Aus dem Fachbereich Medizin
der Johann Wolfgang Goethe-Universität
Frankfurt am Main

aus dem
Zentrum der Radiologie
Klinik für Nuklearmedizin
Direktor: Prof. Dr. Frank Grünwald

betreut am
Bürgerhospital Frankfurt am Main
Deutsches Zentrum für Thermoablation e.V.
Lehrkrankenhaus Universitätsklinikum Frankfurt

Thermoablation von Schilddrüsenknoten

Dissertation
zur Erlangung des Doktorgrades der Medizin
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vorgelegt von
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Inhaltsverzeichnis

Zusammenfassung

Im Rahmen dieser publikationsbasierten Dissertation wurden drei wissenschaftliche Arbeiten veröffentlicht. Als Erstautorenschaft wurde 2022 die Arbeit “Effectiveness of High-intensity Focused Ultrasound (HIFU) Therapy of Solid and Complex Benign Thyroid Nodules - A Long-term Follow up Two-center Study.” im Journal “Experimental and Clinical Endocrinology & Diabetes” veröffentlicht. Im Folgenden wird der Inhalt dieser Arbeit dargelegt. Ein kurzer Überblick über die Ergebnisse der anderen beiden mitpublizierten Arbeiten findet sich im Kapitel „Weitere Ergebnisse der Arbeitsgruppe“.

Durch die hohe Prävalenz benigner Schilddrüsenknoten sind deren Behandlungsalternativen von großem wissenschaftlichem Interesse. Dabei bildet die nebenwirkungsarme, minimalinvasive Thermoablation mittels high-intensity focused ultrasound (HIFU) eine attraktive Alternative zu herkömmlichen Verfahren wie der Schilddrüsenchirurgie oder der Radioiodtherapie. Bei der HIFU-Echotherapie werden die Schilddrüsenknoten auf 80 - 90 Grad Celsius erhitzt, sodass eine irreversible Koagulationsnekrose entsteht. Um den Therapieprozess und die Indikationsstellung von HIFU bei benignen Schilddrüsenknoten zu optimieren, ist es notwendig, genaue Studien durchzuführen.

Ziel der vorliegenden bizentrischen Langzeitstudie war, die Effektivität von HIFU-Echotherapien bei benignen Schilddrüsenknoten zu evaluieren und erstmalig den Einfluss der Knotenmorphologie auf den Therapieerfolg zu untersuchen. Vor der Therapie und in regelmäßigen Intervallen nach der Therapie wurden die Größe und die Morphologie der Schilddrüsenknoten mittels Ultraschall dokumentiert. In der retrospektiven Studie wurden Daten von 58 Patienten ausgewertet. Dabei wurde die Gesamtpopulation in eine Gruppe mit soliden und in eine Gruppe mit komplexen Knoten eingeteilt. Die durchschnittliche prozentuale Volumenreduktion in jeder Gruppe wurde mit dem Wilcoxon-Signed-Rank Test statistisch analysiert.

Die Gesamtpopulation zeigte eine Volumenreduktion der zuvor abladierten Knoten von 38.86 % nach 3 Monaten (Spannweite: 4.03 % - 91.16 %, $p < 0.0001$, $n = 25$), 42.7 % nach 6 Monaten (Spannweite: 7.36 % - 93.2 %, $p < 0.0001$, $n =$

18), 62.21 % nach 9 Monaten (Spannweite: 12.88 % - 93.2 %, p = 0.0078, n = 8) und 61.42 % nach 12 Monaten (Spannweite: 39.39 % - 93.2 %, p > 0.05, n = 4). Die soliden Knoten hatten eine Volumenreduktion von 49.98 % nach 3 Monaten (Spannweite: 4.03 % - 91.16 %, p = 0.0001, n = 15), 46.40 % nach 6 Monaten (Spannweite: 7.36 % - 93.2 %, p = 0.001, n = 11), 65.77 % nach 9 Monaten (Spannweite: 39.39 % - 93.2 %, p = 0.0156, n = 7) und 63.88 % nach 12 Monaten (Spannweite: 39.39 % - 93.2%, p > 0.05, n = 2). Komplexe Knoten hatten eine Volumenreduktion von 35.2 % nach 3 Monaten (Spannweite: 5.85 % - 68.63 %, p = 0.002, n = 10), 36.89 % nach 6 Monaten (Spannweite: 12.23 % - 68.63 %, p = 0.0156, n = 7) und 63.64 % nach 12 Monaten (Spannweite: 52,38 % - 73.91 %, p > 0.05, n = 2).

