57 Co-Bleomycin scintigraphy and 57Co-Bleomycin positron emission tomography. Experimental observations and clinical results in lung cancer

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SUMMARY

It is often difficult to detect a malignant tumor and assess the presence of metastases. Therefore it is important to have a non-invasive test than can visualize these lesions.

^{57}Co-bleomycin (^{57}Co-blm) is a radiopharmaceutical that is used for these purposes especially in patients with lung cancer. The aims of the present study were to determine the value of ^{57}Co-blm scintigraphy as it is used in clinical practice and to improve the radiopharmaceutical and detection procedure. This work is a sequel to the work of Rasker (251).

The properties of the ideal tumor imaging radiopharmaceutical are outlined in *chapter 1.* This hypothetical agent should accumulate in malignant tumors but not in other lesions and not in normal tissues. It should have few side effects, a short half-life, emit radiation with a suitable energy for in vivo detection and be generally available for a reasonable price.

The specific and non-specific mechanisms by which tumor imaging radiopharmaceuticals are accumulated in tumor tissue are discussed.

Tumor imaging radiopharmaceuticals can be arranged roughly into three major groups: metabolite related agents, immunological substances and non-specific compounds. Many radiopharmaceuticals that have been used at one time or another are briefly discussed. In the section on metabolite related agents, special attention is paid to bleomycin (blm) and ^{57}Co-blm. The group of immunological substances consists of radiolabeled antibodies against antigens that are present in tumors. ^{67}Ga-citrate is the best known tumor imaging agent among the non-specific compounds. It is widely used in nuclear medicine. Its history, indications and disadvantages are discussed.

In *chapter 2,* a brief review is presented on lung cancer epidemiology, pathology, etiology, prevention, clinical symptoms and signs, therapy and prognosis. New developments in this field are reviewed. Various techniques to establish the diagnosis of lung cancer and to detect metastases are discussed more extensively. The importance of assessing the correct stage of the disease is stressed.

The labeling procedure of blm with ^{57}Co and the value of ^{57}Co-blm in the detection of primary lung cancer are described in *chapter 3.* Over a 5 year period, ^{57}Co-blm scintigraphy for tumor detection was performed in our

institute with a large field of view gamma camera. The scintigrams of 287 well documented patients with lung cancer, other types of neoplasm, non-malignant lesions or no abnormality in the lung were reviewed. A sensitivity of 96% was found for the detection of lung cancer. False negative and equivocal scintigrams were seen in patients with small lesions.

Nineteen patients proved to have another type of malignant tumor in the lung, mostly metastases from tumors elsewhere in the body. Of these lesions, 13 (68%) were visualized. ^{57}Co-blm scintigraphy cannot differentiate between lung cancer and other malignancies.

It is important to determine the value of ^{57}Co-blm scintigraphy in patients in whom a preoperative pathological diagnosis cannot be obtained by reasonable means. In such a subgroup of 194 cases, sensitivity was 95% and specificity 87%.

Correlation between tumor size and tumor-to-non-tumor ratio (TNT-ratio) was established for squamous cell carcinoma, adenocarcinoma and small cell carcinoma. Adenocarcinomas were smaller and showed lower TNT-ratios than other histological types. A correlation between histological differentiation and TNT-ratio could not be established for squamous cell carcinoma.

Forty of 46 scintigraphic studies in patients with a non-malignant lesion or no abnormality in the lung were true negative. This leads to a specificity or 87%. ^{57}Co-blm scintigraphy results in 512 patients with various non-malignant lesions in the lung were collected from the literature, including the present results. Overall specificity was 81%. Most false positive studies were seen in patients with active tuberculosis and unspecified pneumonia. It is concluded that ^{57}Co-blm scintigraphy is helpful in patients suspected of having lung cancer in whom a preoperative pathological diagnosis cannot be obtained.

In *chapter 4*, the value of ^{57}Co-blm scintigraphy for staging lung cancer was investigated in 174 patients. In the detection of lymph node metastases in the hilus and mediastinum, the sensitivity was 54% and the specificity 98%. ^{57}Co-blm scintigraphy proved to be more reliable than chest radiography and roentgen tomography.

Distant metastases were sought in 44 patients. False positive or false negative results were not found in this group. The ^{57}Co-blm brain scintigrams were of particularly good quality.

