Rabbit Oncology

Diseases, Diagnostics, and Therapeutics

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KEYWORDS

• Lagomorphs • Neoplasia • Neoplastic disease • Oryctolagus cuniculus
• Lymphoma • Thymoma • Uterine adenocarcinoma • Viral-induced tumors

KEY POINTS

- Rabbits may suffer from similar neoplastic diseases as other companion animals, with a tumor incidence reported of 0.5% to 2.7% across the entire rabbit population.
- Common tumors include uterine adenocarcinoma, lymphoma/leukemia, thymoma, mammary gland tumors, and cutaneous neoplasia; other tumor types may also be diagnosed, but seem to occur less frequently.
- Diagnostic workup follows similar guidelines as in other animals and aims to determine the location, type, and extent of the tumor; the clinical stage; and presence of comorbidities.
- Surgery remains the most commonly used method to treat neoplasia in rabbits, but other therapeutic modalities can be used as primary treatment or in conjunction with surgery.
- Preventive measures include ovariohysterectomy, insect control, and vaccination, which are aimed at reducing the incidence of uterine and mammary neoplasia and transmission of viruses known to cause neoplasia, respectively.

INTRODUCTION

Over the past decades, the popularity of rabbits as pets has risen considerably. Together with the increased quality of (veterinary) care and concomitant increases in the rabbits' life expectancy, this has likely led to an increase in the number of rabbits diagnosed with geriatric diseases and neoplasia. Although the actual incidence of spontaneously occurring neoplasia in the rabbit is difficult to provide, retrospective studies have suggested prevalences of 0.5% and up to 2.7% across the entire rabbit population.[1–3] Similar to other animals, older rabbits are more likely to be diagnosed with tumors, with a profound increase in the incidence of neoplastic disease (from 1.4% to 8.4%) reported after the second year of life.[2] These neoplastic changes predominantly involve the urogenital, hemolymphatic, and integumentary systems, with

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uterine neoplasia and lymphoid tumors being the 2 most predominant tumor types. Other tumor types have also been reported in rabbits, but their incidence seems to be much lower, with most of the information being derived from anecdotal evidence and case reports. Nevertheless, the knowledge with regard to rabbit oncology has grown considerably over the past years whereby the availability of new, more advanced diagnostic techniques and treatment modalities have greatly improved the abilities to accurately and appropriately diagnose and manage neoplastic disease in the domestic rabbit.

In this article, the different diagnostic steps and therapeutic interventions that can be considered when confronted with a rabbit suspected of a neoplasia are discussed. In addition, an overview will be given of the various spontaneously occurring neoplasia that have been reported in rabbits, whereby the most commonly seen tumors will be discussed in greater detail.

DIAGNOSTIC EVALUATION

As with any disease, the workup of a patient with (suspected) neoplasia starts with a thorough history and full physical examination, followed by additional diagnostic tests. The major goals of this diagnostic evaluation are to assess the following:

- Location of the tumor,
- Size and local invasiveness of the tumor,
- Tumor type, including biologic activity of the tumor,
- Stage of the disease, including regional and distant metastases, and
- Presence of concurrent disease, secondary complications, and paraneoplastic syndromes that may influence the treatment options and outcome.

Signalment, History, and Physical Examination

Various types of neoplasia are known to affect rabbits of a specific age, sex, or breed. Familiarity with these predispositions may aid in the diagnosis. Examples of tumor predilections in rabbits include:

- Age: most tumors are seen in older patients, but lymphomas and papillomas can also be found in rabbits less than 2 years.[3]
- Sex: although mammary tumors may develop in both sexes, females are most prone.
- Breed: uterine tumors are often seen in, for example, Dutch breeds.[3]

Aside from the signalment, the history may also provide information on potential risk factors such as (lack of) neutering and vaccination status. If the patient is presented with an external mass (**Fig. 1**), specific information needs to be obtained regarding the mass' time of onset, duration, growth rate, and (response to) previous treatment. Moreover, the history should include an evaluation of the potential systemic effects of the neoplasia, which will induce changes in, for example, the rabbit's behavior, activity level, appetite, body condition, or breathing. However, in many rabbits the neoplastic process itself will go unnoticed by the owner (eg, in case of an abdominal mass). As a result, the clinical presentation may be more variable, ranging from unspecific signs (eg, inappetance, weight loss, lethargy, depression) to signs resulting from the local or systemic effects of the neoplasia (eg, hematuria, gastric bloat or gut stasis, dyspnea).

Internal and external masses may occasionally be identified as coincidental findings during a routine physical examination (**Fig. 2**). Any mass that is identified

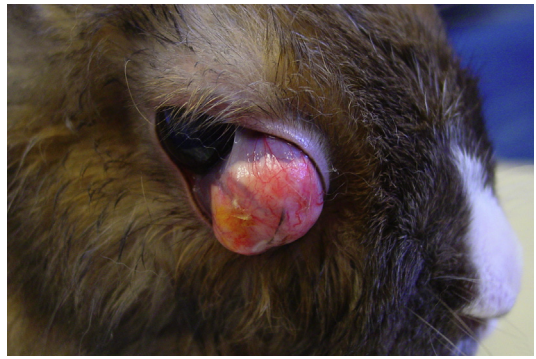

Fig. 1. When a lump or mass is found, such as the one protruding from the third eyelid of this rabbit, the owner will easily associate this with the fact that their rabbit has cancer. Knowledge regarding tumor predispositions will often help to inform the owner adequately and quickly whether and what type of tumor can be involved. In this rabbit, the location and morphologic appearance fit best with a protrusion of the Harderian gland, resulting from a prolapsed third eyelid, although a lymphoma of the Harderian gland cannot be excluded. To differentiate between the 2, cytology or histopathology are required.

should always be evaluated for its location, size, aspect, and association with surrounding tissues because this can provide clues on the involved tumor type and its behavior. Regional lymph nodes will also need to be evaluated for size, consistency, and fixation to adjacent tissues to obtain information on potential metastasis, which is helpful in the staging of the disease. Moreover, a full physical examination is warranted to identify presence of systemic effects (eg, owing to distant metastasis, paraneoplastic syndromes) and comorbidities that may interfere with treatment or negatively influence the prognosis. For example, dyspnea may hint toward the presence of pulmonary metastases and indicate a poor prognosis in does with a uterine adenocarcinoma.

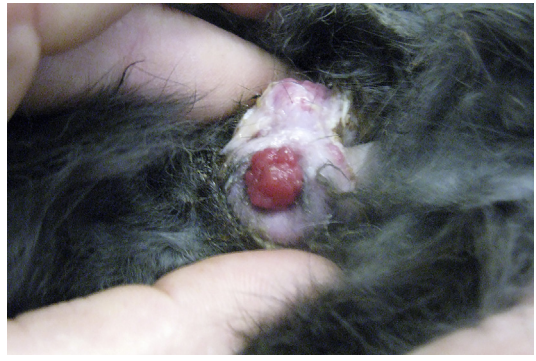

Fig. 2. Neoplasia will not always be directly noticeable by the owner. In this 1-year-old male castrated Flemish giant rabbit, tenesmus was the predominant clinical sign. Only upon closer inspection of the anus, was this anorectal papilloma noticed.

Ancillary Diagnostic Testing

After the history and physical examination, a problem list, and list of differential diagnoses may be constituted to form the basis for planning of further diagnostic steps. Diagnostic modalities that may be used in rabbits are similar to those used in dogs and cats and may include a hematologic and biochemical profile, urinalysis, imaging, and collection of fine-needle aspirates (FNA) or biopsies for cytologic and histopathologic examination.

Hematology and biochemistry

Blood and urinalysis are often performed to establish a baseline of the rabbit's overall health status. Moreover, it can be useful for:

- Diagnosis of leukemia,
- Diagnosis of functional endocrine tumors (eg, hypertestosteronism or prolactinemia in adrenocortical neoplasia or pituitary tumors, respectively),
- Evaluation of paraneoplastic changes such as hypercalcemia[a] (eg, malignant lymphoma) and hyperproteinemia and gammopathy (eg, myeloma), and
- Assessment of organ function (eg, liver, kidneys), especially if these are involved in the primary neoplastic process (eg, generalized lymphoma), or to exclude organ dysfunction before or during a treatment course.

Imaging

Imaging techniques will often provide valuable information with regard to the extent of the tumor and presence of metastases. Similar to other animals, radiography and ultrasonography are most commonly used, because most private practices have easy access to these imaging modalities. In rabbits, radiographs will often aid in the diagnosis of abdominal or mediastinal masses (**Fig. 3**), bony tumors (**Fig. 4**), and pulmonary metastases (**Fig. 5**). In case of abdominal or mediastinal masses, ultrasonography may be used for further evaluating the origin, morphology, and extent of the mass. As in other animals, advanced techniques such as computed tomography

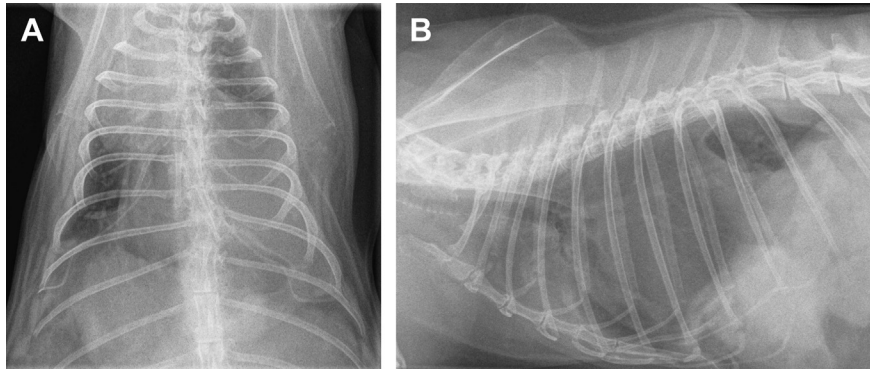

Fig. 3. Ventrodorsal (*A*) and right lateral (*B*) radiographs of a rabbit with progressive dyspnea, displaying a caudal mediastinal mass, and craniolateral displacement of the heart. Histopathology revealed the mass to be a lipoma.

[a] In rabbits, hypercalcemia should always be interpreted with caution because high calcium levels are not necessarily pathologic in rabbits owing to their unique calcium-regulating mechanism.

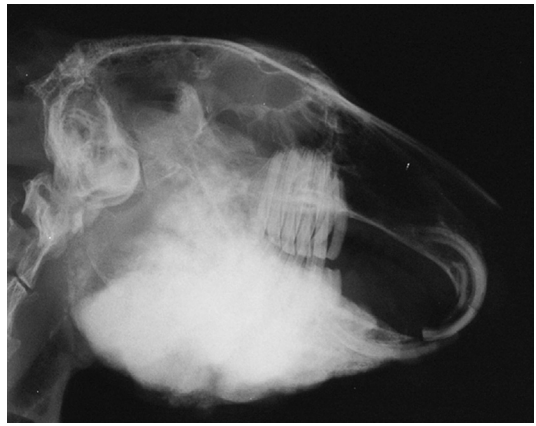

Fig. 4. Radiograph of a mandibular osteosarcoma of a rabbit. Extensive new bone formation may be noted. (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

(CT; Fig. 6), MRI, or nuclear scintigraphy (eg, bone scintigraphy) may be required to gain more detailed information on the extent and invasiveness of the tumor to aid in the planning of a surgical intervention or radiation therapy (eg, in case of nasal tumors or thymomas; Fig. 7).

