Different aspects of hyperthermic isolated limb perfusion
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Hyperthermic isolated limb perfusion with cisplatin in the local treatment of spontaneous canine osteosarcoma: Assessment of short-term effects

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Abstract
To increase the effect of cisplatin on locoregional osteosarcoma, the short term effect of hyperthermic isolated limb perfusion (HILP) with cisplatin (30 mg/L extremity volume) was studied in 28 dogs with spontaneous osteogenic sarcoma using clinical, radiological, and histological parameters. Thirty days postoperative mortality was 14.3 %. Total platinum levels at the start of perfusion were 28.2 ± 14.3 mg/L. A significant improvement (p<0.001) in the clinical score was observed in the overall group at 6 and 12 weeks after perfusion. The radiological parameter showed a stationary X-ray 2 weeks after perfusion and an improved X-ray 6 weeks after perfusion. Overall histological scores showed a moderate effect according to the Huvos classification. No additional therapeutic effect, according to the three parameters, could be demonstrated by increasing the perfusate temperature by 1 °C. HILP with cisplatin is feasible in the local treatment of spontaneous osteosarcoma in dogs with acceptable locoregional toxicity. However the histological results were modest, with none of the dogs showing a complete response 6 weeks after perfusion. Therefore, the search for the ideal perfusion agent with substantial contribution to the limb-sparing treatment in human osteosarcoma, continues.

Introduction
Osteosarcoma is the most frequent primary malignant bone tumor in humans. Until the early 1970s, the most common approach to the management of localized osteosarcoma was surgical resection, amputation or radiation. In most large series of patients treated in this manner, long term survival was only 20%.1,2 During the past few decades, the use and further development of systemic neoadjuvant chemotherapy, e.g., including high-dose methotrexate (HD-MTX) and cisplatin, appears to have a definite influence on the disease free and overall survival for patients with osteosarcoma.3-5 The effect of the systemic neoadjuvant chemotherapy on the primary bone tumor, the improved surgical resection technique, and the development of prosthetic replacement techniques also improved the limb salvage rate for osteosarcomas, especially for the lower extremity. Salvage rates varying from 40 % to almost 80 % are reported.6 However, the potential local tumor effect of the systemic neoadjuvant chemotherapy is not always favorable, although a good response of the local tumor to systemic chemotherapy demonstrated prognostic value.7 Increasing the systemic chemotherapy dose to achieve a higher local tumor response is limited due to the nephrotoxicity and ototoxicity of cisplatin. To avoid systemic toxicity but to raise the effect on the local tumor and thereby facilitate limb preserving procedures, a local treatment of the primary tumor could be the solution.
With hyperthermic isolated limb perfusion (HILP) as a local treatment modality, it is possible to obtain very high local drug concentrations in a limb with minimal systemic toxicity.\textsuperscript{8} The value of cisplatin in HILP has also been demonstrated in humans for melanoma and various soft tissue sarcomas.\textsuperscript{9-11} Fletcher and associates showed that 250 mg/m\textsuperscript{2} was the maximum tolerable dose of cisplatin for lower-extremity perfusions, with improved local control rates for sarcomas and melanoma of the extremities without regional nodal metastases.\textsuperscript{12} Before introducing HILP with cisplatin in the clinical treatment of osteosarcoma of the limb, the short term effect of this treatment modality on the primary tumor was investigated by clinical, radiological, and histological parameters in dogs with spontaneous osteogenic sarcoma of the limb. Biological behavior of osteosarcoma is similar both in human and in dogs; a locally aggressive bone tumor predominantly occurring in the long bones with early hematogenous metastases to the lungs.\textsuperscript{13,14} The differences between canine and human osteosarcoma are that in humans a younger age group (adolescence) is most commonly affected, and the tumor is less common. With the high frequency of occurrence in dogs, allows canine osteosarcoma is a useful model for evaluation of new treatment regimens in humans as rapid case accrual and rapid time to reach measurable end points are possible. The canine osteosarcoma therefore appears to be a valid model for studying the potential treatment of HILP with cisplatin in the local treatment of osteosarcomas of the extremity in humans.

