Radiation Therapy for the Treatment of Thymoma in Rabbits (*Oryctolagus cuniculus*)

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Abstract

The article presents 3 clinical cases of thymoma in rabbits. The diagnosis of thymoma was made in these cases by combining the results of the case history, the physical examination, the blood work, the thoracic and abdominal imaging and the fine needle aspiration of the mass in 2 cases and a biopsy in 1 case. Palliative radiation treatment was elected in all 3 cases. 24 Gy were given in 3 fractions at 8 Gy on day 0, 7 and 21. In all cases the clinical signs and the quality of life significantly improved. Two cases were followed for 6 months post-treatment and no complications or recurrence of the clinical signs were noted, unfortunately the patients were lost for follow up examinations. One case is still in remission at 16 months post-treatment. Copyright 2006 Elsevier Inc. All rights reserved.

Key words: **rabbit; thymoma; radiation therapy; palliation**

Radiation therapy has become the standard treatment for the management of thymomas in dogs and cats.[1-3] To date, there have been limited reports regarding the successful use of radiation therapy as a treatment for thymomas in rabbits. Previous treatment reports were limited to surgical intervention (thoracotomy) to remove thymomas.[4,5] The authors describe 3 clinical cases (case series) of thymoma in rabbits where hypofractionated radiation therapy was used as a palliative treatment.

Clinical Cases

Three rabbits were referred to the Exotic Animal Medicine Service at Cumming's School of Veterinary Medicine at Tufts University, N. Grafton, Massachusetts, for respiratory distress. While the rabbits were under general anesthesia with sevofluorane (Abbott Laboratories, North Chicago, IL USA) delivered by facemask, imaging (thoracic radiographs and/or ultrasound), fine needle aspiration or biopsy, and

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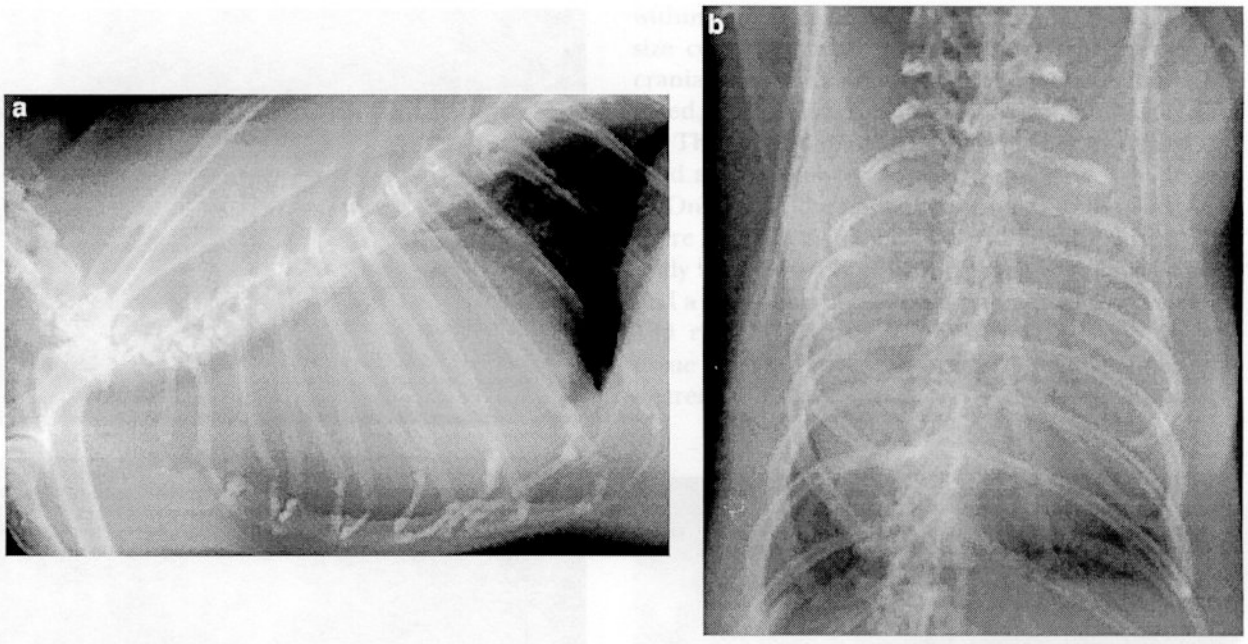


