

Case report

ORTHOVOLTAGE X-RAY THERAPY OF LARGE CELL INVASIVE NASAL LYMPHOMA IN CAT

Alexander ROGACHEV¹, Alexey GAZIN¹, Yuliia ZUENKOVA^{2*}

¹Biocontrol veterinary clinic, 115522, Kashirskoje avenue, 24/10, Moscow, Russian Federation;

²FGAOU VO Peoples' Friendship University of Russia. Address: 117198, Russian Federation, Moscow, st. Miklukho-Maklaya, 6

(Received 09 September, Accepted 15 December 2022)

Feline nasal lymphoma is generally a localized radiosensitive tumor. Treatment options include radiation therapy, chemotherapy, or a combination of both modalities. Radiation therapy (RT) in a combination with chemotherapy lead to median survival from 19 months to 955 days. The objective of this paper is to report a case of a large cell late stage invasive feline nasal lymphoma and to evaluate the results of orthovoltage radiation therapy and its side effects. A 12-year-old female mixed breed cat was presented with nasal discharge, sneezing and hyporexia. Definitive histopathology diagnosis was diffuse large cell lymphoma. Computed tomography revealed an advanced stage of the disease, an intranasal mass, bone lysis, invasion of the orbital space and central nervous system. A radical course of X-ray therapy was performed (SFD = 4 Gy, TSD = 40 Gy, 10 sessions, 3 times a week). Radiation side effects were well tolerated and resolved with supportive treatment. Lymphoma is a systemic process and requires a multidisciplinary approach. On most cases, the penetrating ability of radiation therapy of 3.5 cm in depth is enough for small domestic animals. A significant effect is noted in the middle of the treatment course. The fractionated regime did not cause early radiation damage. The relapse-free period was up to 8 months. The patient had a satisfying quality of life for 5 months. Orthovoltage X-ray therapy can be considered as a treatment choice for local nasal lymphoma. X-ray therapy is a widely used modality in veterinary medicine considering the price of machines and costs of treatment.

Keywords: orthovoltage X-ray therapy, feline, veterinary oncology, nasal lymphoma, radiation therapy.

INTRODCUTION

Lymphoma is the most common oncological disease in cats, accounting for approximately 90% of all hematopoietic neoplasms, and is generally a solitary and radiosensitive tumor [1-3]. Nasal lymphoma is relatively rare, accounting for 1-8.4% of all tumors in cats [4,5]. Lymphomas are typically radiosensitive tumors in humans,

*Corresponding author: e-mail: zuenkova@bk.ru

dogs and cats [6-9]. Chemotherapy was usually considered as a priority treatment in feline nasal lymphoma, because it is generally a systemic disease [10].

Previous larger studies of cats with nasal lymphoma that were treated with chemotherapy alone reported to have a median survival time (MST) ranging from 98 to 456 days [11]. Meanwhile, radiation therapy (RT) is a treatment of choice for localized forms of lymphomas [12,13]. Cats with nasal lymphoma treated with a combination of local radiation therapy and systemic chemotherapy had a MST from 174 to 955 days [8]. A large retrospective study by Haney et al. of 97 cats with nasal lymphoma showed that the response rate for radiation therapy alone was 93% with a median survival time (MST) of 456 days [8]. IAEA developed guidelines on the safe use of radiation for imaging and treatment in veterinary medicine with the objective of ensuring safety and radiation protection of workers and members of the public [14].

Results of previous studies suggest that the addition of higher doses of RT to a cat's treatment protocol may control the localized disease and therefore influence survival [8]. The addition of any RT to a cat's protocol was evaluated for influence on survival, and was found to significantly improve overall survival. There were no differences in survival among the cats treated with different machine energies (orthovoltage versus Cobalt-60 versus 4- or 6-MV linear accelerators) [8].

The objective of this paper is to report a case of a large cell late stage invasive feline nasal lymphoma and evaluate the results of orthovoltage radiation therapy and its side effects.