**Materials and methods**

*Dogs*

Twenty-eight dogs with an average weight of 45 ± 10.0 kg and a mean age of 7 ± 2.5 years with spontaneous, histologically proven, previously untreated, primary osteosarcoma of the extremity, without radiographic evidence of distant metastases, underwent HILP with cisplatin. Preoperatively, all dogs were thoroughly clinically evaluated at the Department of Veterinary Medicine and underwent a complete blood count (CDC), serum chemistry profile, and X-rays of the primary tumor and thorax. The perfusion procedure was performed at the Central Animal Facility of the State University Groningen, while follow-up was performed at the Department of Veterinary Medicine Utrecht. The study was approved by the Animal Welfare Committee of the Faculty of Medicine of the State University Groningen.

*Anesthetics*

All dogs were premedicated with atropine sulfate (0.5 mg, i.m.) and piritramide (15-17.5 mg, i.m.)(Dipidolor, Janssen Pharmaceutica, Tilburg, The Netherlands). The dogs were anesthetized with thiopental (30 mg/kg BW, i.v.)(Pentothal, Abbott,
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Amstelveen, The Netherlands) and after muscle relaxation with pancuroniumbromide (0.08mg/kg BW, i.v.)(Pavulon, Organon, Oss, The Netherlands), the dogs were ventilated by means of a Siemens Servo Ventilator 900B, with a mixture of nitrousoxide and oxygen. The oxygen concentration in the gas mixture, continuously measured by means of an oxygen analyzer (Taylor Servomex OA 272), and minute volume (4-6 L/min), were adjusted to maintain an end-expiratory CO₂ concentration of 4-5% (Siemens CO₂-analyser 930). The dogs were placed in the supine position on a heated mattress to maintain their normal body temperature of 38 °C. During the operations, all dogs were given about 500 ml of Isodex through the cephalic vein.

Operation and perfusion techniques

The iliac or axillary vessels of the affected limb were exposed under sterile conditions and collateral vessels were clipped. Cannulas were inserted into the artery (Bardic, 16F-18F) and vein (Portex, 6-8 mm). Both cannulas were connected to an extracorporeal circuit consisting of an occlusive roller pump, a cardiotomy reservoir and a bubble oxygenator with heat-exchanger. A canvas tourniquet was placed around the base of the extremity to complete isolation of the limb from the systemic circulation. The perfusate consisted of 350 ml of 5% dextran 40 in glucose 5% (Isodex, Pharmacia AB, Uppsala, Sweden), 250 ml red blood cells (typed canine blood donors), 250 ml plasma, 30 ml sodium bicarbonate 8.4%, and 0.5 ml 5000 IU/ml heparin (Thromboliquine, Organon BV, Oss, the Netherlands). A mixture of oxygen, air, and carbon dioxide through the oxygenator was adjusted to maintain the blood gas values within the physiological range and, when necessary, bicarbonate was added to adjust the pH.

All perfusions were performed under hyperthermic conditions. To study the effects of additional heat to the perfusate, two groups of dogs were randomized. In group I (14 dogs), HILP of the extremity was performed at 39-40°C limb temperature; and for group II (14 dogs), HILP was performed at 40-41 °C limb temperature. The arterial line temperature was kept at 40-41 °C in group I and at 41-42 °C in group II. In addition a 1000 Watt infrared lamp was placed at a distance of 90 cm to heat the extremity. Thermistor probes (Electrolaboriet, Copenhagen, Denmark) were inserted into the subcutaneous tissue and into a muscle of the proximal limb just above the knee for continuous monitoring of the temperatures during perfusion. The perfusion time was 1 hour and the perfusion was followed by washout of the extremity with 500 ml of Isodex. Tourniquet, cannulas and clips were then removed and the incisions in the vessels were repaired. Protamine hydrochloride (Hoffman La Roche, Mijdrecht, The Netherlands) was administered to neutralize heparin, in a ratio of 1:1 to the initial dose of heparin. All dogs were observed for one night and allowed to go home.
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with the owner the next day. No anti-inflammatory medications or analgesics were administered during follow up.