Figure 1. a, Case 1, left lateral radiograph of the rabbit prior to the first radiation session. b, Case 1, dorsoventral radiograph of the rabbit prior to the first radiation session.

blood work (complete cell count and chemistry) were performed. Radiographs were examined by a board-certified radiologist, and the fine needle aspiration cytologic sample reviewed by a board-certified clinical pathologist.

Treatment options included surgical resection, definitive radiation therapy, and chemotherapy, and each option was discussed before the decision to use hypofractionated radiation therapy as a palliative therapy was made. Left lateral and dorsoventral radiographs were performed while the rabbits were under general anesthesia, and with sevofluorane by mask, and the radiographs were taken to evaluate response before each dose of radiation therapy. Radiation therapy consisted of palliative doses delivered in 3 fractions (8 Gy × 3 treatments, total 24 Gy) within 4 weeks to the cranial thorax. The standard therapy schedule was based on delivering doses at days 0, 7, and 21. Radiation therapy was delivered by 6-mV linear accelerator (Mevatron 77; Siemens Corporation, New York, NY USA).

Other treatments included lactated ringer's solution (50 mL/kg bolus subcutaneously) administered during and after each treatment and meloxicam (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT USA) (0.2 mg/kg by mouth once a day) to reduce inflammation and control the potential pain associated with tumor progression. The animals were discharged from the hospital the same day of each radiation dose.

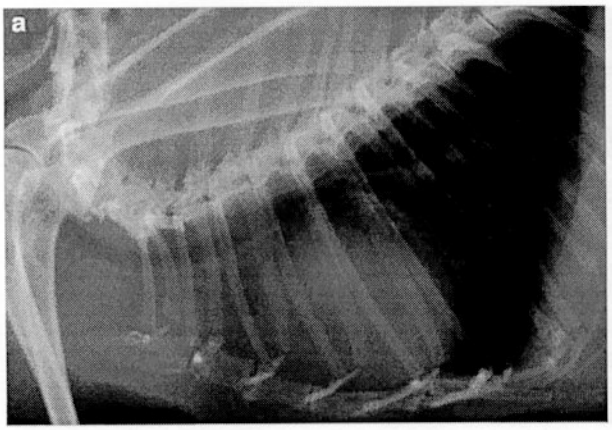
Case 1

A 10-year-old intact male Netherland dwarf rabbit weighing 1.27 kg was presented for a sudden onset of increased respiratory effort and for evaluation of an increased soft tissue density in the mediastinum on thoracic radiographs. On physical examination, the rabbit was quiet, alert, responsive, and was mildly dyspneic. Overall body condition was 5 (on a scale of 1-9), heart rate was 350 beats per minute (bpm), and respiratory rate was 90 respirations per minute (rpm). The rabbit had a >2-year history of a small corneal degeneration with deposits on the left cornea, a subcutaneous mass on the right ventral thorax, and a herniated bladder.

A thoracic ultrasound revealed a 3-cm^3 mass in the cranial thorax. A fine needle aspiration of the mass yielded numerous lymphocytes and occasional epithelial cells (consistent with thymic reticular cells), and suggested a diagnosis of thymic lymphoma or lymphocyte-predominant thymoma. A complete blood count and chemistry panel were unremarkable.

Hypofractionated radiation therapy was delivered to the cranial thorax on days 0, 7, and 17.

