

## **AN OVERVIEW OF RECENT OSTEOSARCOMA CASES IN RABBITS (*Oryctolagus cuniculus*)**

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**ABSTRACT:** *Osteosarcoma is a condition affecting several species. In rabbits, it has been described to be relatively rare and to occur mainly in older animals. The condition is usually treated with surgery, but has a very poor prognosis. Chemotherapy and radiotherapy have been sporadically performed. The limited number of published cases makes it difficult to make sound conclusions about the epidemiology and treatment of the disease.*

*Additionally, no prospective studies have been conducted to assess treatment strategies. Ten additional cases published after 2010 are summarized in the current review. The information included is generally in line with previous reports. The condition occurs in*

*several breeds, in several locations in both the axial and appendicular condition. There were frequent pulmonary metastasis and diagnosis was usually made with radiography. Rabbit OSA is usually treated with surgery, with a poor prognosis.*

*This means further research is needed to get further insights into the epidemiology and novel treatment strategies.*

*Conclusively, recent cases of rabbit OSA mainly supports information from previous case reports. However, the body of literature is still very limited. This makes it difficult to make sound conclusions and warrants further research in the epidemiology and treatment of the condition.*

**Keywords:** *Osteosarcoma, Rabbits, Cases, Research*

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## **INTRODUCTION**

Osteosarcoma (OSA) are bone cancers that have been described in several species such as humans (**Jafari et al., 2022**), dogs (**Szewczyk et al., 2015**), cats (**Heldmann et al., 2000**) and rabbits (**Mazzullo et al., 2004**). Depending on the species, OSA can have specific characteristics (such as site of occurrence), while its biological behaviour can also be similar between species (**Fan and Khanna, 2015**).

In rabbits, OSA occurs mostly in older animals (**Mazzullo et al., 2004; Ishikawa et al., 2012; van Zeeland, 2017**), although cases in young animals have also been described (**Mazzullo et al., 2004**). It has been

mentioned that there is no predisposition of a certain sex or breed in rabbit OSA (**van Zeeland, 2017**). The condition can occur in both the axial (**Mazzullo et al., 2004**) and appendicular skeleton (**Higgins et al., 2015**). Extraskkeletal cases have also been reported (**Wijesundera et al., 2013**).

Diagnosis of rabbit OSA is often based on imaging, including radiography (**Weiss and Müller, 2011; van Zeeland, 2017**). Clinical signs depend on the specific location of the tumour, but can include swelling and lameness (**van Zeeland, 2017**). When possible, surgery has been performed to treat rabbit OSA (**Higgins et al., 2015**). Chemotherapy and radiotherapy have also been used (**van Zeeland, 2017**). The same authors added that OSA has been described to occur infrequently in rabbits. A 2012 case report including a literature review only identified 11 cases (**Ishikawa et al., 2012**). However, it has been noted that the condition may be underreported in the literature (**Renfrew et al., 2001**).

No comprehensive review has been published on recent cases of rabbit OSA, despite further knowledge being required to optimize treatment strategies for the condition and better understand its epidemiology.

Therefore, the current review aims to summarize important aspects of cases of rabbit OSA published in 2010 or later.

### ***Search strategy***

On the 15<sup>th</sup> of October 2022, the Med Line database was searched with search strings consisting of several combinations of the following terms: “rabbit”, “osteosarcoma” and “bone cancer”. Filters were used to limited the results to publications from 2010 or later. A similar strategy was used to search the Google Scholar database. The Google search engine was used to look for additional articles. Additionally, there was a manual search of the literature published in World Rabbit Science and Egyptian Journal of Rabbit Science. Finally, the reference lists of papers of interest was screened for further eligible literature.

The abstracts of potentially eligible publications were read to assess whether they met inclusion criteria. Papers were included if: (1) they described at least one case of rabbit osteosarcoma, (2) at least minimal data was included about animal and tumour characteristics, (3) the tumour occurred spontaneously (*e.g.* not induced experimentally), (4) they were written in English, (5) the full text could be sourced and (6) they were published in 2010 or later.