In der vorliegenden bizentrischen Langzeitstudie wurde deutlich, dass HIFU-Echotherapie eine effektive Behandlungsoption benigner Schilddrüsenknoten ist. Erstmalig gezeigt wurde der Trend, dass solide Knoten besser auf HIFU-Echotherapie ansprechen als komplexe Knoten.

Anhand der gewonnenen Ergebnisse und der neuen Erkenntnisse zum Einfluss der Knotenmorphologie auf die HIFU-Echotherapie benigner Schilddrüsenknoten kann HIFU als Therapieoption besser bewertet werden. Eine differenziertere Indikationsstellung in Bezug auf solide und komplexe Knoten wird ermöglicht und die HIFU-Echotherapie kann gegen andere thermoablative Verfahren abgewogen werden.

Summary

As part of this publication-based dissertation, three scientific papers were published. As first authorship, the paper "Effectiveness of High-intensity Focused Ultrasound (HIFU) Therapy of Solid and Complex Benign Thyroid Nodules - A Long-term Follow up Two-center Study." was published in the journal "Experimental and Clinical Endocrinology & Diabetes" in 2022. The following will now outline the contents of this paper. A brief overview of the results of the other two co-published papers can be found in the chapter "Weitere Ergebnisse der Arbeitsgruppe".

Treatment alternatives for benign thyroid nodules are of great scientific interest due to the high prevalence of thyroid nodules. Minimally invasive thermoablation with few side effects, such as High-intensity focused ultrasound (HIFU), is an attractive alternative to conventional procedures such as thyroid surgery or radioiodine therapy. During HIFU, thyroid nodules were heated to 80 - 90 degrees Celsius, resulting in irreversible coagulation necrosis.

In order to optimize the therapeutic process and indication of HIFU for benign thyroid nodules, it is necessary to perform accurate studies. The aim of the presented study was to evaluate the efficacy of HIFU in benign thyroid nodules and to investigate the influence of nodal morphology on the therapeutic outcome. Before and at regular intervals after therapy, the size and morphology of the thyroid nodules were documented by ultrasound. In this retrospective long-term bicentric study, data from 58 patients were analyzed. Total population was divided into a group with solid nodules and a group with complex nodules. The average percent volume reduction in each group was statistically analyzed using the Wilcoxon signed-rank test.

The overall population had a volume reduction of the treated lesions of 38.86 % at 3 months (range: 4.03 % - 91.16 %, $p < 0.0001$, $n = 25$), 42.7 % at 6 months (range: 7.36 % - 93.2 %, $p < 0.0001$, $n = 18$), 62.21 % at 9 months (range: 12.88 % - 93.2 %, $p = 0.0078$, $n = 8$), and 61.42 % at 12 months after intervention (range: 39.39 % - 93.2 %, $p > 0.05$, $n = 4$). Solid nodules had a volume reduction

of 49.98 % at 3 months (range: 4.03 % - 91.16 %, p = 0.0001, n = 15), 46.40 % at 6 months (range: 7.36 % - 93. 2 %, p = 0.001, n = 11), 65.77 % at 9 months (range: 39.39 % - 93.2 %, p = 0.0156, n = 7), and 63.88 % at 12 months after treatment (range: 39.39 % - 93.2 %, p > 0.05, n = 2). Complex nodules had a volume reduction of 35.2 % at 3 months (range: 5.85 % - 68.63 %, p = 0.002, n = 10), 36.89 % at 6 months (range: 12.23 % - 68.63 %, p = 0.0156, n = 7), and 63.64 % at 12 months after treatment (range: 52.38 % - 73.91 %, p > 0.05, n = 2).

HIFU was shown to be an effective treatment option of benign thyroid nodules. For the first time, it has been demonstrated that solid nodules respond better to HIFU echotherapy than complex nodules. Based on the results obtained, HIFU can be better evaluated as a treatment option. A more differentiated indication with respect to solid and complex nodules is made possible and HIFU-echotherapy can be compared with other thermoablative procedures.

Abkürzungsverzeichnis

RIT	Radioiodtherapie
HIFU	High-intensity focused ultrasound
T3	Trijodthyronin
T4	Thyroxin
TSH	Thyreotropin
MWA	Mikrowellenablation
RFA	Radiofrequenzablation
FNAB	Feinnadelaspirationsbiopsie