On day 0, radiographs showed soft tissue opacity within the cranioventral thorax consistent with a cranial mediastinal mass; this obscured the cranial margin of the cardiac silhouette. The trachea was



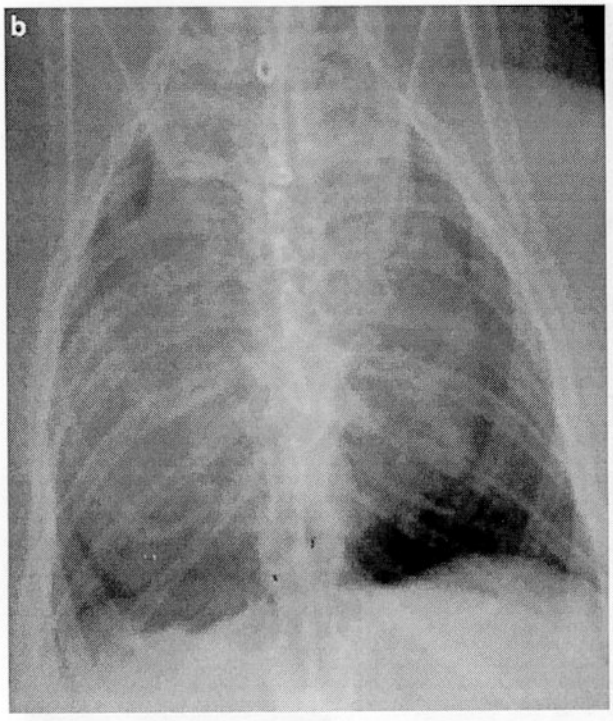
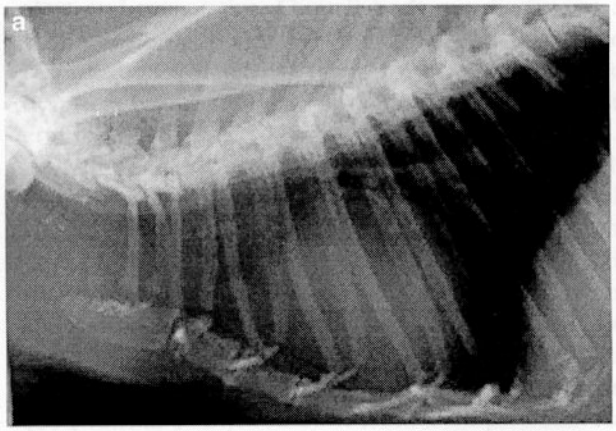


Figure 2. a, Case 1, left lateral thoracic radiograph after the second session of radiation. b, Case 1, dorsoventral thoracic radiograph after the second session of radiation.

dorsally deviated against the vertebral column (Fig 1). The first dose of radiation therapy was delivered. The rabbit exhibited normal behavior and was observed eating hay approximately 5 minutes after recovery with no clinical signs of discomfort or pain observed during the next 5 hours.

On day 7, the owner reported a significant decrease in clinical signs (eg, more active, less respiratory distress) after the first treatment. The respiratory signs were markedly improved: a heart rate of 180 bpm and a respiratory rate of 150 rpm were noted, without clinical signs of labored breathing. The radiographs showed that the soft tissue opacity within the cranial mediastinum had decreased in size compared with previous images. However, the cranial border of the heart could not yet be delineated, and the trachea was less deviated dorsally (Fig 2). The second dose of radiation therapy was delivered and the rabbit recovered uneventfully.

On day 17, the animal continued to improve, and there was no evidence of respiratory distress. The body weight had slightly increased to 1.28 kg, and it had a heart rate of 240 bpm and a respiratory rate of 180 rpm. The radiographs revealed that the soft tissue opacity within the cranial mediastinum had decreased in size compared with previous images,