The dosage of cisplatin (Platinol 0.5 mg/ml, Bristol Myers SAE, Barcelona, Spain) used in the perfusion had been established in a previous study which showed massive edema with necrosis and fibrosis with cellular infiltrates in skeletal muscle throughout the perfused extremity in dogs that received 45 mg cisplatin per liter extremity volume. These local side effects were not seen after a 30% dose reduction to 30 mg/L extremity volume, as used in the present study. The volume of the extremity was determined by submersion in water to the tourniquet border and measurement of displaced water volume. Extremity volumes varied from 1.7 ± 0.27 L. Cisplatin was added to the circulated perfusate in 10 minutes. During perfusion, serum platinum levels were determined in the regional and systemic circulation at 0, 10, 20, 30, 40, 50, and 60 minutes by flameless atomic absorption spectrophotometry (FAAS).

Local effect parameters
Short-term effects on the tumor were determined using three parameters: clinical, radiological, and histological. The clinical score was determined by a veterinarian on the basis of gait analysis: walking on three legs (score I), severe limp (score II), slight limp (score III), walking normally (score IV). This score was determined 1 week before and at 2, 6 and 12 weeks after perfusion. The radiological score was determined by a veterinarian radiologist on conventional X-rays in two directions of the extremity according to methods described earlier. Preperfusion X-rays were compared with 2 and 6 week postperfusion X-rays: progression (score I), stationary (score II), regression (score III), the latter defined as a decrease in tumor volume, increased ossification of intraosseous tumor osteoid, periosteal new bone and soft tissue margin more densely ossified and well-defined resulting in a more benign appearance. Biopsies from the tumor were taken before, and 2 and 6 weeks after perfusion at random in three directions with a 3.5 mm diameter Coombs bone biopsy system. The histological score was determined by a pathologist on the material obtained from the biopsies, according to the criteria of Huvos et al. no reaction (score I), moderate effect (score II), good effect (score III), total necrosis (score IV). The radiological as well as the histological scores describe the response to treatment; therefore, it was not possible to score these parameters 1 week before treatment, as it was with the clinical score. All dogs were followed for local and systemic side effects by the cisplatin perfusion.
Statistical Considerations

Mean clinical, radiological and histological scores of the total group were analyzed with the Pittman test. Differences between group I and II were analyzed with the Yates & Cockran test. The survival curve was calculated according to the Kaplan Meier method. P-values <0.05 were considered significant.

Results

Although the dogs underwent a thorough clinical work-up before treatment, the investigators were confronted with a 30 days postoperative mortality of 14.3% (4 dogs). The first dog, 10 years of age, died at the end of the perfusion from cardiac failure. The other two dogs, both 6 years of age, died postoperatively due to pulmonary and cardiac failure. Postmortem examination of those two dogs was not obtained from their owners. A fourth dog died 1 week after the perfusion from a large myocardial infarction. Postmortem examination of this animal showed a completely necrotic tumor.

No systemic or normal tissue side effects of the perfusion were encountered. The local reaction of the limb to the perfusion consisted of an initial slight edema that reached a maximum on the third postoperative day and disappeared completely within the first week. Total platinum levels in the perfusate ranged from 28.2 ± 14.3 mg/L at the start of perfusion to 12.1 ± 5.3 mg/L at the end of a 1-hour perfusion in the total group. There was no significant difference in platinum levels during perfusion between group I and II. Systemic platinum levels never rose above 0.7 mg/L in both groups (Fig. 1).

Fig. 1 Concentration of total platinum (tPt) measured in the perfusate during cisplatin perfusion. Values are the mean of all dogs; error bars are ± SEM. Time 0 is the time of administration of 30 mg cisplatin per liter extremity volume.
### Table 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1 week</td>
<td>N=28</td>
<td>N=14</td>
</tr>
<tr>
<td>2 weeks</td>
<td>N=11</td>
<td>N=6</td>
</tr>
<tr>
<td>6 weeks</td>
<td>N=11</td>
<td>N=4</td>
</tr>
<tr>
<td>12 weeks</td>
<td>N=7</td>
<td>N=2</td>
</tr>
<tr>
<td>1 week</td>
<td>N=11</td>
<td>N=4</td>
</tr>
<tr>
<td>2 weeks</td>
<td>N=14</td>
<td>N=2</td>
</tr>
<tr>
<td>6 weeks</td>
<td>N=7</td>
<td>N=1</td>
</tr>
<tr>
<td>12 weeks</td>
<td>N=7</td>
<td>N=1</td>
</tr>
</tbody>
</table>