### ***Identified literature***

A relatively small amount of new cases of rabbit osteosarcoma was published since 2010 (Table 1). Seven case reports were identified (**Gibson and Donnelly, 2011; Weiss and Müller, 2011; Ishikawa et al., 2012; Wijesundera et al., 2013; Higgins et al., 2015; van Praag, 2015;**

Table 1: Included case of rabbit osteosarcoma with extracted information

Reference	Age	Breed	Wt	Sex	LPT	Metastasis	Symptoms	Diag. Tech	Treatment	Outcome
Gibson and Donnelly, 2011	18 months	NZW	2.3 kg	Fe	Proximal aspect right femur	Lungs	Anorexia Decreased urine output Decreased stool output Right hind limb lameness	Radiography	None	Euthanized
Wicks and Miller, 2011	2 years	Not specified	1.2 kg	M	Spine	None identified	Angular <del>dermatitis</del> Dermatitis Abscess of pelvic limb Swelling dorsal sacral region Atrophy pelvic limb muscles	Radiography	None	Euthanized
Ishikawa <i>et al.</i> , 2012	7 years	Cross breed	2.6 kg	Fe	Tarsal joint region involving distal tibia	Pulmonary <del>metastases</del> None in liver	Blistering in tarsal region right hind limb Swelling in tarsal region right hind limb	Radiography	Mass excision (CO <sub>2</sub> -laser)	Died 3 days post-surgery
Wijesundera <i>et al.</i> , 2013	9 years	Mixed	1.8 kg	M	Subcutaneous in left forelimb (scapulothoracic)	None	Haemorrhage & edema around left forelimb (initial) Ulcerating mass at scapular site (2 months after resection)	Radiography	Surgical removal (primary tumour) Amputation of limb one month after recurrence	Recurrence 2 months after resection Alive
Higgins <i>et al.</i> , 2015	8 years	mini mix use Rex	1.7 kg	M	Tibia or fibular head	No evidence of pulmonary metastases at presentation No evidence of metastases 4 months after amputation No evidence of metastases 6 months after amputation	Lameness Atrophy left pelvic limb musculature	Radiography Fine needle aspiration	Pre-amputation: tenotomy, meloxicam, gabapentin Amputation of limb after three days	Active 2 weeks after operation Died 190 days after surgery from secondary <del>gastric</del> gastric bleed

Continue Table 1										
Reference	Age	Breed	Wt	Sex	LPT	Metastasis	Symptoms	Diag. Tech	Treatment	Outcome
van Praag 2015	1 year	Rat	Not mentioned	Fe	Periaortic lymphatic metastatic base	Multiple abdominal chest and pulmonary metastases	Lameness Paresis of hind limbs	Radiography Biopsy	None mentioned	Enhanced
Mitchkins <i>et al.</i> , 2020	8 years, 9 months	Long-eared	19 kg	M	Intercostal <del>osteosarcoma</del> Septate pulmonary neoplasms	None (from primary tumor) Septate pulmonary neoplasms	Enlargement of left eye Exophthalmos Respiratory failure	None	None mentioned	Died due to respiratory failure (from pulmonary neoplasms)
Mina <i>et al.</i> , 2019	4 years	Mixed	Not mentioned	M	Mandibular gingiva	Pulmonary metastases	Not mentioned	Computed tomography	Pedal amputation (Primary) Hemicoardiectomy (Panence)	Died 4 months after diagnosis
Mina <i>et al.</i> , 2019	4 years	Lion-headed	Not mentioned	M	Mandibular gingiva	Pulmonary metastases	Not mentioned	Radiography	Laser resection (Primary) Radiation (Panence)	Died 45 months after diagnosis
Mina <i>et al.</i> , 2020	7.2 years	Not mentioned	Not mentioned	M	Intercostal	Not mentioned	Nasal discharge	Radiography	Rhinectomy	Unknown

Fe: Female; M: Male; NZW: New Zealand White; Wt: Weight; LPT: Location primary tumour; Diag. Tech: Diagnostic techniques

**Makishima et al., 2020**). Additionally, two case series of oral and intranasal tumours showed one and two cases of osteosarcoma, respectively (**Miwa et al., 2019; Miwa et al., 2020**). This meant the total number of identified cases was ten. There were no case-control or cohort studies published after 2010 about the condition. Furthermore, no studies comparing therapeutic interventions were available.

