
PET Scanning of Iodine-124-3F9 as an Approach to Tumor Dosimetry During Treatment Planning for Radioimmunotherapy in a Child with Neuroblastoma

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A patient with advanced neuroblastoma who had failed chemotherapy presented with a large abdominal mass and virtually total bone marrow replacement by tumor on repeated marrow biopsies. She was considered a candidate for a Phase I ^{131}I -3F8 radioimmunotherapy trial, (MSKCC 89-141A). As a potential aid to treatment planning, a test dose of ^{124}I -3F8 was injected and the patient was imaged over the 72 hr postinjection using two BGO based PET scanners of different designs. Time activity curves were obtained, and the cumulated activity concentration of radiolabeled 3F8 in tumor was determined. Based on MIRDO, an estimated radiation absorbed dose for ^{131}I -3F8 was 7.55 rad/mCi, in the most antibody avid lesions. Because of low uptake and unfavorable dosimetry in some bulky tumor sites, it was decided not to treat the patient with radiolabeled antibody. Positron emission tomography of ^{124}I -labeled antibodies can be used to measure cumulated activity or residence time in tumor for more accurate estimates of radiation absorbed tumor dose from radioiodinated antibodies and can help guide management decisions in patients who are candidates for radioimmunotherapy.

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Radioimmunotherapy is a promising new modality for treating tumors resistant to conventional chemo- and radiotherapy (1,2). A more detailed knowledge of the radiation dose actually delivered to tumors and normal organs could lead to the development of more effective dosing schemes, better correlations with observed tumor response and normal tissue toxicity and better comparisons of different antibody-therapeutic radionuclide combinations. It is well recognized, however, that there are problems in

obtaining this knowledge (3,4). At the tissue level, inhomogeneities and biologic effects, such as internalization, need to be considered (5). Even at the organ (and large tumor) level, better quantitative information on the time varying concentration and distribution of the radiolabeled preparations is needed. With conventional gamma camera and SPECT imaging, obtaining accurate quantitative information is difficult.

In this paper, we demonstrate that PET can be used to determine the time varying concentration of an ^{124}I -labeled antibody (3F8) in a patient over a period of several days, permitting the prediction of the radiation dose that will be received from a subsequent administration of ^{131}I labeled antibody (6).

MATERIALS AND METHODS

Patient Selection and Case Report

The patient was a 3½-yr-old female with Stage IV neuroblastoma. She was diagnosed at age 1¼ yr with a large right adrenal primary (5 × 8 × 10 cm) and metastatic disease to bone marrow and lymph nodes. Her serum ferritin was 78 (normal). Tumor histology was favorable, with few mitotic figures. She was started on CCSG-P2 which consisted of cisplatin, adriamycin, VP-16 and cytoxan. After 5 cycles, her marrow was harvested and cryopreserved. At 6½ mo postdiagnosis, because of progressive disease in marrow and the primary site, she was started on CCSG 3003P consisting of high dose cisplatin, VP-16, ifosfamide and adriamycin. After 3 cycles, she underwent autologous bone marrow transplantation following high dose cytoxan, VP-16, thiotepa, cytoxan and total body irradiation. She also received local radiation to the primary tumor and left distal femur.

Although her 100 day posttransplant workup showed stable disease, rapid progression was evident by the time of this study, with marrow and lymph node involvement and rapid enlargement of the primary tumor with abdominal extension, anemia, leukopenia and thrombocytopenia. Bone marrow biopsy showed replacement of normal marrow elements with neuroblastoma tumor cells. LDH was 1464 (normal below 250), bone scan (Fig. 1A) negative. An [^{131}I]MIBG scan showed faint abdominal up-

