Letter to the editor

Extracapsular lymph node involvement after neoadjuvant chemoradiation in esophageal carcinoma: how to interpret?

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We thank Dr. Chao, and Dr. Luchini and Dr. Veronese for their interest in and their editorial comments (1,2) on our manuscript entitled "Impact of extracapsular lymph node involvement after neoadjuvant chemoradiation therapy followed by surgery in carcinoma of the esophagus: a multicenter study", recently published in *Annals of Surgery* (3).

Both comments highlight the importance of Extracapsular lymph node involvement (EC-LNI) as the strongest predictor for overall survival in squamous cell EC and even propose to consider revising the current staging system. Nevertheless, several questions about how to translate this finding into clinical practice remain.

Starting with the definition of EC-LNI, we deliberately chose for a definition where tumor cells still had a connection with the lymph node itself. As a result, tumor spread in this definition can only be interpreted as nodal invasion. In colon and rectum carcinoma, tumor deposits (TD) in peri-colonic fat are indeed classified as N1c positive nodes in otherwise pN0 patients according to the 8th edition of the AJCC cancer staging manual, in that way influencing staging. But, as further developed in the 8th edition, TD after neoadjuvant chemo- or chemoradiation therapy may represent different pathological situations, being discontinuous spread (categorized as potential primary tumor response with influence on ypT category), venous invasion with extravascular spread (risk factor defined as lymphovascular invasion without influence on ypTNM staging) or a totally replaced lymph node (being defined as ypN1c) (4). Therefore, TD without any connection to the lymph node will probably be responsible for a higher inter-observer variability. Using our definition of tumor extending through the nodal capsule into the perinodal fatty tissue, we are sure that we are dealing with true lymph node invasion, excluding the previously described possible confounding pathological entities.

Second, the concept of "sterilized" lymph nodes is very interesting, especially in ypN0 patients, were no viable tumor cells can be found anymore in any resected lymph node. Morphologically this is theoretically the other spectrum of therapy response on cN+ patients, compared to EC-LNI. However, in clinical practice, a proper definition of a "sterilized" lymph node is lacking: central fibrosis, capsular fibrosis, tumor necrosis with or without calcification, mucin pools, giant cells, foam cells, … (5,6) are all potential signs of lymph node response on nCR. Here again, inter-observer variability could be important, especially for lymph nodes located in the chest where some of those pathological changes could also be triggered by benign "air-borne" conditions. Therefore, further work needs to be done on a definition of "lymph node response" so that data can be collected and compared to survival,

before integration into the future staging systems.

Third, the comment that the number of lymph nodes with EC-LNI was not mentioned, is correct, but probably not important in clinical practice. In our subanalysis we showed that EC-LNI is mainly important in ypN1 squamous cell EC patients as survival differences are significant in this group. Therefore, it can only involve two lymph nodes. Counting more than two EC-LNI nodes is probably irrelevant as persisting N2 or N3 disease after nCR will have anyway a poor prognosis irrespective of the presence of EC-LNI.

The always recurring question "What do we do with this information?" can be answered as follows: first of all, revision of staging groups (especially the squamous cell EC staging groups including ypN1 patients) should be considered to give adequate prognostic information to patients. Second, adjuvant treatment could be more directed to specific staging groups with higher risk. Third, ultimately one is able to properly predict response on nCR by finding genetic predictors for EC-LNI (7) or imaging techniques showing EC-LNI (8), so that adequate therapy can be adjusted before surgical resection.

Anyhow, progression has been made: AJCC 8th edition recognises a specific staging for esophageal carcinoma after neoadjuvant treatment (ypTNM) and devotes a paragraph on extranodal extension (9), although only referring to our previous work on primary esophageal adenocarcinoma (10) and not yet contributing to the staging itself.

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Footnote

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

References

1. Chao YK. Extracapsular lymph node involvement in patients with esophageal cancer treated with neoadjuvant chemoradiation therapy followed by surgery: the closer you look, the less you see. J Thorac Dis 2017. [Epub ahead of print].
2. Luchini C, Veronese N. Extranodal extension of nodal metastasis is the main prognostic moderator in squamous cell carcinoma of the esophagus after neoadjuvant chemoradiotherapy. J Thorac Dis 2017. [Epub ahead of print].
3. Depypere LP, Moons J, Mariette C, et al. Impact of extracapsular lymph node involvement after neoadjuvant chemoradiation therapy followed by surgery in carcinoma of the esophagus: a multicenter study. Ann Surg 2017. [Epub ahead of print].
4. Amin MB, Edge SB, Green FL, et al., editors. AJCC Cancer Staging Manual, 8th edition. New York (NY): Springer-Verlag 2016:251-74.
5. Bollschweiler E, Hölscher A, Metzger R, et al. Prognostic significance of a new grading system of lymph node morphology after neoadjuvant radiochemotherapy for esophageal cancer. Ann Thorac Surg 2011;92:2020-7.
6. Nieman DR, Peyre C, Watson T, et al. Neoadjuvant treatment response in negative nodes is an important prognosticator after esophagectomy. Ann Thorac Surg 2015;99:277-83.
7. Wang W, Lim WK, Leong HS, et al. An eleven gene molecular signature for extra-capsular spread in oral squamous cell carcinoma serves as a prognosticator of outcome in patients without nodal metastases. Oral Oncol 2015;51:355-62.
8. Su Z, Duan Z, Pan W, et al. Predicting extracapsular spread of head and neck cancers using different imaging techniques: a systematic review and meta-analysis. Int J Oral Maxillofac Surg 2016;45:413-21.
9. Amin MB, Edge SB, Green FL, et al. editors. AJCC Cancer Staging Manual, 8th edition. New York (NY): Springer-Verlag, 2016:185-202.
10. Nafteux PR, Lerut AM, Moons J, et al. International multicenter study on the impact of extracapsular lymph node involvement in primary surgery adenocarcinoma of the esophagus on overall survival and staging systems. Ann Surg 2015;262:809-15; discussion 815-6.

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