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Exogenous Insulin Treatment after Hypofractionated Radiotherapy in Cats with Diabetes Mellitus and Acromegaly

M.D. Dunning, C.S. Lowrie, N.H. Bexfield, J.M. Dobson, and M.E. Herrtage

Background: The optimal treatment for feline acromegaly has yet to be established. Surgical and medical therapies are minimally effective although radiotherapy might have greater efficacy. The purpose of this study was to review the response and outcome of cats with acromegaly and insulin-resistant diabetes mellitus (DM) to radiotherapy.

Hypotheses: That radiotherapy improves glycemic control in cats with acromegaly and that improved glycemic control is due to remission of clinical acromegaly; demonstrated by a fall in serum insulin-like growth factor-1 (IGF-1) concentrations.

Animals: Fourteen cats with naturally occurring acromegaly.

Methods: Retrospective case review; records of all cats treated for acromegaly with radiotherapy were reviewed from 1997 to 2008. Cats were selected on the basis of compatible clinical signs, laboratory features, and diagnostic imaging findings. Fourteen cats received radiotherapy, delivered in 10 fractions, 3 times a week to a total dose of 3,700 cGy.

Results: Thirteen of 14 cats had improved diabetic control after radiotherapy. These improvements were sustained for up to 60 months. DM progressed in 2 cats and 1 did not respond. Seven cats responded before the final treatment. Ten cats were euthanized, 1 as a consequence of radiotherapy. In 8 cats in which IGF-1 was measured after treatment, changes in its concentration did not reflect the clinical improvement in glycemic control.

Conclusions and Clinical Importance: Radiotherapy represents an effective treatment for cats with insulin-resistant DM resulting from acromegaly. IGF-1 concentration after treatment does not provide a suitable method by which remission from either acromegaly or insulin-resistant DM may be assessed.

Key words: Fructosamine; IGF-1; Insulin; Pituitary; Prognosis.

Feline acromegaly (FA) usually results from excessive growth hormone (GH, somatomedin) secretion from a pituitary adenoma.[1] Acromegaly in dogs, by contrast, usually results from ectopic GH production from the mammary gland.[2] Humans with acromegaly, as cats, typically have pituitary neoplasia.[3]

All cases of FA reported in the literature have concurrent insulin-resistant diabetes mellitus (DM).[1] Recognized clinical signs include respiratory stertor because of overgrowth of craniofacial bones and soft tissues, widened interdental spaces, generalized organomegaly, and myocardial hypertrophy.[1] In humans with acromegaly, although glucose intolerance is common, overt DM is present in $<60\%$ of cases.[3,4]

Diagnosis of FA relies on detection of increased serum insulin-like growth factor-1 (IGF-1) concentrations. IGF-1 is synthesized in the liver under the influence of GH and circulates both freely and bound to various binding proteins.[5] IGF-1 is used as a surrogate marker of pituitary somatotroph activity.[1,4] Serum IGF-1 concentrations are often increased in diabetic cats without acromegaly, reducing the specificity of IGF-1.[5–7] However, when used as a screening test in cats where acromegaly is suspected, IGF-1 has a sensitivity and specificity of 84 and 92%, respectively.[8] In the United Kingdom, this assay is commercially available.[a] Feline GH measurement is restricted to research institutions. Serum GH, IGF-1, free IGF-1, and oral glucose tolerance testing (OGTT) are used for diagnosis and follow-up evaluation in human patients.[3,4] However, diagnosis of human acromegaly remains controversial despite a recent consensus statement on the subject[9] as up to 25% of all newly diagnosed acromegaly patients have test results outside specified ranges.[10]

The current literature contains limited numbers of cats with verified acromegaly[11–23] and no large controlled case series identifies the most effective treatment. Limited reports with medical or surgical management suggest low efficacy and high complication rates.[18,20] However, in small numbers of cats with acromegaly, radiotherapy has markedly improved clinical signs.[1,12] In humans, the optimal treatment for acromegaly is surgery by a specialist pituitary surgeon.[3,24] Medical and radiation therapies are used where surgery is not curative, not possible, or declined by the patient.[3,25,26] Treatment with radiotherapy alone remains controversial, with slower responses and a greater reduction in quality of life relative to other treatments.[27–30]

