Objective—To describe the biological behavior, clinical outcome, and prognostic factors of osteosarcoma of the maxilla, mandible, or calvarium in dogs.

Design—Retrospective case series.

Animals—183 client-owned dogs with osteosarcoma of the maxilla, mandible, or calvarium.

Procedures—Medical records for dogs treated for osteosarcoma of the maxilla, mandible, or calvarium from 1986 through 2012 were reviewed. Dogs with a histopathologic diagnosis of osteosarcoma and treated for a primary tumor arising from these bones of the head were included.

Results—Mean age was 9.3 years, and body weight was 31.8 kg (70.0 lb). Most dogs (124/183 [67.8%]) were purebred, and the most common primary tumor site was the maxilla (80 [43.7%]). Treatments included palliative medical treatment only (11/183 [6.0%]), coarsely fractionated radiation therapy (RT; 12 [6.6%]), fractionated or stereotactic RT (18 [9.8%]), surgery (135 [73.8%]), and both surgery and fractionated RT (7 [3.8%]). Eighty-three (45.4%) dogs received adjuvant chemotherapy. Local recurrence or progression occurred in 80 of 156 (51.3%) dogs, and 60 of 156 (38.5%) dogs developed distant metastases. Median survival time for all dogs was 239 days. Dogs that underwent surgery had a median survival time of 329 days. Histologically tumor-free surgical margins were associated with significantly decreased hazards of progression or recurrence (hazard ratio [HR], 0.4) and death (HR, 0.5). Dogs with osteosarcoma of the calvarium had a significantly greater hazard of local recurrence or progression (HR, 2.0).

Conclusions and Clinical Relevance—In this study, tumor excision in dogs with histologically tumor-free margins resulted in better local control and longer survival time than did other treatment types. (J Am Vet Med Assoc 2014;245:930–938)
metastatic disease, which is commonly the cause of death in appendicular osteosarcoma. The mandibular location has been associated with longer reported MST of 14 to 18 months and 1-year survival rates of 35% to 71%. Complete excision and mandibular location have repeatedly been shown to be favorable prognostic factors, although most reports are retrospective and contain small numbers of cases with adequate follow-up. Other prognostic factors commonly associated with outcome for appendicular osteosarcoma have not been extensively evaluated for osteosarcoma of the maxilla, mandible, or calvarium.

Historically, because many patients with osteosarcoma of the maxilla, mandible, or calvarium are reported to die of local disease and not metastatic disease, the role of adjuvant chemotherapy has been questioned. It has been firmly established that chemotherapy combined with local disease control improves outcomes in appendicular osteosarcoma. In a recent report, adjuvant chemotherapy was shown to result in significantly increased metastasis-free interval and OST in dogs with mandibular osteosarcoma treated with excision. The impact of RT for treatment of osteosarcoma of the maxilla, mandible, or calvarium has not been well established.

In comparison, osteosarcoma of the maxilla, mandible, calvarium, and neck in humans represents only 2% to 10% of all osteosarcomas reported and is thought to differ from the more commonly diagnosed osteosarcoma of long bones in several ways. Osteosarcoma of the maxilla, mandible, or calvarium is reported to have a more advanced age of onset in humans (median, 40 to 50 years of age) and to have a more heterogeneous histologic distribution. The reported metastatic rate to distant sites of 6% to 18% is lower than that for appendicular osteosarcoma in humans. Surgery is the mainstay of treatment for osteosarcoma of the maxilla, mandible, or calvarium in humans; tumor size and ability to achieve local control affect outcome. The role of radiation and chemotherapy is not well defined, with conflicting reports of the benefit for either or both combined with surgery.

The purpose of the study reported here was to better describe biological behavior, clinical outcome, and prognostic factors on the basis of retrospectively compiled data on a large number of dogs with osteosarcoma confined to the head. We hypothesized that the metastatic rate for tumors in this location would be less than that reported for tumors of the appendicular skeleton and that on the basis of microscopic findings, complete excision, compared with incomplete excision, would result in better local control and improved outcome.

**Materials and Methods**

**Case selection**—An institutional electronic primary bone tumor database was searched for records of dogs with osteosarcoma of the maxilla, mandible, or calvarium between July 1, 1986, and December 31, 2012. For inclusion in this retrospective case series, dogs required a histopathologic diagnosis of osteosarcoma and a primary tumor arising from the maxilla, mandible, or calvarium. Dogs were excluded if prior treatment other than analgesic medications was administered or if the tumor was primarily arising from soft tissues or within the nasal cavity or paranasal sinuses, because of reported differences in biological behavior, compared with axial osteosarcoma.

**Medical records review**—A retrospective review of hardcopy and electronic medical records was performed to obtain information about baseline characteristics at the time of osteosarcoma diagnosis, including age, sex and neuter status, breed, body weight, date of diagnosis, and anatomic location of the primary tumor (mandible, maxilla, or calvarium). Laboratory blood test results from the time of diagnosis were evaluated, including monocyte and lymphocyte counts and both the serum ALP activity and whether the serum ALP activity was above the institutional reference range limit (> 140 U/L). If diagnostic imaging was used to assess the local extent of the primary tumor, the type of diagnostically imaging was recorded. If CT was performed, the diagnostic imaging report was reviewed to assess the maximum reported diameter of the tumor. If the tumor diameter was not reported, the greatest tumor diameter was determined by performing measurements with the image measuring tool software from sequential CT slices through the tumor. The results of staging tests performed at the time of diagnosis were recorded, and if metastases were present, the sites of metastases were recorded when available.

