Should guidelines take sides on colon cancer sidedness?

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As emphasised in this issue's review by De Weerdt & Van Cutsem, the colon cancer primary tumour location (PTL)'s predictive and prognostic value is currently a hot topic.[1-3]
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A prognostic factor (i.e., related to the patients' general outcome irrespective of any given treatment) is different from a predictive factor (i.e., related to the patients' outcome under a particular therapy).[2,4] *BRAF* mutations, for instance, are correlated with a significantly worse prognosis in advanced and metastatic colorectal cancer (CRC) but do not predict the effects of anti-EGFR (epidermal growth factor receptor) treatments, while *KRAS* and *N-RAS* mutations clearly impair any benefit from anti-EGFR therapies but have no or little influence on the patients' prognosis.[5]

Recent guidelines on the use of PTL in management of CRC rely mostly on data provided by subgroup analysis of retrospective trials. Retrospective studies as compared with prospective studies are not submitted to the same demanding regulatory procedures and allow quicker and cheaper analysis.[6] However, they are also highly susceptible to biases and confusion of variables that may go unrecognised because of inadequate knowledge of their prognostic value. Because of these limitations, retrospective data may suggest associations among variables but should never be used to definitively establish causal relationships that have to be prospectively controlled.[7,8]

Numerous retrospective subgroup analyses and meta-analyses have been conducted to explore the relationship between the CRC's PTL and the patients' outcome. Most of these analyses are conducted on subsets of the initial intention-to-treat (ITT) population, excluding patients with 1) *KRAS* and *N-RAS* mutations, 2) missing tumour blocks, and 3) an unknown or undefined tumour location. Moreover, major differences can be found in study characteristics (patients populations, primary endpoints, inclusion criteria, treatment arms and further treatment lines) along with differences in how the right and left colon are delimitated.

The data from large retrospective studies do associate primary tumours from the left side with a better prognosis as compared with the right-sided ones, independently of the stage and the adjuvant treatment.[9] Moreover, further subgroup analyses from limited populations suggest that left-sided tumours draw more benefit from anti-EGFR as compared with anti-VEGF therapies.[2] This disparity has never been prospectively validated. It may therefore be partially related to the uneven distribution among left- or right-PTL of Cytosin-phosphatidyc-Guanin (CpG) island methylation, microsatellite instability and mutations in genes such as *KRAS*, *NRAS*, *BRAF*, *HER2*, *PIK3CA*, *MET*, *PTEN*, which are more prevalent but not exclusive to the right side.[10] Chance could also explain those differences because of the inherent biases of retrospective subgroup analysis. These observations, however, raise exciting new questions and suggest interesting hypotheses that could potentially lead to further improvement in the patients' care, especially since new biomarkers such as *HER2* and *MET* amplification may add predictive information and help to develop original combinations that are able to cir-

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cumvent the resistance mechanisms to EGFR-antibody therapies.[11]

Large retrospective analyses identify PTL as a prognostic parameter, possibly due to the concentration on the right side of the colon of both bad prognostic factors and markers of non-response to anti-EGFR therapy. However, as cautiously stated by De Weerdt & Van Cutsem, the PTL's predictive value on the treatments' outcome has not been prospectively validated beyond *RAS* mutations and therefore may currently not be used in therapeutic algorithms.[2,3]

The biological patterns driving differences in sidedness represent a fascinating field for future translational and clinical research.

REFERENCES

1. Benson AB 3rd, Venook AP, Cederquist L, et al. Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(3):370-98.

2. Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomised trials. Ann Oncol. 2017;28(8):1713-29.

3. Holch JW, Ricard I, Stintzing S, et al. The relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials. Eur J Cancer. 2017;70:87-98.

4. Kohne CH, Cunningham D, Di Costanzo F, et al. Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. Ann Oncol. 2002;13(2):308-17.

5. Taieb J, Le Malicot K, Shi Q, et al. Prognostic value of BRAF and KRAS mutations in MSI and MSS Stage III colon cancer. J Natl Cancer Inst. 2017;109(5).

6. Ward RA, Brier ME. Retrospective analyses of large medical databases: what do they tell us? J Am Soc Nephrol. 1999;10(2):429-32.

7. Lee KL, McNeer JF, Starmer CF, et al. Clinical judgment and statistics. Lessons from a simulated randomized trial in coronary artery disease. Circulation. 1980;61(3):508-15.

8. Greenberg RS, Bembea M, Heitmiller E. Rainy days for the Society for Pediatric Anesthesia. Anesth Analg. 2012;114(5):1102-3.

9. Petrelli F, Tomasello G, Borgonovo K, et al. Prognostic survival associated with left-sided vs right-sided colon cancer: A systematic review and meta-analysis. JAMA Oncol. 2017;3(2):211-9.

10. Missiaglia E, Jacobs B, D'Ario G, et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Oncol. 2014;25(10):1995-2001.

11. Takegawa N, Yonesaka K. HER2 as an emerging oncotarget for colorectal cancer treatment after failure of anti-epidermal growth factor receptor therapy. Clin Colorectal Cancer. 2017;16(4):247-251.