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LETTERS TO THE EDITOR

Contrast media-assisted visualization of brain metastases by kilovoltage cone-beam CT

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To the Editor

The latest linear accelerator equipped with a kilovoltage (kV) cone-beam CT (CBCT) unit is useful for registration at the time of treatment, and thus reduces the setup error [1–4]. But in the case of intracranial or abdominal tumors, the contours of the tumors are difficult to determine on the CT images without contrast media, since such tumors are located next to normal soft tissue whose Hounsfield unit is close to those of the tumors themselves.

Image registration by CBCT is performed based on the bony structures or soft tissue around the tumor. But this process does not necessarily guarantee that the position of the isocenter at treatment is identical with that at the time of planning CT, since bone or soft-tissue registration is based on a volume-matching process. It is difficult to know the exact tumor location for a low-contrast tumor even if on-board registration of the tumor is intended, since the tumor contour is not well visualized even on planning CT images without contrast media. We attempted to visualize metastatic brain

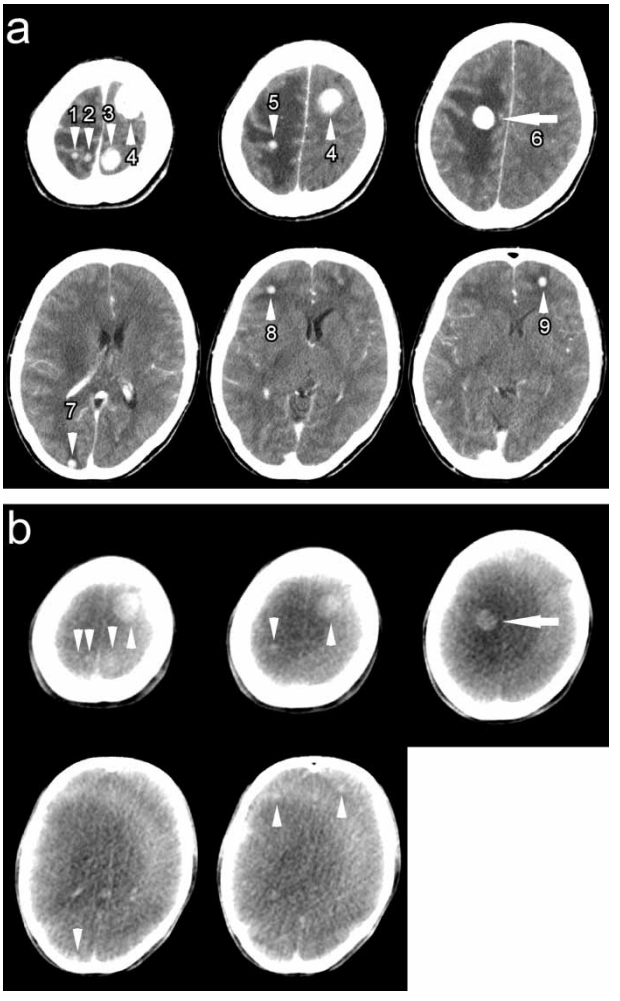

Figure 1 (*Continued*)

Figure 1. Brain tumor images acquired by planning CT (a) and kV CBCT (b) after each intravenous bolus administration of iodized contrast media. The treatment isocenter was set within the tumor indicated by the arrow. Tumors are indicated by the arrowhead. All tumors 6 mm or more in the greatest dimension in the planning CT (a) were also detectable in the CBCT (b). The numbers assigned in the tumor correspond to those in Table I.