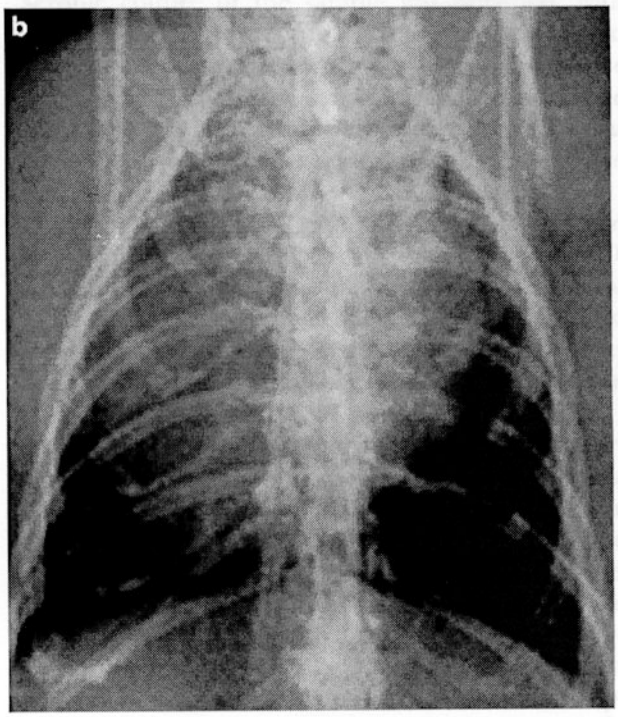


Figure 3. a, Case 1, left lateral thoracic radiograph after the second session of radiation. b, Case 1, dorsoventral thoracic radiograph after the second session of radiation.

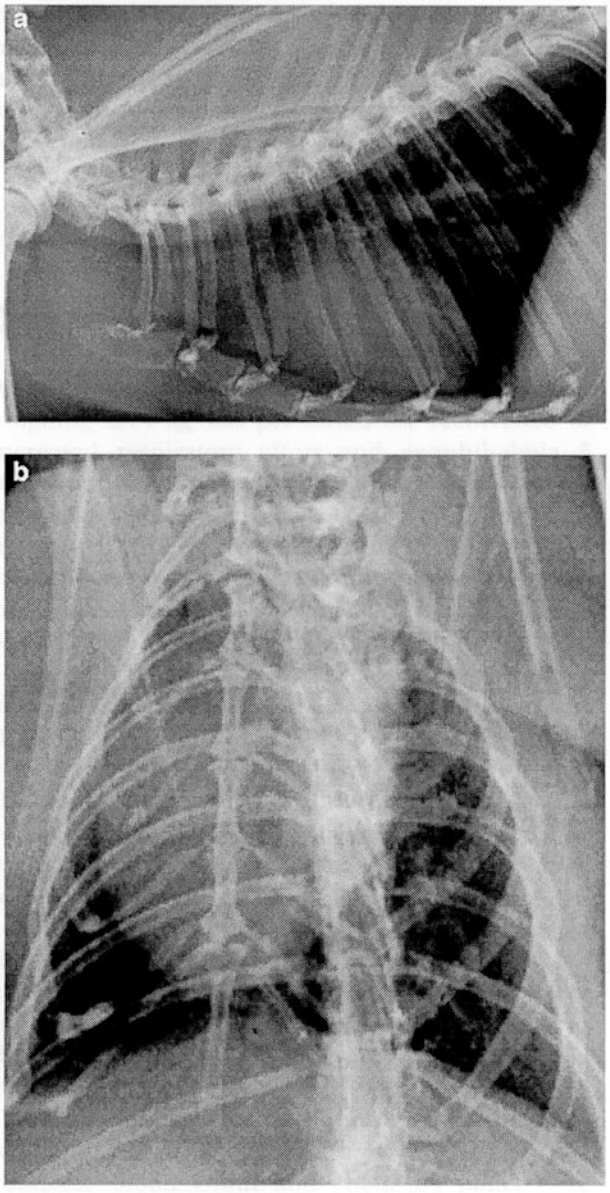


Figure 4. a, Case 1, left lateral thoracic radiograph ninety days after the first session of radiation. b, Case 1, dorsoventral thoracic radiograph ninety days after the first session of radiation.

making it possible to delineate the cardiac silhouette (Fig 3). The third dose of radiation therapy was delivered and the rabbit recovered uneventfully.

