Preliminary results of intratumoral injections with radioactive holmium microspheres in dogs and cats with soft tissue sarcoma

M.N. Holwerda[1]

[1]*Utrecht University, Veterinary Faculty, Department of Clinical Sciences of Companion Animals, Utrecht, The Netherlands*

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Abstract

Twelve client-owned veterinary patients (8 dogs, 4 cats) with unresectable soft tissue sarcoma of different histologic types were treated with intratumoral injections consisting of radioactive holmium microspheres. Nine out of twelve animals underwent subsequent surgery. Tumor response and toxicity were evaluated retrospectively. Overall, holmium treatment was well tolerated with minor side effects. The tumor-absorbed dose varied between 34-5767 Gy and there was no obvious dose-response relation observed. Interestingly, the higher radiation doses were not associated with increased toxicity. Complete response, being >50% tumor volume reduction after holmium treatment allowing for subsequent surgery, was observed in 5 animals. Four animals had partial response, being a tumor volume reduction of 20-50%. Progressive disease, being ≤20% tumor volume reduction, was seen in two cases. Complete remission after having had subsequent surgery was achieved in six animals. Median survival time for all treated patients was 457 days (range 93–1772 days). Six animals were alive at the time of writing, five died and one was lost to follow-up. Two out of five animals died owing to tumor recurrence. Intratumoral insertion of radioactive holmium microspheres appeared to be a safe and effective modality for the downstaging of selected cases of unresectable soft tissue sarcomas allowing for subsequent surgery.

Introduction

Soft tissue sarcomas (STS) are heterogeneous group of mesenchymal tumors with similar biological behavior characterized by being locally aggressive and a low-to-moderate metastatic potential. STS account for approximately 15% of all canine skin and subcutaneous tumors and 7% of all feline skin and subcutaneous tumors. STS arise from a variety of connective tissues including muscle, fibrous, fascial, adipose and neurovascular tissues. Malignant tumors that are grouped under soft tissue sarcomas include fibrosarcoma, hemangiopericytoma, myxosarcoma, rhabdomyosarcoma and liposarcoma.(1)

There are many similarities between canine and feline soft tissue sarcomas. However, feline vaccine-associated sarcomas are known to be more aggressive than non-injection site sarcomas and the majority of the tumors are high-grade.(1) Although FSA is the most common tumor to arise at vaccination sites, other tumor types have also been described including malignant fibrous histiocytoma, myxosarcoma and osteosarcoma.(2) The local aggressive nature of STS necessitates wide surgical excision as the principal treatment for local tumor control. Additional treatment options that have been described include radiation

therapy and chemotherapy, depending on the histologically determined surgical margins and tumor grade.(1) Postoperative radiotherapy may be useful in incompletely excised tumors and adjuvant chemotherapy can be considered for high-grade tumors because of the risk of developing metastasis.(1, 3-4)

In dogs, a median survival time of 1416 days has been reported with surgery alone while a combination of surgery with radiotherapy has been associated with a median survival time of 2270 days.(3)(5) In cats, a median survival time of 576 days has been reported for treatment with surgery alone(6), while median survival time for cats treated with surgery and radiotherapy ranged from 600-730 days.(2, 7-8)

Although a multimodal treatment may improve outcome in some cases, response to radiotherapy and chemotherapy is generally considered poor when gross tumor is present. Therefore, aggressive surgery is the first step to achieve local tumor control.(1) However, wide surgical excision may not always be possible due to tumor size and location (e.g. tumors of the head and extremities), or radical surgery (limb amputation) may not be favored by the owner. For patients with malignancies not amenable for surgery, an experimental treatment option could offer perspectives. This experimental treatment is a form of internal radiation therapy and aims at reducing tumor size by the selective intratumoral administration of microspheres containing the radioisotope holmium-166. The dose that can be administered with external beam radiation is largely limited by the radiosensitivity of the surrounding healthy tissue. Due to the high selectivity of the technique used in this study, radiation is mainly restricted to tumor tissue, enabling very high local radioactive doses without causing extensive damage to surrounding tissue.

The use of holmium microspheres for the radioablation of malignancies has been investigated by the Department of Nuclear Medicine of the University Medical Center of Utrecht, The Netherlands for nearly two decades. Initially, holmium microspheres were clinically explored for transcatheter intra-arterial radioembolization as a treatment of hepatic malignancies in humans. These studies have shown encouraging results.(9-11) This selective internal radiation therapy is thought to be applicable not only in patients with liver malignancies, but also in patients with other tumors, such tumors of the head, trunk and limbs.