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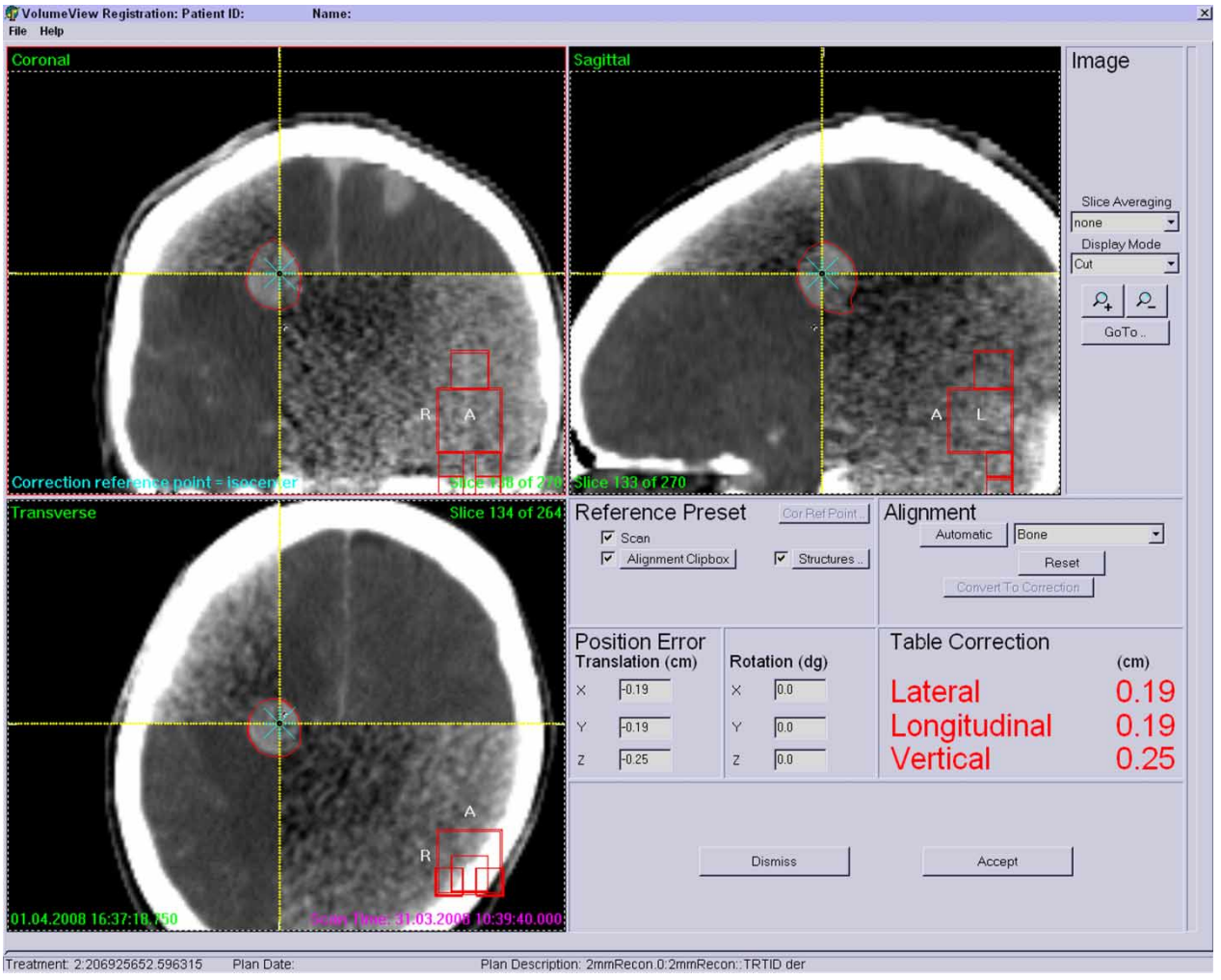

Figure 2. The desktop screen at the time of image registration. After bone registration, the location of the tumor at the isocenter was verified by eye and registered well.

tumors by contrast media administration in kV CBCT images.

A 41-year-old female developed multiple brain metastases from a follicular variant of papillary carcinoma of the thyroid. Radiotherapy planning was performed by Pinnacle[3] (Philips/ADAC, Milpitas, CA) based on CT images acquired by a large-bore CT (Aquilion/LB, Toshiba, Tokyo, Japan) after an intravenous bolus injection of 100 ml of iodized contrast media, Iopamiron 300 (Schering, Berlin,

Table I. Characteristics of the tumors observed in the planning CT.

Tumor No.[1]	Size (mm)[2]	Locus	Possible factors interfering with detectability in CBCT [8]
1	6 × 4	Rt. high frontal	Cupping artifacts Ring artifact
2	7 × 5	Rt. high frontal	Cupping artifacts Ring artifact
3	18 × 16	Lt. high frontal	Cupping artifacts Ring artifact
4	27 × 19	Lt. high frontal	Cupping artifacts Ring artifact
5	7 × 7	Rt. high frontal	Cupping artifacts
6	19 × 16	Rt. frontal	–
7	8 × 8	Rt. occipital	Cupping artifacts
8	7 × 7	Rt. frontal tip	Ring artifact
9	8 × 8	Lt. frontal tip	Ring artifact
10	4 × 4	Lt. frontal	Cupping artifacts Ring artifact

[1]The numbers of the tumors correnspond to those in Figure 1.
[2]Sizes were measured on 5-mm-thick images of the planning CT.
The greatest dimension and its orthogonal dimension in the axial slice was presented.

Germany). Elekta Synergy (Elekta, Crawley, England), equipped with kV CBCT unit, was used for registration and treatment. Immediately before the treatment, on-board CBCT images were taken four minutes after another intravenous bolus injection of 100 ml of Iopamiron 300. The initial estimation of the tumor registration was performed by built-in bone-matching software because it was very quick. Subsequently, the tumor position in the CBCT image and the isocenter imported from the treatment planning system were displayed for further manual adjustment by eye. Written informed consent on these procedures and treatment was obtained from the patient.

