**THOROTRAST**

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**THOROTRAST INVESTIGATIONS TO EVALUATE THE LONG TERM EFFECTS CAUSED BY ARTIFICIAL RADIATION IN MAN (THOROTRAST PATIENTS) FOLLOW-UP STUDY**

From 1985-01-01 to 1992-04-30

**Project details**

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<th>Total cost:</th>
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**Objective**

In 1929 Radt (Berlin) and Oka (Tokyo) introduced a stabilized 25% colloidal solution of thorium dioxide as a radiodiagnostic contrast medium which was sold under the trade name Thorotrast. The predominant form of application was an intravascular injection, especially for cerebral angiography. After intravascular injection the ThO₂ aggregates accumulate in the reticuloendothelial system (RES) and are stored for life.

From the data on the 232Thorium distribution in the tissue and the activity ratios combined with information about the various types of radiation, the average energy per decay of each radionuclide and the cell absorption of alpha-particles in ThO₂ aggregates, Kaul and Noffz calculated mean values for the annual radiation dose of the organs of the RES. A mean intravascular injection of 25 ml Thorotrast in a 70 kg person causes the following absorbed dose rates: liver 25 cGy/year; spleen 70 cGy/year; bone marrow 9 cGy/year; endothelial layer in bone 16 cGy/year; kidneys 0.4 cGy/year. The radiation dose in the lung tissue is mainly caused by the daughter product 220Rn which is exhaled by the breath.

The objective of the German Thorotrast study was:
- to trace the largest possible number of Thorotrast patients who had been given intravascular injection;
- to determine the thorium dioxide quantities incorporated;
- to compare the health and the fate of Thorotrast patients with those of a control group;
- to relate long term effects of Thorotrast found to the radiation dose in the depository organs.

Apart from answering these scientific questions, it was intended to provide a comprehensive treatment for these patients and to advise the physicians as well as the patients themselves.

**Objectives for 1990 and 1991**

The working programme will be continued according to the recommendations of the coordinating committee:
- regular correspondence with about 600 patients of the Thorotrast and control group as well with the respective family physicians;
- outpatient reexaminations of Thorotrast carriers and patients of the control group at two years intervals;
- computer suitable registration of examination data and medical reports of the family doctors as well as the treating hospitals;
- controlling of the stored data and preparation of final statistical evaluation.

The aim of the study was to uncover the late effects of incorporated colloidal thorium dioxide by epidemiological observation and clinical and biophysical examination and to compare the results with those of a corresponding control group.

The final fate of the thorotrast patients is the most important parameter for the calculation of the thorotrast late effects. The following 3 groups of diseases leading to death are discussed:

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diseases with high excess rate in the group of thorotrast patients;
diseases with possible excess rate;
diseases without apparent excess rate.

Diseases with high excess rate:
A significant excess rate was observed in malignant liver tumours, liver cirrhosis, myeloid leukaemias and bone marrow failures. The relative risk of malignant liver tumours for all thorotrast patients is about 200. The latency period of malignant liver tumours ranged from 16 to more than 45 years. In 5 patients sarcoma and carcinoma simultaneously manifested in 1 liver. Cirrhosis was present in about 30% of liver tumour patients and in about 10% of the nonliver tumour patients.

The cumulative rate of malignant liver tumours and leukaemias was calculated with the sum limit method by putting each case of liver cancer in relation to the number of individuals still at risk; this fraction is summed by year by year. The frequency of malignant liver tumours in male patients is significantly higher than in female patients. However, there was no difference between male and female patients. However, there was no difference between male and female patients with regard to age at injection, mean volume of injected thorotrast and exposure time; so it must be stated that males are more sensitive than females to thorotrast induced liver cancer. About 6% of liver cancer patients suffered from a second neoplastic disease.

The induction of malignant liver tumours is caused by the chronic irradiation and not by the foreign body effect. For the calculation of the relation between dose rate and effect 3 cohorts were formed being injected with 1 to 10 ml, 11 to 20 ml, and more than 20 ml thorotrast. The correlation between the dose rate to the liver expressed by the mean volume of administered thorotrast and the cumulative rate of malignant liver tumours is quite evident.

