Gamma Camera Imaging of Platinum in Tumours and Tissues of Patients after Administration of ^{191}Pt-Cisplatin

Johan Areberg, Sven Björkman, Lars Einarsson, Britt Frankenberg, Hans Lundqvist, Sören Mattsson, Kristina Norrgren, Ole Scheike and Ronnie Wallin

From the Departments of Radiation Physics (J. Areberg, B. Frankenberg, S. Mattsson, K. Norrgren), Oncology (O. Scheike), and the Hospital Pharmacy (S. Björkman, R. Wallin), Malmö University Hospital, Malmö, the The Svedberg Laboratory (L. Einarsson), and the Department of Biomedical Radiation Sciences (H. Lundqvist), Uppsala University, Uppsala, Sweden

Correspondence to: Dr Johan Areberg, Department of Radiation Physics, Universitetssjukhuset MAS, 205 02 Malmö, Sweden. Tel: + 46 40 33 31 59. Fax: + 46 40 96 31 85. E-mail: johan.areberg@rfa.mas.lu.se

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The aim of this study was to visualize non-invasively the uptake of platinum in tumours and tissues after treatment with cisplatin. ^{191}Pt-cisplatin was synthesized from $^{191}PtCl_4$ with rigorous pharmaceutical quality control. The uptake of platinum by both tumorous and healthy tissues was studied by gamma camera imaging in 14 patients, 5 of whom showed a clear uptake of platinum in regions corresponding to known tumour sites. Maximum concentrations of platinum in the tumours were on average 4.9 ± 1.0 μg/g, when normalized to an administered amount of 180 mg cisplatin. In all the patients, the liver was the organ that showed the highest uptake. Platinum uptake was also seen in the spleen, gall bladder, gastrointestinal tract, bladder, kidneys, ureter, neck and mediastinum and urogenital region. By using in-house production of ^{191}Pt-cisplatin, it was possible to monitor the uptake of platinum in tumorous tissues and healthy organs.

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The cytostatic agent cisplatin is used as a single drug or in combination with other drugs or radiotherapy for the treatment of a number of cancers. It has been particularly successful in the treatment of testicular cancer (germ cell tumours), where today 90% of the patients treated are cured (1). Cisplatin is also used to treat ovarian, oesophageal and small-cell lung cancer as well as head and neck and bladder cancer.

The cisplatin molecule (cis-dichlorodiammineplatinum(II)) consists of a platinum atom located centrally, surrounded by two chloride and two ammonia ligands in the cis-configuration. It is generally assumed that intact cisplatin penetrates the cell and that hydrated complexes are formed intracellularly (2). The main target for cisplatin is DNA. The drug forms adducts with DNA, on which the intrastrand crosslink is assumed to be responsible for the biological activity (3). Part of the cisplatin is irreversibly bound to plasma proteins that cause loss of the cytotoxic effect (4).

Irreversible renal failure was early considered as a dose-limiting factor. Today, hydration is used to reduce this effect but nephrotoxicity is still the most dose-limiting adverse effect in cisplatin treatment. Other side effects are ototoxicity, myelosuppression, nausea, vomiting and peripheral neurotoxicity. In patients receiving very high doses or overdoses, side effects such as loss of vision and hepatic toxicity have been noted (5, 6).

Individual variations in the therapeutic results have been seen in patients, although they have the same histological form of cancer in the same stage. There is therefore an urgent need to develop quantitative, non-invasive methods to determine the concentration of the cytostatic agent in tumour tissue and in organs at risk. We have previously used in vivo x-ray fluorescence (XRF) to measure the concentration of platinum in the kidneys and tumours in patients (7). This technique made it possible to monitor only the total platinum uptake and not the distribution inside the organ or tissue studied. Another non-invasive method for determining the concentration of platinum in patients receiving therapy with cisplatin is the use of a radiotracer. Cisplatin is synthesized from radioactive platinum and the uptake, and with this technique also the distribution, of platinum in different organs and tissues can be studied using a gamma camera. The first studies

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with cisplatin containing radioactive platinum followed by gamma camera imaging in patients were carried out by Lange et al. (8) and were later continued by other groups (9–11). There were only a few patients included in these studies and both the spatial resolution and the uniformity of the detector system have been improved considerably since then.

