Use of PET/CT and Stereotactic Radiation Therapy for the Diagnosis and Treatment of Osteosarcoma Metastases

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ABSTRACT

This case report describes the use of two new concepts in the diagnosis and treatment of metastatic osteosarcoma (OSA) in one dog. The dog was initially presented for positron emission tomography and computed tomography (PET/CT) as full-body staging following amputation and adjuvant chemotherapy for treatment of OSA of the proximal tibia. The initial PET/CT did not show evidence of metastatic disease. Six mo after OSA, diagnosis pulmonary metastatic nodules were identified and oral toceranib phosphate was initiated. Twelve mo postdiagnosis the dog developed neck pain and non-ambulatory tetraparesis and was diagnosed with a C7 vertebral metastatic lesion based on magnetic resonance imaging. A second PET/CT was performed to screen for further metastatic lesions, and a nodule within the right ischium was identified. The C7 and ischial lesions were treated with stereotactic radiation therapy (SRT). Sixteen mo postdiagnosis, a third PET/CT was performed due to increasing size of the pulmonary nodules and a right-sided liver metastasis was detected. The liver mass was treated with SRT. The PET/CT scans facilitated identification of gross metastatic lesions that were subsequently treated with SRT, which resulted in clinical improvement of the dog's neurological signs. (*J Am Anim Hosp Assoc* 2017; 53:52–58. DOI 10.5326/JAAHA-MS-6359)

Introduction

Osteosarcoma (OSA) is an aggressive primary bone tumor in dogs with a high rate of microscopic metastases at diagnosis.[1] Regular monitoring for development of metastatic disease (staging) is recommended following curative-intent treatment protocols for treatment of canine appendicular OSA. Common staging tests include thoracic radiography, thoracic or full-body computed tomography (CT), full-body nuclear scintigraphy, and abdominal ultrasonography.[2–7] Combined positron emission tomography and computed tomography (PET/CT) is routine in the diagnosis and staging of cancer in humans.[8,9] PET allows for non-invasive characterization of tissue metabolism, blood flow, perfusion, and oxygenation. Limited availability precludes routine use of PET/CT in oncologic management of veterinary patients. Despite this limitation, PET/CT offers potential advantages over currently recommended staging tests, including high sensitivity of detection of metastatic lesions and allowing assessment of soft tissues and bone with full-body imaging.

Reported treatments for gross OSA metastases include pulmonary metastatectomy, fractionated radiation therapy, Samarium-153, systemic and inhalational chemotherapy, and receptor tyrosine kinase inhibitors.[10] Stereotactic radiation therapy (SRT)

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CBC (complete blood count); CT (computed tomography); FDG (2-deoxy-2-[^{18}F]fluoro-D-glucose); MWF (Monday, Wednesday, and Friday); OSA (osteosarcoma); PET/CT (positron emission tomography and computed tomography); SRT (stereotactic radiation therapy); SUV (standard uptake value); TPLO (tibial plateau leveling osteotomy)

has been utilized for treatment of primary appendicular bone tumors, but this treatment has not been reported for metastatic OSA.[11] The purpose of this report describes the use of PET/CT for staging in canine OSA, which facilitated identification of metastatic lesions and allowed for treatment of OSA metastases with SRT.