Details about treatment administered for the primary tumor were evaluated, and dogs were categorized according to the treatment type (palliative medical treatment, coarsely fractionated RT, surgery, finely fractionated RT or SRT, or surgery and finely fractionated RT). Coarsely fractionated RT is administration of relatively large doses per fraction typically given on a weekly basis, with the goal of minimizing acute radiation side effects in spite of potential losses in tumor control due to low total dose of radiation and increased risk for late toxicity due to large fraction size; these protocols are often used with palliative intent. Finely (or conventionally) fractionated RT is a high dose of radiation given as 5 small daily doses/wk for 3 to 4 weeks; such protocols are often used to treat gross or microscopic disease with definitive-curative intent. Dogs that primarily received analgesic medications with or without an NSAID were classified as having received palliative medical treatment.

For dogs that had surgery, histopathologic reports were reviewed to record details about excisional completeness. If no neoplastic cells were described at the edge of the surgical margin, the mass was considered completely excised. If neoplastic cells extended to the edge of the surgical margin, the mass was considered incompletely excised. Two pathologists (DAK and AG) histologically reviewed tumor specimens from a subset of dogs to determine histologic subtype (osteoblastic, chondroblastic, fibroblastic, telangiectatic, giant cell, or small cell). This subset of cases was reviewed as part of an earlier investigation, during review, a high level of accuracy for diagnosis of osteosarcoma was determined.

For dogs that were treated with RT, the type of protocol administered was recorded (coarsely fractionated, finely fractionated RT, or SRT). The RT was delivered by different linear accelerators over the study period.
The total dose, number of fractions used, and dose per fraction were recorded.

If chemotherapy was used, the agents, number of doses administered, and route of administration (IV vs implantable sustained release) were recorded. The use of other treatments such as IV administration of bisphosphonates, oral administration of NSAIDs, and metronomic administration of cyclophosphamide was recorded.

Outcome information was collected prospectively as part of follow-up for an institutional primary bone tumor registry. Information was acquired from recheck visits, referring veterinarians, and owners. The date of tumor progression, local recurrence, or development of metastases was recorded. Tumor progression or local recurrence was determined by the primary clinician and was not prospectively defined on the basis of the Veterinary Cooperative Oncology Group response evaluation criteria for solid tumors because these were not available at the start of the study period. If metastases developed, the site of first detection of metastasis was recorded and classified as pulmonary, other site, or multifocal. The date the dog was lost to follow-up, died, or was euthanized was collected.

Statistical analysis—Continuous data were graphically assessed for normality, and data were described as mean ± SD if normally distributed and median and IQR if nonnormally distributed. Categorical data were described with frequencies (proportions and percentages of dogs). Baseline characteristics (age and body weight at the time of diagnosis, sex and neuter status, serum ALP activity, monocyte and lymphocyte counts, and anatomic location of primary tumor) were compared across treatment groups with a 1-way ANOVA for continuous variables and χ² tests for categorical variables.

Progression-free survival time was calculated as the time from the date of diagnosis to the date of documented local disease progression, local recurrence, or development of metastases. Progression-free survival time was only calculated for dogs that did not have metastases at the time of diagnosis and that received finely fractionated RT or SRT, surgery only, or surgery and finely fractionated RT. Dogs were censored in the PFS analysis if they did not have documented local disease progression, local recurrence, or development of metastases at the time of last follow-up or the time of death. Overall survival time was calculated as the time from the date of diagnosis to the date of last follow-up or death resulting from any cause. Dogs were censored in the survival analysis if they were alive at the time of last follow-up or were lost to follow-up.

The Kaplan-Meier method was used to generate survival curves and calculate the median PFS time, median OST, and 95% CIs. A Cox proportional regression analysis was used to assess for any association between baseline characteristics (age and body weight at the time of diagnosis and breed [purebred vs mixed]), diagnostic test results (monocyte or lymphocyte count, serum ALP activity, and whether the serum ALP activity was > 140 U/L [yes vs no]), anatomic location (mandibular, maxillary, or calvarial), largest diameter of tumor, treatment intent, histologic status surgical margins, use of chemotherapy, use of RT, and outcome measures (PFS time and OST). Hazard ratios and 95% CIs were generated to describe these associations. Statistical analyses were performed with commercial software packages.