The aim of this work was to visualize non-invasively uptake of platinum in tumours and tissues after treatment with cisplatin. In order to do this, an in-house synthesis of radioactive cisplatin was established and imaging conditions optimized.

MATERIAL AND METHODS

^{191}Pt-production

^{191}Pt was produced at the The Svedberg Laboratory in Uppsala. A gold foil, 2 g/cm^2, was irradiated with 75–65 MeV protons, as a result of which three main reactions occurred:

1. ^{197}Au(p,2p5n)^{191}Pt
2. ^{197}Au(p,p6n)^{191}Au → ^{191}Pt
3. ^{197}Au(p,7n)^{191}Hg → ^{191}Au → ^{191}Pt

The first of these three reactions predominates. ^{191}Pt decays with a half-life of 2.9 days by electron capture (EC) to stable ^{191}Ir (12). The characteristic x-rays emitted in this decay have energies of 63–73 keV (104%). Several less abundant γ-rays are emitted, of which the 539 keV (13.7%), 409 keV (8.0%), 360 keV (6.0%), 82 keV (4.9%) and 172 keV (3.5%) dominate.

The irradiations were performed overnight with an integrated beam current of 50–100 μAh. Targets were allowed to decay for 2 days before processing. The separation was started by heating the gold target at 1030°C (close to melting) for about one hour, which quantitatively distilled off the isotopes of mercury produced. The target was then dissolved in 10 mL aqua regia, evaporated to near dryness and dissolved in 5 mL concentrated HCl. The evaporation and the dissolution in concentrated HCl were repeated 2–4 times in order to remove the nitric ions. ^{191}Pt was separated from the target solution by 3–4 liquid-liquid extractions of gold, using methyl isobutyl ketone. No carrier was added. The final solution, containing 2–4 GBq in the form of $^{191}PtCl_4$, was evaporated to dryness. Usually no or only a minor amount of visible solid residue remained.

Synthesis of ^{191}Pt-cisplatin

^{191}Pt was transported from Uppsala to Malmö University Hospital where the synthesis was carried out under aseptic conditions. The process and production facilities were approved by the Swedish Medical Products Agency. The $^{191}PtCl_4$ was dissolved in 12 M HCl, 1–2 mL, and transferred to a small quartz beaker. The solution was evaporated to near dryness. Dissolution and evaporation were repeated using 1 mL of 1 M HCl. The solution was then transferred to a screw-cap centrifuge tube containing 34 mg $PtCl_4$ as carrier. After addition of 200 μL of 2 M NaCl and 20 μL of 1 M HCl, the tube was cooled in ice. The synthesis of cisplatin, beginning with the reduction of Pt(IV) to Pt(II) by means of hydrazine, proceeded as described in a published procedure (13), but with two changes. During the reduction step the final heating to 85–90°C was omitted and the intermediate product K_2PtCl_4 was isolated by precipitation as described in the original, unpublished procedure (14). The recrystallized cisplatin was finally dissolved in 10 mL 0.9% NaCl solution and filtered through an 0.22 μm sterile filter.

Quality control

The radionuclide purity was verified by gamma-spectrometry on an HPGe (High Pure Germanium)-detector (a volume of 161 cm^3 and an energy resolution of 1.7 keV (FWHM) at 1 330 keV). The chemical yield (milligrams cisplatin, as a percentage of theoretically possible), purity and identity of the synthesized cisplatin were determined by high-performance liquid chromatography (HPLC) (15). A 1.0 mM solution of benzalkonium chloride in water was used as the mobile phase on a LiChroCart™ (Merck, Darmstadt, Germany) RP-18 reversed-phase column (250 × 4 mm). The flow rate was 0.7 mL/min and the UV wavelength used for detection was 301 nm. A commercially available cisplatin solution (Platinol™, Bristol-Myers Squibb) was used as a reference for identification and quantification. The activity yield (MBq obtained as a percentage of theoretically possible) of the synthesized cisplatin according to the starting activity of the $^{191}PtCl_4$ was measured by an activity meter (Capintec, CRC—10 RB). One batch was also checked by thin-layer chromatography (TLC) on 0.25 mm silica gel plates, 10 cm × 20 cm (Merck), developed with acetone—0.1 M HCl 7:3. Several batches of final, injectable solution of cisplatin prepared by the general procedure but with carrier $PtCl_4$ only were tested for sterility (n = 7) and absence of bacterial endotoxins (pyrogens) (n = 7), by methods specified in the European Pharmacopoeia, 2nd edition.