CASE PRESENTATION

A 12-year-old female mixed breed cat (domestic housing) was presented with nasal discharge, sneezing and hyporexia (Figure 1). The clinical signs were present from May 2021 and were getting worse.

Computed tomography (CT) and rhinoscopy in August 2021 revealed advanced disease with intranasal mass, bone lysis, invasion of the orbital space and central nervous system. According to the results of the examination, a neoplasm of the left nasal passage with invasion into the orbit of the eye and the latticed bone was found (Figure 2).

Histological examination (pinch biopsy 3-18 mm of the nasal cavity) confirmed the diagnosis of large-cell lymphoma (Figure 3). The excisional biopsies were fixed for 24 hours in 10% neutral buffered formalin, afterwards they underwent standard histological treatment (using isopropyl alcohol as a dehydrating and clarifying agent), as a result of which histological preparations with a thickness of 4 microns stained with hematoxylin-eosin were obtained according to the manufacturer's instructions. A multi-focal subepithelial infiltrative high-cell neoplasm consisting of layers of large rounded cells (2 or more erythrocyte diameter) was suppressed. Tumor cells have a small amount of cytoplasm, a pleomorphic rounded large nucleus with granular

chromatin and more often with 1 central nucleole. Infiltration by small lymphocytes and neutrophils is represented multilocally intratumorally. The sites of necrosis are represented multilocally. Prednisone was prescribed 5 mg 1/2 once per day, Endoxane 50 mg 1/3 tablet 1 time every 3 days. The administered treatment led to positive dynamics and stabilization of the disease.

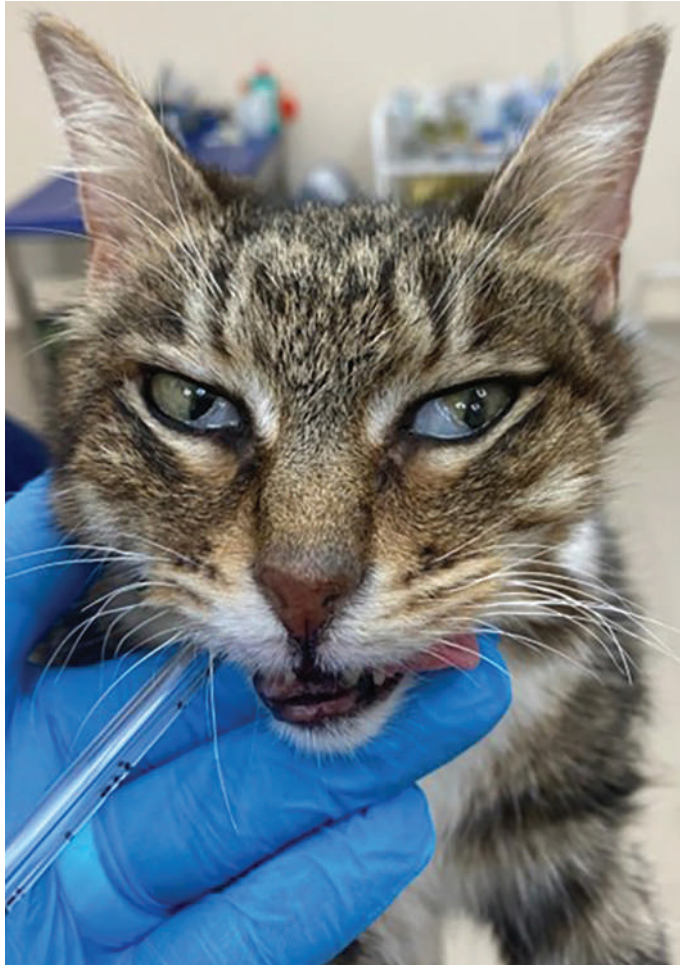


Figure 1. Patient's appearance at admission

After 2 months from the start of treatment, minor discharge from the nasal passages and sneezing appeared (rhinotracheitis was not excluded). Doxycycline (10mg/kg) was prescribed, and the symptoms stopped.