Results

One hundred ninety dogs were treated for osteosarcoma of the maxilla, mandible, or calvarium during the study period. Seven dogs were excluded (2 had an undifferentiated high-grade sarcoma that was diagnosed retrospectively, and 5 had osteosarcoma diagnosed presumptively without histologic evaluation). One hundred eighty-three dogs were treated for osteosarcoma of the maxilla, mandible, or calvarium during the study period. The mean ± SD age was 9.3 ± 2.9 years, and the mean ± SD body weight was 31.8 ± 10.7 kg (70.1 ± 23.5 lb). The majority of dogs were neutered (n = 167 [91.3%]) and were purebred (124 [67.8%]; Table 1). Breeds represented included Labrador Retriever (n = 26 [14.2%]), Golden Retriever (24 [13.1%]), Rottweiler (5 [2.7%]), Border Collie (4 [2.2%]), German Shepherd Dog (4 [2.2%]), Australian Shepherd (4 [2.2%]), Siberian Husky (4 [2.2%]), Standard Poodle (4 [2.2%]), Bernese Mountain Dog (3 [1.6%]), Bassett Hound (3 [1.6%]), Doberman Pinscher (3 [1.6%]), English Springer Spaniel (3 [1.6%]), Great Dane (3 [1.6%]), and Portuguese Water Dog (3 [1.6%]). Another 24 breeds were represented with 1 or 2 dogs each.

The maxilla was the most common primary tumor location (n = 80 [43.7%]), followed by mandible (60 [32.8%]) and calvarium (43 [23.5%]). Metastases were rarely detected at the time of diagnosis (n = 7 [3.8%]). Sites of metastasis were tabulated (Table 1). Serum ALP activity was > 140 U/L at the time of diagnosis in 63 of 180 (35.0%) dogs, and median serum ALP activity (from 64 dogs) was 77 U/L (IQR, 52.0 to 184.0 U/L). The median monocyte and lymphocyte counts (from 159 dogs) were 0.5 ± 0.8 X 10⁶ cells (IQR, 0.3 ± 0.5 X 10⁶ cells to 0.8 ± 1.0 X 10⁶ cells) and 1.3 ± 2.9 X 10⁶ cells (IQR, 0.9 ± 1.0 X 10⁶ cells to 2.0 ± 2.0 X 10⁶ cells). Diagnostic imaging of the primary tumor was performed in 164 (89.6%) dogs, with CT being used most commonly (n = 116 [63.4%]), followed

Table 1—Baseline characteristics of 183 dogs with osteosarcoma of the maxilla, mandible, or calvarium.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>9.3 ± 2.9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>31.8 ± 10.7</td>
</tr>
<tr>
<td>Sex and neuter status</td>
<td></td>
</tr>
<tr>
<td>Sexually intact female</td>
<td>7 (3.8)</td>
</tr>
<tr>
<td>Spayed female</td>
<td>84 (45.9)</td>
</tr>
<tr>
<td>Castrated male</td>
<td>83 (45.4)</td>
</tr>
<tr>
<td>Sexually intact male</td>
<td>9 (4.9)</td>
</tr>
<tr>
<td>Breed</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>59 (32.2)</td>
</tr>
<tr>
<td>Purebred</td>
<td>124 (67.8)</td>
</tr>
<tr>
<td>Anatomic location</td>
<td></td>
</tr>
<tr>
<td>Mandible</td>
<td>60 (32.8)</td>
</tr>
<tr>
<td>Maxilla</td>
<td>80 (43.7)</td>
</tr>
<tr>
<td>Calvarium</td>
<td>43 (23.5)</td>
</tr>
<tr>
<td>Metastases at the time of diagnosis</td>
<td></td>
</tr>
<tr>
<td>Lymph node</td>
<td>7 (3.8)</td>
</tr>
<tr>
<td>Lung</td>
<td>4</td>
</tr>
<tr>
<td>Lung and rib</td>
<td></td>
</tr>
<tr>
<td>Location not stated</td>
<td>1</td>
</tr>
</tbody>
</table>

Values reported are mean ± SD or number (%).
by radiography (40 [21.9%]) and MRI (3 [1.6%]). Twelve (6.6%) dogs had no record of diagnostic imaging prior to surgery, and 7 (3.8%) dogs had a record of diagnostic imaging but the modality was not specified. The mean ± SD tumor size was 56.4 ± 21.0 mm in 75 dogs that had CT scans available for review. In the subgroup of dogs (n = 75) that had the tumor specimens reviewed histologically for subtyping, osteoblastic osteosarcoma was identified most frequently (n = 52 [69.3%]); followed by chondroblastic (13 [17.3%]), giant cell (4 [5.3%]), fibroblastic (3 [4.0%]), telangiectatic (2 [2.7%]), and small cell (1 [1.3%]).

Most frequently, dogs had surgery for treatment of their primary tumor (n = 135 [73.8%]); 11 (6.0%) dogs had palliative medical treatment only, 12 (6.6%) dogs had coarsely fractionated RT, 18 (9.8%) dogs had SRT or finely fractionated RT, and 7 (3.8%) dogs had surgery with adjunct finely fractionated RT. In addition to treatment of the primary tumor, 83 (45.4%) dogs received chemotherapy.

A significantly (P < 0.001) larger proportion of dogs with mandibular tumors had surgery (56/60 [93.3%]) compared with dogs with tumors in other anatomical sites (calvarium, 21/43 [48.8%]; maxilla, 58/80 [72.5%]). A significantly (P = 0.04) lower proportion of dogs that had surgery had serum ALP activity > 140 U/L (40/133 [30.0%]), compared with dogs receiving finely fractionated RT or SRT (10/18), surgery and finely fractionated RT (4/7), and coarsely fractionated RT (7/12), but not compared with dogs receiving analgesics alone (2/10). Of the 75 dogs that had CT scans and measurement of the tumor length, dogs that had surgery for treatment of the primary tumor had significantly (P < 0.001) smaller tumors (mean ± SD, 50.4 ± 21.0 mm) compared with dogs receiving finely fractionated RT or SRT (69.3 ± 22.7 mm). There were no other significant differences between treatment groups in baseline characteristics, including age and body weight at the time of diagnosis, sex and neuter status, breed, and monocyte or lymphocyte counts.