Patients

Fourteen patients gave their written consent to take part in the study, which was approved by the Human Research Ethics Committee of Lund University, the Swedish Medical Products Agency and the Isotope Committee of Malmö University Hospital. The patients' clinical data are presented in Table 1. The tumour sites were localized from CT images or bone scans taken over the tumour region, examinations performed close in time to the ^{191}Pt-cisplatin study.

Administration of cisplatin

The ^{191}Pt-cisplatin synthesized in-house was mixed with cisplatin available commercially and administered by a 2-h infusion (the doses are shown in Table 1). This was done in connection with a standard hydration protocol, including the infusion of 1000 mL of physiological saline before and 1000 mL after the 2-h infusion of cisplatin. The fraction of cisplatin synthesized in-house was limited to a maximum of 10% of the total amount of cisplatin given. This corresponded to a ^{191}Pt activity of 31–50 MBq.

Imaging and quantitative measurements

Imaging was performed using a gamma camera (patients 1–5: Toshiba GCA-901 A, Tokyo, Japan, patients 6–14: Siemens MultiSPECT2, Hoffman Estates, IL) equipped with a high-energy collimator, necessitated by the presence of the high-energy photons. A 20% energy window was centred at 70 keV. In order to quantify the activity content in the tumours, liver and kidneys in the patients, phantom studies were performed. A known activity of ^{191}Pt was filled in spheres with diameters of 15, 20, 25 and 30 mm simulating tumours, a MIRD (16) liver phantom and a kidney phantom consisting of two cylinders, 50 mm in diameter and 62 mm in length. The 'organs' were inserted in a water-filled, elliptical thorax phantom (adult MIRD (16)). The phantom was imaged with the same collimator and using the same collection parameters as for the patients. For both cameras, the system resolution and sensitivity were determined. The system resolution was measured with a line-source of ^{191}Pt at a distance (air) of 10 cm from the camera. The sensitivity was measured with ^{191}Pt in solution in a dish, 100 mm in diameter (3 mm thick), placed directly on the collimator.

Imaging of the patients was started within three hours after the start of the infusion (except for patient 14, where the first image was performed 13 h after the start of the infusion) and then repeated one day later and for some patients up to 10 days after the infusion. Whole-body scanning, anterior and posterior, was done as well as static imaging over the liver and kidneys and over areas with known or suspected tumour tissue. The image matrix was 256×256 pixels for static images with an imaging time of 10–20 min depending on the activity infused and time

Table 1

Characteristics of the patient group (M-VAC: methotrexate, vinblastine, doxorubicin, cisplatin and calcium folinate; PF: 5-fluorouracil and cisplatin; P-VP16: etoposide and cisplatin; BEP: bleomycin, etoposide and cisplatin)

Pat. no.	Sex	Age (years)	Diagnosis	Pathology	Amount of cisplatin infused (mg)[a]	^{191}Pt activity (MBq)	Cytostatic treatment schedule
1	F	72	Bladder cancer+ cancer of urethra	Uroepithelial cancer	100 (7)	34	M-VAC
2	M	61	Oral cancer	Squamous cell carcinoma	102 (2)	31	PF
3	F	53	Chest wall metastases, unknown primary	Squamous cell carcinoma	180 (14)	37	P-VP16
4	M	62	Bladder cancer	Uroepithelial cancer	136 (6)	42	M-VAC
5	M	51	Lung cancer	Bronchoalveolar cancer	153 (3)	40	P-VP16
6	M	62	Oral cancer	Squamous cell carcinoma	109 (9)	50	PF
7	M	32	Testis cancer	Embryonal carcinoma	45 (5)	50	BEP
8	F	69	Lung cancer	Small cell lung cancer	47 (5)	50	P-VP16
9	F	55	Lung cancer	Undifferentiated cancer, non-small cell.	202 (2)	50	P-VP16
10	M	70	Lung cancer	Large cell undifferentiated carcinoma	152 (2)	50	P-VP16
11	M	60	Oral cancer	Squamous cell carcinoma	167 (7)	50	PF
12	M	43	Testis cancer	Mixed type, seminoma and teratoma	44 (3)	50	BEP
13	M	69	Rectal cancer	Cloagenic type	140 (2)	50	PF
14	M	29	Testis cancer	Mixed type: teratoma, embryonal carcinoma	88 (2)	50	BEP

