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ORIGINAL ARTICLE

High intensity focused ultrasound in the therapy of benign thyroid nodules—first German bicentric study with long-term follow-up

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Abstract

Purpose The study evaluated high-intensity-focused ultrasound (HIFU) for benign thyroid nodules in terms of efficiency, complication rate, influence of preablative nodule size, parameters influencing the therapeutic success and hormonal-thyroid-function.

Methods Seventy-two patients with 75 nodules were treated with HIFU at 2 centers from 2014–2019. Median nodule volume was 4.4 ml (range 0.33–53). The therapeutic ultrasound probe (EchoPulse THC900888-H) generated 80–90 °C in the target tissue with 87.6–320.3 J per sonication. Nodal volume was measured at baseline and over 12 months after therapy in a retrospective bicentric-study with long-term follow-up. Hormonal-thyroid function (TSH, T3, T4) was measured before and after ablation. Complications were assessed.

Results Significant volume reduction ($p < 0.05$ Wilcoxon-signed-rank test) of thyroid nodules was 38.98% at 3 months, 37.32% at 6 months, 61.54% at 9 months and 60.66% at 12 months. Volume reduction of nodules <3 ml did not differ significantly from nodules >3 ml ($p > 0.05$ Mann–Whitney test). At 3 months solid nodules had a significant volume reduction of 52.08%, complex nodules of 32.57%, nodules treated under regional anesthesia of 33.07% and under general anesthesia of 49.47%. Hormonal-thyroid function was not influenced significantly by HIFU therapy ($p > 0.05$ Wilcoxon-signed-rank test). Complication rate was 3.8%. No long-term complications occurred.

Conclusion Significant volume reduction of thyroid nodules up to 12 months after HIFU was shown. All complications were reversible. Therapy was more efficient in solid than complex nodules and in nodules treated under general anesthesia than with regional anesthesia. Hormonal-thyroid-function was not affected.

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Keywords Benign thyroid nodules · Thermoablative procedure · Volume reduction · High intensity focused ultrasound

Introduction

Thyroid nodules are a common disease even despite adequate iodine supply [1]. In randomly selected patients, thyroid nodules are diagnosed by ultrasound in 50% of women and 30% of men [2]. Although most (85–95%) thyroid nodules are benign and malignancy can be ruled out by fine-needle biopsy [3–10], they can cause symptoms such as hoarseness, difficulty swallowing, feeling of pressure, dyspnea, hyperthyroidism, intubation difficulty during necessary surgery, and cosmetic impairment [11–13]. In this case, the nodules are usually surgically removed under general anesthesia or treated with radioiodine therapy (RIT) [14, 15]. Whereby possible complications such as bleeding, recurrent laryngeal nerve (RLN) palsy, hypothyroidism, and infections may occur [14–16]. Thermoablation as a minimally invasive procedure offers an alternative [13, 17].

During HIFU therapy, ultrasound waves are focused by a concave ultrasound probe and heat the target area to 85 °C [11, 18–20]. The heat produces irreversible coagulation

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necrosis in the nodule. Vessels supplying the nodule up to 3 mm in diameter are coagulated. Vessels larger than 4 mm are not coagulated by the ultrasound waves but transport the heat away. This is called "heat sink" and protects the nerves in the large nerve and vessel tracts (e.g., internal carotid artery and internal jugular vein) [18] Unlike other thermoablative procedures, HIFU is used only for small superficial nodules [3]. But due to its small focal point it has the advantage of not penetrating the skin and providing very focused therapy.

HIFU is not only an interesting treatment option for benign thyroid nodules. It is already used in many areas such as prostate cancer, uterine fibroids, liver metastases, and bone metastases [21, 22].

Studies have shown that HIFU [23, 24] could be a safe and effective method for treating thyroid nodules [11, 25, 26]. However, more evidence is needed [2]. To evaluate whether HIFU is an alternative treatment option for benign thyroid nodules the study assessed HIFU in terms of its effectiveness, of its parameters influencing the therapeutic success, of its impact on hormonal-thyroid function and of its complication rate in this long-term bicentric study with long-term follow-up.

Material and methods

Study design

The study is a retrospective analysis of data in a bicentric open-label study.

Study population and investigation methods

Seventy-two patients were enrolled in the study from 2014–2019 at two different treatment centers. Twenty-four patients were treated in center 1 and 48 patients were treated in center 2.