One of the 11 dogs receiving palliative medical treatment had pulmonary metastases detected at the time of diagnosis. In addition to oral administration of analgesics, 6 dogs received piroxicam (0.3 mg/kg [0.1 mg/lb], PO, q 24 h) and 1 dog received a combination of doxycycline (2.6 mg/kg [1.2 mg/lb], PO, q 24 h), piroxicam (0.3 mg/kg, PO, q 24 h), and metronomic administration of cyclophosphamide (15 mg/m², PO, q 24 h). None of the 11 dogs that received analgesic medications alone received chemotherapy IV. The MST of dogs in this treatment group was 35 days (95% CI, 4 to 46.0 days). Overall survival time by treatment type was summarized (Figure 1).

Twelve dogs received coarsely fractionated RT for palliative intent. Two dogs had metastases present at the time of diagnosis (1 with pulmonary and 1 with mandibular lymph node metastases). Three dogs were administered piroxicam (0.3 mg/kg, PO, q 24 h). Two dogs were administered pamidronate; one dog received 6 doses (1 mg/kg [0.45 mg/lb], IV, q 4 wk), and the other dog received 2 doses, with the second dose administered 2 months after the first. Dogs received different RT protocols prescribed according to tumor location, surrounding normal tissues, and owner preferences; the most common protocol (4 dogs) used was 2 fractions of 8 Gy (total dose, 16 Gy) given approximately 1 week apart, and 1 dog received 3 fractions of 6 Gy (total dose, 18 Gy). Five dogs received a total dose of 24 Gy, with 4 dogs receiving 3 fractions of 8 Gy each weekly and 1 dog receiving a total dose of 24 Gy in 2 repeated protocols 2 months apart of 2 fractions of 6 Gy within 24 hours. One dog received a total dose of 30 Gy in 5 fractions of 6 Gy administered weekly. The MST of dogs that received palliative coarsely fractionated RT was 97 days (95% CI, 31 to 199 days; Figure 1).

None of the 18 dogs treated with finely fractionated RT or SRT for curative intent had metastases at the time of diagnosis. Of the 18 dogs receiving curative-intent RT, 3 had a finely fractionated radiation protocol and 15 had SRT. Two dogs received a total dose of 54 Gy administered over 18 fractions (3 Gy/fraction). One of these 2 dogs received 5 doses of carboplatin chemotherapy (300 mg/m², IV, q 3 wk) and 4 doses of pamidronate (1 mg/kg, IV, q 1 to 2 mo). The other dog had an open cell polyactic acid polymer impregnated with platinum implanted prior to the first dose of radiation but did not receive chemotherapy IV because of sudden death following radiation. The other dog that received finely fractionated RT received a total dose of 12 Gy in 4 fractions (3 Gy/fraction, q 24 h) but had RT terminated prematurely because of poor performance status. For the 15 dogs treated with SRT, the total dose was 30 Gy administered in 3 fractions in 11 dogs, 27 Gy in 3 fractions in 1 dog, and 48 Gy in 3 fractions in 1 dog. Two dogs received 1 fraction of SRT (total dose, 18 and 20 Gy). One of the dogs receiving SRT had 1 dose of IV pamidronate prior to RT. This dog and 5 other dogs received carboplatin chemotherapy (300 mg/m², IV, q 3 wk) for 1 dose in 2 dogs, 2 doses in 2 dogs, and 4 and 6 doses in 1 dog each.

The PFS time and MST of dogs that received finely fractionated RT or SRT therapy was 132 days (95% CI, 98 to 152 days) and 132 days (95% CI, 98 to 377 days), respectively. Twelve dogs developed local progression of disease (2 had carboplatin chemotherapy), 4 dogs...
had both local progression and distant metastases (3 had carboplatin chemotherapy), and 2 dogs failed to develop local progression or distant metastases at last follow-up (both received carboplatin chemotherapy). The 4 dogs that developed distant metastases had pulmonary metastases; only one of these dogs received treatment for metastases. This dog was administered a combination of doxycycline (4.3 mg/kg [2.0 mg/lb], PO, q 24 h) and carprofen (2.2 mg/kg [1 mg/lb], PO, q 24 h), and also received metronomic administration of cyclophosphamide (19.2 mg/m², PO, q 24 h). One dog that had local progression received a second SRT treatment (255 days after diagnosis) consisting of 3 fractions of 6 Gy administered 24 hours apart.

