INTEGRATED ACADEMIC STUDIES OF MEDICINE

IASM

FACULTY OF MEDICAL SCIENCES

Nuclear medicine in therapy benign thyroid disorders and other benign diseases

- Global prevalence of hyperthyroidism varies from 0.2 to 1.3% in different studies.
- Thyroid dysfunction has important ramifications on health outcome especially in older population like cardiovascular, metabolism, bone and mental health. Undiagnosed and untreated hyperthyroidism causes drastic clinical complications for patients as well as health care delivery system in term of economic burden.
- Hence early diagnosis and prompt treatment are indispensable to reduce mortality and associated costs

- Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected hyperthyroidism and should be used as an initial screening test.
- In less than 5% of patients with thyrotoxicosis, the serum T3 assay may be needed to diagnose T3 toxicosis.
- Subclinical hyperthyroidism is diagnosed when the TSH level is subnormal and T4 and T3 levels are normal.
- To exclude autoimmune based disorders, evaluation of antithyroid antibodies (TRAb, antiperoxidase, and antithyroglobulin antibodies) is needed.

- Radioactive Iodine (RAI) represents as an effective treatment modality for hyperthyroidism, especially in cases who do not respond to medical therapy. RAI therapy is in practice for the last 80 years. It was first used for therapeutic purpose in 1941 by Dr. Saul Hertz. Over the time its therapeutic efficacy was evaluated and evolved, by 1990 it becomes preferred treatment option for Grave's disease in US. Although, previously it was reserved for patients who had a relapse after failed medical treatment. New practice guidelines of National Institute for Health and Care Excellence (NICE) recommends RAI as first line treatment option in cases of Grave's disease.

- Thyroid hormones, L-thyroxine (tetraiodothyronine, T4) and L-triiodothyronine (T3) are the only iodine containing molecules in vertebrates with well-established biological role. Baumann was the first to report the presence of iodine in thyroid hormone in 1895 with iodine accounting for 65% of T4 and 58% of T3 weight. Iodine is an integral component and rate-limiting substrate for thyroid hormone synthesis that is provided exogenously. Ingested iodine is absorbed from small intestine as iodide into the plasma which also contains iodide released by thyroid gland and extrathyroidal deiodination of iodothyronines. This iodide is either transported in plasma and taken up by thyroid or excreted via urine.

- Thyroid follicles, the structural and functional unit of thyroid are responsible for production, storage and secretion of thyroid hormones. Iodide is actively trapped into thyroid follicular cells (thyrocytes) against electrochemical gradient by sodium-iodide symporter (NIS) at basolateral membrane while efflux of iodide across apical membrane into follicular lumen is mediated by Pendrin, a potential iodide transporter. Normally, thyroid concentrates 20–50 times higher iodide as compared to plasma. Inside thyroid follicle iodide is rapidly oxidized to iodine by thyroid peroxidase (TPO) in the presence of hydrogen peroxidase generated by membrane bound NADPH-oxidase. Iodine is then covalently bound to the selected tyrosyl residues of thyroglobulin (Tg) at the apical plasma membrane-follicle lumen boundary resulting in the formation of monoiodotyrosine and diiodotyrosine (MIT, DIT), a process referred to as organification or iodination. Tg is the most abundant protein in thyroid providing polypeptide backbone for thyroid hormone synthesis and storage. Subsequently, two neighboring iodotyrosyl residues on Tg molecule are coupled in the presence of TPO to produce iodothyronine; two DIT form T4 while one DIT and one MIT form T3. Iodinated Tg is stored as colloid in follicular lumen. Upon stimulation, Tg is internalized into follicular cells by pinocytosis and digested by endosomes and lysosomes resulting in release of T4 (~80%) and T3 (~20%). Deiodination of MIT and DIT by intracellular iodotyrosine dehalogenase release iodide which is again recycled for hormone synthesis

Regulation of thyroid hormone synthesis

- Thyroid hormone synthesis is primarily governed by hypothalamic-pituitary-thyroid axis, a prime negative feedback mechanism that respond suitably to any challenge to maintain biochemical equilibrium. Hypothalamic hormone, thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH) or thyrotropin release by anterior pituitary stimulates thyroid hormone synthesis and secretion while thyroid hormones in turns inhibit the production and secretion of both TRH and TSH and vice versa. This complex interaction between TSH and thyroid hormones maintain serum hormone levels within narrow limit. However, this relationship is individual, dynamic and adaptive depending on many factors.
- TSH almost influences every step in thyroid hormone synthesis and release via Gp/phospholipase C and cAMP cascade respectively. It stimulates thyroid cell proliferation and hormone synthesis by inducing expression of Tg, TPO, NIS and iodothyronine deiodinase type I (D1). Clinically serum TSH levels serves as sensitive biomarker for evaluation of thyroid dysfunction even at sub-clinical stage.
- Beside this, genetics factors, endocrine mediators like estrogen and corticosteroids and local factors released by nerve endings, follicular cells and C cells are also involved in the regulation of biosynthesis of thyroid hormones. Sympathetic and immune system are also involved in regulation of thyroid hormone activity, however very less is known in this regard. Antithyroid drugs, iodide and some external compounds also influence thyroid hormone metabolism.