Here we report a series of 14 cats with insulin-resistant DM and acromegaly treated with external beam megavoltage radiotherapy. We tested two hypotheses: that hypofractionated radiotherapy leads to improved glycemic control in cats with acromegaly and that the improvement in glycemic control is because of remission of clinical acromegaly as shown by a fall in serum IGF-1 concentrations.

Materials and Methods

Case records were retrieved from the Oncology Department archive at the Queens Veterinary School Hospital (QVSH).

Cats studied were examined at the QVSH between 1997 and 2008 for assessment of insulin-resistant DM or for treatment of suspected

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acromegaly. All cats had signs of insulin-resistant DM at the time of presentation.

Criteria for including cats in this study were: Acromegaly was diagnosed on the basis of suggestive clinical signs including overgrowth of soft tissues of the head and neck, widened interdental spaces, enlargement of extremities, and cardiac hypertrophy. In addition, supportive evidence of a pituitary micro- or macroadenoma was required on diagnostic imaging (MRI or CT). Increased serum IGF-1 concentrations (>1,000 ng/mL) were used as a surrogate marker of hypersomatotropism. Clinical evidence of insulin-resistant DM was determined by two or more of either an exogenous insulin requirement >1.5 U/kg daily,[31] clinical evidence of poorly controlled DM shown by increased fructosamine or owner's report (n = 14) of continued PD/PU and polyphagia despite insulin treatment. The dose of insulin received by each cat was expressed as a total dose/kg/d to account for differences in body weight and administration frequencies. A number of cats had previously received higher doses of insulin without improvements in glycemic control. This ensured insulin underdosing was not responsible for poor glycemic control in these cases.

External beam radiation using a 4 MV linear accelerator was used to administer 10 fractions of radiation on an escalating dose schedule using a Monday-Wednesday-Friday regime. The starting dose was 200 cGy for 3 fractions, which increased to 300 cGy for the next 2 fractions with 500 cGy being administered for the final 5 fractions. The total dose was 3,700 cGy. This was applied using a bilateral, equally weighted, isocentric, parallel opposed beam configuration, in some cases brass wedges were used to maximize tumor dosage and spare surrounding normal tissues. A custom written computerized planning system[b,32,33] was used to produce an isodose plot of predicted radiation distribution on a transverse section of the cats head. The planning target volume (PTV) was the tumor mass as defined on transverse MRI scan of the skull at the maximum tumor diameter, plus a 1-cm margin in all directions. In all cases the treatment volume was larger than the PTV because of the limitation of the machine, the smallest field achievable on the linear accelerator was 4 × 4 cm, thus a significant proportion of normal brain was also included in the treatment field. The treatment dose was prescribed to the 100% isodose line. The same treatment plan was implemented for delivery of each fraction of radiation. All cats were treated on the same protocol and to the same total dose.

General anesthesia was induced with alfaxolone/alphadolone.[c] After induction, cats were subsequently maintained on isofluorane[d] or sevoflurane[e] inhalation anesthesia, delivered via an Ayers' T-piece. The typical duration of each anesthetic was 10 minutes. Cats were positioned in sternal recumbency for the delivery of the radiation treatment. The tumor was positioned at the isocenter of the machine using anatomical landmarks (particularly the zygoma and ear canals) and distance parameters calculated by the planning program. The parallel (right and left lateral) beams were delivered by rotating the gantry to 90 and 270°, the cat remained in one position during treatment.

The final radiotherapy was used as the starting point for calculating the times to improved glycemic control, remission of DM, and survival times in the individual cats. Response was assessed objectively by measurement of serum blood glucose, fructosamine, and total IGF-1 concentrations along with exogenous insulin dose per unit body weight. Blood samples for serum IGF-1 and fructosamine were obtained at the completion of treatment and thereafter at regular intervals where this was possible.

