Localized Thyroid Tissue Ablation by High Intensity Focused Ultrasound: Volume Reduction, Effects on Thyroid Function and Immune Response

Lokale Ablation von Schilddrüsengewebe durch hochintensiven fokussierten Ultraschall: Volumenreduktion, Auswirkungen auf die thyroidale Funktion und Immunreaktion

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**Key words**
- high intensity focused ultrasound
- thyroid nodule
- thermal ablation
- thyroid hormones
- thyroid function
- thyroglobulin

**Material and Methods:**
Zwölf Patienten (neun weiblich, Durchschnittsalter 56,9 Jahre) wurden ambulant mit HIFU an der Schilddrüse behandelt. Alle Patienten hatten einen einzelnen benignen Schilddrüsenknoten, der in jeweils einer Therapiesitzung behandelt wurde. Das mittlere Knotenvolumen (nodular outline volume) betrug 3,4 ml (Bereich 0,6 – 5,0 ml). Die therapeutische Ultraschallsonde (Echopulse® THC900 888-H), die in dieser Studie verwendet wurde, arbeitet mit einer Frequenz von 3 MHz, erreicht eine mittlere Temperatur von 80 – 90 °C und sendet eine mittlere akustische Leistung von 87,6 bis 192,8 Watt aus. Die Therapieendpunkte (Tak) wurden bei der Aufnahme, 24 Stunden nach der Therapie und drei Monate nach der Therapie gemessen. Die prä-post Thyreo globulin-Reduktion wurde gemessen, um den Erfolg der Ablation einzuschätzen. Außerdem wurde das Knotenvolumen mit der Variable Nodular Outline Volume (NOV) untersucht, um die Effektivität zu bestimmen.

**Results:**
All measured hormone levels were within normal ranges and remained stable (p > 0.05). No clinically meaningful immune reaction was induced (p > 0.05). Thyroglobulin serum levels increased significantly at 24 hours after ablation (p < 0.05) and decreased significantly at the 3-month follow-up (p < 0.05), returning to pre-ablative levels. The median reduction in nodular outline volume (NOV) was 55% (p < 0.05).

**Conclusion:** HIFU is a safe and effective alternative for treating benign thyroid nodules, while preserving thyroid function. Further investigations with multiple treatments should be conducted to eval-
Das mittlere Knotenvolumen (NOV) konnte um 55 % reduziert werden (p<0,05).

Schlussfolgerung: HIFU ist eine sichere und effektive Methode, um benigne Schilddrüsenknoten zu behandeln. Die Funktion der Schilddrüse wird nicht beeinträchtigt. Um eine noch größere Volumenreduktion zu erreichen, könnten mehrfache Sitzungen Erfolg versprechen.

Kernaussagen:
- HIFU ist eine sichere und effektive Methode, um benigne Schilddrüsenknoten zu behandeln.
- HIFU beeinträchtigt die Funktion der Schilddrüse nicht.
- HIFU induziert keine ernste Immunreaktion, wie etwa Morbus Basedow.

Introduction

Thyroid nodules are relatively common in industrial nations [1 – 6] with most being benign and requiring treatment for associated symptoms such as compression, discomfort and cosmetic concerns [7 – 9]. The relatively mild clinical consequences of most benign nodules suggest that standard therapies, like surgery and radiiodine therapy (RIT), may be associated with more harm than benefit [10, 11]. As a result, there has been a search for alternatives to these standard treatments. This has yielded a variety of new techniques including radiofrequency ablation [8], ethanol sclerotherapy [12], microwave ablation [7, 9, 13] and high intensity focused ultrasound (HIFU) ablation. While some of these alternative techniques have already been established in clinical practice [14], a majority have drawbacks that include induction of serious immune reactions such as Graves’ disease, scar formation, hypothyroidism and hyperthyroidism, thyrotoxicosis and inflammation [10 – 18].

