Impact of EGFR expression on colorectal cancer patient prognosis and survival: a response

We recently read the article from Spano et al. [1], which describes the impact of epidermal growth factor receptor (EGFR) detection on colorectal cancer patient survival. Although we found the study of some interest, we have some concerns.

First, the authors affirm that previous studies did not demonstrate any influence of EGFR expression on patient survival and disease-free survival.

In 2003 we published a study [2] which suggested that EGFR may be used as a marker of circulating tumour cells (CTCs) in a series of colorectal cancer patients, since EGFR persistence in blood after surgery identified a subset of patients at high risk of relapse. In that study, where we described the association between EGFR expression and tumour stage, we also found a statistically significant correlation between EGFR expression in blood and relapses. Analogous results have been obtained by our group in bladder cancer patients, where EGFR expression in blood also correlates with worse prognosis [3, 4]. Thus, it is incorrect to say that EGFR expression does not affect patient survival, but would be more correct to affirm that EGFR expression in tumoural tissues does not affect patient survival.

We would like to stress that in our series of patients affected by colon or bladder cancer, we often failed to find a correlation between EGFR expression in the primary tumour and in peripheral blood. This is not surprising, and reflects the biological characteristics of tumour progression: molecular oncologists well know that the genic profile of tumoural cells in the primary tumour is different from that of cells which detach and enter blood flow.

Thus, we are not surprised if EGFR expression at the tumour level does not affect prognosis, but are really interested to know if analysis of EGFR-expressing CTCs may lead authors to the same conclusions.

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Relevance of EGFR expression in colorectal cancer

In a recent issue of Annals of Oncology, Spano and colleagues reported their study of epidermal growth factor receptor (EGFR) expression by immunohistochemistry in 148 patients with colorectal cancer [1]. The aim of this study was to analyse the relationship between EGFR reactivity and various histological and clinical characteristics and survival. Multivariate analysis found significant overexpression in the T3 stage while there was no impact on overall survival. This study suggests some comments. Regarding eventual prognostic impact, the first handicap is the high frequency (80%) of overexpression, which is consistent with other studies. EGFR has been extensively studied in many tumours providing a number of data. Although the authors discuss the expression of EGFR among the different sites of the colon, the notable variation in expression between primary and secondary sites has not been discussed [2]. As rapidly evoked in the last sentence, somatic mutations of the EGFR can play a major role, which has been clearly demonstrated in lung cancer [3, 4]. Until now, about 30 mutations have been determined within the kinase domain of EGFR in lung cancer with a wide variation of frequency.
according to several baseline characteristics including gender, ethnic group or histological subtypes. Thus, there is a relatively high frequency of mutations in women, in smokers, or in Japanese patients with non-small-cell lung cancer. EGFR mutations can enhance tyrosine kinase activity in response to EGF and increase the efficacy of anti-EGFR such as gefitinib or erlotinib [3, 4]. Increased expression of the multiple ligands, including EGF, TGF-α, epiregulin or amphiregulin, can also play a major role. To illustrate this, the prognostic value of EGFR in tumours of the head and neck, oesophagus, larynx, pancreas, lung, ovary, stomach or bladder was generally revealed when combined with increased EGF, TGF-α or both. Of note, the prognostic value of EGFR expression remains unproven in breast and lung cancers. Moreover, the multiple signalling pathways following on from the activation of EGFR have their own impact on the tumoral potential. Thus, many actors interfere with EGFR, minimising its proper impact. In line with this, there is no apparent correlation between the expression of EGFR and response to certain targeted drugs, such as cetuximab, in metastatic colorectal cancer [5]. Tyrosine kinase inhibitors might interfere with the phosphorylation of several of these pathways such as Ras/Raf/mitogen-activated protein kinase, or phosphatidylinositol 3'-kinase-Akt. Thus, eventual prognostic impact of EGFR might be reversed by targeted drugs such as illustrated in patients with metastatic breast cancer overexpressing HER2 and treated by trastuzumab. For all these reasons, the crude expression of EGFR probably does not belong to the most crucial biomarkers such as those selecting candidates to adjuvant systemic therapy among stage II patients, or predicting response to a given drug.

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Reply to the “Letter to the Editor on ‘Relevance of EGFR expression in colorectal cancer’” by C. Alliot

Alliot and co-workers address relevant questions regarding our recent study which appeared in this journal [1]. In our study [1], we analysed epidermal growth factor receptor (EGFR) expression and its relationship with the main histological and clinical characteristics in a group of colorectal cancer patients. We found that EGFR overexpression was significantly associated with tumor stage, especially T3. Nevertheless, we did not analyse the expression of EGFR in case of recurrent disease and we did not have samples available to compare EGFR expression between primary and metastatic sites of the tumour. We agree with the comments by Alliot and co-workers and it is clear that it would be particularly interesting to perform such an analysis bearing in mind the recent data published by Scartozzi et al. [2] emphasising changes in EGFR immunohistocompatibility (IHC) expression between primary- and metastatic-stage disease although these results must, however, be taken with caution knowing the variability in EGFR determination by IHC [3, 4]. Concerning our study, we used an EGFR composite score as described and validated by Goldstein and Armin [5], which remains one of the most accurate scoring systems currently defined for IHC. Above all, we consider that the variability of treatment decision based on EGFR expression measured by IHC remains to be established since there are reports indicating response rate to EGFR-targeting drugs in EGR negative colorectal cancer patients by IHC [6].

The second point advocated by Alliot and co-workers is related to EGFR mutations that can be predictive of response to EGFR targeted therapies. We agree with the view that some EGFR mutations may favour the activity of anti-EGFR drugs, but for the moment these mutations are essentially reported in lung cancer patients [7]. Recent data exclude the presence of such mutations in colorectal cancer patients [8]. In conclusion, efforts must be made to evaluate how we can optimise patient selection for EGFR targeting, especially for colorectal cancer patients. As we underlined in a recently published study [9], other biomarkers are necessary to be evaluated besides EGFR expression itself and, as mentioned by Alliot and co-workers, p-AKT expression, MAPK expression or EGFR amplification are all good candidates for this purpose.

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