In February 2022, nasal discharge and decreased appetite resumed again. The first control CT scan and biopsy were performed (Figure 4). CT-signs of neoplasms of the left and nasal passages with invasion of the latticed bone were recorded.

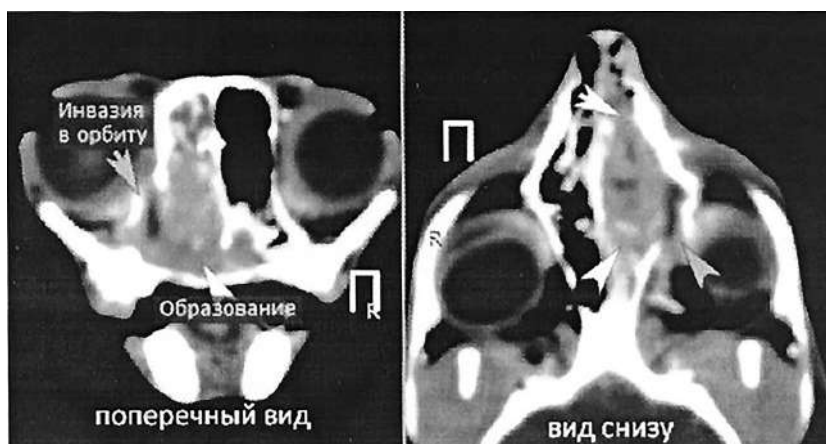


Figure 2. CT investigation axial (left) and coronal (right) view

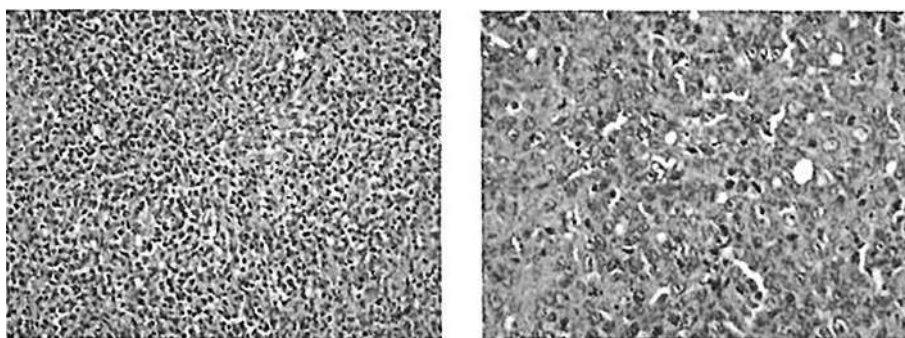


Figure 3. Histologic examination of the nasal cavity tissues

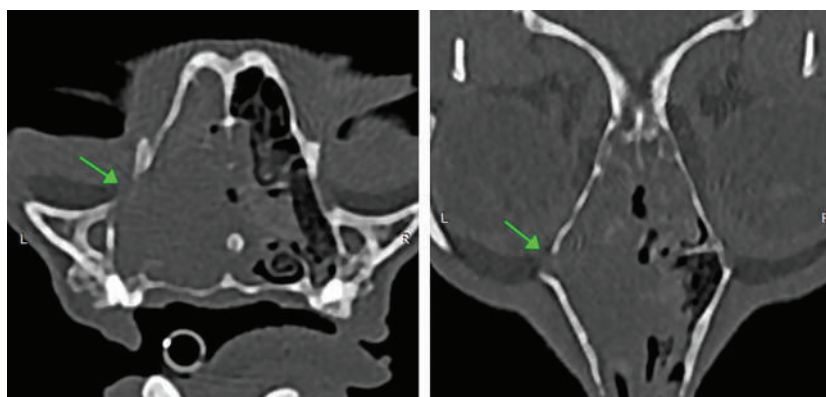


Figure 4. Control CT images transversal (left) and ventral (right) view

The patient received an appointment with an oncologist on 22.02.2022. Endoxan was cancelled and a radiotherapist consultation was recommended.

