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## Percutaneous ethanol injection therapy of autonomous (toxic) thyroid nodules

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Percutaneous ethanol injection therapy (PEIT) has been established as an interventional method of the ablation of hepatic malignancies, especially hepatocellular carcinoma (HCC), since long. Its effects are based on cellular dehydration, toxic and coagulation necrosis and thrombosis of small venules within the tumour. The result is fibrosis of the damaged tissue, loss of function and shrinkage. Hence the "ablative" effect of absolute (95%) ethanol. The more confined ally lesion the better the ablative effect due to the high concentration of the toxic liquid. Highest effects will be achieved in encapsulated nodules which prevent diffusion of the toxic agent into surrounding normal tissue which is the case in HCC.

Since 1990, Livraghi (Milan, Italy) and co-workers as well as Monzani and his group from Pisa/Italy have published the curative effect of ethanol injection into autonomous (toxic) thyroid nodules, and have presented this method as a valuable alternative to surgical ablation or radiotherapy treatment with radioactive iodine-131.

In Europe, 9-10% of hyperfunctioning thyroid glands have toxic, autonomous thyroid nodules (ATN). These may present in a unifocal, multifocal or disseminated form. They must be treated definitely, when there is a constellation of clinical signs of hyperthyroidism. scintigraphically proven inactivity of normal thyroid tissue, elevation of hormone levels (T-3 and T-4) and a depression of basal thyroid stimulating hormone (TSH) under detectability. If those findings are not found in a case of "hot spot" in scintigraphy, the case is less urgent, and one may wait and observe the patient. However, in the natural course of such adenomas 4-6% tend to develop apparent clinical hyperthyroidism within every given year. ATN or toxic adenomas of the thyroid gland may develop when thyrocytes get a mutation of their receptors for TSH, which is in fact a somatic mutation. It

leads to a permanent, constitutifional, TSH-non-responding activation of the receptor cell which produces hormone excessively. Autonomous cells are stipulated in proliferation by iodine deficiency, so that endemic goiters are the main cause for such a development. In accordance to the number of autonomous cells first hormone levels are elevated, and with the ongoing proliferation subclinical hyperthyroidism may change into manifest hyperthyroidism with all clinical signs. Cure of this status is achieved only by removing the nodules surgically or destroying them by radio-iodine treatment. Antithyroid drugs have no curative effect because of universal relapse of hyperthyroidism when they are discontinued.

In the last decade, ethanol (alcohol) ablation of toxic nodules of the thyroid gland has been established as a very effective and secure alternative to the well established methods of operation and radiotherapy. However, in this authors opinion, it has not yet achieved the acceptance it deserves.

Since 1994, in the Municipal hospital of Marl, Germany, we have performed percutaneous ethanol ablations of toxic thyroid nodules in 186 patients with very good or at least sufficient results. Morphologically, ATN present as "hot nodules" in Technetium scintigraphy. Sometimes, the surrounding thyroid tissue is still in function, sometimes, according to the hormone activity and/or the size of the nodule, radioactivity is only found within the nodule (so-called "decompensated" autonomous adenoma).

Ultrasound may detect a rounded lesion with predominantly hypoechoic, homogeneous echo pattern, which is surrounded by a clearly delineated capsule. If scintigraphy and ultrasound are matching, and if T-3 and T-4 levels are elevated and basal TSH suppressed, one can easily make the diagnosis of hyperthyroidism due to toxic adenoma. Sometimes, when laboratory and scintigraphic constellation is equivocal, suppression

scintigraphy may prove the existence of a toxic adenoma. In the last years a linear relation between vascularity in colour Doppler ultrasound studies and the hormone activity of nodules has been described. Hence, colour Doppler ultrasound is a good instrument to evaluate the remaining hyperfunctioning tissue in toxic nodules treated by PEIT.

### Ablation Technique

A small amount of local anesthesia is given to the skin above the nodule. Free hand puncture of the lesion is performed under ultrasound control (preferably a 7.5 MHZ device) using a 20-22 gauge needle. Control of the needle tip is easily done by gently moving it up and down within the nodule: it can be seen by casting a very high acoustic echo. Care has to be taken as not to perforate the posterior border in order not to inject ethanol into the surrounding tissue and to avoid damaging the recurrent laryngeal nerve. Once the needle tip is secured within the center of the lesion a small amount of ethanol is cautiously injected. Immediately, it spreads throughout the nodule and can be seen in form of a "snow shower" phenomenon (enhancement of acoustic impedance by minute air bubbles within the alcohol) which ensures the distribution of the toxic agent strictly within the adenoma. The total amount of alcohol depends on the nodule size (approximately 1.5 ml the estimated volume). However, we advise to inject no more than 1.5 to 3 ml of ethanol per session. It should be delivered very slowly because there will be an increase of pressure within the nodule that may cause pain. If overdone, the capsule may disrupt, and the liquor pours into adjacent tissues causing pain and damage. In our experience, patients do tolerate an extended period of injection sessions (medium 6 times i.e. six weeks) rather than being bothered by a treatment too quick and vigorous and at the risk of damaging the recurrent laryngeal nerve. Also, before injection, aspiration should be done to be sure not to inject into an adjacent vessel (common carotid artery or jugular vein). The procedure is finished by leaving the needle without syringe some seconds in order to let the pressure evade, then withdrawing it by injecting some droplets of anesthetic agent into the needle track. Patient gently compresses the puncture site for at least five minutes to avoid hematoma and is then discharged within the next quarter of an hour, such being treated totally on an

outpatient basis.

