostics and Public Health, University and Hospital Trust of Verona, Verona, Italy; [2]National Research Council, Neuroscience Institute, Aging Branch, Padova, Italy

Correspondence to: Dr. Claudio Luchini, MD. Department of Diagnostics and Public Health, University and Hospital Trust of Verona, Piazzale Scuro, 10, Verona 37134, Italy. Email: claudio.luchini@katamail.com or claudio.luchini@univr.it.

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Several studies, including comprehensive systematic reviews with meta-analyses of our group of research, have demonstrated the negative prognostic impact of the extranodal extension of nodal metastasis (ENE) in different cancer types, including squamous cell carcinoma (SCC) of the vulva, of the penis and of head and neck, as well as in tumors of the digestive and genitourinary systems, in thyroid cancer and others (1-17). ENE is a morphological feature that indicates the presence of a nodal metastasis (LNM) that, through a rupture of nodal capsule by neoplastic cells, can reach perinodal adipose tissue, increasing its local aggressiveness and the possibilities for distant metastasization (1,2). Recent studies and meta-analyses have highlighted the prognostic role of ENE also in esophageal carcinoma (EC), analyzing both patients that received and that not received neoadjuvant treatment (14-17); the meta-analysis, however, did not address this particular issue due to the lack of specific analyzable data (14). Now the gold standard for locally advanced EC is represented by neoadjuvant chemoradiation (NCR) followed by surgery, because of improved loco-regional disease control and survival for patients treated with this strategy (16,17). Of note, it still lacks a comprehensive summary of the prognostic weight of ENE in EC patients treated with NCR followed by surgery.

The recent paper published on the *Annals of Surgery* by Depypere *et al.* tries to answer to this specific question (17). Indeed, this paper explores the prognostic impact of ENE in lymph node (LN)-positive EC after NCR. This study shows that ENE is important at least as pathological nodal stage (pN) for survival in esophageal SCC patients treated with NCR followed by surgery. The Authors specifically analyzed LNM EC patients, 182 with SCC and 391 with adenocarcinoma (AC). ENE was detected in 60 LNM esophageal SCC patients (33% of the total of LNM esophageal SCC) and in 147 LNM esophageal AC patients (37.6% of the total of LNM esophageal AC). Notably, for LNM SCC, ENE emerged as the strongest independent prognosticator for survival in multivariable analysis. At the same time, in AC the prognostic role of ENE was not significant. As stated by the Authors, the main feature of this research is the major importance of ENE in esophageal SCC after NCR, independently from ypN stage. Furthermore, there was no survival difference between incomplete responders with no LNM and ypN1 patients without ENE, indicating that persistent limited number (<2) of LNM without ENE after NCR does not automatically imply a systemic dissemination of cancer for such patients. For AC, the prognostic role of ENE was not retained. This is an important difference and calls for a revision of the current staging system for EC, that should consider also the specific histotypes in the future. The reasons of these

differences are still unclear, but a diverse biology between these two EC subtypes seems to be the most important one. Indeed, a first explanation may be that SCC tends to have a better prognosis on NCR than AC (28% of complete responders in SCC *vs.* 13% in AC). Another may reside in the total number of residual LNM after NCR, with a mean value significantly lower in SCC (0.90) than AC (1.86) in this work (17). Future studies are needed to better explore this topic, also considering that the prognostic impact of ENE may vary not only on the basis of tumor histotypes, but also on the basis of the biological features in the same histotypes. For example, in SCC of the head and neck, ENE plays a negative prognostic role on loco-regional recurrence and distant metastasization, but in HPV-positive oropharyngeal SCC such prognostic role is not retained (9,10). This observation further points out a biological peculiarity of ENE in influencing cancer prognosis.

