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ACCURACY OF COMPUTED TOMOGRAPHY IN DETERMINING LESION SIZE IN CANINE APPENDICULAR OSTEOSARCOMA

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Abstract

Multidetector contrast enhanced computed tomography with acquisition of 0.625-mm thick transverse images was used to measure the extent of appendicular osteosarcoma in 10 dogs. The measured length of tumor based on CT was compared to the true length of tumor using histopathology. There was a statistically significant association with good correlation between the true length of osteosarcoma compared to the length of intramedullary/endosteal abnormalities on CT with a mean overestimation of 1.8% (SD = 15%). There was not a statistically significant association between the true tumor length and the length of periosteal proliferation on CT with a mean overestimation of 9.7% (SD = 30.3%). There was a statistically significant association, but with poor correlation, between the true tumor length compared to the length of abnormal contrast enhancement with a mean overestimation of 9.6% (SD = 34.8%). The extent of intramedullary/endosteal CT abnormalities assessed from submillimeter transverse images may be of value in assessing patient candidacy and surgical margins for limb-sparing surgery

Keywords

canine; computed tomography; CT; dog; OSA; osteosarcoma; multidetector

Introduction

Osteosarcoma is the most common primary bone tumor in dogs and is associated with a guarded prognosis and rapid progression of disease.[1–4] The majority of tumors arise in the appendicular skeleton.[1,3] Treatment for appendicular osteosarcoma includes amputation, limb-sparing surgery, radiation therapy, and chemotherapy. These treatments may be performed in combination or individually, although treatment of the primary lesion by amputation or resection of diseased bone alone is rarely curative due to subsequent metastasis.[5]

Although limb amputation is employed commonly, it may not be an option due to concurrent orthopedic disease, neurologic disease, or owner preference.[6] For these dogs, limb-sparing techniques involving replacement of diseased bone with nondiseased bone or

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an endoprosthesis have been developed. Limb-sparing procedures in the dog have been described for the radius,[7–14] proximal humerus,[13–15] tibia,[13,14,16] and femur.[13,14,17]

With limb-sparing, accurate determination of the surgical excision margin is critical as there is a higher risk of implant failure if greater than 50% of the bone is affected and inadequate excision leads to local recurrence.[8,14,18,19] Local recurrence ranges from 24% to 60% after limb-sparing surgery.[12,15,20,21] The incidence of metastasis may also be influenced by surgical margins. In dogs receiving adjuvant chemotherapy for humeral osteosarcoma, those with incomplete surgical margins were 7.7 times more likely to develop metastasis than those with complete resection.[15] Accurate determination of surgical margins is also critical for stereotactic radiation.[22,23]

Numerous imaging techniques have been used to measure the length of appendicular osteosarcoma. With bone scintigraphy using ^{99m}Tc- labeled methylene diphosphonate and craniocaudal and lateromedial radiographs, there was a mean overestimation of the length of osteosarcoma.[24,25] With magnetic resonance imaging, there was a mean overestimation of osteosarcoma length by 3 ± 13% in one study and an overestimation ranging from 0.4 to 4.4 cm in another.[6,24]

Noncontrast enhanced computed tomography (CT) has also been used to measure the length of appendicular osteosarcoma. There was a mean overestimation of length by 27 ± 36% in one study in which 1.5-mm-thick sagittal images of the entire length of the affected bone were acquired.[24] There was overestimation of tumor margins in eight out of nine dogs ranging from 0.1 to 4.6 cm in another study in which 5-mm-thick transverse images were acquired through the length of the affected bone.[6] Intravenous contrast medium was not administered for these studies.

Because accurate determination of the extent of appendicular osteosarcoma is of importance for surgical margins and patient candidacy for limb-sparing procedures, developing more accurate imaging methods is critical. Therefore, our purpose was to evaluate the accuracy of pre- and postcontrast multidetector CT detection of appendicular osteosarcoma in dogs compared to histopathologic evaluation. The null hypothesis was that multidetector contrast enhanced CT would not correlate with histopathologic measurements in assessing the extent of appendicular osteosarcoma.

Materials and Methods

This was a prospective study of 10 client owned dogs with a histologically confirmed appendicular osteosarcoma. Dogs ranged in age from 4 to 12 years. There were eight Greyhounds, one Saint Bernard, and one Labrador retriever. Tumors were located at the following sites: proximal humerus (four), distal femur (two), proximal tibia (one), distal tibia (one), distal radius (one), and mid-distal ulna (one). No dog had radiographic evidence of a pathologic fracture or had received prior chemotherapy or radiation therapy.

