Therapeutic Options for Thymoma in the Rabbit

James K. Morrisey, DVM, Dip. ABVP (Avian Practice),
Margaret McEntee, DVM, Dip. ACVIM, ACVR (RO)

Abstract

Thymomas are relatively rare tumors that have been reported in a number of rabbits. Clinical signs may be nebulous or a result of the effect of the tumor on the occupied space. Diagnosis is made by aspiration cytology or tissue biopsy and histopathology. Treatment options for thymomas in people and animals include surgery, chemotherapy, and radiation therapy. Surgery appears to offer the best chance for cure and is recommended when possible; however, radiation therapy may also be effective. Chemotherapy alone appears to have limited utility, at least in the rabbit. This article will discuss these treatment options and their use in rabbits with thymoma, both as reported in the literature and based on our experience.

Key words: **Rabbit thymoma; radiation therapy; thymic; thoracotomy**

Thymomas are tumors of thymic epithelial origin found most commonly in the cranial mediastinum. They are relatively rare tumors but have been reported in a number of rabbits;[1-3] a review of 55 cases of rabbits with neoplasia documented an incidence of approximately 8%.[4] Thymomas are also uncommon in other species but have been described in dogs, cattle, cats, horses, pigs, sheep, and goats.[5,6] Although rare, thymoma is still the most common mediastinal neoplasm in adult humans.[7] The relatively low occurrence of thymoma in the rabbit may be related to their short life span; thymomas tend to arise in older individuals regardless of species.

Thymic tumors include thymoma and malignant thymoma or thymic carcinoma. Thymomas tend to be slow growing but have the potential for local invasion, pleural dissemination, and metastasis. Although the likelihood of metastasis is low, there is 1 report describing metastasis to thoracic organs and abdominal lymph nodes in a rabbit with thymoma.[8] The World Health Organization classification system for histologic subtypes of thymoma in humans includes 12 distinct categories (2 benign and 10 malignant).[9]

The 2 most common tumors of the cranial mediastinum in animals are thymoma and lymphoma. Other differential diagnoses for a cranial mediastinal mass in domestic animals include chemodectoma, ectopic thyroid tissue or thyroid carcinoma, thymic branchial cysts, mediastinal granuloma or abscess, thymic hyperplasia, mediastinal hemor-

From the Exotic Animal and Wildlife Medicine Service, Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Box 25, Ithaca, NY 14853 USA and from the Oncology Service, Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853 USA.

Address correspondence to: James K. Morrisey, DVM, Dip. ABVP (Avian Practice), Exotic Animal and Wildlife Medicine Service, Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Box 25, Ithaca, NY 14853 USA. E-mail: jkm27@cornell.edu

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rhage, mast cell tumor, and metastatic tumor. Other than thymoma, the most likely differential diagnoses in rabbits with a cranial mediastinal mass are thymic lymphoma and pulmonary or mediastinal abscess.

Clinical Signs of Thymoma and Associated Paraneoplastic Disorders

The clinical signs associated with thymoma in the rabbit can be quite variable. When present, clinical signs are usually caused by the presence of a space-occupying mass in the thoracic cavity. Although paraneoplastic syndromes are common in other animal species, they are less common in rabbits. Signs associated with a space-occupying mass may include shortness of breath, exercise intolerance, dyspnea, and open mouth breathing. Bilateral exophthalmos has been reported in 2 rabbits,[2,3] and neck, head, and forelimb edema may also be seen. These latter signs are thought to be caused by partial occlusion of the cranial vena cava by the mass (cranial vena caval syndrome).

Immune disorders are frequently reported in association with thymomas in cats, dogs, and people: 50% to 60% of human patients with thymoma are reported to have immune-mediated disease. To date, similar disorders have not been described in rabbits with these tumors.[7,10] Other paraneoplastic syndromes seen with thymoma in people and animals include myasthenia gravis, hypercalcemia, polymyositis, cytopenias, dermatitis, and nonthymic neoplasms. There are reports of rabbits with thymoma and concurrent hypercalcemia,[1,3] with resolution of hypercalcemia observed in 1 rabbit after surgical tumor removal.[1] Hemolytic anemia associated with thymoma has also been documented in a rabbit and was thought to be an inherited condition that has been associated with thymomas in certain strains of laboratory rabbits.[11,12] An elevated total white blood cell count with lymphocytosis was described in a rabbit with mediastinal masses, although it is unclear if this animal had thymoma or thymic lymphoma.[13]