A radical course of orthovoltage X-ray therapy (Xstrahl300, Great Britain) was recommended in the mode of ROD 4 Gy 3 times per week up to SOD of 40 Gy was reached. A 6x6 cm applicator, ionizing radiation filter №9 (Cu 3.0mm) was used. Protection of the right eyeball was carried out with a lead block (2mm) (Figure 5).



Figure 5. Applicator 6x6 cm treatment (left) and eyeball protection with a lead block (right)

Anesthesia

Introductory anesthesia was performed with Propofol, supportive anesthesia was with isoflurane gas. Intubation with a 4.0 mm endotracheal tube was performed to ensure airway patency. During anesthesia, ECG, saturation and blood pressure were monitored. There were no deviations during the course.

Course of treatment

A moderate degree of leukopenia $3.48 \times 10^9/L$ was observed in the incoming clinical blood test (Figure 6).

Dynamic monitoring was prescribed during the course of therapy. Before carrying out the 4th fraction, a control analysis was performed. Leukocytosis was detected $18.9 \times 10^9/L$ (Figure 7) as an inflammatory reaction that appeared in the tumor during the treatment.

The antibiotic Synulox 50 mg was prescribed (1/2 tablet 2 times a day) until the end of the course.

After the 4th fraction, the oncologist was re-admitted and Sorafenib 1/10 tablet was added to the scheme 2 times a day, as well as Maltofer due to the borderline hemoglobin index.

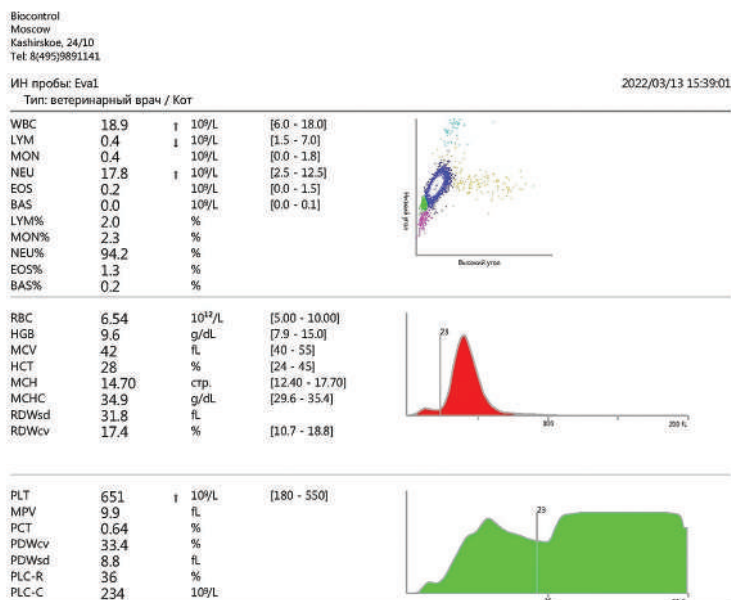


Figure 6. Results of the biochemical blood analysis before radiotherapy

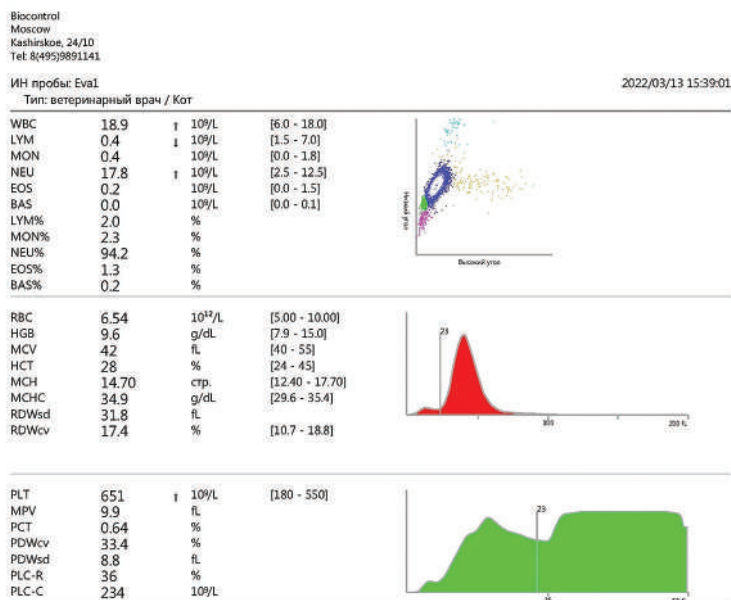


Figure 7. Results of the biochemical blood analysis during the radiotherapy treatment after 3 fractions

