was in agreement with other studies [1, 12 13, 18]. CSF NSE was found to be elevated in various neurological diseases. However, the difference in distribution of CSF NSE between the individual diseases was in no case statistically significant.

Our results suggest that the use of CSF NSE does not improve the diagnostic yield for CNS involvement in either systemic or primary CNS malignancies.

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Tumour Uptake of 57-Cobalt-bleomycin in Patients with Breast Cancer

L. Pace, G. D'Aiuto, C. Acampora, P. Oliviero, G. Botti, F. Tatangelo, M. Cerra and M. Salvatore

17 patients with breast carcinoma were studied with 57-cobalt-bleomycin scintigraphy. Scans showed increased tumour uptake in all patients. Results expressed as percentage of the injected dose (ID) normalised by the size of the tumour region (% ID/pixel) showed higher tumour uptake in patients with T3–T4 breast carcinomas ($n = 5$) than in patients with T1–T2 breast cancer ($n = 12$) ($8.4 \pm 0.55 \times 10^{-3}$ vs. $5.25 \pm 1.71 \times 10^{-3}$ % ID/pixel, respectively, $P < 0.05$). An inverse correlation between tumour uptake of 57-cobalt-bleomycin and progesterone receptor concentration was also found in all tumours tested ($r = -0.60$, $P < 0.05$, $n = 10$) and was confirmed in the group of patients with T2 breast carcinomas ($r = -0.89$, $P < 0.05$, $n = 6$). We conclude that a quantitative analysis of 57-cobalt-bleomycin uptake can give additional information suitable for the presurgical characterisation of a tumour.
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INTRODUCTION

RADIOLABELLED bleomycin is an agent used for tumour detection [1–5]. When given intravenously, radiolabelled bleomycin localises in tumours with a high tumour to normal tissue ratio [3, 6].

On the other hand, unlabelled bleomycin is clinically used in the treatment of several human tumours. DNA strand scission by bleomycin is believed to be responsible for its therapeutic effect. Although the mechanism of DNA damage by bleomycin is not completely understood, there is evidence of a specific recognition and cleavage of DNA by bleomycin [7, 8].

The selective tumour localisation and the peculiar mechanism of interaction with DNA suggest that a quantitative analysis of tumour scintigraphy with radiolabelled bleomycin can give additional information on biological characteristics of tumours. In the present study we analysed tumour uptake of 57-cobalt-bleomycin in patients with breast carcinoma. Our purpose was to assess whether quantitative data on tumour uptake of bleomycin could be related to the prognostic parameters commonly used in the evaluation of breast cancer, such as tumour size, axillary nodal status, tumour grading and hormone receptor expression.

MATERIALS AND METHODS

We studied 17 patients with a histologically confirmed diagnosis of unilateral breast carcinoma prior to any treatment. The mean age was 55 ± 14 (range 29–78 years). Patients received 37 MBq of 57-cobalt-bleomycin by intravenous injection. Dosimetric data were taken into account to select the injected dose (ID) and reduce the radiation dose to bladder, kidneys, and liver [9]. Images were obtained 1 h after the radiotracer injection using a large field of view gamma-camera (SELO, Italy). Maximum tumour uptake of 57-cobalt-bleomycin has been observed 20 min after the injection, with a sensible decrease in tumour concentration at 120 min [10]. In order to achieve a good tumour-to-background ratio with low blood pool activity, a 1-h interval seemed a reasonable choice. Whole body scan and spot views were acquired on a computer (Digital PdP 11/34). In order to compute the net ID the radioactivity in each syringe was recorded before and after administration.

The scans were first evaluated by two investigators to identify areas of increased activity and then regions of interest were drawn over the tumour area in both anterior and posterior view. The counts per minute recorded in each area were divided by the number of pixels to normalise for the region's size. The geometric mean of the anterior and posterior counts/pixel was then computed. Dividing this value by the net ID the tumour uptake (TU) was expressed as percentage of the ID per pixel (% ID/pixel). In order to compute tumour to lung ratio a region of interest was also drawn over the omolateral lung.

Histological typing of the tumours was done according to WHO classification. Nuclear grading was used to define the degree of malignancy (G-III: poorly differentiated; G-II: intermediate; G-I: well differentiated) [11]. Other histopathological features, such as tubular formation and mitotic activity, were evaluated semiquantitatively. Oestrogen and progesterone receptors were measured using the dextran-coated charcoal technique according to the EORTC recommended methods [12].