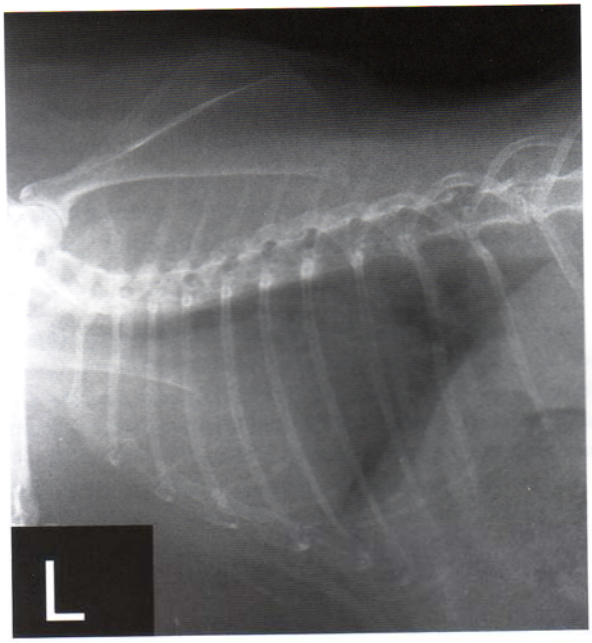

Figure 1. Lateral radiograph of a 5-year-old rabbit with thymoma. Note the difficulty in distinguishing tumor from normal thoracic structures. This emphasizes the benefit of contrast and noncontrast CT scanning.

Figure 2. Photograph of a rabbit positioned in left lateral recumbency in a Vac-Lok positioner for radiation therapy. The rabbit was placed in the Vac-Lok for acquisition of the CT images used for treatment planning, and then the positioner was used to reposition the rabbit for each radiation treatment.

Diagnosis

Thoracic radiographs are useful for the initial identification of a cranial mediastinal mass. Ultrasonography can be used to verify the presence of a mass and characterize its consistency (solid versus cystic); it is also useful in performing guided aspirates and needle biopsies. However, cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging provides the most detailed information regarding the full extent of disease and consistency of the mass (Fig 1).[14] Thoracic CT scan with intravenous contrast provides a means of assessing the texture of a cranial mediastinal mass as well as its invasiveness and the presence of pulmonary metastasis. The appropriate algorithm should be used, and window and level settings should be adjusted to fully evaluate the lung parenchyma. A preliminary CT scan is also necessary if radiation treatment is to be

Table 1. Staging System for Thymoma

Stage	Definition
I	Macroscopically encapsulated tumor, with no microscopic capsular invasion
IIa	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
IIb	Microscopic invasion into the capsule
III	Macroscopic invasion into neighboring organs
IVa	Pleural or pericardial metastases
IVb	Lymphogenous or hematogenous metastasis

used, and follow-up scans can be performed to follow progress and adjust the treatment as discussed below. A repositioning device (Vac-Lok, MedTec, Orange City, IA USA) can be used to maintain the same position for radiation therapy (Fig 2). Both pre- and postcontrast CT scans are recommended because of the extensive nature of thymomas in most rabbits on initial presentation; intravenous contrast assists in identifying the tumor and distinguishing it from the normal intrathoracic structures such as the heart.

Definitive diagnosis of thymoma requires fine-needle aspiration or biopsy. Diagnostic cytologies may reveal small, mature lymphocytes or an admixture of variably sized well-differentiated lymphocytes and epithelial cells. Lymphoma is the primary differential for a cranial mediastinal mass in a rabbit, but the presence of a homogeneous population of small, well-differentiated lymphocytes is suggestive of thymoma rather than lymphoma. Other cells that may be present in fine-needle aspirations of thymomas include mast cells, eosinophils, macrophages, melanocytes, plasma cells, and neutrophils.[6] Unfortunately, fine-needle-aspiration cytologies of thymomas are often nondiagnostic; a core needle biopsy, or thoracotomy and open incisional or excisional biopsy is frequently required for definitive diagnosis. Thoracoscopy and biopsy is another option for obtaining a diagnostic sample.

