Prof. Dr. Christoph Reiners

NUCLEAR THERAPY IN THYROID DISEASES

Клиника ядерной медицины университета Вюрцбурга (Германия)

Oral administration of I-131-sodiumiodide is a commonly accepted procedure for treatment of benign and malignant thyroid diseases since the 1940's (8). Today, approximately 60.000 patients are treated with radioiodine in Germany; the majority because of benign thyroid diseases and a minority of 5-10% because of thyroid cancer.

Background

Radioiodine is taken up by the normal thyroid and by tissue of differentiated thyroid cancer. The maximum uptake and the effective half-life depend on the functional state of the thyroid and on the nature of the underlying thyroid disease (4). In the euthyroid state, the normal thyroid takes up between 30% and 60% of the radioiodine administered. In addition, the maximum uptake depends on the nutritional iodine supply (sufficient nutritional iodine supply up to 30% uptake, iodine deficiency more than 60% uptake). In the euthyroid state, the maximum uptake of radioiodine during treatment is usually reached 24 hours after application of a test activity.

In the hyperthyroid state, the maximum uptake may be increased and reach levels up to 80%; the effective half-life of radioiodine, which is in the range of 7 days in the euthyroid state, may be shortened to 4-5 days.

For radioiodine treatment of thyroid diseases, Iodine-131 is used in form of sodiumiodide. Its Я-emission with a maximum energy of 0.61 meV, an average energy of 0.192 meV and a range in tissue of 0.8 mm accounts for approximately 90% of its therapeutic effect on the thyroid. For diagnostic purposes, the г-emission of I-131 (360 keV) may be used. I-131 is produced as a by-product of nuclear fission in a nuclear reactor. This accounts for its relatively low cost. For radioiodine treatment, I-131 is administered orally in solution or capsule form. For radiation protection purposes, the capsule preparation should be favoured.

Indications for radioiodine in the treatment of diseases of the thyroid

Benign diseases

Radioiodine treatment is indicated for the treatment of benign and malignant thyroid diseases. According to the guidelines of the Society of Nuclear Medicine (8) and the German Society of Nuclear Medicine (2) the indications are

- manifest hyperthyroidism in patients with Graves' disease or functional autonomy
- latent hyperthyroidism in case of focal functional autonomy or autonomous (toxic) goiter
- non-toxic multinodular/diffuse goiter (mainly after unsuccessful resection).

In Germany, between 70-80% of the patients treated with radioiodine for benign diseases suffer from functional autonomy, whereas only 20-30% from Graves' disease. The primary aim of radioiodine treatment in benign thyroid diseases is the elimination of hyperthyroidism and functional autonomy. In addition, thyroid volume or volume of autonomous nodules should be reduced (3, 7).

Malignant diseases

Radioiodine treatment in patients with differentiated papillary or follicular thyroid cancer follows adjuvant, curative or palliative strategies (4, 6). According to the guidelines of the American Society of Nuclear Medicine (8) and the German Society of Nuclear Medicine (1) the indications for radioiodine treatment in thyroid cancer patients are:

- adjuvant ablation of thyroid remnants after thyroidectomy
- curative treatment of residual thyroid cancer, local recurrences and metastatic disease (lymph-node metastases, distant metastases) after partial or complete surgical resection

Radioiodine treatment is only indicated, if a surgical resection can not or only incompletely be performed. The results of radioiodine treatment correlate negatively with the size of remnant tissue so that operative resection is the primary therapeutic option (1).

Radioiodine treatment is not indicated (1) in case of small differentiated thyroid cancers (papillary microcarcinoma pT1a N0 M0 with a tumor diameter of J 1,0 cm).

Contraindications for radioiodine treatment

Contraindication of radioiodine treatment generally is given during pregnancy and for breast-feeding women. No consensus has been reached on contraindication for radioiodine treatment of benign diseases with respect to young patients. On the background of the high cancer risk of children and young adults after exposure to radioiodine – as observed after the Chernobyl reactor accident – we advise against treating children or young adults for benign thyroid diseases with radioiodine (4).

Dose concepts, results and side effects

Benign diseases

According to the general principles of radiation therapy, radioiodine treatment of benign thyroid diseases should be performed by application of a "single dose" of I-131, which is to be determined taking into consideration the individual parameters for the thyroidal iodine kinetics of a given patient. This means, consequently, that fractionated radioiodine treatment is not permitted and that a radioiodine test has to performed before application of a therapeutic activity (2, 4). For application of the Quimby-Marinelli formula, the thyroid volume to be treated, the maximum uptake and the effective half-life has to be measured. Instead of fixed standard activities or calculated activities referring only to thyroid volume, the radiation dose should be selected as basis for the calculation of the therapeutic activity.

Typical therapeutic radiation doses to be applied range between 300-400 Gy for unifocal or multifocal functional autonomy, 200 Gy for disseminated autonomy and 200-250 Gy for Graves' disease under application of an optimised concept. For

patients with recurrent or complicated course of Graves' disease, ablative treatment with a radiation dose of 300 Gy may be favoured (2, 4).