Student's *t*-test and regression analysis were used as appropriate.

RESULTS

Typical scan findings are shown in Fig. 1 for one of the patients studied. Table 1 summarises clinical data, histological findings, and receptor status of each patient. All patients except 4 (patients 4, 6, 10 and 16) underwent radical surgery within 1 week from 57-cobalt-bleomycin scan. Patients 4 and 16 showed locally advanced disease and surgery was planned after a complete course of chemotherapy or radiation therapy. Because of impaired left ventricular function patient 6 did not undergo surgery, while in patient 10 only a simple mastectomy was performed.

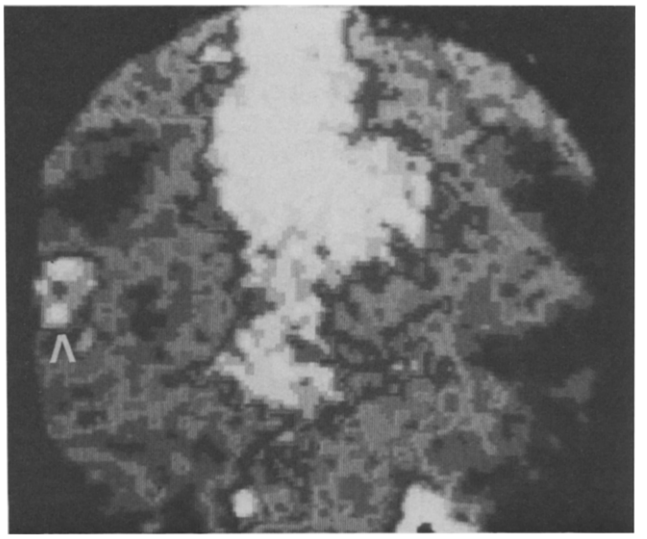

Fig. 1. 57-Cobalt-bleomycin scintigraphy in a patient with breast cancer. Anterior view of the thorax acquired 1 h after intravenous administration of the radiocompound. A high tumour uptake of 57-cobalt-bleomycin is clearly visible at the right breast (arrowhead). Blood pool activity is observed along the midline.

All breast carcinomas showed increased uptake of radiolabelled bleomycin at visual inspection of the scans. Table 2 shows the results of the region of interest analysis. In order to compare the percentage ID/pixel to the TNM stage, patients were sub-

Table 1.

Patient	Age	Pathological diagnosis	Stage	Nuclear grading	Receptors	
					ER	PgR
1	55	Invasive ductal	pT2N0M0	G-II	6	5
2	40	Invasive ductal	pT2N0M0	G-I	228	600
3	29	Invasive ductal	pT3N1M0	G-III	269	98
4	67	Ductal (a)	cT4cN0M0	ND	ND	ND
5	52	Invasive lobular	pT2N0M0	G-II	172	72
6	72	Ductal (a)	cT2N0M0	ND	ND	ND
7	40	Invasive ductal	pT3N1M0	G-I	ND	ND
8	65	Invasive ductal	pT2N1M0	G-I	ND	ND
9	41	Invasive ductal	pT2N0M0	G-I	6	7
10	78	Invasive ductal	pT1NxM0	G-II	11	32
11	62	Invasive lobular	pT2N0M0	G-III	ND	ND
12	40	Invasive lobular	pT1N1M0	G-I	ND	ND
13	62	Invasive ductal	pT2N1M0	G-II	213	134
14	72	Invasive lobular	pT1N0M0	G-III	69	106
15	50	Invasive ductal	pT2N1M0	ND	4	19
16	65	Tumour cells (a)	cT4cN0M0	ND	ND	ND
17	46	Invasive ductal	pT3N1M0	G-III	8	5

Receptors are expressed as fmol/mg of protein of cytosol; (a): oncytological smears; ND: not done; ER: oestrogen receptor; PgR: progesterone receptor.

