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Assessment of Anthracycline-related Myocardial Adrenergic Derangement by [^{123}I]Metaiodobenzylguanidine Scintigraphy

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Myocardial adrenergic neuron integrity and function were evaluated in 21 patients who had received doxorubicin or epirubicin for various malignancies. Myocardial uptake of iodine-123 metaiodobenzylguanidine ([^{123}I]MIBG), a marker suitable for the study of myocardial neuron injury, was calculated from planar scintigraphic images after 4 h and the washout between 15 min and 4 h. In 13 patients with normal left ventricle ejection fraction (LVEF) analysed at three cumulative dose levels (no, low and middle dose), [^{123}I]MIBG uptake tended to be significantly impaired ($z = -2.772$, $P = 0.0056$), at higher cumulative dose levels, before significant LVEF changes were observed. [^{123}I]MIBG values were considerably decreased in 2/7 patients investigated at low cumulative dose and in 3/8 cases at the middle dose level. On follow-up, 1 of these patients, who had normal LVEF after completion of chemotherapy but whose [^{123}I]MIBG values had progressively deteriorated during anthracycline therapy, subsequently developed congestive heart failure; another patient, whose [^{123}I]MIBG values were impaired at the middle dose level, developed persistent reduced LVEF 5 months after completing therapy. In 8 patients, who had developed persistently, reduced LVEF at high doxorubicin cumulative dose levels, [^{123}I]MIBG, performed in the period after chemotherapy discontinuation, was invariably abnormal. These data suggest that myocardial adrenergic derangement plays a role in anthracycline-associated cardiotoxicity: its appearance, even at low cumulative anthracycline dose levels, may reflect impairment of the intravesicular norepinephrine storage by incipient anthracycline-associated cardiac neuron injury. [^{123}I]MIBG scintigraphy may be useful to assess myocardial adrenergic derangement during and in the follow-up of anthracycline therapy and potentially detect patients who are at risk.

Key words: [^{123}I]MIBG, anthracycline therapy, myocardial adrenergic derangement
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INTRODUCTION

THE ASSESSMENT of anthracycline-associated injury of one or more components of the cardiac function by non-invasive and specific methods is valuable since it may enable the design of better strategies to overcome dose-related cardiotoxicity from anthracyclines. Traditionally, the monitoring of cardiotoxicity has been based on serial assessment of endomyocardial biopsy or left ventricle ejection fraction (LVEF). Although endomyocardial biopsy is, until now, the only recognised technique to detect myocyte damage, and correlate the abnormal cellular changes with the cumulative anthracycline dose [1, 2], the monitoring of heart muscle histology requires a repeated, invasive, expensive procedure and highly specialised histological knowledge of early toxicity. Moreover, histological findings do not necessarily correspond with the clinical evolution, as early myocardial injury is scattered throughout the heart [3], which easily leads to sampling error during biopsy. A decrease in LVEF, reflecting cardiac systolic dysfunction secondary to myocardial injury, is useful to predict congestive heart failure. However, a decrease in LVEF is often preceded by histological changes [1, 2] and focal impairment of wall motion [4,5], demonstrating its limited sensitivity for early detection of cardiac injury from cumulative anthracycline doses.

Recently, the introduction of Indium-111 antimyosin (Fab) antibodies has enabled the direct visualisation of heart muscle cell injury in humans and animals [6, 7]. The degree of myocardial uptake of this tracer has been found to correlate with the cumulative dose of anthracycline [8]. Since, in anthracycline-associated cardiotoxicity, injury of myocytes plays a major role, and a wide spectrum of mechanisms has been listed to explain the cell damage [9], mapping of myocyte damage by [^{111}In]antimyosin cardiac scintigraphy may have important clinical implications, enabling the measurement of the effect of several factors on myocardial cells, such as intensification of chemotherapy, different regimens, different anthracyclines and cardioprotective agents.