Observation at 3 months after the last radiation dose showed the rabbit to be clinically normal, without any signs of dyspnea or exercise intolerance. The body weight was 1.31 kg, a heart rate of 180 bpm and a respiratory rate of 150 rpm. The radiographs showed no significant changes (Fig 4) from the radiographs taken 3 months earlier (Fig 3). There were no negative side effects associated with the radiation therapy. A complete blood count and chemistry panel were unremarkable. The rabbit was again presented for a check-up 9 months after the last dose of radiation, with no apparent complications. When last contacted, the owner reported no signs of respiratory distress 6 months after the treatment. Follow up was lost after 6 months.

Case 2

A 5-year-old spayed, female, Netherland dwarf rabbit weighing 1.5 kg was presented for increased respiratory effort over a two-and-a-half-month period and for evaluation of a thoracic mass diagnosed on radiographs. On physical examination, the rabbit was alert and responsive. Overall body condition was 5 (on a scale of 1-9), heart rate was 250 bpm, and respiratory rate was 104 rpm. She also showed mild dyspnea, bilateral ocular discharge, and slight bilateral exophthalmia.

A thoracic ultrasound revealed an approximately 4-cm^3 mass in the cranial thorax. A fine needle aspiration of the mass showed small to moderate numbers of nucleated cells; small lymphocytes predominated, with lesser numbers of medium-sized lymphocytes and occasional lymphoblasts, eosinophils, and neutrophils. The high percentage of small lymphocytes suggested aspiration of lymph from thymic tissue (normal or thymoma) or from a lymph node. An aerobic culture of the sample was obtained, with negative results. The complete blood count revealed a white blood count of 22×10^3 μL (reference range, 5.2-12.5 $\times$ 10^3 μL) and 89% lymphocytes. The morphology of the lymphocytes was described as significantly enlarged and the cells considered to be reactive.

Hypofractionated radiation therapy was delivered to the cranial thorax on days 0, 7, and 21. On day 0, when the first dose of radiation therapy was delivered, the rabbit exhibited normal behavior and was observed to eat hay approximately 5 minutes after recovery with no clinical sign of discomfort or pain observed during the next 4 hours.

On day 7, the owner reported that the respiratory signs improved and the eyes were noticeably less exophthalmic. Radiographs revealed a decrease in size of the mass. The complete blood count revealed a white blood count of 9×10^3 μL (reference range, 5.2-12.5 $\times$ 10^3 μL) and 71% lymphocytes; at this time, the morphology of the cells appeared to be within normal limits. The chemistry profile was unremarkable. The second dose of radiation therapy was delivered and the rabbit recovered uneventfully.

On day 21, the owner reported that dyspnea and exercise intolerance were no longer apparent, and

the exophthalmia was significantly decreased. The radiographs showed no significant changes compared with the previous visit. The third dose of radiation therapy was delivered and the rabbit recovered uneventfully.

The owner reported that the rabbit was in good condition 6 months post-treatment radiation. Follow up was lost after 6 months.

Case 3

A 7-year-old spayed, female, Jersey wooly rabbit weighing 2.14 kg was presented for recurrence of increased respiratory effort and exophthalmia 3 months after a thoracotomy and debulking of a thoracic mass. The mass was diagnosed by histopathology as a thymoma. On physical examination, the rabbit was quiet, alert, and mildly dyspneic. Overall body condition was 3 (on a scale of 1-9), heart rate was 280 bpm, and respiratory rate was 160 rpm.

On day 0, radiographs revealed a significantly large mass in the cranial thorax, obscuring the cardiac silhouette and displacing the trachea dorsally. Hypofractionated radiation therapy was delivered to the cranial thorax on days 0, 7, and 21. The animal recovered uneventfully from the procedure. The rabbit exhibited normal behavior and was observed to be eating within 10 minutes of recovery.

On day 7, radiographs showed a mild decrease in the size of the mass within the cranial thorax. A complete blood count and chemistry panel were unremarkable. The second dose of radiation was delivered and the rabbit recovered with no complications.

On day 21, radiographs showed that the mass within the cranial thorax appeared unchanged. The complete blood count and chemistry panel were repeated, and the results were within accepted reference ranges. The third dose of radiation was delivered and the rabbit recovered uneventfully. The owner reported no evidence of respiratory symptoms 24 months after the last dose of radiation.

