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Clinical and computed tomography tumour dimension assessments for planning wide excision of injection site sarcomas in cats: how strong is the agreement?

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Abstract

In injection site sarcoma (ISS) in cats lateral as well as deep margins should be correctly planned for a successful surgical outcome. The discrepancy between clinical and computed tomography (CT) measurements of dimension in resectable tumour has led to possible bias that affects the subsequent surgical dose. The aim of this study was to prospectively investigate the agreement between clinical and CT measurements of dimension in newly diagnosed ISS in cats. Fifty-three client-owned cats that underwent both clinical and CT measurements of the length and width of ISS were included. CT measurements showed a tendency towards being larger than clinical dimensions, and this difference increased with increasing tumour size. Based on our results, in further studies focusing on ISS in cats, the kind of assessment used to define tumour dimensions (CT versus clinic) should be declared and specified to properly consider surgical results and prognostic impact of this variable.

Introduction

Injection site sarcoma (ISS) in cats is a well- recognized soft tissue sarcoma characterized by very aggressive local behaviour with a high probability of local recurrence and a relatively low probability of distant dissemination.1 – 7 Although multimodal therapeutic approaches have been proposed, wide margins or radical surgical excision based on tumour extent remains the primary therapeutic procedure.6 –8. Despite the peculiar presence of asymmetric and infiltrating long tumour extensions departing from the main mass making the estimation of the dimensions of ISS objectively difficult to achieve,9 –11 many studies have used clinical measurements for prognostic and surgical purposes.4,5,7,9 The use- fulness of advanced diagnostic imaging, such as magnetic resonance imaging (MRI) and/or computed tomography (CT), to plan preoperatively the surgical excision of ISS has been previously dis-cussed and suggested,8,9,11 – 15 but it has not always been applied for surgical planning.4,5,7,9 The avail- able veterinary literature discuss on the amount of lateral margins that should be excised around ISS in cats, whereas regarding the deep margins it has been suggested to consider one or (more recently) two not infiltrated underlying muscles layers.6,7,9 In those studies in which both clinical and advanced imaging measurements have been reported, the tumour dimensions obtained with CT have generally been larger than those obtained with clinical measurements.13,16,17 Recently differ- ent amount of lateral margins was hypothesized for surgical excision of ISS in cats based on the possibil- ity that the same wide lateral margins could not be equally wide if a surgeon consider the clinical or the computed tomographic measurements of the same tumour.16 Size discrepancies between clinical and CT mea- surements of the same tumour size can impact the surgical dose applied. The aim of the study was to prospectively investigate the agreement between the clinical and CT measurements of tumour dimension in newly diagnosed ISS in cats.

Materials and methods

Client-owned cats affected by histologically con- firmed, newly diagnosed ISS18 and referred to our clinic from January 2002 to December 2013 were included. Before surgery, all the cats underwent a whole-body CT examination for staging of onco- logic disease, and clinical and CT evaluations of tumour dimensions were performed on the same date by the same clinician and the same radiologist, respectively. The surgeon and the radiologist were blinded to the CT and clinical measurements, respectively. All the owners provided written con- sent before the clinical and diagnostic procedures.

The clinical measurements were obtained before a whole-body CT examination of the anaesthetised cats. The cats were placed in sternal recumbency when the tumour was localized on the dorsal thorax and dorsal abdomen or in lateral recumbency when it was localized on the lateral thorax or abdomen. The clinical dimensions (CD) obtained by the surgeon were the longest length (CD-l) and the longest width (CD-w) of the palpable tumour, measured with digital callipers. All the CT measurements were performed with the patients in sternal recumbency with the forelimbs extended cranially, even when the ISS was localized in the interscapular region, and double positioning was performed with the forelimbs flexed/extended.11 The dimensions obtained by CT (CTDs) were measured by the radiologist (Aycan Workstation OsiriXPRO Manager, Aycan Digitalsysteme GmbH, Würzburg, Germany) and consisted of the longest length (CTD-l) and the longest width (CTD-w) of the tumour with a soft tissue window (Window Width 350, Window Level 40), based on post-contrast CT images (PQ2000S, Philips, Amsterdam, the Nether- lands; single slice fourth generation CT, with slice thickness of 1 – 3 mm, pitch = 1, 200 –250 mA)after an intravenous injection via the cephalic vein of non-ionic contrast medium (Iohexol 350 mgI mL−1, Omnipaque GE Healthcare, Milan, Italy)at a dose of 600 mg I kg−1.19 For both the clinical and CT dimensions, we defined ‘length’ as the cranio- caudal axis of the tumour and ‘width’ as the transversal axis for an