Currently, it is possible to study yet another component in

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anthracycline-associated cardiotoxicity, that is, the injury of the cardiac adrenergic neurons by scintigraphy using radioiodinated metaiodobenzylguanidine (MIBG), a norepinephrine-uptake analogue which is not metabolised by monoamine oxidase or cathechol-o-methyltransferase. Diminished myocardial accumulation of [125I]MIBG, indicating adrenergic neuron injury, has been found in animals treated with doxorubicin in a dose-dependent manner [10]. In 6 patients with cardiotoxicity from anthracyclines, decreased myocardial retention of [123I]MIBG was reported, and the degree of myocardial adrenergic derangement appeared to correlate with the decrease in left ventricle ejection fraction (LVEF) [11]. In the present study, we report data of [123I]MIBG heart scintigraphy in 21 patients who have received doxorubicin or epirubicin for various malignancies. The aim of the study was to evaluate both the feasibility of quantitative heart scintigraphy, using [123I]MIBG to detect abnormalities of the cardiac adrenergic neuron activity in patients treated with anthracyclines; and the degree of myocardial adrenergic derangement, in relation to the LVEF.

PATIENTS AND METHODS

Patients

21 patients (19 female, 2 male; aged 31–56 years, median 42.5 years) with a variety of malignancies (16 advanced breast carcinoma, two malignant lymphoma, three soft tissue tumours) were studied. 13 consecutive patients (group A) referred to the department of nuclear medicine for cardiac monitoring were evaluated during chemotherapy including doxorubicin or epirubicin; 3 of these patients underwent [123I]MIBG studies at three different cumulative dose levels of anthracyclines and 2 patients at two different levels. At the time of [123I]MIBG scintigraphy, none of these patients had any evidence of ECG abnormalities or a decreased LVEF at rest. Group B consisted of 8 patients with documented cardiotoxicity, who had developed a persistently decreased LVEF at cumulative doses of doxorubicin varying from 400 to 600 mg/m^2. In these patients, chemotherapy was discontinued, and in 5 cases, the decrease in LVEF was complicated by the onset of congestive heart failure.

Criteria for the evaluation of congestive heart failure were defined according to the New York Heart Association (class III–IV). Informed consent was obtained from all patients in this study and the protocol of investigation was approved by the scientific and ethical review committees of The Netherlands Cancer Institute.

[123I]MIBG heart scintigraphy

In patients of group A, [123I]MIBG studies were performed in the same week as the LVEF determination and at least 3 weeks after the last chemotherapeutic course. In patients of group B, [123I]MIBG studies were performed in the period after discontinuation of chemotherapy (4–12 weeks in 5 cases, 1–3 years in 3 cases). The thyroid was blocked for the uptake of iodine-123 by oral administration of 100 mg potassium iodide about 30 min before intravenous injection of the radiopharmaceutical. [123I]MIBG was prepared with a high radionuclide purity of >99.95% iodine-123 (pR14 method, Cygne, Eindhoven, The Netherlands), and had a specific activity of 925 MBq/mg on calibration. At the time of [123I]MIBG scintigraphy, none of the patients used drugs which are known or may be expected to interfere with MIBG uptake, such as tricyclic antidepressants, sympathicomimetic and antihypertensive drugs, and they were asked to abstain from coffee or caffeine-containing beverages before and during the radionuclide study. Following a 20-min resting period, planar static images of the heart were obtained 15 min and 4 h after administration of 185 MBq (5 mCi) [123I]MIBG containing 0.2 mg MIBG. Anterior and left anterior oblique (LAO) images were acquired in a 128 × 128 × 16 matrix. Acquisition in LAO projection was done with an inclination of 30° and identical positioning of the patient for both the early and late images was ensured using fixed anatomical reference points. Images were made with a large field of view gamma camera (Siemens Rota-2/Adac Genesys) equipped with a low energy high resolution collimator.

Quantification of [123I]MIBG scintigraphy was performed on an Adac Pegasys computer. Washout rates were calculated as follows: regions of interest were drawn around the left ventricular myocardium in the LAO position; background subtraction was performed using a mediastinal regular region of interest [12]. The same regions of interest were applied for the early and late images and, to calculate the 4-h washout rates, the counts were normalised for injected dose and corrected for decay [11]. For quantification of [123I]MIBG cardiac uptake, heart-to-mediastinum ratios (HMR) were calculated from the 4-h views. Cardiac [123I]MIBG parameters were measured twice by two independent observers in a series of 25 examinations in order to assess the intra- and interobserver variations.