Long-term follow-up data were obtained by means of telephone conversations with the referring veterinary surgeons and owners.

Statistical analysis was performed using Wilcoxon's rank distribution test, Mann-Whitney *U*-test statistic, Spearman's rank correlation coefficient and Student's *t*-tests. Survival data were calculated using a Kaplan-Meier product limit method.

Results

Fourteen cats met the entry criteria and were treated with radiotherapy as described in the "Materials and methods." The mean age at presentation was 10 years (range 6–12.5 years) and the average weight of the cats was 6.1 kg (range 5–7 kg). There was no breed predisposition; 13 cats were domestic short hairs with a single purebred Burmese. Males were significantly overrepresented, comprising 12/14 cats.

The mean individual dose of insulin at presentation in this study was 4.69 U/kg/d (range 2–10.2). Of the 10 cats that had paired concentrations of IGF-1 and fructosamine measured on enrolment into the study, all but 1 cat had increases in both parameters (Fig 1). The mean duration of DM before referral was 10.6 months (range 4–28).

Thirteen of 14 cats had an improvement in clinical signs after radiotherapy. The cat that failed to respond had an initial improvement in clinical signs and glycemic control; however, some difficulties were subsequently experienced with management of his DM and he was discovered dead by the owner 5 months after treatment. Of the 13 cats that responded to therapy, 7 showed improvement before completing the radiotherapy course. The rate of response to radiotherapy did not correlate with duration of improvement in glycemic control.

Significant reduction in the insulin dose per unit weight was observed after treatment ($P < .004$). The mean time to improved glycemic control measured using insulin per kilogram was 5 weeks after completing radiotherapy (range 0–20 weeks). The lowest insulin dose in those cats that responded to therapy represented an average reduction of 74% (SD ± 32%) of the enrolment dose. The cats that responded to radiotherapy had clinically improved glycemic control for variable proportions of their subsequent follow-up periods (Fig 2). The mean duration of improved glycemic control represented 70% (SD ± 36%) of the respective follow-up periods. Complete resolution or remission of DM was achieved in 6 cats during the follow-up period; the mean time to ces-

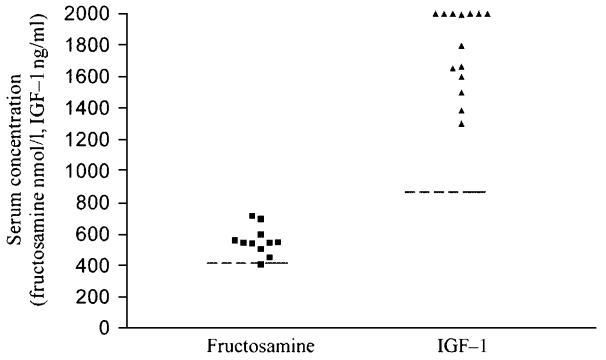

Fig 1. Graph showing enrolment concentration data for fructosamine (solid squares) and insulin-like growth factor-1 (IGF-1) (solid triangles) for cats (n = 14) satisfying inclusion criteria for unstable diabetes mellitus (DM) and acromegaly. Hatched lines represent poor control of DM and acromegaly for each respective parameter. All data points lie above the hatched lines except a single fructosamine value.