Cytology

Cytologic examinations of buffy coat preparations, bone marrow aspirates or FNA from solid masses (Fig. 8) or peripheral lymph nodes are often valuable in the diagnosis of primary neoplastic lesions or regional metastases to lymph nodes.[4,5] Owing to the low cytologic yield, this technique is predominantly considered helpful in case of lipomas, and tumors comprising round cells (eg, lymphoma, mast cell tumor) or epithelial cells (eg, squamous cell carcinoma, melanoma, adenocarcinoma).[6,7]

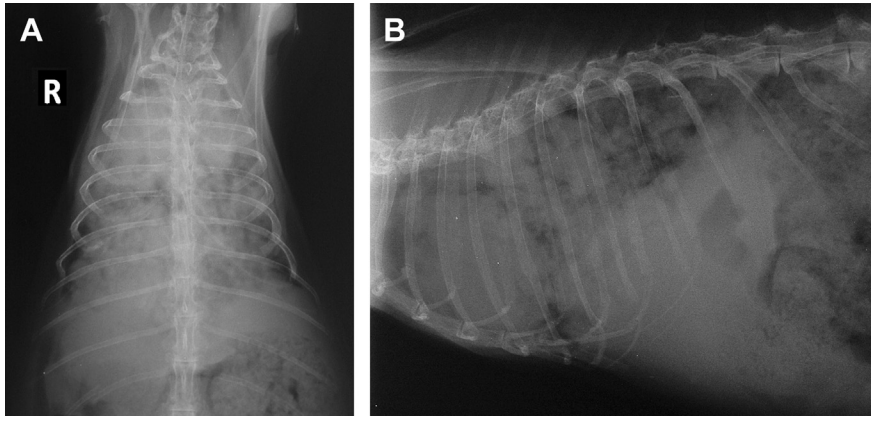

Fig. 5. Ventrodorsal (*A*) and right lateral (*B*) radiographs revealing extensive pulmonary metastases in an intact doe with uterine adenocarcinoma. (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

Fig. 6. Advanced imaging techniques, such as computed tomography, are ideal for localizing masses that may remain unnoticed with conventional radiographs (eg, nasal adenocarcinomas).

Histopathology

The collection of biopsies in rabbits follows similar guidelines as those described in dogs and cats.[8–10] However, extra caution is warranted when collecting surface-biting biopsies from the hollow viscera, because these pose an increased risk of perforation, peritonitis and associated mortality owing to their thin-walled and delicate nature.[5] Once tissue samples have been collected, histopathologic evaluation may take place to establish a definite diagnosis and verify whether complete resection has been achieved (in case of excisional biopsies). Classification of the tumor type follows similar guidelines as those used in other animal species, whereby a morphologic diagnosis generally can be obtained based on the primary tumor's site of origin, tissue type, and histologic grade (**Box 1**).[11] Accurate typing of the tumor may furthermore be

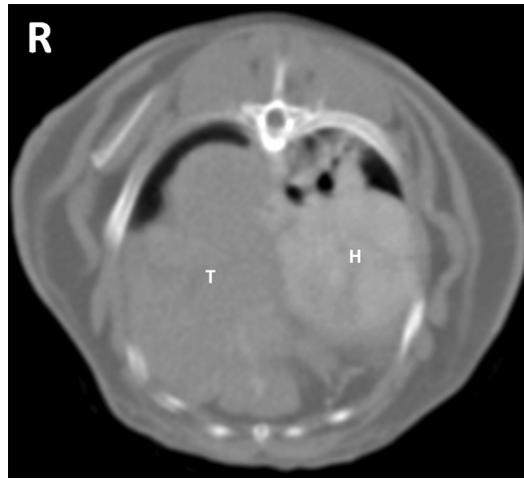

Fig. 7. Computed tomographic image from a 6-year-old male castrated rabbit with clinical signs of progressive dyspnea and bilateral exophthalmos owing to a thymoma. After intravenous administration of iodinated contrast medium, the tumor (T), which occupies approximately one-half of the thorax and causes the heart (H) to deviate to the left, can be identified clearly.

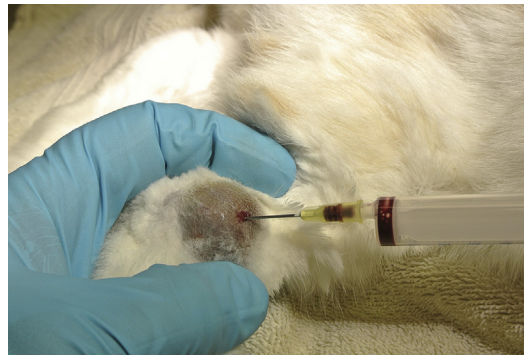

Fig. 8. Fine needle aspiration biopsy of a mass at lateral surface of the hock joint, which was diagnosed as a malignant melanoma. To obtain good quality samples, a needle size of at least 22 Gauge should be used. (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

achieved using tumor markers. These comprise either substances that are produced (in greater amounts) by or in response to the presence of tumor cells in the body or patterns of gene expressions that are characteristic for certain types of cancer (**Table 1**). Tumor markers can be identified in the tissue or bodily excretions (eg, blood, feces, urine) using immunohistochemical stains or laboratory tests Although these are not yet routinely used in exotic animal practice, tumor markers can provide crucial information regarding the nature and behavior of the tumor. As a result, they do not only serve a diagnostic purpose, but also aid in the management, monitoring, and estimation of the prognosis for an oncologic patient.[12]

Tumor staging

Aside from classification of the tumor based on its location, tumor type, and grade, tumors may also be classified by stage using the TNM system (**Box 2**).[13] This type of staging is not applied routinely in rabbit medicine, but may follow similar guidelines to those described in dogs and cats.

THERAPEUTICS

Once the diagnosis and staging have been completed, treatment options may be evaluated and discussed with the owner. The primary goal of any intervention will be to treat the neoplasm without compromising the welfare of the rabbit. Patients at increased risk for morbidity or mortality (eg, rabbits with severe anemia as a result from bleeding tumors) may require stabilization before attempting other treatment options. Moreover, rabbit patients may require close monitoring and supportive care during the treatment course, to prevent them from deteriorating. For patients in which this seems to be unlikely or impossible to achieve, euthanasia should be considered.

Surgical Intervention

Similar to other companion animals, treatment of neoplasia in rabbits often involves surgical intervention. If possible, complete surgical excision, whereby guidelines with regard to margins are comparable with those in other species (ie, 1–3 cm dependent on malignancy of the tissue). However, in smaller rabbits, smaller margins may need to be used because the remaining defect may otherwise be too large to close.

Box 1
Classification of tumors

Classification by site of origin

Anatomic location where the primary tumor originated from

Examples:
- Uterine neoplasia
- Renal tumor
- Liver tumor
- Cutaneous neoplasia
- Mammary gland tumor
- Brain tumor
- Lung tumor

Classification by tissue type

Tumors may be classified into 6 major categories based on the tissue type involved:
- Epithelial tumors: originating from epithelial cells lining the body surface or internal organs (eg, squamous cell carcinoma, adenocarcinoma).
- Mesenchymal tumors: originating in connective and supportive tissues including bone, cartilage, muscle and fat (eg, fibroma; fibrosarcoma, osteosarcoma, lipoma; leiomyoma, rhabdomyosarcoma).
- Hematopoietic tumors originating from the bone marrow:
  - Leukemia: originating from cells that normally mature in the blood stream (eg, myelocytic leukemia, lymphatic leukemia);
  - Lymphoma: originating from cells that normally mature in the lymphatic system, representing solid tumors that may be present in various organs and lymph nodes;
  - Myeloma: originating from plasma cells;
- Germ cell tumors (eg, teratoma); and
- Mixed cell types: composed of 2 or more components (eg, mixed Müllerian duct tumor).

Classification by histologic grade

Differentiation between benign and malignant tumors based on the following criteria:
1. Differentiation (well vs poorly differentiated)
2. Growth rate (slow vs rapid with many mitoses)
3. Growth pattern (expansile vs invasive growth without a capsule)
4. Metastasis (no vs frequent metastasis)
5. Microscopic features (eg, presence of pleiomorphism, hyperchromasia and multiple nucleoli in malignant tumors)

If the tumor is malignant, the degree of malignancy may be determined. Based on the level of tissue differentiation, cellular growth activity and extent of necrosis within the tumor, a grade from 1 to 4 may be assigned.

Grade 1: Low grade; well-differentiated cells that bear close resemblance to the normal cells of the parent tissue.

Grade 2: Intermediate grade; moderately differentiated cells that still bear considerable resemblance to the parent cells and tissue but abnormalities are commonly seen and complex features are often not well-formed.

Grade 3: High grade; poorly differentiated cells that bear little resemblance to the parent tissue. Abnormalities are evident and more complex architectural features are usually rudimentary.

Grade 4: Undifferentiated or anaplastic; cells are immature, primitive, and undifferentiated, and bear no significant resemblance to the corresponding parent cells and tissues.

Similar to dogs and cats, the regional lymph node may also be aspirated, biopsied, or removed as part of the diagnostic workup to enable reliable tumor staging.[14]

If complete resection of the tumor is not feasible, palliative surgery may be considered to relieve the pain and discomfort associated with the tumor. Palliative surgery

Table 1
Examples of tumor biomarkers that have been used in the characterization of neoplasia in rabbits in both experimental and clinical settings

Tumor Marker	Associated Tumor Types
CD3	T-cell lymphoma
CD79α	B-cell lymphoma
Cytokeratin (various types: TPA, TPS, Cyfra21–1)	Many types of carcinoma, some types of sarcoma
Desmin	Smooth muscle sarcoma, skeletal muscle sarcoma, endometrial stromal sarcoma
Immunoglobulin	Lymphoma, leukemia
Keratin (various types)	Carcinoma, some types of sarcoma
Ki-67 (MKI67)	Prostate, brain and mammary carcinomas, nephroblastoma
Melan-A (MART-1)	Melanoma, steroid-producing tumors (adrenocortical carcinoma, gonadal tumors eg, granular cell tumor, testicular interstitial cell tumor)
Osteocalcin	Osteoid containing tumors (eg, osteosarcoma)
Smooth muscle actin	Gastrointestinal stromal tumor, leiomyosarcoma
S100 protein	Melanoma, sarcoma (neurosarcoma, lipoma, chondrosarcoma), astrocytoma, gastrointestinal stromal tumor, salivary gland tumors, some types of adenocarcinoma, histiocytic tumor (dendritic cell, macrophage)
Vimentin	Sarcoma, renal cell carcinoma, endometrial cancer, lung carcinoma, lymphoma, leukemia, melanoma

Box 2
Staging of neoplastic disease based on the TNM system

TNM staging

T: size or direct extent of the primary tumor
- Tx: tumor cannot be evaluated
- T0: no tumor detectable
- T1 to T4: different grades in dimensions of the primary tumor

N: degree of spread to nearby (regional) lymph nodes
- Nx: lymph nodes cannot be evaluated
- N0: absence of tumor cells from the regional lymph nodes
- N1: regional lymph node metastasis present (or spread to closest or small number of regional lymph nodes)
- N2: tumor spread to an extent between N1 and N3
- N3: tumor spread to more distant or numerous regional lymph nodes

M: presence of distant metastasis
- M0: no distant metastasis
- M1: metastasis to distant organs (beyond regional lymph nodes)

Clinical staging

Stage 0: Cancer in situ or limited to surface cells

Stage I: Cancer limited to the tissue of origin

Stage II: Limited local spread of the cancer

Stage III: Extensive local and regional spread of the cancer

Stage IV: Advanced cancer with distant spread and metastasis

may include both debulking surgery and limb amputation, for example, in case of osteosarcomas. This procedure is generally well-tolerated by rabbits.[15,16] In contrast, explorative laparotomy for gastrointestinal tumors, which often present as acute cases owing to gastrointestinal obstruction and ileus, is often associated with high mortality.[17] Aside from conventional surgical techniques, newer techniques involving laser and electrosurgery may also be used in rabbits, especially if precise cutting and coagulating are required (eg, in case of anorectal papillomas; **Fig. 9**).[8] Cryotherapy, which relies on the destruction of cells by repeated freeze–thaw cycles, may be used in treatment of small (<1 cm), superficial tumors found on the skin, lips, eyelids, and perianal region, such as trichoblastomas and papillomas.[18]

Chemotherapy

Chemotherapy may be considered as the primary means of therapy in case of nonresectable tumors or metastases (eg, lymphoma, leukemia). In addition, chemotherapy may be used as adjunct therapy before or after surgical resection. Various types of chemotherapeutic agents are available for use in rabbits (**Table 2**), which may be administered either systemically or intralesionally. Systemic chemotherapy may be attempted in cases of lymphoma and leukemia, as a good response after this type of treatment has been reported in other species, but thus far no specific protocols have been published regarding their clinical use of efficacy in rabbits. However, experimental studies have demonstrated good effects of platinum and pirarubicin in rabbits with induced uterine, bladder, or mammary carcinomas.[19–21] Dosages are usually based on body surface area rather than weight, whereby a recent study determined a reliable method for calculating body surface areas in rabbits based on CT imaging.[22]

