Use of stereotactic body radiation therapy for treatment of a pancreatic tumor in a cat

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CASE DESCRIPTION

A 16-year old castrated male domestic shorthair cat was evaluated at a veterinary teaching hospital because of polyuria, polydipsia, and weight loss of 2 months' duration.

CLINICAL FINDINGS

Hematologic and biochemical examination results were within respective reference ranges except for moderately high pancreas-specific lipase concentration. Ultrasonographic and cytologic evaluation revealed a hepatic mass with findings consistent with mild cholestasis and inflammation and a pancreatic mass that was initially identified as a neuroendocrine tumor.

TREATMENT AND OUTCOME

The cat underwent additional CT assessment and stereotactic body radiation therapy (SBRT; 3 fractions of 8 Gy, administered every other day) for treatment of the pancreatic tumor. Follow-up ultrasonographic and CT examinations indicated a partial response to SBRT, with a maximum CT-measured size reduction from 3.6 X 4.8 X 4.0 cm at the time of treatment planning to 2.0 X 2.0 X 1.9 cm 8 months later. Increased pancreatic tumor size and signs of carcinomatosis were detected 15 months after SBRT treatment; the initial cytologic diagnosis was changed to exocrine pancreatic carcinoma on reevaluation of the slides by another veterinary pathologist. Carboplatin treatment was elected, and signs of carcinomatosis resolved. The cat was euthanized without further testing because of weakness 589 days after SBRT was started.

CLINICAL RELEVANCE

To the authors' knowledge, this is the first report of SBRT for suspected exocrine pancreatic carcinoma in a cat. Further investigation is needed to determine optimal fractionation schedules for SBRT of pancreatic tumors and utility of SBRT of exocrine pancreatic carcinoma in cats. (*J Am Vet Med Assoc* 2021;259:184–189)

A 16-year-old 6.31-kg (13.88-lb) castrated male domestic shorthair cat was referred to the Internal Medicine Department of the Colorado State University veterinary teaching hospital. Clinical signs included polyuria, polydipsia, and moderate weight loss of 2 months' duration. Concurrent medical conditions were hyperthyroidism (deemed well controlled, with a 5-year history), bilateral degenerative joint disease of the stifle joints, bilateral cataracts, mild dental disease, and allergic dermatitis.

Results of routine CBC and serum biochemical analysis at the time of initial evaluation were within the respective reference ranges. The feline pancreas-specific lipase concentration was high (50.0 µg/L; reference range, 0 to 3.5 µg/L), and urinalysis revealed mild isosthenuria (urine specific gravity, 1.022). Abdominal ultrasonography identified a hyperechoic, mildly cystic, heterogenous mass arising from the left aspect of the liver (lobe not determined) near the hilus and an isoechoic, solid, irregular mass arising from the right caudal liver lobe partially surrounding the portal vein. The liver was diffusely hyperechoic. Other relevant findings included pancreatic enlargement with hypoechoic nodules and chronic bilateral degenerative changes of the kidneys.

ABBREVIATIONS

SBRT Stereotactic body radiation therapy

Results of a second, confirmatory ultrasonographic examination revealed 1 or 2 masses: a cystic 3.5 X 3.0 X 3.9-cm, left midliver mass and a 3.7 X 3.9 X 3.5-cm mass caudal to the liver on the right side and adjacent to the pancreas (origin indistinguishable, with possible transposition). Fine-needle aspirates of the cystic liver mass and presumed pancreatic mass were obtained from the sedated cat with 25-gauge needles and submitted for cytologic analysis by a board-certified pathologist. Cytologic findings for the liver mass were considered indicative of cholestasis, mild suppurative inflammation, and hepatocellular damage. Pancreatic mass cytology results at this time were initially interpreted as a suspected neuroendocrine tumor.

