Does tumor side represent a relevant factor for prognosis and treatment decision in metastatic colorectal cancer?

“The results of some clinical trials subanalysis revealed that right-sided colon cancer has a worse prognosis compared with left-sided colon cancer...”

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Colorectal cancer represents a major public health challenge; it is the third most frequent cancer worldwide [1]. With the approval of biologic agents (anti-EGFR and anti-VEGFR) next to chemotherapeutic agents in the treatment of metastatic cancer, the median survival of these tumors in the metastatic setting reached 30 months [2]. Determining prognostic and predictive factors to personalize the therapy is necessary allowing the administration of the right treatment to the right patient.

Different clinic, pathologic and biologic prognostic factors are validated in metastatic colorectal cancer (mCRC). Performance status and lactate (LDH) level are the two major prognostic clinical and biological factors of mCRC [3]. In some previous studies, number of metastatic sites, alkaline phosphatase level and white blood cell count were considered as prognostic factors, but they were not validated [4]. At the molecular level, *BRAF*

mutation is the most relevant prognostic factor of mCRC [5].

Tumor location within the colon represented a controversial issue regarding its role as predictive or prognostic factor in metastatic colon cancer. It is well documented that right-sided and left-sided colon cancers have different embryologic origins, genetic and mutational profile [6]. Cancers proximal or distal of the splenic flexure were classified as right-sided or left-sided, respectively in some trials, while in others the rectal cancers were classified as a third entity. Many trials evaluated the effect of the location of the primary colic tumor to elucidate its potential role in determining the prognosis of the disease and the choice of the treatment. The results of some clinical trials subanalysis revealed that right-sided colon cancer has a worse prognosis compared with left-sided colon cancer; while in other studies, no difference in prognosis was found. Many articles published during

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“...it is hard to confess that the oncologic community has missed for a long period of time a simple and obvious prognostic and predictive factor in metastatic colorectal cancers...”

the last 2 years and many abstracts in American Society of Clinical Oncology (ASCO) 2016 highlighted the role of tumor location within the colon as predictive and prognostic factor in metastatic colon cancer. The predictive value of the location was mainly related to the response to biologic agents, cetuximab and bevacizumab.

In the Loupakis study, where the results of three independent cohorts were analyzed from PROVETTA pharmacogenetic prospective trial and AVF2107g and NO16966 randomized Phase III trials, the data demonstrated that primary tumor location is an important prognostic factor in previously untreated metastatic colon cancer. This study concluded that side of tumor origin should be considered for stratification in randomized trials and that in both randomized studies, the efficacy of bevacizumab was independent of tumor location [7]. In line with these results, van Erning *et al.* found after analyzing more than 7000 metastatic colon cancers that patients with left-sided tumors had favorable overall survival (OS) as compared with patients with right-sided tumors [8].

Recent results presented by SEER program from more than 40,000 patients with stage III and IV colon cancer in ASCO 2016 concluded that patients with right-sided tumors had a worse survival compared with left-sided tumors. In this analysis, rectal cancer was considered as an independent third entity. This study suggested further research including molecular subtyping to better understand the mechanisms underpinning this phenotypic difference in prognosis [9].

Another retrospective analysis on the CALGB/SWOG 80405 (Alliance) evaluated the impact of primary tumor location on OS and progression-free survival (PFS) in patients with mCRC. It is important to mention that 80,405 did not find any difference in OS or PFS when bevacizumab or cetuximab was added to first-line FOLFOX or FOLFIRI in mCRC. The results of this analysis showed that in wild-type *KRAS* metastatic colon cancer, left-sided colon cancers have a better OS (34.2 vs 19.2 months) and PFS (11.5 vs 8.9 months) compared with right-sided. The difference was more important between the left and right side cancer in patients receiving bevacizumab (32.1 vs 24.5 months) compared with those treated with cetuximab (37.5 vs 16.4 months). These data support the use of bevacizumab in first-line treatment for right-sided primary tumor mCRC regardless of *KRAS* status [10].

Another study evaluated the primary tumor location and bevacizumab effectiveness in metastatic colon cancer. Patients with right side metastatic colon cancer did not benefit from the addition of bevacizumab to chemotherapy with an OS 20.2 versus 20.5 months, while patients having left side metastatic colon cancer presented a better OS when receiving bevacizumab 26.3 versus 23.1 months [11].

Von Einem *et al.* study analysis investigated the impact of primary tumor location on outcome of patients in AIO KRK-0104 trial comparing first-line therapy of mCRC with cetuximab, capecitabine and irinotecan to cetuximab, capecitabine and oxaliplatin. They concluded that left-sided primary tumor location might be a predictor of cetuximab efficacy since it was associated with significantly longer OS and PFS as compared with right-sided tumors; these effects were only present in the *KRAS* codon 12/13 wild-type population [12].

Sunakawa *et al.* investigated the prognostic impact of primary tumor location on outcomes of Japanese patients enrolled in JACCRO CC-05 or CC-06 trial, which evaluated efficacy of cetuximab in combination with FOLFOX or SOX, respectively, for mCRC with *KRAS* exon 2 wild-type tumors. Left-sided tumors were significantly associated with longer OS (36.2 vs 12.6 months) and PFS (11.1 vs 5.6 months) compared with right-sided tumors. Authors concluded that primary tumor location may serve as a predictor of prognosis of metastatic colorectal patients treated with cetuximab plus oxaliplatin-based therapy [13].