In rabbits, reported side effects include inappetance and gastrointestinal stasis, and clinical manifestation of subclinical pasteurellosis or Encephalitozoonosis.[5] If side effects are present, immediate attention and supportive therapy are warranted.[5] Routine monitoring may include a hematologic and biochemical profile to monitor liver and kidney function and evaluate bone marrow function. In case of decreased heterophil/lymphocyte counts, chemotherapy should be delayed until white blood cell counts have returned to normal. Subsequent dosages may be reduced by 20% to avoid recurrence of problems.[5] To reduce the risk of systemic effects, intratumoral administration of chemotherapeutic agents may also be considered, especially in solid tumors in locations where surgery is less ideal (eg, for cosmetic or functional

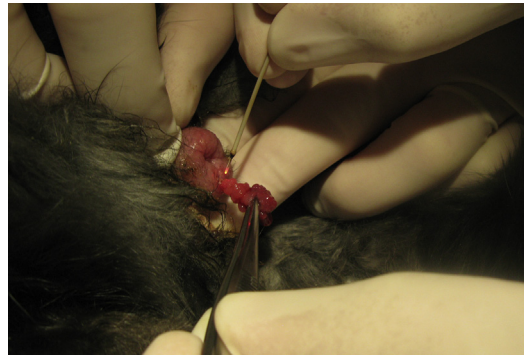

Fig. 9. Removal of an anorectal papilloma using laser surgery. Compared with conventional surgical techniques, laser enables precise cutting and helps to maintain hemostasis by immediate coagulation of blood vessels.

reasons). Cisplatin is currently the drug of choice because it is nonnecrotizing and has a good effect on solid tumors (<2 cm) of various types, including squamous cell carcinomas, soft tissue sarcomas, and round cell tumors. In combination with a collagen matrix or water/sesame oil suspension, a high tumor-to-plasma drug concentration ratio will result.[23] Standard protocols include 4 consecutive chemotherapy sessions performed at-1 week intervals during which cisplatin is administered intratumorally at a dose of 1 mg of cisplatin/cm^3 of tissue.[4,23]

Radiation Therapy

In rabbits, radiation therapy (**Fig. 10**) has been used predominantly for the treatment of thymoma, whereby good results have been achieved with both coarse (ie, palliative) and definitive (ie, curative) fractionated radiation therapy using dosages of 24 to 48 Gy.[24,25] Other tumor types that are likely to respond well to radiation therapy include lymphoma, myeloma, seminoma, and nasal adenocarcinoma.[5,26–28] Adverse effects seen after irradiation are similar to those in other species and may include hair loss and discoloration, tissue swelling and associated nerve pain, and skin irritation that—in rare instances—may lead to self-mutilation. Incidentally, more severe side effects, such as radiation-induced myocardial failure and radiation pneumonitis may also be noted, particularly in cases where the thorax is irradiated.[24]

Other Treatment Modalities

Aside from the previously mentioned options, other treatment modalities such as photodynamic therapy,[29] whole body and local hyperthermia,[30,31] and immunotherapy may also be considered in the management of oncologic rabbit patients. Their use in rabbits has, however, been limited to experimental studies.[32–35]

Supportive Care

Neoplastic disease will often induce changes in the metabolism of fat, protein, and carbohydrates, thereby resulting in gradual loss of muscle and fat tissue and, eventually, a state of cachexia. Similarly, anorexia will be a common sequela to neoplastic disease in rabbits, thereby further deteriorating the animal's condition. Provision of high-quality foods and adequate nutritional support will therefore be important in any rabbit presented with a neoplasia. In some rabbits, assisted feeding may be necessary, whereby placement of a nasogastric or esophagostomy tube may be considered for patients that need long-term care. Aside from nutritional support, rabbit patients may also benefit from administration of analgesics (eg, nonsteroidal anti-inflammatory drugs, opioids) to provide pain relief. The use of other drugs (eg, motility-enhancing drugs, gastroprotectants, prednisone, vitamin A) may also be considered as symptomatic treatment, although the potential risks of administering these drugs should be considered. Caution is required particularly when using prednisone or other corticosteroids, because the immunosuppressive effects of these drugs could predispose rabbits to develop secondary pasteurellosis or Encephalitozoonosis.

Follow-up

After treatment, regular checkups are routinely advised because they will facilitate timely diagnosis of recurrent disease or metastases. Guidelines in companion animals suggest rechecks to be scheduled at 1, 2, 3, 5, 7, 9, and 12 months after treatment, with increasing intervals for the years thereafter.[36] During each of these rechecks, a thorough physical examination should be performed, during which the tumor site is carefully examined for evidence of recurrence. Other tests that might be indicated

Table 2
Chemotherapeutic agents used in rabbits

Drug Class	Mechanism of Action	Indications	Side Effects	Dosing Regimen
Alkylating agents (cyclophosphamide, chlorambucil, melphalan, lomustine)	Formation of bonds between alkyl groups in DNA thereby affecting DNA replication (effect is greater in cells with faulty DNA replication). Effect is independent of cell cycle.	Lymphoma	Bone marrow suppression, neutropenia; GI toxicity; hemorrhagic cystitis. Corticosteroids may be given to mitigate side effects. Hepatic and renal toxicity reported when using lomustine.	Cyclophosphamide • 50 mg/m^2 PO q24 h for 2–3 d/wk • 100–200 mg/m^2 IV q1-3 wk (often combined with doxorubicin) Lomustine • 50 mg/m^2 PO q 3–6 wk
Antitumor antibiotics (doxorubicin, mitoxantrone)	Multiple modes of action: affect functionality of DNA and RNA polymerase and topoisomerase I; stimulate formation of free radicals and directly damage DNA/RNA and cell membrane. Action independent of cell cycle.	Lymphoma; leukemia; myeloma; hemangiosarcoma; carcinomas (various types)	Neutropenia; renal failure; GI toxicity; neuropenia; cardiac toxicity (doxorubicin); tissue necrosis at extravasation sites; allergic reactions reported. Corticosteroids and antihistamines may be considered to counteract effects.	Doxorubicin • 1 mg/kg IV q 2–3 wk Mitoxantrone • 5–6 mg/m^2 IV q3 wk
Vinca alkaloids (vincristine, vinblastine)	Inhibition of intracellular microtubule formation (action dependent on phase of the cell cycle).	Lymphoma	Tissue necrosis with extravasation; GI toxicity and neutropenia (at higher dosages); peripheral neuropathy (may result in ileus and constipation).	Vincristine: • 0.5–0.7 mg/m^2 IV q 1–2 wk

Platinum products (cisplatin, carboplatin)	Cross-linking between DNA strands (independent of cell cycle).	Carcinoma (various forms); osteosarcoma (alone or in conjunction with doxorubicin)	Severe myelosuppression; neutropenia; GI toxicity; nephrotoxicity. Decrease dose in presence of renal failure. Fluid therapy required before, during and after administration.	Carboplatin: • 150–180 mg/m^2 IV q 3–4 wk
Crisantaspase; L-asparaginase	Degradation of L-asparagine, an amino acid required for protein and DNA synthesis.	Lymphoma; leukemia	Anaphylaxis; pancreatitis and GI toxicity reported in other species.	400 IU/kg IM or SC
Prednisone	Induction of apoptosis in certain lymphoid cell populations. Exact mechanism is not fully understood. Corticosteroids may potentially induce resistance to other chemotherapeutic agents thereby decreasing their effects.	Lymphoma; also effective to treat side effects and as palliative treatment for many other cancer types	Potential immunosuppression which may predispose to pasteurellosis or Encephalitozoonosis. Concurrent use of gastroprotectants (eg, ranitidine or omeprazole) is advised. PU/PD, polyphagia and skin changes may be noted after long-term treatment.	0.5–2.0 mg/kg PO

Body surface area (BSA) can be calculated using the following formula: BSA = 99 $\times$ (body weight in grams)$^{2/3}$/10,000.

Abbreviations: GI, gastrointestinal; IM, intramuscularly; IV, intravenous; PO, orally; PU/PD, polyuria/polydipsia; SC, subcutaneous.

Data from Refs.[4,5,19]

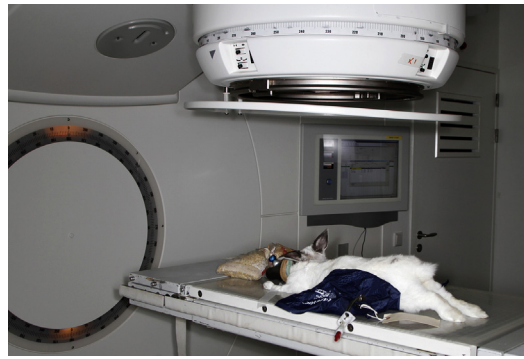

Fig. 10. Radiation therapy in a rabbit with a thymoma. To enable proper positioning, the rabbit was placed on an inflatable cushion whereby landmarks on the rabbit and cushion were used to ascertain that during the consecutive radiation sessions (every 2–3 days for a total of 10 sessions) the rabbit is placed in exactly placed in the same position. A combination of low-dose ketamine (5 mg/kg) and medetomidine (100 μg/kg) produced anesthesia of a depth sufficient to immobilize the rabbit for the duration of the session; supplemental oxygen was provided through a face mask.

include (thoracic and/or abdominal) radiographs, ultrasound, CT-imaging, MRI, bone marrow aspirates, and FNA or biopsy of the original tumor site or regional lymph nodes. Whether and which tests will be performed will depend on the tumor type involved.

DISEASES

Rabbits can suffer from many types of neoplastic disease (**Table 3**). As in other animals, classification is based on their primary site of origin (eg, mammary gland, bone), type of tissue involved (epithelial vs mesenchymal), and growth behavior of the neoplastic cells (benign vs malignant). Although primary neoplasia can originate in any organ system, the degree to which organ and organ systems are affected varies considerably. In both laboratory and pet rabbits, adenocarcinoma of the uterus continues to be the most frequently diagnosed neoplasia, followed by lymphoma/lymphoid leukemia.[3] In laboratory animals, the 2 next most common tumors include embryonal nephroma and bile duct adenoma, whereas in pet rabbits mammary gland tumors and skin tumors are seen more commonly.[3] The differences seen in the frequency with which certain tumor types are seen may, at least in part, be explained by differences in age composition of the groups as well as differences in exposure to pathogens (eg, Shope fibroma virus) or frequency of postmortem examinations performed in apparently healthy animals (resulting in a higher percentage of tumors found by coincidence).

COMMON TUMORS AND THEIR CLINICAL PRESENTATION, DIAGNOSIS AND TREATMENT

Uterine Neoplasia

Uterine adenocarcinoma (**Fig. 11**) is the most commonly diagnosed neoplasia in pet rabbits.[3,37] Although all intact female rabbits are susceptible to develop uterine adenocarcinoma, certain breeds, such as the Tan, French silver, Havana, and Dutch breeds, are considered particularly prone.[37] Incidence significantly increases with age, varying

Table 3
Reported (spontaneous) neoplasia in rabbits

Organ System	Tissue of Origin	Reported Tumor Types	Incidence	Clinical Signs	Diagnosis and Workup	Treatment and Prognosis
Reproductive tract (female)	Ovary; uterus; cervix; vagina; vulva	Uterine adenocarcinoma; leiomyoma/ leiomyosarcoma; mixed Müllerian duct tumor; choriocarcinoma; deciduosarcoma; squamous cell carcinoma (vaginal wall); teratoma; hemangioma; granulosa cell tumor; ovarian adenocarcinoma	Entire females; uterine adenocarcinoma is the most common tumor, affecting 50%–80% of does >3 y; certain breeds and family lines may be overrepresented. Other tumors are diagnosed more sporadically.	• Hematuria • Anemia • Firm, irregular uterus on abdominal palpation • Cystic mammary glands • Weight loss, lethargy • Dyspnea (if lung metastases are present)	• Clinical signs (abdominal palpation) • Urinalysis (in patients with hematuria) • Radiography (including thorax to check for lung metastases) • Ultrasonography • Cytology (FNA) • Histopathology • Exploratory laparotomy	Ovariohysterectomy. High rate of metastasis (mainly to lungs and liver but occasionally also to other locations) reported and thus potentially life-threatening without treatment. Up to 3 y may pass from time of diagnosis until metastases-related death occurs.
Reproductive tract (male)	Testes; Prostate	Seminoma; Sertoli cell tumor; interstitial cell tumor (Leydig cell tumor, granular cell tumor); teratoma; adenocarcinoma; Neoplasia of different tumor types can occur simultaneously in both testes and can be nonfunctional or hormone secreting (functional)	Entire males; cryptorchid rabbits are at higher risk; incidence increases with age, but generally considered a rare finding in rabbits.	• Unilateral or bilateral testicular enlargement; contralateral testis may be small • Change in consistency of 1 or both testes • Change in libido and associated behaviors • Reproductive failure • Scrotum skin necrosis (rare) • Gynecomastia (rare) • Gait changes (if testes are severely enlarged) • Weight loss	• Clinical signs • Ultrasonography • Histopathology • Thoracic radiographs to check for lung metastases	Bilateral orchidectomy; palliative care in case surgical intervention is not feasible. Prognosis usually good to excellent after complete excision and lack of metastases.