Hyperthyroidism and thyrotoxicosis

- **Hyperthyroidism** is pathological condition characterized by inappropriately high levels of thyroid hormones due to its excess production and release by thyroid gland. The most common causes of hyperthyroidism are diffuse toxic goiter (Grave's disease), toxic multinodular goiter (Plummer disease) and toxic adenoma.
- The term **thyrotoxicosis** is often interchangeably used with hyperthyroidism and is characterized by elevated level of circulating thyroid hormones secondary to exogenous intake or excess release of preformed stored hormones. Thyroiditis, inflammation of thyroid gland resulting in release of stored hormones is the most frequent cause of thyrotoxicosis.

  Other rare causes of thyrotoxicosis are iodine-induced hyperthyroidism, post-partum thyroiditis, suppurative thyroiditis, beta human chorionic gonadotropin induced thyrotoxicosis and thyrotoxicosis factitia. Follicular thyroid carcinoma, TSH secreting pituitary adenoma and struma ovarii can also cause excess thyroid hormone levels.

Clinical presentation

- The spectrum of clinical presentation depends on age, duration and severity of illness, comorbidities and underlying cause and may range from asymptomatic in subclinical disease to life threatening in thyroid storm.
- restlessness, tremors, anxiety while older patients lack sympathetic symptoms and tend to presents with less obvious symptoms like weight loss, decrease appetite, shortness of breath and cardiac manifestations like atrial fibrillation and tachycardia. Older patients are at increased risk of congestive heart failure and embolic stroke due to atrial fibrillation.
- Some symptoms are specific to underlying cause, like Grave's disease characterized by orbitopathy and pretibial myxedema.
- Patients with untreated or uncontrolled hyperthyroidism may land up in thyroid storm preceding severe physical or mental stress like infection or trauma. Thyroid storm is a rare life-threatening endocrine emergency. It is acute exaggerated clinical manifestation of thyrotoxic state and may cause death from multiorgan failure. Patient may present with agitation, delirium, convulsions, chorea like abnormal movements, severe hyperthermia, excessive diaphoresis, hypertension and refractory dysrhythmias.

Grave’s disease

- is the most frequent cause of hyperthyroidism in developed countries. It is one of most commonly encountered autoimmune disorder with peak incidence in second to fifth decade of life. Women are 5–10 times more affected.
- It is an autoimmune disorder in which antibodies against TSH receptors (TRAb) cause unopposed activation of TSH receptors triggering hormone synthesis. The usual negative feedback mechanism is not effective as the antibodies are directed against TSH receptors. This result in excessive production and release of T3 and T4, an enlarged thyroid gland and increased iodide extraction. Since TSH receptors are present in almost all tissues, extrathyroidal manifestations may be observed. Commonly observed extrathyroidal TRAb driven features are orbitopathy, pretibial myxedema and thyroid acropathy.
- Genetic predisposition accounts for 79% while environmental factors account for 21% of the risk factors. Smoking, iodine excess, selenium and vitamin D deficiency are important environmental risk factors. Person with family history of hyperthyroidism or other autoimmune disease such as myasthenia gravis, type I diabetes mellitus are at increased risk of Grave’s disease.

Toxic multinodular goiter (TMNG, Plummer's disease)

- is the second most common cause of hyperthyroidism after Grave's disease and most common in elderly living in iodine deficient areas. It was first described by Henry Plummer in 1913.
- Thyrotoxicosis occurs in long-standing goiter, with peak incidence in sixth or seventh decade of life. It is characterized by release of thyroid hormones by multiple autonomously functioning nodules or single autonomous nodule in thyroid gland. This functional autonomy is result of activating somatic mutations of TSH receptors genes in most of the cases (~60%). Autonomous nodules appear hots (hyperactive) on thyroid scintigraphy while non-autonomous appears as cold (hypoactive). TMNG has indolent progression with mild clinical symptoms. Clinical features are similar to thyrotoxicosis except presence of Grave's orbitopathy, dermopathy and acropathy. Compressive symptoms may also be present depending on size of gland.

- Toxic adenoma is a benign autonomously functioning thyroid nodule with clinical and biochemical features suggestive of thyrotoxicosis. Iodine deficiency is well established risk factor in pathogenesis of adenoma besides other environmental and genetic factors. Like TMNG, activating mutations in TSH receptor genes results in toxic adenoma. The incidence is higher in women and after 50 years of age. Hyperfunctioning adenoma is usually considered as benign lesion with less than 1% chances of malignant transformation.

Diagnosis

- Diagnosis is made on the basis of history, clinical examination and relevant investigations. Older patients should also be evaluated for potential cardiovascular complications.
- **Laboratory:** Serum TSH and T4 estimation should be done as initial screening test. Serum TSH is more sensitive than direct thyroid hormone estimation in assessment of thyroid hormone excess. Majority of the patients (~90%) with thyrotoxicosis have raised T4 and suppressed TSH levels. However, in patients with T3 toxicosis (~5%), T3 is raised while T4 is normal. Therefore, in patients with suspected thyrotoxicosis and normal T4 levels, T3 should be done to rule out T3 toxicosis. This represents autonomously functioning thyroid nodule or initial disease stage. In patients with pituitary dependent thyrotoxicosis TSH is usually normal with raised T3 and T4. In subclinical hyperthyroidism, TSH levels are suppressed with normalized T3 and T4 while in overt hyperthyroidism T3 and T4 are elevated with suppressed TSH
- TRAb can confirm the diagnosis of Grave's disease with sensitivity and specificity of 97 and 99% respectively. TRAb are detected in almost all patients with Grave's disease. Thyroid peroxidase (TPO) antibodies are less sensitive and specific for Grave's disease, detected in only 70–80% of patients. They are greatly influenced by environmental factors such as iodine intake.
- **Ultrasound** is inexpensive, non-invasive and radiation free modality to assess thyroid blood flow and suspicious thyroid nodules warranting further testing like FNAC. Doppler ultrasound examination has greatly improved accuracy specially in cases where vascularity is needed. Increased thyroid vascularity is seen in Grave's disease while decrease vascularity is indicative of destructive thyroiditis. Thyroid echogenicity assessed by ultrasonography can be used to predict remission after initiation of medications and can also identify patients who are at increased risk of recurrence after withdrawal. However, ultrasound does not precisely establish the underlying etiology of thyrotoxicosis and is reserved for cases where RAIU is contraindicated (pregnancy and breast feeding) or unavailable according to American Thyroid Association (ATA) guidelines.