During the last five years, a select group of veterinary patients with unresectable malignancies have been experimentally treated with this form of internal radiation therapy at the Utrecht University Clinic for Companion Animals (UUCCA), in close collaboration with the department of Nuclear Medicine of the University Medical Center Utrecht. Only in these veterinary patients, holmium microspheres were injected directly into the tumor rather than a transcatheter approach.

A total of 34 veterinary patients have been experimentally treated by intratumoral injections with holmium microspheres at UUCCA between 2009 and 2013 including 18 dogs, 15 cats and 1 parrot. The most common tumor types that have been included are oral squamous cell carcinomas and soft tissue sarcomas.

Neutron-activated holmium-166 (holmium) has favorable properties and can therefore be considered an ideally suited device for internal radioablation of malignancies. Holmium is a high-energy beta-emitting radionuclide with a maximum soft tissue penetration range of 8.7 mm (effective range 3.2 mm), and emits γ-radiation as well. Whereas the β particles can be used therapeutically, the γ-radiation allows visualization of the holmium distribution by nuclear imaging (SPECT). Because of the paramagnetic nature of holmium, the microspheres can be visualized with MRI. Moreover, its high attenuation coefficient enables visualization by CT as well.(12)

Selective intratumoral administration of holmium allows high dose of radiation to be delivered to tumor tissue while largely sparing surrounding healthy tissues. Because of its favorable half-life of 26.8 h(12), irradiation continues for several days after administration, depending on the amount of injected activity.

It is anticipated that internal radioablation using holmium microspheres could relieve clinical signs associated with the tumor by decreasing tumor size, this technique may however not provide for a complete cure for these tumors. It is thought that the use of holmium microspheres for the downstaging of unresectable tumors might allow subsequent excision of the residual tumor after having reduced its size. For this reason, a combination of holmium treatment with subsequent surgery was investigated in this study. The purpose of the study reported here was to evaluate the efficacy and toxicity of intratumoral injections with holmium microspheres in vetetinary patients with unresectable STS.

Materials and methods

Selection criteria
Eligible patients had unresectable, histologically confirmed soft tissue sarcomas with no evidence of metastases, as assessed on CT. Life expectancy should be at least 12 weeks and blood analysis should reveal no major abnormalities (e.g. no signs of renal- or liver failure). Patients should have had no chemotherapy or surgery within 4 weeks of entry. Animals were excluded from this study if they had a severe comorbidity at presentation.

Animals
Twelve client-owned dogs and cats presented to the Utrecht University Clinic for Companion Animals (UUCCA) for the treatment of soft tissue sarcomas (STS) between 2009 and 2013 were included in this study. Eight dogs and four cats had unresectable soft tissue sarcomas of different histologic type. Seven dogs had hemangiopericytoma (HPC), four cats had fibrosarcoma (FSA) and one dog had rhabdomyosarcoma (RMS). Three of the cats with FSA had injection site sarcomas and one cat had oral FSA. HPC and RMS were located on the extremities (n=8) and FSA were located on the back (n=3) and in the oral cavity (n=1). The tumors of four animals had been locally excised prior to presentation but had recurred. The ages ranged from 7 to 13 years. Six dogs were females and two dogs were males. From the cats, two were males and two were females. Dog breeds included cross breed (n=3), Shiba Inu (n=1), Dutch Shepherd (n=1), Irish Setter (n=1), Stafforshire Terrier (n=1) and Welsh Springer Spaniel (n=1). Cat breeds included domestic shorthair (n=3) and British shorthair (n=1). Clinical signs associated with the tumor were dependent on the site of the tumor and were not present in most cases. For tumors affecting the limbs and the back, there were no signs other than the presence of the mass. In the cat with oral FSA increased vocalization was noted by the owner. All patients underwent a complete clinical workup prior to treatment consisting of a physical examination and blood analysis. Furthermore, CT imaging was used to accurately define tumor extension, involvement of adjacent structures and to detect metastases. In most cases, tumor grade was determined after surgical excision. Seven animals had low-grade tumors, two had high-grade tumors and tumor grade was unknown for three animals.
One cat with FSA had detectable metastases and signs of advanced disease at referral. Although thoroughly informing the owner that holmium treatment would be palliative in this case and was generally against advice, the owner still wished to proceed with the treatment.