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Table 3
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Organ System	Tissue of Origin	Reported Tumor Types	Incidence	Clinical Signs	Diagnosis and Workup	Treatment and Prognosis
Mammary glands		Adenocarcinoma; papilloma; fibroadenoma	Common in multiparous, intact female rabbits >2 y; often associated with uterine hyperplasia and adenocarcinoma (hyperestrogenism) and prolactin-secreting pituitary adenomas. Reports of familial occurrence in Belgian and English breeds.	• Mammary gland enlargement; single or multiple coalescing firm masses palpable in the mammary glands; usually nonpainful • Brown-red discharge from teat(s); teat(s) may be enlarged with hair loss present around it • General malaise with lethargy, depression, inappetance, weight loss and dyspnea if tumor has metastasized to the lungs	• Cytology (FNA) • Histopathology • Thoracic radiographs to check for lung metastases	Mastectomy and ovariohysterectomy. Prognosis depends on the presence of metastasis (poor if lung metastases are present).

Hematopoietic and lymphatic systems	Blood; lymph nodes; thymus; spleen; bone marrow; blood vessels	Lymphoma/ lymphosarcoma; lymphoid/myeloid/ erythroid leukemia; thymoma/ thymosarcoma; thymic carcinoma; hemangioma/ hemangiosarcoma/ hemangioepithelioma; epithelioma; histiocytoma; eosinophilic granulocytic sarcoma; plasma cell tumors/ myeloma	Lymphoma/ lymphosarcoma is most common neoplasia in young rabbits <2 y and second most common neoplasia overall; may be of B- or T-cell origin and occur in variety of different tissues (lymph nodes, spleen, liver, bone marrow, eye, skin, GI tract). Thymomas more common in older rabbits. Other tumors are considered very rare in rabbits and generally diagnosed on postmortem examination.	• Highly variable in lymphoma, depends on the site affected (eg, enlarged lymph nodes, reno/spleno/hepatomegaly, general malaise, cutaneous or ocular lesions, diarrhea) • Presenting signs of thymoma may include dyspnea, exercise intolerance and bilateral exophthalmos. • Paraneoplastic syndromes have been reported for both lymphoma (hypercalcemia) and thymoma (exfoliative dermatitis) • Animals with hemangiosarcoma may bleed out from the tumor without premonitory signs	• Clinical signs • Ultrasound, thoracic radiographs or CT imaging • Cytology (FNA) • Histopathology • CBC or blood smear may reveal marked lymphocytosis and neoplastic cells • Protein electrophoresis may reveal monoclonal gammopathy (in case of myeloma) • Necropsy	Similar to other animals, radiation therapy or chemotherapy may be attempted for lymphoid tumors, although no specific chemotherapeutic protocols have been published in rabbits. Surgical treatment of thymomas is possible, but is technically challenging and poses high risks of perioperative mortality. Radiation therapy also poses a risk owing to repeated anesthetic episodes but is considered to have good effect. Chemotherapy is reported as an option in humans. Hemagiosarcomas may require surgical excision followed by (doxorubicin-based) chemotherapy.

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Organ System	Tissue of Origin	Reported Tumor Types	Incidence	Clinical Signs	Diagnosis and Workup	Treatment and Prognosis
Integument	Skin (squamous epithelium, adnexa); ears; eyelids; lips	Basal cell tumor; trichoblastoma; squamous cell carcinoma; sebaceous gland adenoma/ adenocarcinoma; spindle cell sarcoma; collagenous hamartoma; trichoepithelioma; trichoblastoma; malignant melanoma; fibroma/fibrosarcoma; papilloma; apocrine (adeno)carcinoma Viral-induced skin tumors include papilloma, myxoma; shope fibroma	Nonviral skin tumors are reported infrequently and mostly seen in older rabbits; viral-induced tumors may be seen at various ages. Of the nonviral tumors, trichoblastoma appear most frequently diagnosed in rabbits, comprising 20%–25% of all skin neoplasia	• Generally present as solitary, well-circumscribed cutaneous or subcutaneous masses with or without ulceration. Tumors may be pigmented in case of trichoblastoma or melanoma or appear as wartlike growths in case of papillomas. • May be located anywhere on the body surface, although predilection sites may be recognized for some tumors (eg, ear, eyelid, toe or genital area for malignant melanoma; head, neck and limbs for trichoblastoma; head and mucosa for papillomas).	• Clinical presentation • Cytology (FNA) • Histopathology (excisional/incisional biopsy) • Imaging may be required in case of malignant tumors to check for metastases	Treatment of choice is surgical excision of the mass. Adjunct chemotherapy or radiation may be considered depending on the tumor type involved. Prognosis varies depending on the type of neoplasia and location with prognosis for benign tumors such as trichoblastoma generally being excellent, the whereas prognosis for malignant melanoma may be more guarded as tumors tend to be locally invasive and metastasize to the lymph nodes and other tissues, including lung and liver. Adjunct therapy using radiation therapy may thus be necessary. In addition, a melanoma vaccine, developed for dogs, may be used, but its efficacy in rabbits needs to be studied further.

Gastrointestinal tract	Stomach; small and large intestines; caecum; rectum and anus; liver and bile duct; exocrine pancreas	Bile duct adenoma/ adenocarcinoma; carcinoma; hepatic hamartoma; pancreatic adenoma/ adenocarcinoma; tumors of the stomach and intestines (carcinoma; adenoma/ adenocarcinoma, leiomyoma/ leiomyosarcoma); papilloma; liver metastases (particularly uterine carcinoma)	Uncommon. Most common tumor includes the bile duct adenoma/ adenocarcinoma, which has been speculated to arise as a result from *Eimeria steidae* infection	• Bile duct adenomas/adenocarcinomas are often an incidental finding at necropsy. If diagnosed antemortem these may involve solitary growths or multiple masses that are sharply circumscribed from normal liver and may contain honeylike fluid and can be palpated in the abdomen during the physical examination. • Animals with gastric or intestinal tumors may present with anorexia, gastric dilatation (bloat), abdominal pain; ileus; diarrhea, ascites, lethargy or chronic wasting. Some animals may present with acute death. • Anorectal papillomas present as small, friable fungating masses originating from the anorectal junction. Clinical signs include constipation, discomfort, hematochezia, and occasionally rectal prolapse.	• Clinical presentation (anorectal papillomas) • Ultrasound, radiography or CT imaging • Cytology (FNA; often nondiagnostic) • Histopathology • Biochemistry may reveal elevated liver enzymes (eg, GGT), increased bile acids, hypoproteinemia and hypoalbuminemia but often only in advanced cases • Explorative laparotomy • Necropsy	Surgical excision of solitary growths. Chemotherapy may be attempted for multifocal hepatic tumors or infiltrative lymphomas, but is primarily considered a palliative treatment. Metastasis of hepatic and biliary tumors may occur to the lungs or surrounding tissues (peritoneum, diaphragm, mesentery). Most gastric and intestinal tumors are likely to be diagnosed only in an advanced stage, thereby carrying a grave prognosis. Surgical excision, laser therapy or cryotherapy may be attempted for anorectal papillomas and carry a good prognosis. Spontaneous regression may also occur in asymptomatic cases.

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Table 3
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Organ System	Tissue of Origin	Reported Tumor Types	Incidence	Clinical Signs	Diagnosis and Workup	Treatment and Prognosis
Urinary tract	Kidney; ureters; bladder; urethra	Benign embryonal nephroma; renal carcinoma; leiomyoma	Benign embryonal nephromas are a reportedly common tumor in laboratory rabbits, both in young and older animals (range, 1.5 - >5 y)	• Commonly presented as a coincidental finding at necropsy with no antemortem clinical signs noted; may occur as single or multiple masses in one or both kidneys. • Unilateral renal enlargement. • Acute death or clinical signs resulting from metastases to distant sites.	• Ultrasound, radiography • Necropsy • CBC may reveal secondary polycythemia; kidney values often remain normal (especially in case of unilateral involvement)	Often no therapy indicated for benign embryonal nephromas, although successful nephrectomy has been described in rabbits with secondary polycythemia. Treatment of renal carcinoma may be difficult, with poor response to chemotherapy noted in other species. At the time of diagnosis, metastasis has often occurred to the regional lymph nodes, contralateral kidney, liver, and lungs. Chemotherapy has not been considered effective in these tumors.

Respiratory tract	Nasal cavity; sinuses; trachea; lungs	Adenocarcinoma; primary carcinoma; primary epithelioma; pulmonary metastases of any tumor (particularly uterine adenocarcinoma); histiocytic sarcoma	Uncommon	• Unilateral or bilateral nasal discharge; epistaxis; sneezing; snoring. • Progressive dyspnea and tachypnea. • General malaise, including anorexia, lethargy, and depression.	• Radiography or CT imaging (particularly for the upper respiratory tract) • Rhinoscopy and biopsy collection for histopathologic examination • Cytology (FNA)	Surgical excision is often not feasible; certain tumors (eg, adenocarcinoma) may respond well to radiation therapy or chemotherapy; otherwise, palliative treatment may be considered.
Musculoskeletal system (including mesenchymal tissues)	Bone; muscle; joint tissue; tendons and ligaments; connective tissue	Osteosarcoma; osteochondroma; adamantinoma; acanthomatous ameloblastoma; fibroma; fibrosarcoma; sarcoma; spindle cell sarcoma; round cell sarcoma; leiomyoma/leiomyosarcoma; mesothelioma; lipoma/liposarcoma;	Rare, with most tumors involving osteosarcomas of the appendicular skeleton (eg, tibia), ribs, skull or facial bones. Mainly diagnosed in older rabbits (>6 y)	• Swelling of the affected area. • Progressive, unilateral lameness. • In case of facial involvement, anorexia, weight loss, and ocular and nasal discharge may be noted. • Metastasis may occur to the lungs, resulting in dyspnea.	• Biochemistry may reveal elevated alkaline phosphatase activity • Radiographs may reveal proliferative bone density mass and potential lung metastases. • CT imaging may be useful to determine the extent of the tumor (also for surgical planning) • Histopathology	In case of appendicular tumors, amputation of the affected limb is recommended. Hemimandibulectomy has been attempted in cases involving the mandible. Chemotherapy using doxorubicin or platinum compounds may be attempted as adjunct therapy, similar to dogs. Palliative treatment may consist of the use of NSAIDs and other pain medication.

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Organ System	Tissue of Origin	Reported Tumor Types	Incidence	Clinical Signs	Diagnosis and Workup	Treatment and Prognosis
Nervous system	Brain; spinal cord; peripheral nerves; eyes	Teratoma; neurinoma; ependymoma; neurofibrosarcoma; peripheral nerve sheath tumor; intraocular sarcoma	Uncommon	Clinical signs will depend on the location of the tumor and may include ataxia, seizures, paresis/paralysis and other neurologic deficits.	• Use of advanced diagnostic techniques such as CT or MRI is generally required • Necropsy	Surgical resection is often not considered feasible unless the tumor is located peripherally, in which case radical surgical resection (eg, amputation of the limb) may be attempted followed by radiation therapy or chemotherapy. Similar to other animals, radiation therapy may be considered as palliative treatment but overall prognosis is considered poor.