In a number of patients, complementary single photon emission computed tomography (SPECT) was performed in order to study the myocardial distribution of [123I]MIBG, and to evaluate the feasibility of this technique in patients after left mastectomy, who often have reduced capacity to sustain the arm in wide abduction as required for SPECT of the heart. SPECT studies were performed by means of 180° rotation with a single-head ADAC-Genesys camera equipped with a low energy high resolution collimator (30 s/frame, 64 × 64 ×8 matrix, 6° angle interval).

LVEF values were obtained from gated angiocardioscintigraphic studies performed in the LAO position after administration of 740 MBq (20 mCi) of ^{99m}Tc-labelled human serum albumin, acquiring 24 frames per cardiac cycle. LVEF was measured using a semi-automatic processing with a varying region of interest.

Analysis

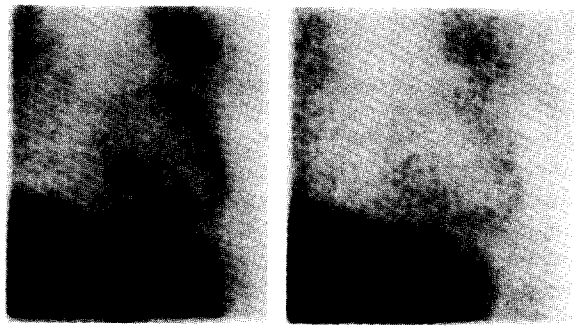
Myocardial [123I]MIBG uptake, 4-h washout and LVEF values of group A were analysed at three cumulative anthracycline dose levels: no dose, low dose (150–200 mg/m^2 of doxorubicin or 240–300 mg/m^2 of epirubicin) and middle dose (300–350 mg/m^2 of doxorubicin or 450–500 mg/m^2 of epirubicin). Differences of [123I]MIBG and LFEV values between data of groups A and B were analysed using the two sample Wilcoxon rank sum for equality of medians. To test a trend across different anthracycline dose levels of group A, a Wilcoxon-type test for trend (Altman, Cuzick) was used. Results were expressed as mean ± S.D. and median values.

RESULTS

A total of 30 [123I]MIBG examinations were performed: 22 in group A, eight in group B. The quality of the planar images was generally satisfactory, and an abnormal pattern could easily be distinguished from a normal one (Figure 1).

The intra-($r = 0.98, P < 0.001$) and interobserver ($r = 0.99$, $P < 0.0001$) correlations indicated no essential differences in [123I]MIBG measurements.

In group A (Table 1), HMR tended to deteriorate significantly at higher dose levels ($z = -2.772$, $P = 0.0056$), but although



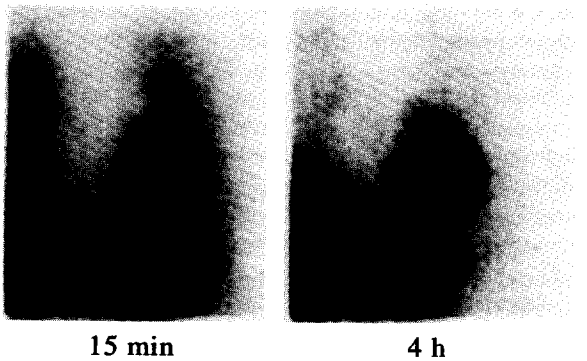
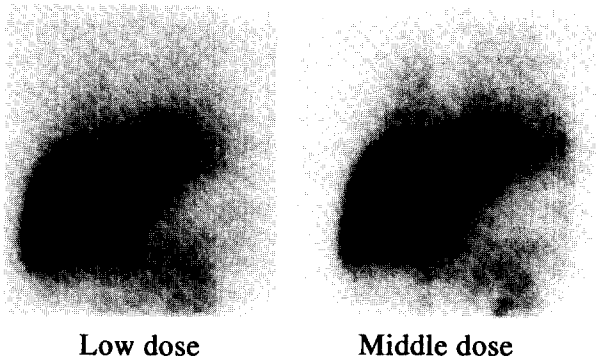


