Quantitative contrast-enhanced CT attenuation evaluation of osseous metastases following chemotherapy

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**Title: QUANTITATIVE CT DENSITY EVALUATION OF OSSEOUS METASTASES
FOLLOWING CHEMOTHERAPY**

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ABSTRACT

Purpose: Osseous metastases often undergo an osteoblastic response following chemotherapy also known as the “flare” phenomenon. The purpose of our study was to demonstrate the quantitative CT changes in density of osseous metastases before and after chemotherapy.

Materials and Methods: Our study was IRB approved and HIPAA compliant. Our cohort consisted of 48 consecutive cancer patients with studies both before chemotherapy/at the time of diagnosis of osseous metastases and 14 ± 3 (12-20) months after the initiation of treatment 60 ± 10 (range: 37-80) years, 26 F, 22 M). CT density of all lesions was measured by two fellowship trained MSK radiologists. The largest possible region of interest was selected to measure the average and maximum densities in Hounsfield Units (HU). If multiple lesions were present, the largest lesion was evaluated. Treatment effects were assessed using paired *t*-tests, using $P < 0.05$ as statistically significant. Intraclass correlation coefficient (ICC) was calculated for the two readers.

Results: The distribution of primary tumors was as follows: breast (20/48, 42%), lung (10/48, 21%), prostate (5/48, 10%), pancreatic (5/48, 10%), renal (2/48, 4%), and other (6/48, 13%). The measured lesions were in the following locations: spine/sacrum (35/48, 73%), pelvis (10/48, 21%), sternum (3/48, 6%). The distribution of lesion types were as follows: lytic (14/48, 29%), blastic (25/48, 52%), and mixed lytic-blastic (9/48, 19%). Mean and maximum CT densities (Reader 1) of all metastases before chemotherapy treatment were 328 ± 206 HU and 580 ± 391 HU, respectively and after chemotherapy treatment were 511 ± 263 HU and 789 ± 439 HU, respectively. There was a significant increase in mean and maximum CT densities of metastases following chemotherapy for all lesions collectively but also when separated into lytic, blastic, and mixed lytic-blastic lesions ($P < 0.05$). ICC was almost perfect for average density and moderate to substantial for maximum density.

Conclusion: Quantitative assessment of osseous metastatic disease using CT density measurements confirms a statistically significant increase in density 12-20 months after initiation of chemotherapy.

Clinical Application: Measuring changes in CT density of osseous metastases may have a significant role in evaluating chemotherapy effect.

INTRODUCTION

Osseous metastatic disease is common, affecting approximately 280,000 adults in the United States, and with approximately 68% of cases occurring in patients with primary breast, prostate, or lung cancer. Accurate evaluation of the imaging findings of osseous metastatic disease is important for staging, outcome prediction, and treatment planning [1–5].

Osseous metastases often undergo an osteoblastic response following chemotherapy also known as the “flare phenomenon.” Initially observed in skeletal scintigraphy, a discordance between apparent clinical improvement of the patient and unexpected additional bony lesions with greater Technetium-99m-methylene diphosphonate uptake, was thought to reflect a healing response to the chemotherapy [6–11]. A similar response has been seen in CT density of metastases where an increase in density may be considered to be a positive response to treatment [5]. Although this has been demonstrated qualitatively, it has not been proven with a systematic study of a cohort. Therefore, it is not known if this difference is statistically significant and consistently reproducible. Also, the numeric values associated with the densities before and after chemotherapy and the change in density is not known.

The purpose of our study was to demonstrate the quantitative CT changes in density of osseous metastases before and after chemotherapy.

MATERIALS AND METHODS

Patient Cohort

Our study was IRB approved and HIPAA compliant.

Inclusion criteria were age ≥ 18 years, history of cancer, presence of osseous metastases, and contrast-enhanced CT of the chest, abdomen and pelvis before chemotherapy as well as 12 or more months after the initiation of chemotherapy treatment.

