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Reply: Comment on 'KRAS and BRAF mutations are prognostic biomarkers in patients undergoing lung metastasectomy of colo-rectal cancer'

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Sir,

It is with great interest that we read the letter entitled 'KRAS and BRAF mutations are prognostic biomarkers in patients undergoing lung metastasectomy of colo-rectal cancer. Variation in survival associated with proto-oncogenes is not evidence for effectiveness of metastasectomy'.

In their comment on the prognostic value of proto-oncogenes in lung metastasectomy of colo-rectal cancer (CRC) (Renaud *et al*, 2015), Cardillo and colleagues stated that 'no difference in survival attributable to surgical removal of lung metastases has been shown in a control trial' and reached the conclusion on 'the doubt on effectiveness of metastasectomy in colorectal cancer' (Cardillo *et al*, 2015). However, as stated by the authors, no randomised controlled trial has shown a survival benefit for follow-up compared with surgery. The very large majority of the published series shows that in metastatic CRC, medical treatment alone leads to poor overall survival (OS) (Rooney *et al*, 2015), while surgery leads to 5-y OS up to 70% (Riquet *et al*, 2010; Hawkes *et al*, 2012; Renaud *et al*, 2014).

At this point a word of caution is essential and we would like to emphasise several points that we consider to be important.

First, we agree that patients who underwent surgery were highly selected. However, the proper selection of candidates for surgery is the basis of surgical oncology. As an example, stereotactic ablative radiotherapy and radio-frequency are offered as alternatives to surgery in resectable NSCLC unfit for surgery, since poor medical condition is associated with worse outcomes (Boily *et al*, 2015; Dupuy *et al*, 2015). Consequently, the doubt of hyperselection can be applied to all the fields of surgical oncology.

Second, the authors relevantly stated that 'the study shows the influence of oncogenes on survival but these are likely to be general prognostic factors'. They are right! Our aim was to identify new prognostic factors. Indeed, despite known prognostic factors, there are wide variations of OS among patients after metastasectomy of CRC. It seems that, from the primary CRC tumour, the molecular status could predict the course and the aggressivity of CRC (Renaud *et al*, 2015). Consequently, molecular markers might help to a better selection of patients, from the primary CRC surgery. In addition, we further think that molecular analysis could be even more helpful. Indeed, it seems that *KRAS* specific amino-acid substitutions is associated with different activations of downstream effectors, which can induce different behaviours (Garassino *et al*, 2011; Ihle *et al*, 2012; Izar *et al*, 2014; Nadal *et al*, 2014). In particular, in CRC cell lines, *KRAS* G12V is known to overexpress CXCR4, implied in metastasis process, promoting higher aggressivity (Alamo *et al*, 2015). These interesting preliminary results may lead in the future to a molecular prognostic classification, which may help to select the best patients for surgery.

Third, in the meta-analysis of Gonzalez *et al* (2013), CEA remained significant in multivariate analysis in only 9 out of 19 selected studies. Furthermore, CEA only reflects the total tumour mass. On the other hand, the absence of impact of disease free survival in our work probably reflects the proper selection of patients.

Fourth, meta-analyses cited by the authors, such as the latest one, does not add supplementary reflexion to our discussion (Gonzalez *et al*, 2013). Indeed, it only identifies four risk factors of poor outcome, which have been included in our analysis.

Fifth, CEA second look trial recruited patients who were randomised between surgery and follow-up according only to CEA elevation (Treasure *et al*, 2014). Obviously, this study cannot be generalised to lung metastasectomy of CRC: (1) patients with extra-abdominal recurrence were excluded, and different regimen of peri-operative treatment were used; (2) the use of CEA alone may have probably led to the inclusion of patients without recurrence, for whom surgery was futile. Indeed, patients were included in case of CEA $>10\,\mathrm{ng\,ml^{-1}}$. However, when $<30\,\mathrm{ng\,ml^{-1}}$, many conditions can induce CEA increase, in particular smoking and alcohol. Excluding these conditions by simple questioning exposed to information biases. Otherwise, Primrose *et al* (2014) did not reach the conclusion that treatment of recurrence was unnecessary, but that intensive follow-up after surgery, even if detecting earlier recurrence, does not significantly diminish the mortality in comparison with minimum follow-up (Primrose *et al*, 2014). Furthermore, they clearly stated that 'detection of recurrence that was treatable surgically with curative intent was chosen as the main outcome measure' (Primrose *et al*, 2014), and 'that the statistical power of their trial to assess a mortality advantage of intensive follow-up was limited' (Mant and Primrose, 2014). Finally, in their work, recurrence was treated by various regimen forbidding to conclude on the benefit of surgical treatment of recurrence.