Figure 1a presents representative axial images of the planning CT of this patient. Figure 1b shows kV CBCT images of the corresponding slices taken immediately before the treatment. The isocenter was set within the tumor in the right frontal lobe indicated by the arrow in the Figure 1a. No further manual adjustment was performed after bone matching in this study. The tumor position was directly registered (Figure 2). Thus, it was shown that direct tumor registration was feasible by contrast media-assisted kV CBCT. The patient was treated with whole-brain irradiation.

All the tumors with diameters of 6 mm or more in the greatest dimension observed in the 5-mm-thickness planning CT image were also visible by CBCT (Table I). Ring artifacts of the concentric circle that centers on the treatment isocenter, possibly due to the skull, were seen in the CBCT images (Figure 1b). But these artifacts did not degrade the accuracy of visual verification insofar as the tumor was detectable. Other smaller metastases sized less than 6 mm in the planning CT were undetectable in the CBCT images.

This is the first report of direct tumor visualization and registration in the linear accelerator-mounted CBCT by contrast media administration. It had been reported that sufficient soft-tissue contrast could not be obtained in kV CBCT images by contrast media administration [5]. This is an obstacle for direct tumor registration. To overcome this difficulty, Guckenberger et al. used mobile in-room CT with contrast media just before the treatment [5,6]. The idea of their report is interesting, but the tumor image obtained by in-room CT does not warrant exact tumor position during the treatment. Through our procedure, we can know the exact position of the small tumor itself in an organ with soft-tissue density on-board even during the treatment by simultaneous dual exposure of kV x-ray for CBCT and megavoltage x-ray for treatment [4]. In addition, we determined the minimum size of brain tumors that can be visualized by kV CBCT in this study.

Metastatic brain tumors 6mm or more in the greatest dimension were visualized in the CBCT. This means that tumors 6 mm or more in the greatest dimension are candidates for direct tumor registration by contrast media-assisted kV CBCT. The possible reasons why smaller tumors could not be detected in the CBCT were low contrast of the image, low resolution of the image, the ring artifacts described above, and artifacts due to beam hardening. Most of them had been pointed out previously [7,8], and some problems have already overcome by improvement of the systems [7].

The tumors of the patient involved in this report were strongly and homogeneously enhanced by contrast media. Such characteristics of the tumor appeared suitable for this procedure of visualization. In our preliminary experience, soft-tissue contrast of cystic tumors or heterogeneously enhanced tumors was insufficient in the CBCT images. It is expected that the radiological characteristics of the tumor influence the minimum size of the tumor that can be visualized by CBCT. In the future, we should clarify such relationships by further studies incorporating more patients.

Conflict of Interest Statement

Dr. Nakagawa receives research funding from Elekta K.K. All other authors have no financial or personal relationship with other people or organizations that could inappropriately influence this work.

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Small cell carcinoma of unknown primary presenting with disease confined to the central nervous system

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To the Editor

We refer to an article published recently in your journal [1], in which the authors stated that extrapulmonary small cell carcinoma (EPSCC) "has been recognized at all sites of the body except the central nervous system". We disagree with this statement and find it ambiguous. If the authors are referring to EPSCC with brain metastases, we argue that this in fact has been widely described [2–9].

Small cell carcinoma of unknown primary (SCUP) is a subset of EPSCC, constituting between 8% [10] to 31% [11] of all EPSCC diagnoses. If the authors are referring to SCUP presenting with central nervous system (CNS) disease, although rare, we have identified one previously reported case in the literature [10]. Furthermore, our institution has recently treated two patients with SCUP who presented with disease isolated to the CNS and who also experienced relapse in the CNS alone.

Both patients were previous smokers, the first a 56-year-old male and the second a 71-year-old female. Both initially presented with a solitary intracranial lesion that was resected. Histology was consistent with small cell carcinoma, and no other sites of disease were found on staging investigations (computed tomography of the chest, abdomen and pelvis and whole body bone scan). Both patients received whole brain radiotherapy (30 Gy in 10 fractions). After 16 and 21 months respectively, both patients relapsed with isolated spinal intradural extramedullary disease that was surgically debulked. Histology was again consistent with small cell carcinoma. Both patients received radiotherapy to the involved spine (30 Gy in 10 fractions), followed by carboplatin (AUC 5, Day 1) and etoposide (120mg/m^2 Days 1–3) chemotherapy. The first patient completed four cycles and remains alive and well 33 months after the initial diagnosis. The second patient developed pneumonia and an acute myocardial infarction after cycle 1, and died shortly thereafter (24 months after the initial diagnosis). In a recent retrospective study, median survival for SCUP was only 2.5 months [11]. By comparison, our patients experienced prolonged disease-free and overall survival.

In summary, not only does EPSCC metastasise to the brain, but SCUP can also present initially in the CNS as demonstrated by the two cases we have described.

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