Patients with symptomatic benign thyroid nodules that caused thyrotoxicosis, swallowing problems, pain, or hoarseness and non-symptomatic benign thyroid nodules that caused cosmetic impairment were included. Only patients who did not want to undergo surgery or RIT or had contraindications to the same were included.

Patients with asymptomatic nodules, malignant nodules, nodules with retrosternal growth, and nodules in proximity to sensitive structures such as the trachea, esophagus, and recurrent nerve and carotid artery were excluded from the study. None of the patients had been treated with RIT or surgery before.

Malignancy of the nodules was excluded preinterventionally in all patients. Blood tests before and after therapy including thyroid hormone status with triiodothyronine (T3) (normal range 1.0–3.3 nmol/L), thyroxine (T4) (normal range 55–170 nmol/L), and thyrotropin (TSH) (normal range 0.3–4.0 mU/L) were performed.

Morphology, size, and location of the nodules were assessed pre- and post-ablatively by B-mode ultrasound (SonixTouch Ultrasound System, UltrasonixMedical, Richmond, Canada). Since nodule volume reduction is the decisive parameter for patient symptom improvement and thus treatment success, it was chosen as an objective outcome parameter. In previous studies the nodules had a significant volume reduction up to 12 months after HIFU [3, 27, 28]. Therefore, in the present study a followed up of 12 months after therapy was chosen. The patient population was divided into two groups based on nodule size to investigate if there is a different therapeutic success of large and small nodules. Because of the expected efficacy of therapy, the guideline value of 3 ml was chosen [3] Group A includes all nodules with a preablative volume of < 3 ml. Group B includes all nodules with a preablative volume of > 3 ml. In addition, at 3-month follow-up, the volume reduction of complex, solid, autonomous, nonautonomous nodules and patients under local or general anesthesia were separately statistically evaluated. For baseline characteristics see Table 1.

Treatment procedure

Therapy was performed at both centers using the EchoPulse ultrasound system (THC900888, Teraclion, Malakoff, France). At center 1, one doctor performed the HIFU treatments, and at center 2, 2 doctor performed the treatments. The probe of the device contained a diagnostic head with 7.5–12 MHz and a concave therapeutic head with 3 MHz. The therapeutic head focused the ultrasound beams in the target area and generated 87.6–320.3 J in the focus per session per nodule. By absorbing the acoustic energy and converting it into thermal energy, the tissue in the focus was heated. The focus was approximately 2 × 9 mm in size. The device required 10 s to heat 1 ml of the nodule.

Therapy was performed on an outpatient basis. A cooling kit was installed before each therapy. Local skin and fascia infiltration with Mecain 1%, general anesthesia, or no anesthesia was performed, depending on patient characteristics and preference. The therapeutic probe was positioned on the patient's hyperextended neck under ultrasound monitoring.

The system automatically created a sonication map of the tissue. The doctor defined on the map the area to be treated and the structures to be protected. Test pulses of approximately 4 s were emitted before starting therapy pulses. The system performed the ablation in a spiral pattern automatically. Figure 1 shows a nodule before and after therapy.

To ensure patient safety, following safety distances ware selected: 0.5 cm from the skin, 0.3 cm from the trachea, and

Table 1 Baseline characteristics of benign thyroid nodules <3 ml and >3 ml treated with HIFU

	Number of patients	Preablative nodule size	Average patient age	Nodule morphology		Indication for therapy		Type of anesthesia during HIFU		Applied Energy per nodule volume [kJ/ml]	Complication rate	Volume reduction after HIFU
				Complex	Solid	Nodule autonomy	Pressure symptoms	General anesthesia	Regional anesthesia			
Group A (<3 ml nodule size)	23	1.29 ml (range 0.33−2.8 ml)	54 (26–82)	14	13	8	15	11 (47.83%)	12 (52.17%)	3.96 kJ/ml	0%	3 months: 40% ($p < 0.008$) 6 months: 37.5% ($p < 0.001$) 9 months: 60.66% ($p > 0.05$) 12 months: 60,66% ($p > 0.05$)
Group B (>3 ml nodule size)	49	6.83 ml (range 3.3–53 ml)	53 (24–85)	19	26	13	36	31 (63.27%)	18 (36.73%)	1.18 kJ/ml	6.12%	3 months: 37.14% ($p < 0.001$) 6 months: 37.14% ($p = 0.001$) 9 months: 71.21% ($p = 0.031$) 12 months: 63.93 ($p > 0.05$)