Anesthesia and analgesia
Anesthetic protocols varied, and were chosen according to the medical and physical condition of the individual patient. Pre-anesthetic agents included dexmedetomidine, midazolam, methadone and butorphanol. In most animals, general anesthesia was induced using propofol. Only in the dog with concurrent cardiac disease, alfaxalone was used as an anesthetic agent for induction as it has less cardiovascular effects than propofol. After endotracheal intubation, anesthesia was maintained by inhalation of 1.0-2.0% isoflurane in O2/air (1:1) in all but one animal. In this dog, maintenance of general anesthesia was achieved with a continuous rate infusion (CRI) of alfaxalone. Peri- and postoperative analgesia consisted of buprenorphine, meloxicam, tramadol and/or carprofen. Antibacterial prophylaxis was provided by amoxicillin/clavulanic acid or cefovecin. Lactated Ringer's solution was administered throughout anesthesia in all cases. In cases where dexmedetomidine was used as premedication, atipamezole was used as antagonist during the recovery of anesthesia. The cat with oral FSA had an esophageal tube placed prior to treatment to ensure adequate feeding on the days following the procedure.

Microsphere preparation
The microspheres were prepared as described by Nijsen *et al*. and Bult *et al*.(13-14)
Either Ho-PLLA-MS (mean size 37 μm; Ho content: 17.0% (w/w)) or Ho-AcAc-MS (mean size 15 μm; Ho content 45.0% (w/w)) were used.
Ho-AcAc-MS have a substantially higher holmium content per microsphere.(14)
The microspheres were prepared by a solvent evaporation method. Subsequently, the microspheres were activated by neutron irradiation in the nuclear reactor of the Delft University of Technology (Delft, The Netherlands).

Treatment
The tumor volume (in cm^3) was calculated by the formula: $4/3 \cdot \pi \cdot (½\ d^1 \cdot ½\ d^2 \cdot ½\ d^3)$, where d^{1-3} represent the length, width and height of the tumor in cm, respectively. The tumor-absorbed dose (Gy) was calculated using the following formula:
15.87 (mJ/MBq) · activity (MBq) / tumor weight (grams). Assumed tumor tissue density is 1 g/cm^3.

The tumors were visually approached and the radioactivity was administered through 22G needles under visual guidance. Radiation dose to the hands during administration was limited by placing the syringes into an acrylic glass cylinder. To minimize untreated areas within the tumor, multiple injections into various sites of the tumor were given for adequate delivery of radioactivity. Immediately post treatment, distribution of the holmium microspheres was assessed using gamma scintigraphy (SPECT). The activity in the syringes were measured before and after administration, to determine the injected amount of activity. The tumor-absorbed dose varied between 34-5767 Gy (table 1). Animals were discharged from the clinic when the radiation rate was < 40 mSv/h at 100 cm distance.

Table 1. Overview activity and dosage

Tumor type	Tumor volume (cm^3)	Activity (MBq)	Dose (Gy)	Survival
HPC[a]	41	843	673	Yes
HPC	16	1048	1028	Yes
HPC	110	1281	185	No
FSA[b]	66	616	148	No
FSA	0,87	642	5767	No
	1,53	109	753	
FSA	0,18	3,3	298	Yes
HPC	52	2173	515	No
FSA	55	1800	345	LTF[d]
HPC	165	2372	152	No
HPC	261	2647	157	Yes
RMS[c]	46	1106	255	Yes
HPC	543	1747	34	Yes

[a]HPC=hemangiopericytoma
[b]FSA=fibrosarcoma
[c]RMS=rhabdomyosarcoma
[d]LTF=lost to follow-up