- **RAIU** measures the percentage of radioactive iodine trapped and organified by thyroid gland after a fixed interval. It is recommended to establish the underlying etiology of thyrotoxicosis (ATA guidelines) and is preferred over TRAb estimation except in cases where RAIU is contraindicated (pregnancy and breast feeding) or unavailable.
- A gamma camera is used to measure the percentage of iodine uptake by gland. RAIU scan shows diffusely increased homogenous uptake in Grave's disease, focal area of increased uptake in toxic adenoma and asymmetrically irregular uptake in TMNG with multiple focal areas of increased and suppressed uptake.
- RAIU will be reduced or near zero in painless and subacute thyroiditis or in those with exogenous ingestion of thyroid hormones, excess iodine intake or exposure to iodinated contrast media in preceding 4–8 weeks. RAIU is also helpful in calculating therapeutic radioactive iodine dose.
- Technetium scintigraphy utilizes pertechnetate which is taken up by thyroid but not organified resulting in low range of uptake. The radiation exposure is less as compared to RAIU however RAIU provides more physiological information. It can also determine the underlying pathology in toxic nodular thyroid disease

- Iodine occurs naturally in stable form as I-127 with 37 known isotopes. All radioactive isotopes of iodine are produced in nuclear reactors by process of fission.
- I-131 is the most commonly used radioisotope of iodine with physical half-life of 8.02 days. I-131 decays to Xe-131 by emitting beta (β) particle and gamma (γ) photons.
- β-particles make I-131 a therapeutic agent as they have the propensity to ablate thyroid tissues. β-particles with these energies can only travel few millimeters ~3 mm, causing only local destruction. The second emission product is γ-photon (10%) with end point energy of 0.364 MeV (80.9%). It travels far from its source before depositing its energy with relatively little impact on thyroid tissue, hence cannot be employed for therapeutic purposes.

Pharmacokinetics of RAI-131

- is similar to normal dietary iodine. After oral ingestion, sodium iodide I-131 is absorbed from small intestine into extracellular fluid. About 90% absorption occurs in first hour after ingestion. From extracellular compartment it is predominantly taken up by thyroid gland or eliminated through kidneys. NIS is responsible for active uptake of iodide in thyroid gland against electrochemical gradient. Under normal physiological condition, NIS can concentrate iodide 20–50 times of plasma concentration and this may increase up to 10 times in hyperthyroidism. Thyroid achieves its maximum uptake of iodide after 24–48 hours with 50% of maximum uptake after 5 hours. Normally thyroid has iodide clearance of about 10–50 ml/min. Iodide uptake is influenced by many factors including patient age, thyroid gland size, circulating iodide level and functional status of kidneys. After radioactive iodide uptake by thyroid, it is further oxidized to iodine and follow normal metabolism of thyroid hormone.

- NIS also mediates active RAI uptake in extrathyroidal tissues like salivary glands, lactating mammary glands, gastric mucosa, lacrimal sac and choroid plexus. However, these structures lack the system to oxidize iodide. RAI elimination from the body is mainly through renal pathway accounting for 37–75% while fecal excretion accounts for 10% of administered dose. Excretion through sweat glands is negligible.

Pharmaceutical preparations of RAI-131

- I-131 is supplied as sodium iodide (NaI-131) in either capsule form or solution form for oral administration. Capsule are available in different activity ranging from 0.75–100 mCi. These are opaque white gelatin capsules packaged in shielded cylinders.
- I-131 is also available as stabilized aqueous solution in vial with activity ranging 5–150 mCi at the time of calibration. The pH of the solution is adjusted between 7.5 and 9. NaI-131 utilized in the preparation of solution at the time of calibration contains more than 99% I-131

- Common well-established clinical indications for RAI-131 therapy are:

- Benign thyroid disease (Grave's disease, TMNG, toxic adenoma and non-toxic nodular goiter)

- Differentiated follicular and papillary carcinoma; residual or recurrent disease after thyroidectomy, metastatic disease after near-total thyroidectomy

- RAI-131 therapy has been considered as a safe, cost-effective and durable treatment option for thyroid pathologies particularly benign thyroid disease for the last eight decades with known risk and benefits. However, optimal method of calculating RAI-131 activity to be administered to achieve therapeutic objectives is still controversial.
- Fixed dose method and calculating a personalized dose using either clinical scoring or scintigraphy findings are frequently used methods

Standard fixed dose RAI-131 therapy

- is simple, with early and higher cure rate and minimal remission. In this method, nuclear physician based on his personal judgment and experience prescribed a fixed dose usually ranging from 2 to 20 mCi. Higher fixed dose is associated with high cure and reduced remission rate but concomitant risk of hypothyroidism. Studies show that approximately 69% patients achieve hypothyroidism at 1 year with 10 mCi RAI-131 while 75% became hypothyroid at 6 months after receiving 15 mCi. However, it has been observed that same results can be obtained with different doses indicating that therapeutic outcome is not dependent only on administered activity.
- European society still advocates administering fixed dose for benign thyroid disease owing to early therapeutic outcome and decrease need of retreatment.