Patients were anesthetized and positioned in dorsal or ventral recumbency, depending on patient conformation and ease of positioning. The affected and contralateral bones were positioned symmetrically within the CT gantry, parallel to the table. A series of 0.625-mm-thick contiguous transverse images were acquired perpendicular to the long axis of the affected bone*. The field of view extended at least 1 cm proximal and distal to the articular margin of the affected and contralateral bones. Images were acquired using a bone algorithm (window width = 2500–3500, window level = 250–350) and reconstructed into a standard

*Lightspeed 3.X, GE Healthcare, Waukesha, WI.

algorithm (window width = 350–400, window level = 40–50) (Fig. 1). Iohexol 240 mg I/ml (Omnipaque[†]) at a dose of 2 ml/kg was hand injected intravenously and the initial acquisition was repeated immediately using a standard algorithm and identical limb positioning. The CT scan was followed by limb amputation.

The CT images were evaluated as a group consisting of two ACVR Diplomates and a radiology resident (E.M.G., V.F.S., K.S.K.). Window width and window level were adjusted as needed. The following three CT features were measured for each osteosarcoma affected bone: (1) length of intramedullary/endosteal abnormalities, (2) length of periosteal proliferation, and (3) length of abnormal contrast enhancement. The contralateral bone was used as a control for comparison. The criteria for intramedullary/endosteal abnormalities included any change in intramedullary attenuation or irregularity adjacent to the internal cortical margin that was not seen in the contralateral bone at the same level (Fig. 2). The criterion for periosteal proliferation was the presence of any periosteal new bone that was not seen along the contralateral bone in the identical region. Abnormal contrast enhancement was confirmed by measuring the Hounsfield units (HU) using regions of interest within the medullary cavity of the affected versus contralateral bone at the same level (Fig. 3). Any increase in HU relative to the contralateral bone was considered abnormal. The length of the lesion was measured from the articular surface closest to the tumor to the furthest extent of disease. Transverse images were used to make the measurements using digital software (eFilm[‡]). The soft tissues surrounding the bones were not evaluated.

Histopathology served as the gold standard for measuring the true extent of neoplasia. Following amputation, transverse sections were made through the affected bone using a band saw. Each section was measured individually using electronic calipers to within 0.01 mm. The bone loss caused by the band saw was taken into consideration by adding the width of the blade between individual sections. The sections were placed in 10% buffered formalin for at least 72 h followed by a decalcification solution of 50% formic acid for 2–5 weeks. These sections were cut transversely and embedded in paraffin. Transverse 5-μm-thick slices were made at 500-μm increments through the processed sections using a microtome (Leitz 1512[§]), mounted on slides and stained with hematoxylin and eosin.

The slides were evaluated by a board certified veterinary pathologist (S.E.W.) for evidence of periosteal, intramedullary, and/or endosteal neoplasia. The extent of neoplasia was determined to be the furthest extension of neoplastic cells regardless of periosteal, intramedullary, or endosteal involvement. The extent of neoplasia was determined to be at the slice between the presence and absence of neoplastic cells to within 500 μm. In the event that the transition between neoplastic and nonneoplastic cells occurred at the junction of a band saw or blade cut, the extent of neoplasia was considered to be between the two sections, 500 μm distal or proximal to the last section containing neoplastic cells.

Linear regression analysis was used to create a statistical model based on lesion length obtained for each patient from CT and histopathology. The length of each CT lesion was then compared to the true length of neoplasia using the predictive model. Statistical tests were performed using statistical software[**].

[†]GE Healthcare, Princeton, NJ.
[‡]Merge Healthcare, Milwaukee, WI.
[§]Leitz, Wetzlar, Germany.
[**]SAS, Cary, NC; Excel, Microsoft, Redmond, WA.

Results

Based on histopathologic analysis, intramedullary neoplasia extended further than endosteal and periosteal neoplasia in all patients, thus this histologic parameter was selected as the indicator for tumor extent and used for comparison to CT parameters.