Before the 7th fraction, a control clinical blood test was performed, the indicators stabilized (Figure 8).

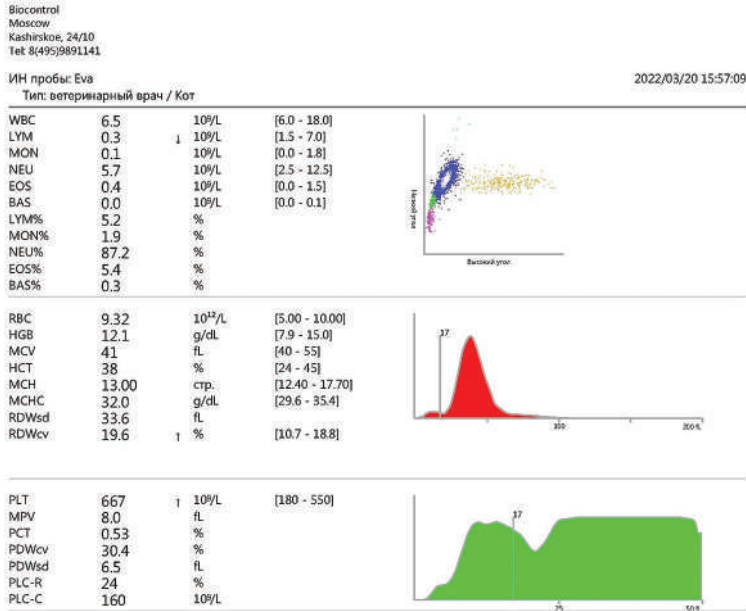


Figure 8. Results of the biochemical blood analysis during the radiotherapy treatment after 6 fractions

Further, the course continued without complications, after the 10th fraction, the patient was discharged with a recommendation to perform a CT scan of the head 3-4 weeks after the end of the course.

Observation after therapy

After 3 weeks, a CT scan of the skull was performed, the result of which revealed a significant regression of the neoplasm (Fig. 9).

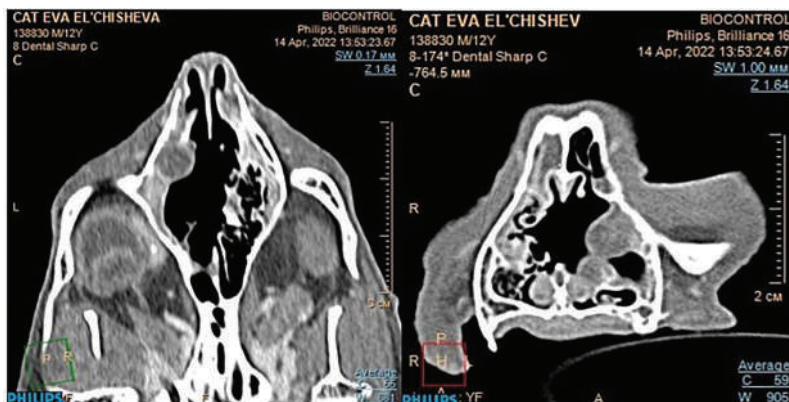


Figure 9. CT scan of the skull 3 weeks after treatment (horizontal profile - left) and (vertical profile - right)

CT demonstrated a picture of bilateral rhinitis, the area of locally thickened nasal mucosa on the left probably corresponds to rhinitis (the residual volume of formation cannot be completely excluded) (Fig. 9). At a checkup by an oncologist after 3 weeks no discharge from the nose detected and appetite was partially restored.