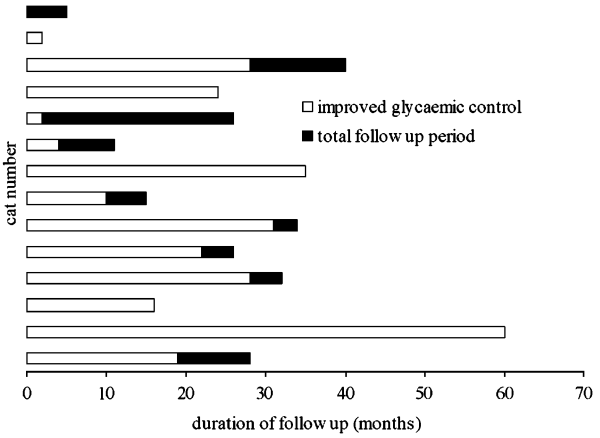

Fig 2. Graph representing duration of treatment response in each cat enrolled into the study (n = 14). The reduction in daily insulin dose over that at enrollment is used to represent this response. $T = 0$ represents the time point for completion of the radiotherapy course. The white bar represents the proportion of the total follow-up period (black bar) for which each cat had daily insulin requirements lower than pretreatment levels. Where no black bar is shown the insulin requirement remained lower than pretreatment levels for the entire follow-up period.

sation of insulin therapy was 3.6 months (range 0–6 months). Three of these cats remained insulin-free for up to 32 months. In the remaining 3 cats, this response was sustained for 3, 17, and 24 months, respectively.

At the time of writing, the average follow-up is 22 months (range 4–60 months). Eleven cats are no longer alive, none of which received postmortem examinations. The median survival time was 28 months for cats dying from any cause; however, the median survival time was not reached as a consequence of progression of DM due to insufficient cats dying of this cause (Fig 3). Two cats suffered progression of DM, 19 and 21 months after radiotherapy. These cats were euthanized at the owners request due to an unacceptably poor quality of life. Eight cats were euthanized for reasons unrelated to either DM progression or treatment complications. Two of these became unwell, 26 and 35 months after radiotherapy. Clinical examination in each case revealed an abdominal mass, further evaluation was declined by each respective owner and both cats were subsequently euthanized. Neither cat showed deterioration in glycemic control before euthanasia. One cat was euthanized at the owner's request due to acute onset gastroenteritis, which was unresponsive to symptomatic therapy. One further cat was euthanized after 60 months for complications associated with megacolon and chronic obstipation. Two cats were euthanized after 15 and 40 months, respectively, due to chronic renal failure. One cat was euthanized, at the owner's request, due to seizures unrelated to hypoglycemia. One cat was euthanized at the referring veterinary practice for reasons that were unclear. The remaining cat as described above was discovered dead by the owners.

Of the cats that are still alive (n = 3), 1 cat is receiving less insulin per kilogram than before treatment and 2 remain in remission from DM.

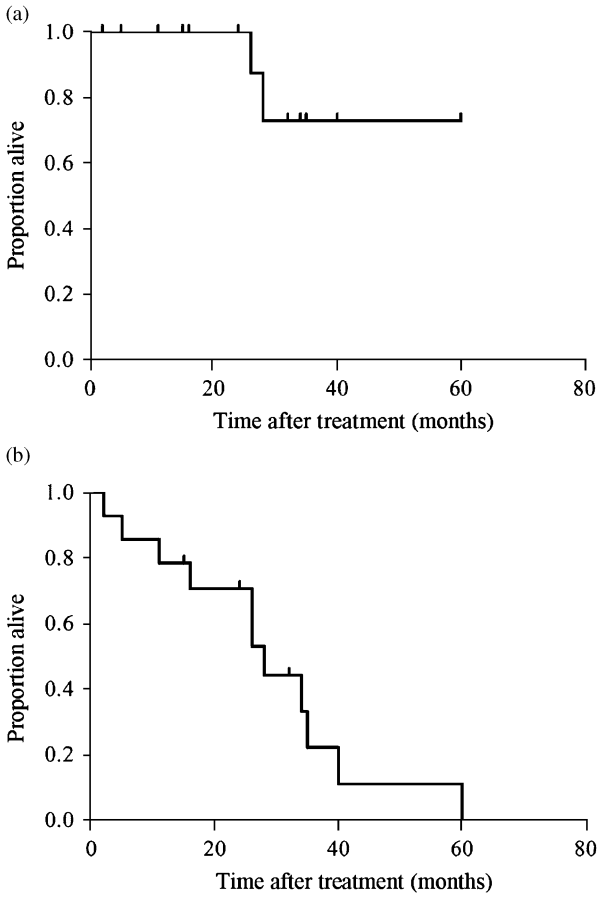

Fig 3. (a) Kaplan-Meier survival curve showing those cats surviving after radiotherapy. Deaths recorded are as a result of diabetes mellitus progression. (b) Kaplan-Meier survival curve showing those cats surviving after radiotherapy. Deaths recorded are because of any cause.