All 10 dogs had CT abnormalities within the intramedullary cavity of the affected bone on CT. There was a significant association between the true extent of neoplasia and the length of intramedullary/endosteal abnormalities measured on CT (Fig. 4). There was a mean overestimation of tumor length of 1.8% (SD = 15%). CT overestimated the length of neoplasia based on intramedullary/endosteal abnormalities in 7 of 10 dogs ranging from 0.08% to 27.1%. CT underestimated the length of neoplasia in 3 of 10 dogs ranging from 3.3% to 29.5%.

All 10 dogs had CT evidence of periosteal proliferation of the affected bone. The association between the true extent of neoplasia and the length of periosteal proliferation measured on CT was not statistically significant (Fig. 5). There was a mean overestimation of tumor length of 9.7% (SD = 30.3%). CT overestimated the length of neoplasia based on periosteal proliferation in 7 of 10 dogs ranging from 0.03% to 60.9%. Of the seven dogs wherein tumor length was overestimated based on intramedullary/endosteal abnormalities, tumor length was also overestimated in six based on periosteal proliferation. In the other dog, periosteal proliferation overestimated tumor length by 26.3% whereas it was underestimated by 3.3% using intramedullary/endosteal abnormalities. Periosteal proliferation on CT underestimated tumor length in 3 of 10 dogs ranging from 3.7% to 46.4%. Of the three dogs in which intramedullary/endosteal abnormalities underestimated the extent of tumor, two of the same dogs were also underestimated using periosteal proliferation. In the other dog, the extent of periosteal proliferation underestimated the length of tumor by 23.9% whereas it was overestimated by 0.08% using intramedullary/endosteal changes.

All 10 dogs had abnormal contrast enhancement within the medullary cavity of the affected bone. The association between true extent of neoplasia and length of abnormal contrast enhancement was statistically significant but the correlation was poor (Fig. 6). There was a mean overestimation of tumor length of 9.6% (SD = 34.8%). CT overestimated the length of neoplasia based on abnormal contrast enhancement in 7 of 10 dogs ranging from 0.47% to 62.8%. These were also the same seven dogs in which tumor length was overestimated using the extent of periosteal proliferation. Of the seven dogs in which the intramedullary/endosteal abnormalities on CT overestimated tumor length, six of the same dogs were also overestimated using abnormal contrast enhancement. In the other dog, the extent of abnormal contrast enhancement overestimated tumor length by 35.8% whereas it was underestimated by 3.3% using intramedullary/endosteal abnormalities. CT underestimated tumor length based on abnormal contrast enhancement in 3 of 10 dogs ranging from 22.5% to 47.4%. These were the same three dogs in which tumor length was underestimated based on the extent of periosteal proliferation. Of the three dogs in which intramedullary/endosteal abnormalities underestimated the extent of tumor, two of the same dogs were also underestimated using abnormal contrast enhancement. In the other dog, the extent of abnormal contrast enhancement underestimated the length of tumor by 47.4% whereas it was overestimated by 0.08% using intramedullary/endosteal abnormalities.

Discussion

Based on this preliminary study, there was a significant correlation of the extent of tumor on CT compared to histology, rejecting the null hypothesis. The CT characteristic that was the best predictor of tumor length was intramedullary/endosteal abnormalities. Even with this

predictor, however, tumor length was underestimated in three patients, which would have lead to incomplete tumor resection (Fig. 7). In one dog with a proximal humeral tumor, the extent of tumor was underestimated by 29.5% or 34.8 mm. If the mean ± 1 standard deviation of estimated tumor length were used to guide the surgical resection, tumor would have been resected completely in all but this one patient.

Tumor length was overestimated by 27.1% in one patient. Overestimation of tumor length has the potential to exclude suitable patients as candidates for limb-sparing surgery. Although the mean overestimation of tumor length was 1.5%, there was wide variation.