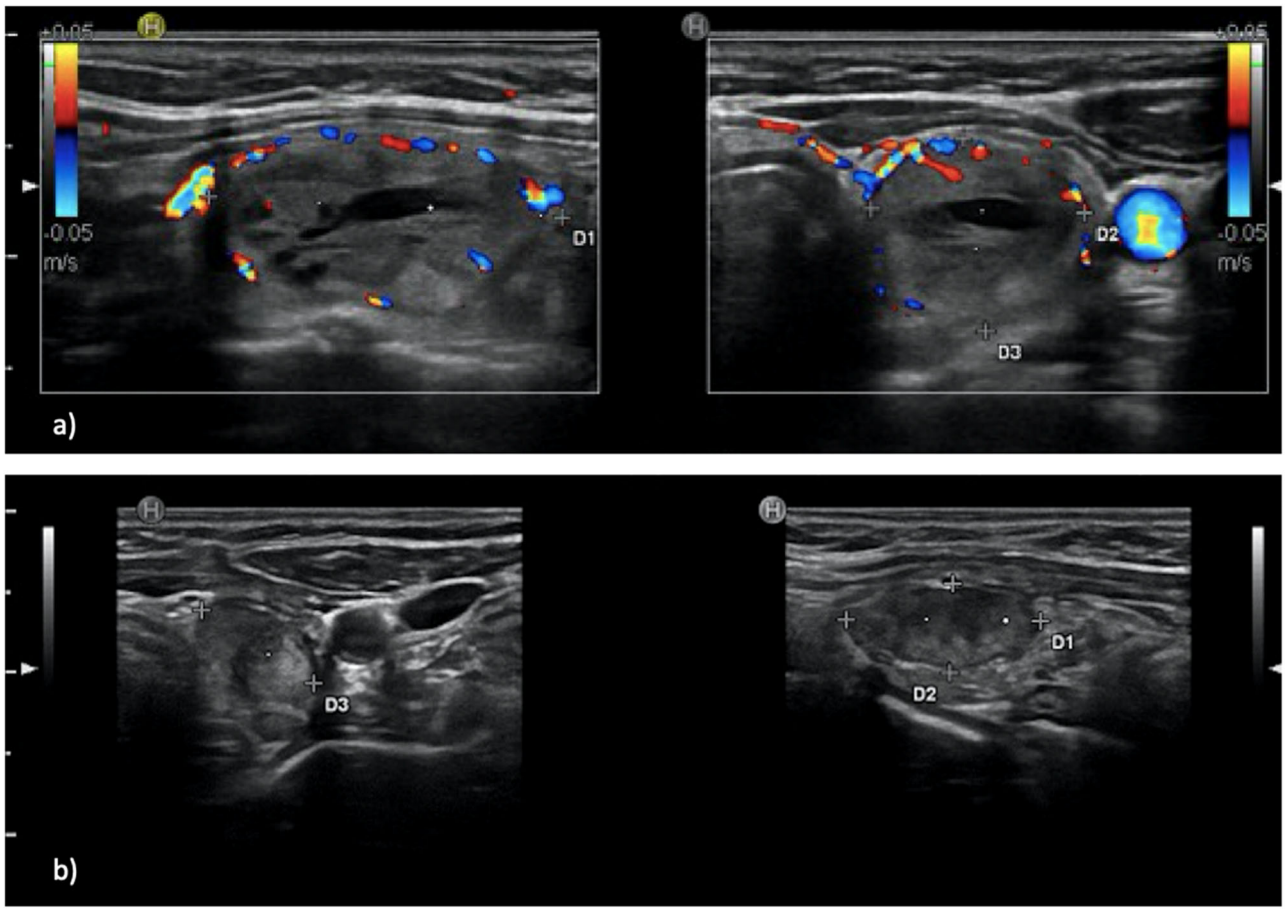

Fig. 1 **a** Screen capture of ultrasound examination before HIFU therapy (Diameter 1 [D1]: 31.8 mm, D2 19.1 mm, D3 17.4 mm, nodule volume: 5.55 ml). **b** Screen capture of ultrasound examination after HIFU therapy (D1: 24.1 mm, D2 11.1 mm, D3 16.6 mm, nodule volume: 2.32 ml)

0.2 cm from the carotid artery. The EchoPulse system is equipped with a laser that—in case the patient moves—detects deviations of 1 mm or more between the planned point and the actual position of the probe. If the laser registered a change in position, the system stopped immediately. If the treating doctor noticed a deviation or tissue damage such as heat bubbles in ultrasound, he or she could manually intervene at any time [3, 18, 25]. After treatment, patients were observed for one hour and then discharged.