Calculated dose protocol

- is based on individualized dosimetry taking into account patients anatomical and biological parameters. Idea is to calculate minimum effective dose to acquire therapeutic goals and to prevent unnecessary radiation exposure. Individual patient dosimetry is essential for determining dose–response relationship. Calculation of personalized activity to be administered depends on variables like thyroid mass, I-131 uptake values, effective half-life and dose to thyroid in grays (Gy).
- Radiation dose needed to be delivered to thyroid for therapeutic purposes following this protocol is controversial varying from low calculated dose (80 Gy) to high calculated dose (300 Gy). Low radiation dose activity is associated with less chances of hypothyroidism but increased rate of hyperthyroidism. Different algorithms are also used to calculate dose like Marinelli's formula which takes in account RAI-131 uptake and effective half-life

Patient preparation: Pre-therapy evaluation must emphasize on following:

- Patient should be properly educated regarding procedure, its possible outcome, adverse events, complications, radiation safety measures they have to follow and need for long term follow-up by providing written as well as verbal information. Informed consent should be obtained prior to therapy containing all relevant information.
- History including disease duration, previous treatment (ATD or RAI-131 therapy), use of iodinated contrast media or other iodine containing medications, medical therapy for other comorbid like amiodarone and urinary incontinence. Thyrostatic drugs lower radioiodine uptake and effective half-life, so they should discontinue before RAI-131 therapy. Usually, carbimazole and methimazole should be stopped 2–3 days before therapy while propylthiouracil should be discontinued 2–3 weeks prior to therapy due to more radioprotective effect because of presence of sulfhydral group. Exposure to iodine alter the timings of RAI-131 therapy. After administration of iodinated water-soluble contrast agent, therapy should be postponed for 6–8 weeks. In case of amiodarone use for underlying cardiac issue, therapy is usually not preferred because it leads to delay in excess iodine elimination for an average period of 6 months. Similarly, other iodine containing medications like lugols iodine, potassium iodide and topical iodine should be stopped 2–3 weeks before therapy.
- Laboratory investigations including serum free T3, T4, TSH, TRAb levels.
- Recent thyroid scintigraphy and radioiodine uptake studies (< 6 months) to look for tracer uptake values and cold nodules.
- Recent ultrasound neck (< 3 months) for volume assessment and evaluation of nodules.
- Fine needle aspiration cytology of suspicious appearing nodules on ultrasound and hypo-functioning (cold) nodules on scintigraphy to exclude malignancy.
- Fasting for at least 4 hours prior to therapy and 2 hours after therapy is recommended to improve gastrointestinal absorption.
- Breast feeding and lactation are absolute contraindications for RAI-131 therapy.
- In patients with uncontrolled urinary incontinence, proper catheterization should be done or even in-patient therapy should be considered. *Literature also suggest lifelong ATD therapy in such cases if surgery is risky.*

Thyroid drugs and iodide-containing substances that can reduce radioiodine thyroid uptake

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Type of medication	Recommended time of withdrawal
Water-soluble intravenous radiographic contrast agents	6–8 wk*, assuming normal renal function
Lipophilic intravenous radiographic contrast agents	3–6 mo#
Thyroxine	3–4 wk*
Triiodothyronine	10–14 d§
Antithyroid drugs:	
Methimazole Propylthiouracil	2–5 d§ before RAI therapy 2–8 wk* if RAI therapy is performed by fixed-activity method (4–7 d§ if RAI therapy is performed after personalized dosimetric approach)
Nutrition supplements containing iodide	7–10 d§
Kelp, agar, carrageenan, Lugol solution	2–3 wk*, depending on iodide content
Saturated solution of potassium iodide	2–3 wk*
Topical iodine (e.g., surgical skin preparation)	2–3 wk*
Amiodarone	3–6 mo# or longer

Adapted from SNMMI Procedure Standard 2012

§*d* days; **wk* weeks; #*mo* months

- Patients with overt hyperthyroidism and free T4 levels 2–3 times upper limit should be pre-treated with beta adrenergic blockers and ATD (methimazole) to prevent post-therapy worsening of symptoms. Elderly patients and those with comorbid like atrial fibrillation, heart failure, diabetes mellitus, pulmonary hypertension, renal failure and infection should get pre-therapy ATD along with optimization of their medical conditions. ATD should be stopped 3–5 days before therapy and again given 3–7 days after therapy till normalization of thyroid functions where it is tapered off. Levothyroxine substitution is started once patient become hypothyroid.