Figure 1. Planar anterior [^{123}I]MIBG images showing reduced myocardial uptake and retention in a patient who developed severe cardiotoxicity (upper panels). By contrast (lower panels), normal uptake and myocardial retention are observed in another patient investigated at low cumulative anthracycline dose.



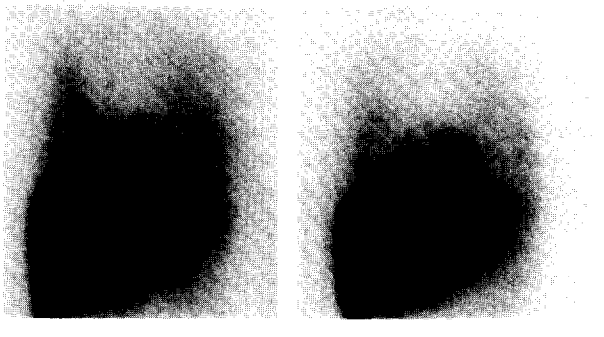


Figure 2. Sequential 4-h planar [^{123}I]MIBG left anterior oblique images at low and middle cumulative anthracycline dose levels. Myocardial uptake (H) of the tracer remains normal (upper panels), whereas in another patient there is a tendency to impairment at middle dose (lower panels).

4-h washout tended to increase (z = 1.355), it did not reach statistical significance. HMR was clearly reduced in comparison to reference values at the no dose level in 2/7 cases at low dose and in 3/8 at middle dose, as illustrated in Figure 2. An abnormal LVEF or ventricular enlargement was not observed in any patient during chemotherapy. In contrast to the MIBG tendency, LVEF did not deteriorate significantly (z = −0.579) at different dose levels (Figure 3). No correlation (r = 0.176) was found between LVEF and HMR. The negative correlation between LVEF and [^{123}I]MIBG washout (r = −0.258) was also non-significant.

On follow-up, 1 of the patients of this group who had a LVEF of 59% after completion of chemotherapy, but whose HMR had deteriorated from 1.92 to 1.35, and the 4-h washout increased from 12.9 to 42.9%, subsequently developed congestive heart failure; another patient, whose HMR was 1.53 and 4-h washout 50.2% at middle anthracycline dose level, developed persistently reduced LVEF 5 months after completing chemotherapy.

Table 1. [^{123}I]*MIBG and LVEF data of patients of group A in relation to anthracycline cumulative dose level. Principally* [^{123}I]*MIBG cardiac uptake after* 4 *h measured by heart-to-mediastinum ratio (HMR) tended to impair at higher cumulative anthracycline dose levels*

	[^{123}I]MIBG						Left ventricle ejection fraction (LVEF)		
	4-hour cardiac uptake (HMR)			4-h washout					
Dose	None	Low	Middle	None	Low	Middle	None	Low	Middle
n	7	7	8	7	7	8	7	7	8
Mean	1.91	1.77	1.72	14.8	16.5	22.5	60.1	57.4	58.1
S.D.	0.08	0.11	0.18	6.5	10.9	15.5	6.3	4.9	6.7
Median	1.90	1.79	1.72	13.2	14.5	17.1	59.0	58.0	58.0
Range	1.81–2.06	1.56–1.86	1.35–1.9	5.8–25.4	4.0–34.1	6.0–50.2	50.0–70.0	51.0–65.0	50.0–68.0
		z = −2.772 (P = 0.0056)			z = 1.355 (n.s.)			z = −0.579 (n.s.)	