Case Report

A 10-year-old, female, spayed rottweiler was presented to Colorado State University Veterinary Teaching Hospital for a PET/CT for OSA staging. A left mid-femoral hind limb amputation had been performed 4 mo prior to presentation, for treatment of a left proximal tibial OSA at the site of a tibial plateau leveling osteotomy (TPLO) performed 5 yr prior. The dog was subsequently treated with an IV chemotherapy protocol consisting of carboplatin[a] (300 mg/m^2) and doxorubicin hydrochloride[b] (30 mg/m^2) with administration of one agent every 2 wk on an alternating schedule for three doses of each agent. Following completion of the chemotherapy protocol, thoracic radiographs and thoracic and abdominal CT were performed and did not show evidence of metastatic disease, but the owner was interested in PET/CT assessment for metastases. On physical examination, the dog had muscle atrophy of the remainder of the amputated left hindlimb, but no other abnormalities were detected. The dog was anesthetized for a PET/CT scan using a premedication of subcutaneous hydromorphone[c] (0.1 mg/kg) and atropine[d] (0.02 mg/kg) and induced with IV propofol[e] (2.3 mg/kg) and midazolam[f] (0.2 mg/kg) with maintenance of a mixture of isoflurane[g] and oxygen. Following induction, the dog was transported to the PET/CT suite, where 6.3 mCi 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) was injected intravenously. During the 1-hr uptake period, pre- and post-IV contrast (iohexol[h]; 770 mg/kg) whole-body CT scans were performed. One hr after FDG injection, whole-body PET images were obtained in multiple bed positions. The PET/CT was performed using a scanner[i]. The PET/CT scan identified multiple areas of increased radionucleotide uptake (maximum lesion standard uptake values $[SUV]_{max}$ of minimal to 5.3), none of which were thought to be consistent with metastases. Increased FDG uptake at the left distal femoral margin (SUV_{max} of 2.1) was thought to be most likely a result of postsurgical extraosseous and medullary fibrosis with mild inflammation. Residual tumor was thought unlikely based on CT appearance and low level of FDG uptake. Other abnormalities evident included ankylosing spondylosis, sternebritis and costosternitis (minimal FDG uptake suspected to be inflammatory due to lack of soft tissue reaction to suggest an infectious cause), bilateral elbow osteoarthritis, previous TPLO, and extensive right stifle osteoarthritis. No obvious metastatic lesions were detected. A fine needle aspirate and cytology of the distal aspect of the left femoral amputation site were performed when the dog returned to background radiation levels, and results were consistent with reactive bone.

A thoracic CT was performed for routine staging 2 mo following the PET/CT scan (6 mo post OSA diagnosis). A circumscribed 5 mm diameter soft tissue nodule was identified in the ventral aspect of the right cranial lung lobe. This nodule was suspected to represent pulmonary metastasis from OSA. At that time, the dog was started on oral toceranib phosphate[j] (2.35 mg/kg) administered on Monday, Wednesday, and Friday (MWF). A recheck thoracic CT was performed 1 mo later (7 mo post OSA diagnosis). The pulmonary nodule was unchanged in size and no additional nodules or masses were seen. Following the CT scan, oral cyclophosphamide[k] (9.25 mg/m^2) and oral furosemide[l] (1 mg/kg) were prescribed, in addition to toceranib phosphate, to be administered on Tuesday, Thursday, Saturday, and Sunday. The pulmonary nodule remained unchanged on thoracic radiographs performed every 1 to 2 months. On a recheck of complete blood count (CBC) 2 mo after starting cyclophosphamide, a leukopenia (WBC 2.8 $\times$ 10^3/μL; reference range, 5.7–16.3 $\times$ 10^3/μL) was detected, so the toceranib phosphate, cyclophosphamide, and furosemide were discontinued. The toceranib phosphate was reinitiated (2.35 mg/kg) 4 days later; however, within 2 wk, the dog was leukopenic (2.6 $\times$ 10^3/μL; reference range, 4.0–15.5 $\times$ 10^3/μL) once more, so the toceranib phosphate was discontinued for 4 wk.

Two wk following discontinuation of toceranib phosphate, the dog was noted to have neck pain and was ataxic. Over the 2-wk period the dog was increasingly paretic and became non-ambulatory. Three days prior to presentation, the dog was presented to a local veterinary neurologist and an MRI of the cervical spine was performed. The MRI showed evidence of an expansile and aggressive bone lesion involving the C7 vertebra that was suspected to be an OSA vertebral metastasis. Neither fine needle aspirate nor biopsy were performed.