Four of 135 dogs that had surgery had metastases detected at the time of diagnosis (2 lung, 1 lung and rib, and 1 unknown site). Surgical resection of the primary tumor resulted in complete excision in 87 (64.4%) dogs and incomplete excision in 44 (32.6%) dogs. In 4 (3.0%) dogs, tumor status of the surgical margins could not be determined from the histopathologic report. Following surgery, 8 dogs were administered piroxicam (0.3 mg/kg, PO, q 24 h) and 1 dog was administered carprofen (2.2 mg/kg, PO, q 12 h). Chemotherapy was administered in 65 (48.1%) dogs following surgery, with 56 dogs receiving chemotherapy IV, 7 receiving cisplatin formulated as an implant, and 2 receiving chemotherapy both IV and as an implant. Various chemotherapy protocols were followed (Table 2). Of the 7 dogs that received chemotherapy as an implant only, 3 dogs had a single implantation of open cell polylactic acid polymer sponges impregnated with platinum and 4 dogs had implantation of a liquid polymer solution at 2 visits 8 weeks apart.

The PFS time and MST of 135 dogs that underwent surgery was 239 days (95% CI, 190 to 358 days) and 329 days (95% CI, 259 to 424 days), respectively. Forty-one (30.4%) dogs had local recurrence, 34 (25.2%) developed distant metastases, and 18 (13.3%) had local recurrence and distant metastases concurrently diagnosed. In the 5 dogs with distant metastases, pulmonary metastases were most common (27 [51.9%]), followed by metastasis to other sites (11 [21.2%]) and multifocal metastases (13 [25.0%]). In 1 dog, the sites of metastasis were not recorded. Only 27 dogs received treatment for either recurrence of local disease or metastases; 15 of these dogs received RT with various protocols being used, 3 of the dogs received chemotherapy IV and RT (1 dog each received doxorubicin [30 mg/m², IV, q 3 wk for 5 doses], carboplatin [250 mg/m², IV, q 3 wk for 5 doses], toceranib [2.7 mg/kg [1.2 mg/lb], PO, given on Monday, Wednesday, and Friday], and cyclophosphamide [19.8 mg/m², PO, on alternate days to toceranib]). Three dogs had further surgery to treat local disease recurrence. Three dogs received chemotherapy IV, with 1 dog each receiving 2 doses of carboplatin (300 mg/m², IV, q 3 wk), 2 doses of doxorubicin (30 mg/m², IV, q 3 wk), or 2 doses of doxorubicin (30 mg/m², IV, q 3 wk) and 1 dose of cisplatin (121 mg/m², IV). Two dogs received piroxicam (0.3 to 0.7 mg/kg [0.1 to 0.3 mg/lb], PO, q 24 h), and 2 further dogs received metronomic administration of chemotherapy including doxycycline (only in 1 dog; 5.5 mg/kg [2.5 mg/lb], PO, q 24 h), deracoxib (1.1 mg/kg [0.5 mg/lb], PO, q 24 h), or carprofen (2.2 mg/kg, PO, q 24 h) and metronomic administration of cyclophosphamide (27.3 to 31.6 mg/m², PO, q 48 h). One dog received intraluminal administration of carboplatin (unknown dose and frequency) and prednisone (2 mg/kg [0.9 mg/lb], PO, q 24 h for 1 week and then 1 mg/kg, PO, q 24 h).

None of the 7 dogs that underwent surgery and finely fractionated radiation had evidence of metastases at the time of diagnosis. Six dogs had incomplete excision, and 1 had complete excision as determined by histologic evaluation of the surgical specimen. The total doses were 54 Gy administered in 18 fractions (3 Gy/fraction, 5 d/wk) in 4 dogs, 57 Gy in 1 dog given in 19 fractions (3 Gy/fraction, 5 d/wk), and 36 Gy given in 1 dog in an unknown number of fractions. For 1 dog, the total dose and number of fractions were unknown. Six of the 7 dogs had open cell polyactic acid polymer impregnated with platinum implanted at the time of surgery. Four of these dogs received chemotherapy IV; 2 dogs received carboplatin (300 mg/m², IV, q 3 wk) for 2 and 4 doses, 1 dog received 1 dose of doxorubicin (30 mg/m², IV), and 1 dog received 2 doses of cisplatin (IV, unknown dose). The dog that did not have open cell polyactic acid polymer implanted with platinum implanted received 5 doses of cisplatin (9 mg/m², IV, q 3 to 4 days).

The PFS time and MST of dogs that underwent surgery and received adjuvant finely fractionated RT was 162 days (95% CI, 88 to 388 days) and 162 days (95% CI, 88 to 498 days), respectively. The dog with complete excision developed local recurrence, 88 days from diagnosis. Two other dogs developed local recurrence (at 104 and 267 days), and 2 further dogs developed local recurrence and distant metastasis concurrently (at 162 and 388 days). Two dogs developed distant metastases at 102 and 811 days. In the 4 dogs that developed metastases, 1 had pulmonary metastases and the other 3 had metastases at other sites. A second surgery was performed to treat the local disease recurrence in 2 dogs; no other dogs received treatment for local recurrence or metastatic disease.

In the study population, excluding the 11 dogs that received palliative medical treatment only, 12 dogs that received coarsely fractionated RT and 4 dogs that were...
treated with surgery had metastatic disease at diagnosis. Local recurrence or progression of disease was detected in 80 of 156 (51.3%) dogs, and 60 of 156 (38.5%) dogs developed distant metastases. Local disease progression, recurrence, and metastatic rates for each anatomic site were summarized (Table 3).