Of existing alternatives to standard therapies, HIFU appears to be one of the most promising in that its advantages include: (a) non-invasiveness, (b) patient wellbeing due to avoidance of scar formation (c) low risk of immune responses as will be discussed below, (d) accuracy and (e) ease of use, the latter two based on our own clinical experience. HIFU is already widely applied in clinical practice and is used to treat, among other diseases, breast lesions [19], uterine fibroids [20] and prostate cancer [21]. It is also further being developed to treat kidney and liver tumors [22]. However, to our knowledge there have been only few published studies except our own recent publications [23 – 25] investigating the ablation of human thyroid tissue with HIFU [26 – 28] and few other publications describing preclinical work in the area [28 – 30].

The objective of the current study was to assess HIFU’s effectiveness in reducing nodule volume while preserving thyroid function, as measured by thyroid hormone and relevant antibodies, and so to provide much needed additional data on procedure outcome in the indication. A successful treatment in this study was achieved if the following criteria were achieved: (a) volume reduction > 30 %, (b) symptom score improvement, (c) euthyroid hormone status.

Materials and Methods

Patients

Patients were enrolled at the nuclear medicine department of the University Hospital Frankfurt. Eligible patients had a symptomatic thyroid nodule and cosmetic concerns and had either refused surgery or were contraindicated for it. Patients were excluded for having asymptomatic nodules, nodule volume exceeding 10 ml, histological evidence for malignancy or positive Tc-99 m MIBI uptake in cold nodules or conspicuous calcitonin measurement.

12 patients (9 females) whose average age was 56.9 years (37 – 81) were treated with HIFU in an ambulatory setting. All patients had a single benign thyroid nodule treated in one HIFU session. The median nodular outline volume (NOV) was 3.4 ml (range 0.6 – 5.0 ml).

Study Design

This was a single-arm, open-label, baseline control study. The study complied with institutional review board ethics committees, informed consent regulations, International Committee on Harmonization Good Clinical Practice Guidelines, the Declaration of Helsinki, and local regulations.

Treatment Procedure and Equipment

The system used in this study (Echopulse® THC900 888-H, THERACLIION SA, Malakoff – France) has two separate ultrasound systems. The imaging system works between frequencies of 7.5 and 12 MHz and the therapeutic system with frequencies of 3 MHz, reaching temperatures approximately 80 – 90 °C. Heat is produced by absorption of acoustic energy and its conversion into thermal energy.

A probe with a maximal penetration depth of 1.5 cm and an exchangeable cooling kit was used. The system automatically selected the following safety margins: (a) 0.5 cm from the skin, (b) at least 0.3 cm from the trachea and (c) 0.2 cm from the carotid. The mean output per treated voxel varied between 87.6 and 192.8 W. Before each treatment, a cooling kit was installed and the system underwent a general test of function. The nodular volume was measured using US (Fig. 1). Local anesthesia (Mecain 1 %) was given, followed by positioning of the ultrasound probe on the hyoeprected neck and primary marking of relevant structures. The system automatically generated a voxel map of the intended nodule and the marked structures around it. Following the computed voxel map in a screw pattern while adjusting the energy level, the system executed ablation by automatically alternating a four-second treatment beam with a cooling pause and positioning. Throughout the procedure the voxel map and sonographic images, showing the actual and planned images of the current voxel, were visible to enable control of the ultrasound probe location.

Throughout the treatment it was possible to manually pause, reposition, select or remove particular voxels and terminate the treatment. If patient movement occurred during a beam, a laser-
controlled movement detector directed at the laryngeal prominence automatically stopped the treatment and lead to manual repositioning or recalibration of the measured laser distance.

**Baseline Assessment and Endpoints**

All patients underwent a pre-ablation assessment, including laboratory blood tests, ultrasound imaging and fine-needle aspiration biopsy of the target nodule. B-mode ultrasound (Sonix Touch Ultrasound system, Ultrasonix Medical Corporation, Richmond, Canada) was used to evaluate the volume, size, number and composition of the nodules. Serum levels were determined with commercially available immunoradiometric assay and radioimmunoassay kits. Laboratory blood tests included a complete thyroid hormone status with triiodothyronine (T3, normal range: 1.0 – 3.3 nmol/L) determined by RIA (T3\textsuperscript{125I} RIA Kit, Izotop, Budapest, Hungary), thyroxine (T4, normal range: 55 – 170 nmol/L) determined by RIA (T4\textsuperscript{125I} RIA Kit, Izotop, Budapest, Hungary), thyrotropin (TSH, normal range: 0.3 – 4.0 mE/L) determined by IRMA (SELco\textsuperscript{®} TSH rapid, Medipan GmbH, Dahlewitz, Germany) and thyroglobulin (Tg, normal range: 2 – 70 ng/mL) determined by IRMA (Riason\textsuperscript{®} Tg c.t., Jason GmbH, Graz-Seiersberg, Austria). Calcitonin level, blood count and coagulation diagnostic were measured.