Usually it takes 2-3 months until the effects of radioiodine on thyroid function and volume can be fully evaluated. In patients with functional autonomy, hyperthyroidism is eliminated typically in more than 90% of the cases. The rate for hypothyroidism in cases with functional autonomy is relatively low (10-20%). In patients with Graves' disease, hyperthyroidism may be eliminated in more than 90% of the cases, when 300 Gy are applied in an ablative treatment regime (4, 7); however, the rate of hypothyroidism may then be as high as 90%. Applying an optimised concept, which is to be preferred for patients with uncomplicated course of Graves' disease, 200 Gy lead to elimination of hyperthyroidism in approximately 80% and to development of hypothyroidism in 50% of the cases (3). With respect to the volume of the thyroid, reductions in autonomous nodules lying within the range of 30% and in autonomous goiters (Fig. 1) within a range of up to 40% may be observed (6). In cases of Graves' disease, thyroid volume decreases frequently by 40% or more (3).

As a side effect of I-131 treatment of benign thyroid diseases, radiation induced thyroiditis may develop. However, patients very rarely complain of pain induced by radioiodine therapy. In 15-30% of the cases suffering from Graves' disease and endocrine ophthalmopathy, the exophthalmos symptoms may worsen, if prophylactic administration of corticosteroids is not undertaken. Typically, hypothyroidism develops in patients treated according to an ablative therapeutic concept. However, hypothyroidism is no longer considered to be a side effect, but rather the proof of definitive elimination of hyperthyroidism.

Malignant diseases

For prophylactic ablative treatment of thyroid remnants following surgery for thyroid cancer, 1-3 GBq of I-131 are usually administered as the standard activity (1). Alternatively, an individually calculated activity for a given radiation dose of 300 Gy may be administered to eliminate thyroid remnants after surgery. For curative treatment of tumor remnants or for recurrences and metastases, 5-8 GBq of I-131 are usually administered as the standard activity (1). Where possible, individual dosimetry should be performed, leading to the administration of an activity delivering a therapeutic dose of more than 80 Gy to the tumor tissue. However, it is frequently very difficult or even impossible to quantify correctly tumor volume and the kinetics of a I-131 test activity, with the result that fractionated treatment with standard activities is rather to be favoured in the treatment of cancer patients (Fig. 2).

The prognosis for differentiated thyroid cancer is usually excellent. Applying a standardised interdisciplinary treatment protocol, consisting of thyroidectomy, radioiodine therapy and TSH-suppressive hormone therapy, the 10-years survival rates for patients suffering from papillary thyroid cancer range between 85 and 90%, for those with follicular cancer between 75 and 80% (7).

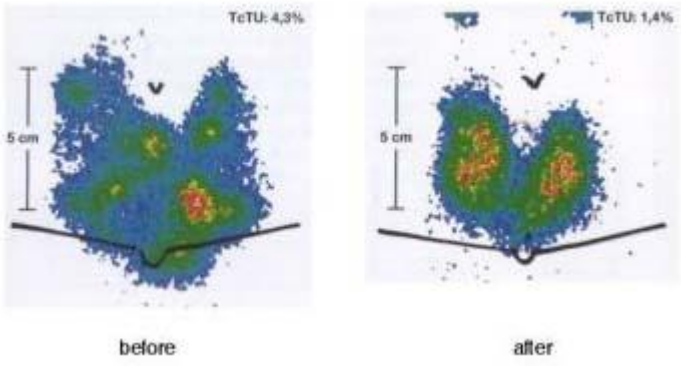

Fig 2. Successful treatment of a 74-years old female patient with 200 Gy for a hyperthyroid goiter with disseminated functional autonomy: Normalisation of Technetium thyroid uptake and volume decrease by approximately 50%.

Due to the relatively high activities necessary in adjuvant, curative or palliative treatment of differentiated thyroid cancer, a number of late side-effects have to be taken into account (1, 6). In 10-20% of the patients, painful reactions in thyroid remnants and metastases due to radiation-induced thyroiditis are possible. 30% of the patients complain of gastritis after oral administration of I-131, and 30% of the patients may show sialadenitis symptoms. In certain rare cases, patients also complain of hoarseness, pain in the throat and impaired ability to taste and swelling of salivary glands. Sicca syndrome develops as a late side-effect, due to radiation-induced sialadenitis in 10-20% of the patients. In parallel, dryness of the eyes due to reduced production of the lacrimal glands may occur. Typically, clinically irrelevant transient thrombo- or leucopenia may be observed. On rare occasions, bone marrow depression may develop in patients after the application of high therapeutic activities of radioiodine. In approximately 1% of the patients requiring multiple courses of radioiodine treatment, radiation-induced leukemia may be observed 5 or more years after treatment. Pulmonary fibrosis may develop in approximately 1 % of patients with lung metastases with high and diffuse uptake of radioiodine (after several courses of treatment). Very rarely, azoospermia may be observed as a side-effect of repeated high dose radioiodine therapy for metastatic thyroid cancer.