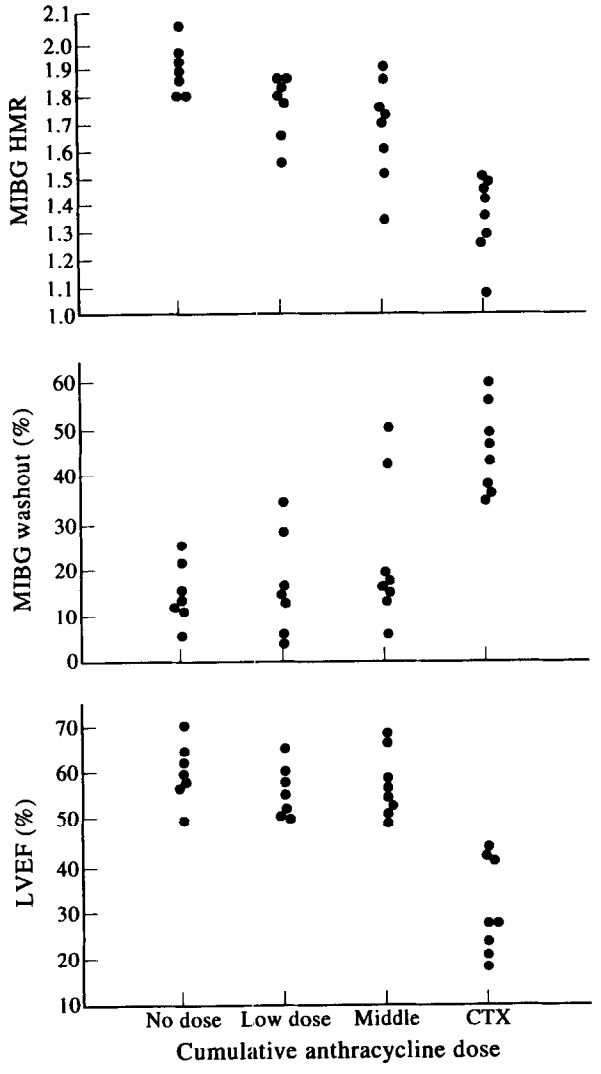


Figure 3. Myocardial uptake (HMR) and 4-h washout of [123I]MIBG compared with the left ventricle ejection fraction (LVEF) in patients investigated at three cumulative anthracycline dose levels (group A) and in patients with decreased LVEF (CTX).

In patients of group B, values of both [123I]MIBG and LVEF were abnormal and considerably reduced in comparison to group A (Table 2).

Analysing the overall data (group A + B), HMR correlated negatively with 4-h washout ($r = -0.835, P < 0.001$).

Complementary SPECT studies were performed in 15 cases: in patients with abnormal [123I]MIBG parameters, a patchy myocardial distribution of the tracer at 4-h images was usually observed (Figure 4); generally, SPECT contributed to identification, with better precision, of the segment abnormalities compared with planar images. Although quality of early and late SPECT was very high in patients with normal myocardial retention of the tracer, 4-h images of patients with abnormal retention were of poorer quality due to the reduced heart uptake. The relatively long acquisition time of the studies was the major burden, especially for patients after left mastectomy.

DISCUSSION

The kinetics of radio-iodinated MIBG are considered to reflect norepinephrine flux in the myocardium directly [13]. Because its uptake in the heart reflects myocardial neuron integrity and its release the adrenergic function, [123I]MIBG has been found to be a suitable marker to study myocardial adrenergic innervation and neuron injury [14]. After intravenous administration of [123I]MIBG, the left ventricle myocardium can be visualised within the first few minutes. This initial concentration, apparently depending primarily on blood flow [15], reflects both the extra- and intravesicular accumulation of the tracer in cardiac neurons. Whereas the extravesicular concentration of radio-iodinated MIBG decreased rapidly in the first few hours, the intravesicular concentration remains relatively constant, reaching a plateau after 4 h and indicates the adrenergic neuron terminal concentration [16]. In this way, 4-h parameters of [123I]MIBG in the heart may be used to explore specific neuron injury and impairment of the norepinephrine uptake function due to various pathological conditions. In a rat model, however, myocardial uptake was found to depend strongly on the specific activity of the tracer, tended to decline when the specific activity was low and was only stable if the total loading dose of MIBG did not exceed 12 μg per kg body weight [17]. The use of MIBG with a high specific activity revealed high levels of intravesicular storage in cardiac neurons a few hours after administration, accounting for 80% of the primary myocardial uptake [10]. The [123I]MIBG used in our study complied with these requirements.