Staging of thymomas is based on assessment of local disease, presence of microscopic versus macroscopic invasion into mediastinal tissues, and metastasis (see Table 1).[15] Stage is an important factor in selecting a treatment protocol in people and has also been correlated with response and survival. This information is not yet available for animals with thymoma.

Treatment Options

Surgery, chemotherapy, and radiation therapy are the primary treatment options for thymoma in people and animals. The treatments most commonly used in rabbits are surgery and, increasingly, radiation therapy. However, these treatments can be expensive and may also carry considerable risk to the animal, so it is important to recognize that more data are needed to fully evaluate their efficacy. Survival time without treatment has been documented in only 1 case: a rabbit with thymoma lived without treatment for 4 months after diagnosis, when it developed severe respiratory distress and was euthanized.[2]

Surgery

Surgery is the treatment of choice for thymoma in all species when there is a solitary mass, because it provides the best chance of removing the entire tumor and effecting a cure. Although the use of preoperative imaging (CT scan) may assist in identifying animals with less invasive tumors that are better surgical candidates, it can sometimes be difficult to determine the true extent of pleural and pericardial invasion with this modality. Exploratory thoracotomy may be required to obtain biopsies and fully assess resectability in animals without cross-sectional imaging studies or in cases where imaging results are equivocal.

Surgical removal of benign, noninvasive thymomas in dogs and cats results in long- term disease control and survival. Surgical removal of thymomas has been reported in 2 rabbits.[1,3] One rabbit developed persistent pneumothorax after surgery and was euthanized, whereas the second rabbit survived the perioperative period but was euthanized 9 months later because of recurrent sarcomas. Necropsy in this rabbit revealed no evidence of the thymoma. We are aware of 2 other rabbits that underwent surgical removal of a thymoma, 1 of which continues to do well 18 months after surgery. (K. L. Rosenthal, personal communication, 01/05) The preferred surgical approach is a median sternotomy, which provides improved access and visualization of the intrathoracic anatomy for removal of a cranial mediastinal mass.[1]

The most common complication after surgical removal of thymoma in rabbits is acute perioperative death. This may be related to pain, stress, anesthetic complications, or inability to remove the tumor. Given the "prey-species" physiology and behavioral adaptations of rabbits, excellent perioperative analgesia is required. Cardiovascular evaluation should

be performed before surgery to rule out tumor-related cardiac dysfunction. Finally, animals should be kept in quiet areas before and after surgery, including throughout the initial recovery period.

Chemotherapy

Chemotherapy is an option for metastatic or invasive thymomas as the primary means of therapy, as neoadjuvant therapy before surgical resection, or as adjunct therapy after surgical resection. Although the efficacy of chemotherapy has not been evaluated in rabbits with thymomas, it has been shown to be effective in the management of thymomas in people. Chemotherapy protocols used in people include combination cisplatin, doxorubicin, and cyclophosphamide, with or without prednisone; combination cisplatin, doxorubicin, vincristine, and cyclophosphamide; and combination cisplatin, etoposide, and epirubicin. Response rates of 79% to 100% are reported with these protocols.[7] Single-agent ifosfamide has also shown activity.[9] Resectability rates after neoadjuvant chemotherapy range from 36% to 69% in people.[7] For invasive tumors, the most common approach is to administer neoadjuvant combination chemotherapy and follow with surgical resection. Postoperative radiation therapy may be considered if the resection is incomplete. There is limited information regarding the efficacy of chemotherapy in the management of thymomas in dogs and cats.

The complications of chemotherapy are dependent on the drugs used but may include bone marrow suppression, renal or hepatic toxicity, and weight loss. We are also aware of a rabbit with thymoma that became very weak and collapsed within 2 hours of receiving doxorubicin; a mild anemia also developed (J. Bryan, personal communication, 03/05). These signs resolved with supportive care, and no further chemotherapy was administered.