Radioiodine treatment on an out- or in-patient basis?

Regulations in Europe

Iodine-131 therapy for patients with thyroid cancer who require the application of high therapeutic activities is performed in nearly all European countries in hospitals where controlled areas and adequate equipment for radiation protection are at hand. However, radioiodine therapy involving the application of lower activities in the treatment of patients with benign thyroid diseases is permitted on an out-patient basis in many European countries (4). Activity limits for out-patient treatment vary considerably. In 14 countries , up to 555 MBq I-131 may be applied, in 8 countries up to 1.1 GBq, and in 2 countries even greater levels are permitted. In 3 European countries, I-131 therapy in out-patients is not permitted. It is remarkable, however, that no significant differences exist between countries belonging to the European Union (EU) compared to Non-EU countries and Eastern Europe. The new EURATOM directive 97/43 on the “Health Protection of Individuals Against the Dangers of Ionising Radiation in Relation to Medical Exposures” and the “Guidance for Radiation Protection Following Iodine-131 Therapy Concerning Doses to Out-

Patients or Discharged In-Patients" proposed by the Expert Group Ex-Article 31 EURATOM lay down the general rule, "that treatment on an out-patient basis or discharged in-patient basis will be permitted only if the dose to third persons, the general public and to family and close friends due to the (residual) activity in the patient, is not expected to exceed dose constraints approved by competent authorities. As a general rule, treatment of thyroid cancer using radioactive radioiodine should only be performed in in-patients." On the basis of the recommendations for the discharging of patients, made by the Expert Group Ex-Article 31 EURATOM, the following dose constraints have been proposed:

- Family and close friends:

Children (including the unborn child) 1 mSv
Adults of up to 60 years old 3 mSv
Adults of more than 60 years 15 mSv

- Third persons/general public: 0.3 mSv

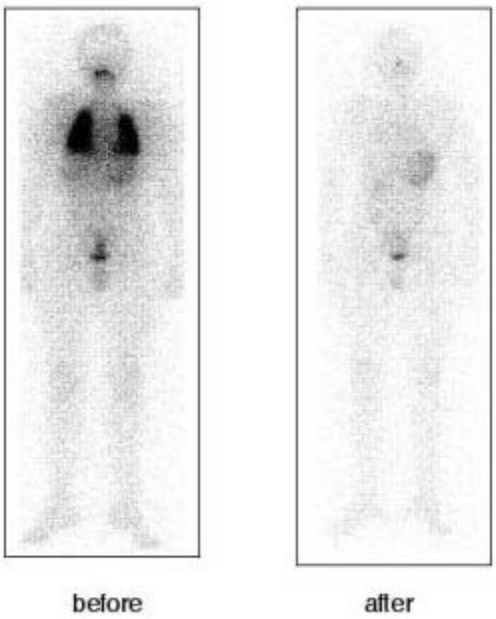

Fig 1. Successful treatment of a 15-years old boy with disseminated pulmonary metastases of papillary thyroid cancer with 3 GBq of I-131: Complete elimination of lung metastases.

"Dose constraints are defined for optimisation purposes and not expected to be exceeded, but they are not legal dose limits."

In accordance with the directive on Medical Exposure 97/43 EURATOM, "in the case of a patient who is undergoing treatment with radionuclides, member states shall ensure that practitioners provide the patient or legal guardian, before the former leaving the hospital or clinic, with written instructions as these may be appropriate, on the reduction of doses to persons in contact with the patient, and with information on the risks associated with ionising radiation."

German regulations for I-131 therapy in in-patients

In German, radioiodine treatment in out-patients is not permitted. Radioiodine treatment must be performed in a ward with a controlled area where the patient must remain for at least 48 hours (4). The controlled area has to be equipped with

installations for the adequate implementation of radiation protection measures (i.e. a waste water decontamination unit, filters for exhaust air etc.). As laid down in the German Guideline for Radiation Protection in Medicine, individual dosimetry before and during treatment is mandatory. The data which are available on quality assurance and radiation protection document the fact that the German regulations concerning the minimum period of stay in a controlled area of 48 hours for patients who have been treated with I-131 have proven to be both useful and effective (5).
Until recently, the activity level affecting the discharge of patients treated with I-131 was 95 MBq, as defined in the German Guideline for Radiation Protection in Medicine. The new Guideline 2001 permits the discharge of in-patients, when activity levels in the patients reach levels below 250 MBq I-131; it has been estimated, using a conservative approach, that the exposure to a person remaining permanently at a distance of 2 meters from the patient would not exceed 1 mSv/a: Taking this, and the obligatorily issued instructions on the reduction of doses to persons coming into contact with the patient into account, the dose constraints recommended by the Expert Group Ex-Article 31 EURATOM will not be exceeded.

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