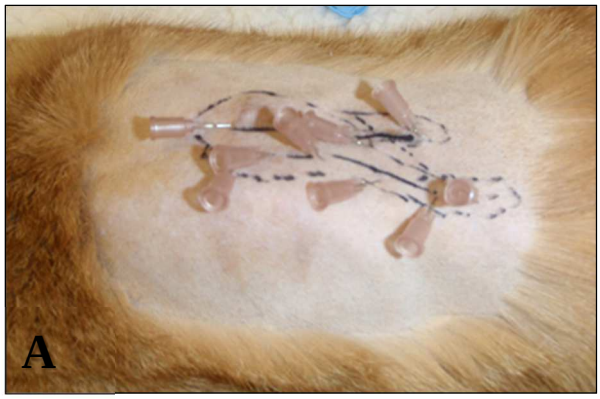
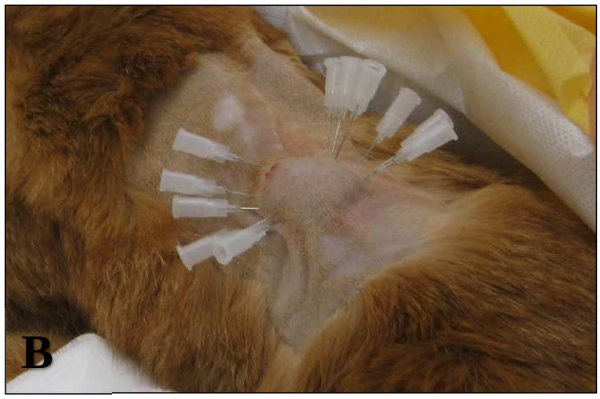


Figure 1. Photograph showing the planned treatment area (scar tissue) for the first (A) and second (B) holmium treatment of the feline patient with recurring FSA.



Follow-up

The follow-up consisted of regular visits to the clinic to evaluate the effect of the treatment by measuring tumor size. Next to the visits to the clinic, regular contact with the owner was maintained as well. Tumor response was evaluated based on clinical or imaging changes in tumor size. Complete response after holmium treatment was defined as >50% tumor volume reduction for subsequent surgery. Partial response was defined as 20-50% reduction of tumor volume. A tumor volume reduction of ≤20% was defined as progressive disease. In animals that had no visible lesions following holmium treatment and surgery, complete remission was achieved. Recurrence free interval was defined as the number of days from initiation of holmium treatment to confirmed recurrence of the tumor. Metastasis free interval was defined as number of days from initiation of holmium therapy until confirmed metastases. Survival time was defined as number of days from initiation of holmium treatment until death.

Patient information was obtained from the medical records, database, previous reports or through phone calls with referring veterinarians or owners regarding recurrence of the tumor, date and cause of death.

Results

Six dogs and four cats with STS of different histological types were treated with intratumoral injections containing holmium microspheres. The intended amount of activity was based on tumor volume, as determined on pre-treatment CT or manual measurements of the tumor. Post-treatment nuclear imaging confirmed that the microspheres had been deposited selectively in the tumor in all cases.

Complete and partial response rate after holmium treatment alone was 45% and 36%, respectively. These response rates exclude one animal that was lost to follow-up, since no data were available to evaluate tumor response. Two animals had progressive disease after holmium treatment based on tumor volume. Mean tumor volume reduction when excluding those with progressive disease was 53%. Complete remission was achieved after having had subsequent surgery in six animals, but in two of those animals amputation of the limb had to be performed due to recurrence.

Overall, holmium treatment was well tolerated by all animals and adverse effects were minimal. Two of the HPC dogs had delayed wound healing after surgery. One HPC dog showed ulceration of the skin which was leading to a chronic inflammation. One dog with HPC had a chronic wound infection postoperatively.

Holmium treatment was followed by surgery in nine out of twelve animals. Two dogs with HPC and RMS first had local tumor excision, but postoperative recurrence necessitated amputation of the affected limb. One cat with injection site FSA was treated twice with holmium before surgical excision was performed. One FSA cat had progressive disease after treatment and surgery was not feasible. One dog with HPC was detained from surgery on request of the owner. One FSA cat was lost to follow-up and was therefore not subjected to surgery.

Tumor response and outcome

For one dog with HPC on the right radius/ulna, amputation of the limb was not feasible at the time of presentation due to a fracture at the concurrent front limb. Holmium treatment resulted in a partial tumor response of 32% and the remaining tumor was surgically excised. When the tumor recurred after 223 days, amputation was performed. This dog is alive at the time of writing, 1775 days post treatment but since the tumor was radically excised, long-term tumor control after holmium treatment cannot be evaluated.

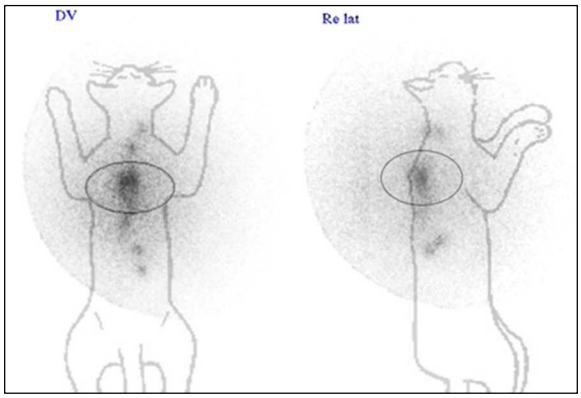


Figure 2. Gamma scintigraph acquired after first holmium treatment of the FSA cat shown in figure 1.