We have successfully used prednisolone (0.5-2 mg/kg orally twice a day) as adjuvant therapy in rabbits undergoing radiation treatment for thymomas. This drug is used for its antineoplastic as well as its antiinflammatory effects. Corticosteroids are of potential benefit in rabbits undergoing radiation therapy to ameliorate the side effects associated with irradiating the thoracic structures, most notably the lung, where development of radiation pneumonitis is a concern.

Radiation Therapy

Radiation therapy has been used for the treatment of thymoma in people, cats, dogs, and rabbits.[9,13,16-19] Thymomas are radiosensitive, but their proximity to critical normal tissues (heart, lung) may limit the radiation dose that can be delivered based on the extent and location of the tumor. Radiation pneumonitis and fibrosis may develop, with the probability related to the volume of lung irradiated. Radiation therapy is recommended after incomplete surgical resection of thymomas or if the patient is not considered a good surgical candidate. A retrospective study of radiation therapy in 17 dogs and 7 cats with thymomas documented a median survival of 248 days in dogs and 720 days in cats.[18] The overall response rate among assessable cases was 75% (15/20), although there were a limited number of complete responses (4/20).

The use of radiation therapy was reported in 1 rabbit with thymoma at a dose of 8 Gy per treatment on days 0, 7, and 21.[13] The tumor was notably smaller after the first treatment, but the rabbit was euthanized 1 month after the final treatment because of pleural effusion and poor clinical condition. The necropsy revealed fibrosis of the tissue at the radiation site and thrombosis of mediastinal vessels, compatible with radiation damage to the tissues in the radiation field caused by high-dose hypofractionated radiation therapy.

We have irradiated 2 rabbits with thymoma. Both rabbits were treated with a linear accelerator based on CT images and using a three-dimensional radiation treatment planning computer (Pinnacle3, Milpitas, CA USA). One 5-year-old buck rabbit received 3.6 Gy per fraction for 8 treatments (total dose of 2880 cGy) over a 6-week period. The radiation protocol was devised based on the ability of the owner to bring the rabbit in for treatment, as well as the large size of the original mass which necessitated irradiation of almost the entire thorax. The initial CT scan was performed with the rabbit in sternal recumbency, because other positions resulted in some level of respiratory distress. Baseline tumor volume in this animal was 39.56 cm^3 (Fig 3). The treatment fields for the first 4 fractions were right and left ventral oblique fields with 45° wedges. A CT scan performed on day 17 after 4 fractions of radiation therapy revealed a dramatic reduction in the size of the tumor (tumor volume, 9.12 cm^3). At this time, the treatment fields were changed to parallel opposed lateral radiation fields to partially spare the heart and lung (Fig 4). The rabbit developed mild respiratory signs and a diffuse increase in pulmonary opacity on radiographs approximately 3 months after radiation therapy that was thought to be compatible with radiation pneumonitis. Survival time for this rabbit was 23 months after the last radiation treatment, when it was euthanized because of chronic respiratory difficulties, muscle wasting, and weight loss.

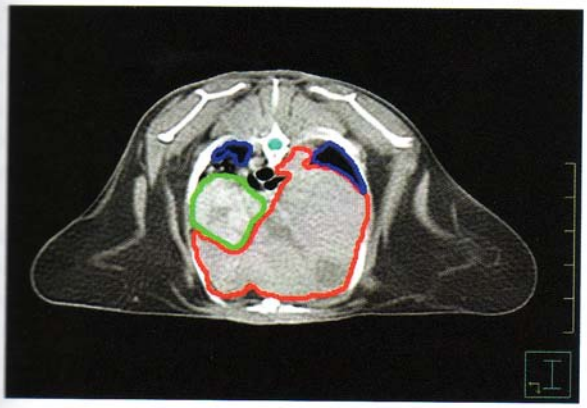

Figure 3. Transverse CT image of the thorax of case 1, with the rabbit in sternal recumbency before the start of radiation therapy, showing the extent of the tumor (red) and displacement of the heart (green) and lung (blue).