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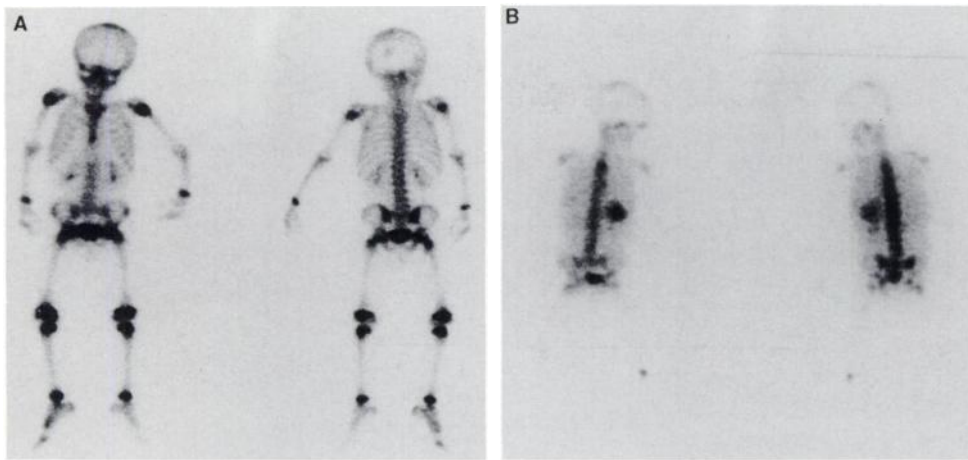


FIGURE 1. Planar whole body images. (A) ^{99m}Tc -MDP bone scan: normal. (B) 24-hr ^{131}I -3F8 scan. There is extensive replacement of the intramedullary space, with very active uptake of ^{131}I -3F8, indicating extensive marrow involvement by tumor.

take. The patient now weighed 14.7 kg, with a height of 39 in. and a body surface area of 0.6 m^2 . Conventional treatment having failed, she was being considered for therapy with ^{131}I -3F8 monoclonal antibody under an ongoing Phase I trial (7) and was about to receive the required ^{131}I -3F8 tracer dose and scan (Fig. 1B).

Radiolabeled Antibody

The ^{124}I was obtained from King Faisal Specialist Hospital, as NaI in 0.1 N NaOH. Following purification of the ^{124}I reagent, 3F8, a murine antibody developed by Cheung (8,9), was labeled using a chloramine-T method (10). Immunoreactivity, measured by a solid phase microtiter radioimmunoassay technique, (11) was 44% and protein incorporation was 24%. This was somewhat lower than observed with ^{131}I , probably because of oxidants in the ^{124}I reagent (10).

PET Imaging Studies

Serial PET studies were performed using a Cyclotron Corporation PC4600 (12) head scanner modified to accommodate pediatric patients. Following a transmission scan, 2.2 mCi ^{124}I -3F8 (3 mg 3F8) was infused intravenously over a half hour period. The patient's abdomen was imaged at 0, 18, 25 and 71.5 hr postinfusion. Scan time increased progressively from 15 to 45 min. A 60-ml syringe, initially containing $48.6\ \mu\text{C}$ of ^{124}I , was scanned each time as a reference standard.

To obtain higher resolution images and also image other body areas, the patient was transported elsewhere and scanned on a Siemens/CTI ECAT 931 PET scanner at 48 hr only (scan duration 30 min). This also permitted comparison of concentration values obtained with each scanner. Transmission scans were performed with the ^{124}I present in the patient. This was later shown to result in a ^{124}I activity determination error of less than 1% in this case.

On both scanners image reconstruction included standard corrections for detector nonuniformity, deadtime, random coincidences and attenuation and filtered backprojection using a Hanning filter. Activity concentrations were determined by comparing the counts within a region of interest in a patient image to the counts in a similar region in a reference standard image.

Dosimetry

Activity concentration was plotted against time for abdominal and vertebral tumors. Exponential fits were used to determine

initial uptake, clearance time and cumulated concentration. Radiation dose was determined using the MIRD schema.

RESULTS

Figure 2 shows the resultant PET images and a CT image for anatomic correlation. Uptake in tumor infiltrating marrow space is clearly seen, but uptake in the intraabdominal mass is significantly less.

Figure 3 shows time activity curves generated from these images. Note that the single time point obtained on the ECAT 931 scanner, although not at exactly the same anatomic location, is consistent with the values obtained on the PC4600 scanner. The maximum uptake was within the intramedullary space, 0.059% dose/g, with a biological half-life of 24.7 hr. These values are consistent with previous biopsies of ^{131}I -3F8 in neuroblastoma (13).

