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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

never an issue for skull base tumours. We wonder whether laryngectomies were done for late unexpected toxicity?

It should be stressed that choosing to employ intra-arterial monochemotherapy and not systemic polychemotherapy could have reduced the positive effect of systemic therapy in preventing disease metastatisation. This fact should be discussed also in light of the fact that 50% of the recurrences in the experimental arm was at a distant site.

The paper presents long-term data about outcome, but no data about late toxicities are reported. Previous studies showed late effects (brain necrosis, osteonecrosis, hearing or visual problems) as possible limiting toxicities of intra-arterial chemotherapy (Homma *et al*, 2009, 2013).

Keeping all these observations in mind, it is hard to agree with the authors' conclusions, suggesting that this new method of chemotherapy could be safe and with promising applications for advanced paranasal sinus cancer.

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