ISS located on the dorsal thorax and dorsal abdomen or as the dorsum– ventral axis for an ISS located on the lateral side of the body.

The shape of each tumour was also considered and was categorized as 'regular-shaped' when the tumour had a spheroidal (the two axes beings approximately equal) or oval (when one axis was longer than the other) shape and 'irregular-shaped' when a geometric shape was not recognizable. This variable was obtained both by clinical evaluation (CD-shape) and by CT imaging (CTD-shape).

For each cat, the following data were also recorded: breed, age, sex, weight, body condition score (BCS – from 1 to 5)20 and site of the tumour.

Statistical analysis

In the absence of a 'gold standard' method for defining the tumour size of ISS, the agreement between dimensions retrieved by clinical and CT measure- ments was evaluated according to the Bland and Altman approach,21 representing the relationship between the differences between the two methods (CTD −CD) versus the average [1/2(CTD + CD)]. The limits of agreement were than obtained as the values containing 95% of the differences between the two measurements. If, on the basis of clinical consideration, the limits of agreement were considered too wide, it can be concluded that the two measurements disagree, and they cannot be considered 'interchangeable'. In the simplest situation, differences and their variability do not depend on the tumour size being measured, and the lack of agreement can be simply summarized by the bias (estimated by the mean of the differences) and the standard deviation of the differences. In the absence of a gold standard method, neither of the two measurements can be assumed to be 'true', and the average of the two measurements is considered an estimate of the tumour size being measured. The assumption of constant difference between the two measurements was evaluated by a regression model of the differences as a function of the aver- ages and by assessing whether the estimated slope was equal

to 0. The assumption of constant variability was evaluated by a regression model of the absolute value of the residuals of the above-cited regression model as a function of the averages and by assessing whether the estimated slope was equal to 0.22 In the case of non-constant differences and non- constant variances, the bias and approximate limits of agreement were obtained by considering a linear relationship between differences and averages and between standard deviations and averages.22,23 A measurement of overall concordance, using the concordance correlation coefficient (CCC), was obtained according to Lin et al.24 The value of CCC ranges between −1 (perfect discordance) to 1 (perfect concordance). A value of 0 corresponds to the lack of a relationship between the two measurements. The CCC is subdivided into its components: precision and accuracy. The 95% confidence interval (95% CI) of the CCC was obtained by the boot-strap method. Because of the limited number of cases, only an overall analysis was performed for all of the cases, and for a subsample of cases in which the tumours were retained as 'regular-shaped' by both measurement methods, without considering other clinical characteristics of the subjects.

The 95% CI for the proportions of the disagreement between the classification of the tumour shape as regular-shaped or irregular-shaped on the basis of clinical and CT evaluations was obtained by the 'exact method' procedure suggested by Clopper and Pearson.25

To evaluate the risk of failure in eliminating over- all tumour mass, using a safety margins of 3 and 5 cm starting from each side of the clinical measurement, length and width of clinical measurements were firstly added by 6 and 10 cm, respectively and then the percentages of clinical measures exceeding CT measurement were calculated with the corre- sponding exact 95% CI. The statistical analysis was performed using the R and MethComp software packages (www.r-project.org). A P value ≤0.05 was considered statistically significant.