One yr after original OSA diagnosis, the dog was presented again to Colorado State University Veterinary Teaching Hospital for further investigation of the probable metastatic lesion in the C7 vertebra. On physical examination, the dog was non-ambulatory and tetraparetic. Proprioceptive deficits were present in all 3 limbs. There was hyperreflexia of the patella, gastrocnemius, and cranial tibial reflexes. The forelimb withdrawal reflex was weak bilaterally, and there was severe cervical pain, with movement of the neck being resisted both laterally and dorsoventrally. The neuroanatomic localization based on the examination was C1-T2. Blood work was unremarkable. To treat the cervical pain, an IV catheter was placed and fentanyl[m] (0.001-0.005 mg/kg/hr) was administered as a

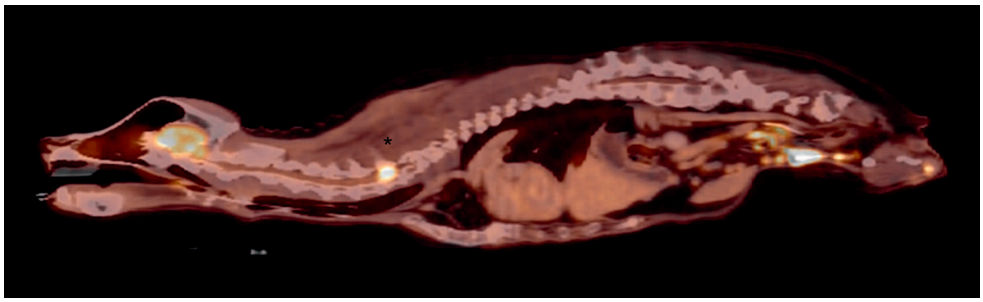

FIGURE 1 *Sagittal PET/CT image of increased FDG uptake in C7 vertebral body and pedicle. The* black asterisk *indicates position of C7 vertebral metastatic lesion. The right ischial lesion cannot be seen on this view. Increased FDG uptake is present in the brain and urinary tract. FDG (2-deoxy-2-[18F]fluoro-D-glucose); PET/CT (positron emission tomography and computed tomography).*

continuous rate infusion in combination with oral gabapentin[n] (8.6 mg/kg *q* 12 hr), methocarbamol[o] (21.4 mg/kg *q* 12 hr), and prednisolone[p] (0.9 mg/kg *q* 12 hr).

A second PET/CT was performed (using the aforementioned protocol) for the purposes of both additional staging and radiation planning. The dog was positioned in sternal recumbency with the right hindlimb extended caudally in an immobilization device consisting of a bite block, thermoplastic mask, and cushion[q] to ensure replicable patient positioning.[12] The PET/CT revealed an extradural, mildly osteolytic and osteoproductive, soft tissue mass lesion in the left aspect of the C7 cervical vertebral canal (measuring 2 cm x 3 cm x 1.4 cm). The mass was hypermetabolic with an SUV_{max} of 4.5 (**Figure 1**). This lesion caused severe spinal cord compression and spinal cord displacement. An osteoproductive and osteolytic bone lesion (2.1 cm diameter) was identified in the right ischium with a SUV_{max} of 4.5. There was a 1 cm diameter soft tissue nodule identified in the ventral aspect of the right cranial lung lobe (SUV_{max} 2.3), and a 3 mm soft tissue nodule in the dorsal aspect of the right cranial lung lobe (SUV_{max} 0.8). There were multiple 1-2 mm soft tissue to mineral attenuating foci throughout the lungs, thought to be osteomata. The leading differential diagnosis for the C7 and ischial lesions identified on PET/CT was OSA metastases. Given the high level of clinical suspicion and potential difficulty obtaining diagnostic samples, an aspirate or biopsy of the lesions was not performed. A urinary catheter was placed, as the dog was weak and non-ambulatory. SRT was planned with the palliative goals of decreasing pain associated with the C7 lesion, to prevent future pain at the ischial site, and to try to improve ambulation to maintain quality of life. The C7 lesion was treated with three fractions of SRT administered on a Friday, Monday, and Wednesday. The right ischial lesion was treated with two fractions of SRT on Monday and Wednesday. SRT was administered with a linear accelerator[r] following computer-based inverse planning at treatment planning workstation[s] and was delivered with intensity modulation and image guidance (see **Table 1** for treatment details). Quality assurance was performed for each plan (using Varian's Portal Dosimetry system) by an American Board of Radiology certified medical physicist. Normal tissue constraints were applied from the American Association of Physicist in Medicine guidelines.[13] For each radiation treatment, the dog was anesthetized as previously described. The urinary catheter was removed on the day of the second SRT treatment for the C7 lesion, oral prazosin[t] was initiated (1 mg/kg *q* 8 hr), and the dog was able to voluntarily urinate. During hospitalization, the dog received repeated neurological and clinical assessments to monitor neurological status and pain control. Rehabilitation was performed three to four times daily, including passive range of motion of all joints, assisted standing, and walking. Significant improvements in the neck pain and strength were noted and the dog was ambulatory with assistance prior to discharge. The dog was discharged 2 days after the last fraction of SRT with oral methocarbamol (21.4 mg/kg *q* 12 hr), tramadol[u] (2.1 mg/kg *q* 6 hr), prednisolone (0.9 mg/kg *q*12 hr), and gabapentin (8.6 mg/kg *q* 12 hr).

