has been described for the transformation of *EGFR* mutation-positive adenocarcinoma to SCLC associated with EGFR-TKI treatment [3]. In addition, loss of retinoblastoma protein (RB) expression has been associated with transformation to SCLC in EGFR-TKI-treated patients [4], and we detected loss of RB expression in the tumor specimens obtained after alectinib treatment (Figure 1I and J). Our findings thus suggest that loss of RB is also associated with the development of acquired resistance to alectinib in *ALK* rearrangement-positive NSCLC.

In summary, as far as we are aware, this is the first case of adenocarcinoma transformation to SCLC after ALK-TKI treatment confirmed by robust histological examination. Our case suggests that SCLC transformation is a mechanism of acquired resistance to such treatment, in particular for alectinib.

N. Takegawa[1], H. Hayashi[1*], N. Iizuka[2], T. Takahama[1], H. Ueda[1], K. Tanaka[1], M. Takeda[1] & K. Nakagawa[1]

[1]Department of Medical Oncology, Kinki University Faculty of Medicine, Osaka-Sayama;
[2]Department of Pathology, Kishiwada City Hospital, Kishiwada, Japan
(*E-mail: hayashi_h@dotd.med.kindai.ac.jp)

## disclosure

KN has received honoraria from Astellas Pharma, Inc. and AstraZeneca K.K., grants from AstraZeneca K.K. and Taiho Pharmaceutical Co. Ltd, and research funding from Taiho Pharmaceutical Co. Ltd. HH has received lecture fees from AstraZeneca K.K., Chugai Pharmaceutical Co. Ltd, Eli Lilly Japan K.K., and Taiho Pharmaceutical Co. Ltd, as well as advisory fees from AstraZeneca K.K., Boehringer Ingelheim Japan, Inc., and Eli Lilly Japan K.K. All remaining authors have declared no conflicts of interest.

## references

1. Isozaki H, Takigawa N, Kiura K. Mechanisms of acquired resistance to ALK inhibitors and the rationale for treating ALK-positive lung cancer. Cancers (Basel) 2015; 7: 763–783.
2. Stewart EL, Tan SZ, Liu G, Tsao MS. Known and putative mechanisms of resistance to EGFR targeted therapies in NSCLC patients with EGFR mutations—a review. Transl Lung Cancer Res 2015; 4: 67–81.
3. Oser MG, Niederst MJ, Sequist LV, Engelman JA. Transformation from non-small-cell lung cancer to small-cell lung cancer: molecular drivers and cells of origin. Lancet Oncol 2015; 16: e165–e172.
4. Niederst MJ, Sequist LV, Poirier JT et al. RB loss in resistant EGFR mutant lung adenocarcinomas that transform to small-cell lung cancer. Nat Commun 2015; 6: 6377.

doi: 10.1093/annonc/mdw032
Published online 24 January 2016

# Prognostic impact of extracapsular lymph node involvement in colorectal cancer

We read with great interest the article by Veronese et al. [1] on 'Prognostic impact and implications of extracapsular lymph node involvement in colorectal cancer', they found that extranodal extension (ENE) was associated with a significantly increased risk of all-cause mortality and recurrence of disease. We congratulate and applaud their interesting and important work on this topic, but we feel that one important issue should be noticed.

There were low to moderate heterogeneity across studies (studies with an $I^2$ statistic of 25%–50% were considered to have low heterogeneity, those with an $I^2$ statistic of 50%–75% were considered to have moderate heterogeneity [2]), the heterogeneity might be related with demographic characteristics of patients and types of tumor, so we carried out subgroup analyses by demographic characteristics of patients (Europe or Japan) and types of tumor (colon, rectum, both colon and rectum cancer) to text the robustness of results.

After subgroup analysis, we found all-cause mortality [relative risk (RR)] and recurrence of disease [RR and hazard ratio (HR)] were consist with the results of Veronese et al., but the all-cause mortality were HR 1.396 (0.848, 2.3) in colon cancer and HR 1.513 (0.968, 2.365) in both the colon and the rectum cancer, both results did not show statistical significance. HR 1.991 (1.747, 2.27) in rectum cancer showed statistical significance. Perhaps, the prognostic impact of ENE on colon cancer need to be further validated. However, as only five cohort studies included in the subgroups analysis, results should be interpreted with caution. Further researches should pay more attention to specific cancers (colon cancer and rectal cancer).

Q. Huang & X. Qin*

Department of Vascular Surgery, First Affiliated Hospital of Guangxi Medical University, Nanning, China
(*E-mail: qinxiaoyahoo@sina.com)

## disclosure

The authors have declared no conflicts of interest.

## references

1. Veronese N, Nottegar A, Pea A et al. Prognostic impact and implications of extracapsular lymph node involvement in colorectal cancer: a systematic review with meta-analysis. Ann Oncol 2016; 27: 42–48.
2. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557–560.

doi: 10.1093/annonc/mdw031
Published online 22 January 2016

# Extranodal extension is an important prognostic parameter for both colonic and rectal cancer

We thank Qin and Huang [1] for their positive comments on our recent meta-analysis [2], in which we assessed the potential relationship between extranodal extension (ENE) of nodal

metastasis and prognostic indexes in colorectal cancer. We found consistent evidence that ENE is associated with mortality and recurrence of disease, across multiple sensitivity analyses [2], which remained robust after adjustment for publication bias. Moreover, we conducted meta-regression analyses to explain the low-moderate heterogeneity we encountered (see supplementary Table S8, available at *Annals of Oncology* online) in line with best practice. Nonetheless, Qin and Huang [1] have proposed two new subgroup analyses using the same database on geographical location (Europe versus Japan) and site of tumor (colon, rectum, both colon and rectum cancer) to test the robustness of our results. Qin and Huang replicated all of our findings, except from the all-cause mortality in colon cancer [hazard ratio (HR) 1.396, 0.848–2.3] and colon and rectum cancer together (HR 1.513, 0.968–2.365).