In one dog with HPC on the left tarsus, ulceration of the skin at the injection site developed after treatment. The ulceration progressed over time, presumably due to automutilation. The most likely explanation for the skin ulceration is the superficial deposition of the microspheres leading to a high radiation dose to the skin. Despite the ulceration, a tumor volume reduction of 64% was achieved after holmium treatment. The remaining tumor was then surgically removed. Histopathological analysis was performed revealing both an extended inflammatory process and necrosis, most likely associated with the deposition of the microspheres (figure 5). There was only minimal residual tumor tissue left. This dog is alive at the time of writing 1683 days after treatment, and there are no signs of local recurrence or metastatic disease.

One dog with HPC on the left femur had a tumor volume reduction of 62% after holmium treatment which was followed by subsequent surgical excision. The clinical condition of this dog remained stable for two years until the animal spontaneously collapsed due to an acute hemoabdomen which was probably caused by rupture of an intra-abdominal mass. It was decided to euthanize the dog 755 days post treatment.

One cat with a large injection site FSA on the back had no apparent benefit from holmium treatment (figure 3). The cat had progressive disease and there was only a minimal change in consistency of the tumor after holmium treatment. Follow-up CT revealed substantial progression of the tumor and signs of metastatic disease in the left axillar lymph node and lungs 29 days after

treatment. Consequently, the cat was not subjected to surgery. This cat died of an unrelated cause 93 days post treatment. At the last contact, clinical signs associated with the disease were absent, despite the confirmed metastases and tumor progression.

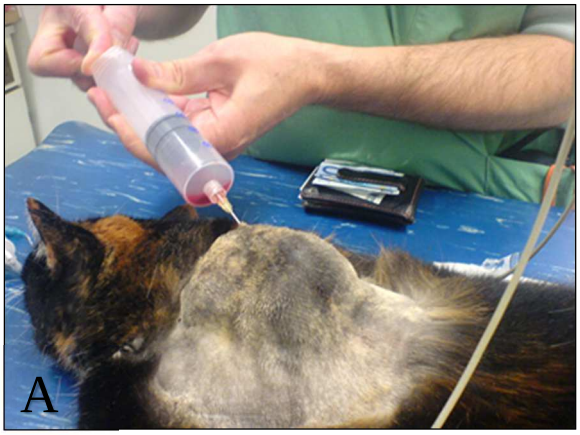
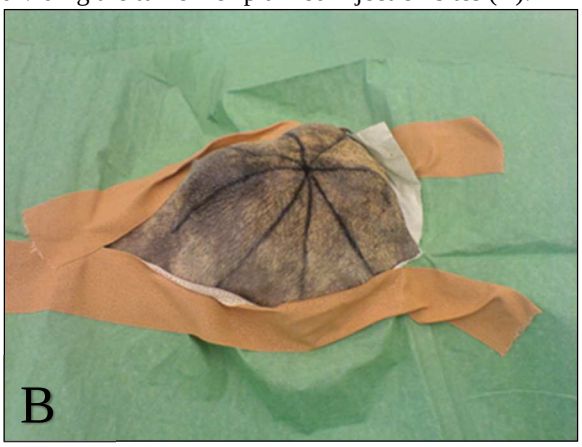


Figure 3. Feline patient with a large injection site FSA. Centesis of fluid prior to treatment (A) and marked lines dividing the tumor for planned injection sites (B).



One feline patient had an incompletely resected injection site FSA (figure 1). The scar tissue had a volume of 0,87 cm^3 and an initial complete response was observed after holmium treatment. However, follow-up CT revealed extension of the tumor into the dorsum and the presence of pulmonary metastases 10 months post treatment. Despite recurrence and metastases, the cat was not manifesting any clinical signs associated with the disease and the owner was still motivated to continue further treatment. For this reason, a second holmium treatment was given. After the second treatment, the cat was subjected to surgery. The clinical condition of this cat remained stable for five more months, after which the cat developed a mass on the chest wall and its clinical condition was deteriorating. The cat was euthanized 514 days after treatment. Necropsy revealed the presence of metastasis in several tissues including subcutis, muscle, fascia en ligaments of left front leg, the chest wall and thoracic vertebrae.