The extent of periosteal proliferation seen on CT was a poor predictor of tumor length, with a mean overestimation of tumor length of 9.7% (SD = 30.3%). Periosteal hyperplasia without evidence of neoplasia extended further than intramedullary neoplasia in 4 of 10 dogs and did not extend as far as intramedullary neoplasia in 5 of 10 dogs. This discrepancy between tumor length and length of periosteal reaction is not surprising as there are several causes of periosteal bone proliferation other that neoplastic infiltration, including ischemia.[26]

The extent of abnormal contrast enhancement was a poor predictor of tumor length. Using linear regression analysis, there was a mean overestimation of tumor length of 9.6% (SD = 34.8%) based on abnormal contrast enhancement as the predictor. Tumor necrosis may have contributed to the underestimation of tumor length based on abnormal contrast enhancement. The lack of vascularity in necrotic regions could have lead to a lack of contrast enhancement despite the presence of neoplastic cells. In fact, there were gaps of abnormal contrast enhancement within the intramedullary cavity of some patients. These gaps may have represented regions of tumor necrosis. Another explanation for the gaps of contrast enhancement could be skip metastasis, which refers to a simultaneous smaller focus of osteosarcoma separate from the primary lesion within the same bone or on the opposing side of the adjacent joint.[27] We did not evaluate skip metastasis as only the first transition from neoplastic to nonneoplastic cells was considered to be the extent of tumor. The entire bone was not evaluated histologically.

In addition, it was difficult to evaluate contrast enhancement in regions of sclerotic or cancellous bone. Subtle changes in contrast enhancement did not cause a significant change in HU in these regions due to the inherently high HU values in bone. This may have also contributed to the poor predictive value of abnormal contrast enhancement.

Based on our data, multidetector CT with acquisition of submillimeter thick images appeared to be a better predictor of the extent of neoplasia compared with nonmultidetector CT studies performed previously.[6,24,25] This was likely due to the acquisition of transverse images as thin as 0.625 mm, which allowed for more precise measurements. In addition, although sagittal and dorsal reformatted images were available, measurements were made from contiguous transverse images. This enabled evaluation of the entire cross section of bone at once for any abnormalities.

The acquisition of transverse submillimeter thick images through the entire length of bone took an average of 8–10 min. This was repeated following contrast medium administration for a total of 16–20 min. The long acquisition time could have lead to dissipation of contrast medium prior to completion of imaging. However, since contrast enhancement was not a good predictor of tumor length, contrast medium administration may not be necessary in identifying the leading edge of tumor, thereby reducing scan and anesthesia time.

There was some inaccuracy in measuring the histologic sections. Each section was processed individually and placed in a paraffin block and the tissue block may not have been

level, leading to asymmetric slicing. Also, the number of slices of paraffin that were sectioned prior to actually reaching bone was not quantified and this had the potential to result in mild over or underestimation of the histopathologic measurements. Tissue processing may have also lead to dehydration and subsequent shrinkage of the specimens leading to a change in tissue thickness. In a porcine model, there was no change in bone volume or diameter measured by magnetic resonance imaging following formalin fixation.[28]

In addition, if the transition of neoplastic to nonneoplastic cells occurred at the junction of a band saw or blade cut, the tumor was assumed to be 500-μm distal or proximal to the last neoplastic slice. This may also have lead to mild over or underestimation of the true extent of neoplasia.

In summary, the length of intramedullary/endosteal abnormalities detected on transverse submillimeter thick transverse CT images was related to the length of appendicular osteosarcoma. This should be of value in assessing patient candidacy and surgical margins in limb-sparing surgery. However, there was wide variation between patients and relying on CT alone would have resulted in incomplete excision of tumor in one of 10 dogs.

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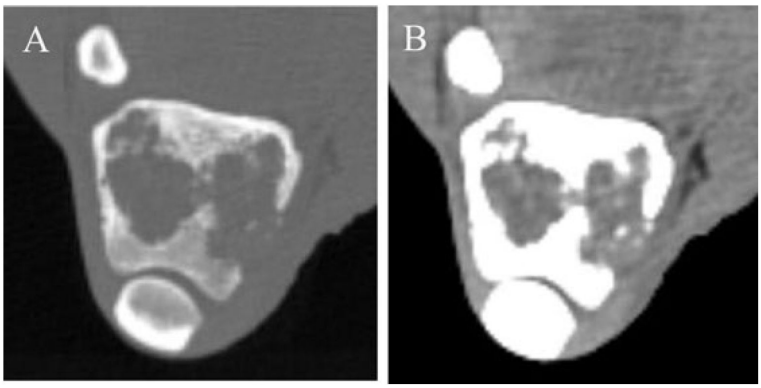

Fig. 1.
(A) Transverse image of the distal femur in a bone algorithm (window width = 2500, window level = 250). There is multifocal medullary and cortical lysis. (B) Same image reconstructed into a standard algorithm (window width 400, = window level = 40).