Endocrine system	Pituitary gland; adrenal glands; thyroid gland; endocrine pancreas	Pituitary adenoma/ carcinoma; prolactinoma; adrenocortical adenoma/carcinoma; thyroid carcinoma	Rare; adrenocortical neoplasia have incidentally been reported in older, male (and 1 female) neutered rabbits,	• Recurrence of sexual and aggressive behavior (chasing, biting, mounting). • Inappropriate urination. • Enlarged mammary glands (in case of prolactinoma). • Other tumors often diagnosed as coincidental findings at necropsy, with no obvious clinical signs noted (nonfunctional tumors?).	• CT or MRI may potentially be used in the diagnosis of pituitary adenoma • Ultrasound • Hormone analysis • Necropsy	Adrenalectomy has been successfully used in rabbits with adrenocortical neoplasia. Leuprolide acetate (GnRH agonist) was reported to only have moderate effect on the behavior. Therapy for other tumors has not been described, but most likely follows similar guidelines as those in dogs and cats.

Abbreviations: CBC, complete blood count; CT, computed tomography; FNA, fine needle aspirate; GGT, gamma-glutamyl transferase; GnRH, gonadotropin-releasing hormone; NSAIDs, nonsteroidal anti-inflammatory drugs.

Data from Refs.[2,3,5,37,64,67]

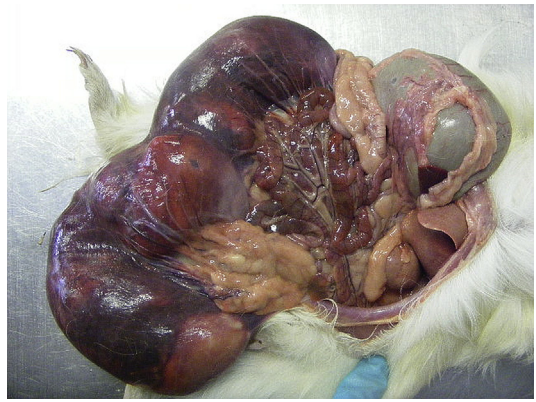

Fig. 11. Severely abnormal uterus of a rabbit. Pathology confirmed this to be a uterine adenocarcinoma. Often the abnormal uterus may be noted on abdominal palpation as a large, firm, irregular mass in the caudal abdomen.

from 4% in 2- to 3-year-old rabbits up to 80% in animals older than 5 years.[38–41] Degree of parity does not affect tumor incidence,[42] whereas the role of hormones (estrogen, progesterone) remains unclear, although involvement of these hormones in the development of tubular or solid uterine carcinomas has been suggested.[43] Aside from uterine adenocarcinomas, adenomas, leiomyomas, leiomyosarcomas, malignant mixed Müllerian duct tumors, deciduosarcomas, hemangiomas, carcinosarcomas, choriocarcinomas, and squamous cell carcinomas (particularly of the vaginosquamocolumnal junction) have also been diagnosed.[3,40,41,44–46]

Clinical signs

In breeder rabbits, reproductive disturbances (eg, decreased fertility, fetal retention, resorption or abortus, still births, reduced litter size) represent one of the first signs of uterine carcinoma.[38] In these animals, clinical detection of the tumor may be delayed by as much as 6 to 10 months.[3] In pet rabbits, hematuria or hemorrhagic vaginal discharge is often the first sign to be noted by the owner (**Fig. 12**).[40,41] In some individuals, mammary gland enlargement may also be observed. However, in many patients, uterine neoplasia will go unnoticed until its presence is discovered during an abdominal palpation or until metastasis to other organs has occurred.[41] At this time, the rabbit may present with a more severe clinical signs such as anorexia, weight loss, depression, dyspnea (in case of pulmonary metastases), or lameness owing to pathologic fractures (in case of bone metastases).

Diagnosis

A tentative diagnosis of uterine carcinoma can usually be made based on the history and clinical examination of the patient, during which the enlarged uterus or uterine masses can be palpated. Radiography or ultrasonography (including FNA for cytology) may be used for confirmation (**Fig. 13**). Thoracic radiographs are indicated to identify pulmonary metastasis. In patients that present with hematuria, urinalysis may be performed to determine whether the patient suffers from true hematuria or porphyria.

Treatment and prognosis

Uterine adenocarcinoma usually comprises a slowly growing tumor, but if left untreated it may locally invade the myometrium and peritoneal cavity or metastasize

Fig. 12. Hematuria or presence of hemorrhagic vaginal discharge is one of the clinical signs that may be noted in rabbits with uterine pathology.

to the lungs, liver, brain, or bone.[47,48] Treatment of choice therefore consists of ovariohysterectomy (**Fig. 14**), with periodic follow-up recommended to monitor for metastases that were undetectable at the time of surgery. If no metastases have occurred, prognosis is usually good with more than 80% of ovariohysterectomized rabbits reported to still be alive 6 months after surgery.[41] Chemotherapy may be attempted in case of metastases, although this is generally not considered to result in a successful outcome.[5] These cases may therefore better be managed palliatively until euthanasia is warranted (eg, in case of progressive dyspnea owing to advanced metastatic lung disease).

Prevention

Anecdotally, ovariectomy in rabbits less than 6 months or breeding at a young age have been suggested as ways to reduce the risk of uterine adenocarcinoma. However, there are anecdotal reports of diagnosed uterine adenocarcinomas in rabbits despite these measures, suggesting that these do not (completely) eliminate the risk of tumor development (2012, personal communication). Prevention can therefore best be achieved by ovariohysterectomy, which is preferably performed in the first year of life (if the rabbit is not intended to be bred).

Testicular Neoplasia

Tumors of the testicle are infrequently reported in rabbits. Older, intact male rabbits, especially those with undescended testes, are considered to be at greater risk.[3] Reported tumor types in rabbits include seminomas, interstitial (Leydig or granular) cell tumors, Sertoli cell tumors, teratoma, adenocarcinoma, testicular nephroma,

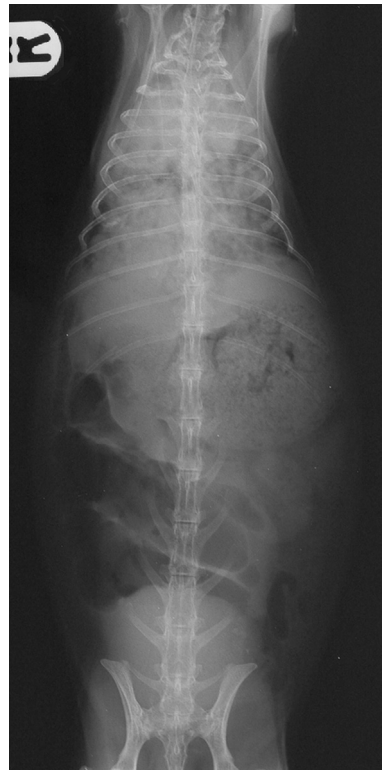

Fig. 13. Ventrodorsal radiograph of a rabbit with a metastasized uterine adenocarcinoma. Both the enlarged uterus and extensive pulmonary metastases may be visualized on this radiograph. (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

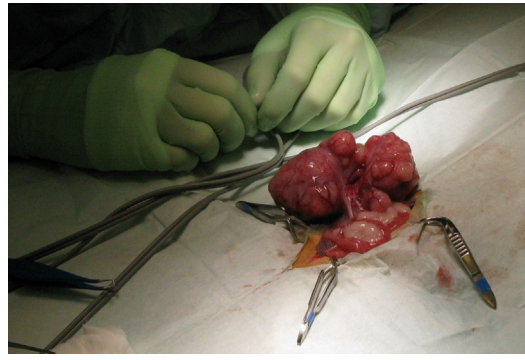

Fig. 14. Ovariohysterectomy in a rabbit with a uterine adenocarcinoma. If the tumor has not metastasized, ovariohysterectomy is the recommended choice of therapy. When performing the surgery, care must be taken to also resect the cervix because tumors have been reported to recur if uterine tissue is left behind.

lymphoma, and mixed cell tumors, also referred to as gonadoblastoma.[3,49–55] Of these, the Leydig cell tumors are the most commonly reported,[53,55] although different tumor types have been reported to occur simultaneously in both testes.[50,51]

Clinical signs

Animals with testicular tumors often present with unilateral or bilateral enlargement of the testes. In general, testicular tumors will present as firm, nodular, nonpainful masses, but occasionally there may be no gross evidence of neoplasia present.[3,49–55] In some animals, fertility may be decreased. If the tumor is functional (eg, estrogen-producing Leydig cell tumors), gynecomastia and behavioral changes (including changes in libido) may be observed.[52] Owing to the negative feedback mechanism, the contralateral testis may be decreased in size in these animals. If the tumor is large, it may interfere with locomotion and/or cause scrotal skin necrosis. Metastases are rare, but have been reported to the regional (sublumbar) lymph nodes and lungs.[56] In these patients, progressive weight loss and other signs of general malaise can also be part of the presenting signs.

Diagnosis

A presumptive diagnosis can usually be made based on the presenting signs and palpation of the testicle. However, to differentiate between a testicular neoplasia and other causes of unilateral or bilateral testicular enlargement (eg, bacterial orchitis, abscesses, testicular torsion, hematoma) further workup will be required. An ultrasound examination may be helpful to evaluate tissue morphology and presence of blood flow. Confirmation of the diagnosis and tumor type will require histopathologic examination.

Treatment and prognosis

Unilateral or bilateral orchidectomy is the recommended choice of treatment for testicular tumors. Prognosis is usually good to excellent unless the tumor has metastasized. If surgery is not an option, palliative care may be considered.

Mammary Gland Neoplasia

Mammary gland tumors have frequently been reported in laboratory rabbits, but are also regularly seen in pet rabbits. Predisposing factors include age (older rabbits with a mean age of 5.5 years; range, 2–14), breed (New Zealand White, English, and Belgian breeds), gender (intact female), and multiparity.[3,57] On various occasions, these tumors have been seen in conjunction with uterine hyperplasia or adenocarcinoma, suggesting a direct link between the two processes.[40,58,59] In addition, their onset may be influenced by hyperestrogenism, prolactinemia, or the presence of prolactin-secreting pituitary adenomas.[3,60,61] Reported tumor types include cystadenoma, fibroadenoma, adenoma, adenocarcinoma, papilloma, carcinoma, and carcinosarcoma, of which malignant tumors (>70%), in particular invasive carcinomas, are the most frequently diagnosed.[3,57,62,63] Development of the tumor seems to be preceded frequently by cystic changes of the mammary gland.[3]

Clinical signs

Mammary tumors often present as mammary gland enlargement and/or presence of 1 or multiple fluctuant or firm masses in the mammary gland(s). Masses can be variable in size, and are often nonpainful on palpation. Other clinical signs that may be noted include alopecia, ulceration, and/or discoloration of the gland(s) and/or teat(s) and milky or amber-colored discharge from the teat(s).[3,64] Rabbits will generally be bright, active, and alert, unless metastasis (to regional lymph nodes, lungs, liver, kidney,

pancreas, adrenal glands, ovary, and bone marrow) has occurred, at which time the rabbit will become cachexic, depressed, and lethargic.[64]

Diagnosis

Definite diagnosis can be made after FNA or biopsy. This is particularly important, because differential diagnoses include a number of conditions with similar presentation such as pseudopregnancy, prolactin-driven cystic hyperplasia, bacterial mastitis, cyclosporine-induced hyperplasia, and testicular interstitial cell tumor-induced gynecomastia.[52,65,66] Thoracic radiographs or ultrasound imaging may furthermore be useful to check for potential metastases.