Results

Fifty-three cats were prospectively included in the study. Forty-eight were domestic short-hair cats, two were Persian, two were Norwegian forestcats, and one was a Chartreux. Thirty-two cats were female (of which 31 were spayed), and 21 cats were male (of which 19 were castrated). The median age at presentation was 10 years old (range:4 – 16 years). The median body weight was 4.5 kg (range, 3 –8.5 kg). The body weight was not avail- able for two cats. Eight cats had a BCS of 2 of 5, 31hada BCS of3 of 5,9 had a BCS of 4 of5 and5 had a BCS of 5 of 5. Thirty-one tumours were located on the inter- scapular region, 13 were on the lateral thorax, 8 were on the lateral abdomen and 1 was on the lumbar region. Forty-eight tumours were histologically diagnosed as fibrosarcomas (2/48 with areas of chondroid metaplasia) and five as malignant fibrous histiocytomas. Moderate to abundant inflammation was seen in all tumours. Inflammatory cells were mainly represented by lymphocytes and fewer macrophages.

The median CD measured was 3 cm (range: 0.5 –10 cm). Both the median CD-l and median CD-w were 3 cm (range: 0.5 –10 cm and 0.7 – 10 cm, respectively). The CD-shape evaluation considered 46 cases as regular-shaped tumours (spheroidalin 34 cases, oval in 12 cases) and seven cases as irregular-shaped tumours.

The median CTD measured was 5 cm (range: 0.6 –13 cm). The median CTD-l was 5 cm (range: 0.9 –12.7 cm), and the median CTD-w was 4.4 cm (range: 0.6 – 13 cm). The CTD-shape evaluation considered 41 cases as regular-shaped tumours (spheroidal in 18 cases, oval in 23 cases) and 12 cases as irregular-shaped tumours. Concerning the shapes of the tumours, 36 cases were classified as regular-shaped, and 3 tumours were classified as irregular-shaped by both measurement methods. Five of 53 cases (9.4%; 95% CI: 3.13 –20.66%) were classified as irregular-shaped according to clinical measurements and as regular-shaped according to CT measurements, whereas 9 of 53

146 cases (17%; 95% CI: 8.07 – 29.80%) were classified as regular-shaped according to clinical
147 measurements and as irregular-shaped according to CT measurements.

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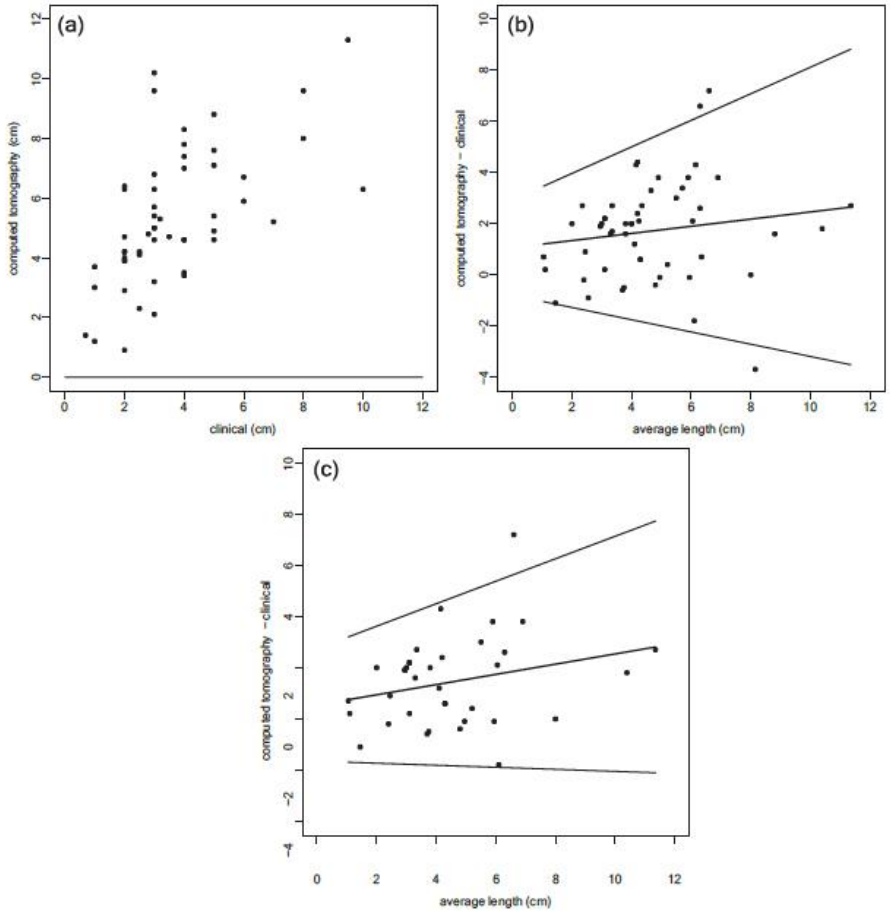

