

Nodal downstaging in esophageal and esophagogastric junction cancer: more important than ever

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Esophageal and esophagogastric junction cancers are still highly deadly malignancies. Nonetheless, multimodal approaches improved survival and gave clinicians some more weapons and patients some more hope. Multimodal approaches include surgery as the mainstay of treatment, together with chemotherapy (ChT) and radiotherapy (RT). Different protocols of associations of ChT and RT have been proposed, but now the most accepted approach considers induction, also called neoadjuvant, treatment with concurrent chemoradiotherapy (CRT) followed by surgery for squamous cell carcinoma and Siewert type I and II adenocarcinoma. For Siewert III adenocarcinoma normally only ChT is used. This multimodal approach showed significant survival advantage, especially in case of good response to treatment (1-4). Induction treatments created a big staging issue, though. Indeed, while TNM has always been pretty good in determining prognosis after upfront surgery, with improvements in staging with the latest versions (5,6), it historically lacked of definition of pathologic post-induction changes and staging. The suffix ypTNM indicates pathologic post-induction staging, and until the last TNM version (8th ed.), it did not have precise definitions and survival curves. In the 8th ed., TNM at last considered and defined ypTNM staging, due to the widely use of induction treatments. Nevertheless it demonstrated to be less distinctive between groups compared to pTNM after upfront surgery (7). The issue of post-treatment pathologic staging is not new. The most used classification

of response to treatment was first proposed by Mandard in 1994 (8). Authors, after noticing that TNM was unable to correctly define prognosis after induction treatments, proposed a Tumor Regression Grade that considered regression on primary tumor according to the presence of residual cancer cells and degree of fibrosis. The main drawback of this invaluable intuition is that Authors did not consider nodal involvement. In a previous paper of our group (9), we proposed a classification of response to CRT that considered also nodal involvement. Indeed, when nodal involvement was added to Mandard's TRG in our case series, this classification was no more informative. On the contrary, our classification, called size-based pathological response (SPR) classification, was able to define classes of different prognosis.

Many other Authors proposed different classification of response to CRT, most of them considering response both on T and N (10-12). All these classifications, although with some limitations, seemed able to stage patients post-operatively according to residual cancer on T and N.

Probably, although the final stage, i.e., the pathological stage, is extremely relevant, also the concept of regression or downstaging is important. And due to the prognostic impact of nodal status, which is one of the most relevant prognostic determinants along with complete curative resection, it can be hypothesized that nodal downstaging might be even more important than downstaging on the primary tumor.

Indeed, we recently demonstrated (13) that not only the final nodal stage after treatment is important, but also the concept of downstaging, with clinical nodal staging before treatment becoming crucial: in our series, node negative patients both before and after treatment (cN0 and ypN0: named “natural N0”) showed significantly improved survival compared to patients who downstaged from cN+ to ypN0 (named “downstaged N0”), and the latter had significantly better survival than yN+ patients. Our findings introduced the concept of downstaging from a cN stage to a ypN stage, indicating that every effort should be made to improve clinical staging.

In parallel with these findings, Shapiro and coworkers (14) tried to determine the pre-treatment stage by measuring the extent of residual cancer and regression changes on the pathologic specimen.

These Authors considered 180 patients with both squamous cell carcinoma and adenocarcinoma treated with induction CRT followed by surgery.

The method used to estimate the original cancer area was based on the extent of regression changes (e.g., fibrosis, mucinous lakes, keratin pearls, foreign body giant cell reactions) along with residual tumor cells in the surgical specimen. This defined the “pretreatment pathological T-stage” (prepT-stage), which according to the Authors was supposedly the estimated original invasion of the primary tumor. The presence of the same regression changes in lymph nodes defined the “pretreatment pathological N-stage” (prepN-stage), which reflected the presence of originally involved lymph nodes. Nodes that showed regression changes, without the presence of residual tumor, were considered by the Authors to have been sterilized by induction CRT. Coupling prepN and ypN-stage, patients were categorized into three groups: “patients who never had nodal involvement, patients who had nodal involvement pre-treatment, but became node-negative, and patients who remained node positive”.

The three upper-GI pathologists who scored the specimens showed pretty successful interobserver agreement, indicating that the method seems promising and reproducible and hence deserves to be further tested in other studies, possibly in other institutions.

The results of this study are extremely interesting: first of all prepT and cT stage showed comparable prognostic strength, meaning that accuracy of clinical imaging staging on T is pretty accurate and use of prepT in clinical practice seems limited. Second, and extremely more decisive, prepN

proved to have more prognostic strength than cN stage and also than ypN stage. Indeed almost 40% of cN0 showed signs of tumor regression, hence were defined prepN+. Likewise, almost 40% of cN+ patients did not show signs of regression and were defined prepN0. This high discordance indicates that clinical nodal staging as routinely performed needs to be drastically improved and explains why prognostic strength of cN stage was poor.

But the main result, the one that needs to be highlighted and stressed with force is the prognostic strength of prepN compared to ypN. Patients who never had nodal involvement (i.e., no residual tumor and no regression changes) had a better survival compared with patients who had nodal involvement pre-treatment, but became node negative after induction CRT, and the latter had better survival than patients who remained node positive after induction CRT. This is exactly what we reported in our investigation (13): hence how you get to ypN0 matters and nodal downstaging is even more important than the final ypN stage. What is convincing about these findings is that two different studies in different countries, starting from slightly different aims, being published online nearly simultaneously obtained almost identical results. This might be the evidence of the importance of this intuition. Other groups (15,16) previously observed that prognosis was better in pN0 patients after upfront surgery compared to ypN0 patients undergoing induction treatment followed by surgery, and attributed this difference to heterogeneity of ypN0 patients. These Authors speculated on the possibility that not all ypN0 patients were equal and that there might have been a group of patients downstaged to ypN0 by eradication of lymph node metastases. What both our group and Shapiro demonstrated is that nodal downstaging truly exists and downstaged patients do have statistically significant decreased survival with respect to natural N0 patients, but better than ypN+ patients. This has a significant clinical implication: indeed, downstaged patients, although with worst prognosis compared to natural N0, still have greatly better survival than ypN+ patients. Hence downstaging positively impacts on survival and those patients with initial nodal involvement who downstaged to ypN0 had significantly improved prognosis. All patients with clinical nodal involvement should then undergo induction treatments to increase the possibility to downstage and improve survival. Detecting clinical nodal involvement before treatment would be of utmost importance.

Compared with Shapiro and coworkers, we obtained our statistically significant results using CT scans with an improved method, where lymph nodes were reckoned metastatic when presenting at least 2 of the following features: short axis ≥ 10 mm, round shape, non-homogeneous density.

Our results indicate that this improved CT scan method is promising and deserves further investigation and, probably, a study using both this CT scan method and prepN might add some more important prognostic information. Improving clinical staging would allow detecting clinical nodal metastases before treatment allowing treatment modifications along the way. Unfortunately, for now, we can only conjecture about all possible clinical implications of this discovery, but confirming these results with other studies and improving clinical staging are further steps toward tailoring treatment.

There is still a long road ahead, but the way is paved for the introduction of nodal downstaging into staging classifications. Nodal downstaging in esophageal and esophagogastric junction cancer is now more important than ever.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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