Discussion

In recent years, multiple reports of thymoma in different pet species have been published. Species in which thymomas have been diagnosed include rabbits,[6,4] ferrets,[7] rats,[8] african bullfrog,[9] and the carp.[10] Thymomas appear to be an uncommon cancer in rabbits.[11,6]

A thymoma is a neoplasm that arises from the epithelial cells of the thymus in the cranioventral portion of the mediastinum and displaces thoracic structures caudodorsally. The space-occupying lesion may cause dyspnea, tachypnea, coughing, exercise intolerance, and cranial vena cava syndrome (edema of the head, neck, and forelimbs). Clinical signs of respiratory distress, which were observed in all 3 cases, and bilateral exophthalmus, which was observed in 2 out of the 3 cases, have also been described in the literature.[12,4] Thymomas can be encapsulated or locally invasive, and local and distant metastases have been reported in other species.[13] The etiology of the thymoma remains unclear. One case of a thymoma in a rabbit was reported after an intramuscular injection of human T-cell leukemia virus type 1 DNA.[14] Interestingly, the human T-cell leukemia virus type 1 provirus was detected in thymocytes and neoplastic epithelium isolated discretely from the thymoma, suggesting a potential role of this virus in the tumor formation.

Thymomas must be differentiated from thymic hyperplasia and/or lymphoma. Enlargement of the thymus to 3 or 4 times normal size due to hyperplasia is not uncommon in adult rabbits, and its gross appearance is similar to that of tumor.[15] Thymic lymphoma denotes lymphoma involving the thymus, with or without other organ involvement.[16]

The presumptive diagnosis of thymoma was made combining the results of the case history, physical examination, blood work, thoracic and abdominal imaging, and fine needle aspiration of the mass in cases 1 and 2. Blood work and thoracic and abdominal imaging did not demonstrate evidence of other organ involvement, thereby supporting the diagnosis of thymoma (case 1). Blood work in case 2 was initially suggestive of systemic lymphoma; however, no other organs were affected and the chemistry panel did not show any evidence of organ dysfunction. A thymic biopsy would have been a useful test for confirming a histological diagnosis in cases 1 and 2; however, this procedure was declined by the owners. The diagnosis of thymoma was established by histopathology after surgical resection via thoracotomy in case 3. The radiological appearance of the tumor was similar in all 3 cases.

Diagnosis of thymoma early in the course of the disease is extremely difficult. A presumptive diagnosis can be made by combining clinical signs with several diagnostic tests. Definitive diagnosis is obtained by histology. In humans, a fine needle aspirate of a mediastinal mass is considered to be diagnostic for thymoma, but it may still lead to confusion with other thymic pathologies.[17] Frequently, different pathological structures affecting the thymus and alternating its macroscopic structure are being

called a thymoma. According to Levine and Rosia, "It is apparent, however, that thymoma, thymic carcinoid, various lymphomas, and germ cell tumors that arise in the thymus differ not only pathologically but also in their clinical behavior. Thymoma is regarded as an epithelial neoplasm and ultrastructurally is characterized by many desmosomes and tonofilaments. The lymphocytes do not behave in a malignant manner, and lymphomas of the thymus should be sharply separated from true thymoma."[18] From the point of diagnosis and treatment, it cannot be over emphasized that an accurate diagnosis should be made to discuss the long-term prognosis with the owner.

Palliative radiation therapy is defined as a noncurative treatment with the goal to improve quality of life, alleviate clinical signs, and provide short-term control of disease progression.[19] Palliative radiation therapy uses hypofractionation to deliver a larger size of fraction in a small number of treatments. Hypofractionated radiation therapy was delivered in these rabbits, and the main organ at risk in the radiation fields was identified in the lungs. Although the acute and late side effects associated with irradiation of the lungs are not well studied in rabbits, the tissues are likely to respond in a similar way to other mammals where more data is available. In these cases, acute side effects, such as pneumonitis, were not observed on thoracic radiographs obtained during and after the course of the radiation therapy. The occurrence of late side effects such as lung fibrosis, which may occur months or years after treatment, needs to be followed up and documented by radiographs. Although the volume of the lungs being irradiated is potentially large, the risk of developing clinical late complications due to fibrosis is relatively small for these rabbits because of the relatively short lifespan of rabbits. During treatment, all efforts were made to spare as much lung from irradiation. In patients surviving longer than expected (more than 1-2 years), risk of late complications may increase. In the cases described above, follow-up at 6 months after radiation therapy revealed no side effects.