The value of mediastinoscopy and roentgen CT-scanning in the detection

of metastases in the hilus and mediastinum is discussed on the basis of data reported in the literature.

It is concluded that ^{57}Co-blm scintigraphy has a limited potential to detect lymph node metastases in the hilus and mediastinum. However, a positive scintigram is highly suggestive of the presence of metastatic disease. ^{57}Co-blm scintigraphy is a reliable technique to visualize brain metastases.

Staging of lung cancer patients in our hospital routinely includes ^{57}Co-blm scintigraphy in addition to conventional roentgen tomography. Mediastinoscopy is rarely done nowadays. When ^{57}Co-blm scintigraphy shows extensive mediastinal involvement, surgery is not performed. When scintigraphy indicates limited hilar or mediastinal involvement, extensive surgery including removal of the affected lymph nodes is considered. When scintigraphy does not show metastases, radical resection is carried out when otherwise no contra-indications are present. In a number of patients in this latter group, lymph node metastases will be found during surgery, but this is always limited and rarely modifies the intended radical resection.

^{67}Ga-citrate is a widely used radiopharmaceutical for the detection and staging of lung cancer. A comparative study of ^{67}Ga-citrate and ^{57}Co-blm in 63 patients with proved lung cancer is described in *chapter 5*. ^{67}Ga-citrate showed the primary tumor in 34 patients (54%) and ^{57}Co-blm in 58 (92%) ($p<0.05$). The mean difference in TNT-ratios in individual patients was significant in favor of ^{57}Co-blm scintigraphy.

Proven metastases in the lung hilus and mediastinum were visualized with ^{67}Ga-citrate in only 8 out of 18 patients (45%) and with ^{57}Co-blm in 16 (89%) ($p<0.05$). These results indicate that ^{57}Co-blm scintigraphy is more suitable for detecting and staging lung cancer than is ^{67}Ga-citrate scintigraphy.

Blm, as it is commercially available, is a mixture of various blm fractions. Blm-mixture and the isolated fractions blm-A2, blm-A5 and blm-B2 were labeled with 57Co.

In *chapter 6* the tumor seeking properties of these compounds were investigated. Biodistribution was determined in rats bearing Walker carcinoma, Yoshida sarcoma or rhabdomyosarcoma. Tissue concentrations of ^{57}Co-blm-mixture and ^{57}Co-blm-A2 were generally similar. ^{57}Co-blm-B2 showed a higher uptake in most tissues. Tumor-to-tissue ratios of these three compounds were similar. ^{57}Co-blm-A5 showed clearly inferior tumor

seeking properties. It is concluded that, in the experimental models that we used, the investigated labeled blm fractions are not superior to ^{57}Co-blm-mixture for tumor detection.

^{57}Co-blm, as it is administered to patients, contains a considerable amount of unlabeled blm. To limit side effects to the patients and to reduce costs, the quantity of blm should be as low as possible. Reduction of the amount of blm however should not result in an increase in the percentage of free $^{57}Co^{2+}$ ions, since these are largely retained in the body and considerably add to the radiation dose. Variations in the ratio of ^{57}Co and blm in the labeling procedure were investigated in *chapter* 7. A fixed amount of 7.4 MBq (0.2 mCi) ^{57}Co was added to successively 21.0, 9.0, 0.9, 0.09 and 0.009 mg (weight) blm in the preparation of ^{57}Co-blm.

When the smallest amount of blm was used, the labeling yielded a percentage of $^{57}Co^{2+}$ that was far too large. The percentage of free $^{57}Co^{2+}$ in the other four compounds was acceptable, being less than 3% of the total activity.

Biodistribution of radioactivity of all five compounds was investigated in rats bearing Yoshida sarcoma. Of the compound with excess $^{57}Co^{2+}$, radioactivity uptake in the tumor was similar to uptake of the other compounds, but uptake in normal tissues was clearly higher. This resulted in inferior tumor-to-tissue ratios. Tissue concentrations and tumor-to-tissue ratios of the other four compounds were similar.

It is concluded that, compared to the quantity traditionally used, the amount of blm in the labeling procedure can be reduced without increase in the percentage of free $^{57}Co^{2+}$ and without reduction in the tumor seeking properties in rats with Yoshida sarcoma. On the basis of these results, the quantity of blm administered to patients for ^{57}Co-blm scintigraphy (1.5 mg weight) will be reduced.