[a] Dose in milligrams of in-house synthesized cisplatin is shown in parentheses.

elapsed since infusion. Scanning was done using a 256 × 1024 pixel matrix and a scanning speed of 10 cm/min. The images were studied by two physicians, one with previous knowledge of the type and localization of the tumours and one without this information. Tumour visualization was graded as not visible, borderline case, visible and clearly visible. For quantification of uptake from the gamma camera images, regions of interest (ROI) were drawn over the whole body, tumours, liver and kidneys in anterior and posterior images.

In patients 5–11 and 13, urine samples were collected for up to 48 h from the start of the infusion, and the fraction of ^{191}Pt excreted was determined. These data were also used to compensate for the fact that the whole-body content of platinum directly after the end of the infusion will be less than 100%, as platinum is lost by urine excretion during the infusion. For the patients whose urine was not collected, the platinum loss was estimated as the average value for the other patients.

RESULTS

Cisplatin synthesis and quality control

The radionuclide purity of the synthesized ^{191}Pt-cisplatin was 99%. About 1% of the total activity was in the form of ^{188}Pt at the time of infusion. ^{188}Pt has a physical half-life of 10.2 days and decays by electron capture (12). Impurities such as ^{191}Au and ^{188}Ir (daughter to ^{188}Pt) were present in the $^{191}PtCl_4$ solution at the start of the synthesis, but were not carried through the synthesis and were not found in the final product. HPLC of the cisplatin synthesized in-house gave a single peak corresponding to that of cisplatin from Platinol™. The chemical yield of cisplatin, calculated from the height of the HPLC peak, varied between 18 and 52%, while the activity yield varied between 10 and 36%. TLC measurements gave a single radioactive spot with $Rf = 0.82$. All batches tested passed the sterility and pyrogen tests.

Gamma camera calibrations

For the Toshiba single-headed camera, the system resolution for ^{191}Pt at 70 keV was found to be 12.5 mm (FWHM) and the sensitivity 190 cps/MBq. The corresponding values for the Siemens two-headed camera system were 12.1 mm (FWHM) and 190 cps/MBq.

Biodistribution and kinetics

The two physicians who studied the images agreed on the uptake of platinum in tumours and tissues stated below.

Tumours. Uptake of platinum in known tumour sites was observed in 5 of the 14 patients at seven different tumour sites, since in patients 10 and 12 two tumours were visualized. Of these seven tumours, four were located in the head and neck region, two in the lung and one in the intestine (see Table 2). Fig. 1 shows two examples of uptake of platinum in tumours. The uptake of platinum was visualized directly after the infusion was completed and remained observable in the later images. The maximum concentrations of platinum in the tumours were in the range 1.0 to 4.7 μg/g tissue (see Table 2), corresponding to an average maximum concentration of 4.9 ± 1.0 μg/g when normalized to an administered amount of 180 mg cisplatin.

Whole-body. The whole-body retention of platinum is shown in Fig. 2 for the ten patients who were scanned more than two days after the infusion of ^{191}Pt-cisplatin. The heart and larger blood vessels were visualized during the first hours after infusion.