Consequently, so far, we strongly advocate that no data allows concluding that lung metastasectomy is a futile procedure in CRC.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Is it the creatine or the anabolic androgenic steroids? Need for assessing the steroids role in testicular cancer

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Sir,

We have read with considerable interest the case-control study by Li *et al.* (2015), in which muscle building supplement (MBS) use was found as an associated factor with testicular germ cell cancer. It is important to remark that the association remained statistically significant even after controlling for important potential confounders. However, we consider that there is one non-assessed variable that might be relevant in the multi-causal model for testicular cancer.

Previous research shows that the frequency of anabolic androgenic steroid (AAS) use within practitioners of recreational physical activity can be as high as 30 (Abrahin *et al*, 2014) to 50% (Dodge *et al*, 2011). Therefore, there is high probability of concomitant AAS and MBS use. In addition, AASs have been associated with the development of some types of cancer. Nandrolone and stanozolol, two of the most used AASs, have proven to enhance Leydig cell proliferation, increasing the risk of tumour development in rats (Chimento *et al*, 2012). There is also suggestive evidence that involves AAS in Leydig cell tumour growth in humans (Belli *et al*, 2013). In this scenario, AAS could be playing an undetected role in malignancy development instead of or in conjunction with MBS.

Moreover, two recently published articles detected the presence of AAS in products marketed as dietary supplements (Abbate *et al*, 2014; Odoardi *et al*, 2015). Thus, the MBS consumed by Li's study participants could have been contaminated with AAS. This highly probable mix of substances does not allow us to convincingly blame one specific compound.

In summary, Li's results provide valuable information suggestive of MBS use as a potential risk factor for testicular cancer. However, future research considering the potential AAS effect should be carried out in order to clarify the real influence of this substance.

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Comment on 'Impact of intra-arterial chemotherapy including internal carotid artery for advanced paranasal sinus cancers involving the skull base'

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Sir,

We read with great interest the paper by Yokoyama J *et al*, 2014. 'Impact of intra-arterial chemotherapy including internal carotid artery for advanced paranasal sinus cancers involving the skull base'.

There are some major issues that in our opinion strongly limit the possibility of drawing any conclusions.

The paper presents the experience of intra-arterial cisplatin chemotherapy (46 patients) compared with historical controls (11 patients) not employing infusion of the internal carotid artery, presenting survival data of both series. However, it is difficult to make any comparison, as there is no histology specification about the treated cancers, which can have a significant prognostic impact in paranasal sinus cancers (Ganly *et al*, 2005; Llorente *et al*, 2014).

The inclusion criteria of this study have not been specified. For example, it is unclear how many patients were considered and how many were eligible; this would help in understanding the feasibility of this approach. How many cases were judged as unresectable? This is the group of patients having the worst prognosis, which indeed would benefit from alternative approaches such as intra-arterial chemotherapy (Hoppe *et al*, 2008); on the other hand, when a paranasal sinus cancer is resectable, surgery represents the standard treatment followed by radiotherapy (Dulguerov and Allal, 2006).

Moreover, it is very unclear if the adopted therapeutic strategy was the same for all cases. The authors stated that 29 of 32 patients with invasion of orbital apex were treated with preservation of the orbital contents, probably suggesting that radiotherapy was given in a preoperative setting.

Therefore, it is vital to clarify whether radiotherapy was administered with radical intent or preoperatively. The reported total dose of 60 Gy to tumour and nodal metastasis with standard fractionation could hardly be curative if definitive treatment was planned. In fact, receiving a total dose of at least 65 Gy is known to be a significant prognostic factor for both tumour local control and overall survival at least in unresectable paranasal sinus cancers (Hoppe *et al*, 2008). Furthermore, no specific data on surgery has been provided in the paper.

In the statistical part, larynx-preservation rates are calculated and compared between the two groups. In our experience larynx preservation is