Correspondence to L. Pace.
L. Pace and M. Salvatore are at the Cattedra di Medicina Nucleare, Istituto di Scienze Radiologiche, II Facoltà di Medicina, Università "Federico II", Napoli; C. Acampora is at the Medicina Nucleare, Istituto Nazionale Tumori, Napoli; G. D'Aiuto and P. Olivero are at the Divisione di Chirurgia, Istituto Nazionale Tumori, Napoli; G. Botti and F. Tatangelo are at the Divisione di Anatomia Patologica, Istituto Nazionale Tumori, Napoli; and M. Cerra is at the Divisione di Biochimica, Istituto Nazionale Tumori, Napoli, Italy.
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Table 2.

Patient	%W.B.	T/Lung%	ID/Pixel ($\times 10^{-3}$)
1	1.36	1.94	5
2	0.99	1.37	2
3	1.08	1.68	9
4	1.41	1.41	9
5	0.78	1.23	6
6	1.01	1.49	9
7	1.2	1.6	8
8	0.75	1.6	6
9	0.96	1.94	7
10	1.56	1.53	4
11	2.38	1.81	5
12	1.48	1.9	5
13	0.95	1.18	5
14	0.81	1.57	4
15	0.93	1.52	5
16	2.81	2.0	8
17	1.3	1.79	8

%W.B.: Tumour uptake as % of whole body; %ID/pixel: tumour uptake as % of net injected dose; T/lung: tumour to lung ratio.

grouped according to their stage. Patients with T1–T2 breast carcinoma were compared with patients with T3–T4 breast cancer. In the first group ($n = 12$) the tumour uptake was 5.25 $\pm$ 1.71 $\times 10^{-3}$ % ID/pixel while in the second group ($n = 5$) a mean value of 8.4 $\pm$ 0.55 $\times 10^{-3}$ % ID/pixel was found ($P < 0.05$). No significant difference in tumour uptake was found between patients without lymph node involvement [6.11 $\pm$ 2.37, $n = 9$] and patients with metastatic lymph nodes [6.57 $\pm$ 1.72, $n = 7$]. When we compared the tumour uptake of 57-cobalt-bleomycin with receptor status of all tumour tested, a negative correlation was found between tumour uptake and progesterone receptors concentration ($r = -0.60$, $P < 0.05$, $n = 10$), while no significant correlation was found for oestrogen receptors. Since the tumour uptake appears to be related to the size of the tumour, we repeated the analysis only in patients with T2 breast carcinoma. In this group a significant correlation ($r = -0.89$, $P < 0.05$, $n = 6$) was confirmed between tumour uptake and progesterone receptors concentration, while no correlation was found for oestrogen receptor expression. None of the histopathological features (nuclear grading, tubule formation, or mitotic activity) considered in the study appeared to be related to the tumour uptake of 57-cobalt-bleomycin.

DISCUSSION

The present study reports the results of a quantitative analysis of tumour uptake of 57-cobalt-bleomycin in patients with breast cancer. Our study showed that tumour uptake, although normalised to the size of tumour region, was significantly higher in T3–T4 breast tumours than in T1–T2 carcinomas. No significant correlation was found between tumour uptake of 57-cobalt-bleomycin and lymph node status. When we correlate the tumour uptake to progesterone receptor values a significant negative correlation was found.

A possible explanation of these findings could be found in the interaction mechanism of 57-cobalt-bleomycin with DNA of tumour cells. Specific binding sites for metallobleomycin have been identified in DNA fragments [8]. Furthermore, the *in vitro* interaction of radiolabelled bleomycin with tumour cells showed that a saturable binding exists [13]. Since radiolabelled bleomycin forms an equimolecular complex with DNA binding sites, the higher uptake in T3–T4 tumours could be due to the higher content of DNA in those tumours. Flow cytometric DNA analysis of breast carcinomas showed that large primary tumours had a significant increased incidence of aneuploidy compared with small tumours [14, 15].

The presence of oestrogen and progesterone receptors in breast tumours is usually considered expression of a high degree of differentiation. A shift from a high percentage of oestrogen/progesterone receptor-positive tumours in early breast cancer to low percentage of this phenotype in advanced disease has also been reported [16]. The loss of progesterone receptors in an increasing state of the disease is more marked than the loss of oestrogen receptors [17]. Since 57-cobalt-bleomycin uptake is higher in large breast tumours compared with small tumours, it is not surprising to find in our patients an inverse correlation of tumour uptake with progesterone receptors expression. What remains unexplained is the confirmation of this inverse correlation when we analysed only T2 tumours.