Übergreifende Zusammenfassung

1. Einleitung

Durch die hohe Prävalenz benigner Schilddrüsenknoten ist deren Therapie von großer klinischer Relevanz. Schilddrüsenknoten treten bei 20 % der 20 – 79-Jährigen und bei 30 – 50 % der 70 – 74-Jährigen auf.[1] Eine Differenzierung zwischen benignen und malignen Knoten ist durch Dopplersonographie, Szintigraphie und durch zytologische Untersuchungen mittels Feinnadelpunktionen gut möglich. 85 - 95 % der Knoten sind benigne und müssen nur im Falle einer Symptomatik therapiert werden. Klassischerweise werden Schilddrüsenknoten mittels Schilddrüsenchirurgie oder Radioiodtherapie (RIT) behandelt, wobei Blutungen, Rekurrenzparesen, eine Hypothyreose und Infektionen auftreten können.[2, 3, 4] In Deutschland werden jährlich insgesamt ca. 80 000 Schilddrüsenoperationen durchgeführt, davon 59 000 Operationen aufgrund einer Struma nodosa.[2, 3, 5] Von den operierten Schilddrüsenknoten ist jedoch nur jeder 15. Knoten maligne.[5]

Ein symptomatischer gutartiger Knoten muss nicht zwingend chirurgisch entfernt werden. Thermoablative Verfahren stellen durch Minimalinvasivität, weniger Nebenwirkungen und mehr Patientenkomfort eine attraktive Alternative dar.[6] Es werden Risiken einer Operation vermieden und es kann ambulant therapiert werden.

Unter den thermoablativen Verfahren ist high-intensity focused ultrasound (HIFU) das am wenigsten invasivste und das zugleich präziseste Verfahren.[7] Dabei wird der Schilddrüsenknoten auf 80 - 90 Grad Celsius erhitzt, sodass eine irreversible Koagulationsnekrose entsteht und der Knoten durch das Immunsystem abgeräumt wird. Verschiedene Studien konnten zeigen, dass HIFU eine sichere und effektive Methode ist, benigne Schilddrüsenknoten zu behandeln.[8-15] Jedoch wird in den aktuellen Leitlinien weitere Evidenz großer Langzeitstudien gefordert, bevor HIFU als Therapieoption bei soliden und komplexen Knoten empfohlen werden kann.[16, 17] Die Datenlage zum Einfluss der Knotenmorphologie auf die Effektivität der HIFU-Echotherapie ist gering. Eine gute Evidenz dahingehend ist notwendig, um eine differenziertere Indikationsstellung in Bezug auf solide und

komplexe Knoten zu ermöglichen und die HIFU-Echotherapie gegen andere thermoablative Verfahren abzuwägen.
In der vorliegenden Arbeit wurden die Effektivität der HIFU-Echotherapie und der Einfluss der Knotenmorphologie auf den Therapieerfolg in einer retrospektiven, baseline kontrollierten, bizentrischen Langzeitstudie analysiert.

2. Fragestellung

- Erreicht die HIFU-Echotherapie eine signifikante Volumenreduktion bei benignen Schilddrüsenknoten?
- Wie ist die Effektivität der HIFU-Echotherapie bei soliden und komplexen Schilddrüsenknoten?
- Ist die HIFU-Echotherapie bei soliden und komplexen Knoten ein sicheres Verfahren zur Behandlung von benignen Schilddrüsenknoten?

3. Darstellung der Publikation

3.1. Material und Methoden

Das in der Studie verwendete HIFU-Gerät besitzt ein CE-Zertifikat gemäß den Anforderungen des Medizinproduktegesetzes. Die Sicherheit und Wirksamkeit der Therapie wurde bereits in klinischen Studien nachgewiesen.[8,10,13] Die Datenauswertung im Rahmen der retrospektiven Doktorarbeit wurde nach dem Erhalt des Ethikvotums der Ethik-Kommission (Geschäfts-Nr. 2852, Zeichen: 2020-1728-evBO) begonnen.
Es wurde nach einer ausführlichen Literaturrecherche eine Arbeitshypothese erstellt. Die Daten wurden erhoben, strukturiert und vervollständigt. Nach Abschluss der Datenerhebung wurden die Daten statistisch mittels MedCalc analysiert und die Arbeitshypothese wurde überprüft. Drei Paper wurden eingereicht und mehrere Peer-Review-Verfahren wurden durchgeführt. Anschließend wurde unter anderem das hier vorliegende Paper publiziert.

3.1.1. Patienten

Von 2014 bis 2019 wurden insgesamt 75 Patienten in zwei Behandlungszentren mittels HIFU behandelt. 27 Patienten wurden dabei in Zentrum 1 (Universitätsklinikum Frankfurt am Main) und 48 Patienten in Zentrum 2

(Bürgerhospital Frankfurt am Main) behandelt. Es wurden nur die Patienten, bei denen eine Follow-up Untersuchung zu den Zeitpunkten 3, 6, 9 und 12 Monaten stattgefunden hatte, in die Studie eingeschlossen. Zudem wurden nur Patienten mit symptomatischen Knoten (Heiserkeit, Schluckprobleme, Schmerzen oder ästhetischen Beeinträchtigungen), die eine Operation oder RIT verweigerten bzw. Kontraindikationen gegen dieselben hatten, eingeschlossen.