- Grave's orbitopathy can be temporary and improves after definitive treatment of Grave's disease. In some instances, it can persist or even deteriorates after treatment. The risk of developing orbitopathy after RAI therapy is 15–30%, while its 10 and 16% after ATD and surgery respectively and it can develop any time after treatment. The deterioration of Grave's orbitopathy after RAI therapy is attributed to post-therapy hypothyroidism and increase serum level of thyroid autoantibodies. This deterioration is transient and can be managed by early initiation of thyroxin replacement and corticosteroids. Patients with pre-existing thyroid eye disease should be treated with higher radioiodine dose to achieve quick and sharper response and to avoid slow rise in autoantibodies level due to slow destruction of thyroid follicular cells. This higher dose activity along with early initiation of levothyroxine substitution can prevent worsening of disease. Euthyroid status in such patients before therapy is usually recommended. Smoking is a risk factor and predictor of therapeutic outcome and is associated with more frequent worsening and severe symptoms. A short course of low dose corticosteroids can be added with RAI therapy in non-smokers with mild active eye disease and smokers with mild or inactive eye disease. Patients with moderate to severe active thyroid eye disease should be consider for thyroid surgery or ATD. However, therapeutic efficacy of RAI in such cases needs to be evaluated.

Toxic nodular goiter

- RAI and thyroidectomy are the two effective and safe treatment options for toxic nodular disease. The decision to select a particular treatment option is based on many factors taking into account patient preference as well. RAI is usually preferred in old age patients, patients with significant comorbids, prior surgery or irradiation to neck, small sized goiter and lack of experienced surgeon. The goal of therapy is long term alleviation of hyperthyroid state and achieve euthyroidism and volume reduction. Euthyroidism is achieved 50–60% at 3 months and 80% at 6 months after RAI therapy. Risk of hypothyroidism is very low as compared to Grave's disease. The incidence of hypothyroidism after therapy is 3% at 1 year while 64% after 20 years and more common in patients under 50 years of age.

- Pretreatment with beta blockers is recommended in patients who are at risk of worsening of symptoms after therapy including elderly or those with comorbids and overt hyperthyroidism however the use of ATD before therapy needs careful monitoring and caution. ATD use before therapy can cause normal or raised TSH levels resulting in increased radiation dose to peri-nodular and contralateral thyroid tissue leading to hypothyroidism. Focal uptake in nodule with suppressed uptake in surrounding parenchyma and TSH levels is the basis of RAI treatment. Adequate radiation should be administered in single dose to achieve therapeutic goals. RAI is either given as fixed dose activity (10–20 mCi) or calculated on the basis of thyroid size and radioiodine uptake values using 150–200 μCi/gm calculated fixed dose. There is estimated 20% risk of treatment failure of TMNG and 6–18% for adenoma.

Non-toxic nodular goiter

- Although radioiodine therapy is less commonly indicated treatment option in this group, it is still preferred in patients with recurrent goiter after surgery and comorbids which makes surgery riskier. The aim of therapy is to relive compression symptoms by volume reduction. Radioiodine uptake in non-toxic nodular goiter is usually low, sometimes even 15–20% after 24 hours of administration effecting the efficiency. This radioiodine uptake can be enhanced by low iodine diet consumption for at least 2 weeks before therapy, lithium, avoiding diuretics and recombinant human TSH (rhTSH). rhTSH can increase radioiodine uptake up to 100% without effecting half-life. However, its use is only limited in treatment of thyroid cancer. ATD can be used to increase endogenous TSH seems promising and needs further studies

- patient respond to therapy with normalization of thyroid function test within 4–8 weeks. Hypothyroidism commonly occur between 2 and 6 months but can occur after 4 weeks after therapy. First TSH and free T4 levels should be done 4–6 weeks after therapy to detect the early effects of therapy. Subsequent visit should be done after 3 months because some patients develop severe hypothyroidism followed by yearly follow-up depending on clinical condition. Decision to start thyroxin replacement therapy depends on serum fT4 and TSH level along with clinical features.

- In cases of overt hyperthyroidism, 3–5 days after therapy ATD are usually recommended. For patients with persistent thyrotoxicosis especially Grave's disease, re-therapy is considered after 6–12 months. However, re-therapy is usually less effective due to stunning effect. In some cases, a third session may be needed if patient is still hyperthyroid. In refractory cases patient is referred for surgery

Side effects

- Patients with large goiter may develop painful swelling of thyroid mimicking as sore throat lasting for up to 1 week following therapy. It is usually managed with ice, NSAIDs and steroids if not resolved spontaneously. Slight discomfort of salivary (sialadenitis) with associated dry mouth (xerostomia) may occur in about 39% of the patients, but these are transient effects and permanent damage is very uncommon. Sialogogues or lemon juice can be used to accelerates radioiodine excretion by stimulating salivary glands resulting in approximately 40% reduction in dose to glands. This treatment should not be given in first 24 hours after therapy as it will result in increased absorbed dose due to rebound phenomena. Dry eyes (xerophthalmia) is very rare after radioiodine therapy. Mild leukopenia and thrombocytopenia can occur in some patients but it is usually temporary (6–10 weeks). Nausea and rarely vomiting can occurs immediately after therapy in some patients and resolve withing 24–72 hours.
- Transient rise in serum thyroid hormones level may occur due to release of stored hormones leading to thyrotoxicosis. This transient rise in hormone level depends on pre-treatment status. Patients who have been poorly controlled before therapy usually leads to exacerbation of hyperthyroidism requiring therapy. To reduce this risk, pre-treatment with ATD before therapy can be done to deplete intrathyroidal hormone stores.
- Post-treatment hypothyroidism is an expected result following RAI-131 therapy indicating actual therapeutic response. Some authors consider it as a side effect of therapy.
- Radioiodine induced thyroid damage can lead to immunological response due to release of thyroid autoantibodies peaking approximately 3–6 months after therapy. TRAb usually return to baseline within 1 year but remains detectable for many years. This thyroid autoimmunity results in thyroid associated orbitopathy, seen in approximately 15–30% of patients with Grave's disease and more common in patients with previous history of thyroid eye disease. The risk is associated with release of autoantibodies and development of hypothyroidism. Steroids have shown promising results in such cases. In patients with toxic or non-toxic nodular goiter, about 1–5% patients may develop de novo TRAb and occasionally orbitopathy. The risk is more pronounced in patients with previously circulating autoantibodies (TPO) and usually resolve spontaneously.
- Fertility issues with radioiodine therapy are rare and late side effects.
- In patients with large goiter and retrosternal extension, tracheal compression can occur after therapy. In such cases therapy should be done in collaboration with otolaryngology department to address compressive emergency. Laryngeal edema, dysgeusia and recurrent laryngeal nerve palsy can occur rarely.