The group PFS time was 229 days (95% CI, 175 to 287 days). Forty dogs were censored from the PFS analysis. Four of the dogs had no documented local disease progression or metastases before loss to follow-up, 7 were alive with no evidence of local disease progression or metastasis at the time of last follow-up, and the remaining 29 dogs died or were euthanized without documented evidence of metastasis before death. Median follow-up on the censored dogs for the PFS analysis was 1,102 days (95% CI, 637 to 1,356 days).

The group median time to development of metastasis was 498 days (95% CI, 354 to 811 days). Metastasis was 498 days (95% CI, 354 to 811 days). Metastasis was 498 days (95% CI, 354 to 811 days).

The group MST was 253 days (95% CI, 200 to 303 days). For the dogs with local recurrence or progression, the median time to progression was 341 days (95% CI, 234 to 533 days).

The group MST was 253 days (95% CI, 200 to 303 days). One hundred sixty-nine dogs died or were euthanized, and 21 dogs were censored at a median of 1,471 days (95% CI, 1,414 to 2,612 days); 16 were lost to follow-up, and 5 were alive at last follow-up.

Baseline characteristics and treatment characteristics were evaluated for associations with PFS time and OST in the univariable Cox proportional hazards analysis (Table 4). In the multivariable Cox proportional hazards analysis, complete excision was associated with a decreased hazard of developing progression or recurrence (HR, 0.4; 95% CI, 0.2 to 0.7; P < 0.001) following adjustment for age, body weight, breed, monocyte count, serum ALP activity > 140 U/L, anatomic location, margin status, use of chemotherapy, and use of RT. Purebred dogs had a significantly (P = 0.007) lower hazard of developing progression or recurrence (HR, 0.5; 95% CI, 0.3 to 0.8) following adjustment for age, body weight, monocyte count, serum ALP activity > 140 U/L, anatomic location, margin status, use of chemotherapy, and use of RT. Purebred dogs had a significantly (P = 0.007) lower hazard of developing progression or recurrence (HR, 0.5; 95% CI, 0.3 to 0.8) following adjustment for age, body weight, monocyte count, serum ALP activity > 140 U/L, anatomic location, margin status, use of chemotherapy, and use of RT. No other factors, including use of chemotherapy, were significantly associated with PFS time.

Every 1,000-cell increase in the monocyte count was associated with a 76% increase in hazard of death (HR, 1.8; 95% CI, 1.2 to 2.7; P < 0.001) following adjustment for age, body weight, breed, anatomic location, use of chemotherapy, and use of RT. Complete excision was associated with a decreased hazard of death (HR, 0.5; 95% CI, 0.3 to 0.7; P < 0.001) following adjustment for age, body weight, breed, monocyte count, anatomic location, use of chemotherapy, and use of RT.

Discussion

In this study population, dogs with osteosarcoma of the maxilla, mandible, or calvarium were commonly

### Table 3—Local progression or recurrence and metastatic rates for each anatomic site.

<table>
<thead>
<tr>
<th>Anatomic location</th>
<th>No. of dogs</th>
<th>Local progression or recurrence</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvarium</td>
<td>30</td>
<td>24 (80.0)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td>Mandible</td>
<td>57</td>
<td>16 (28.1)</td>
<td>26 (45.6)</td>
</tr>
<tr>
<td>Maxilla</td>
<td>69</td>
<td>40 (58.0)</td>
<td>22 (31.9)</td>
</tr>
</tbody>
</table>

Values reported are number (%).

### Table 4—Univariable associations with PFS time and OST in 183 dogs with osteosarcoma of the maxilla, mandible, or calvarium.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PFS time</th>
<th>P-value</th>
<th>OST</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purebred dog</td>
<td>0.7 (0.5–1.0)</td>
<td>0.03</td>
<td>0.8 (0.6–1.1)</td>
<td>0.25</td>
</tr>
<tr>
<td>Serum ALP activity &gt; 140 U/L</td>
<td>1.7 (1.2–2.5)</td>
<td>0.007</td>
<td>1.6 (1.2–2.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>Monocyte count (1,000-cell increase)</td>
<td>1.8 (1.3–2.7)</td>
<td>0.002</td>
<td>1.8 (1.3–2.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tumor-free surgical margins</td>
<td>0.4 (0.2–0.7)</td>
<td>0.002</td>
<td>0.3 (0.2–0.4)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values reported are HRs (95% CI).