One wk after discharge, pamidronate[v] (1.4 mg/kg IV) was administered as a continuous rate infusion over 2 h. At this visit to a local veterinary medical oncologist, the dog was ambulatory with mild tetraparesis, and at that time the toceranib phosphate (2.35 mg/kg *per os* MWF) was reinstituted. Pamidronate was repeated 1 mo later (1.4 mg/kg IV). At this visit, a small (5 mm) dermal mass was noted on the medial aspect of the right thigh, and leukopenia ($2.7 \times 10^3/\mu L$; reference range, $4.0\text{-}15.5 \times 10^3/\mu L$) was noted on CBC. A fine needle aspirate was performed, and cytologic findings suggested a mesenchymal cell tumor. The toceranib phosphate was temporarily discontinued and a punch biopsy of the nodule was performed. Histopathology of the nodule was suggestive of a mesenchymal tumor with narrow excision; although no evidence of osteoid production was seen, this was considered a likely skin metastasis. Toceranib phosphate was reinstituted (2.0 mg/kg *per os*

TABLE 1

Details of Stereotactic Radiation Treatment Administered to the C7, Ischial, and Liver Lesions

	C7 Lesion	Ischial Lesion	Liver Lesion
Prescription			
D/F (Gy)	10	15	8
Total (Gy)	30	30	8
GTV (cc) or CTV (cc)	7.2	12.5	237.7
PTV (cc)*	24	53.6	370.4
Dose delivered to 99% GTV or CTV (Gy)	22.3	31.2	7.9
Dose to PTV			
95% (Gy)†	21.3	29.7	7.7
Range (Gy)	14.5-33.4	23.9-32.7	5.3-23.2
Mean (Gy)	29.6	31.1	12.5
Simultaneously integrated boost(s)	1.3 cc	2.9 cc	108.5 cc
	99% 31.2 Gy	99% 31.2 Gy	99% 13.7 Gy
	Range: 30.2-33.4 Gy	Range: 31.1-31.7 Gy	Range: 10.4-23.2 Gy
	Mean 32.4 Gy	Mean 31.5	Mean; 18.9

D/F, dose per fraction; GTV, gross tumor volume, defined as the gross tumor volume visible via a fusion of CT and PET; CTV, clinical target volume, which was equivalent to the GTV for the three radiation plans; PTV, planned target volume, which was the GTV plus 5 mm (C7 and liver) or 8 mm (ischium) minus the skin thickness.
†Refers to the minimum dose delivered to 95% PTV.