Statistical analysis

Because a normal distribution could not be assumed, non-parametric testing was performed. Preablative nodal volume and nodal volumes at 3, 6, 9, and 12 months after therapy were compared using the Wilcoxon-signed-rank test. Percentage nodal volume reductions of group A and B at 3, 6, and 12 months were compared using the Mann–Whitney test. The volume reduction of complexes and solid, autonomous and nonautonomous nodules, and nodules with therapy under local and general anesthesia was analyzed with the Wilcoxon-signed-rank test. Correlation between delivered energy and volume reduction was tested using Kendall tau. Laboratory parameters before and after therapy were compared using the Wilcoxon-signed-rank test. P values < 0.05 were considered statistically significant. Therapeutic success was defined as volume reduction of more than 50% compared to baseline volume [3, 15, 25]

Results

As shown in Table 1, 72 patients (59 women) with a total of 75 nodules were included in the study. One patient had 2 nodules, one patient had 3 nodules, and 70 patients had one nodule. Average age of patients was 53 years (range 24–85). Preablative total volume of treated thyroid nodules was in median 4.4 ml (range 0.33–53 ml, $n = 75$). Group A had a median volume of 1 ml (range 0.33–2.8 ml, $n = 24$). Group B had a median volume of 6.83 ml (range 3.3–53 ml, $n = 51$). 58,33% ($n = 42$) of patients were treated under general anesthesia and 41.67% ($n = 30$) of patients were

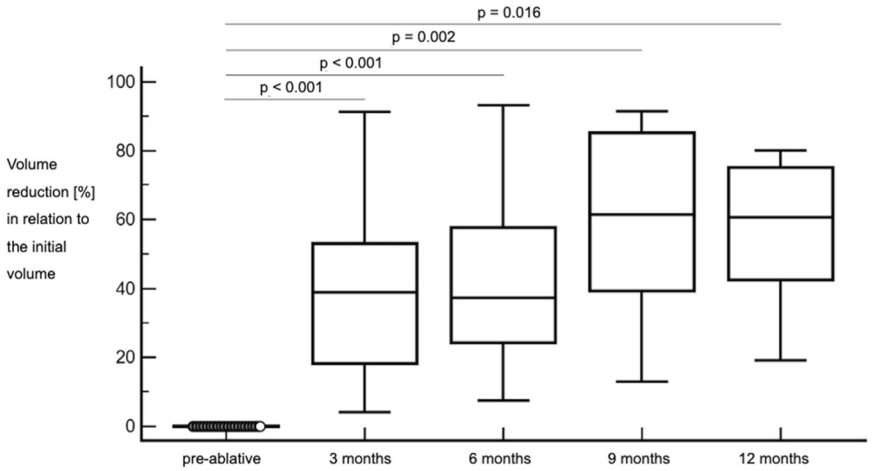

Fig. 2 Median volume reduction of benign thyroid nodules compared to initial volume 3, 6, 9 and 12 months after therapy. A volume reduction with $p < 0.05$ in the Wilcoxon-signed-rank test was considered significant

Table 2 The table shows how many patients with benign thyroid nodules had nodule volume reductions of 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100% at the 3-, 6-, 9-, and 12-month follow-up time points, after high-intensity focused ultrasound (HIFU) therapy

Volume reduction of benign thyroid nodules after HIFU	0–10%	10–20%	20–30%	30–40%	40–50%	50–60%	60–70%	70–80%	80–90%	90–100%
3 months after HIFU	3 patients	6 patients	1 patient	7 patients	4 patients	1 patients	4 patients	2 patients	0 patients	1 patient
6 months after HIFU	1 patient	4 patients	4 patients	4 patients	3 patients	1 patient	2 patients	2 patients	0 patients	1 patient
9 months after HIFU	0 patients	1 patient	0 patients	2 patients	0 patients	0 patients	2 patients	0 patients	3 patients	1 patient
12 months after HIFU	0 patients	1 patient	0 patients	1 patient	0 patients	1 patient	1 patient	2 patients	1 patient	0 patients

treated under local anesthesia. 29% ($n = 21$) patients had nodal autonomy and 71% ($n = 51$) patients had pressure symptoms. 54% ($n = 39$) of the nodules were solid and 46% ($n = 33$) of the nodules were complex.