At a follow-up examination by an oncologist after 5 weeks a purulent discharge from the nose was found, while lymph nodes were normal. The appetite was poor, forced feeding recommended. Symptoms of renal failure presented: creatinine 207 mmol/l and leukopenia $2.9 \times 10^9/L$.

Prescribed treatment:

1. Physiological solution subcutaneously 50 ml 1 time in 2 days;
2. Prednisone 10 mg (0.3 ml);
3. Synulox 50 mg 1 tablet 2 times a day;
4. Heptral 150 mg 1/4 tablet 1 time a day;
5. Mirtazapine (Calixta) 30 mg 1/15 tablet 1 time a day for 5-7 days;
6. Renal advance according to the instructions.

A follow-up examination by an oncologist in 7 weeks showed a positive trend. Appetite was restored, purulent discharge decreased, creatinine decreased down to 150 mmol/l. Leukocytes increased to $4.5 \times 10^9/L$.

The progression of the disease is noted 3 months after the end of the radiotherapy course. While there was no discharge from the nasal passages and appetite was normal a new single formation caused suspicions about metastases to the lungs. For this the CT scan was performed (Figure 10). Left and middle pictures are free from metastases, while the right one depicts one. No biopsy was performed.

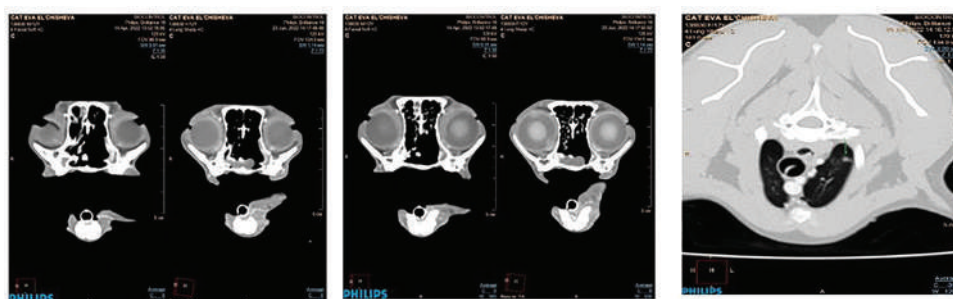


Figure 10. Lung CT after 3 months of radiotherapy (Axial section of lungs)

After 4 months, serous outflows from the nasal passages were observed. There was no discharge from the eyes. Lymph nodes were normal. Patient's follow-up is continuing.

DISCUSSION

Lymphoma is a systemic process and requires a multidisciplinary approach and close monitoring by the oncologist, radiologist and other professionals. In many cats, the FeLV antigen is detected. Prednisolone is a routine pre-treatment practice for cats due to the lymphoma cell sensitivity [15].

On most cases a penetrating ability of 3.5 cm in depth is enough for small domestic animals, providing a sufficient therapeutic effect with the low risk of late radiation reactions from the skull bones. A significant effect is noted usually in the middle of the treatment course. The fractionated regime (SFD = 4 Gy, TSD = 40 Gy, 10 sessions, 3 times a week) was chosen to avoid the risk of complications from general anesthesia. The fractionated regime did not cause early radiation damage to the skin, even alopecia. The lens falling into the irradiation zone may become cloudy and lose its functionality, but no such changes were detected when examined by an ophthalmologist in this patient.

There was a complication in the form of purulent conjunctivitis, but there is no data for the involvement of radiation therapy, because both eyes were affected and not only the one that was in the irradiation zone. Against the background of treatment with Floxal for 10 days, the expiration stopped.

Treatment of this pathology should always be accompanied by the use of prednisone. In the case of manifestations or insufficient response to orthovoltage X-ray as a monotherapy, it is necessary to add chemotherapeutic drugs to the treatment. According to the experience of Biocontrol clinic, the relapse-free period after irradiation is about 5-8 months without the use of chemotherapy. The patient demonstrates a satisfactory quality of life for 5 months, despite the continued growth of the neoplasm.