A CT examination was recommended to further characterize the masses visualized ultrasonographically. The cat was premedicated with butorphanol tartrate[a] (0.3 mg/kg [0.14 mg/lb], SC), and anesthesia was induced with propofol[b] (1.5 mg/kg [0.68 mg/lb], IV) and maintained with isoflurane[c] in oxygen. Non–contrast-enhanced volumetric (helical) CT of the thorax and abdomen was performed with a 16-slice CT scanner,[d] followed by IV administration of iohexol[e] (2

mL/kg [0.91 mL/lb]) for contrast-enhanced imaging. Images were reconstructed at 2.0-mm contiguous intervals with a 512 × 512-pixel matrix and a smoothing algorithm.

Evaluation of the CT images confirmed a lobulated, soft tissue–attenuating, contrast-enhancing mass, measured as 3.5 × 4.5 cm, in the midbody of the pancreas causing moderate ventral and (right) lateral deviation of the portal vein. Multiple well-defined, round, hypoattenuating, non–contrast-enhancing nodules were observed in the left limb and body of the pancreas. A round, hypoattenuating, contrast-enhancing, well-defined mass was noted occupying a large portion of the left aspect of the liver, with the lobe of origin unknown. Mild lymphadenomegaly in the cranial portion of the abdomen was also observed. The CT findings for the pancreas were consistent with pancreatic neoplasia, pseudocysts, or nodular hyperplasia. Differential diagnoses for the hepatic findings on CT were hepatocellular carcinoma, metastatic endocrine tumor, nodular hyperplasia, hematoma, and abscess or granuloma.

The owners initially declined treatment and instead elected for a follow-up CT 1 month later. The weight loss, polyuria, and polydipsia continued, but the owners reported the cat appeared comfortable at home. Anesthetic and imaging protocols for the follow-up CT were similar to the previous procedure. The cat was immobilized in sternal recumbency in a head and neck cushion[f] prior to imaging. The CT findings were largely unchanged, compared with the initial examination. The pancreatic and liver masses were measured as 3.6 × 4.8 × 4.0 and 4.3 × 4.7 × 4.4 cm, respectively. The intra-abdominal lymphadenopathy had resolved. Because the pancreatic mass enveloped the main portal vein, the cat was a poor candidate for surgery. Stereotactic body radiation therapy was offered as a treatment option, and the owners were informed that there was no known information on this modality for pancreatic tumors in cats. The owners elected treatment, and the cat was hospitalized for delivery of 8 Gy every other day to a total dose of 24 Gy. Whereas most SBRT treatments are administered daily, every other day dosing was elected after considering the novelty of the procedure and the risk of toxic effects on adjacent organs. The pancreatic tumor volume prior to radiation was 29.99 cm^3. The hepatic mass was not treated to avoid excessive radiation dose to the liver and stomach.

The 2.0-mm reconstructed contrast-enhanced CT images were used for the 3-D inverse treatment planning system.[g] The organs at risk were contoured by one of the authors (CKG) and included liver, stomach, duodenum, jejunum and ileum, colon, kidneys, and spinal cord. Grossly evident tumor in the pancreas was delineated on the postcontrast CT image, and the gross tumor volume was determined with the plan-