Liver, spleen, gall bladder and gastrointestinal tract. For all 14 patients, the liver was the organ that showed the highest uptake of platinum. Maximum fractional uptake was on average 8.8% (range 6.4–12.6%) of the platinum administered. Normalized to an administered amount of 180 mg cisplatin, this corresponds to an average concentration of 5.7 ± 0.5 μg/g, assuming the weight of the liver to be 1800 g (17). The uptake was seen in the first scintigrams directly after the end of the infusion and the liver continued to be clearly visible in all later scintigrams (see Fig. 3). For two of the patients (nos. 1 and 5) a higher value was found one day after the end of the infusion. No correlation was found between the amount of cisplatin given and the maximum fractional uptake of platinum.

For three patients (nos. 6, 8 and 11), the spleen was observed in all images but most distinctly in later images. For patients 2, 7, 8, and 12 the gall bladder was seen in the images taken one day after the end of the infusion. In the images taken directly after the infusion and at two days or more after the infusion, the gall bladder was not visualized.

Platinum was visible in the gastrointestinal region one day after infusion and remained so for about five to six days (see Fig. 3). On later images, taken seven to ten days after infusion, there was no indication of the presence of platinum. Platinum was first seen in the gall bladder, then in the small intestine and later in the large intestine, consistent with intestinal transit.

Kidneys and urine excretion. The initial fractional uptake in the kidneys (both kidneys together) was 0.4–0.6% of the platinum administered. Normalized to an administered amount of 180 mg cisplatin, this corresponds to 1.9 ± 0.3 μg/g, assuming the total weight of the kidneys to be 310 g (17). The uptake after one day after infusion was of the same order, but on later days the kidneys were not visible, so that the retention pattern could not readily be described.

There was an initial, rapid excretion of platinum via the urine. Six hours after the start of the infusion, on

Table 2

Visualization of tumour tissue in the ^{191}Pt-cisplatin scintigrams. The scale of visualization, '−', '+/?', '+' and '++', indicates not visible, borderline case, visible and clearly visible, respectively. For the cases where tumour tissue was visualized, the depths and concentrations of platinum are given

Pat. no	Localization of tumour tissue	Visualization	Depth for visualized tumours (cm)	Maximum platinum concentration (μg/g)	Verification of the presence of the tumour
1	Bladder and ureter	−			
	Inguinal lymph nodes	+/?			
2	Head and neck	+/?			
3	Lung	+	2	4.7 ± 0.8	CT
4	Pelvis region	−			
5	Lung	−			
6	Head and neck	++	2	4.1 ± 1.2	CT, bone scan
7	Pelvis region	−			
8	Lung	−			
9	Lung	−			
	Right leg	−			
10	Lung	+	12	3.3 ± 1.0	CT
	Head and neck	++	2	3.5 ± 1.0	CT
11	Head and neck	+	2	3.0 ± 1.3	CT, bone scan
12	Head and neck	++	1	1.8 ± 0.9	CT
	Intestine	+	2	1.0 ± 0.4	CT
13	Rectum	−			
14	Lung	−			

average 28% (range 15–42%) of the platinum administered had been excreted. At 48 h, the amount of platinum excreted was on average 42% (range 28–62%). The bladder and ureter were clearly visualized directly after the infusion in all patients.

A significant correlation ($p < 0.05$, $r = 0.96$, by Pearson product moment correlation) was found between the cumulated urinary platinum and the loss of platinum calculated from the whole-body images taken one day after the end of the infusions.

Other organs and tissues. In all 14 patients and in all images, directly after infusion as well as in all later images post infusion, there was a diffuse uptake of platinum centrally in the neck and mediastinum regions (see Fig. 3). An uptake of platinum in the urogenital region, below the bladder, was clearly visible in all patients, both men and women, from the first images directly after the end of the infusion and on all later images (see Fig. 3). The scintigrams clearly showed lack of uptake of platinum in the brain. In later scintigrams, an uptake of platinum in the elbows, knees and ankle joints was seen.

DISCUSSION

The activity yield of the ^{191}Pt-cisplatin synthesis, 10–36%, was lower than reported by other groups. Baer et al. (18) achieved an activity yield of 60–75% for ^{191}Pt-cisplatin. In contrast to the present study, they used Na_2PtCl_6 as carrier instead of $PtCl_4$, which means that they could exclude some steps of the synthesis. We sometimes had a problem with too much acid in the early steps of the synthesis, which partly explains the large variation in the yield. Temporarily, we also had problems with the separation of ^{191}Pt from the target where ^{191}Pt was also present as a compound other than $^{191}PtCl_4$ and hence we lost that activity in the first step of the synthesis.