None of the cats in the study had complications arising from anesthesia or radiotherapy while hospitalized. Adverse effects of treatment reported by the owners were personality change 1/14, seizures 1/14, and weight loss 2/14.

In attempting to determine prognostic indicators from the data, the duration of clinical DM before diagnosis of acromegaly, degree of insulin resistance, IGF-1 concentration at diagnosis, rate of reduction in insulin dose, and relative dose reduction after treatment were all examined against the duration of improved glycemic control (outcome). None of these parameters was correlated with outcome.

Glycemic control after radiotherapy was monitored using serum fructosamine concentrations. Alterations in fructosamine concentrations reflected the clinical impression of glycemic control in all cases. In the subset of cats (n = 8) in which IGF-1 concentrations were also measured after radiotherapy, changes in the concentration of IGF-1 did not reflect the clinical improvement in the glycemic control. Eight of the paired IGF-1 and fructosamine samples gave discordant results (Fig 4). Two of the paired samples suggested poor glycemic control with increased fructosamine concentrations despite normal IGF-

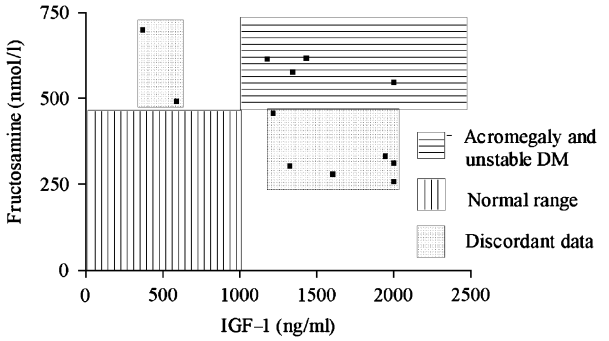

Fig 4. Graph representing paired insulin-like growth factor-1 (IGF-1) and fructosamine concentrations taken from cats after radiotherapy (n = 8). The box with vertical hatching represents IGF-1 concentrations within the normal range and fructosamine concentrations for normal animals and those with well controlled diabetes mellitus (DM). The horizontal hatching represents those samples with concentrations consistent with acromegaly and poorly controlled DM. Data points lying outside of these boxes (highlighted in gray boxes) represent discordant results. Points in the left upper quadrant of the graph represent unusually poor DM control despite normal IGF-1 concentrations (n = 2). Those in the lower right quadrant of the graph represent evidence of IGF-1 concentrations consistent with acromegaly despite well controlled DM (n = 6).

1 concentrations. Six of the paired samples showed IGF-1 concentrations within the range considered diagnostic for acromegaly, despite fructosamine concentrations suggesting good glycemic control. The reduction in fructosamine concentrations with improved glycemic control showed no significant correlation with the corresponding IGF-1 concentration ($P > .9$).

Discussion

This study is the largest to report the efficacy of a standardized radiotherapy regime to treat insulin-resistant DM secondary to FA. Thirteen of 14 treated cats had sustained improvements in glycemic control and 5 cats had remission of DM, hereby demonstrating the efficacy of radiotherapy in this disease. These results contrast to the limited efficacy of radiotherapy alone for human acromegaly.[3,25,26,34]

A small number of studies reporting results of radiation therapy for pituitary tumors in cats have included acromegalic cats as well as those presenting with neurologic signs, the results of these studies support our findings.[12,13,15,35] Six of 8 cats with poorly controlled DM showed improved diabetic control after radiation and in 5 cats, insulin therapy was discontinued at a median time of 17 weeks from the start of radiotherapy,[16] in contrast to our study where the mean time to improvement was 5 weeks. The other studies also report that the diabetic cats considered poorly responsive to insulin at the start of treatment all became more clinically responsive to insulin after radiotherapy; however, they do not quantify this improvement in glycemic control.