Treatment and prognosis

Mastectomy is the treatment of choice, provided a preoperative screening does not reveal the presence of metastases. If a single small lump is present a nodulectomy may be performed, whereas chain mastectomy may be necessary if multiple mammary glands are affected. In intact females, additional ovariohysterectomy may be considered. Even though this is not necessarily proven to decrease the likelihood of mammary tumor development in future, this may help to prevent the more common uterine neoplasias. However, in females that have been spayed at an older age, additional tumors may still develop as a result of previous hormonal sensitization of the mammary tissue.[3] If complete resection is not feasible, radiation therapy may be considered to stop or slow regrowth.[67] In analogy to dogs and cats, chemotherapy with doxorubicin, antiestrogen medication (eg, tamoxifen), or a cyclooxygenase-2 inhibitor (piroxicam, meloxicam) may be attempted for nonresectable or metastasized mammary gland tumors.[67]

Lymphoid Neoplasia: Lymphoma, Lymphosarcoma, and Leukemia

Lymphoid tumors, including lymphoma, lymphosarcoma, and lymphoid leukemia, are the second most common tumor diagnosed in rabbits. Although these tumors may occur in rabbits of all ages (range, 7 weeks to 9.5 years), they are most commonly seen in rabbits less than 2 years of age.[3,68] Lymphomas have been reported in various breeds, including New Zealand white rabbits, Japanese white rabbits, English breeds, and Dutch dwarf breeds.[64] Lymphoid tumors may either be of B-cell or T-cell origin and can be found in practically any organ or tissue, including the lymph nodes, spleen, liver, kidneys, skin, eye, and lymphoid tissues of the gastrointestinal tract and lungs.[3,69] Systemic forms with multiple organ involvement (in particular the liver, spleen, kidneys, and thoracic and mesenterial lymph nodes) are considered the most common.[3] In addition, leukemias in association with lymphoma in multiple organs have been reported.[70–72]

Clinical signs

Clinical manifestations of lymphoma can be extremely variable, depending on the location of the tumor. Clinical signs observed in rabbits with lymphoma include aspecific signs of generalized illness such as anorexia, anemia, lethargy, weight loss, diarrhea, and depression. In addition, peripheral lymphadenopathy and/or an enlarged liver, spleen, or kidneys may be present. In case of skin involvement, lesions may be localized to bilateral blepharitis or cutaneous nodules or plaques with or without ulceration, crusts, erythema, and/or alopecia.[68,73] Ocular lymphoma and retrobulbar lymphoma of the Harderian gland may present as intraocular (white) masses (**Fig. 15**), or unilateral exophthalmos, whereas bilateral exophthalmos and progressive dyspnea may be noted in case of mediastinal lymphomas.[3,64,72,74–76]

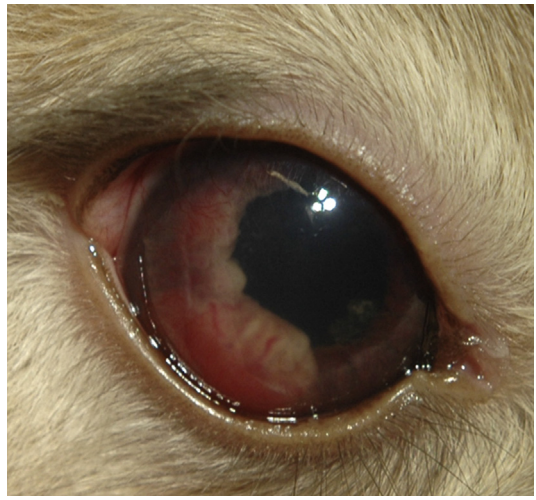

Fig. 15. Ocular lymphoma in a rabbit. After enucleation, the eye was sent in for histopathology revealing the lymphoma to be of T cell origin. (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

Diagnosis

Diagnosis can be achieved by FNA or biopsies of affected lymph nodes or organs. In case of leukemia, increases in total white cell count, lymphocytosis, and/or the presence of lymphoblasts in a blood smear may be observed.[5] In many cases, diagnosis will be made postmortem, revealing hepatosplenomegaly with diffuse small (0.5 mm) pale foci (**Fig. 16**); enlarged, pale kidneys with an irregular lumpy surface; and lymphadenopathy, pale bone marrow, and skin and/or pulmonary nodules.[37,77,78] Confirmation of the diagnosis can be achieved after histopathologic examination, which will reveal the affected lymph nodes and organs to be infiltrated with neoplastic lymphoid cells.

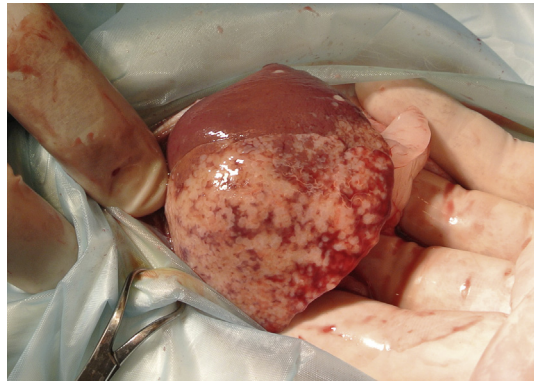

Fig. 16. Lymphoma commonly affects many internal organs, such as the liver in this rabbit. (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

Treatment

In most species, lymphoma is considered to be systemic at the time of diagnosis. Although no chemotherapeutic protocols have been published for rabbits, chemotherapy (using similar chemotherapeutic agents as in other animals) should be considered as the treatment of choice.[5,64] In case of localized forms, surgical excision may be attempted. Similarly, radiation therapy may be considered useful in case of mediastinal masses or after excision of localize masses. Treatment protocols using alpha-interferon and isotretinoin have been reported in rabbits with T-cell lymphomas, but showed no effect.[68]

Thymic Neoplasia

Thymomas are tumors originating from the epithelial cells of the thymus. In contrast with other animal species, the thymus of the rabbit is large and persists into adulthood. In mature animals (median, 6 years; range, 1–10), cells may become neoplastic, giving rise to both benign (thymoma) and malignant (thymic lymphoma [malignant thymoma], thymic carcinoma) tumors, with benign forms being most common.[79] An incidence approaching 8% has been reported.[59] Thymomas tend to be slow growing but may locally invade tissues and metastasize locally to the pleura and other (thoracic and abdominal) organs, although the likelihood of this occurring seems low.[80]

Clinical signs

Clinical signs in rabbits with thymomas may range from an incidental finding of a cranial mediastinal mass on radiographic examination to signs of progressive dyspnea and exercise intolerance owing to the presence of a space-occupying mass in the thorax. Moreover, bilateral exophthalmos; prolapse of the third eyelids; head, neck, and forelimb edema; and pleural effusion associated with cranial vena cava syndrome may be seen (**Fig. 17**).[79,81] Other paraneoplastic syndromes that have been associated with thymomas include systemic immunopathy and/or hemolytic anemia[82,83] and exfoliative dermatitis[84,85] (**Fig. 18**). Hypercalcemia has also been reported in 2 rabbits,[86,87] with 1 rabbit showing resolution of the hypercalcemia after surgical removal of the neoplasia.[87] Nonetheless, caution is warranted when attributing the presence of a hypercalcemia to the neoplastic disease because hypercalcemia may also be present as a result of the rabbit's unique calcium metabolism and dietary influences.[88]

Fig. 17. Bilateral exophthalmos in a rabbit with a thymoma. As a result of the compression on the large veins by the tumor, venous return to the heart is diminished, leading to cranial vena cava syndrome. Typically, the bilateral exophthalmos can be exacerbation by changing the body position.

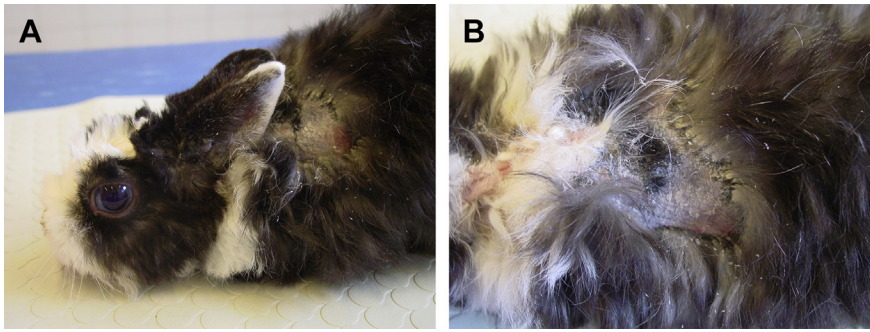

Fig. 18. (*A, B*) A 6-year-old female rabbit was presented with alopecia, scaling, and severe pruritus. Prior treatment against mites and dermatophytosis was unsuccessful. Skin biopsies were consistent with sebaceous adenitis. This skin condition is considered as a potential paraneoplastic syndrome of a thymoma.

Diagnosis

History and clinical signs are usually suggestive of a mass in the cranial mediastinum, especially if the clinical examination reveals one of the following abnormalities: position-dependent worsening or improving of bilateral exophthalmos, decreased compliance of the thoracic wall, absence of breath sounds in the cranial thorax, and caudal displacement of the heart and ictus cordis. The presence of a soft tissue mass in the cranial mediastinum (and potential accompanying pleural effusion) may be confirmed using thoracic radiographs, ultrasound examination, or CT imaging (the latter technique also being helpful in planning of subsequent surgery or radiation therapy; see **Fig. 7**). As lymphoma, abscesses, thymic hyperplasia, and thymic carcinoma are important differential diagnoses, (ultrasound-guided) FNA (**Fig. 19**) or tissue biopsies are required for a definite diagnosis. FNAs will not always be diagnostic, but if the sample contains sufficient material, thymomas can easily be identified by the presence of a mixture of epithelial cells and small, well-differentiated lymphocytes.[25,79]

Treatment

Surgery and radiation therapy are currently the preferred options to treat thymomas. Surgical excision after explorative thoracotomy (**Fig. 20**) is often considered to provide

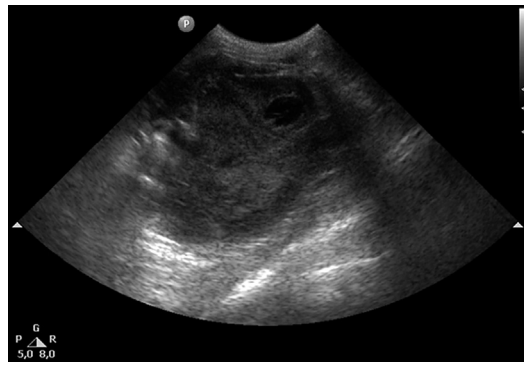

Fig. 19. Ultrasound imaging of a rabbit diagnosed with a mass in the cranial mediastinum. A fine-needle aspirate was collected of the mass for cytology, after which a definite diagnosis of thymoma was obtained.

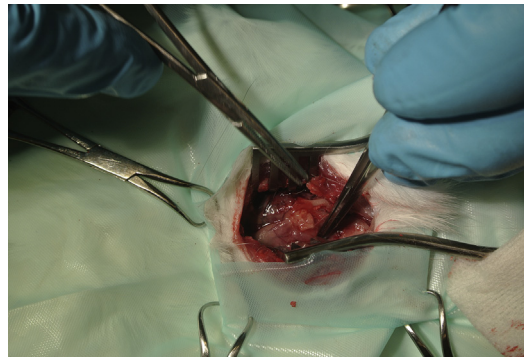

Fig. 20. In rabbits diagnosed with thymomas, a midline sternotomy may be performed to gain access to the thoracic cavity and enable optimal visualization of the tumor. (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

the best chances of removing the entire tumor and long-term control of the disease. However, recurrence has been reported.[79,87] In addition, surgery poses a high risk for perioperative and postoperative morbidity and mortality with reported survival rates varying between 25% and 50%.[79,80] If the decision is made to surgically excise the mass, a median sternotomy is the preferential route to be used, because this provides optimal access and visualization of the thoracic cavity for removal of the mediastinal mass. Owing to the high risks associated with surgery, and the tumor's sensitivity to irradiation, radiation therapy has received growing attention over the past years. Various authors have demonstrated good results of radiation therapy (**Fig. 21**) with resolution of clinical signs seen after 4 to 42 days and a median survival time of 1 to 2 years (range, <14 days to 3 years).[24] Complications that may be seen after the procedure included anesthetic-related death and radiation-induced alopecia, pneumonitis, pulmonary fibrosis, myocardial failure and thrombosis of the thoracic vessels.[24,80] To ameliorate these side effects, the use of nonsteroidal anti-inflammatory drugs or prednisone[b] may be considered.[80] In humans, chemotherapy protocols (eg, using octreotide, ifosfamide, or combinations of eg, cisplatin, doxorubicin, cyclophosphamide, and vincristine) have also been used with good success, with response rates of greater than 79% reported with certain protocols.[89] In rabbits, the use of doxorubicin was attempted in 1 rabbit diagnosed with thymoma, but after its administration the animal developed severe side effects (including anemia, weakness, and collapse), thereby resulting in a discontinuation of the treatment.[80] Aside from doxorubicin, chemotherapy using octreotide has also been attempted in 2 rabbits. Although initial results of this treatment were more promising, treatment in these animals also needed to be discontinued owing to the occurrence of side effects associated with the medication.[5]

Skin Neoplasia

Skin neoplasia can present in various forms (for an overview and description, see Kanfer and Reavill [2013]).[67] Two retrospective studies indicated between 20% to 35% of all submitted skin tumors to comprise trichoblastoma (previously referred to as basal

[b] Caution is warranted when using corticosteroids in rabbits owing their potential to induce immunosuppression, thereby rendering the rabbit susceptible to secondary infections. The risks and benefits should therefore be weighed carefully before making a decision whether or not to use these drugs.