Non-invasive studies of the concentration of platinum in tumours in humans are rare, thus little is known about the uptake and retention of platinum in tumours during and after treatment with cisplatin. Shani et al. (11) found concentrations of ^{195m}Pt in astrocytoma tissue three to ten times higher than in the surrounding normal brain tissue after intra-arterial infusion of cisplatin. Iosilevsky et al. (19) reported on uptake of ^{195m}Pt in a small-cell carcinoma of the lung and in a glioblastoma of the brain. Visualization of platinum in brain tumours is theoretically easier than in other tissues because the concentration of platinum after treatment with cisplatin is very low in normal brain tissue. In the present work we show that visualization of platinum in tumour tissue after therapy with cisplatin is possible, not only in the brain and the lungs but also in the region of the head and neck and intestine. The average maximal concentration of platinum in tumour tissue, 4.9 ± 1.0 μg/g normalized to an administered amount of 180 mg cisplatin, is comparable to the 1.6–4.2 μg/g tissue that Hecquet et al. (20) found in tumour biopsies (head and neck, uter-

ine cervix and breast) taken 48 h after cisplatin administration (100 mg/m^2).

The important factor for the visualization of an organ or tissue is the concentration of platinum, or more correctly the ratio between the concentration in the organ/tissue of interest and the surrounding tissue. Even if platinum was observed in tumours in our patients, the concentrations were not particularly high. Tumours in tissues with normally a low concentration of platinum, such as the brain and lungs, are more readily visualized than tumours in tissues with a high concentration of platinum such as the liver, mediastinum and kidneys. It is also evident that a marked limitation to visualization with this technique is the depth of the tissue to be imaged, because of increasing attenuation of the photons as the depth increases. Our method does not differentiate between the various forms of platinum present in the body, but since only intact cisplatin can penetrate the cell, a large uptake of platinum indicates a large uptake of intact cisplatin.