It is difficult to make direct survival comparisons as the other studies included cats with neurologic signs. However, it appears that cats with acromegaly may expect prolonged survival after radiotherapy with studies reporting median survival times of 71 weeks[16] and 17.4 months (~69 weeks).[13] The median survival time from our study was 28 months, which compares favorably with previous reports.

It is interesting that these studies reporting irradiation of feline pituitary tumors achieve similar outcomes with very different radiation treatment protocols, ranging from a total dose of 37 Gy (4 MeV photons) in 5 coarse fractions, to a total dose of 36–40 Gy (20–30 MeV photons) in 10–12 fractions on Monday/Wednesday/Friday schedule to 45–54 Gy (6 MeV photons) in 15+ fractions.[16,35] The unconventional escalating dose regime used in the present study was devised as a modification of that described by Brearley et al[36] in an earlier study. Up to 50% of dogs with brain tumors treated with large fractions of radiation have clinical deterioration after the 1st fraction, thought to result from reactive tumor swelling. The incidence of this problem was subsequently reduced using an escalating dose regimen.[36] The QVSH routinely uses an escalating dose schedule to treat canine brain tumors, which was modified to the 10 fraction regime described here. It is arguable that postirradiation brain swelling would be less likely using a 10 fraction regime of 350–400 cGy per fraction, as previously described,[35] which is a more rational treatment protocol.

In humans with pituitary disease, although radiation is not the first-line treatment, conventional radiation protocols treat to a total dose of 45–50 Gy in 25–28 fractions of 1.8 Gy over 5 weeks. In radiobiological terms this is far superior to the more coarsely fractionated regimes used in this and other veterinary studies, because the large number of small fractions of radiation optimize tumor control and minimize normal tissue toxicity. Hence, the advantages of the 10 fraction protocol used in this study including the less frequent anesthesia and lower cost would be outweighed by the potential disadvantages of using higher doses per fraction, ie, higher risk of late effects and lower probability of tumor control due to a lower dose.

No acute adverse effects of radiation were observed in the present study, nor in 2 earlier studies.[16,35] Epilation and mild otitis externa were reported using higher total doses[13] and mild skin reactions and transient alopecia were reported as later events.[35] As outlined above, it might be expected that coarse fractionation regimes would result in greater late intoxication, particularly ischemic brain necrosis, which would likely present as a rapidly progressive neurologic problem, usually appearing from 5–6 months onward after brain irradiation.[35] It has been suggested that cats are more tolerant of irradiation than dogs or humans and this observation may be supported by the apparently low incidence of brain necrosis across the feline studies. Acute neurologic deterioration was not reported in any of the 12 cats by Brearley et al.[16] One cat in the present study developed seizures 15 months after radiotherapy and was euthanized; postmortem examination was not performed. Two cats were examined postmortem in the Kaser-Hotz et al[35] study, 1 at 18 months had no pathology indicating late radiation effects and the other, euthanized for signs unrelated to the brain, had small areas of necrosis

of the 3rd ventricle and the hypothalamus, possibly due to radiation. At the higher total doses of 45–54 Gy, Mayer et al[13] reported 1 cat with a focal area of brain necrosis found on postmortem examination, adjacent to an area of tumor regrowth and 1 cat that died 523 days after radiation due to progressive neurologic deterioration, tumor regrowth was suspected but no postmortem examination was performed. The higher total dose was also associated with several other late effects of radiation, including cataracts (2 cats) and hearing impairment (2 cats). Although postmortem examination of the cat's brains was not undertaken to look for necrosis, only 1 cat in the present study had seizures that could have been consistent with late radiation damage to the brain.