A 5.5-year-old doe rabbit was given 3 Gy per fraction with parallel opposed lateral fields 3 times a week for 2 weeks, with a planned total radiation dose of 45 Gy. This rabbit did well during the treatment and multiple anesthetic episodes, although it developed mild gastrointestinal stasis several times during the 2 weeks of treatment. A repeat CT scan was performed on the day of the sixth treatment to facilitate radiation treatment planning for a cone-down field and revealed a decrease in tumor size from an initial 26.11 cm^3 (Fig 5) to 3.5 cm^3 (Fig 6) after just 15 Gy of radiation. Unfortunately, the rabbit died of anesthetic complications after the sixth radiation treatment.

We are also aware of other rabbits treated with radiation therapy for thymoma. One case was treated

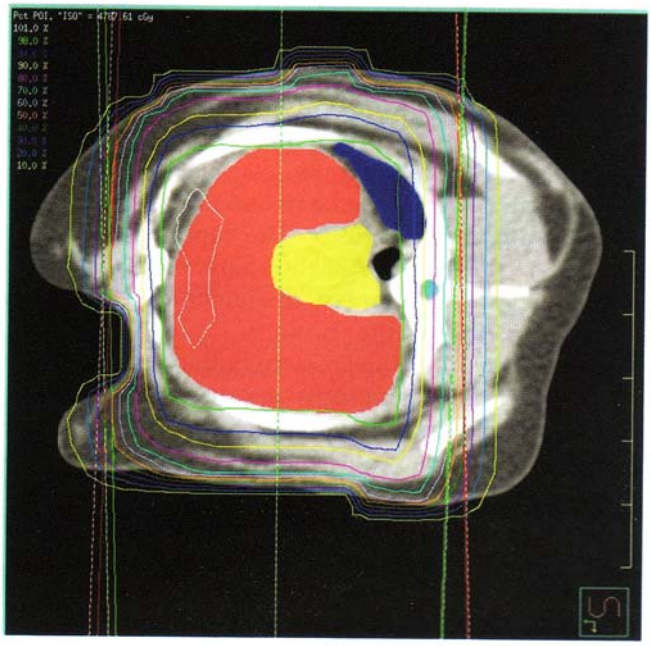

Figure 5. Transverse CT image of the thorax of case 2 before the start of radiation therapy, with the rabbit in left lateral recumbency, showing the tumor (red), heart (yellow), and lung (blue).

with 4 Gy 3 times weekly for 4 weeks and did well for 6 months after treatment, at which time the thymoma recurred (K. L. Rosenthal, personal communication, 01/05). Another case involved a rabbit being given 3 Gy twice weekly for 8 treatments (J. Dennis, personal communication, 03/05). There was a 1-week break in therapy after the second treatment, because the animal developed inappetence, tachypnea, and pyrexia. These signs responded well to the addition of prednisolone to the treatment

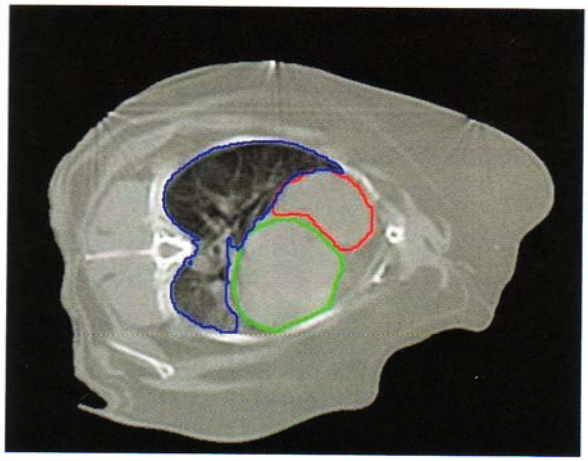

Figure 4. Transverse CT image of the thorax of case 1, with the rabbit in left lateral recumbency for the repeat CT scan after having received 14.4 Gy, showing reduction in the size of the mass (red) and increased lung capacity (blue).