Radiation safety procedures

- The amount of radiation received by a person from treated patient depends on activity retained in patient, distance and duration of contact. Mostly radioiodine therapy is administered as outpatient in registered and authorized facility.
- Patient should be encouraged to drink plenty of water during first 8 hours and empty bladder frequently to eliminate excessive activity. Flush toilet twice and rinse sink and tub after use. Wash hands for 20 seconds. Maintain a distance of at least 3 feet from surrounding people for first 8 hours and use private car to drive home, if not possible maintain a distance of at least 3 feet from driver and passengers. Public transport should be avoided.
- Do not share utensils, towels or wash clothes for 48 hours. Wash bed linen, towels and garments stained with urine, sweat or other body fluid. After washing these can be used by others.
- Patient should sleep alone in separate room and avoid close physical contact for at least 7 days. Maintain a distance of 3–6 feet from pregnant females and children below 18 years of age. Infant and small children requiring nursing care should be provided with caretaker for at least 1 week. Avoid activities requiring close contact for more than 5 min for first week like public transport, movie theater, class room etc.
- Both men and women should avoid pregnancy for at least 6 months. Breast feeding should not be resumed for current child. Small amount of radiation can trigger radiation sensors at airports, hospitals and sensitive buildings for up to 3 months. In such cases documentary proof regarding therapy can be obtained from concerned doctor

Radiosynoviorthesis (Radiation Synovectomy)

- Radiosynoviorthesis (RSO) is a proven important instrument for local treatment of chronic inflammatory joint diseases in the context of medical and orthopaedic efforts. The term radiosynoviorthesis was created by Delbarre et al. 1968, meaning the restoration (orthesis) of the synoviumbymeans of radionuclides. By local administration of radioactive agents an attempt is made to influence the synovial process favourably as an alternative to surgical synovectomy.
- In the Anglo-American literature the term “radiosynovectomy” or “radiation synovectomy” came into use.

- **Indications**
- Basically RSO is indicated for the local treatment of almost all kinds of chronic synovitis. The main indications for radiosynoviorthesis are:

Rheumatoid arthritis

Seronegative spondyloarthropathy (i.e., reactive arthritis, psoriatic arthritis)

Haemarthrosis in haemophiliacs

Recurrent joint effusions (i.e., after arthroscopy)

Pigmented villonodular synovitis (PVNS)

Osteoarthritis (activated arthrosis)

After joint prosthesis: persistent effusions, polyethylene disease

Undifferentiated arthritis (where the arthritis is characterized by synovitis, synovial thickening or

effusion)

- **Absolute contraindications:** Pregnancy, Breast feeding, Local skin infection, Acute rupture of popliteal cyst (Baker's cyst)

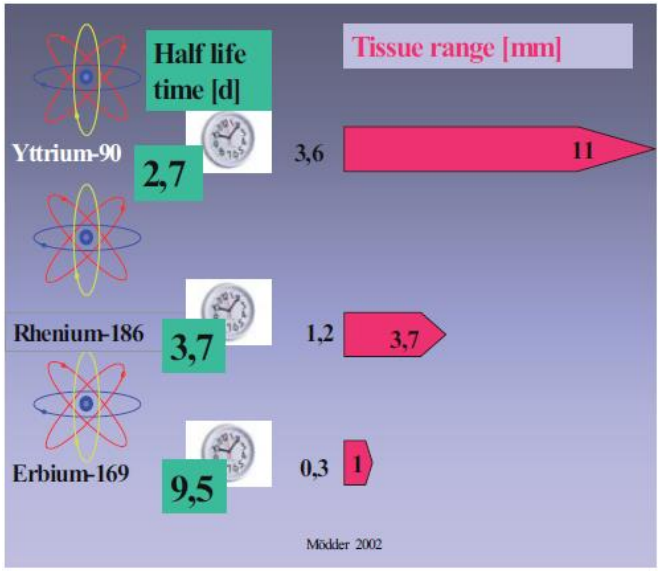
- **Relative contraindications:**RSO should only be used in children and young patients (<20 years) if the benefit of treatment is likely to outweigh the potential hazards. But it is routinely applied in haemophilic children. Extensive joint instability with bone destruction