One cat with FSA on the back was treated with surgery and chemotherapy two years prior to admission and the tumor had now recurred. In this case, due to the local aggressive aspect of the tumor and because of the strong suspicion of lung metastases as assessed on CT, holmium treatment would be of palliative intent. At the request of the owner, holmium treatment was initiated. Unfortunately, this cat was lost to follow-up immediately post treatment and no tumor response data were available for this cat.

One feline patient was presented with an oral FSA located on the dorso-medial side of the right mandibula and caudal of the last molare. Pre-treatment CT imaging also revealed an incidental meningioma located at the dorsal right side of the falx cerebri which was characterized as asymptomatic. After intralesional holmium treatment, a partial response of 28% was evident and the remaining tumor was treated with subsequent debulking laser surgery. This cat has not shown any signs of recurrence since and has no symptoms caused by the incidental meningioma.

One dog with HPC on the left front limb had a tumor volume reduction of 54% after holmium treatment. Even though subsequent surgical removal was recommended for optimal local tumor control, this dog was detained from surgery on request of the owner. This dog was euthanized one year post treatment due to local tumor recurrence.

One dog was presented with a high-grade ulcerated RMS on the left tarsus. Injections with holmium microspheres were aimed at the basis of the tumor and the deeper tumor layers, due to the local aggressive nature of the tumor. The tumor became necrotic and was surgically debulked two weeks post treatment. A postoperative curative protocol of external beam radiotherapy was performed because of the likelihood of incomplete surgical margins owing to the local aggressive behavior of the tumor. Accordingly, 17 fractions of 12 MeV were administered with a total dose of 54 Gy. Initially, the dog was weight bearing on the treated limb. However, local recurrence was evident 130 days after holmium treatment. The only remaining treatment option would be radical removal of the tumor, thus amputation was performed. Since the dog was treated with adjuvant external beam radiation therapy and radical surgery, it is not possible to evaluate the

