Reviewer’s report

Title: The dog as a naturally-occurring model for insulin-like growth factor type 1 receptor-overexpressing breast cancer: an observational cohort study

Version: 1 Date: 1 June 2015

Reviewer: Patrícia Dias Pereira

Reviewer’s report:

The dog as a naturally-occurring model for insulin-like growth factor type 1 receptor-overexpressing breast cancer: an observational cohort study

This is an interesting and well-written manuscript focusing on IGF1R immunohistochemical expression in a series of canine mammary carcinomas. The authors also assess the prognostic value of IGF1R immunoexpression.

There are, however, several points that require attention/clarification:

Minor Essential Revisions

Fig 1a does not seem to represent normal mammary gland tissue; it reminds me of hair follicles instead.

Line 67 – reference 7 does not support the author’s statement; in fact, Kim and colleagues found only 18.7% of triple-negative cases in a large cohort (n=241) of canine mammary carcinomas.

Lines 97-98 and 281-282 – the role of IGF1R in canine mammary carcinogenesis is not discussed in this manuscript.

Line 135 - Ref Elston and Ellis (1991) is missing from the references list.

Ref 29 does not constitute the official WHO classification system for canine mammary tumors.

On what basis did the authors classify canine mammary carcinomas into luminal and triple-negative subtypes? This is not explicit in the text and is not supported by bibliographic references in canine species.

Line 209 – “date of diagnosis”: do the authors mean “date of surgery”?

The authors do not interpret and do not present reasonable biological explanations for the inverse association they observed between IGF1R and ER expression, nor for the correlation found between IGF1R overexpression and aggressive clinicopathological features. The authors restrict their discussion to the presentation of data obtained previously by others which is, in my opinion, insufficient.

Discretionary Revisions

IGF1R immunoexpression is not well characterized in canine normal mammary tissue. In fact, the authors describe that “IGF1R was strongly expressed in the normal mammary tissue adjacent to the tumors”, while ref 21 documents “weak
to moderate IGF1R expression in canine normal mammary gland”, similarly to
data obtained by Bhargava and colleagues (ref 39) in human breast tissue. The
authors do not provide a rational explanation for this finding. It would be very
interesting to include samples of normal mammary gland (obtained from animals
free of neoplastic disease) instead of considering the mammary tissue
surrounding the tumour as normal. IGF1R lower- or over-expression should be
defined considering the immunoreactivity of the normal mammary tissue as
reference.
The authors do not explain why they decided to stratify tumor size into <2 and
#2cm categories and body size into >10 and #10 Kgs.
Despite the low number of carcinomas scored 0 for IGF1R expression, it would
be interesting to know if those cases share similar clinicopathological features.

Major Compulsory Revisions
I have serious reservations regarding the follow-up study:
- Phone call (to the owners or to the clinicians) is an unreliable follow-up method.
Animals included in this study were not submitted to standardized periodical
clinical examination, as recently recommended by Matos et al (2012), which may
bias some of the clinicopathological features evaluated in this investigation,
namely date and histological confirmation of local recurrence, development of
new tumoral lesions, lymph node metastasis and/or distant metastasis.
- Furthermore, I don’t find “overall survival” (as defined by the authors) a useful
prognostic parameter as it includes death from any cause, that may not be
related to the tumoral lesion. I suggest eliminating this prognostic indicator.

Level of interest: An article whose findings are important to those with closely
related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests