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Significance of the prognostic stratification of extranodal extension in colorectal cancer

We have to thank Huang and Yang for their very interesting letter [1], in which they comment a recent meta-analysis of our group of research [2], as well as a subsequent letter on the same topic [3]. We recognize as important points those highlighted by Huang et al., particularly when they pointed out that colon and rectal cancer are different in anatomic site, embryological origin, function and also in metastatic patterns. At the same time, we still consider of value the results of our manuscript, in which we present the analysis on the prognostic value of extranodal extension (ENE) of nodal metastasis considering colon and rectal cancer as one entity only. Notably, we have also presented the hazard ratios of a significant number of studies and, in the subsequent letter, we have indicated that the location has not been recognized as a probable moderator of our findings ($P = 0.229$). The approach to consider colon and rectal cancer together was further justified by the fact that the staging systems do not consider separately such neoplasms. Notably, the prognostic role of ENE has been shown in diverse other cancer types [4, 5] and its importance independently from specific anatomic subdistinctions is further suggested by the case of carcinoma of pancreas versus that of papilla of Vater [5].

In our meta-analysis and in our letter, we address the prognostic impact of ENE in both colon and rectal cancers, but without suggesting a unique staging system for these two neoplasms. Indeed, we recognize that the current TNM staging system needs improvements, and the inclusion of ENE might be one of these.

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disclosure

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Positron emission tomography (PET) as a predictive measure in patients with metastatic pancreatic cancer and normal CA19-9 levels at baseline

Two recent MPACT subanalyses (Chiorean et al. and Ramanathan et al. *Ann Oncol*. 2016) demonstrated evidence that decreases from baseline in carbohydrate antigen 19-9 (CA19-9) and tumor uptake of radioactively labeled glucose (^{18}F-FDG) as measured by positron emission tomography (PET) imaging were each significantly associated with longer overall survival (OS) in patients who received first-line treatment with *nab*-paclitaxel plus gemcitabine or gemcitabine for metastatic pancreatic cancer [1, 2]. These modalities are complementary approaches to monitor treatment efficacy in most patients. However, we raised the question of whether tumor response measured by PET could predict outcome for a subset of patients (15%–20%) with pancreatic cancer who do not secrete elevated levels of CA19-9 [3, 4]. In the MPACT trial, more patients experienced a metabolic response (MR) measured by PET imaging than a tumor response measured by computed tomography. PET imaging may be particularly valuable to predict outcomes in patients without elevated baseline CA19-9 levels.

Table 1. Overall survival by metabolic response in patients without elevated baseline CA19-9 levels treated with *nab*-paclitaxel plus gemcitabine or gemcitabine alone (pooled)

	Patients without elevated CA19-9 levels at baseline in the PET cohort		HR (*P*-value)
	Yes PET MR	No PET MR	
Week 8	*n* = 21	*n* = 17	
Median OS, months	13.2	8.0	0.34 (0.001)
(95% CI)	(9.20–17.05)	(3.38–14.69)	
One-year survival rate	52%	35%	
Best response during treatment	*n* = 24	*n* = 16	
Median OS, months	13.6	6.9	0.31 (0.003)
(95% CI)	(9.26–22.83)	(3.38–10.22)	
One-year survival rate	58%	25%	

CA19-9, carbohydrate antigen 19-9; MR, metabolic response; OS, overall survival; PET, positron emission tomography.

We carried out a post hoc, pooled treatment-arm analysis of OS by PET response in patients without elevated CA19-9 levels at baseline (defined as <37 U/ml). Results for OS by MR (defined by European Organization for the Research and Treatment of Cancer [EORTC] criteria [5]) are summarized in Table 1. MRs at week 8 and at best response during the study were each significantly associated with longer OS in patients with no CA19-9 elevation at baseline. Specifically, the median OS in patients with an MR at week 8 was 5.2 months longer than that in patients without one. In addition, patients with an MR at any time during the study had a nearly twofold longer median OS than those without one.

These results illustrate that PET imaging may serve as a valuable tool to monitor treatment response in the subset of patients without elevated CA19-9 levels at baseline. Future trials may examine this issue more systematically as a preplanned end point.

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The challenge to one-course carboplatin in seminoma clinical stage 1

The Swenoteca report [1] on treatment results of seminoma clinical stage 1 (CS1) is of utmost importance to clinicians caring for these patients because it documents, for the first time, the uncertain efficacy of the one-course regimen of carboplatin.

When carboplatin was introduced into the adjuvant management of seminoma in the 1990s, the standard regimen consisted of two courses of the drug to be applied with 4 weeks apart. The outcome was similar to that of traditional abdominal radiotherapy with relapses in the range of 3%–4%.

In 2005, a large prospective MRC/EORTC trial suggested equal efficacy of just one course of carboplatin [2], and subsequently, international guidelines adopted this recommendation as one standard therapy of seminoma CS1 [3]. However, that trial had merely documented the non-inferiority of one-course carboplatin to traditional radiotherapy. A formal trial comparing the standard two-course regimen with the experimental one-course treatment has never been conducted. So, according to the rules of the evidence-based medicine, the true efficacy of