| Number of dogs | N=28 | N=24 | N=13 |

| III Slight limp| 6 (21%) | 5 (25%) | 3 (24%) |
|                | 6 (21%) | 7 (50%) | 1 (8%)  |
|                | 6 (21%) | 6 (46%) | 3 (23%) |
|                | 6 (21%) | 7 (50%) | 1 (8%)  |

| IV Walks normally| 2 (4%)  | 1 (2%)  | 6 (15%) |
|                  | 1 (4%)  | 1 (2%)  | 4 (10%) |
|                  | 1 (4%)  | 1 (2%)  | 4 (10%) |

**Clinical**

Distribution of clinical parameters at 1 week before and at 2, 6, and 12 weeks after perfusion.
The clinical scores in the total group before and after treatment could be compared. Before perfusion: 6 dogs (21%) walked on three legs; 15 dogs (54%) walked with a severe limp; 6 dogs (21%) walked with a slight limp; and 2 dogs (4%) walked normally. Two weeks after perfusion: 5 dogs (21%) walked on three legs; 6 dogs (25%) walked with a severe limp; 11 dogs (46%) walked with a slight limp; and 2 dogs (8%) walked normally (Table 1). At 6 and 12 weeks after HILP therapy, the improvement of walking with a severe limp towards a normal walking pattern continued.

Radiological scores for the total group 2 weeks after perfusion: progression in 3 dogs (12%); stationary in 13 dogs (52%); and an improved X-ray was found in 9 dogs (36%). Radiological scores 6 weeks after perfusion: progression in 6 dogs (25%); stationary in 3 dogs (12%) and an improved X-ray was found in 15 dogs (63%) (Table 2). These scores illustrate a change from a stationary X-ray, 2 weeks after perfusion toward an improved X-ray 6 weeks after perfusion.

The histological effect of cisplatin on the tumor was classified according to Huvos et al. Biopsy scores for the total group two weeks after perfusion showed: no reaction, Huvos I in 5 dogs (20%); moderate effect, Huvos II in 8 dogs (32%); good effect, Huvos III in 7 dogs (28%); total necrosis, Huvos IV in 5 dogs (20%). Six weeks after perfusion, biopsy scores were as follows: no reaction, Huvos I in 3 dogs (14%); moderate effect, Huvos II in 12 dogs (57%); good effect, Huvos III in 6 dogs (29%); total necrosis, Huvos IV in none of the dogs (Table 3). At 2 and at 6 weeks after perfusion, the overall histological score is one of moderate effect according to Huvos et al.

After summation of the individual scores, there was a significant improvement (p<0.001) in the clinical score in the total group 6 and 12 weeks after perfusion; respectively; 2.04 before perfusion to 3.04 6 weeks and 3.18 at 12 weeks after perfusion (Table 4). Radiological and histological scores only classify the response to treatment; therefore, mean radiological and histological scores before and after perfusion could not be compared. However, a comparison of the radiological and histological scores between 2-6 weeks could be made. There was no significant improvement or deterioration in radiological and histological mean scores between 2-6 weeks in the total group. Analysis of the distribution and the mean scores of all three parameters demonstrate that additional hyperthermia of 1°C (group I versus group II) did not improve the results of the measured parameters. Retrospective analysis of survival time showed a median survival for all dogs of 115 days (Fig. 2). Three dogs underwent a resection or amputation of the affected limb and survived 12, 24 and 43 months, respectively, after perfusion without evidence of disease.
Table 2  Distribution of radiological parameters at 2 and 6 weeks after perfusion

<table>
<thead>
<tr>
<th>Radiological Parameter</th>
<th>Group I and II</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 2 weeks N=25</td>
<td>6 weeks N=24</td>
<td>2 weeks N=12 *</td>
</tr>
<tr>
<td>I progression</td>
<td>3 (12%)</td>
<td>6 (25%)</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>II stationary</td>
<td>13 (52%)</td>
<td>3 (12%)</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>III improved</td>
<td>9 (36%)</td>
<td>15 (63%)</td>
<td>2 (17%)</td>
</tr>
</tbody>
</table>

*The radiological score of the dog that died 1 week after perfusion from a myocardial infarction included.