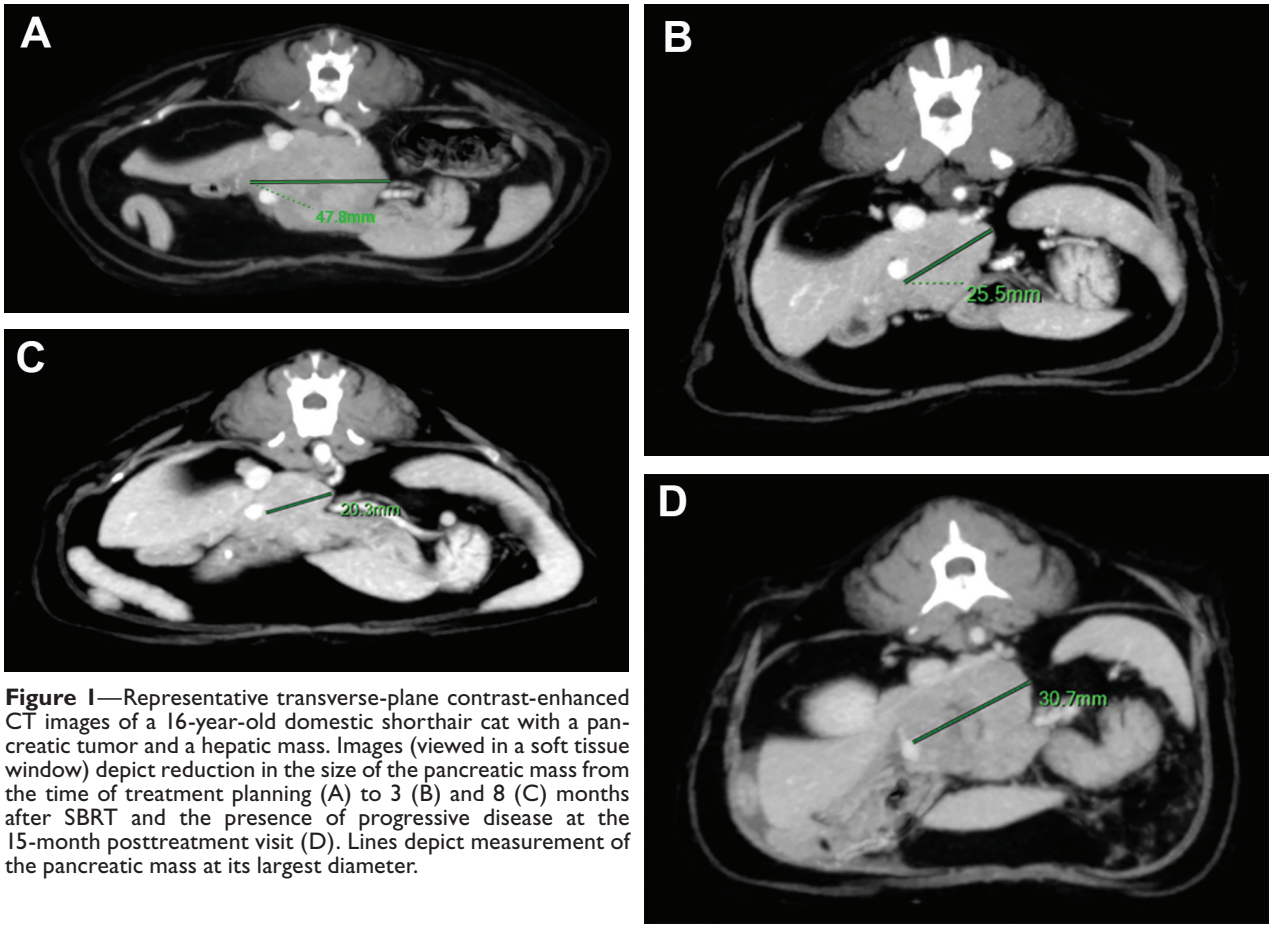

Figure 1—Representative transverse-plane contrast-enhanced CT images of a 16-year-old domestic shorthair cat with a pancreatic tumor and a hepatic mass. Images (viewed in a soft tissue window) depict reduction in the size of the pancreatic mass from the time of treatment planning (A) to 3 (B) and 8 (C) months after SBRT and the presence of progressive disease at the 15-month posttreatment visit (D). Lines depict measurement of the pancreatic mass at its largest diameter.