The two most relevant findings of this feasibility study were the demonstration of reduced myocardial uptake of [123I]MIBG in patients with reduced LVEF studied after chemotherapy, and the tendency to myocardial adrenergic derangement with increasing cumulative dose levels of anthracyclines, observed in patients with normal LVEF during chemotherapy. [123I]MIBG was abnormal in all patients with reduced LVEF, and the impairment of [123I]MIBG parameters tended to be proportional to the severity of LVEF decrease. By contrast, in patients receiving anthracyclines, deterioration of [123I]MIBG myocardial kinetics was observed in cases without any evidence of abnormal LVEF or dilatation of the left ventricle. We assume that the deterioration of MIBG parameters in relation to the cumulative anthracycline dose, observed in patients with normal LVEF, may reflect an impairment of intravesicular norepinephrine storage function by incipient neuron injury. Although ventricular enlargement may influence the uptake of MIBG, the correlation between these factors has been found to be weak in patients with heart failure [18], and is also assumed to play a minor role in the present series.

Various authors have used both heart-to-mediastinum ratios and 4-h washout to study MIBG kinetics in the myocardium [12, 18–20]. In this study, we generally found concordance between both parameters; each may be used independently. However, in one case investigated, at the middle cumulative dose level of anthracycline, a normal washout was found in the presence of reduced myocardial uptake of [123I]MIBG. This observation is interesting since an initially decreased cardiac concentration, influenced by reduction of blood flow and/or extraneuronal compartment, may cause spuriously normal washout values even under conditions of impaired intravesicular storage. In this context, the acquisition of both early and late MIBG images may not only detect injured myocardial areas, but also enable a better quantitative evaluation of the neuronal and extraneuronal compartments.

Various technical limitations, principally related to other organ activities in the cardiac region, which requires an adequate correction for background, have been described for the quantification of myocardial activity on planar scintigraphic images [18].

Table 2. [^{123}I]*MIBG and LVEF data of patients without LVEF decrease, studied during chemotherapy (group A), and patients with decreased LVEF, studied after anthracycline therapy (group B)*

	[^{123}I]MIBG				Left ventricle ejection fraction (LVEF)	
	4-h cardiac uptake (HMR)		4-h washout			
	A	B	A	B	A	B
n	22	8	22	8	22	8
Mean	1.78	1.38	18.2	45.3	58.6	31.1
S.D.	0.16	0.1	11.7	9.5	5.8	10.3
Median	1.85	1.39	14.9	45.5	58.5	28.0
Range	1.35–2.06	1.08–1.5	4.0–50.2	35.0–60.0	50.0–70.0	21.0–44.0
	$P < 0.0001$		$P < 0.0002$		$P < 0.0001$	

In spite of this, ^{123}I-MIBG heart scintigraphy is easy to perform, and may become a useful tool in the monitoring of cardiotoxicity, provided that technical aspects are standardised. The technique has good reproducibility, and appears to be sensitive enough to detect abnormalities of the myocardial adrenergic innervation due to anthracyclines before LVEF is reduced. Moreover, as seen in 2 patients of this study, [^{123}I]MIBG may potentially predict which patients are at risk. In a recent report [21], the reduction in myocardial accumulation of MIBG in a rat model was found to be larger and more dose-dependent than alterations in LVEF and morphological changes in myocytes.

Furthermore, the demonstration of impaired [^{123}I]MIBG parameters in patients studied in the period after chemotherapy suggests a role for [^{123}I]MIBG in the study of late effects of anthracyclines. Recognition of late cardiac sequelae has become of major concern in children and adolescents treated for cancer [22–24]. Recently, we found impaired [^{123}I]MIBG parameters in 2 adult patients 4 and 5 years after completing treatment with anthracyclines. Both patients, referred to the Department of Nuclear Medicine for re-evaluation before retreatment, were asymptomatic and had borderline LVEF.