Radiopharmaceuticals

- The most common and approved radiopharmaceuticals used for RSO are:
- [90Y]yttrium citrate or silicate ([90Y]colloid), only used for RSO of knee joints
- [186Re]rhenium sulphide ([186Re]colloid), used for RSO of middle sized joints
- [169Er]erbium citrate ([169Er]colloid), used for RSO of small joints

Table 29.1. Proven dosages for the most frequently treated joints

Joint	Radioisotope	Dose (MBq)
Knee joint	Yttrium-90	185 – 222
Glenohumeral joint	Rhenium-186	74
Elbow joint	Rhenium-186	74
Wrist joint	Rhenium-186	55 – 74
Hip joint	Rhenium-186	111 – 185
Ankle joint	Rhenium-186	74
Talonavicular/subtalar joint	Rhenium-186	55
Metacarpophalangeal joint (MCP)	Erbium-169	20 – 40
Proximal interphalangeal joint (PIP)	Erbium-169	10 – 20
Distal interphalangeal joint (DIP)	Erbium-169	10 – 15
Metatarsophalangeal joint (MTP)	Erbium-169	30 – 40
Thumb base	Erbium-169	30



Mechanism of Action

- “Synovitis is the villain of the drama” (Mannerfeldt), in rheumatic diseases causing brutal destruction of cartilage, bone, tendons and ligaments correlated with pain, swelling and loss of function. After intra-articular administration the radioactive particles in colloidal form are taken up by phagocytosis in synovial macrophages. A particle size of about 5±10 nm is essential to avoid leakage and provide homogenous distribution on the surface of the synovium.
- q -radiation leads to coagulation necrosis, sclerosis and fibrosis of the synovial tissue including vessels and pain receptors, resulting in reducing effusion, swelling and pain of the joint. Due to the fact that cartilage has no ability to phagocytose, this tissue is not a target for the radiation effects .

- Simultaneous intra-articular injection of corticosteroids (i.e., triamcinolone hexacetonide or triamcinolone acetonide) is recommended because this might reduce local inflammation due to radionuclide instillation and prolong residence time of the radiopharmaceutical agent in the joint. An additional reason is the reduction of the often superposed layer of oedema on the synovium so that the thin film of radioisotopes gets closer to the destructing pannus – resulting in improvement of the effect of RSO.

- Side Effects
- Early: Temporarily increased synovitis (rapid relief by local application of ice)
- Late: Local radionecrosis (rare)

Patient Selection

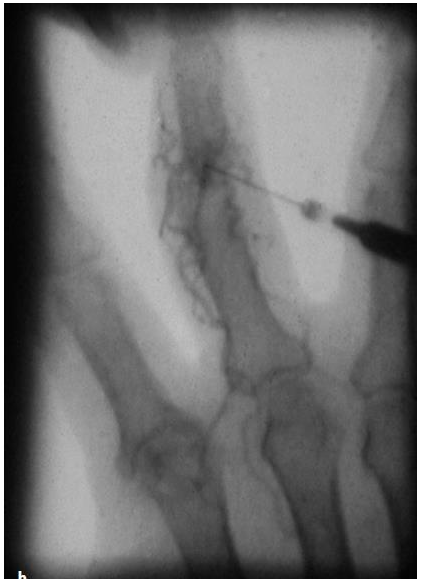
- Rheumatic patients need systemic treatment with antirheumatoid drugs because rheumatism is a systemic disease. If after at least 6 months a few joints do not show adequate improvement even after corticosteroid injections into the affected joints, these joints are selected for RSO, thus avoiding escalation of systemic therapy with its possible side effects. In monarthritis or oligoarthritis RSO could be the therapy of first choice, after failure of locally administered corticosteroids
- Orthopaedic patients should be selected after failure of local corticoid injection and/or ineffective conservative treatment. But also after plenty of surgical interventions RSO might improve the complaints of the patient, i.e., after total knee replacement or effusions after arthroscopy.
- Some authors recommend RSO after arthroscopy as a routine method to improve results. The time interval between arthroscopy or joint surgery (i.e., villonodular synovitis) and RSO should be planned as (4–)6 weeks.

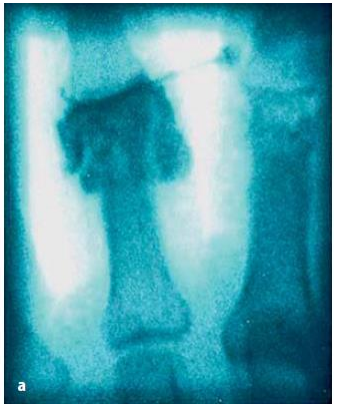
Diagnostic Studies Prior to RSO

- Medical history, clinical inspection, examination of joint function.
- X-ray images provide basic information about the joint.
- Ultrasound study evaluates joint space, synovial structure and thickness and extent of effusion, and assesses tenosynovialitis or rotator cuff tear (shoulder). Ultrasound is obligatory prior to performing RSO to rule out a Baker's cyst
- Multiphase scintigraphy with 99mTc-MDP (or similar radiopharmaceuticals) is the best diagnostic tool for detecting and demonstrating inflammation of the synovium, thus – including findings of the clinical examination – selecting joints for RSO. In the first step (10 min p.i.) soft tissue scintigraphy detects the degree of active inflammation of synovium. In the second step (3 h p.i.) bone scintigraphy assesses the bone involvement in the painful process. The study reveals nearly indispensable information in activated arthrosis (osteoarthritis) and gives the best overview over multiple joint involvement especially in (also seronegative) polyarthritis
- Magnetic resonance imaging might be suitable for additional information in a few patients (i.e., bone oedema, femur head necrosis).