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150 *Figure 1. (A) Tumour length on the whole tumour series: clinical measure against computed*
151 *tomography measure. The couple of measurements for each tumour are represented by points and*
152 *the line represents the putative perfect agreement between the two measures. (B) Bland–Altman*
153 *plot describing the agreement between the computed tomography measure of tumour length and*
154 *the clinical measure of tumour length on the whole tumour series. The couple of measurements for*
155 *each tumour are represented by points. The central line is the estimated bias and lower and upper*
156 *lines are the estimated limits of agreement. (C) Bland–Altman plot describing the agreement*
157 *between the computed tomography measure of tumour length and the clinical measure of tumour*
158 *length on the subsample of regular-shaped tumours. The couple of measurements for each tumour*
159 *are represented by points. The central line is the estimated bias and lower and upper lines are the*
160 *estimated limits of agreement.*
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Length

The relationships between the CT and clinical measurements are reported in Figure 1A. In the majority of tumours, the CT measurement was larger than the clinical measurement (Figure 1B). A plot of the differences between the two measurements (CTD − CD) against their averages suggested a tendency of the differences to increase with increasing of the estimated tumour length (slope of the estimated regression coefficient is 0.1403, P = 0.27) and a tendency of the variability of the differences to increase with increasing of the estimated tumour length (slope of the estimated regression coefficient is 0.15194, P = 0.06). Because of the small size of the case series, although the estimated regression coefficients were not significantly different from 0, a conservative approach was applied, accounting for possible increases in difference and variability. The corresponding estimated bias and limits of agreement are reported in Figure 1B. The estimated bias ranged from 1.2 cm for an estimated tumour size of 1 – 2.18 cm for an estimated tumour size of 8 cm. The estimated limits of agreement became wider with increasing estimated tumour length, starting with values of bias of ±2.24 for an estimated tumour length of 1 cm to bias of approximately ±4.9 for an estimated tumour size of 8 cm (Figure 1B). The CCC between the two measurements was 0.52 (95% CI: 0.27 –0.69) with corresponding precision of 0.66 and accuracy of 0.78. The value of this CCC also suggested unsatisfactory concordance between the clinical and CT dimensions.

Considering the analysis of the subsample of 36 tumours classified as 'regular-shaped' using both clinical and CT evaluations, the results were similar (Figure 1C). The estimated regression slopes for the difference between measurements as a function of the estimated length and for the variability of the difference as a function of estimated length were 0.20 (P = 0.12) and 0.09 (P = 0.21), respectively. The estimated bias and limits of agreement started at 0.74 ± 2.44 for an estimated tumour length of 1 cm and ranged to 2.14 ± 4.12 for an estimated tumour length of 8 cm (Figure 1C). The estimated CCC was 0.63 (95% CI: 0.36 –0.81).

Width

The relationships between CT and clinical measurements of width are reported in Figure 2A. The tendency of a CT measurement to be larger than the clinical measurement was less evident than the observed pattern for length (Figure 2A). A plot of the difference between the two measurements (CTD −CD) against their average suggested a tendency of the differences to increase with increasing estimated tumour width (slope of the estimated regression coefficient was 0.1453; P = 0.32). The increase in the variability of the differences with increasing estimated tumour width was evident and was confirmed by the regression analysis (slope of the estimated regression coefficient was 0.25055; P = 0.0062). Although the estimated regression coefficients were not both significantly different from 0, a conservative approach was applied, accounting for the possible increase in difference and variability as a function of the estimated tumour width. The corresponding bias and limits of agreement are reported in Figure 2B. The estimated bias ranged from 0.5 for an estimated tumour width of 1 cm to 1.55 for an estimated tumour width of 8 cm. The limits of agreement became wider with increasing estimated tumour width, ranged from values for bias of approximately ± 2.1 for an estimated tumour size of 1 cm to bias of approximately ± 6.44 for an estimated tumour size of 8 cm (Figure 2B). The CCC between the two measurements was 0.52 (95% CI: 0.27 –0.68) with corresponding precision of 0.57 and accuracy of 0.92. The value of this CCC also suggested an unsatisfactory concordance between the clinical and CT measurements.