The long half-life of ^{57}Co (272 days) has discouraged the widespread acceptance of ^{57}Co-blm. Because a major fraction of the radioactivity is quickly excreted by the kidneys, the contaminated urine should be collected and stored to prevent environmental contamination. Since the labeling of blm with other radionuclides did not lead to a useful tumor imaging agent, we investigated ^{55}Co (half-life 17.5 hours) as potential label. The results are described in *chapter* 8.

^{55}Co is produced by the ^{56}Fe(p, 2n)^{55}Co reaction in the cyclotron of the

University of Groningen. After purification, ^{55}Co is attached to blm with the procedure as described for ^{57}Co in chapter 3. Fifty patients with proven lung cancer were investigated with ^{55}Co-blm. A dose of 37 MBq (1.0 mCi) was administered intravenously. The results were compared with ^{57}Co-blm scintigraphy. Since ^{55}Co is a positron emitting radionuclide, a positron camera was used for imaging. The characteristics of this device are briefly described. Tomographic images were obtained and proved to be of good quality. Sensitivity in the detection of primary tumors was 96% for ^{55}Co-blm positron imaging, whereas for ^{57}Co-blm imaging this was 98%. TNT-ratios of ^{55}Co-blm scintigraphy were significantly lower than those of ^{57}Co-blm scintigraphy. TNT-ratios obtained with ^{55}Co-blm after computerized filtering were significantly higher than those obtained with ^{57}Co-blm. However, the filtered images were not always easy to evaluate.

^{55}Co-blm and ^{57}Co-blm were equally sensitive in the detection of lymph node metastases in the hilus and mediastinum. One false positive ^{55}Co-blm study was found versus no false positive ^{57}Co-blm studies. In all six patients with a brain metastasis, this was clearly demonstrated on the ^{55}Co-blm tomograms.

Advantages and disadvantages of ^{55}Co-blm positron scintigraphy are discussed. It is concluded that the results are good enough to replace ^{57}Co-blm scintigraphy. The more refined positron imaging equipment that has recently become available will probably improve the results in the near future.

In *chapter 9*, organ radiation doses and somatically effective total body dose to the adult patient from a study with ^{57}Co-blm or ^{55}Co-blm were calculated using the MIRD (Medical Internal Radiation Dose) scheme. The radioactivity is mainly concentrated in bladder, kidneys and liver. It is assumed that the rest of the radioactivity is distributed homogeneously throughout the remainder of the body.

Residence times — cumulated activities per unit of injected amount of radioactivity — for these three organs and the remainder of the body were derived from ^{57}Co-blm clearance measurements in patients. The radiation dose was calculated for the gonads and all organs that contribute to the somatically effective total body dose. The somatically effective total body dose is 70 ± 8 μGy/MBq (0.26 ± 0.03 rad/mCi) for ^{57}Co-blm and 170 ± 24 μGy/MBq (0.63 ± 0.09 rad/mCi) for ^{55}Co-blm ($\pm$ 1 s.d.). The influence of the ^{56}Co impurity in ^{55}Co and the ^{55}Fe daughter activity of ^{55}Co on the

radiation dose are discussed. The calculated somatically effective total body dose of both radiopharmaceuticals is comparable to that of other scintigraphic studies.

New developments in tumor imaging are described in *chapter 10*. Testing new blm fractions might lead to a component that has better tumor seeking properties. Research in the labeling of a ligand of non-radioactive cobalt and blm with radionuclides that emit a suitable gamma energy might lead to a compound that carries no risk of environmental contamination and that can generally be used for imaging with a gamma camera.

In the near future, the introduction of a rotatable double headed gamma camera, adapted for positron imaging, offers the opportunity to quantify the amount of radioactivity in a certain area in the body. This feature might enable us to guide tumor therapy more accurately.

Two main directions can be discerned in the search for more specific tumor imaging agents: metabolite related agents (such as amino acids labeled with the positron emitting ^{11}C, ^{13}N, ^{15}O) and (monoclonal) antibodies against tumor specific antigens.

Nude mice bearing human tumors might make it possible to test tumor imaging radiopharmaceuticals in animals and obtain results that are highly predictive for human beings.

When a truly specific tumor imaging agent is found, we should consider converting this compound into a therapeutic agent by labeling it with a radionuclide with suitable physical characteristics.

Nuclear magnetic resonance (NMR) is another new clinical imaging technique. Its potential in tumor imaging is briefly discussed.

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