The three rabbits responded to hypofractionated radiation therapy in a very similar fashion. Clinical signs improved significantly after the first radiation therapy in all rabbits. The radiographic imaging of the thorax showed a reduction of the mass after treatments, coinciding with improvement of clinical signs. Other treatment options for thymomas, including definitive radiation therapy (eliminating all disease for long-term control with high-dose radiation therapy), chemotherapy, and/or surgical excision, were offered and discussed with the owners.

To the authors' knowledge, these are the first case reports of successful hypofractionated radiation therapy used for palliative therapy of thymoma in rabbits. Andecdotal reference can be found in the literature, in which a single clinical case was treated with palliative radiation therapy.[16] The rabbit was given 8 Gy per treatment on days 0, 7, and 21. The tumor was notably smaller after the first treatment, but the rabbit was euthanized 1 month after final treatment because of pleural effusion and poor clinical condition. Most recently, Morrisey and coworkers, in 2005, reviewed the therapeutic options for thymoma in the rabbit and reported short-term and long-term complications in 2 rabbits treated with a different radiation therapy protocol.[20] One rabbit was given 3.6 Gy per fraction for 8 treatments over a 6-week period and developed mild respiratory signs 3 months after radiation therapy. This animal was euthanized 23 months after the last radiation treatment because of chronic respiratory difficulties, muscle wasting, and weight loss. The other rabbit was given 3 Gy 3 times a week for 2 weeks and died of anesthetic complications after the sixth radiation treatment. The effects of radiation on soft tissue masses have been studied in rabbits used as experimental models.[11,21]

The protocol used in the discussed cases is considered to be a palliative treatment and not curative. Complete eradication of the disease will not be achieved with the palliative approach, but a significant alleviation of the clinical signs can be expected because of the reduction in the size of the mass. Treatment response was described by Hitt et al[1] in 1987, when the mass of a dog treated with orthovoltage radiation resulted in an approximate 60% reduction in tumor mass and freedom from clinical signs for 6 months.

Definitive radiation therapy is accomplished by delivering a small fraction of radiation in a large number of treatments. These treatments will be delivered over a period of 4 weeks and may require the animal to be hospitalized for this time, because daily radiation therapy is given under general anesthesia.

Surgical excision of thymic masses can be performed with 2 different methods. Left lateral thoracotomy can be performed for small masses, but in general, many thymic masses are large and median sternotomy is required for adequate access.[22] This treatment is considered significantly more invasive, and owners are often reluctant to choose this aggressive treatment. In theory, a combination of surgery

and radiation would offer one of the best solutions to this condition.

Surgery and chemotherapy are commonly used as therapeutic modalities in other species, and can provide significant relief and sometimes a cure. Chemotherapy alone appears to have limited utility, at least in the rabbit.[20] In dogs and cats with thymomas, a combination of surgery and radiation therapy has been shown to offer an excellent prognosis. Radiation therapy alone may also be an effective therapy in the management of dogs with thymomas.[23]

Conclusion

Thymomas can be treated in rabbits with radiation therapy alone or in conjunction with surgery. Radiation therapy can be delivered as a palliative, noncurative treatment or as a definitive treatment, and owners should be informed of the difference in treatment goals. The 3 cases presented involve palliative radiation treatment therapy and have shown to significantly improve the clinical signs and overall quality of life. In all cases, no clinical side effects were noted up to 6 months after the last dose of radiation. At the time of writing, 26 months after the initial treatment, case 3 is still in remission.

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