Considering the analysis of the subsample of 36 cases classified as ‘regular-shaped’ tumours using both clinical and CT evaluations, the trend towards an increase in the difference between measurements with the increase in estimated tumour width is very weak (slope of the estimated regression coefficient was 0.05; P = 0.68), as was the trend towards an increase in the difference in variability with the increase in estimated tumour width (slope of the estimated regression coefficient was 0.04, P = 0.57). The average bias between the two measurements was approximately

0.56 cm, and the average limits of agreement were approximately −2.67 and 3.80, respectively (Figure 2C). The estimated CCC was 0.73 (95% CI: 0.50 – 0.86). Considering the addition of a lateral margins to each side of the clinical measurement, only in two cases CTD-l was greater than CD-l added by 6 cm (3.78%: 95% confidence interval 0.46 – 12.98%) and only in one case CTD-w was greater than CD-w added by 6 cm (1.89%: 95% confidence interval 0.048 –10.07%). Overall, if 3 cm for each side are added to CD, the risk of failure to eliminate the corresponded tumour highlights by CT should be 3/53 (5.7%, 95% confidence interval 1.18 –15.66%). If 5 cm for each side were added to CD, no CTD was greater than CD added by 10 cm. The risk was estimated to be 0/53 = 0%, nevertheless, after com- puting 95% CI, the upper limit was 6.72%.