Another trial presented also in ASCO 2016 investigated whether primary tumor location affects cetuximab efficacy in patients with *RAS* wild-type metastatic colon cancer determined by extended *RAS* genotyping. The results showed in 170 patients included (23 of them right-side colon cancer) that PFS was significantly shorter in right-side colon cancer compared with left side (2.0 vs 4.9 months) and OS was 4.1 versus 13 months. It is noteworthy to report that more mutant *BRAF* (39.1 vs 5.4%), poorly differentiated (17.4 vs 3.4%) and mutant *PIK3CA* (13 vs 1.4%) tumor and peritoneal involvement (26.1 vs 8.8%) were observed in right-sided colon cancer [14].

In a recent study published in 2015 dealing with refractory metastatic colon cancer, tumor location within the colon is strongly predictive of PFS benefit from cetuximab therapy: *KRAS* wild-type patients having left side colon cancer

had significantly improved PFS when treated with cetuximab compared with best supportive care (BSC; median: 5.4 vs 1.8 months), whereas those with right-sided colon cancer did not (median: 1.9 vs 1.9 months) [15].

Based on all these findings, the primary location of colon cancer should be routinely included in study design, reporting and patient counseling. The trend in all these studies is that right-sided colon cancer play the role of poor prognostic factor. The main weakness in all these studies is being a retrospective analysis of subgroups with different parameters probably not well balanced between the two arms. The first step to confirm these results is to launch a prospective study having the difference in survival between right-sided and left-sided colon cancer as primary end point, with well-balanced clinical, biological and molecular parameters between the two arms and to exclude rectal cancer that have different characteristics.

Concerning the predictive value of the location of the primary tumor on biologic agents, cetuximab is probably not efficient enough

in the right-sided wild-type *KRAS* metastatic colon cancer and bevacizumab could therefore be administered. Also before its application in clinical practice, a prospective study should confirm these results.

Finally, it is hard to confess that the oncologic community has missed for a long period of time a simple and obvious prognostic and predictive factor in mCRCs, which is the tumor location, while molecular complicated and expensive factors such as *RAS* and *BRAF* were universally used for prognosis and treatment decision.

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References

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J. Clin.* 61, 69–90 (2011).
- Lenz H, Niedzwiecki D, Innocenti F *et al.* CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with expanded RAS analyses untreated metastatic adenocarcinoma of the colon or rectum (mCRC). *Ann. Oncol.* 25(Suppl. 5), v1–v41 (2014).
- Köhne 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.* 13(2), 308–317 (2002).
- Chibaudel B, Bonnetain F, Tournigand C *et al.* Simplified prognostic model in patients with oxaliplatin-based or irinotecan-based first-line chemotherapy for metastatic colorectal cancer: a GERCOR study. *Oncologist* 16(9), 1228–1238 (2011).
- Yokota T, Ura T, Shibata N *et al.* *BRAF* mutation is a powerful prognostic factor in advanced and recurrent colorectal cancer. *Br. J. Cancer* 104(5), 856–862 (2011).
- Glebov OK, Rodriguez LM, Nakahara K *et al.* Distinguishing right from left colon by the pattern of gene expression. *Cancer Epidemiol. Biomarkers Prev.* 12(8), 755–762 (2003).
- Loupakis F, Yang D, Yau L *et al.* Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J. Natl Cancer Inst.* 107(3), dju427 (2015).
- van Erning FN, Elferink MA, Bos AC *et al.* RE: primary tumor location as a prognostic factor in metastatic colorectal cancer. *J. Natl Cancer Inst.* 107(9), djv203 (2015).
- Schrag D, Weng S, Brooks G *et al.* The relationship between primary tumor sidedness and prognosis in colorectal cancer. *J. Clin. Oncol.* 34(Suppl.), Abstract 3505 (2016).
- Venook A, Niedzwiecki D, Innocenti F *et al.* Impact of primary (1°) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). *J. Clin. Oncol.* 34(Suppl.), Abstract 3504 (2016).
- He WZ, Jiang C, Liao F *et al.* Primary tumor location and bevacizumab effectiveness in metastatic colorectal cancer patients. *J. Clin. Oncol.* 34(Suppl.), Abstract 3593 (2016).
- von Einem JC, Heinemann V, von Weikersthal LF *et al.* Left-sided primary tumors are associated with favorable prognosis in patients with *KRAS* codon 12/13 wild-type metastatic colorectal cancer treated with cetuximab plus chemotherapy: an analysis of the AIO KRK-0104 trial. *J. Cancer Res. Clin. Oncol.* 140(9), 1607–1614 (2014).
- Sunakawa Y, Ichikawa W, Tsuji A *et al.* Prognostic impact of primary tumor location on survival time in patients (pts) with metastatic colorectal cancer (mCRC) treated with cetuximab plus oxaliplatin-based chemotherapy: a subgroup analysis of the JACCRO CC-05/06. *J. Clin. Oncol.* 34(Suppl. 4S), Abstract 613 (2016).
- Kim D, Hong YS, Kim JE *et al.* Association of right-sided colon cancer with poor efficacy of cetuximab in patients with *RAS* wild-type metastatic colorectal cancer. *J. Clin. Oncol.* 34(Suppl.), Abstract 3601 (2016).
- Brulé SY, Jonker DJ, Karapetis CS *et al.* Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. *Eur. J. Cancer* 51(11), 1405–1414 (2015).