ning software[g] algorithm, which counted the number of voxels within any contoured structure. The voxels were predetermined with a parameterized 2-D grid and the slice thickness of the acquired CT image. When a voxel overlapped the determined boundary of the structure, the voxel was counted once on the side of the boundary that contained the largest portion of the voxel. The apparently normal portions of the pancreas were not contoured because there were no radiation dose constraints for this organ available in the published human medical reference[1]; no veterinary reference has been published. There was no field expansion to account for potential subclinical disease. A uniform expansion of 3 mm was applied to the gross tumor volume to account for interfractional and intrafractional motion, penumbra, and setup inaccuracies and was designated as the planning target volume. Three millimeters was considered sufficient, as the CT images for reconstruction were acquired while the cat was spontaneously breathing, and the cat would also be spontaneously breathing during the SBRT. No respiratory management beyond positioning in semirigid immobilization[f] was used. Volumetric and maximum dose constraints to normal tissues **(Appendix)** were determined with published guidelines.[1] The dose distribution was illustrated in the dose-volume histogram (**Supplementary Figure S1**, available at: avmajournals.avma.org/doi/suppl/10.2460/javma.259.2.184).

Anesthetic protocols for treatment were similar to those used for imaging. Once anesthetized, the cat was repositioned in immobilization devices. Daily patient position verification was performed by online registration of the simulation CT to images of the daily setup obtained via on-board cone beam CT. Intensity-modulated radiation therapy was delivered with a linear accelerator[h] with 7 static beams equally spaced out around the cat (**Supplementary Figure S2**, available at: avmajournals.avma.org/doi/suppl/10.2460/javma.259.2.184). The dosing goal was for 99% of the gross tumor volume and 95% of the planning target volume to receive the total prescribed dose of 24 Gy. Lower doses were accepted to meet dose constraints to the organs at risk (Supplementary Figure S1). A simultaneous integrated boost was not used.

Following completion of SBRT with no complications, the cat was discharged from the hospital. At a recheck examination 1 month after completing treatment, the cat continued to have a good appetite and energy level, with no reports of abnormal elimination or vomiting. The cat was returned for multiple follow-up visits over the next 15 months. During this time, multiple abdominal ultrasonography and CT examinations were performed to monitor the hepatic and pancreatic masses. The size of the pancreatic mass gradually decreased, with the maximum size reduc-