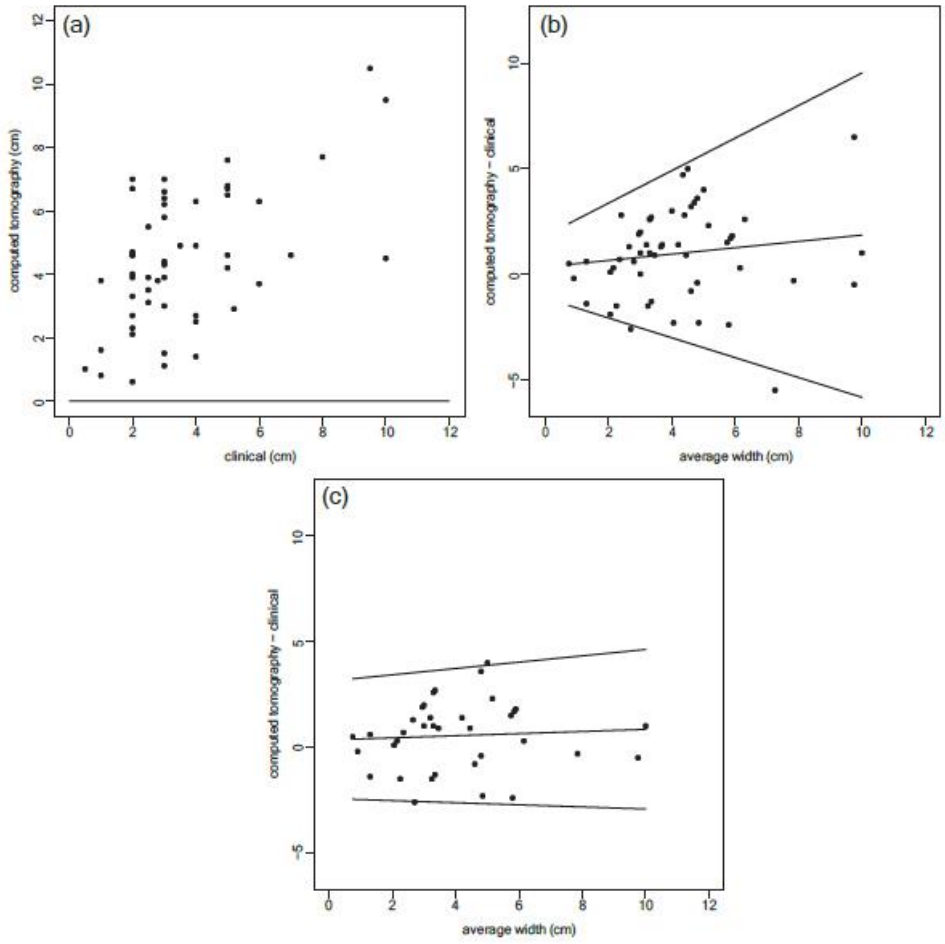

Figure 2. (A) Tumour width on the whole tumour series: clinical measure against computed tomography measure. The couple of measurements for each tumour are represented by points and the line represents the putative perfect agreement between the two measures. (B) Bland–Altman plot describing the agreement between the computed tomography measure of tumour width and

the clinical measure of tumour width on the whole tumour series. The couple of measurements for each tumour are represented by points. The central line is the estimated bias and lower and upper lines are the estimated limits of agreement. (C) Bland–Altman plot describing the agreement between the computed tomography measure of tumour width and the clinical measure of tumour width on the subsample of regular-shaped tumours. The couple of measurements for each tumour are represented by points. The central line is the estimated bias and lower and upper lines are the estimated limits of agreement.

Discussion

Tumour dimension is one of the first aspects evaluated in the pre-operative setting, to outline the prognostic consultation, as well as to calibrate the surgical dose. These considerations are particularly relevant for ISS in cats because the correct surgical approach is crucial for ensuring clean surgical mar- gins and increasing the probability of a cure.6,10,15 In addition, the dimensions of ISS in cats influence the surgical time and therefore indirectly impacted the risk of wound healing complications, which could induce postoperative morbidity and postpone other adjuvant therapies.16 Despite the relevance of such aspects, a standardized approach for measuring the dimensions of ISS in cats is not currently available. In small animal oncology, especially when dealing with feline ISS, the use of advanced imaging techniques in the pre-surgical setting has recently increased, but their use is still not a rule, and it is mostly left to surgeon choice.4,7,9,15,16

In this study, tumour dimensions, both length and width, evaluated by CT showed a tendency towards being larger than the dimensions measured with calipers, consistent with previous reports.13,16,17 In addition, in a proportion of cats, the shapes retrieved by the two methods demonstrated discrepancies. These findings could be related to the specific characteristics of ISS and specifically to the presence of non-palpable tumour extensions departing from the clinically palpable tumour. These thin tumour peripheral projections are mostly detectable only with CT contrast medium or histologically.10,11,17 Actually, these extensions are not always composed of neoplastic cells because inflammatory infiltration (small lymphocytes and rarer macrophages) and the rich neovascularization that often histologically characterizes ISS can also be highlighted by CT

contrast medium.11,12,18 A distinction between neoplastic and inflammatory tissue can be achieved only histologically; however, it has been suggested that inflammatory tissue around an ISS should also be excised.11 Therefore, the tumour burden in this study included all the tissue enhanced by the CT contrast medium. The difference between tumour dimensions obtained with the two techniques was also corroborated by the statistical analysis, which revealed a weak concordance between clinical and CT evaluations of tumour dimensions. This weak concordance was confirmed even when considering the subsample of 'regular-shaped' tumours, in which greater agreement was expected. Moreover, other results also showed wide limits of agreement, particularly with increasing tumour size, indicating that, when the surgeon clinically measures the tumour, a wide range of possible CT measurements is possible. In addition, this range of possible values became wider if the tumour increased in size. This could be explain by the hypothesis that a tumour that has the ability and/or the time to grow also has a greater likelihood of infiltrating the surrounding tissues, forming longer tumour extensions and thus increasing the discrepancy between the two methods of measurement by increasing the tumour dimensions. Another explanation could be that, while CT images allow for the precise evaluation of only the tumour edges, when the tumour was clinically measured with calipers, the thickness of the skin and soft tissues that covered the mass could not be subtracted from the value obtained, and other variables related to the single cat, such as BCS and the anatomical site of the tumour, could contribute to that variability. These findings suggested that it is not correct to estimate the tumour size only using one method of assessment but rather than both methods should be applied.