In each age group a marked increase in the liver tumour rate occurs 30 to 40 years after injection.

The risk estimates for malignant liver tumours in the German thorotrast study were calculated for all patients that had either whole body counting or the injected thorotrast volume recorded in the patient file with the following assumptions. Patients who have died within the first 15 years of exposure were excluded from the evaluation as they are not at risk for malignant liver tumours. The dose delivered during the last 10 years before clinical manifestation of the malignant liver tumours will be looked upon as wasted dose because the tumour already exists growing from microscopical to clinical dimensions. There is a clear difference between the risk for male and female patients, which comes up after 40 years to 500 and 300 malignant liver tumours per E4 person Gy, respectively. In the thorotrast patients with liver cancer, the 3 lowest doses at 10 years before diagnosis were 1.88, 2.65 and 2.71 Gy in female and 1.98, 2.06 and 2.30 Gy in male patients.

Myeloproliferative diseases (n=37) were observed about 10 times more often in the thorotrast group as compared to the control group. The majority were classified as acute myeloid leukaemias (25 cases); the reminder were described as erythroleukaemia (3 cases), monocyctic leukaemia (5 cases) and chronic myeloid leukaemia (4 cases). The relatively high number of erythroleukaemia, which was also described in the Japanese thorotrast study is remarkable. The shortest latency period in a leukaemia case was 5 years. A close correlation between dose rate in the bone marrow and frequency of leukaemia could not yet be proved. The 3 smallest accumulative doses to the red bone marrow at time of death in myeloid leukaemia patients were 0.23, 0.69 and 0.73 Gy. The term bone marrow failure was used collectively for aplastic anaemia, agranulocytosis and thrombocytopenia. It is well known that these diseases may be caused by a variety of drugs, however, they are clearly more frequent in the group of thorotrast patients.

Diseases with a probable excess rate:
An excess rate of some neoplastic diseases in the thorotrast group is possible. However, consideration must be given to the fact that these figures may change in the following years. The last years have shown an increase of carcinomas of the extrahepatic bile ducts including carcinoma of the gall bladder. Daughter products in the bile and irradiation of the gall bladder wall by thorium aggregates in the surrounding liver could be the source of irradiation. The excess rate of oesophageal cancer and pancreatic cancer is difficult to explain. The excess or laryngeal cancer, however, might be related to the exhaled thoron. There is a constant small excess of the non-Hodgkin lymphoma during the last years. The same is true with regard to bone sarcomas; these 4 patients were injected at the end of their skeletal growth phase and had long exposure times of more than 30 years. According to the results induction of plasmacytomas by internal irradiation is possible. Malignant mesotheliomas of the pleura and the peritoneum occurred only in the thorotrast group and not in the control group. The diagnoses of these patients are histologically confirmed. Of special interest are the peritoneal mesotheliomas arising from the peritoneum surrounding liver and spleen. The tumours could be explained by the fact that the adjacent layer of peritoneal cells can be reached by the alpha particles emitted from the thorium aggregates of liver and spleen. These tumours appeared after a long latency period of more than 30 years. A problem which needs a special comment are the paravascular deposits. In the group of the examined patients 256 paravascular deposits of very different extension were detected. 146 patients suffered from late effects after more than 15 years of latency. Tumours close to the deposits are extremely rare and only 1 sarcoma of the soft tissue was observed. In 2 other cases a causal connection to the thorium deposits is possible but uncertain.