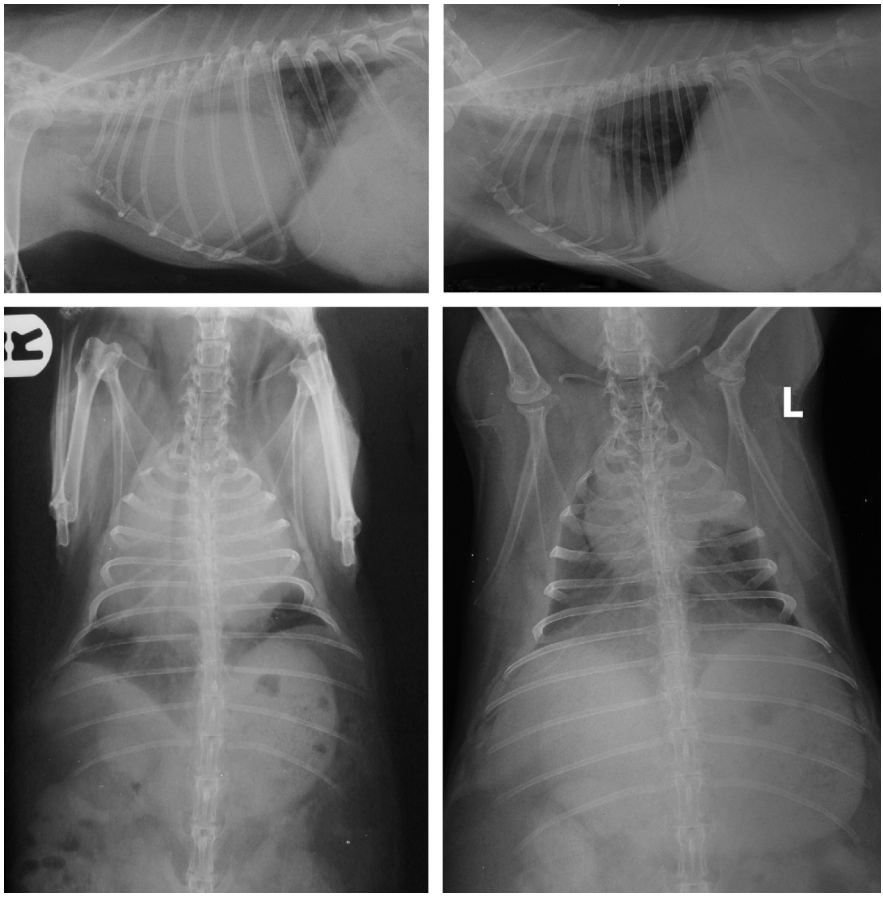

Fig. 21. Ventrodorsal and right lateral radiographs of a rabbit diagnosed with thymoma before (*left*) and after 10 sessions of radiation therapy (administered over a period of 3 weeks), showing a marked decrease in tumor size after treatment (*right*). The total dose of radiation used was 40 Gy. (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

cell tumors; **Fig. 22**).[58,90] Other tumors that were reported as common include collagen nevi (hamartomas), squamous papillomas, squamous cell carcinomas, melanomas, lipomas, and spindle cell sarcomas.[67,90]

Clinical signs

Skin neoplasia generally present themselves as solitary, well-circumscribed cutaneous or subcutaneous masses that are grossly visible to owners and often the reason for presentation to the veterinarian. Their appearance may vary, depending on the type of tumor involved. For example, tumors may be pigmented in case of trichoblastoma or melanoma or appear as wartlike growths in case of papillomas. Ulceration may also be seen. Skin neoplasia may be found anywhere on the body. However, predilection sites have been recognized for specific types of tumors (eg, ear, eyelid, toe, or genital area for malignant melanoma; head, neck, and limbs for trichoblastoma; and head and mucosa for papillomas).[67]

Fig. 22. Trichoblastomas, previously referred to as basal cell tumors, are the most common spontaneous skin tumors found in rabbits. Trichoblastomas can be found anywhere on the body, but the head, neck, and forelegs are favored locations. Generally, they comprise solitary, well-circumscribed tumors. However, they may become very large and ulcerated, as can be seen in this rabbit. (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

Diagnosis

Diagnosis of the type of skin neoplasia involved can usually be made using cytology of FNA or impression smears, or after histopathologic evaluation of excisional or incisional skin biopsies. In case of malignant tumors (eg, malignant melanoma, squamous cell carcinoma), FNA of regional lymph nodes and imaging (radiographs, ultrasound examination, CT imaging) may be considered to check for regional and distant metastases.

Treatment

The treatment of choice for most skin neoplasia is surgical excision. This may be curative in many cases, especially if the tumor is benign and/or wide margins are adhered. However, this may be challenging in small animals, thereby posing a risk for incomplete tumor removal and regrowth. Additional therapy may therefore be considered, depending on the type of tumor and presence of tumor-free margins. In case of tumor regrowth or incomplete excision, adjunct radiation therapy or (intralesional) chemotherapy may be considered. For small tumors (<1 to 2 cm), intralesional chemotherapy, cryotherapy, or photodynamic therapy may be considered as a standalone treatment modality. Prognosis will be highly dependent on the location and type of neoplasia involved.

Bone Neoplasia

Although bone neoplasia has been suggested to be rare in rabbits, in these last few years an increasing number of reports have been published on the presence of osteosarcomas in rabbits. Generally, this type of neoplasia will be found in middle-aged to older rabbits, but osteosarcomas have been diagnosed in rabbits as young as 1 year.[91] No sex or breed predilection has been reported. Osteosarcomas have been reported to affect both the axial (skull, spine, ribs; **Fig. 23**)[91–98] and appendicular (scapula, humerus, tibia, tarsus; **Fig. 24**) skeleton.[16,37,99,100] In addition, extraskeletal osteosarcomas have also been incidentally reported.[101,102] In comparison with dogs, whereby the appendicular skeleton is most commonly involved, osteosarcomas in rabbits seem to involve the facial bones (mandible, frontal bones) in the majority of cases.[100] Various subtypes of osteosarcomas have been reported, of which the

Fig. 23. A 5-year-old female lop-eared rabbit with a significant, painful swelling of the lower jaw, resulting in difficulty with eating. The tumor was diagnosed to be an osteosarcoma. (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

osteoblastic osteosarcoma is reported as the main type to be found in rabbits.[100] Other subtypes reported in rabbits include fibroblastic, giant cell, and poorly differentiated (osteolytic) osteosarcoma.[98,99,102] Similar to dogs, osteosarcomas metastasize rapidly, with multiple (micro)metastases present in the lungs and other tissues (eg, subcutis, pleura, peritoneum, pericardium, heart, liver, kidney, intestines) in more than 50% of animals at the time of diagnosis.[91,93,97,100]

Clinical signs

The clinical signs seen in rabbits with osteosarcoma will often depend on the area that is affected. Appendicular osteosarcomas often present as chronic, progressive lameness, often with a detectable swelling of one of the limbs.[16,37,99,100] Osteosarcomas in other locations also commonly present as a mass or swelling, which may be accompanied by other nonspecific signs, such as decreased appetite, dysphagia, and weight loss.[16,91,93,95,98] Pathologic fractures (**Fig. 25**), bleeding, fever, urine scald, and (severe) pain can also be noted.[16,99,100]

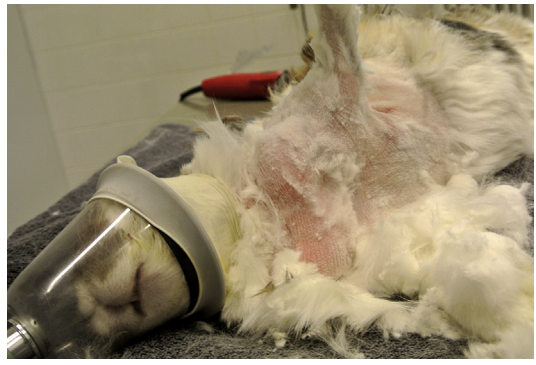

Fig. 24. Significant swelling of the humerus owing to the presence of an osteosarcoma. This rabbit also presented with severe lameness resulting from a pathologic fracture (see **Fig. 25**). (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

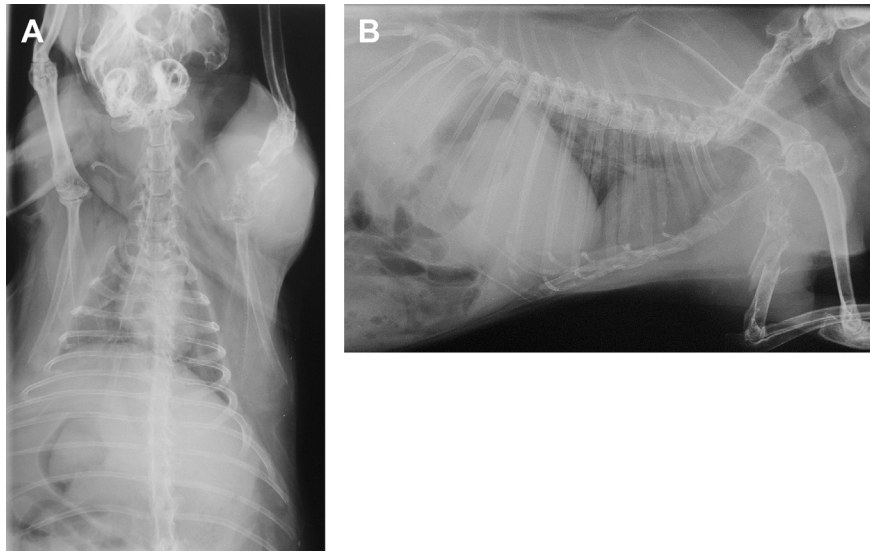

Fig. 25. (*A*, *B*) Ventrodorsal and left lateral radiographs of the rabbit from Fig. 24, showing the presence of both the neoplastic process and a pathologic fracture of the left humerus. (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

Diagnosis

Radiographs and other advanced imaging techniques (CT, MRI) will usually be helpful in establishing a tentative diagnosis. Radiographic findings may range from lytic to proliferative, sclerotic or mixed lesions.[16,91,95,97–100] In 2 rabbits with appendicular tumors, lesions were found to have crossed the joint space.[99,100] Aside from identifying bone abnormalities at the affected site, imaging is helpful to identify (pulmonary) metastases. Cytologic examination of FNAs has been found useful to obtain a definite diagnosis.[16,100] In case FNA is inconclusive, a histopathologic examination of the biopsied bone (including the use of specific immunohistochemical stains using antiosteocalcin monoclonal antibodies)[99,100] can be used for confirmation. Osteosarcomas have furthermore been associated with increased plasma alkaline phosphatase concentrations, resulting from bone production and remodeling.[16,93,97,99,100] Aside from diagnostic purposes, alkaline phosphatase may also serve as a prognostic indicator,[99] although currently no studies exist with regard to this aspect in rabbits.

Treatment and prognosis

Whenever possible, surgical removal of the tumor is considered most effective. In case of appendicular tumors, amputation of the affected limb is recommended,[16] to which rabbits generally respond favourably.[15,103] In case of tumors involving the mandible, partial mandibulectomy has been found successful.[104] If complete removal is not feasible, debulking surgery followed by radiation therapy or chemotherapy may be attempted. However, in many cases, (micro)metastases may already be present, thereby greatly diminishing the prognosis. Unfortunately, systematic studies into survival times of rabbits with osteosarcoma after surgical intervention (with or without adjunct therapy) are currently lacking. In rabbits with

confirmed metastases, palliative treatment using analgesic drugs (nonsteroidal anti-inflammatory drugs, opioids, gabapentin) or irradiation may be considered.