As shown in Fig. 2, the overall population had a median volume reduction of 38.98% (range 4–91.16%, $p < 0.001$) at 3 months, 37.32% (range 7.36–93.2%, $p < 0.001$) at 6 months, 61.54% (range 12.88–93.2%, $p = 0.002$) at 9 months and 60.66% (range 19.13–93.2%, $p = 0.016$) at 12 months. Detailed number of nodules with their percentage volume reduction is shown in Table 2. Statistical analysis was performed using the Wilcoxon-signed-rank test. Significant volume reduction was observed up to 12 months. Therapeutic success (>50% volume reduction of nodules after HIFU) was achieved at 9 months follow-up.

As shown in Fig. 3, the volume reductions of group A (<3 ml) and B (>3 ml) did not differ significantly in the Mann–Whitney test. For group A, a median volume reduction of 40% (range 15–62.5%, $p < 0.008$) was observed at 3 months, 37.5% (range 16.67–75%, $p < 0.001$) at 6 months, 60.66% (range 12.88–89.01%, $p > 0.05$) at 9 months and 60.66% (range 19.13–73.91%, $p > 0.05$) at 12 months. For group B, a median volume reduction of 37.14% (range: 4.03–91.16%, $p < 0.001$) was observed at 3 months, 37.14% (range 7.36–93.2%, $p = 0.001$) at 6 months, 71.21% (range 37.35–93.2%, $p = 0.031$) at 9 months and 63.93% (range 39.39–93.2%, $p > 0.05$) at 12 months. In group A and in group B the therapeutic success was achieved after 9 months.

Autonomous nodules had a volume reduction of 44.73% ($n = 10$, $p = 0.002$) after 3 months. Nodules without autonomy had a volume reduction of 33.26% ($n = 18$, $p < 0.0001$) after 3 months. Therapeutic success was not achieved.

Patients with local anesthesia had a volume reduction of 33.07% ($n = 16$, $p < 0.0001$) after 3 months. Patients under anesthesia had a volume reduction of 49.47% ($n = 15$, $p = 0.0001$) after 3 months. Under local anesthesia the therapeutic success was not achieved. Under anesthesia it was missed slightly.

Complex nodules had a volume reduction of 32.57% ($n = 12$, $p = 0.0005$) at 3 months. Solid nodules had a volume reduction of 52.08% ($n = 15$, $p = 0.0001$) after 3 months. Solid nodules achieved therapeutic success, complex nodules did not.

The delivered energy per ml of the nodule did not correlate significantly ($p > 0.05$) with postablative volume reduction.

As shown in Fig. 4, there was no significant effect of HIFU therapy on serum TSH levels ($p > 0.05$ by Wilcoxon-signed-rank test). 4 patients were latently hyperthyroid before therapy. After therapy, only 2 patients were latently hyperthyroid.

The overall complication rate was 3.8%. Postintervention, transient left RNL palsy occurred in two patients. In