Joint Puncture

- A suitable room and strict asepsis are necessary.
- Apart from the knee, all joints have to be punctured for RSO by fluoroscopy and often by arthrography. Dye distribution predicts the distribution of radionuclide which is injected immediately afterwards. Using this procedure perfect needle position in the cavity of the joint is ensured





After RSO/Follow-up

- A distribution scintigram confirms the appropriate intra-articular distribution of the radiopharmaceutical.
- Scintigraphy is enabled after use of yttrium- 90 by its Röntgen-bremsstrahlung, after use of rhenium-186 by its gamma portion (140 keV). After the use of erbium-169 no scintigram is available.
- The joint has to be immobilized to avoid necrosis of injection channel or skin caused by reflux and to avoid transport of radioactive particles through the lymphatic vessels (leakage). A splint is required for 48 h. After removal of the splint the joint should be treated with care for 1 week, but then the patient should go into training of the joint and muscles.
- Sometimes an effusion fluid or a Baker’s cyst has to be punctured before the development of the definitive effect of RSO. Clinical examination and ultrasound scans, sometimes control of scintigraphy, should take place 12 months after treatment.

Repetition of Radiosynoviorthesis

- Radiosynoviorthesis should be performed at an early stage of the disease, when cartilage damage is minimal. Reasons for non-satisfactory results of RSO might be, e.g., rapidly recurrent effusions, strongly developed thickness of synovial villus, enlargement of the joint cavity by additional cavities (Baker's cyst, bursa subdeltoidea), unfavourable Larsen stage, etc.
- Then a repetition of RSO (Re-RSO) may be indicated, normally not earlier than 6 months after the previous procedure. Re-RSO of the wrist will not only treat the proximal wrist joint but will additionally reach the intercarpal compartments. And after total knee replacement the deeper layers of polyethylene disease can be attacked by Re-RSO. A new fraction is more effective than a primarily enhanced dose

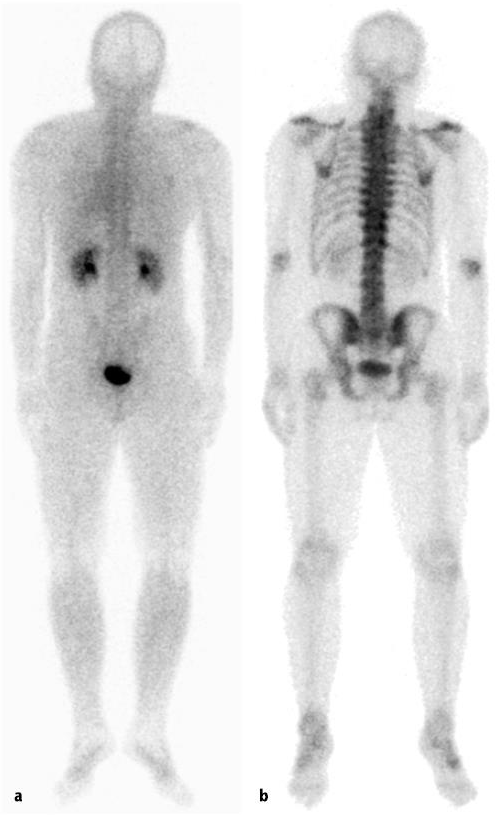
Treatment in Ankylosing Spondylitis

- Radiopharmaceuticals Employed -The isotope 224Ra is an [-emitter with a physical half life of 3.6 days and a radiation energy of 5.7 MeV. The effective half-life is 1.7 days in the human body. It behaves like a homologue of calcium with preferential accumulation in zones of calcification and ossification.
- The pharmacological effects in ankylosing spondylitis are anti-osteoblastic and anti-inflammatory with subsequent relief of pain, improvement of mobility, and reduced spinal ossification.

Clinical Indications

- Therapy with 224Ra was considered to be indicated with radiologically proven early ankylosing of one or two parts of the spine with ongoing inflammation diagnosed by a value of the C-reactive protein (CRP) above 10 mg/l, clinical progression failing to respond to nonsteroidal anti-inflammatory drugs (NSAIDs), and/or if analgesic/anti-inflammatory drugs are contraindicated.
- Contraindications for this therapy were considered to be diseases of the blood formation system, recent fractures, severe liver damage, pregnancy and lactation, age of patient less than 21 years, and acute infection.
- First two phase whole body bone scan is shown with positive signs for AS. During the treatment we performed weekly measurements of full blood count, liver enzymes, CRP and ESR (erythrocyte sedimentation rate).
- For the evaluation of the response to therapy, pain evaluation can be done by oral interview; the function mainly of the spinal column can be evaluated by the standardized Bath Ankylosing Spondylitis Functional
- Index (BASFI) questionnaire, which is a rheumatological index for the measurement of movement restrictions in everyday situations; the course of the medication should be questioned by oral interview; and the acute phase-reactants can be measured by CRP/ESR evaluation.

- Complications of this therapy are a drop of the leukocyte count by 27%, platelets by 21% with unchanged hemoglobulin value and liver enzymes.



Two-phase whole body bone scintigraphy in the posterior view of a patient with ankylosing spondylitis. **a** Early soft tissue phase with typical paravertebral accumulation of the radiopharmaceutical. **b** Late bone phase with typical hot spots in the small vertebral joints

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