CT Technique

Lesions were evaluated using either a 16 or 64-slice CT (Siemens Biograph 16 or 64, Siemens, Erlangen, Germany or GE Healthcare discover, Milwaukee, Wisconsin, USA).

All metastatic lesions were identified and evaluated on either a CT of the chest or a CT of the abdomen and pelvis (slice thickness, 2.5 mm for chest and 5 mm for abdomen/pelvis; table

feed, 15 mm/sec; pitch 1.5; tube voltage, 120 kVP; tube current, 200 mAs; sagittal and coronal reconstruction thickness, 2 mm with 2 mm intervals) with IV and oral contrast.

Density Measurements

Density measurements were performed on a Picture Archiving and Communication System (PACS) workstation (Agfa, Morstel, Belgium) by two musculoskeletal radiologists with 5 and 4 years of experience.

The CT of the chest, abdomen and pelvis was reviewed, and the largest lesion on axial slices was selected. The round region of interest (ROI) tool was used to draw the largest possible ROI over the lesion without extending beyond lesion margins or including an adjacent cortex to measure the average density in Hounsfield Units (HU). The same slice was used to measure the maximum density using the square histogram tool. If necessary, the square was permitted to extend beyond the margins of the lesion while excluding any adjacent cortex. The histogram tool provided the range of densities and the number of pixels for each density value. The maximum density in HU was recorded.

The lesion location was provided to the second observer to perform the measurements, but all measurements were performed independently by the two readers.

The type of lesion (lytic, blastic, mixed lytic-blastic) and the patient's overall disease status in terms of CT and clinical follow-up based on patient notes were recorded.

Statistical Analysis

The means and standard deviations for each patient's largest lesion were calculated, and groups were compared using the Student's *t*-test (JMP, version 12 Pro, SAS Institute, Cary, NC). $P < 0.05$ was considered statistically significant. Interreader reproducibility was assessed using intraclass correlation coefficient (ICC) with 95% confidence interval (CI) (MedCalc Statistical Software version 16.4.3, Ostend, Belgium). ICC value of 0-0.2 indicated slight agreement, 0.21-0.40 indicated fair agreement, 0.41-0.60 indicated moderate agreement, 0.61-0.80 indicated substantial agreement, and 0.81-1.0 indicated almost perfect agreement.

RESULTS

Patient Cohort

The patient cohort consisted of 48 patients, with 22 (46%) males and 26 (54%) females, ages 60 ± 10 (range 37-80) years. The distribution of primary tumors was as follows: breast (20/48, 42%), lung (10/48, 21%), prostate (5/48, 10%), pancreatic pancreas (5/48, 10%), renal (2/48, 4%), and other (liver, bladder, kidney, rectum, esophagus, melanoma) (6/48, 13%). The average time between CT studies was 14 ± 3 months, with a range of 12 to 26 months.

The measured lesions were in the following locations: spine/sacrum (35/48, 73%), pelvis (10/48, 21%), sternum (3/48, 6%). The distribution of lesion types were as follows: lytic (14/48, 29%), blastic (25/48, 52%), and mixed lytic-blastic (9/48, 19%).

CT Density of Metastatic Lesions

The average and maximum CT densities of all metastases before and after chemotherapy for both readers are detailed in Table 1 and Table 2. There was a significant increase in average and maximum CT densities of metastases following chemotherapy for lytic (Figure 1), blastic (Figure 2), and mixed lytic-blastic (Figure 3) metastases. The increase in average density (Reader 1) was 183 ± 220 HU for all lesions, 159 ± 193 HU for lytic lesions, and 159 ± 208 HU for blastic lesions, and 287 ± 279 HU for mixed lytic-blastic lesions. The increase in maximum density was 209 ± 278 HU for all lesions, 230 ± 325 HU for lytic lesions, and 143 ± 215 HU for blastic lesions, and 369 ± 325 HU for mixed lytic-blastic lesions.