In contrast to the human experience, it would appear from this and other studies that radiotherapy can lead to rapid and sustained improvement in glycemic control in cats. This suggests that the resultant reduction in GH secretion leads to a fall in insulin antagonism.[37] This comparative difference may reflect a heightened radiosensitivity of feline adenoma cells. However, the difference may also relate to the fractionation regime and relative biological radiation dose. As a follow-up MRI was not performed, it is impossible to know what magnitude of tumor remission (if any) was actually achieved with radiotherapy. Although a clear clinical response, this does not indicate tumor regression per se, as radiation may influence cellular function or secretory activity of adenoma cells without necessarily causing lethal damage.[38,39] Thus a lower intensity radiotherapy schedule may inhibit secretion from slowly growing tumors.

A further important observation from our study was the time over which remission from DM developed and persisted. One cat remained in remission for 2 months, while another for 24 months. In addition, those animals requiring reintroduction of insulin due to recrudescence of DM remained stable on a lower dose per kilogram than before radiotherapy (data not shown). This variable response to treatment may result from tumor size or histologic variation, factors that were not addressed in this study.

Our 2nd hypothesis was that the improvement in glycemic control after radiotherapy resulted from remission of clinical acromegaly. Diagnosis of FA currently relies on demonstration of increased serum IGF-1 concentrations. In this study a reduction in IGF-1 after treatment was used as a surrogate marker of GH secretion and therefore disease remission. Upon enrollment, all cats had increased IGF-1 and all but one had fructosamine levels consistent with poor glycemic control. However, only 4/12 samples measured after radiotherapy had IGF-1 and fructosamine concentrations within expected ranges. The remaining 8 paired tests were discordant, showing persistent increase in IGF-1 concentration despite reduced fructosamine and improved clinical signs of DM. From this we can determine that an increased IGF-1 concentration after radiotherapy has only a 37.5% chance of predicting persistently poor glycemic control (positive predictive value for poorly controlled DM). Similarly, normal IGF-1 cannot predict good glycemic control in cats treated for acromegaly. The power of this statement is, however, limited due to the small number of cases but remains an important observation. It is particularly relevant when considering the difficulties in assessing clinical response in human acromegaly patients.[9,40]

The cohort of cats with persistently increased IGF-1 concentrations after radiotherapy still satisfied the diagnostic criteria for acromegaly. This suggested ongoing somatotrophic abnormalities despite improved glycemic control.[41] Intuitively it would seem that if acromegaly is the sole cause of DM, unless complete remission is achieved after radiotherapy, acromegaly must persist in some capacity in the absence of pancreatic exhaustion. That pituitary hyperfunction still exists after treatment, despite improved glycemic control, relies on the specificity of IGF-1 as a surrogate marker of GH. It is possible, yet unlikely, that the established reference range for a diagnosis of FA using IGF-1 is flawed. A further possibility, which is currently unclear, is the specificity of the IGF-1 assay in FA. A number of other IGFs and their binding proteins exist in feline serum and may interfere with the IGF-1 assay should their abundance or affinity in FA change. Pre- and posttreatment discordance between disease activity and IGF-1 concentration is well accepted in humans with acromegaly.[9,40,42] Normalization of IGF-1 concentrations and other serological markers after treatment often takes decades.[43,44] As a result it remains unclear in humans when IGF-1 measurement should occur after intervention, therefore serial IGF-1 measurements are taken over many months.[41] The timing of the samples in our study was empirical. As a result it may be that over time, IGF-1 concentrations gradually return to normal in those cats showing improved glycemic control. Importantly these data suggest IGF-1 concentrations do not provide prognostic information in FA. At present those cats remaining alive are being regularly sampled to determine the kinetics of IGF-1. Measurement of free IGF-1 concentrations in humans is being developed and standardized, this is hoped to circumvent some of the problems associated with total IGF-1 assays.[45–47] Initial reports from human studies suggest that free IGF-1 may fall more rapidly than total IGF-1 after treatment.[47]

The typical large stature and overgrown facial features persisted in all cats in our study regardless of their response to radiotherapy. Human patients similarly retain these signs after treatment[3,4] making their persistence unhelpful for evidence of continued pituitary hyperfunction. Many of the subjective abnormalities in human acromegaly such as sweating, headaches, and arthralgia are difficult to identify in cats. As a result, the incidence of such abnormalities remains unclear, making persistent disease activity after remission of DM difficult to identify. This study has failed to demonstrate a role for total IGF-1 in this respect. As a result, this often subtle human disease may remain impossible to identify before the onset or after remission of DM until more sensitive markers of disease activity are established.