From these data and the MIRD formula for nonpenetrating radiation, the radiation absorbed dose to the tumor sites of maximum uptake for a therapeutic administration of ^{131}I -labeled 3F8 was estimated to be 7.55 rad/mCi. The dose to the abdominal mass would be 1.9 rad/mCi. Dose from the remainder of the body was estimated to be no more than 0.4 rad/mCi.

The Phase I ^{131}I -3F8 treatment protocol requires inspection of the ^{131}I -3F8 tracer dose scan before beginning therapy. If there is clear distinction in uptake between known tumor sites and normal tissues, therapy proceeds. This scan (Fig. 1B) also shows markedly abnormal uptake of antibody throughout the marrow cavity, but little in the abdominal mass, consistent with the ^{124}I -3F8 PET studies.

Because of lack of uptake of ^{131}I -3F8 in the enlarging abdominal mass, and unfavorable tumor dosimetry, the patient was started on chemotherapy: high dose cytoxan, adriamycin and vincristine. The patient's disease rapidly progressed, however, and she died of hepatic and renal failure 2 wk after the start of therapy.

DISCUSSION

In radioimmunotherapy, accurate dosimetry requires accurate quantitative imaging. The widespread use of ra-

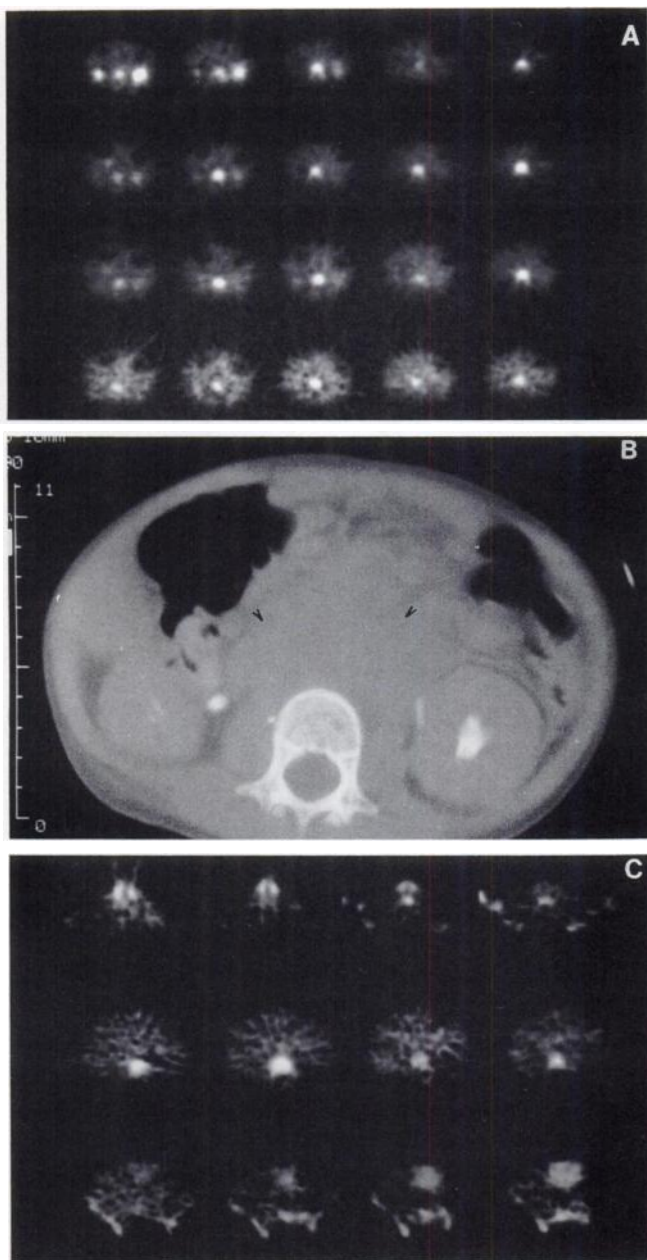


FIGURE 2. Transaxial PET and CT images. (A) PET images obtained on the PC4600 at four time points (0, 18, 25, 71.5 hr) postinfusion of 2.2 mCi of ^{124}I 3F8. Each row represents one time point, with images normalized to the maximum marrow activity in that row. The first image in each row is at the approximate level of the L-1 vertebra, subsequent images extending inferiorly. Note the appearance of activity in the renal area, most evident on early images. Uptake within the vertebral marrow is evident on all images. At 18 hr and at 25 hr in Slice 1, there is a definite "hot-spot" which is just anterior to the region of the patient's primary tumor, in the right adrenal, and may represent a site of tumor that is taking up the ^{124}I -3F8 more avidly than the large mid-abdominal mass. Lack of visualization at the other time points is probably due to patient movement. (B) A CT scan at approximately the level of Slice 1 of the PET scans of Figure 2A, showing the large intra-abdominal mass which does not concentrate the radiolabeled antibody as much as the tumor infiltrating the vertebral marrow. (C) Images taken approximately 48 hr postinfusion on the ECAT 931 body scanner. Images in each row are normal-