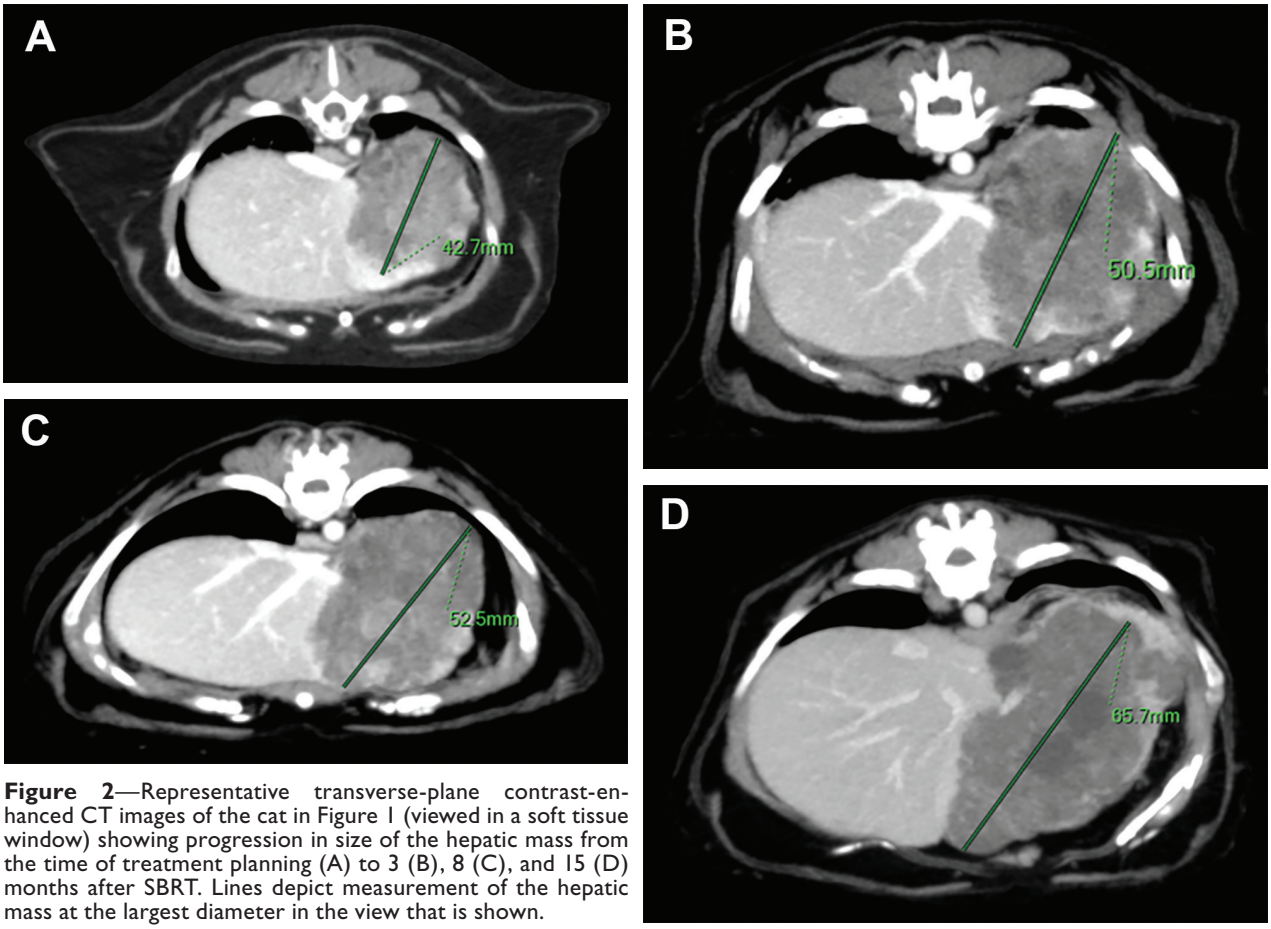

Figure 2—Representative transverse-plane contrast-enhanced CT images of the cat in Figure 1 (viewed in a soft tissue window) showing progression in size of the hepatic mass from the time of treatment planning (A) to 3 (B), 8 (C), and 15 (D) months after SBRT. Lines depict measurement of the hepatic mass at the largest diameter in the view that is shown.

tion observed 8 months after the completion of SBRT (from 3.6 × 4.8 × 4.0 cm at the time of treatment planning to 2.0 × 2.0 × 1.9 cm), until an increase (to 2.5 × 3.1 × 2.5 cm) was observed at the 15-month visit **(Figure 1)**. The untreated hepatic mass gradually increased in size from 4.3 × 4.7 × 4.4 cm at the time of treatment planning to 6.6 × 4.6 × 5.3 cm at the 15-month visit **(Figure 2)**.

At the 15-month recheck CT examination, suspected carcinomatosis and peritoneal effusion were noted. This indicated a discrepancy in the initial diagnostic findings, and the pancreatic cytologic preparations that were obtained prior to treatment were reevaluated by a second board-certified pathologist. The cytologic diagnosis was changed to pancreatic carcinoma. Possible treatment options discussed were further radiation therapy or IV chemotherapeutic treatment. The owners elected chemotherapy consisting of 4 doses of carboplatin[i] (180 mg/m^2), administered 3 weeks apart at the referral clinic. Abdominal ultrasonography revealed no evidence of carcinomatosis by the third administration of carboplatin. The cat continued to have weight loss and developed diarrhea that was treated symptomatically. On day 589 after the first day of SBRT, the cat was presented to the same referral clinic for weakness and was euthanized without further diagnostic tests.