MWF) 1 mo later and pamidronate (as above) was repeated. The dog was reassessed every 1-2 wk by the local medical oncologist, allowing assessment of the dog and discussion with the owner as to whether the palliative treatments were effectively decreasing pain and maintaining quality of life. During this time, the owner and local oncologist were happy with the progress of the dog given the improvement in ambulation, resolution of cervical pain, and improved quality of life shown.

Chest radiographs were performed for restaging 15 mo after OSA diagnosis and showed a mild increase in the size of the pulmonary nodule within the ventral aspect of the right cranial lung lobe; pamidronate (as above) was administered at this visit. The dog was presented again to Colorado State University Veterinary Teaching Hospital for a recheck PET/CT scan 16 mo after diagnosis of OSA; CBC and serum biochemistry performed the week prior to presentation was unremarkable. On physical examination, there was a small alopecic area over the right ischium. The skin in this area was not inflamed or ulcerated, and the changes were consistent with a grade I late radiation toxicity.[14] The dog was ambulatory with mild ataxia and moderate right hind limb weakness. No neck pain or resistance to movement was present. Mild proprioceptive deficits were present in all three limbs. All reflexes were normal, and the neuroanatomic localization of C1 to T2 was given based on this examination.

The dog was anesthetized for an FDG PET/CT scan (using previous PET/CT protocol and a dose of 5.4 mCi FDG). The dog was positioned in dorsal recumbency using a cushion. The PET/CT abnormalities detected included a heterogeneous, mixed attenuating variably FDG hypermetabolic mass within the right medial and right lateral liver lobes (SUV_{max} 19), multiple pulmonary nodules (SUV_{max} 0.7–4.2), a hypermetabolic nodule in right intercostal muscles (SUV_{max} 3.8), a focal sclerotic, hypermetabolic nodule in the right scapula (SUV_{max} 3.3), contrast enhancing splenic nodules (SUV_{max} 0.7–0.8), multiple well-defined, non-contrast enhancing hypoattenuating areas (consistent with cysts) within the liver (SUV_{max} 0.92–1.17), and previously described benign osseous changes. The differential diagnoses considered for the right-sided liver mass included primary liver neoplasia or metastatic neoplasia, and for the splenic nodules included nodular regeneration, extramedullary hematopoiesis, or metastasis. The C7 vertebral and right ischial lesions showed decreased metabolic activity (C7 lesion SUV_{max} 3.6 versus 4.5; right ischial lesion SUV_{max} 0.9 versus 4.5) and decreased extradural compression at C7. An abdominal ultrasound was performed the following day to facilitate ultrasound-guided aspirates of the liver mass (measured at 8 cm by 9 cm), liver nodules, and splenic nodules. Cytology suggested that the right-sided liver mass was a sarcoma, the liver nodules result were

possibly well-differentiated hepatocellular carcinomas, and the splenic nodules represented extramedullary hematopoiesis and lymphoid hyperplasia. A bile acid stimulation test performed to assess liver function was normal. Given the previous history of OSA, the right-sided liver mass was suspected to be metastatic OSA.

Three days after the PET/CT, the dog was anesthetized for a single fraction of SRT, which was delivered to the right-sided liver mass (Table 1). The anesthesia protocol and patient positioning were the same as described for the PET/CT scan. However, the dog was placed on a ventilator and atracurium[w] (0.1 mg/kg IV) was administered; this allowed for management of respiratory motion during delivery of SRT (radiation dose was only administered with the patient held at maximal expiration). Following discharge, toceranib phosphate (2.1 mg/kg orally *q* MWF) and chlorambucil[x] (0.13 mg/kg orally on alternating days to toceranib phosphate) were prescribed.

