Editorial Commentary

Prognostic relevance of tumor response after neoadjuvant therapy for patients with esophageal cancer

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Comment on: Kröll D, Noser L, Erdem S, *et al.* Application of the 8th edition of the AJCC yTNM staging system shows improved prognostication in a single center cohort of esophageal carcinomas. Surg Oncol 2018;27:100-5.

Submitted Jul 08, 2019. Accepted for publication Aug 08, 2019.
doi: 10.21037/atm.2019.08.36
View this article at: http://dx.doi.org/10.21037/atm.2019.08.36

Introduction

In recent years, pre and perioperative chemotherapy or chemoradiotherapy have been successfully implemented for advanced esophageal carcinoma (1,2). Traditionally, the resected specimen and lymph nodes (LN) have been evaluated according to the Union for International Cancer Control (UICC)/TNM system. The gold standard for evaluation of the prognosis after surgical therapy is the pathological TNM (pTNM) staging system. UICC established the 7th edition of the TNM system for esophageal cancer in 2009 (3). This was followed in 2018 by the current 8th edition (4,5). The 7th and earlier editions used data from patients treated surgically and without other interventions. Therefore, the TNM staging system offers limited value for patients receiving pre-operative chemotherapy or chemoradiation. The 7th edition used a simple "y" to distinguish pre-treated from treatment-naïve tumors. One of the major changes in the 8th TNM edition was the introduction of a distinct post-neoadjuvant pathological stage group (ypTNM) (4,6). This modification is found in the TNM8 classification of the AJCC (6), but not the UICC (5).

Surgeons and pathologists from the University Hospital in Bern/Switzerland re-evaluated the data of patients with esophageal cancer treated with neoadjuvant therapy over the past 15 years (7). In total, 198 cases had received neoadjuvant therapy. These were re-evaluated and classified using the TNM7 and ypTNM8 systems. Accurate staging was possible using ypTNM8 for neoadjuvant-treated esophageal cancer, and the prognostic value was slightly better than with TNM7.

Many questions remain. For one, should the same classification system be used for naïve tumors and for those post-neoadjuvant therapy? The 7th and 8th editions of the TNM classification define pT and ypT categories for esophageal cancer as ypT0 (no residual cancer; pCR); ypT1 (carcinoma within the subepithelial tissue, e.g., the lamina propria, muscularis mucosa or submucosa); ypT2 (carcinoma within the muscular layer (muscularis propria); ypT3 (carcinoma within the external esophageal layer, i.e., adventitia); and ypT4 (carcinoma within nearby structures) (5,6).

This classification is based on the idea that in naïve tumors, invasion begins at the epithelial layer of the esophagus. Deeper tumor invasion correlates with worse prognosis; this has been shown in several studies. The pT category is a valid prognostic factor. However, there is no evidence that tumor regression begins at the deepest point of invasion, e.g., that a pT4 tumor with little regression after chemotherapy necessarily becomes a ypT3 tumor, with medium regression a ypT2 tumor, and so on. And it is possible that a small number of residual tumor cells in the esophageal adventitia could be a ypT3 tumor. Thus, prognostic differentiation of the ypT categories is not very good. Several studies have confirmed this. Kröll *et al.* (7) found that patients with ypT0, ypT1 or ypT2 had the same prognosis. Similar results have been reported by other authors (8,9).

Regression in the primary tumor

To improve the prognostic relevance of tumor response

after neoadjuvant therapy a great number of systems and classifications has been developed for evaluating the histopathological response. These can be further broken down into qualitative versus (semi)-quantitative systems according to histopathological criteria. These consider first and foremost the cytologic and topographic characteristics associated with tumor regression and tumor cell vitality. For esophageal cancer, the Mandard Classification and the Cologne Regression Scale are used most frequently in clinical studies (10-12).

The Mandard classification was published in 1994 and uses semi-quantitative assessment of the ratio of fibrosis to tumor within the primary tumor (10). Initially, it was used in squamous cell esophageal cancers to estimate tumor regression after neoadjuvant cisplatin and radiotherapy (10). Since that time, a number of studies have evaluated the Mandard system regarding prognostic relevance for esophageal adenocarcinomas and for different types of chemotherapy (13-15). One early study classified regression of the primary tumor based on histopathological changes according to the original publication by Mandard (10). It offered five tumor regression grades (TRGs). TRG1 (complete pathologic regression) is characterized by the absence of residual cancer (on histological examination) and presence of fibrosis reaching various layers of the esophageal wall, plus or minus granuloma; TRG2 has occasional residual cancer cells scattered within fibrosis; TRG3 shows more residual cancer cells, but overriding fibrosis; TRG4 has more residual cancer than fibrosis; and TRG5 is characterized by a lack of regressive changes.

The Cologne Regression Scale was initially used to evaluate lung carcinoma (16). It showed good prognostic relevance when used in esophageal squamous cell and adenocarcinoma (11,12). This scale classifies according to quantifiable histological measures and vital/necrotic tumor proportions, as well as reactive changes after treatment. Reactive changes are measured within the residual cancer tissue and given as the percentage of vital tumor cells (VTCs) (11,12). Primary tumor regression is then assigned to four histomorphologic categories. Grade I has a complete response; grade II a nearly complete response with <10% vital residual tumor cells (VRTCs); Grade III has 10% to 50% VTCs; and Grade IV has >50% VTCs.