*Chemotherapy category includes implantable, IV, or both.
middle-aged purebred neutered dogs, which is consistent with the signalment information reported in other studies.\textsuperscript{4,9,20-25} Metastases were rarely present at the time of diagnosis in this study population (7/183 [3.8%]); however, when it did occur, lungs were the most common site. Previous studies\textsuperscript{3-4} evaluating axial osteosarcoma have found a higher metastatic rate at the time of diagnosis (11% to 42%). Given the retrospective nature of this study, it is possible that the metastatic rate could be low as a result of an underappreciation of metastatic disease, with most dogs developing local recurrence or progression and lack of local control resulting in euthanasia prior to development of metastasis. Alternatively, underrecognition may have occurred as a result of the nonstandardized approach to staging on the basis of individual clinician recommendations. Most dogs in this study were treated surgically (135/183 [73.8%]), and complete excision of the tumor on the basis of histologic assessment was achieved in most cases (87/135 [64.4%]). Following treatment for head osteosarcoma with finely fractionated RT or SRT, surgery only, or a combination of surgery and finely fractionated RT in cases with no metastases at diagnosis, 80 of the 156 (51.3%) dogs developed local progression or recurrence of disease, confirming the findings of other studies that osteosarcoma of the maxilla, mandible, or calvarium is a locally aggressive disease with anatomic constraints complicating treatment.\textsuperscript{3,20} Of 156 dogs receiving these treatments (with no metastases at diagnosis), 60 (38.5%) subsequently developed metastatic disease, indicating a propensity of osteosarcoma of the maxilla, mandible, or calvarium to metastasize at a rate similar to that previously reported.\textsuperscript{5,7}

A higher proportion of maxillary tumors (80/183 [43.7%]) were present in this case series, compared with other sites. Heyman et al\textsuperscript{1} observed 27% and 22% of the axial osteosarcoma cases occurred in the mandible and maxilla, respectively, reflecting a larger proportion of dogs with mandibular osteosarcoma, contrary to our study findings (60/183 [32.8%]). This may be because of differences in study populations resulting from factors including increased willingness of owners to seek treatment of oral tumors at all sites or a referral bias, with maxillary tumors being referred to centers such as our institution with multidisciplinary teams where advanced diagnostic imaging, surgery, or RT are possible.

Most dogs in this study (119/183 [65.0%]) had cross-sectional diagnostic imaging for assessment of the primary tumor and to allow for treatment planning. A number of dogs had radiographs alone or did not have diagnostic imaging recorded prior to surgery (19/183 [10.4%]); these dogs were evaluated at the start of the study period, when cross-sectional diagnostic imaging was not available at our institution. It is likely that some of these dogs had undergone diagnostic imaging at the referring veterinarian’s office or that treatment was determined on the basis of gross disease. Given these temporal differences, we did not attempt to evaluate the effect of use of cross-sectional diagnostic imaging on treatment outcome. However, cross-sectional diagnostic imaging allows assessment of transverse images to facilitate assessment and planning of surgical margins, but it has not been evaluated as to how this affects treatment outcome.

Wide surgical resection is recommended for treatment of the primary tumor for osteosarcoma of the maxilla, mandible, or calvarium. The MST of surgery for all sites was slightly lower (MST, 329 days) than has been reported\textsuperscript{4,5} for dogs undergoing surgery for mandibular or maxillary osteosarcoma sites. This difference may be the result of inclusion of all sites and difficulty of achieving wide resection especially in some areas of the maxilla and calvarium. Complete excision, as determined on the basis of histologic evaluation, resulted in a lower hazard of development of local recurrence or metastases and death. This finding makes intuitive sense with respect to the reduction of the risk for recurrence and increasing survival time and is consistent with other studies\textsuperscript{23,24} in dogs and humans. Because of the retrospective nature of this study, we were unable to assess the intended surgical margins or the quality of the surgical margins. In addition, tumor location (cranial vs caudal) within the different anatomic categories was not assessed because of lack of detail in the early study period records and lack of availability of radiographs for review.

Seven dogs had resection of their primary tumor with planned finely fractionated RT to follow because of the likely presence of residual microscopic disease; 6 of these dogs had histologically reported incomplete excision. Because of low case numbers, this study provides insufficient evidence to evaluate the impact of finely fractionated RT after surgery on outcome. Considering that local recurrence was a factor in 59 of 135 (43.7%) dogs that underwent surgery in this study, further evaluation of adjuvant radiation for local disease control may be warranted.