CONCLUSION

Orthovoltage X-ray therapy can be considered as a treatment choice for local nasal lymphoma. The penetrating ability of the orthovoltage X-ray with energies of 40-320kV is up to 10 cm while the therapeutic effect of 3.5 cm in depth is enough for small domestic animals.

Orthovoltage X-ray therapy is a widely used modality in veterinary medicine and often becomes a modality choice instead of megavoltage units considering the price of machines and costs of treatment [16]. The simplicity of the modality provides wide opportunities for its integration into veterinary clinical practice and forecasting the patients flow [17].

Ethical approval

No ethical approval was obtained because this study did not involve laboratory animals and only involved non-invasive procedures. Informed consent by the owner for all appropriate use in scientific and educational purposes has been received (see the doc. Inform Consent, Clause 5).

Author's contributions

AR contributed to the conduct of the experiment, critical revision of the manuscript, and literature review. AG performed pathomorphological investigation and critically revised the manuscript. YZ performed the literature review, developed the concept of the paper, and wrote it. All authors read and approved the final manuscript.

Declaration of conflicting of interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Statement of Informed Consent

The owner understood procedure and agrees that results related to investigation or treatment of their companion animals, could be published in Scientific Journal Acta Veterinaria-Beograd.

REFERENCES

1. Allen HS, Broussard J, Noone, K: Nasopharyngeal diseases in cats: a retrospective study of 53 cases (1991-1998). *J Am Anim Hosp Assoc* 1999, 35:457-461.
2. Henderson SM, Bradley K, Day MJ, Tasker S, Caney SM, Hotston Moore A, Gruffydd-Jones TJ: Investigation of nasal disease in the cat--a retrospective study of 77 cases. *J Feline Med Surg* 2004, 6(4):245-257.
3. Mukaratirwa S, van der Linde-Sipman JS, Gruys E: Feline nasal and paranasal sinus tumours: clinicopathological study, histomorphological description and diagnostic immunohistochemistry of 123 cases. *J Feline Med Surg* 2001, 3(4):235-245.
4. Madewell BR, Priester WA, Gillette EL, Snyder SP: Neoplasms of the nasal passages and paranasal sinuses in domesticated animals as reported by 13 veterinary colleges. *Am J Vet Res* 1976, 37(7):851-856.
5. Cunha SC, Corgozinho KB, Ferreira AM: Treatment of two cats with advanced nasal lymphoma with orthovoltage radiation therapy and systemic chemotherapy. *Acta Sci Vet* 2016, 44(Suppl 1):180.
6. Axiak SM, Carreras JK, Hahn KA, Endicott MM, Parshley DE, King GK: Hematologic changes associated with half-body irradiation in dogs with lymphoma. *J Vet Intern Med* 2006, 20(6):1398-1401.