In conclusion our study shows that a quantitative analysis of 57-cobalt-bleomycin uptake can give additional information suitable for the presurgical characterisation of the tumour. Further studies are needed to assess more directly whether a close relationship between 57-cobalt-bleomycin uptake and DNA content of the tumour exists, and the potential prognostic significance of this uptake. Finally, we believe that this kind of approach may be applied to other radiopharmaceuticals that are able to trace molecules or functions important for the presurgical characterisation of tumour phenotype.

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Clinical Usefulness of Serum Assays of Neuron-specific Enolase, Carcinoembryonic Antigen and CA-50 Antigen in the Diagnosis of Lung Cancer

Bengt Bergman, Fred-Thomas Brezicka, Carl-Peter Engström and Sture Larsson

Serum concentrations of neuron-specific enolase (NSE), carcinoembryonic antigen (CEA) and CA-50 antigen were determined in 168 consecutive patients with lung cancer. All three markers were significantly elevated compared with levels in 102 patients with non-malignant chest diseases. NSE and CEA varied significantly across histological lung cancer types, with most highly elevated serum levels in small cell lung cancer and adenocarcinomas, respectively. The overall diagnostic accuracy was 0.66 for NSE, 0.74 for CEA, and 0.62 for CA-50, implying that CEA best discriminated between lung cancer and benign chest diseases, while CA-50 was less efficient as a diagnostic marker. In multivariate analysis of the three markers combined, a positive predictive value of 95% for lung cancer could be achieved with a diagnostic sensitivity of 57%, with a cut-off level defined as $0.037 \cdot NSE + 0.052 \cdot CEA + 0.011 \cdot CA\text{-}50 > 1$. In 22% of the cancer patients, the time from admission to histological or cytological lung cancer diagnosis exceeded 1 month. In 52% of these patients, the initial weighted tumour marker index was > 1, strongly implying the cancer diagnosis. The study lends support to the potential use of combined analysis of NSE, CEA and CA-50 as a complementary tool in the diagnosis of lung cancer.
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INTRODUCTION

DURING THE last decade a considerable interest has been taken in defining the role of tumour markers in the clinical management of lung cancer, e.g. diagnosis, staging, prognosis and monitoring of treatment [1, 2]. Patterns of correlations between various tumour markers and different histological types of lung cancer have been investigated, but no single substance has yet been identified as a diagnostic marker of major clinical importance in relation to established diagnostic procedures. Multiple-marker assays have been performed to enhance the diagnostic efficacy [3–8]. However, there is still a need for a clinically useful multivariate model for diagnostic purposes in the evaluation of lung cancer.

Correspondence to B. Bergman.
B. Bergman is at Renströmska Hospital, Box 17301, S-402 64 Göteborg, Sweden. B. Bergman, F.-T. Brezicka and C.-P. Engström are at the Department of Pulmonary Medicine; F.-T. Brezicka is also at the Department of Medical Microbiology and Immunology; and S. Larsson is at the Department of Thoracic Surgery, University of Göteborg, Göteborg, Sweden.
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For lung cancer patients in general, carcinoembryonic antigen (CEA) was one of the first markers described [9]. CEA is a glycosylated protein that is primarily associated with carcinomas within the gastrointestinal tract. In larger lung cancer series (> 100 patients), elevated serum CEA levels have been detected in 50–55% of the patients [10, 11]. CEA has been related to tumour burden in groups of patients, with possible prognostic implications in the preoperative assessment of lung cancer patients [12].

Neuron-specific enolase (NSE) has been extensively tested in small cell lung cancer (SCLC) [13]. NSE is a glycolytic enzyme found in neurons, peripheral neuroendocrine tissue and in tumours of the amine precursor uptake and decarboxylation system (APUD) cell series, the most important of which are SCLC and neuroblastoma. Elevated levels of NSE have been found in approximately 70% of SCLC patients. It has been related to the stage of disease both in groups of patients and in individuals, and has been shown to be an important prognostic factor in the treatment of SCLC [14]. In non-small cell lung cancer (NSCLC), elevated serum NSE levels have been reported in 10–20% of the patients. Recent studies imply that the