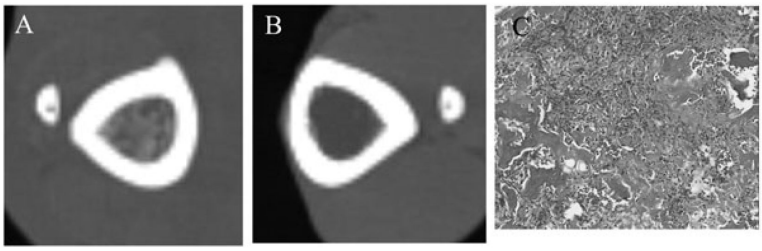

Fig. 2.
(A) Transverse image at the level of the mid tibia. There is patchy hyperattenuation within the medullary cavity of the affected limb which is absent in the contralateral limb (B) at the same level. (C) A histologic slide made at the level of (A). There is mesenchymal neoplasia with osteoid production.

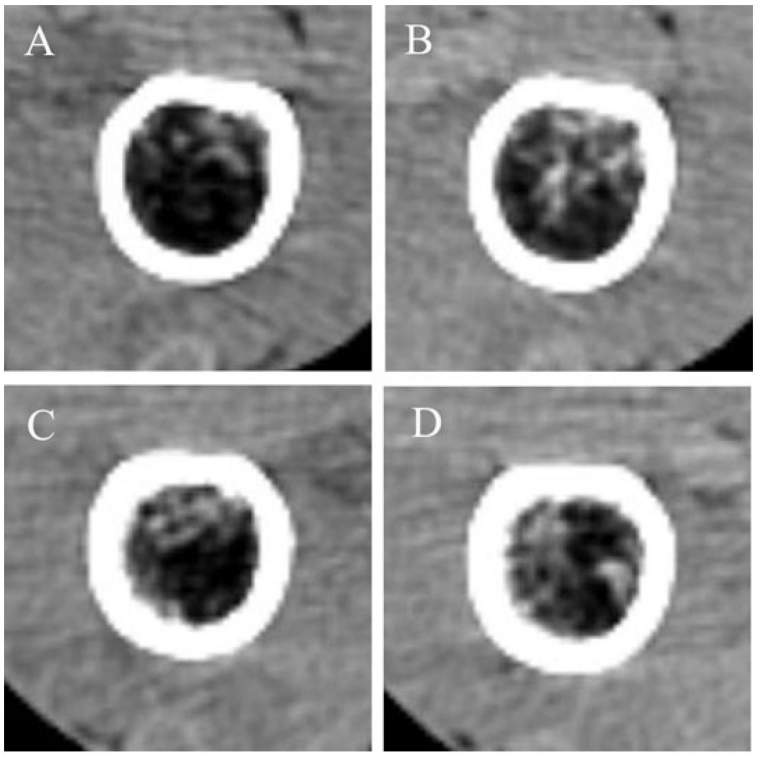

Fig. 3.
Abnormal contrast enhancement of distal femoral osteosarcoma. Transverse image of the affected limb precontrast (A) and postcontrast (B) and the contralateral limb at the same level precontrast (C) and postcontrast (D). There is an intramedullary increase of 53.6 HU in the affected limb compared to 5.2 HU in the contralateral limb (window width = 350, window level = 50).

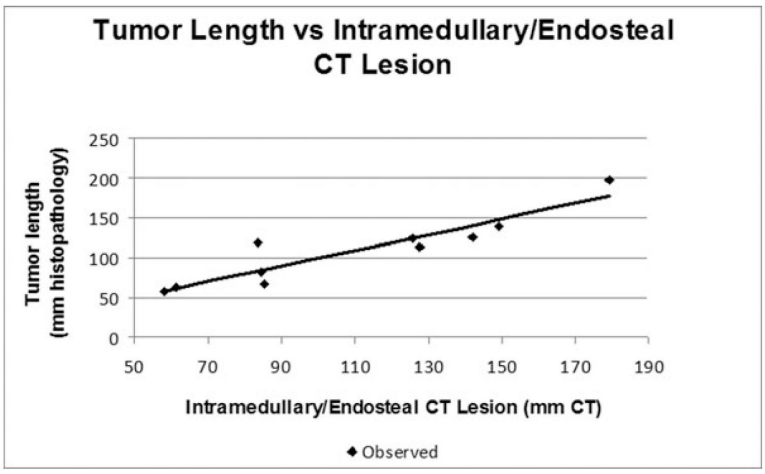

Fig. 4.