Diseases without apparent excess rate:
The 2 subgroups of organs which have to be considered are organs which are exposed to a small dose rate and organs which are exposed to an extremely low dose rate at least the dose arising from the daughters in the blood stream. Morbus Hodgkin is found equally distributed in the thorotrast and in the control group. An important result of the study is the similar number of lung cancer in both groups, though the bronchi are exposed to chronic alpha irradiation by the exhaled thoron. Hornik et al (1989) reevaluated the calculations of the dose to the bronchi. The results give an explanation of the fact that up to now there is no excess of bronchogenic carcinomas in the thorotrast group. The kidneys are exposed to a mean dose of 40 mGy/year. No increase in renal cancer could be observed. Cancer of the urinary bladder and the adrenals (which are part of the reticuloendothelial system) have the same frequency in both groups.
Life spans of thorotrast patients: During the past years there is a constant trend that thorotrast patients die earlier compared to patients of the control group. This phenomenon is dependent on the amount of thorotrast injected. However, as the frequency of malignant liver timours increases with the incorporated volume of thorotrast, this result could be caused by the high numbers of liver cancer. It can be stated that there is a thorotrast volume dependent influence to the age at death with regard to neoplastic and nonneoplastic diseases, but we are not yet able to give a fundamental explanation.

The German Thorotrast Study has been setup in order to uncover the late effects of incorporated colloidal thoriumdioxide by epidemiological observations and clinical and biophysical examination of the patients. The results of those of a corresponding control group have been compared to assess the relationship between late effects and radiation dose. Furthermore appropriate diagnostic facilities and if possible therapeutic facilities are offered and advice is given to the family physicians of the patients.

The German Thorotrast Study comprises 2326 Thorotrast patients and 1890 contemporary matched patients in the control group to be evaluated. 899 Thorotrast patients and 662 controls and clinical and biophysical follow up examinations every 2 years since 1969. The recent most important results of the study are: a high excess rate of primary liver cancer (Thorotrast/control) (411/2) was observed beginning after the 15th year of exposure. 31% of the tumours are combined with cirrhosis and 6% with other neoplastic diseases. A clear (mean) dose rate effect relationship exists. The tumour frequency depends on the time of exposure or the cumulative dose to the liver respectively and not primarily on the age at injection. The lowest cumulative dose at 10 years before diagnosis of liver cancer were about 2 Gy. Risk estimates for liver cancer after 40 years of exposure are 500 malignant tumours per 1 E4 person-Gy for man and 300 for women.

A high excess rate exists also for nonlymphocytic leukaemia starting already 5 years after Thorotrast injection (39/4). The lowest cumulative doses to the red bone marrow at time of death were about 0.5 Gy. According to the present results an excess rate can be expected for carcinomas of the extrahepatic bile ducts, pancreas, oesophagus, larynx, as well as non-Hodgkin's lymphoma, bone sarcomas, plasmacytomas and mesotheliomas.

Patients and methods of examination

Most of our patients were injected intravascularly with Thorotrast in the period between 1937 and 1947. The names and addresses of more than 5000 patients who had cerebral arteriography (70%) or arteriography of the upper and lower limbs (30%) with Thorotrast were obtained from the records of different hospitals in West Germany. In none of our patients was Thorotrast injected for the actual detection of liver disease.

A pseudorandomized non-Thorotrast control group was set up. It was made up of persons who had been inpatients at the same hospital and in the same year as the Thorotrast patients. To set up the roster, only patients with a surname starting with the letter B were used. The conditions for which either the Thorotrast patients or the controls were admitted to hospital was not considered in the selection. The control group and the group of Thorotrast patients were only matched for age and sex of the patients. In 1968 when the study was started a large number of the Thorotrast patients had already died. The causes of the death of those patients were clarified by hospital records, postmortem examinations, etc. Patients who died in the first three years after Thorotrast injection were excluded from the evaluation to minimize the influence of the underlying diseases. Excluding the patients who died within the first three years, patients who are not traceable and those not responding, the German Thorotrast study comprises 2326 Thorotrast patients and 1890 control patients of which 2151 Thorotrast patients and 1493 controls have died up to 1990).

Organs with extremely low doses from the locally incorporated Thorotrast are reached, however, by the daughter product radon which is distributed by the blood stream. It is of high interest to calculate the cumulative dose for those organs which show no cancer excess rate.

During the past years there has been a constant trend for Thorotrast patients to die earlier compared to controls. This phenomenon depends on the amount of Thorotrast injected. Excluding from the analysis those patients who died from Thorotrast specific diseases (liver cancer, cirrhosis or leukaemias) we see similar results in dose-rate dependent life shortening. So it is most probable that there is a Thorotrast dependent influence on age at death.