One mo after hepatic SRT, the dog was presented again to its local oncologist with a 4-day history of mildly decreased appetite and lethargy. Restaging with chest radiographs showed multiple soft tissue pulmonary nodules with mild increases in size of three visible pulmonary nodules. An abdominal ultrasound performed at that time showed a small amount of peritoneal effusion, with mild increase in size of the liver mass (measured 10.6 × 8.6 cm). Toceranib phosphate and chlorambucil were continued as previously prescribed.

The dog experienced worsening in appetite and lethargy and was presented to Colorado State University Veterinary Teaching Hospital (17 mo after OSA diagnosis) for euthanasia and necropsy examination. Necropsy showed disseminated metastases of OSA. The liver mass was larger (30 cm x 30 cm x 40 cm) than measured on the initial ultrasound scan (8 cm by 9 cm). The right lateral liver lobe mass was characterized by prominent central necrosis with numerous pockets containing thick, opaque, yellow exudate. Nodules of highly pleomorphic neoplastic cells multifocally infiltrated the liver and spleen. There were about 10 masses within the omentum and mesentery, and the kidneys contained three nodules (2–3 cm in diameter). Other metastatic nodules were found in the heart, lungs, adrenal, and thoracic wall. There was extensive necrosis of the neoplastic lesions in the C7 vertebra and the right ischium. Assessment of the spinal cord adjacent to the C7 lesion revealed some mild axonal swelling and some dilation of the myelin sheathes in all white matter funiculi; these changes were thought to be due to compression and not consistent with side effects from radiation therapy.

Discussion

Osteosarcoma is reported most commonly in middle-aged large breed dogs; the rottweiler breed is one of the breeds most at risk of OSA in the United States.[10] Development of OSA at the site of a previous TPLO has been rarely reported in the veterinary literature.[15,16] Appendicular OSA is a biologically aggressive tumor necessitating close monitoring for development of metastases following treatment. Recent investigations have focused on comparison of staging tests and determined that thoracic CT detected more pulmonary lesions than digital radiography but that whole body CT was not a suitable alternative to bone scintigraphy.[2,3] PET/CT has not been reported for staging of canine OSA.

Positron emission tomography can be performed with different tracers (or radiopharmaceuticals) to allow assessment of tissue characteristics including perfusion, oxygenation, proliferation, and metabolism. FDG is a glucose analogue that is commonly used as a tracer in human oncology, as tumor cells use glycolysis to generate more than half their energy, which should result in accumulation of FDG compared to normal cells.[17] However, FDG can also accumulate in non-cancerous tissues that are metabolically active, including inflammatory lesions and muscles. Standard uptake value (SUV) is a semi-quantitative measurement of the degree of FDG accumulation that is calculated using the concentration of FDG in a tissue divided by the dose of FDG injected and body weight.[18] The SUV of tissues or lesions accumulating FDG has been characterized in normal dogs but has not been fully characterized in spontaneous inflammatory or neoplastic diseases, thus limiting the utility of FDG-PET with regard to definitively distinguishing neoplastic from non-neoplastic lesions.[17] Given the incomplete characterization of cut-offs for SUV_{max} for malignant and benign lesions in veterinary species, any area that was hypermetabolic on PET images were thoroughly evaluated on CT. The SUV and CT characteristics were used together in this case to assess lesions leading to identification of several neoplastic and non-neoplastic lesions. PET/CT offered assessment of the entire body for detection of soft tissue or bone metastases and resulted in detection of both bone and soft tissue OSA metastases that were later confirmed by histopathology. Lesions smaller than 8 mm could potentially be overlooked by PET/CT due to the limited spatial resolution.[18] Further investigation into FDG PET/CT for staging of canine OSA and the sensitivity for detection of metastases compared to other imaging modalities may be merited.