The presence of antibodies was also examined, specifically those against thyroid peroxidase (TPOAbs, positive: > 50 U/mL) determined by RIA (anti-TPO magnum, Medipan GmbH, Dahlewitz, Germany), thyroglobulin (TAbs, positive: > 50 U/mL) determined by RIA (anti-Tg magnum, Medipan GmbH, Dahlewitz, Germany) and thyrotropin receptor (TRAbs, positive: > 1.5 IU/L) determined by RIA (TRAK Human RIA, Brahms GmbH, Henningsdorf, Germany).

Patients with “cold” nodules were evaluated with a Tc-99 m methoxy-isobutyl-isonitrile (MIBI) scan to exclude malignancy. Images were taken 10 and 60 minutes after injection of 500 MBq (13.5 mCi) Tc-99 m MIBI. Further a fine-needle aspiration biopsy was performed. No evidence of malignant transformation was found in any of the subjects. The patients had follow-up laboratory blood tests at 24 hours and 3 months after ablation treatment.

**Statistical Analysis**

Statistical analyses were done with the R statistical software [29]. Because of the small sample size and the fact that normality could not be assumed, all statistical testing was non-parametric. Differences between time points were compared by the Wilcoxon sign-rank test and correlation using Kendall’s tau.

**Results**

**Safety and Tolerability**

HIFU treatment sessions were completed successfully for all twelve patients. All patients tolerated the treatment and interruption was not necessary.

**Laboratory Tests**

With the exception of thyroglobulin (hTg), no laboratory parameter, antibody measurement or blood count changed significantly at all follow-ups. Thyroglobulin levels increased significantly (p < 0.05) 24 hours after ablation and decreased significantly at the 3-month follow-up relative to the 24-hour time point (p < 0.05). Comparison of 3-month hTg values to the baseline was not significant (Fig. 2).

**Efficacy**

The median reduction of the NOV at the three-month follow-up was 55% (p < 0.05). In three patients the therapy was not successful, because a volume reduction of more than 30% was not achieved.

**Antibody Measurement**

No patient showed signs of Hashimoto’s thyroiditis or Grave’s disease. Yet one patient had elevated levels of anti-TPO before HIFU. After HIFU the levels remained stable. Antibody measurement is summarized in Table 1.

**Discussion**

HIFU is currently the least invasive method for the treatment of thyroid nodules, with the most favorable safety profile, posing low risk for infection and other side effects [27]. The study present-
ed in this article found no indication that HIFU either interferes with thyroid gland function or induces thyrotoxicosis. Furthermore, no indications for serious thyroid diseases like Graves’ disease or Hashimoto’s thyroiditis were found. The hormone status of all patients remained stable and substitution was not necessary. HIFU ablates with temperatures of about 80 to 85 °C. Irreversible tissue damage by heat occurs at temperatures higher than 60 °C [30, 31] while high temperatures under 60 °C induce reversible damage, with a high risk of leaking functional thyroid hormones inducing transient thyrotoxicosis [16]. Other thermal ablative treatments use rather large ablation areas and a long ablation time and thus leak significant energy into the surrounding tissue. In comparison to other thermal ablative treatments, HIFU works with small focal points, great accuracy, short ablation times and a constant cooling system whereby very little energy is spread to the surrounding not targeted tissue [26–28]. This is likely the reason that there have yet to be reports of HIFU inducing thyrotoxicosis, which may in fact not occur at all when using this procedure. Adding to the safety of the procedure is that structures like blood vessels or the trachea are protected by automatic safety margins and planning accuracy.

A successful volume reduction of more than 30 % of the pre-ablation volume was achieved in 9 of the 12 patients in this study. However, it is possible that a further volume reduction will be observed at later follow-ups, since not all damaged tissue might be biologically degraded 3 months after ablation.