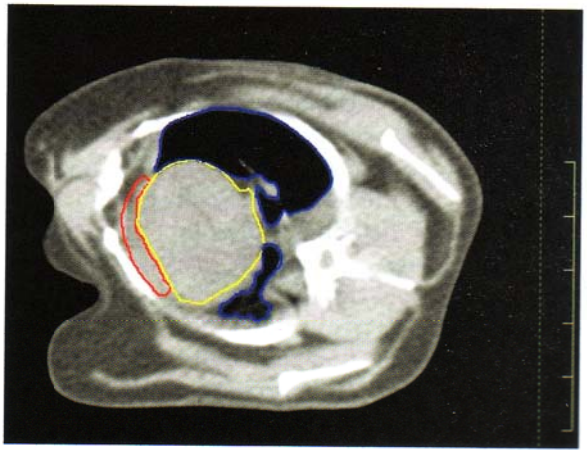

Figure 6. Transverse CT image of the thorax of case 2 after having received 15 Gy, showing marked reduction in the size of the tumor (red) and more normal position of the heart (yellow) and increased lung expansion (blue).

protocol. This rabbit died of pneumonia and pulmonary granulomas 6 months after treatment ended.

Complications of thymic radiation therapy in a rabbit have been reported and include pulmonary fibrosis and thrombosis of thoracic vessels.[13] Normal tissue damage should be considered with large masses that contact the heart and fill a large percentage of the thoracic cavity. The repeated anesthetic episodes needed for radiation carry some risk, especially if cardiopulmonary dysfunction secondary to the mass effect of the thymoma is present. We have also seen an interstitial pattern in the lungs and mild to moderate respiratory signs develop over many months following radiation therapy; these signs have responded to antibiotics and bronchodilators. Although *Encephalitozoon cuniculi* infections and chronic active pyelonephritis have been seen in a rabbit treated with radiation therapy and prednisolone,[13] we have not seen this problem in the clinical cases treated thus far.

Choosing a Treatment Protocol

Until more information can be gathered on the efficacy of various treatment modalities for thymoma in rabbits, the most appropriate treatment for a particular animal should be determined on a case-by-case basis. It is difficult to advocate the use of chemotherapy as the sole treatment at this time, and this modality is probably best used as an adjunct treatment after surgery or radiation therapy. Whether to recommend radiation therapy or surgery depends on thoughtful consideration of several factors. Concurrent diseases and the health status of the animal are important in deciding which treatment modality to pursue. Cardiopulmonary function should be fully evaluated, because anesthesia is required for either radiation therapy or surgery. Surgical removal involves a single, long anesthetic episode and requires meticulous perioperative monitoring and support. The surgical skills required to perform a thoracotomy are considerable, and finding a qualified surgeon can be difficult. Intensive postoperative care and monitoring including a chest tube and excellent analgesia are also needed. Radiation therapy involves shorter but more frequent anesthetic episodes, as often as every other day in some cases. Patient monitoring after radiation treatment is generally less intensive, but prolonged hospitalization may be required unless the owners live close to the treatment facility. The availability of a radiation treatment facility is a significant limiting factor, although veterinary radiation facilities are becoming more accessible. The physiologic and behavioral stress that is placed on the animal by hospitalization, surgery, radiotherapy, and anesthesia should also be considered. The facility used for either radiation therapy or surgery must provide the low-stress environment that is needed for rabbits. Rabbits should be kept away from the sight, sounds, and smell of predatory species such as dogs and cats.

Obviously, the treatment protocol chosen for an individual rabbit with thymoma is ultimately the owner's decision. Owners must be made aware of the considerable costs and time commitment that may be involved with each option. Home care and monitoring schedules should be clearly outlined, and an estimate of prognosis provided. Based on the information gathered for this article, the perioperative survival rate for rabbits with thymoma appears to be approximately 50%, with a good chance for clinical cure of the disease. The likelihood of a rabbit with thymoma surviving radiation therapy is higher, about 80%, but the chance of recurrence and post-treatment complications is greater than with surgical tumor removal.

Summary

Thymoma is an uncommon tumor in the rabbit but should be considered in any rabbit displaying respiratory signs, and especially if there is bilateral, non-painful exophthalmos. Diagnosis of thymoma requires fine-needle aspiration or, preferably, a tissue biopsy; epithelial cells and small lymphocytes are the predominant cells present. Preferred treatment options at this time include surgery and radiation therapy. Although surgical excision is the best treatment, it carries significant perioperative risk to the animal. Radiation therapy has a definite role and can be of benefit in the treatment of rabbits with thymomas. Further work is needed to develop a standardized protocol that minimizes the number of anesthetic episodes while maximizing the beneficial effect of the radiation.

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