There was a subgroup of 9/48 (19%) patients whose osseous metastases decreased in average density. The distribution of lesion types were as follows: lytic (3/9, 33%), blastic (4/9, 44%) (Figure 4), and mixed lytic-blastic (2/9, 22%). There was no significant difference in the distribution of lesion type between patients whose metastases increased or decreased in density ($P = 0.7$). In the patients with a decrease in density, an overall progression of disease (primary tumor or metastatic disease) was seen in 6/9 (67%), improvement of disease was seen in 0/9 (0%), and stable disease was seen in 3/9 (33%). In the patients with an increase in lesion density, an overall progression of disease was seen in 20/39 (51%) patients; in 4/39 (10%) patients' disease improved and in 15/39 (38%) patients' disease was stable. There was no statistically significant difference between these groups ($P = 0.8$).

The ICC for Reader 1 and Reader 2's average density measurements was 0.83 (95% CI, 0.0.71-0.90; almost perfect agreement) before chemotherapy and 0.97 (95% CI, 0.97-0.98, almost perfect agreement). The ICC for Reader 1 and Reader 2's average density measurements

was 0.42 (95% CI, 0.16-0.63; moderate agreement) before chemotherapy and 0.65 (95% CI, 0.045-0.79, substantial agreement).

DISCUSSION

Our quantitative assessment of osseous metastases using CT density measurements confirms a statistically significant increase in density more than 12 months after initiation of chemotherapy.

Pollen et al initially described osteoblastic response after chemotherapy as an increase in number and sclerosis of metastases in patients with prostate cancer on radiography without corresponding increased uptake on bone scan [12]. A bone scan “flare” phenomenon has also been described, where follow up bone scans showed “new” lesions, which was contradictory to overall clinical improvement of the patient’s oncologic status, and subsequent clinical and imaging follow up confirmed regression of the patient’s disease [7,8]. A similar finding has also been described with positron emission tomography (PET) in gastric cancer patients [13–15]. Stattaus et al demonstrated an osteoblastic response with an average increase in CT density of 153 HU in a series of 24 patients with small cell lung cancer patients. However, CT density measurements were only performed in the 15 patients who demonstrated an increase in number of metastases [16]. Similar qualitative studies were also performed for prostate, gastric, and small cell lung cancer patients [14,16,17]. Quattrocchi et al demonstrated a quantitative increase of CT density in lytic and sclerotic metastases after 3 months of bisphosphonate (zoledronic acid) administration but did not study chemotherapeutic agents [18].

To our knowledge, no series has been performed to evaluate the quantitative changes of CT density after chemotherapy administration. When evaluating osseous lesions on follow up CT examinations, the results of this study confirm that the increase in density can be interpreted as an effect of the chemotherapy, especially in the setting of overall clinical improvement. We explored a temporal relationship between the initiation of chemotherapy and a change in the CT density of osseous metastases. Our observed increase in CT density following chemotherapy is consistent with the prior studies showing increased CT density following therapy. Questions to be explored include temporal relationship of CT density changes following therapy. We picked one year as the minimum duration of follow-up in order to capture changes in CT density. The

change in density likely occurs much earlier. In the study by Quattrocchi et al, an increase in CT density was detected after 3 months of therapy [18]. Our observed decrease in CT density of some lesions also poses interesting questions. We explored the possibility that the lesion type (lytic, blastic, mixed lytic-blastic) or the patient's overall disease status may be a contributing factors of this change. Although we did not see a statistically significant difference between the groups, the number of lesions which decreased in density was small ($n = 9$). For our study we only measured the density of the largest lesion in each patient, but in a previous study done by the authors, we found that there was no significant variation in osseous metastasis density within the same patient [19].

Limitations of our study include our retrospective nature, which precludes standardization of the chemotherapy regimen and the interval of the follow-up studies. A lower agreement between the readers in the measurement of the maximum density was observed, which may be related to the heterogeneity of treated lesions.

In conclusion, osseous metastatic disease on average increases in density before and after chemotherapy. Measuring changes in CT density of osseous metastases may have a significant role in evaluating chemotherapy response.