The main goal of treatment of metastatic disease in this dog was to decrease pain and recover ambulation to improve quality of life. It is well known that following development of metastatic

disease, survival times can be short (median survival time 76 days) despite treatment.[19] Palliative treatments are often employed to decrease signs associated with metastatic OSA, such as pain from bone metastases. SRT is a promising option for palliative treatment to decrease local OSA metastatic progression and pain. Precise treatment delivery and a small number of fractions are required, which is of benefit when considering palliative treatments for metastatic disease. In human medicine, SRT is commonly used for inoperable head and neck sarcomas and has been reported for vertebral tumors, hepatic tumors, and brain metastases. The use of SRT for treatment of the OSA bone and soft tissue metastases has not been reported in dogs. The stereotactic radiation treatments were planned for this dog using the PET/CT scans to identify the location and extent of the metastatic lesion. SRT was successful in palliating the neurological clinical signs, including severe neck pain resulting from the C7 vertebral metastasis, and was well tolerated (only a grade I skin toxicity over the right ischium). Decreased PET avidity of the two OSA bone metastatic lesions occurred following SRT and systemic anti-neoplastic therapy. This could be consistent with decreased metabolic activity of the tumor resulting from cell death occurring due to the SRT or anti-neoplastic treatment. Multimodal treatment for metastatic disease in canine OSA may result in longer survival times due to improved palliation of the clinical signs of disease or control of disease progression. In the Boston et al. study, the dogs receiving palliative radiation and chemotherapy had significantly longer survival times than dogs receiving other treatments (including NSAID-opioids, surgery, chemotherapy, or combinations of these treatments or radiation therapy alone), but the median survival time was 130 d.[19] The combination of treatments for metastatic disease used in this dog provided 1-y survival following diagnosis of metastatic disease and improved the quality of life of the dog. Further investigation of multimodal treatment for metastatic OSA and the effect on quality of life may be merited.

Conclusion

The case report highlights the potential utility of PET/CT in canine OSA for staging and facilitating treatment of suspected metastases with SRT. In addition, the report describes the use of SRT for treatment of gross OSA metastatic lesions.

FOOTNOTES

[a] Carboplatin; Hospira, Lake Forest, Illinois
[b] Adriamycin; Bedford Laboratories, Bedford, Ohio
[c] Hydromorphone HCl; Baxter Healthcare Corp., Deerfield, Illinois
[d] Atrophine sulfate; Vedco Inc., St. Joseph, Missouri
[e] Propoflo; Abbott Labs, North Chicago, Illinois
[f] Midazolam hydrochloride; Hospira Inc., Lake Forest, Illinois
[g] Isoflo; Abbott Labs, North Chicago, Illinois
[h] Omnipaque; General Electric Healthcare Inc., Princeton, New Jersey
[i] Philips Gemini TF Big Bore 16-slice scanner; Philips Medical Systems Nederland B.V., Eindhoven, Netherlands
[j] Palladia; Pfizer, New York, New York
[k] Cyclophosphamide; Roxane Laboratories Inc., Columbus, Ohio
[l] Furosemide; Vedco Inc., St. Joseph, Missouri
[m] Fentanyl citrate; Hospira Inc., Lake Forest, Illinois
[n] Gabapentin; TEVA pharmaceuticals USA, Sellersville, Pennsylvania
[o] Methocarbamol; West-Ward Pharmaceutical Corp., Eatontown, New Jersey
[p] Prednisolone; Vedco Inc., St. Joseph, Missouri
[q] Vac-Lok cushion; CIVCO Medical Supplies, Orange City, Iowa
[r] Varian Trilogy linear accelerator; Varian Medical Systems Inc., Palo Alto, California
[s] Eclipse treatment planning workstation; Varian Medical Systems Inc., Palo Alto, California
[t] Prazosin HCl; TEVA Pharmaceuticals USA, Sellersville, Pennsylvania
[u] Tramadol HCl; TEVA Pharmaceuticals USA, Sellersville, Pennsylvania
[v] Pamidronate disodium; Hospira, Lake Forest, Illinois
[w] Atriacurium besylate; Hospira, Lake Forest, Illinois
[x] Leukeran; Aspen Global Inc., Prasco Laboratories, Mason, Ohio

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