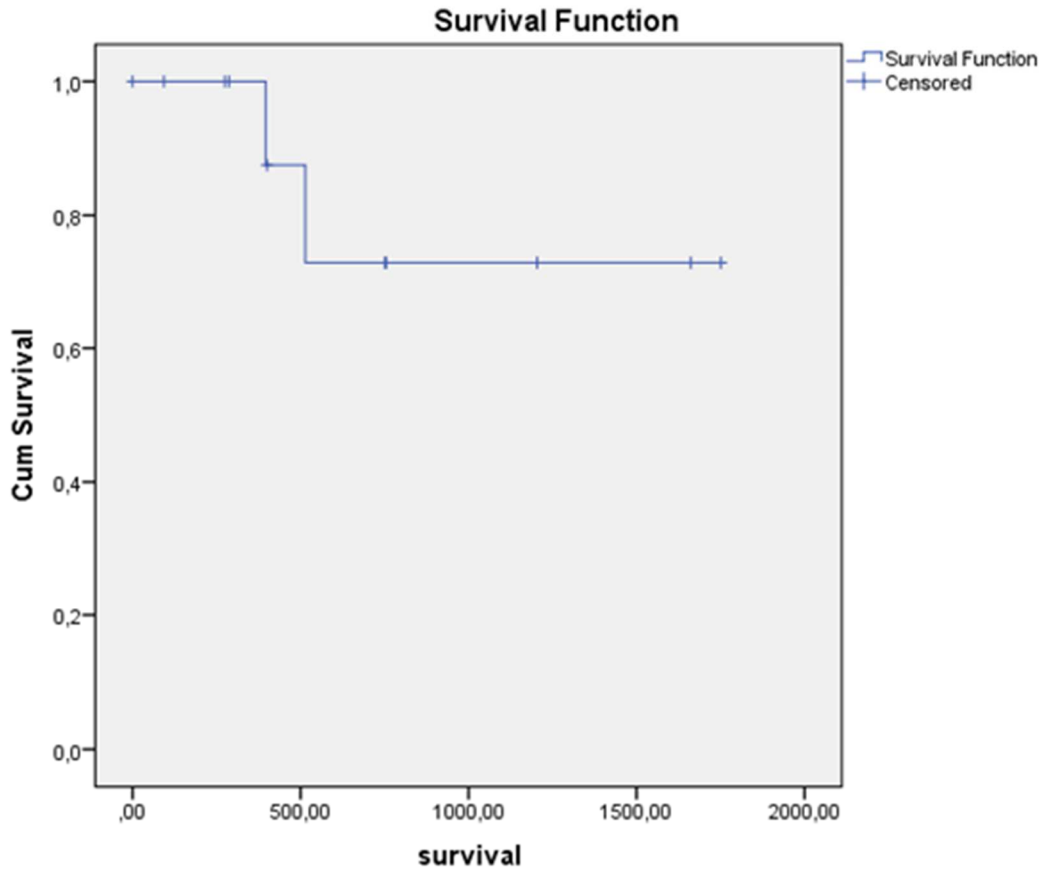


Figure 4. Kaplan-Meier survival curve showing only two animals died owing to recurrence, the remaining ten animals are censored.

long-term effect of the holmium treatment. This dog was metastasis free until 400 days post treatment.

One dog with HPC on the hip had severe arrhythmias, second degree AV block and mitral and tricuspid insufficiency at presentation which were associated with an increased anesthetic risk. Preoperative antiarrhythmic treatment with diltiazem and mexiletine was attempted and no major incidents occurred during the anesthetic procedure. A tumor volume reduction of 53% was achieved 21 days after holmium treatment. However, three weeks post treatment, tumor size was increasing again and in addition, two masses were discovered in the mammary glands. Surgical resection of the tumor and mastectomy of the affected glands was performed. Surgical margins of the excised tumor appeared to be incomplete upon histological examination. Eight months post-treatment, this dog developed a severe anemia with unknown underlying cause, and repeated blood transfusion only had a short term effect. There was no evidence of tumor recurrence or metastases. The animal was euthanized 275 days months post-treatment, because of a rapidly declining clinical condition.

One dog had a HPC on the left hip mainly consisting of fluid. CT evaluation showed a soft tissue mass within the fluid-filled mass. Prior to holmium treatment, about 500 ml of clear fluid was drained from the mass and holmium was selectively injected in the soft tissue mass using ultrasound guidance. CT imaging of the mass was repeated 37 days post treatment to determine the soft tissue volume reduction. The tumor volume was reduced with 41% and the remaining mass was surgically removed. Surgical margins appeared to be complete on histologic examination. At the time of writing, there have been no signs of tumor recurrence and the dog is alive 777 days post-treatment.

One dog with a large HPC on the right elbow had an initial tumor response of 43% after holmium treatment. Narrow marginal resection was performed after holmium treatment since deep margins were difficult to obtain due to involvement of the underlying muscles. Histological evaluation of the excised tumor

confirmed incomplete margins, but the tumor appeared to be low grade and therefore was associated with a low metastatic- and recurrence rate. Six weeks post-surgery, the wound appeared to be chronically infected and methyciline-resistant staphylococcus pseudointermedius (MRSP) was isolated from the exudate. The infection resolved within several weeks with conservative treatment. At the time of writing, 313 days post-treatment, the dog is showing signs of local recurrence proximal of the surgical scar.

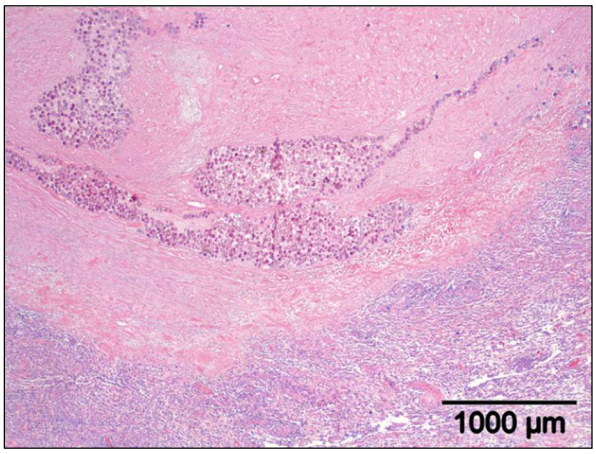


Figure 5. Histopathological evaluation of a HPC. Note the tissue necrosis around places with large amounts of holmium microspheres.