7. Berlato D, Schrempp D, Van Den Steen N, Murphy S: Radiotherapy in the management of localized mucocutaneous oral lymphoma in dogs: 14 cases. *Vet Comp Oncol* 2012, 10(1):16-23.
8. Haney SM, Beaver L, Turrel J, Clifford CA, Klein MK, Crawford S, Poulson JM, Azuma C: Survival analysis of 97 cats with nasal lymphoma: a multi-institutional retrospective study (1986-2006). *J Vet Intern Med* 2009, 23(2):287-294.
9. Wilder RB, Rodriguez MA, Tucker SL, Ha CS, Hess MA, Cabanillas FF, Cox JD: Radiation therapy after a partial response to CHOP chemotherapy for aggressive lymphomas. *Int J Radiat Oncol Biol Phys* 2001, 50(3):743-749.
10. Nakazawa M, Tomiyasu H, Suzuki K, Asada H, Fujiwara-Igarashi A, Goto-Koshino Y, Ohmi A, Ohno K, Fujita M, Tsujimoto H: Efficacy of chemotherapy and palliative hypofractionated radiotherapy for cats with nasal lymphoma. *J Vet Med Sci* 2021, 83(3):456-460.
11. Taylor SS, Goodfellow MR, Browne WJ, Walding B, Murphy S, Tzannes S, Gerou-Ferriani M, Schwartz A, Dobson JM: Feline extranodal lymphoma: response to chemotherapy and survival in 110 cats. *J Small Anim Pract* 2009, 50(11):584-592.
12. Sfiligoi G, Théon AP, Kent MS: Response of nineteen cats with nasal lymphoma to radiation therapy and chemotherapy. *Vet Radiol Ultrasound* 2007, 48(4):388-393.
13. Williams LE, Pruitt AF, Thrall DE: Chemotherapy followed by abdominal cavity irradiation for feline lymphoblastic lymphoma. *Vet Radiol Ultrasound* 2010, 51(6):681-687.
14. International Atomic Energy Agency, Radiation Protection and Safety in Veterinary Medicine, Safety Reports Series No. 104, IAEA, Vienna, 2021.
15. Hlavaty J, Ertl R, Mekuria TA, Rütgen B, Tsujimoto H, Walter I, Wolfesberger B: Effect of prednisolone pre-treatment on cat lymphoma cell sensitivity towards chemotherapeutic drugs. *Res Vet Sci* 2021, 138:178-187.
16. Zuenkova J, Izurov L: Forecasting the kilovoltage therapy unit with the mathematical model. *RAD Conf Proc* 2020, 4:7-10.
17. Zuenkova YA: Analysis of the technical characteristics of X-ray therapy systems and the potential for their further improvement. *Biomed Eng* 2022, 55(5):370-374.

ORTOVOLTAŽNA TERAPIJA X-ZRACIMA INVAZIVNOG NAZALNOG *LARGE CELL* LIMFOMA MAČAKA

Alexander ROGACHEV, Alexey GAZIN, Yuliia ZUENKOVA

Nazalni limfom felida je uopšteno govoreći lokalizovani tumor, osetljiv na radijacionu terapiju. Opcije terapije obuhvataju radijacionu terapiju, hemioterapiju ili kombinaciju ove dve metode. Radijaciona terapija (RT) u kombinaciji sa hemioterapijom dovodi do preživljavanja u periodu od 19 meseci do 955 dana. Cilj rada je bio da se prikaže slučaj nazalnog limfoma velikih ćelija, kod mačke u kasnom stadijumu bolesti i evaluacija rezultata ortovoltazne radio terapije kao i postrani efekti tretmana. Na prijemu, mačka, mešanac stara 12 godina sa simptomima nosnog iscedka, suzenja i hipopoksijom. Konačna histopatološka dijagnoza bila je difuzni *large cell* limfom. Kompijuterska

tomografija je otkrila da se radi o uznapređovalom stadijumu oboljenja, sa prisustvom tumorskih tvorevina u nosu, lizom kostiju, invazijom orbita i centralnog nervnog sistema. Obavljena je terapija X-zracima (SFD=4Gy, TSD=40Gy, 10 ciklusa, tri puta nedeljno). Životinja je dobro podnela prateće efekte radijacione terapije uz potpurnu terapiju. Uopšteno govoreći, limfomi predstavljaju sistemski patološki proces koji zahteva multidisciplinarni prilaz. U većini slučajeva, penetrirajuća sposobnost radijacione terapije je u dubini od 3.5 cm i dovoljna je u slučaju malih životinja. Značajni efekti terapije su mogli da se uoče na sredini perioda tretmana. Frakcionisani režim tretmana nije izazvao rana oštećenja usled radijacije. Period slobodan od relapsa, bio je do 8 meseci. Pacijent je imao zadovoljavajući kvalitet života u periodu vremena od 5 meseci. Ortovoltazna terapija X zracima, može da se smatra kao tretman izbora u slučaju lokalizovanih nazalnih limfoma. Terapija X zracima je široko prihvaćena u veterinarskoj medicini imajući u vidu cenu aparata kao i cenu tretmana.