Discussion

Exocrine pancreatic carcinoma is a rare neoplasia in cats, with reported incidences of < 0.5%.[2–6] Similar to its characteristics in human patients, it is an aggressive disease in cats with a reportedly poor prognosis and limited effective treatments available.[7–9] Clinical signs are often nonspecific, as observed for the cat of the present report, with the primary signs including weight loss accompanied by a normal appetite, vomiting, and diarrhea.[3,10–16]

Differential diagnoses for pancreatic masses include neuroendocrine tumors, benign pseudocysts, nodular hyperplasia, and carcinomas or other forms of metastatic neoplasia.[2] In dogs, radiography and ultrasonography have reported sensitivities of 19% and 75%, respectively, for identification of pancreatic tumors.[16] Ultrasonography can be used to guide fine-needle aspiration or for core needle biopsy.[5] Carcinomas and chronic pancreatitis can have similar ultrasonographic characteristics, including hypoechogenicity of the pancreatic parenchyma, hyperechogenicity of the surrounding pancreatic mesentery, generalized pancreatic enlargement, and dilation of bile ducts.[5,17–20] For the cat of the present report, the pancreatic tumor identified with abdominal ultrasonography and confirmed by CT examination was ultimately identified as an exocrine pancreatic carcinoma on reevaluation of cytologic slides after the development of metastatic disease. Without aggressive treatment, clinical conditions in cats with exocrine pancreatic carcinoma do not appear to improve, and treatment options are limited.[2,7–9] In a study[3] that included 8 cats, treatment was focused on supportive care consisting of IV fluid therapy and administration of fentanyl, vitamin K, prednisone, and antimicrobials. Most cats died or were euthanized ≤ 7 days after diagnosis.[3] The standard of care is currently surgical resection of the mass, chemotherapy, or both. In a retrospective study[2] of 34 cats with exocrine pancreatic carcinoma, the overall median survival time was 97 days for animals that underwent chemotherapy and 165 days for those that underwent surgical removal of the mass. Gemcitabine was the primary cytotoxic drug administered and is currently the chemotherapeutic drug of choice in human medicine for treatment of exocrine pancreatic carcinoma.[2,19] Eighty-two percent of the cats treated with gemcitabine had improvement of clinical signs; however, the improvement was not durable.[2] Adverse effects of chemotherapeutic treatment included neutropenia, vomiting, diarrhea, lethargy, and anorexia.[2] For the cat of the present report, surgical resection was not elected because of the extent of the disease near the portal vein at the time of diagnosis.

Stereotactic body radiation treatment shows promising results for treatment of pancreatic adenocarcinoma in people. In a clinical investigation[21] of 20 patients with locally advanced, nonmetastatic pancreatic adenocarcinoma, 3 doses of gemcitabine were administered prior to a single-fraction SBRT treatment, and 2 doses were administered afterward. Throughout the investigation, no grade 3 or greater acute gastrointestinal toxic effects were reported.[21] Clinically relevant late adverse effects included gastric and duodenal ulcers, with duodenal perforation developing in 1 patient. Median survival time was 11.8 months, with 1- and 2-year survival rates of 50% and 20%, respectively.[21] The radiation dose delivered to the cat of the present report was similar to palliative-intent SBRT doses administered to human patients, which range from 25 to 33 Gy delivered in 1 to 5 fractions.[21,22] Radiation doses to the tumor volume in our patient were well below the total prescribed dose to achieve sparing of the normal tissues. To our knowledge, this technique has not previously been reported for veterinary patients with pancreatic tumors.

In the clinical investigation[21] of pancreatic adenocarcinoma in human patients, adverse effects following SBRT were minimal. In the cat of the present report, clinical signs of weight loss and diarrhea were seen prior to SBRT treatment and continued afterward. It is difficult to differentiate these signs from adverse radiation effects, exocrine pancreatic insufficiency secondary to the tumor, or hyperthyroidism, without any further diagnostic testing. Measurements of thyroid hormones and indicators of pancreatic function were not consistently evaluated before or after SBRT for this cat. Certain other limitations were associated with the case described here and should be considered when interpreting the information. A CT reconstruction with slice thickness of 2 mm creates a degree of uncertainty when considering small

tumor contours and radiation dose estimates for SBRT planning. Finally, the initial cytologic diagnosis of neuroendocrine tumor was changed to exocrine pancreatic carcinoma on reevaluation of the sample by a second board-certified veterinary pathologist 1.5 years after the initial referral examination and sample collection. The change in diagnosis was arrived at after consultation with colleagues and considering the progression to carcinomatosis. A histologic diagnosis was not obtained, so a degree of uncertainty in the diagnosis remains.