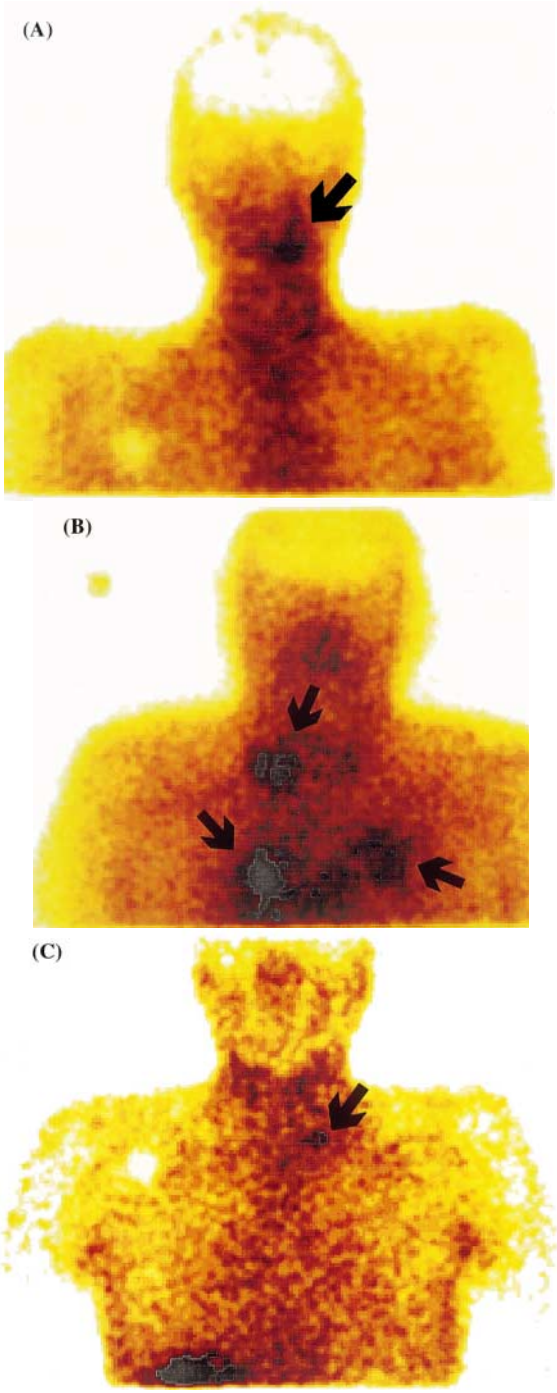

Fig. 1. Static anterior images over the head and neck and thorax region of patient 6 (A), patient 10 (B) and patient 12 (C) directly after the end of the infusion of ^{191}Pt-cisplatin. Tumours are indicated with arrows.

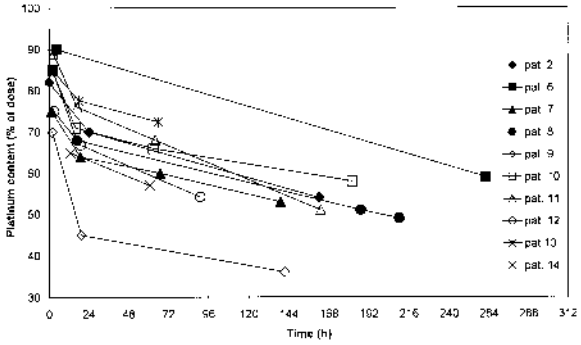

Fig. 2. Fraction of platinum administered remaining in the whole body of the patients at different times after the end of the infusion of ^{191}Pt-cisplatin, calculated from whole-body scans.

The extent of the uptake of platinum in the liver seen in our images is consistent with data reported by Smith et al. (9). Furthermore, studies on tissues obtained from autopsies from patients who had received cisplatin ante-mortem demonstrated a high concentration of platinum in the liver. Both Stewart et al. (21) and Uosumi et al. (22) found a linear relationship between cumulative cisplatin dose and hepatic platinum concentration. Tothill et al. (23) found the platinum concentration in the liver at autopsy to be much higher than that in any other organ, 2.0% of the dose administered following cisplatin administration at least two months before death.

In some patients, the gall bladder was visualized, and an uptake of platinum was seen in the gastrointestinal tract, indicating that a proportion of the platinum was excreted into the gastrointestinal tract and not only through the kidneys. Other groups have also reported excretion of platinum into the gastrointestinal tract (8–10), but no data are reported in the literature on platinum elimination via faeces. To our knowledge, the presence of platinum in the spleen has not previously been demonstrated by non-invasive measurements. Tothill et al. (23) found the concentration of platinum in the spleen to be approximately one-seventh of the concentration in the liver in autopsy

material from patients following cisplatin administration at least two months before death.

The uptake of platinum in the kidney was lower than expected from XRF measurements (7) but consistent with other studies using radioactive cisplatin. Owens et al. (10), who studied the distribution of platinum after a bolus injection of ^{191}Pt-cisplatin in three patients, found a peak uptake in the left kidney, after 6 min, of on average 1.89% of the platinum administered. After 24 h. 0.27% was retained. This is consistent with our results of 0.4–0.6% of the amount of platinum administered in the two kidneys together during the first day. When studying autopsy material from patients receiving cisplatin, Stewart et al. (21) found no correlation between renal cortical platinum concentrations and total cumulative platinum dose, whereas Uozumi et al. (22) found a correlation between the platinum concentration in the kidney and the total cumulative platinum injected within a 6-month period