***Case characteristics:***

Several breeds of rabbits were mentioned in the case reports, including New Zealand White (**Gibson and Donnelly, 2011**) and Rex breeds (**van Praag, 2015**). Due to the small number of reports, it is difficult to assess whether specific breeds have a predisposition for OSA. However, the wide variety of breeds reported could suggest that these tumours can occur in all rabbit breeds. Seven out of ten cases occurred in male rabbits.

The average age of the rabbits in the cases include was 5.25 years, but ranged from 18 months to 9 years. In the included cases, three animals were very young (**Gibson and Donnelly, 2011; Weiss and Müller, 2011; van Praag, 2015**). This is contrast to the general belief that OSA occurs mainly in older rabbits. The small amount of cases however means it is difficult to draw conclusions. Further research is warranted regarding a potential link between age and developing OSA.

The weight of the animals with OSA in the included cases ranged from 1.2 to 2.6 kg. No previous assessments have been made regarding a link between weight and OSA risk in rabbit, but such a link has been described in dogs (**Boerman et al., 2012**). Based on the information currently available, it is not possible to make conclusions about the situation in rabbits. Further research could compare the normal weight range in different rabbit breeds and compare this to the weight of individuals suffering from OSA.

***Disease characteristics, treatment and outcomes:***

OSA occurred at several locations, including the femur (**Gibson and Donnelly, 2011**), spine (**Weiss and Müller, 2011**), tarsal joint (**Ishikawa et al., 2012**) and mandibular gingiva (**Miwa et al., 2019**). This confirms previous statements that canine OSA can occur in both the axial and appendicular skeleton (**van Zeeland, 2017**). Additional extraskeletal cases were also identified (**Wijesundera et al., 2013; Makishima et al., 2020**).

The described symptoms varied between the different case reports. Bleeding, swelling and lameness were described in several cases. This is expected since symptoms can vary according to the location of the primary tumour. Future research could define which symptoms can occur across different tumour locations and which symptoms are linked to disease in

certain locations. This can also aid the development of treatment directed to mitigate location-specific symptoms.

Metastases were reported in six cases. In the overwhelming majority, these metastases occurred in the pulmonary system. This in line with previous reports (**Ishikawa *et al.*, 2012**). Therefore, presence of pulmonary metastases should be included in the clinical examination and be included as a subject of potential future research in novel treatment strategies.

Radiography was utilized in almost all cases where diagnostic imaging was performed. In one report, computed tomography was performed (**Miwa *et al.*, 2019**). In selected cases, a biopsy or fine needle aspiration was performed (**Higgins *et al.*, 2015; van Praag, 2015**).

In six cases, surgery was performed to remove at least part of the tumour. In the other cases, no treatment was mentioned, which may suggest that these rabbits did not actually receive treatment. No reports of chemotherapy or radiotherapy were made. These results mean there is still a large opportunity for further research in the treatment of rabbit OSA.

Unfortunately, a large proportion of animals were either euthanized or died from complications from the disease. This usually happened within months of the diagnosis. Only one animal was described as being alive (**Wijesundera *et al.*, 2013**).

#### ***Future research:***

The amount of literature available on rabbit OSA is very limited. Additionally, only case reports and series are available, which means that the evidence is of relatively low quality. Therefore, further research is urgently needed. It is important that more cases are published about this condition. The epidemiology of rabbit OSA is poorly understood. Large, multi-institutional retrospective studies should be performed to assess possible correlations between factors such as breed, age, sex and medical history and OSA occurrence and prognosis.

Currently, surgery is the main treatment strategy performed in rabbit OSA. Effective surgical methods should be developed and tested for OSA occurring in different regions. Additionally, research is needed to assess whether combination between surgery and (neo) adjuvant chemotherapy and radiotherapy is effective. Furthermore, the use of chemotherapy and radiotherapy as standalone treatment should be explored in OSA not amenable to surgery.

***Conclusively***, recent cases of rabbit OSA mainly supports information from previous case reports. However, the body of literature is still very limited. This makes it difficult to make sound conclusions and warrants further research in the epidemiology and treatment of the condition.

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