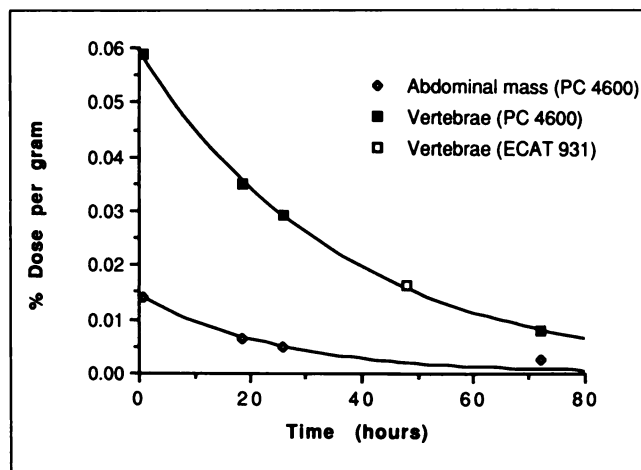


FIGURE 3. Time-activity curves generated from the images in Figure 2A for the large abdominal tumor and intravertebral tumor.

dioiodine isotopes as labels for antibodies would seem to make PET and ^{124}I a natural combination. Unfortunately, ^{124}I has a complex decay scheme with many high energy gamma rays and a positron abundance of only 25%. It was therefore virtually ignored in PET, until the combination of favorable chemical properties, half-life (4.2 days) and upsurge of clinical antibody studies awakened interest.

Concerns about the use of ^{124}I for quantitative imaging led to a previous study with phantoms and animals under realistic imaging conditions using the PC4600 (14) and several other PET scanners (15) to confirm that quantitative imaging is feasible. This paper extends this work to show that quantitative PET imaging of ^{124}I -labeled antibodies can be carried out in a patient over a period of several days to permit predictive radiation dose estimates prior to radioimmunotherapy.

PET and ^{124}I -iodide were used by Ott et al. (16) to estimate radiation dose to the thyroid. The ^{124}I -labeled antibodies were first used by Miraldi and Cheung to image neuroblastoma heterografts in nude rats (17), with subsequent animal studies performed by Snook et al. (18). These investigators clearly recognized the quantitative potential of ^{124}I versus ^{131}I . Subsequently, we and others, e.g., Wilson et al. (19), have employed ^{124}I -labeled antibodies in both animals and human studies.

In summary, we have demonstrated a dosimetric approach for radioimmunotherapy based on PET and ^{124}I , permitting estimation of radiation absorbed dose for subsequent therapeutic administrations of antibody labeled with ^{131}I or other radionuclides of iodine. Consistency of measurement between two very different PET scanners was also demonstrated.

ized to the maximum for that row and are in descending order within each row. Row 1: Neck and shoulder region. Images show iodine accumulation in the thyroid, and radiolabeled antibody uptake in cervical and other marrow spaces. Row 2: Lumbar spine. Activity seen in vertebral marrow spaces. Row 3: Pelvic region. Activity seen in pelvic marrow and bladder.

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