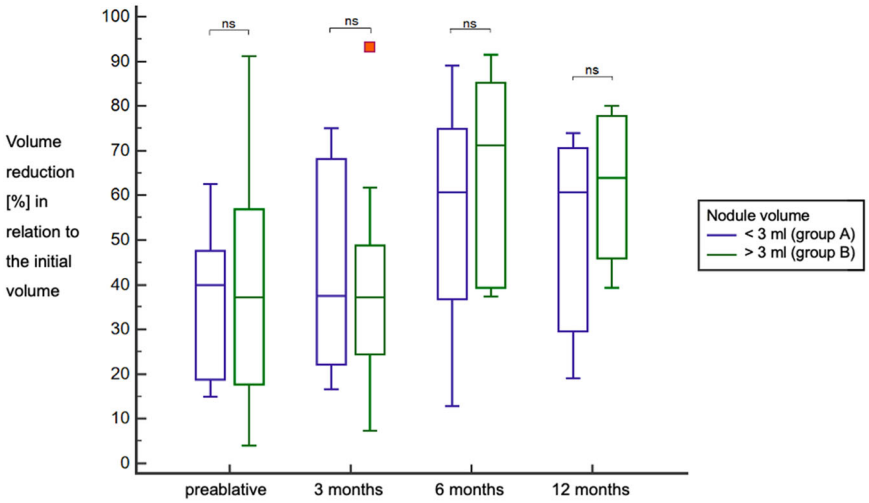

Fig. 3 Comparison of median volume reduction between benign thyroid nodules with an initial nodule volume <3 ml and >3 ml preablatively and at the time points 3, 6, and 12 months after therapy. $P < 0.05$ by Mann–Whitney test was considered significant. There was no significant difference in volume reductions at any time point

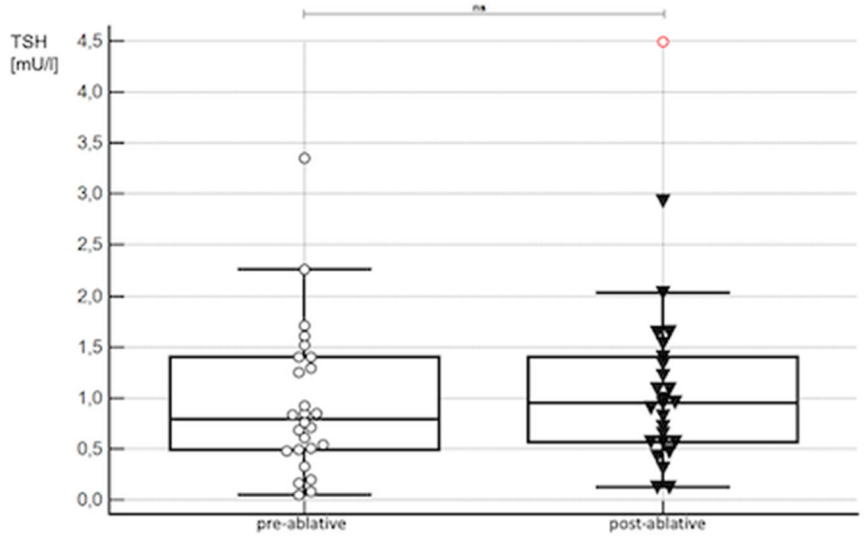

Fig. 4 Effects of HIFU of benign thyroid nodules on hormonal-thyroid-function. Preablative and postinterventional serum TSH levels compared with Wilcoxon-sign-rank test. With $p > 0.05$, no significant change is presented

both patients, the vocal cords were freely movable again after two months of speech therapy. The third patient had a transient right vocal cord weakness 3 months after an initially regular postinterventional result, which was also reversible with speech therapy. All three patients had nodules larger than 3 ml.

Discussion

The presented bicentric study with long-term follow-up demonstrates that HIFU produces significant volume reduction of benign nodules and that hormonal-thyroid function is not affected by the procedure.

Therapeutic success - more than 50% volume reduction compared to baseline volume—was achieved after 9 months. Thus, HIFU is an effective treatment alternative for benign thyroid nodules. Volume reduction achieved by HIFU was greatest in the first 3 months. This is due to coagulation necrosis after heating the nodules. After the initial volume reduction within the first 3 months, the volume reduction decreased. Other studies confirm this observation [3, 11, 26, 28]. Thus, volume reduction in the first 3 months indicates whether HIFU was successful or not.

All patients had volume reduction of the nodules after HIFU therapy. However, the volume reduction was subject to a wide range. Parameters influencing the therapeutic success of HIFU and contributing to the wide range of volume reduction were investigated in the presented study. The study shows no significant correlation between the delivered energy [kJ] per milliliter [ml] of the nodules and the postablative volume reduction. This indicates that other parameters influence the therapeutic outcome. The study

also shows that solid nodules achieved the therapeutic success of 50% volume reduction, while complex nodules did not. Furthermore, nodules under general anesthesia missed the therapeutic success only narrowly and nodules with local anesthesia missed it widely. Autonomous and nonautonomous nodules didn´t achieved therapeutic success after 3 months. The study indicates that nodal morphology and type of anesthesia during therapy have an influence on the therapeutic success of HIFU of benign thyroid nodules. Solid nodules and nodules treated under general anesthesia respond better to therapy. However, this should be confirmed in further studies.