Thyroglobulin serum levels were measured to evaluate the success of ablation. In clinical diagnosis thyroglobulin constitutes a

Table 1 Thyroid function parameter medians at baseline and follow-ups.

<table>
<thead>
<tr>
<th>parameter</th>
<th>baseline</th>
<th>24 hours after HIFU</th>
<th>3 months after HIFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3 [nmol/L]</td>
<td>1.7 (1.4 – 2.3)</td>
<td>1.7 (0.9 – 2.7)</td>
<td>1.5 (1 – 2.2)</td>
</tr>
<tr>
<td>T4 [nmol/L]</td>
<td>84 (69 – 144)</td>
<td>92 (74 – 146)</td>
<td>87 (60 – 164)</td>
</tr>
<tr>
<td>TSH [mE/L]</td>
<td>0.9 (0.5 – 5.6)</td>
<td>0.7 (0.1 – 3.0)</td>
<td>1.2 (0.1 – 1.8)</td>
</tr>
<tr>
<td>TgTg [ng/mL]</td>
<td>29.6 (0.1 – 459)</td>
<td>702.0 (28.9 – 3431.0)</td>
<td>15.3 (0.09 – 155)</td>
</tr>
<tr>
<td>TPOAbs [IU/L]</td>
<td>10 (6 – 1119)</td>
<td>12 (6 – 986)</td>
<td>7 (3 – 791)</td>
</tr>
<tr>
<td>TAbs [IU/L]</td>
<td>9 (5 – 110)</td>
<td>7 (5 – 63)</td>
<td>9 (3 – 108)</td>
</tr>
<tr>
<td>TRAbs [IU/L]</td>
<td>0.02 (0 – 0.92)</td>
<td>0.30 (0 – 0.74)</td>
<td>0.3 (0 – 0.74)</td>
</tr>
</tbody>
</table>

Median laboratory parameters at baseline and follow-ups. Normal ranges of hormones and antibodies are: T3: 1.0 – 3.3 nmol/L, T4: 55 – 170 nmol/L, TSH: 0.3 – 4.0 mE/L, TgTg: < 1 after thyroidectomy, TRAbs: positive > 1.5 IU/L, TAbs: positive > 50 IU/mL, TPO > 50 IU/mL. The increase of hTg levels 24 hours after ablation and the following decrease 3 months after ablation are significant (p < 0.05). Data are presented as median and range. Blood count, coagulation diagnostics and calcitonin were within normal limits in all patients at all dates of measurement. Die Tabelle zeigt die Mittel der Laborparameter zum Zeitpunkt vor der HIFU-Therapie und bei den Kontrollen. Der normale Bereich der Hormone und Antikörper sind: T3: 1.0 – 3.3 nmol/L, T4: 55 – 170 nmol/L, TSH: 0.3 – 4.0 mE/L, TgTg: < 1 nach Thyreoidektomie, TRAbs: positiv > 1.5 IU/L, TAbs: positiv > 50 IU/mL, TPO > 50 IU/mL. Die einzigen signifikanten Veränderungen waren im hTg-Wert zu beobachten (p < 0.05). Die Daten sind als Median und Bereich präsentiert. Das Blutbild, die Gerinnungsdiagnostik und die Calcitoninwerte waren bei allen Patienten an allen Messungen im Referenzbereich.

1 p < 0.05

Fig. 2 Boxplots of hTg serum levels. The increase of hTg levels 24 hours after ablation and the following decrease three months after ablation are significant (p < 0.05).

Abb. 2 Diese Grafik zeigt einen Boxplot der hTg-Blutserum-Werte. Sowohl der Anstieg der Werte 24 Stunden nach der Ablation, als auch der darauf folgende Rückgang drei Monate nach der Ablation sind signifikant (p < 0.05).
Conclusion

HIFU treatment in benign thyroid nodules is safe, effective and easy to use. The procedure preserves thyroid gland function and there is no indication of it causing autoimmune diseases or thyrotoxicosis. Volume reduction is significant and in most cases sufficient.

Due to small sample size and missing long-term outcome, findings of this study need to be verified by larger studies.

References

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