The overall message of the paper by Depypere *et al.* is important; it represents one of the most important manuscripts for the consideration of ENE by future staging systems. In our opinion they should consider this fundamental parameter in EC also on the basis of the histotypes, and also in other cancer types. The most important clinical implication is that patients with esophageal LN positive SCC and ENE+ could benefit from adjuvant treatment after NCT followed by surgery. Notably, in pancreatic ductal AC, post-operative chemo-radiation or chemotherapy alone was found to have no significant effect on overall survival or disease-free survival. Interestingly, a subgroup of ENE+ patients was demonstrated by Sergeant *et al.* to have an improvement in overall survival and in disease-free survival with adjuvant chemo-radiation, but not with chemotherapy alone (18). These findings should be explored also for EC, since, due to the poor survival, not only NCR but also adjuvant treatment seems to be important in ENE+ patients. If it will be possible to predict ENE before surgery, even NCR could be adapted to this patient group. For example, for bladder cancer Smith and colleagues have developed a 20-gene panel able to stratify patients into low or high risk of nodal metastases (19,20). Notably, a recent work has suggested the molecular marker PIM-1 is a significant predictor for nodal metastasis in EC (21). Speaking about ENE, for SCC of head and neck a specific predictive genetic panel already exists (22); future studies are needed to identify ENE genetic predictors also in EC, starting from genes already known to be important drivers in gastrointestinal malignancies (23,24). ENE genetic predictors may have potential implications not only for NCR and adjuvant treatment, but also for genetic-targeted therapy.

Points of strengths of the paper by Depypere *et al.* are for sure represented by the rigorous selection of the patients (all patients underwent standard NCR followed by surgery), the multicentric design, the use of a standard and specific definition of ENE (e.g., exclusion of tumor deposits in adipose tissue and of vascular invasion out of LN from ENE definition), the reliable method of LN sampling for ENE detection (LN larger than 1 cm or suspicious for metastasis were bisected preparing two slides for histopathologic evaluation) and the adequacy of the follow-up (median 42.5 months, mean 70.5 months, very long considering the highly malignant potential of EC). As potential limitation, as also partly acknowledged by the Authors, there are the retrospective design and the lack of a re-evaluation of histology. In our opinion, this latter limitation may be the most important one, since in ENE assessment, despite of the use of a specific ENE definition by all the involved centers, a significant inter-observer variability can exist.

In the last edition (8^{th}) of the new TNM staging system for esophageal cancer (25), there is no modification about pN. Indeed, N0 still corresponds to no regional LNM, as well as N1 to 1–2 regional LNM, N2 to 3–6 regional LNM and N3 to 7 or more regional LNM. Interestingly, although not yet taken into account in pN, there is a new paragraph in this new TNM edition entitled "Extranodal Extension". The prognostic value of this morphologic moderator is classified as AJCC Level of Evidence II. In the AJCC classification, this level is the second in a four-tiered scale of reliability, and indicates that the available evidence is obtained from at least one large, well-designed and well-conducted study in appropriate patient populations with appropriate end points and with external validation. The presence of this new paragraph on ENE in this new AJCC edition may be seen as anticipation for its inclusion in the next edition. At least, the insertion of this new paragraph highlights that the importance of ENE has been acknowledged starting from this TNM edition. The consideration of the number of LNM as the unique moderator in the pN category appears in our opinion not sufficient to guarantee an adequate sub-staging of patients with LNM. This inadequacy is not a peculiarity of EC only, but can be extended to all cancer patients with LNM, in which many morphological features should be considered in the future for a better stratification of patients' prognosis. Speaking about ENE, it has been already taken into account

by the TNM and FIGO classification for SCC of the vulva and of the penis and it is a novelty of the new edition its consideration for SCC of the head and neck (6,9,10,25). Notably, it seems that the histotype might play an important role in influencing the prognosis of metastatic cancer based on the presence of ENE: indeed, the most robust evidences of ENE considered by AJCC regard now SCC only. Also in the paper by Depypere *et al.* the squamous histotype is the one mainly affected by the presence of ENE. However, and of note, recent manuscripts and meta-analyses pointed out that ENE may play an important and independent prognostic role in many other tumors or histotypes. In this line, further investigations are needed to better clarify this prognostic scenario, but the paper by Depypere *et al.* could represent an excellent point of start to this aim.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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