### Follow-up

If the nodule diameter does not exceed 3 centimeters, 6 injections in weekly repetition will be sufficient to destroy the lesion entirely. Two weeks after the end of treatment technetium scintigraphy should be performed to secure the ablation of the hot nodule and to see whether normal thyroid tissue has regained its activity. If ultrasound also is repeated a shrinkage of the nodule can be seen (to one half or one third of the size before therapy) and a slight elevation in echogenicity confirms the fibrotic nature of the "ablated" lesion. Doppler colour sonography then should show a complete loss in vascularity, if not, and if scintigraphy shows substantial parts of the hot nodule still viable, one should proceed to another series of 2-4 injections into the still functioning areas. In very big nodules over 5 cm and in the very old patient it may be wise not to aim at a total destruction of the nodule rather than re-establishing euthyrosis. The serum T-3 and T-4 levels fail to normal levels within 6-8 weeks, and the basal TSH reaches normal values within the same time or little later. Scintigraphy should be repeated at yearly intervals to look for local recurrence (under 5% in our experience) and to detect new autonomous nodules that may be generated independently.

### Favorable indications for PEIT in ATN

Patients with toxic adenomas referred for diagnostic evaluation present in three groups:

I. Toxic cases: FT-3 and FT-4 elevated, TSH suppressed 70%.

II. Nontoxic: FT-3 and FT-4 normal, TSH suppressed 20%.

III. Compensated: FT-3, FT-4 and TSH normal 10%.

Scintigraphy in group I and II: uptake only in "hot nodule"-decompensated nodules.

Scintigraphy in group III: little uptake also outside nodule.

In our collection of 186 patients two thirds were female, one third male. They had a mean age of 59 years (31-78) and presented with one hot nodule in the majority of cases (87%). The median nodule size, in terms of the largest diameter, was 2.9 cm (1.8-6.7 cm

). We believe that ATN should be treated in the following conditions ;

I . ATN with hyperthyroidism .

II . ATN with normal peripheral hormone levels .

-in the elderly patient with nodule size > 3 cm , suppressed TSH and borderline levels of FT-3 and FT-4 .

-in patients with cardiac disease( tachycardia , atrial arrhythmias and/or heart failure .

- when iodine exposure is necessary ( such as coronary or peripheral angiography or CT-scanning with contrast medium or the like ) .

## Results

There have been no failures in terms of complete ineffectiveness to cure hyperthyroidism in 186 patients so far . There have been very few ( 31 pts . ) incomplete ablations of toxic nodules , but all patients responded by having normal peripheral hormone values ( TSH remained depressed ) . These figures include 11 patients in whom we performed a second treatment series of 4 injections that lead to total exclusion of the hot nodule . Choice of treatment operation , radiotherapy or ethanol ablation- depends on the informed patients decision , the interventional experience of the doctor , the size of the goiter , the age of the patient ( radiotherapy not in the younger patient ) and the concomitant multimorbidity of the patient . Facts in favour of PEIT are :

1-2 adenomas only

diameter under 4 cm

patient older then 40 years

multimorbidity

hesitation against surgery , radiotherapy and hospitalization

Unfavorable conditions and contraindications for ethanol therapy in ATN coagulopathy very young patients ( no very long term observations so far ) . Size over 4 cm big goiter ( operation may be needed anyway ) Rejection of PEIT because it may cause pain .

## Side effects and complications

Overall , the procedure is very safe in the hands of the interventionally experienced , and seldom major complications do occur , in our series , we found the

following :

- pain( very often , but mostly slight , due to the repeated punctures during the treatment period , sometimes , when leakage through the capsule occurs ) None asked for interruption of the therapy .

- transient damage of the recurrent laryngeal nerve ( hoarseness ) in 5 cases . No permanent damage .

- hematoma of the puncture side in 21 cases , all mild and within sequelae , and without need of interruption of the series ( within a total of  $6 \times 186$  i. e. 1116 punctures ) .

- no infection , no skin necrosis .

## Costs of therapy of autonomous thyroid nodules


In our country , proven by dates that the insurance companies provide , PEIT of ATN has a tremendous effect on cost reduction : Operation and radiotherapy for the cure of ATN cost about 4500 DM and 4200 DM , respectively , where as PEIT produces costs of about 150 DM which represents a factor of about 30( thirty ) ! .

## Discussion and conclusion

All patients gave informed consent to this therapy which is not yet fully established yet no longer experimental . After the therapy series , when asked again whether they would prefer the PEIT method again or rather choose operation or radiotherapy , 95% voted in favour of ethanol ablation therapy . May PEIT of ATN jeopardize an operation carried on later ? In their article : "Surgical and Pathologic Changes after Percutaneous Ethanol Injection Therapy of Thyroid Nodules ( Thyroid Vol. 10 , 2000 , p. 1087-1092 ) Monzani and colleagues stated : " In conclusion , our data suggest that patients previously treated by PEIT can be subjected to surgery without particular concern " . We do believe that PEIT of ATN is a safe , highly effective , very low-cost therapy which deserves more consideration as an alternative to operation and radiotherapy . It furthermore has an extremely high acceptance by patients , and in this authors view it could become the treatment of choice before considering other therapeutic modalities .

( 收稿日期 2004-06-05 )

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英文刊名: [JOURNAL OF INTERVENTIONAL RADIOLOGY](#)  
年, 卷(期): 2005, 14(1)  
被引用次数: 0次

本文链接: [http://d.wanfangdata.com.cn/Periodical\\_jrfsxzz200501038.aspx](http://d.wanfangdata.com.cn/Periodical_jrfsxzz200501038.aspx)

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