TABLES

Table 1: Average densities

	Reader 1			Reader 2		
Lesion Type	Pre-Chemotherapy Density (HU)	Post-Chemotherapy Density (HU)	P	Pre-Chemotherapy Density (HU)	Post-Chemotherapy Density (HU)	P
All	328 ± 206 (23-863)	511 ± 263 (-7-1047)	<0.0001	306 ± 188 (35-800)	511 ± 258 (0-959)	<0.0001
Lytic	117 ± 73 (23-240)	276 ± 197 (-7-615)	0.01	117 ± 52 (35-211)	272 ± 203 (35-211)	0.02
Blastic	435 ± 189 (70-863)	594 ± 247 (56-1047)	0.0006	404 ± 176 (133-800)	609 ± 232 (58-959)	0.0002
Mixed Lytic-Blastic	323 ± 147 (84-546)	610 ± 186 (289-911)	0.01	298 ± 133 (66-499)	574 ± 184 (232-783)	0.006

Table 2: Maximum densities

	Reader 1			Reader 2		
Lesion Type	Pre-Chemotherapy Density (HU)	Post-Chemotherapy Density (HU)	P	Pre-Chemotherapy Density (HU)	Post-Chemotherapy Density (HU)	P
All	580 ± 391 (128-1744)	789 ± 439 (108-2176)	<0.0001	455 ± 241 (78-869)	707 ± 289 (145-1202)	<0.0001
Lytic	316 ± 341 (128-1416)	546 ± 426 (110-1567)	0.03	208 ± 70 (78-333)	489-280 (145-972)	0.006
Blastic	600 ± 221 (144-1068)	743 ± 262 (108-1230)	0.002	555 ± 209 (225-869)	753 ± 247 (159-1088)	0.0002
Mixed Lytic-Blastic	905 ± 581 (263-1744)	1275 ± 528 (389-2176)	0.009	526 ± 243 (99-862)	890 ± 247 (431-1202)	0.001

FIGURES:

Figure 1: 50 year old woman with lung cancer. A) Axial contrast-enhanced CT at initial cancer diagnosis demonstrates a lytic osseous metastasis in the right sacrum (*). The average density is 87 HU and the maximum density is 304 HU. B) Axial contrast-enhanced CT 13 months after initiation of chemotherapy demonstrates increased density of lytic osseous metastasis in the sacrum (*). The average density is 184 HU and the maximum density is 975 HU.

Figure 2. 72 year old man with prostate cancer. A) Axial contrast-enhanced CT at initial cancer diagnosis demonstrates a blastic osseous metastasis in the right half of the L5 vertebral body (arrows). The average density is 228 HU and the maximum density is 459 HU. B) Axial contrast-enhanced CT 14 months after initiation of chemotherapy demonstrates increased density of the blastic osseous metastasis in the L5 vertebral body (arrows). The average density is 473 HU and the maximum density is 670 HU.

Figure 3: 59 year old woman with breast cancer. A) Axial contrast-enhanced CT at initial cancer diagnosis demonstrates a mixed lytic/blastic osseous metastasis in the T7 vertebral body (arrow). The average density is 330 HU and the maximum density is 716 HU. B) Axial contrast-enhanced CT 13 months after initiation of chemotherapy demonstrates increased density of mixed lytic/blastic osseous metastasis in T7 (arrow). The average density is 859 HU and the maximum density is 1107 HU.

Figure 4: 65 year old woman with breast cancer. A) Axial contrast-enhanced CT at initial cancer diagnosis demonstrates a mixed lytic/blastic osseous metastasis in the L1 vertebral body (arrow). The average density is 542 HU and the maximum density is 786 HU. B) Axial contrast-enhanced CT image at initial cancer diagnosis demonstrates a normal liver. C) Axial contrast-enhanced CT 16 months after initiation of chemotherapy demonstrates decreased density of mixed lytic/blastic osseous metastasis in L1 (arrow). The average density is 258 HU and the maximum density is 528 HU. D) Axial contrast-enhanced CT 16 months after initiation of chemotherapy demonstrates new diffuse hepatic metastases (*).

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