A current study by Puetz *et al.* compared prognostic relevance of ypT categories, the Mandard Classification, and the Cologne Regression Scale in 216 patients with advanced esophageal carcinoma after preoperative chemoradiation (8). They found better prognostic discrimination for subgroups using the Mandard and particularly the Cologne Regression Scale versus ypT category. However, only the Cologne Regression Scale was relevant in terms of prognosis, with hazard-ratios increasing continuously for each subgroup. The authors also found very good inter-rater agreement with the re-evaluated Cologne Regression Scale compared to routine pathological classification, with kappa value 0.891 (8).

Prognostic relevance of lymph node metastasis (LNM)

The UICC /TNM system classifies ypN category according to the number of LNM. Thus, ypN0 is no LNM, ypN1 has 1 to 2 LNM, ypN2 has 3 to 6 LNM, and ypN3 has more than 6 LNM. This classification does not consider the number of resected and analyzed LNs. The quantity of LNs resected can be lower in patients receiving preoperative chemoradiation for advanced esophageal cancer (17). The smaller number of resected LNs might be due to the effects of chemoradiation on metastatic LNs. A study by Castoro *et al.* investigated 402 patients treated consecutively for cancers of the esophagus or esophagogastric junction (18). They compared patterns of nodal metastasis in patients treated with surgery alone versus those receiving pre-operative chemotherapy or chemoradiation. After neoadjuvant therapy, there were fewer lymph node metastases, and localization and patterns of the nodes also changed (18). The quantity and dimensions of metastatic LNs are significantly reduced when there is a good response to neoadjuvant chemoradiation, regardless of cancer histology (17). The ypN0 patient group is of particular interest. Hölscher *et al.* found that patients with minor response in the primary tumor (10% or more VTCs) and ypN0 had comparable prognosis to patients with major response (<10% VTCs) and ypN+ (19).

Therapy-induced changes in lymph nodes

There have been a number of reports in the past few years that signs of regression within metastatic lymph nodes and the primary tumor are relevant to prognosis (20-22).

One study analyzed histomorphologic signs of tumor regression within 1,270 lymph nodes in 40 patients (20). Central fibrosis of the LN showed prognostic relevance as a sign of regression. The most important factor affecting prognosis for advanced esophageal cancer patients receiving preoperative chemoradiotherapy was the lymph node regression grading system (LNMRG) created for the study.

Patients having no LN metastasis and those with isolated signs of tumor regression. The most relevant factors affecting prognosis were ypN category and number of LNs with central fibrosis. Better prognoses were found in ypN0 patients (no LNM) with two or fewer LNs with central fibrosis compared to ypN0 patients with three or more LNs with central fibrosis or those with a limited number of LNM (20). This study included only a small number of patients. However, the results were confirmed in another study with 400+ patients (21). The prognoses of the three groups of patients with the defined LNMRG system differed significantly. The group of ypN0 patients with major primary tumor response (<10% VTCs) and two or fewer LNs with central fibrosis had the best prognoses.

Davies *et al.* studied lymph node regression in 268 patients undergoing preoperative chemotherapy (22). They found subgroups of prognostic relevance in patients with LNM. Lymph node negative patients had negative nodes, no evidence of previous tumor involvement, or negative with complete regression. Lymph node positive patients were given a regression score according to the ratio of fibrosis to residual tumor. The regression score ranged from (I) complete response; (II) less than 10% of residual tumor; (III) 10% to 50% residual tumor; (IV) more than 50% viable tumor; and (V) no response. "Responders" scored 1, 2 or 3, and "Non-Responders" scored 4 or 5. LN regression had a strong effect on prognosis, possibly larger than primary tumor response.

Perspectives

There are many factors that influence the prognosis of esophageal cancer patients. The effect of pre-operative therapy on the primary tumor or metastatic lymph nodes and is probably just one factor among many individual and environmental factors affecting prognosis.

There is clear evidence that response to chemotherapy or chemoradiation is of prognostic relevance. For prognostic grading of the response, standardized histomorphologic evaluation of the primary tumor and resected lymph nodes is necessary. The ypT categories did not differentiate low pT-categories, and thus, combined staging systems based on ypT category are problematic. The evaluation of primary tumor regression using quantitative analysis of histomorphologic signs (percentage of VTCs) showed the best prognostic differentiation.

Along with analysis of primary tumor regression, evaluation of the influence of neoadjuvant therapy on lymph nodes must be performed. Further studies are needed to establish evidence-based and practical lymph node grading systems. Better outcomes are clearly found in patients whose primary tumor shows complete or major response after chemoradiation. However, it remains unclear whether these outcomes are a true benefit of treatment, i.e., showing eradication of the occult systemic disease, or whether these responses are a marker of tumors with more favorable biological characteristics.

Other questions remain: do we need different grading systems for squamous cell carcinoma and adenocarcinoma? Or, what is the influence of different preoperative therapy—chemotherapy or chemoradiation—to the grade of regression and to the prognosis?

Acknowledgments

None.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Bollschweiler E, Hölscher AH. Prognostic relevance of tumor response after neoadjuvant therapy for patients with esophageal cancer. Ann Transl Med 2019;7(Suppl 6):S228. doi: 10.21037/atm.2019.08.36