Renal Neoplasia

Renal neoplasia is occasionally found in rabbits. Although malignant tumors (eg, lymphoma, renal carcinoma)[3,105] may occur, benign embryonal nephromas are more commonly reported, especially in laboratory animals where it is the second most common tumor after uterine adenocarcinomas.[3,37,106] Embryonal nephromas have been found in both young and old rabbits, most commonly as an incidental finding during postmortem examinations.[3] Both single and multiple, unilateral or bilateral tumors have been found, with both kidneys being equally affected.[3] Embryonal nephromas are generally slow growing, with metastasis rarely occurring.[107]

Clinical signs

In many rabbits, the presence of renal tumors will go unnoticed, because they do not affect renal function. As a result, these tumors will mainly be diagnosed during postmortem examinations, representing as large whitish, well-circumscribed nodules of 1 to 2 cm in diameter, projecting above the cortical surface of the kidney.[3,108] Incidentally, secondary polycythemia may be present, resulting in hyperemic mucous membranes, lethargy, tachypnea, and exercise intolerance.[109–112] In addition, single or multiple masses in the kidney, or renomegaly, may be noted on abdominal palpation.[64,112]

Diagnosis

In most rabbits with renal tumors, diagnosis will be made postmortem. If an abdominal mass is palpated during a (routine) physical examination, ultrasonography and/or radiography may be helpful to diagnose where the mass originates from. A complete blood count may reveal a marked increase in erythrocytes, most likely resulting from increased erythropoietin production by the tumor.[109–112] Unfortunately, no validated tests exist to confirm these suspicions. Renal function will rarely be affected.

Treatment and prognosis

Treatment is usually not required in case of benign embryonal nephromas. However, in case of secondary polycythemia, resolution of the clinical signs may occur after nephrectomy.[109,112] Before surgery, intravenous urography may be considered to evaluate function of the contralateral kidney.[110,112] Nephrectomy may also be considered in rabbits with renal carcinomas after checking for the presence of metastases, which may be found in either the regional lymph nodes, contralateral kidney, liver, and/or lungs.[64] In these animals, as well as those with bilateral renal involvement, prognosis is generally considered poor, with chemotherapy not considered effective to treat these tumors in other species.[113]

Adrenal Neoplasia

Adrenal neoplasia has infrequently been reported in (older) rabbits, with male rabbits being overrepresented.[114–117] Both functional and nonfunctional adenomas and adenocarcinomas have been diagnosed.[114–118] Similar to ferrets, the disease has been associated with gonadectomy, whereby the loss of negative feedback from the gonads to the hypothalamic–pituitary axis leads to chronically increased plasma luteinizing hormone concentrations that exert a stimulatory effect on the synthesis and secretion of sex steroids by the adrenal gland.[119,120]

Clinical signs

Similar to functional adrenal tumors in ferrets, adrenal neoplasia in rabbits has been linked to increased sexual behavior and aggression. Clinical signs in these animals may include chasing, biting, mounting, and humping on various objects or people's legs.[114–117] In addition, urine spraying and fecal marking have been observed as well as aspecific signs of disease (ie, reduced appetite, weight loss).[114–117] Female rabbits may furthermore present with clitoral enlargement.[117] Nonfunctional adrenal tumors may go unnoticed until they may accidentally be discovered during a physical examination or on abdominal imaging.

Diagnosis

Diagnostic workup of rabbits with suspected adrenal neoplasia include hormone analysis, which may reveal elevated concentrations of sex hormones (ie, progesterone, 17-hydroxyprogesterone, testosterone).[114–117] Moreover, abdominal ultrasound may reveal an unilaterally or bilaterally enlarged adrenal gland.[114–117]

Treatment and prognosis

The treatment of choice for unilateral adrenal neoplasia is adrenalectomy, resulting in alleviation of the clinical signs.[116,117] Similar to ferrets, removal of the right adrenal gland may be challenging owing to the close association with the caudal vena cava,[117,121] whereas removal of the left adrenal gland may be complicated by the close association with the left renal vein.[116] In case of incomplete removal, recurrence of the clinical signs may be noted.[114] Medical management using gonadotrophin-releasing hormone agonists (leuprolide acetate, deslorelin) as well as other drugs used in the treatment of adrenal disease in other companion animals (ie, trilostane, finasteride, flutamide) have been attempted with variable

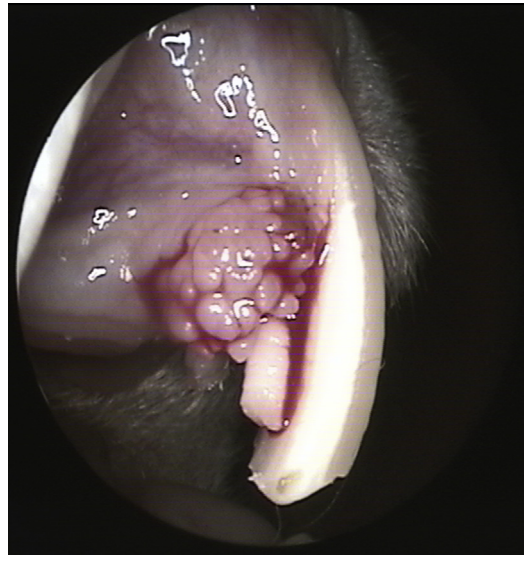

Fig. 26. Endoscopic view of an oral papilloma located just caudal to the upper incisors. Growth of these tumors may be induced by rabbit oral papillomavirus. (*Courtesy of* Evert-Jan de Boer, DVM, Dierenkliniek Wilhelminapark, The Netherlands.)

success.[116,117] More research will therefore be needed to evaluate the efficacy and safety of these drug therapies in rabbits. In case of adenocarcinomas, local metastases to the liver, duodenum, and periadrenal fat and connective tissue have been reported.[114,118]

Viral-Induced Tumors

In rabbits, viral-induced tumors have been reported. Viruses that are known to cause tumors in rabbits include Shope fibroma virus, Shope papilloma virus, or rabbit cutaneous papillomavirus, rabbit oral papilloma virus (**Fig. 26**), and myxomavirus (**Fig. 27**).[5,122–126] More information on the causative agents, routes of transmission, and clinical signs can be found in **Table 4**. In addition to the aforementioned viruses, a malignant rabbit fibromavirus has also been isolated. This virus is closely related to the Shope fibroma virus and the Moses strain of rabbit myxoma virus and presumably causes immunosuppression and malignant tumors.[127,128]

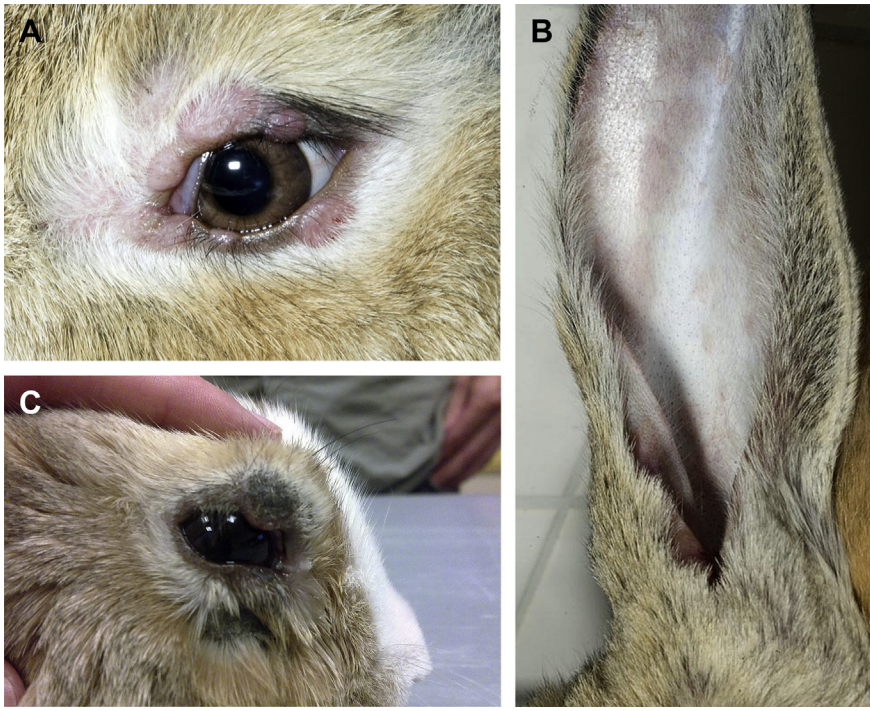

Fig. 27. Rabbit with myxomatosis, a virus from the family Poxviridae, causing a severe and fatal disease in pet rabbits (*Oryctolagus cuniculus*) in Europe. Rabbits with myxomatosis typically develop tumorlike lesions, so-called myxomas, on the eyelids (*A*), ears (*B*), and face, which may subsequently spread to the rest of the body. The virus furthermore induces a severe immunosuppression, rendering the rabbit susceptible to secondary infections (eg, Pasteurellosis) and associated mortality. Vaccination is generally effective to prevent the disease, but may, in rare instances, also result in the formation of self-limiting nodules (*C*). Unlike rabbits with clinical myxomatosis, these rabbits will remain bright, alert, and active, without signs indicative of systemic disease.

Table 4
Viral infections associated with tumor growth in rabbits

Virus	Family	Susceptible Species	Route of Transmission	Clinical Signs	Treatment	Prevention
Shope papilloma virus (also known as cottontail rabbit papillomavirus	Papovaviridae	Pet rabbits (*Oryctolagus cuniculus);* Cottontail rabbits *(Sylvilagus spp.*)	Biting insects; direct contact through skin trauma.	Wartlike, keratinous tumors on or around the head; large tumors may cause problems with food intake	Surgical resection (nodules may become malignant and develop into squamous cell carcinomas); lesions may also spontaneously regress after a few months.	Insect control
Rabbit oral papilloma virus	Papovaviridae	*O cuniculus*	Direct contact with infected rabbits; rabbits may become infected when suckling. Infection may remain latent until trauma of the oral mucosa allows papilloma development.	Oral papillomas; occasionally conjunctival or anal papillomas may also be seen. Generally affects rabbits 2–18 mo of age. May be asymptomatic as well.	Often no treatment indicated; lesions will often regress within 60 d.	Not applicable
Shope fibroma virus	Poxviridae	Wild rabbits (*Sylvilagus spp., Lepus spp.*)	Biting insects	Endemic disease in wild rabbits in North America; may sporadically cause disease in pet rabbits, resulting in fibromatous growths on feet, legs, face and back. Large growths (>7 cm) may interfere with eating and cause mobility problems. In immunocompromised or newborn rabbits, generalized fibromatosis may occur.	Tumors are benign and will usually resolve within 12–24 mo in wild rabbits and more rapidly in *Oryctolagus spp.* Supportive care may be required; surgical intervention may be considered if the size or position of the tumor inhibits normal functioning of the rabbit.	Vaccination (shope fibroma vaccine); insect control

Myxomavirus	Poxviridae	*Oryctolagus cuniculus; Sylvilagus brasiliensis, S bachmani*)	Biting insects or direct contact	Life-threatening systemic disease in *O cuniculus*: edema around the eyelids, nose and face, nodules on body face and legs 10–14 d after infection; high mortality rate associated with viremia and secondary infections. Virus causes mild cutaneous disease in *Sylvilagus spp.* (natural host). Rabbits that have been vaccinated may develop 'atypical myxomatosis' resulting in scabbing around the eyes and nose and multiple nodules over the body, which may regress over time.	Nodules may resolve in 3–4 wk in immunocompetent host. Supportive care, pain relief, and antibiosis may be indicated in affected rabbits. Euthanasia considered in severe cases. Generally no treatment needed for atypical myxomatosis; surgery may be considered if nodules are causing pain or distress to the animal.	Vaccination (bivalent myxomatosis/ rabbit hemorrhagic disease vaccine); Insect control
Malignant rabbit fibroma virus	Poxviridae	*O cuniculus*	Biting insects or direct contact	Rapidly progressing disseminated disease. Development of a large primary tumor with secondary tumors in the extremities including the nose, ears and feet. Tumors resemble myxosarcomas.	Often fatal disease owing to occurrence of metastases and immunosuppression leading to secondary infections (eg, pasteurellosis). Death often occurs within 12–24 d.	Insect control

Data from Refs.[5,122–128]

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