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: 5 July 2015

Reviewer: Josef Singer

Reviewer's report:

The article 'The dog as a naturally-occurring model for insulin-like growth factor type 1 receptor-overexpressing breast cancer: an observational cohort study' by Laetitia Jaillardon, Jérôme Abadie, Tiffanie Godard, Delphine Loussouarn, Mario Campone, Brigitte Siliart and Frédérique Nguyen is a well-elaborated and concise observational cohort study of IGF1R expression in canine mammary carcinoma within the context of Comparative Oncology.

150 patients were included in the cohort and monitored for 2 years with respect to disease-free interval, overall survival and specific survival.

The size of the cohort is appropriate and their main experimental method, immunohistochemistry, is well performed and in the supplementary information also well described. As many clinical oncologists are used to the HercepTest™ classification, it is suitable to score also IGF1R expression analogous to this scoring system. Fig. 1 nicely depicts the different scoring intensities, and it is creditable that only 3+ lesions were considered as IGF1R positive.

Another positive aspect of this study, which should be highlighted, is that each specimen was classified by five independent pathologists.

A rather astonishing finding of this study is, that the authors could not find any HER-2 overexpressing carcinoma in 150 patients. As this is against other published studies, it is interesting whether this finding is real or a methodological issue. In human medicine and in several veterinary oncology studies, pathologists use the HercepTest™ to evaluate HER-2 expression. As this was not used in this study, but the authors reference to the scoring system, I would suggest to stain the sections also with this staining kit. The side-by-side comparison of the two different staining systems (Monoclonal rabbit anti-human Clone 4B5 vs. Polyclonal rabbit HercepTest™) will be also interesting for other researchers working in the field.

The results of the study are well-elaborated, the prognostic value of IGF1R expression in canine mammary carcinoma is well-investigated, especially within the important context of luminal subtype or triple negative mammary carcinoma.

These findings are also put in line with current literature and the similarities and differences between human studies are discussed, which is of uttermost importance for Comparative Oncology. However, only for the human situation possible mechanistic explanations are discussed by mentioning in vitro studies investigating the crosstalk between the IGF1R and ER. As this study shows, that
both subtypes of mammary carcinoma, luminal and triple negative, have worse prognosis upon IGF1R overexpression in dogs, it would be interesting to know, whether eventual crosstalk between the IGF1R and the ER have also been investigated in canine tumor cells. If not, please indicate in the paper, that here possible differences within the receptor biology can be expected and should thus be further investigated.

Apart from that, the discussion is clear and informative, the structure of the paper is well designed to navigate the reader through the experiments and the quality of written english is excellent.

Summarizing, this manuscript is of good quality and an article of importance not only for veterinary oncology but within the context of Comparative Medicine also for human clinical and experimental oncology.

The article 'The dog as a naturally-occurring model for insulin-like growth factor type 1 receptor-overexpressing breast cancer: an observational cohort study' by Laetitia Jaillardon, Jérôme Abadie, Tiffanie Godard, Delphine Loussouarn, Mario Campone, Brigitte Siliart and Frédérique Nguyen is a well-elaborated and concise observational cohort study of IGF1R expression in canine mammary carcinoma within the context of Comparative Oncology.

150 patients were included in the cohort and monitored for 2 years with respect to disease-free interval, overall survival and specific survival.

The size of the cohort is appropriate and their main experimental method, immunohistochemistry, is well performed and in the supplementary information also well described. As many clinical oncologists are used to the HercepTest™ classification, it is suitable to score also IGF1R expression analogous to this scoring system. Fig. 1 nicely depicts the different scoring intensities, and it is creditable that only 3+ lesions were considered as IGF1R positive.

Another positive aspect of this study, which should be highlighted, is that each specimen was classified by five independent pathologists.

A rather astonishing finding of this study, however, is, that the authors could not find any HER-2 overexpressing carcinoma in 150 patients. As this is against many other published studies, it is interesting whether this finding is real or a methodological issue. In human medicine and in several veterinary oncology studies, pathologists use the HercepTest™ to evaluate HER-2 expression. As this kit, which employs polyclonal antibodies against HER-2, was not used in this study, but a monoclonal antibody against human HER-2 (4B5), I would suggest to stain the sections also with this staining kit, as normally higher cross-reactivity within two species can be expected with polyclonal antibodies. The side-by-side comparison of the two different staining systems (Monoclonal rabbit anti-human Clone 4B5 vs. Polyclonal rabbit HercepTest™) will be also interesting for other researchers working in the field.

The results of the study are well-elaborated, the prognostic value of IGF1R expression in canine mammary carcinoma is well-investigated, especially within the important context of luminal subtype or triple negative mammary carcinoma (however, one has to keep in mind that triple negative includes absence of
HER-2, which could be due to methodological issues).

These findings are also put in line with current literature and the similarities and differences between human studies are discussed, which is of uttermost importance for Comparative Oncology. However, only for the human situation possible mechanistic explanations are discussed by mentioning in vitro studies investigating the crosstalk between the IGF1R and ER. As this study shows, that both subtypes of mammary carcinoma, luminal and triple negative, have worse prognosis upon IGF1R overexpression in dogs, it would be interesting to know, whether eventual crosstalk between the IGF1R and the ER have also been investigated in canine tumor cells. If not, please indicate in the paper, that here possible differences within the receptor biology can be expected and should thus be further investigated.

Apart from that, the discussion is clear and informative, the structure of the paper is well designed to navigate the reader through the experiments and the quality of written english is excellent.

Summarizing, this manuscript is of good quality (if the HER-2 issue can be addressed) and an article of importance not only for veterinary oncology but within the context of Comparative Medicine also for human clinical and experimental oncology.

Major compulsory revisions:
Please stain again for HER-2 with the HercepTest™ kit, as it is highly unlikely to have not a single positive tumor overexpressing HER-2 in 150 mammary carcinoma patients. As this finding would be against many published studies, this has to be investigated in more depth. Moreover, HER-2 status is part of the classification as triple negative, therefore it is important to exclude methodological issues. All positive controls for HER-2 of this study are expressing human HER-2, so maybe there is a lack of cross-reactivity of the monoclonal antibody 4B5 to the canine counterpart. For the polyclonal HercepTest™, cross-reactivity could already be demonstrated.

Minor essential revisions:
In the methods section of the abstract:
Please change the last sentence to ‘The prognostic value of the IGF1R expression was assessed in terms of overall AND specific SURVIVAL AS WELL AS disease-free interval (DFI).’ to make it easier to grasp for the reader.

Please change the sentence from:
Anyway, the expression and prognostic value of IGF1R overexpression is of particular interest in the triple negative subtype since it is associated with a poor prognosis, particularly in young women for which this type is more frequent.

To:
NONETHELESS, the expression...
Level of interest: An article of importance in its field

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.