Table 3  Distribution of histological parameters at 2 and 6 weeks after perfusion

<table>
<thead>
<tr>
<th>Histology</th>
<th>Group I and II</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 2 weeks N=25 *</td>
<td>6 weeks N=21</td>
<td>2 weeks N=12 *</td>
</tr>
<tr>
<td>I no reaction</td>
<td>5 (20%)</td>
<td>3 (14%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>II moderate</td>
<td>8 (32%)</td>
<td>12 (57%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>III good</td>
<td>7 (28%)</td>
<td>6 (29%)</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>IV necrosis</td>
<td>5 (20%)</td>
<td>2 (17%)</td>
<td>2 (17%)</td>
</tr>
</tbody>
</table>

*The histological score of the dog that died 1 week after perfusion from a myocardial infarction included.

Table 4  Mean clinical, radiological and histological scores

<table>
<thead>
<tr>
<th>Mean scores</th>
<th>Clinical</th>
<th>Radiological</th>
<th>Histological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>-1 wks</td>
<td>2 wks</td>
<td>6 wks</td>
</tr>
<tr>
<td>Mean group I</td>
<td>1.93</td>
<td>2.55</td>
<td>3.18</td>
</tr>
<tr>
<td>Mean group II</td>
<td>2.14</td>
<td>2.31</td>
<td>2.92</td>
</tr>
<tr>
<td>Mean group I + II</td>
<td>2.04</td>
<td>2.42</td>
<td>3.04 **</td>
</tr>
</tbody>
</table>

*p < 0.05 group I versus group II; ** p < 0.001 compared with the pre-perfusion score.
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Discussion
In the treatment of osteogenic sarcoma a distinction can be made between systemic therapy and locoregional treatment. Systemic therapy is primarily concerned with eradicating possible micrometastatic disease and its use was a major breakthrough in the clinical treatment of osteosarcomas in the 1970s. About 60% of patients with resectable primary tumors and no metastases at diagnosis will be cured.
The primary objective in locoregional treatment is to prevent local recurrence and allow limb salvage procedures in an attempt to preserve limb function. New surgical techniques and the development of endoprosthetic materials, coupled with the systemic neo adjuvant chemotherapy, have offered less radical surgery for 40% - 80% of patients with osteosarcoma in the 1980s. Procedures that increase tumor necrosis of the primary tumor, and with that reduction of viable tumor cells and tumor volume, could contribute to limb preservation strategies. At first changes in systemic chemotherapy regimens were investigated to achieve this goal. In 1978, cisplatin exhibited activity in the treatment of osteogenic sarcoma. Since its first use, cisplatin has been one of the most effective chemotherapeutic agents and has been incorporated in most systemic treatment regimens for osteosarcoma. The potential local tumor effect of systemically administered cisplatin, however, is limited due to the nephrotoxicity and ototoxicity of cisplatin. Techniques that administer cisplatin locally have been introduced to surmount these systemic side effect restrictions. Powers et al. demonstrated the superiority of the intra-arterial administration of cisplatin to the intravenous route in canine osteosarcoma. Jaffe et al. reported a 50% response rate from intra-arterial infusion with cisplatin in osteosarcoma and recommended it for use in inoperable tumors, to render them suitable for limb salvage. On the other hand, Wile et al. demonstrated the superiority regional perfusion with cisplatin to the intra-arterial or intravenous route in an experimental pharmacokinetic study.
In a study of cisplatin pharmacokinetics during HILP in humans with recurrent melanoma, cisplatin levels were 10-20 times higher than those found in systemic treatment and about 5 times higher than those found in intra-arterial infusion. During these perfusions, high total platinum concentrations in the limb were reached that would be unacceptably toxic for systemic use. A substantial drug extraction occurred with minimal leakage to the systemic circulation.