Tumor length determined histopathologically as a function of the length of intramedullary/endosteal abnormalities from CT. $Y = 0.98x + 1.1$; $r^2 = 0.85$, $P = 0.0001$.

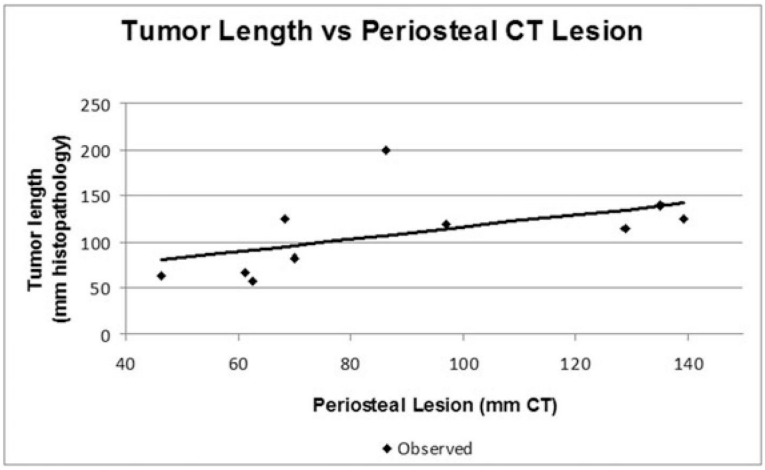

Fig. 5.
Tumor length determined histopathologically as a function of the length of periosteal proliferation from CT. $Y = 0.67X + 49.4$; $r^2 = 0.27$, $P = 0.1225$.

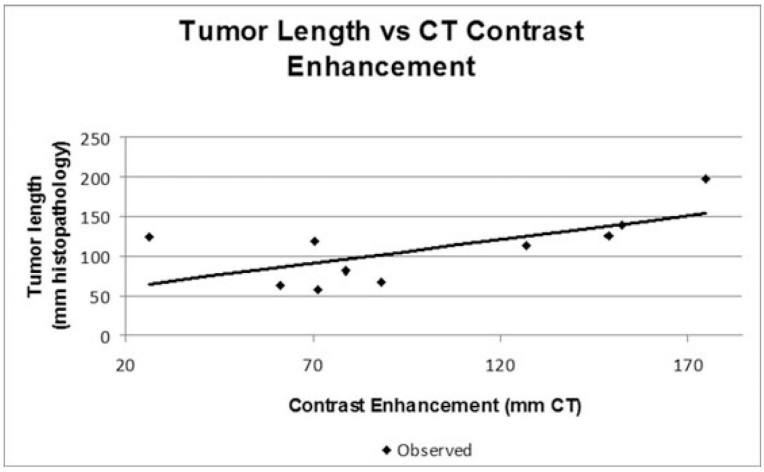

Fig. 6.

Tumor length determined histopathologically as a function of the length of abnormal contrast enhancement from CT. $Y = 0.59X + 50.1$; $r^2 = 0.42$, $P = 0.0419$.

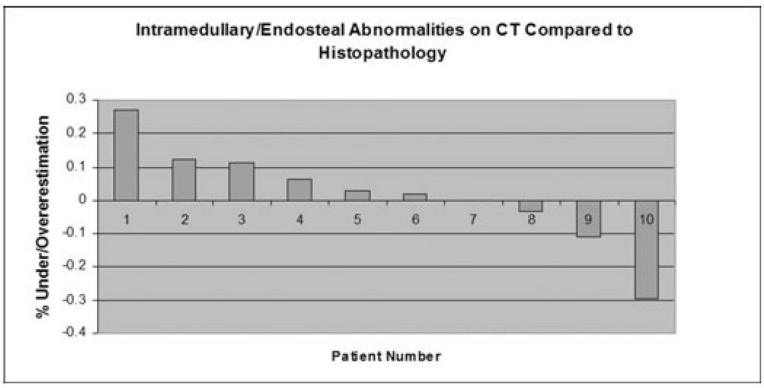

Fig. 7.
Distribution of percent overestimation and underestimation of intramedullary/endosteal abnormalities on CT compared to true tumor length.