The gold standard for measuring tumour dimensions should be the method that provides a value closer to the real dimensions of the tumour. In human breast cancer, another tumour category in which surgery is the mainstay of treatment, the gold standard is to obtain the tumour size measured by pathology, and with calibration, it is possible to record which technique of measurement

278 applicable in the pre-surgery setting was closer to that gold standard.26 Unfortunately, in the
279 specific case of ISS in cats, the gold standard method for tumour measurement remains unknown.
280 Some studies have emphasized the utility of advanced imaging techniques for better clarifying
281 tumour edges and planning excision,8,9,11 – 15 but the real impact of this procedure on surgical
282 and oncologic outcomes, rather than being applied for clinical evaluation only, has not been well
283 documented.8 In the absence of a gold standard, it is not possible to determine the perfect pre-
284 surgical approach. The wide margins proposed for ISS excision have ranged from 3 to 5 cm,6,8 as
285 previously hypothesized,16 the results of the study emphasized the necessity for the surgeon to
286 approach the same ISS in a different manner, depending on whether the tumour dimensions were
287 obtained with CT or calipers. In cases of clinical measurement the widest margin should be required,
288 whereas in cases of tumour dimensions obtained with CT this margin could be reduced. Recently, in
289 fact, a wider margin of excision of 5 cm of healthy tissue around clinically palpable margins of ISS in
290 cats that did not undergo a pre-surgical CT examination was proposed.7 In the case series of this
291 study the addition of 10 cm (5 cm of margins for each side of the linear measurement) to the value
292 obtained clinically led to include all the measures retrieved by CT. Simplistically this result seemed
293 to suggest that using a safety margin of 5 cm around palpable mass almost all tumour detectable
294 tomographically would be excised. At the same time it is also probable that for some of these
295 tumours a 5 cm margins in clinics correspond to a marginal excision of the tumour highlighted by
296 the CT contrast-medium. Based on this consideration, a perspective randomized study comparing
297 the two methods of size assessment (and consequent margin of excision) in relation to onco- logical
298 outcome should be deal in further studies.
299 The dimensions of the tumours in cats are often reported as maximum diameters,7,9,15 but in this
300 study, two perpendicular axes were considered because the major axis between length and width
301 on clinical evaluation is not necessarily the major axis even on CT evaluation, thus making the

comparison between the two methods susceptible to bias. The third axis was not calculated because of presence of anatomical limits, such as underlying bone or cavities, making it impossible to measure clinically with calipers the thickness of the tumour. These data are therefore not available for comparison with CT measurements. In addition, the surgeon calibrates the depth of the excision based on the infiltration of fascial planes and not based on linear measurement of the thickness. Regarding this practice, the use of CT evaluation could facilitate the identification of deep soft and bone tissue infiltration,11,15 the detection of which is not always easy to perform in a clinical fashion. The use of other measurements, e.g. area, was not applied because these data could only be retrieved using a mathematical formula that approximates the real extension of the tumour, particularly in 'irregular-shaped' tumours, so a comparison of linear measurements was considered more appropriate.

This study emphasized that dimension of a ISS in cats obtained with CT are often larger than those measured with calipers. This finding suggested that the margin of excision in cases of clinical measurements should be larger than in cases of CT evaluation. These difference highlighted the necessity to declare and standardize the method of tumour dimension assessment in studies focusing on ISS in cats in order to properly consider surgical results and prognostic impact of this variable. As it has already been reported in the literature, the useful- ness of contrast-enhanced whole-body CT for ISS in cats is not only linked to the role of planning lateral excision margins, but it also has the ability to estimate deep margins and to detect distant metastasis.11,27 These aspects are crucial points to discuss before surgery with surgical staff and the owner. Further studies are necessary to evaluate other advanced imaging techniques, such as MRI, and to introduce a gold standard method to create guidelines for the pre-surgical evaluation of the dimension of ISS in cats.

Conflict of interest

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of this paper.

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