Further investigation is needed to determine optimal fractionation schedules for SBRT of pancreatic tumors in cats. In addition, tolerance of the pancreas in cats to various radiation doses is unknown. In the future, the apparently normal portion of the pancreas could be contoured to allow for reduction of dose to this organ. Although no overt adverse effects of radiation were noted in the cat of this report, it was possible that radiation-induced fibrosis could have contributed to subclinical pancreatic insufficiency. In people, SBRT has been shown to cause less severe toxic effects than traditional chemotherapy and to shorten treatment periods.[22] Serial imaging for the cat of the present report confirmed that the pancreatic mass was partially responsive to radiation according to the Response Evaluation Criteria in Solid Tumors guidelines for dogs[23] (no similar guidelines presently exist for cats), and the cat survived 589 days after the start of SBRT. Although SBRT appeared to be well tolerated and local control of the pancreatic tumor was achieved for an extended period of time, the results cannot be extrapolated to other patients, and prospective controlled studies are needed to confirm the efficacy of this treatment in cats.

Footnotes

a. Stadol, Geneva Pharmaceuticals, Dayton, NJ.
b. Diprivan, Fresenius Kabi, Bad Homburg, Germany.
c. Aerrane, Baxter, Haryana, India.
d. Gemini TF Big Bore, Philips, Amsterdam, Netherlands.
e. Omnipaque, GE Healthcare, Chicago, Ill.
f. Vac-lok, CIVCO Radiotherapy, Coralville, Iowa.
g. Eclipse, Varian, Palo Alto, Calif.
h. Trilogy, Varian, Palo Alto, Calif.
i. Paraplatin, Bristol-Myers Squibb, New York, NY.

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Appendix—The reported normal tissue volumes, radiation dose statistics (ie, maximum, minimum, mean, and median doses) for individual tissues, and radiation dose delivered to specific tissue volumes (ie, the maximum volume of tissue that received the radiation dose shown) during 3-fraction abdominal SBRT treatment of a 16-year-old domestic shorthair cat.

		Radiation dose (cGy)				Volume-dose constraint*	
Structure	**Volume (cm³)**	**Maximum**	**Minimum**	**Median**	**Mean**	**Volume (cm³)**	**Dose (cGy)**
Liver	258.9	2,356.5	8.2	40.8	206	NR	1,920
Stomach	37	1,572.2	18.7	438.4	426.2	NR	1,650
Duodenum	8.2	1,625.8	60.3	594.7	577.9	0.24	1,140
						NR	1,650
Jejunum and ileum	195.9	2,216.8	4.3	31.7	202.6	0.4	1,770
Colon	100.1	2,052.4	0.6	29.5	264.3	1.4	1,600
						NR	2,400
Urinary bladder	10,094.1	71.7	2.4	8.8	11.1	NR	1,680
Right kidney	30	1,161.9	17.1	121.5	252	0.004	1,060
						NR	1,600
Left kidney	9.9	520.5	18.9	42.6	64.3	NR	1,060
Spinal cord	4.5	1,379.5	2.6	25.8	230.8	0.1	1,230

Radiation statistics for the patient were compared with published radiation planning guidelines in human literature for acceptability.[1] Maximum and minimum radiation values are point doses (ie, the highest and lowest dose within a single voxel of the contoured organ volume on the imported CT images).

*Volume-dose constraints represent the maximum volume of a tissue that received the radiation dose shown. Some tissues (duodenum, colon, and kidney), have multiple volume-dose constraints in the published guidelines, and radiation doses delivered to ≥ 1 volume are reported where applicable.

NR = Not reached (the volume of the tissue that received the described radiation dose was 0 cm³).