Although these additional analyses are of potential interest, we respectfully share a number of limitations. First, our initial analyses had low-moderate heterogeneity and our meta-regression analyses already significantly explained large portions of the heterogeneity we encountered. Second, Qin and Huang did not report any heterogeneity metric in their new analyses, so it is unclear to what extent their additional analyses addressed their own primary concern that our paper found low-moderate heterogeneity. Third, Qin and Huang included a limited number of studies in each subgroup (only five studies reported HR estimates: two studies for colon, two for rectum and one regarding colorectal cancer). Indeed, they only included 5 studies out of the 13 considered in our meta-analysis, thus type II error might be a factor in their null findings. Moreover, the *P* for the interaction for this subgroup analysis is 0.229, suggesting that this factor is not a probable moderator of our findings. Notably, the staging system does not separately consider colon and rectum cancer [2], further justifying our approach. Moreover, the meso-rectal adipose tissue, the main anatomical difference between a surgical specimen of colonic and of rectal cancer, contains very few lymph nodes: also from this point of view (i.e. number of lymph nodes and possible metastasis) colonic and rectal cancer can be studied together. Interestingly, the morphologic aspect most similar to ENE, that is represented by the free tumor deposits in adipose tissue (N1c category), is already considered in TNM staging system for both rectal and colonic cancer. Lastly, in other cancer types ENE appeared as a significant prognostic index [3, 4], and also of importance independently from specific anatomical subdistinction (e.g. carcinoma of pancreas versus of ampulla of Vater) [5].

In conclusion, we partly agree with the analyses of Qin and Huang and are grateful that they echo our calls for further research considering the prognostic role of ENE in colorectal cancer. However, we have a number of potential concerns that do not shift our stance, based on the data, that future research should consider colon and rectum cancer as only one entity.

C. Luchini[1,2,3*], A. Nottegar[1], A. Pea[4], M. Solmi[5], B. Stubbs[6], P. Capelli[1], G. Sergi[7], E. Manzato[7], M. Fassan[7], L. D. Wood[8], A. Scarpa[1,2] & N. Veronese[7]

[1]Department of Pathology and Public Health;
[2]ARC-NET Research Center, University and Hospital Trust of Verona, Verona;
[3]Surgical Pathology Unit, Santa Chiara Hospital, Trento, Italy;
[4]Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore, USA;
[5]Department of Neuroscience, University of Padua, Padua, Italy;
[6]Health Service and Population Research Department, King's College London, De Crespigny Park, London, UK;
[7]Department of Medicine, DIMED, University of Padua, Padua, Italy;
[8]Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, USA
(*E-mail: claudio.luchini@katamail.com; claudio.luchini@univr.it)

## disclosure

The authors have declared no conflicts of interest.

## references

1. Huang Q, Qin X. Prognostic impact of extracapsular lymph node involvement in colorectal cancer. Ann Oncol 2016; 27: 955.
2. Veronese N, Nottegar A, Pea A et al. Prognostic impact and implications of extracapsular lymph node involvement in colorectal cancer: a systematic review with meta-analysis. Ann Oncol 2016; 27: 42–48.
3. Luchini C, Veronese N, Pea A et al. Extra-nodal extension in N1-adenocarcinoma of pancreas and papilla of Vater: a systematic review and meta-analysis of its prognostic significance. Eur J Gastroenterol Hepatol 2016; 28: 205–209.
4. Luchini C, Nottegar A, Solmi M et al. Prognostic implications of extra-nodal extension in node-positive squamous cell carcinoma of the vulva: a systematic review and meta-analysis. Surg Oncol 2015 Sep 14 [epub ahead of print], doi: 10.1016/j.suronc.2015.09.005.
5. Veronese N, Luchini C, Nottegar A et al. Prognostic impact and implications of extra-nodal extension in lymph-node positive thyroid cancers: a systematic review and meta-analysis. J Surg Oncol 2015; 112: 828–833.

doi: 10.1093/annonc/mdw034
Published online 22 January 2016

# Prognostic impact of extra-nodal extension on colon and rectal cancer should be investigated separately

We thank Luchini et al. [1] for replying to our comments [2] on a recent meta-analysis [3]. A recent review by Tamas et al. [4] pointed out that colon and rectal cancer were different in anatomic site, embryological origin, function and metastatic patterns and further subgroup analyses would have a great effect on treatment option and prognosis evaluation of colon and rectal cancer, so we thought that the results (all-cause mortality and recurrence of disease) of colon and rectal cancer should not be combined. In addition, $I^2$ values showed low to moderate heterogeneity across studies, but $I^2$ statistic was a value of statistical heterogeneity; there were clinical heterogeneity and methodological heterogeneity besides statistical heterogeneity, so we thought that subgroup analyses by geographical location and types of tumor were of potential significance. Finally, for survival data, the end points and the time to reach the end points were considered in the hazard ratio (HR), but the relative risk (RR) just considered the end points, so we thought that the HR was more appropriate than RR for all-cause mortality and