Discussion

Holmium treatment appeared to be well tolerated and a high radiation dose could be administered without occurrence of severe radiation-related toxicity. One HPC dog had skin ulcerations at the injection site and delayed wound healing was seen in two HPC dogs postoperatively. One HPC dog had a chronic wound infection which could be due to the radiation effects of the holmium treatment. Six out of twelve animals are still alive at the time of writing, and median survival time including all animals was 457 days (figure 4). One FSA cat and one HPC dog died of disease recurrence with a survival time of 514 and 396 days, respectively. However, three animals died of other causes and one animal was lost to follow-up so the actual median survival time in this study was not reached. Survival time did not seem to be associated with specific tumor types. Three feline injection site sarcomas have been subjected to holmium treatment in this study. Injection site sarcomas are known to be locally aggressive and invasive and recurrence in those tumors is common. At the time of initial evaluation, one cat with FSA was subjectively assessed as an unsuitable candidate for holmium therapy, as the cat had metastatic disease. This cat was lost to follow-up before tumor response could be evaluated. Another FSA cat with a tumor volume of 66 cm^3 had no apparent benefit from holmium treatment. Follow-up CT revealed progression of the tumor and the presence of metastases one month post treatment. Despite confirmed disease progression, this cat was not showing any clinical signs associated with the disease and the clinical condition remained stable until the cat was euthanized due to an unrelated cause. For the third feline patient with injection site FSA, holmium treatment alone was associated with a 10-month period of local tumor control. After recurrence and metastatic disease were confirmed, a second holmium treatment was performed followed by surgical excision. The clinical condition of this cat remained stable for five more months before being euthanized with a total survival time of 514 days.

Because of the size and invasiveness of the tumors that were included in this study, it was anticipated that holmium therapy as a single treatment modality would not be curative. Combining holmium treatment with surgery however appeared to be an effective means for local tumor control in most cases. Holmium has a short half-life of 26.9 h, and most visible radiation effects were expected within the first 4 weeks after treatment. However, in some cases surgical intervention was chosen before this 4-week period because tumor size reduction allowed surgical removal of the residual tumor or because surgery was recommended due to severe tumor necrosis. Mean time to optimal effect of holmium treatment was 30 days in this study.

Even though holmium treatment alone only requires a single anesthetic episode, multiple anesthetic procedures are necessary for pretreatment assessment of the patient and possible subsequent surgery and may be undesirable as the anesthetic risk is increased. In general, there were no complications observed during anesthesia in this study.

Information regarding original tumor size and tumor size after treatment was available in most records, but methods used for measuring tumor size varied, as well as time after treatment.

Not all patients were treated with the same type of holmium microspheres as both Ho-PLLA-MS and Ho-AcAc-MS were used. The holmium content of the Ho-AcAc microspheres was markedly higher than of Ho-PLLA microspheres. Because of the increased holmium content per microsphere, smaller volumes of HoAcAc were necessary to

obtain tumoricidal doses after direct intratumoral injection.(14) Although the use of different microspheres was not likely to impact outcome, a large injection volume could increase the chance of deposition of microspheres outside the lesion, whereas a smaller volume could possibly leave tumor areas untreated. The amount of radioactivity to be administered during treatment should be higher than the amount needed according to the calculated dose due to activity remaining in the syringes after injections and possible spillage so that the difference between the calculated and actual administered dose is minimal. However, this unpredictable value may lead to a higher or lower administered dose than calculated prior to treatment.

Four animals had a partial response and two animals had progressive disease based on tumor volume reduction. The number of partial responders may be explained by a suboptimal distribution of microspheres within the tumor after administration. Whereas the short tissue penetration depth of β-radiation emitted by holmium microspheres offers an advantage over conventional external beam radiotherapy since surrounding tissues are mostly spared from radiation damage, it also necessitates proper distribution of the microspheres throughout the entire tumor and the target tissue must be fully accessible for injections. When looking at tumor volume reduction for evaluating treatment response, the dog with high-grade ulcerated RMS would be characterized as having had progressive disease since there was no obvious tumor volume reduction after treatment. However, since the tumor became almost completely necrotic within one week post treatment, adequate volume reduction could not be determined. Tumor necrosis is seen as a response to holmium treatment, and in this case tumor volume did not appear to be an adequate means for evaluating tumor response. The necrotic tumor became infected and was a source of discomfort for this dog and therefore surgery was performed two weeks after holmium treatment.

Conclusion

The results of this study demonstrate that intratumoral injections of holmium microspheres can be used effectively for decreasing tumor size in selected cases of unresectable STS. However, surgical excision of the residual tumor was needed to provide sufficient local control of canine and feline STS. In conclusion, combining holmium treatment with surgery offers the highest chance of achieving local tumor control in patients with unresectable STS. Studies evaluating the effects of holmium treatment on tumors of varying origin in dogs and cats are ongoing.

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