The aim of the present study was to investigate the short-term effect of HILP with cisplatin in dogs with spontaneous osteosarcoma. All three parameters used to evaluate the short-term effect showed a trend toward improvement. However, only the clinical score reached statistical significance for the total group with 1.93 before perfusion, 2.42 (n.s.), 3.04 (p<0.001), and 3.18 (p<0.001) at 2, 6 and 12 weeks, respectively, after perfusion. The mean radiological score was 2.24 and 2.38 at 2 and 6 weeks after perfusion, i.e. 15 out of 24 (63%) dogs had an improved radiological picture 6 weeks after perfusion, compared with the picture before perfusion. The histological results showed a moderate effect at 2 weeks (mean score 2.48) with a slightly lower mean score at 6 weeks (2.14). This could be an indication that viable tumor cells are growing out between 2 and 6 weeks after an initial favorable response to perfusion, meaning that a limb salvage procedure should be planned 2 weeks after perfusion. Surprisingly none of the dogs showed a complete histological response of the tumor 6 weeks after perfusion. Three dogs with total necrosis 2 weeks after perfusion, showed viable tumor cells 6 weeks after perfusion. Sampling error could account for these observations. Although high total platinum levels in the perfusate were reached, the histological outcome were modest and comparable with those observed in the systemic treatment of osteogenic sarcoma.

Although several authors report an enhanced toxicity of cisplatin combined with hyperthermia, due to phenomena of enhanced blood flow, enhanced cellular drug uptake, tissue extraction, DNA cross-linking and decreased DNA repair, no additional therapeutic effect, according to the three parameters, could be demonstrated by increasing the limb temperature by 1°C (group II). The mean clinical, radiological and histological scores for both groups were comparable at 2 and 6 weeks. At 12 weeks however the second group deteriorated in clinical score significantly with regard to the first group (p < 0.05). Elevated normal tissue damage, occurring at higher perfusion temperatures could be a reasonable explanation for this observed difference in clinical performance of the dogs.

Median survival time in our series for all dogs was 115 days, similar to survival times in dogs that had amputation alone without any adjuvant chemotherapy. This may not be a surprising, as it is estimated that 90 % of the dogs with osteosarcoma already have micrometastatic disease predominantly in the lungs. An improvement
of survival is only to be expected when the locoregional treatment is combined with effective systemical therapy to eradicate micrometastatic disease. Mc Ewen et al. improved the overall median survival time from 77 to 222 days (p<0.002) using adjuvant treatment with liposome-encapsulated muramyl tripeptidephophatidylethanolamine (liposome/MTP-PE) after amputation for osteosarcoma in dogs. Combining HILP for local treatment together with adjuvant liposome/MTP-PE as the systemic component, may improve local control and increase disease free survival in canine osteosarcoma.

The present study shows that a single HILP with cisplatin in dogs having extremity osteosarcoma is feasible with acceptable locoregional toxicity, improved functional outcome at 6 and 12 weeks and a steadily improving radiological picture. However, the histological results were modest with none of the dogs showing a complete response 6 weeks after perfusion. Results of recent publications and of our own experience with a new perfusion modality, which combines tumor necrosis factor (TNF), Interferon (IFN), and melphalan in patients with recurrent melanoma or soft tissue sarcoma, are very promising. Since the endothelial cells are supposed to play a key role in the working mechanism of TNF, osteosarcomas with a high extent of tumor vessels, are of particular interest. Therefore the combination of TNF and Interferon with cisplatin could theoretically induce more tumor necrosis in osteosarcoma than could perfusion with cisplatin alone. A similar study designed to investigate the additional effect of TNF with cisplatin in the treatment of canine osteogenic sarcoma, is being initiated. If results are as good as they are in the treatment of recurrent melanoma and soft tissue sarcoma a step forward could be made in the locoregional treatment of osteosarcoma.

Conclusions

HILP with cisplatin is feasible in the local treatment of spontaneous osteosarcoma in dogs with acceptable locoregional toxicity, improved functional outcome at 6 and 12 weeks, and a steadily improving radiologic picture. However the histological results were modest with none of the dogs showing a complete response 6 weeks after perfusion and no additional therapeutic effect, according to the three parameters, could be demonstrated by increasing the perfusate temperature by 1° C. Therefore, the search for the ideal perfusion agent with substantial contribution to the limb sparing treatment in human osteosarcoma continues.
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