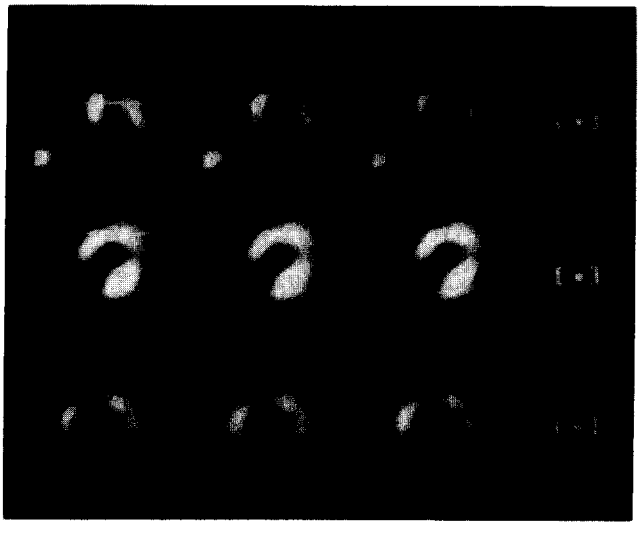


Figure 4. SPECT images after 4 h of a patient with reduced myocardial retention of [^{123}I]MIBG.

In the present study, complementary SPECT, in many cases, contributed to obtaining, with better precision, the distribution of the tracer in the myocardial segments. However, the relatively long acquisition time of SPECT, using a single-head gamma camera, may limit its feasibility, particulary in patients after left mastectomy. The introduction of dual head cameras with variable-angle detection or gamma cameras with a triple-head detection system may help to overcome this problem by significantly reducing the acquisition time.

In conclusion, this study demonstrates the feasibility of [^{123}I]MIBG heart scintigraphy to detect abnormalities of the myocardial adrenergic neuron activity in patients receiving chemotherapy containing anthracyclines. Obtained data suggest that anthracycline-associated cardiac adrenergic derangement may occur in advance of any systolic dysfunction. A further assessment of the clinical value and the place of [^{123}I]MIBG heart scintigraphy in the monitoring of anthracycline-related cardiotoxicity is warranted.

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Post-irradiation Soft Tissue Sarcoma

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From 1975 to 1993, 11 of 375 patients treated for soft tissue sarcoma presented with post-irradiation sarcoma. The mean time interval between irradiation therapy and onset of the second neoplasm was 15.8 years (4–31 years). The total radiation dosage ranged from 12 to 60 Gy with a mean of 40 Gy. All patients had complete staging including CT or MRI of the tumour site, and CT of the lung. Surgical resection was the treatment of choice. Wide margins could be achieved in 10 patients. One had a marginal resection. Tumours included malignant fibrous histiocytoma, haemangiosarcoma, rhabdomyosarcoma, malignant schwannoma, fibrosarcoma and undifferentiated sarcoma. All patients were reassessed in our outpatient clinic. After a mean follow-up of 4.7 years (1.0–11.5 years), only 1 patient had died because of the tumour. Although post-irradiation sarcomas are rather infrequently observed, these tumours must be suspected when alterations or symptoms occur in a previously irradiated region. Early detection provides the chance of curative, wide margin resection.

Key words: soft tissue sarcoma, irradiation, surgical treatment
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INTRODUCTION

KNOWLEDGE OF the aetiology of soft tissue sarcoma is poor. Malignant transformation of a benign mesenchymal tumour to soft tissue sarcoma is accepted in Von Recklinghausen's disease [1, 2], while it has been doubted as a general process in the pathogenesis of sarcoma [3]. Chronic lymph oedema, induced by radiotherapy, may lead to lymphangiosarcoma, known as Stewart-Treves-Syndrome [2]. Post-irradiation soft tissue sarcoma comprise another rare but well recognised entity [4–6]. This long-term complication of radiotherapy is poorly character-