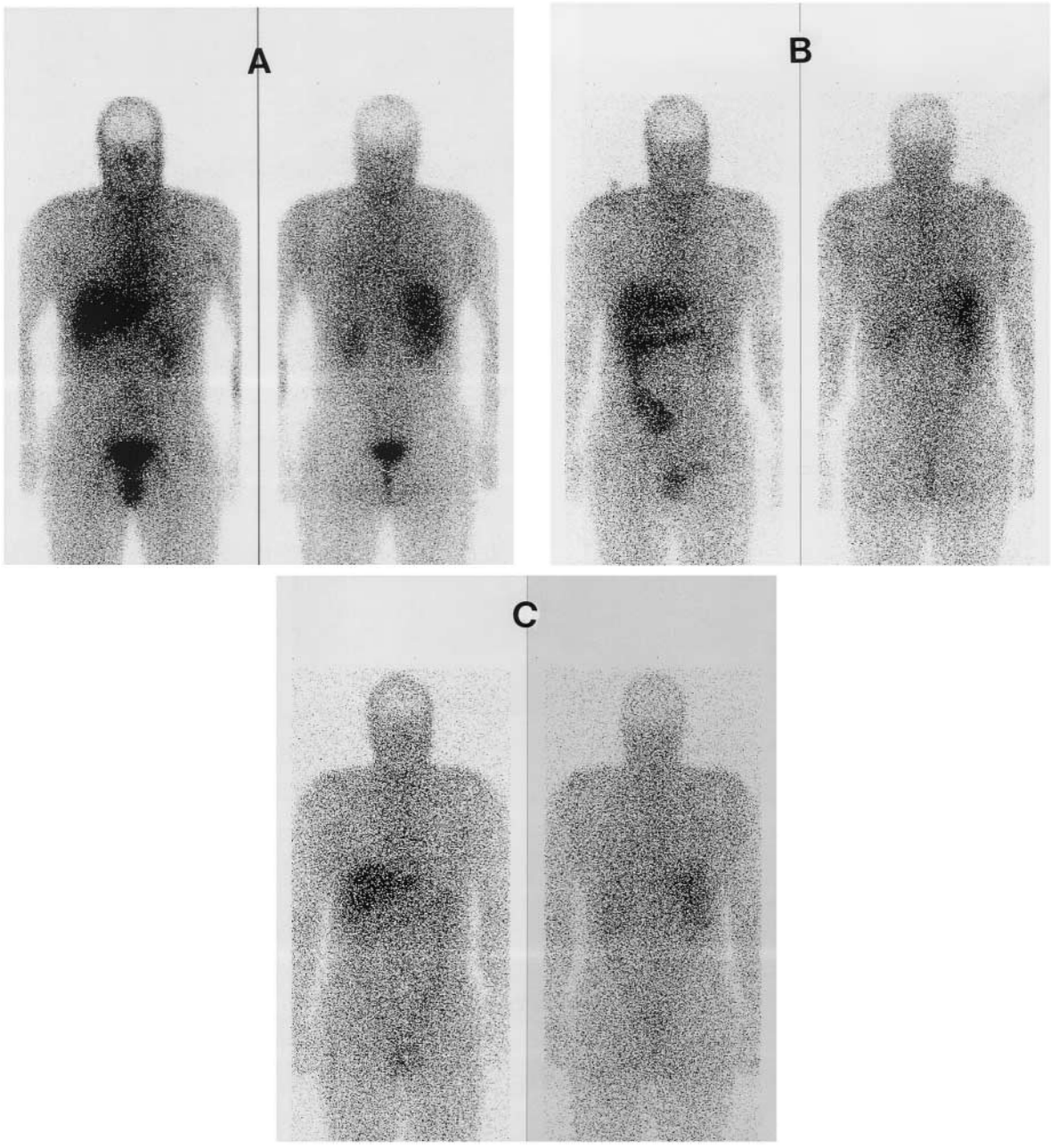

Fig. 3. Whole-body images (anterior to the left and posterior to the right) of patient 7 at 1 h (A), 65 h (B) and 163 h (C) after the end of the infusion of ^{191}Pt-cisplatin. The imaging performed 17 h after the end of the infusion (image not shown) was similar to the 1-h image except for lower uptake in the bladder.

prior to death in their autopsy material. The excretion of platinum via the urine is in good agreement with other studies (9, 23–26).

There was an uptake of platinum in the urogenital region. Tothill et al. (23) found high concentrations of platinum in the uterus, prostate and testes in autopsy tissue from patients who had been given cisplatin at least two months before death. The concentrations of platinum in these organs were higher than the concentrations of platinum in the kidneys and spleen.

We have shown that non-invasive visualization of platinum uptake in tumours after treatment with cisplatin is possible. However, more data are necessary before any predictions about the clinical value of the method can be drawn.

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