Editorial

Editorial on role of p53 in esophageal cancer from a meta-analysis of 16 studies by Fisher *et al.*

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Esophageal adenocarcinoma (EAC) is the predominant form of distal esophageal cancer in the western world. The incidence has increased markedly over the past two decades due to known risk factors, i.e., obesity and gastroesophageal reflux. EAC typically arises from Barrett's esophagus (BE), a metaplastic transformation of the native esophageal squamous epithelium into columnar epithelium in response to gastroesophageal reflux with a risk of malignant progression among patients with BE of 0.22% to 0.5% per year.

The incidence of EAC continues to increase with an estimated 17,460 new cases reported in the USA, and the survival is dismal with a 5-year overall survival (OS) of 15%, irrespective of tumor stage.

In their systematic review of 16 studies (11 with OAC only and 5 with mixed histology) with more of 800 patients, on the prognostic role of p53, Fisher *et al.* conclude that patients with EAC with *TP53* gene mutations have worse OS compared with wild-type patients and the effect is independent of tumour stage (1).

This systematic review analyzes two potential confounders that two previous studies on the prognostic role of p53 did not consider: tumor stage and TP53 mutation analysis methods.

The effect of mutant TP53 on patient OS was larger in studies that had adjusted their analyses for tumor stage compared with the estimates from studies that reported unadjusted risk estimates.

As regard the method to evaluate p53 status, half of the studies (n=8) assessed TP53 mutation status by IHC (immunohistochemistry), one study assessed TP53 mutations through 17p/17p.13 loss of heterozygosity (LOH), one through SSCP (single-strand conformation polymorphism) and the remaining six studies performed TP53 gene sequencing to determine the presence of mutations. Using these methods, a median of 57% of all OACs (range 33–79%) were classified as harboring TP53 mutations.

The effect of TP53 mutation status on survival appeared to be smaller among studies performing IHC compared with studies performing direct TP53 gene assessments (sequencing and SSCP) or LOH analyses, but this difference was not statistically significant. This is probably linked to the use of different antibodies, antibody dilutions and variable scoring systems for immunopositivity.

Considering that the presence of low-moderate heterogeneity across studies is not statistically significant, this systematic review shows that TP53 mutation is associated with a statistically significant negative effect on patient OS with an HR 1.48 (95% CI: 1.16 to 1.90, P=0.002). Fourteen of the total 16 studies reports that the median survival time of patients assessed as having mutated TP53 was 18.9 months compared with 26.2 months for patients with non-mutated TP53.

Molecular analysis has uncovered potential driver mutation in EAC and many of these occur in tumor

suppressor genes, such as p53 and SMAD 4. P53 is mutated at high frequency (80%) and ubiquitously across studies and, interestingly, this genetic alteration is also described in 69% of BE. However the majority of patients with BE do not evolve into cancer, so other genetic pathways are probably involved (2-4). Singhi *et al.* show that the loss of Smad4 protein expression is an independent prognostic factor for time to recurrence and OS; it also correlates with increased propensity for disease recurrence and poor survival in patients with EAC. However, Smad 4 mutation are described in only 13% of EAC and BE, so it has less impact than p53 as a prognostic index to be used in a clinical setting (5). Another pathway with prognostic importance in EACs is TGF-β: the loss of an important TGF-β adaptor, β2SP, in EAC leads to activation of Notch signaling and increased expression of SOX9; high levels of nuclear SOX9 expression are associated with poor survival and adverse disease status (lymph node metastasis). Moreover, nuclear SOX9 expression in tumor tissue increases along with tumor stage and indicate an adverse clinical outcome (6). Also the up-regulation of some miRNAs (miR-143, miR-199a_3p, miR-199a_5p, miR-100 and miR-99a) in EAC would be an index of worse survival as shown by Feber *et al.*, in a study based on specimens from esophagectomy for adenocarcinoma without neoadjuvant chemotherapy (7). In a recent paper by van Olphen *et al.* they also investigate the predictive role of p53 in EAC patient submitted to neoadjuvant chemoradiation prior to surgery. They found that aberrant expression of p53 (both overexpression or complete loss of expression) was associated with a major response, with an odds ratio of 4.9, even after adjusting for age, sex, tumour grade, clinical T and N stage in the primary cohort, with a trend toward significative response in the validation cohort (8).

But what can be the role of p53 mutations in the complex picture of genetic profiling of EAC? TP53 mutations are early driver events in EAC and are almost ubiquitously found. This is well demonstrated by Murugaesu *et al.* in a study based on multi-region exome sequencing (M-seq) on eight tumors from patients with operable EACs in which they assessed tumor evolution both spatially (biopsy taken in different regions of the primary tumor) and temporally (samples obtained in different moments before and after neoadjuvant treatment) (9).

Recently, integrative genomic analyses led to the proposal of a molecular classification of gastric cancer into four subtypes: MSI (microsatellite-instable), EBV (Epstein-Barr virus-positive), chromosomal-instable (CIN), and GS (genomically stable). Molecular classification of gastric cancer advances our knowledge of the biology of the disease and may have implications for diagnostics and patient treatment (10).

Integrated genomic characterization was also published on January 2017 for esophageal carcinoma. The study is based on a molecular analysis of 164 carcinomas of the esophagus (90 squamous, 72 adenocarcinomas, 2 undifferentiated) and clearly shows that EAC and squamous cells carcinoma are distinct in their molecular characteristic. But probably the most intriguing evidence is that, according to molecular analysis, EACs and CIN gastric cancers jointly form a group distinct from EBV, MSI or GS tumors, as they share defining features such as chromosomal instability and p53 mutations.

Moreover, no EACs were positive for MSI or EBV, but among gastroesophageal junction adenocarcinomas, they were able to identify a minority of MSI-positive and EBV-positive tumors (11). Probably, the latter are p53 negative cancers with a different origin pathway, while the notable molecular similarity between EACs and CIN gastric cancers provides indirect support for the gastric origin of BE and EAC.

CIN-EACs and CIN gastric cancer could have a common origin, but this group includes cancers with different prognosis. We know, in fact, from survival analysis that EACs behave better than proximal gastric cancers, and the latter do universally poorer that distant gastric cancers (12,13).

In conclusion, the role of P53 mutation is of a driver mutation in the development of EAC. It is also a defining molecular feature together with CIN of EACs and CIN gastric cancers making them a distinct group from other gastric cancers. Emerging evidence also shows a predictive role to response to neoadjuvant therapy. However, more studies are needed to know molecular features to differentiate between EAC and CIN gastric cancer.

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Footnote

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

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