In this study, dogs treated with curative intent fractionated RT or SRT experienced low MST (132 days) and high rates of local progression (16/18), compared with the MST (329 days) and rate of local recurrence (59/135 [43.7%]) in dogs treated with surgery alone. This difference may be the result of other confounding factors such as case selection bias. In this study, dogs receiving these RTs had significantly larger tumors reflecting cases where the chance of complete resection with surgery was low, surgical risks were high, or the tumor was deemed inoperable by a surgical oncologist, resulting in the owner preference for RT rather than surgery. Size was not adjusted for in the multivariable analysis because more than half of the dogs did not have size information. Little outcome information is available in the literature concerning the effectiveness of RT in dogs with axial osteosarcoma locations. The MST of 132 days associated with definitive treatments including finely fractionated RT and SRT in this study was lower than has been previously reported for 8 dogs with axial osteosarcoma sites (MST, 265 days).\textsuperscript{20} The location of affected sites in dogs receiving definitive RT was unclear in that study.\textsuperscript{20} It is possible that restrictions to delivery of RT dose because of the location of the primary tumor could result in differences in local control rates and survival time. No previous information describing treatment outcomes of dogs receiving SRT for osteosarcoma of the maxilla, mandible, or calvarium exists in the literature for comparison.
Prognostic factors that have been identified in other studies evaluating axial osteosarcoma and osteosarcoma of the maxilla, mandible, or calvarium have included histologic status of the surgical margins, tumor location, histologic subtype and grade, body weight, age, and serum ALP activity.\textsuperscript{2,23} Calvarial tumor location was associated with a significantly ($P = 0.04$) greater hazard of local progression or recurrence and development of metastasis (HR, 2.1; 95% CI, 1.0 to 4.1), compared with mandibular tumor location, following adjustment for baseline signalment and tumor characteristics. Poorer prognosis with this anatomic location has not been previously identified, but very few calvarial osteosarcoma cases have been reported with associated treatment outcomes in the veterinary literature. This increased hazard of recurrence or local tumor progression for this tumor location could be related to late time of detection of these tumors, given the temporal muscle coverage of the calvarium and potential for unperceived inward growth. In addition, calvarial tumors are difficult to treat surgically with wide excision and present a type I error. This finding is opposite to the finding reported by Dickerson et al\textsuperscript{20} for treatment of axial osteosarcoma with RT, who found that mixed-breed dogs had improved survival times but not PFS times, compared with purebred dogs and retriever-type dogs. Increases in circulating monocytes were significantly ($P = 0.01$) associated with increased hazard of death (HR, 1.8; 95% CI, 1.2 to 2.7) following adjustment for baseline signalment, tumor, and treatment characteristics. This has not been shown to be associated with survival time in osteosarcoma of the maxilla, mandible, or calvarium in dogs in previous studies. Sottnik et al\textsuperscript{6} reported that an increased circulating monocyte count ($> 0.4 \times 10^9$ cells/µL) was associated with a decreased disease-free interval in appendicular osteosarcoma. A proposed reason for this finding in the study by Sottnik et al\textsuperscript{26} was that the increase in circulating monocytes could represent the presence of myeloid-derived suppressor cells, which have been implicated in enhancing the pathogenesis of cancer. This may be another important prognostic factor to consider for osteosarcoma of the maxilla, mandible, or calvarium in future studies.

The predominant histologic subtype in this study was osteoblastic osteosarcoma (52/75 [69.3%]), which is consistent with the findings of another study\textsuperscript{26} in which osteoblastic osteosarcoma was the predominant subtype (in 68/144 [47.2%] dogs with osteosarcoma at any site). In the present study, telangiectatic histologic subtype was associated with an increased hazard of local recurrence or progression and metastases (HR, 7.1; 95% CI, 1.5 to 33.6) but not death, compared with osteoblastic subtype. This is consistent with previous findings that telangiectatic osteosarcoma was associated with a worse prognosis in dogs with axial osteosarcoma.\textsuperscript{1} In the present study, only 2 dogs had telangiectatic osteosarcoma and this factor was not used in the multivariable Cox proportional hazards analysis because it was not available for all dogs.

Concurrent chemotherapy did not result in a significantly decreased hazard of disease progression or death. This may be the result of several factors. First, local recurrence or progression occurred more commonly than metastases in this study population. Incomplete excision resulting in residual cells at the surgical site may not respond favorably to systematic chemotherapy. Additionally, different chemotherapy protocols were used, including implantable and IV administered chemotherapy, which could result in dilution of the result of effect of this factor. Other studies\textsuperscript{1} have failed to clarify the role of chemotherapy in treatment of head osteosarcoma. One recent study\textsuperscript{6} assessing treatment outcomes of mandibular osteosarcoma found adjuvant chemotherapy was prognostic for metastasis-free interval and survival time. Our study failed to find evidence of a survival benefit with the use of chemotherapy, but given the rate of development of metastatic disease, it is reasonable to consider the use of adjuvant chemotherapy for dogs treated for osteosarcoma of the maxilla, mandible, or calvarium. As is the case in osteosarcoma of the maxilla, mandible, or calvarium in humans, the role of treatment modalities beyond surgery remains undefined.

In this study, metastases were diagnosed in 60 of 136 (36.9%) dogs following treatments other than palliative medical treatment or coarsely fractionated RT. Although this result is within the range previously reported for head and axial osteosarcoma (35% to 58%), it could be that the number of dogs developing metastatic disease was underrecognized by this retrospective study, given that follow-up staging was at the owner’s discretion, albeit recommended every 2 to 3 months.\textsuperscript{6,5} In addition, local recurrence or progression may have occurred before development of detectable metastases, which could further interfere with determination of the metastatic rate in dogs in this study. This rate is much lower than that reported following treatment of appendicular osteosarcoma.\textsuperscript{2}

In conclusion, osteosarcoma of the maxilla, mandible, or calvarium is a locally aggressive disease; dogs treated with surgical excision had the longest PFS time (239 days) and MST (329 days). Surgery resulting in complete excision improved prognosis, whereas calvarial tumor location and increased monocyte count were associated with a poorer prognosis. As is the case in osteosarcoma of the maxilla, mandible, or calvarium in humans, the role of treatment modalities beyond surgery remains undefined.

\textsuperscript{a} SAS, version 9.3, SAS Institute Inc, Cary, NC.
\textsuperscript{b} Prism for Windows, version 6, GraphPad Software Inc, San Diego, Calif.
\textsuperscript{c} OPLA-Pt, THM Biomedical Inc, Duluth, Minn.
\textsuperscript{d} Atriplat, Atrix Laboratories, Fort Collins, Colo.
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