FA has yet to be reliably diagnosed in the absence of DM. This contrasts with a much lower incidence of overt DM in humans with acromegaly.[4] It is possible that cats

with FA remain undiagnosed until DM develops reflecting insidious disease progression. It is therefore possible that noninsulin resistant diabetics may be suffering from low-grade pituitary hyperfunction. Indeed, increases in IGF-1 are well accepted in long-term diabetics.[5–8] These increases may therefore reflect true pituitary hyperfunction rather than an alteration in the pancreas-liver axis and IGF-1 synthesis. A previous study investigated the incidence of pituitary tumors among diabetic cats; however, numbers were limited and not all cats included in the study received pituitary imaging.[11] A current project screening diabetic cats for pituitary abnormalities (The Royal Veterinary College, North Mymms, London, UK) will yield greater insight into this possibility. However, the onset of overt DM is not correlated with the duration of human acromegaly[3,4] (Gurnell, personal communication). This may also be true in cats and might suggest that the feline pancreas is more sensitive to antagonism by GH than in humans. Certainly the response of the feline pituitary is different to that of the human pituitary when similar stimuli are used.[48] A different sensitivity to GH may mean that in cats, smaller reductions in pituitary GH production may be sufficient to improve glycemic control whilst acromegaly persists. As a result, DM may truly be an earlier complication of FA reflecting a difference in disease pathophysiology.

Although the majority of cats responded favorably to treatment, the duration of response was variable; however, only 1 cat was a nonresponder. Prognostic indicators would be useful for owners to make informed consent. In humans, the duration of disease, OGTT results and long-term normalization of IGF-1 concentrations after treatment are all used for prognosis.[41,42] In this study, the duration of overt clinical DM before radiotherapy had no influence on the chances of improved glycemic control postradiotherapy. The extent of insulin resistance in individual cats, measured using insulin dose per kilogram, was also unable to predict the subsequent response to radiotherapy. In addition, both the rate and magnitude of the decline in insulin requirement after radiotherapy could not predict the long-term change in glycemic control for individual cats. We therefore conclude that parameters associated with DM do not provide prognostic information regarding treatment response in FA.

This study confirms that serum IGF-1 concentration appears to be a good screening test for FA. However, IGF-1 concentrations have poor predictive value and low specificity in identifying improved glycemic control after radiotherapy over the time period studied here. Further studies evaluating more sensitive and specific markers of prognosis for cats with FA, eg, free IGF-1, OGTT, or serial GH monitoring may be valuable and require further investigation.

Footnotes

[a] CSL Laboratories, Cambridge, UK

[b] Software written by Dr S Thomas, Dept Medical Physics, Addenbrookes Hospital, Cambridge (tested in accordance with IPEMB (Institute of Physics and Engineering in Medicine and Biology) 1996. Report 68. A guide to commissioning and quality control of treatment planning systems. Ed J.E. Shaw (York, IPEM)

[c] Saffan, Pitman-Moore, Uxbridge, UK

[d] Isoflo, Schering-Plough Animal Health, Uxbridge, UK

[e] Abbott Laboratories, Kent, UK

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Isodose plot showing the parallel opposed beam configuration for treatment of a feline pituitary macroadenoma. The outline of the cat's head (blue line), the brain (large red circle), and the pituitary mass (small red circle) are manually digitized into the computer program from the MRI scan. The program calculates the dose distribution resulting from beams applied at ports 1 and 2 and displays these as isodose lines, where 100 is equivalent to 100% of applied dose.

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