The complication rate was at 3.8%. However, all complications were transient. Irreversible complications did not occur. All observed complications involved the posterior RLN. This is the only vulnerable structure that is difficult to visualize by ultrasound. To avoid compromising the deep lying RLN, the HIFU device allows only a certain depth of therapy. If there are anatomic abnormalities, the RLN may lie more anteriorly and be damaged. Moreover, in the present study, the RLN was damaged mainly during therapy of large nodules. A big nodule size increases the probability that the nodule is located near the nerve and damaged during therapy. The lack of complications on other vulnerable structures can be explained by their good visibility on ultrasound. They are protected by small ablation zones and automatic safety distances.

In alternative procedures for the removal of benign thyroid nodules, RNL palsy occurs with similar frequency as in HIFU. Surgery causes transient RLN palsy in 5–11% of cases and permanent RLN palsy in 1–4% of cases [27–29]. With other thermoablative procedures, such as RAF, RLN palsy has been observed in 0–8.3% of cases [30, 31]. With MWA it has been observed in 9.1% of cases [32]. Therefore, HIFU does not have a higher risk of causing RLN palsy than other therapy options. In addition, unlike thyroid surgery, HIFU has no risk of other side effects such as bleeding, infection, hypothyroidism [14–16]. Continuous intraoperative neuromonitoring (CIONM) would be a way to reduce the risk of RLN palsy after HIFU. This is already used in thyroid surgery and RFA [30, 33, 34].

To be able to intervene quickly in case of possible side effects such as vocal cord paresis, a 3–6-month follow-up should be performed after therapy. If vocal cord paresis is treated with speech therapy, it is reversible.

Other studies observed that large nodules had a smaller volume reduction relative to initial volume than small nodules. The patient moves more during a long treatment period and any movement interrupts the ongoing treatment. An only partially heated lesions and thus a smaller ablation zone result [3, 18].

However, in this study, no significant difference was observed between the volume reduction of large and small nodules. The patients with larger nodules included in the study were more frequently treated under general anesthesia than the patients with small nodules. General anesthesia minimizes patient movement, resulting in fewer incomplete lesions despite long treatment times. Presumably as a result, patients with large nodules in the study did not have a lower volume reduction than patients with small nodules treated with local anesthesia.

Another option to optimize HIFU treatment of large nodules would be to treat patients in multiple sessions so that the individual sessions are shorter. For multiple sessions, HIFU is better suited than other termoablative procedures because it is noninvasive and therefore can be repeated as often as necessary.

Based on the analysis of TSH, T3, and T4, this study showed that HIFU had no significant effect on hormone function. This result is consistent with other studies [25, 35]. In contrast to thyroid surgery and RIT, no general risk of inducing thyrotoxicosis or bleeding was observed with HIFU. The other termoablative procedures, like surgery and RIT, have the risk of inducing transient thyrotoxicosis. Because of large ablation areas, they deliver much more energy to the surrounding tissue and have a greater risk of damaging too much enclosed tissue [16, 18, 36]. The fact that no thyrotoxicosis occurred with HIFU is due to the smaller focus and constant cooling.

Thus, HIFU induces significant volume reduction in benign thyroid nodules and does not affect hormonal-thyroid function, in contrast to thyroid surgery and RIT. The complication rate was 3.8%. HIFU has no higher risk of RLN palsy than RFA and thyroid surgery. In addition, no other side effects were observed. It should be further evaluated how to optimize the protection of RLN during HIFU therapy.

Conclusion

The study shows that HIFU is a safe and effective alternative for treatment of benign thyroid nodules in terms of both efficacy and potential side effects compared to other treatment options. It was shown that HIFU not only achieves significant volume reduction in benign thyroid nodules >3 ml and <3 ml but also has the advantage of preserving thyroid function. HIFU Therapy was more efficient in solid than complex nodules and in nodules treated under general anesthesia than with regional anesthesia. A complication rate of 3.8% occurred. All complications were transient.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by C.V., A.F. and H.K. The first draft of the manuscript was written by C.V., A.F. and H.K. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date 16.06.2020/No. 2020-1728-evBO).

Informed consent Informed consent was obtained from all individual participants included in the study.

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