Kontraindikationen gegen die HIFU-Therapie und somit gegen die Aufnahme in die Studie waren Malignität der Knoten, Nervenanomalien des Patienten, retrosternales Wachstum der Knoten, asymptomatische Knoten, sowie die Nähe zu wichtigen Strukturen wie der Luftröhre, der Speiseröhre und der Arteria carotis.

Dementsprechend wurden insgesamt 58 Patienten (50 Frauen und 8 Männer, durchschnittliches Alter: 52 Jahre, Alterspanne: 24 – 85 Jahre) in die Studie eingeschlossen. Von diesen 58 Patienten wurden 23 Patienten in Zentrum 1 (Universitätsklinikum) und 35 Patienten in Zentrum 2 (Bürgerhospital) behandelt. Präablativ wurde bei allen Patienten eine Malignität ausgeschlossen, sowie Laboruntersuchungen (Trijodthyronin [T3], Thyroxin [T4], Thyreotropin [TSH]) durchgeführt.

Vor der HIFU-Echotherapie sowie in regelmäßigen Abständen nach der Therapie wurden bei allen Knoten Lage, Volumen und Echogenität mittels B-Mode-Ultraschall (Sonix Touch Ultrasound System, Ultrasonix Medical Corporation, Richmond, Kanada) dokumentiert.

Knoten mit einem Flüssigkeitsanteil > 50 % aber ≤ 90 % des Knotenvolumens wurden als komplexe Knoten definiert. Knoten mit < 50 % Flüssigkeitsanteil wurden als solide Knoten definiert.[18, 19]

		Insgesamt	Komplexe Knoten	Solide Knoten
Patientenzahl		58	23	35
Patientenalter [Jahre]		52 (24 – 85)	52 (26 – 82)	53 (24 – 85)
Medianes Volumen [ml]		4,4 (0,13 - 23,1)	4,7 (0,2 - 23,1)	4.3 (0,13 - 17)
Knotenlokalisation	Rechter Lappen	32	15	17
	Linker Lappen	24	7	17
	Isthmus	2	1	1
HIFU-Indikation	Autonomie	26	9	17
	Drucksymptome	32	14	18

3.1.2.HIFU-Gerät und Prozedere

Die HIFU-Echotherapie wurde in beiden Zentren mit dem EchoPulse-Gerät (Teraclion, Malakoff, Frankreich) durchgeführt. Das in der Studie verwendete HIFU-Gerät besitzt ein CE-Zertifikat gemäß den Anforderungen des Medizinproduktegesetzes. Es besteht aus einem therapeutischen Ultraschallkopf (3 MHz) und einem diagnostischen Ultraschallkopf. Der konkave therapeutische Kopf erhitzt mit 87,6 bis 320,3 J pro Sitzung einen 2 x 9 mm großen Brennpunkt auf 80 - 90 Grad Celsius. Zur Erhitzung eines Milliliter des Knötchens benötigt das Gerät etwa 10 Sekunden. Präablativ wird eine Voxelkarte des Gewebes erstellt, auf der der zu therapierende Bereich und die zu schützenden Strukturen vom Arzt definiert werden.

Das Gerät nutzt einen Laser, um Abweichungen zwischen dem geplanten Brennpunkt und der tatsächlichen Position der Sonde zu erkennen. Wird das Muster verschoben, stoppt das Gerät automatisch den Vorgang und die Einstellung kann erneut vorgenommen werden. Zugleich überwacht der Arzt den Therapieprozess mit einer diagnostischen Ultraschallsonde. Er kann jederzeit manuell eingreifen und den Prozess korrigieren.[7, 8, 10, 12, 14, 15, 20-22]

3.1.3. Wirksamkeitsbewertung und Follow-up

Um die Effektivität von HIFU bei soliden und komplexen Knoten zu untersuchen, wurde die Volumenreduktion der Knoten statistisch analysiert. Die Volumenreduktion ist der entscheidende Parameter für die Symptombesserung des Patienten und somit für den Therapieerfolg.
Vorherige Studien haben eine signifikante Volumenreduktion der Knoten bis zu 12 Monate nach einer HIFU-Echotherapie festgestellt.[10] Daher wurde in der vorliegenden Studie ein Follow-up von 12 Monaten gewählt. Die Volumenreduktion der Knoten wurde drei, sechs, neun und zwölf Monate nach der Therapie untersucht und dokumentiert. Da es zum neunmonatigen Follow-up nur wenige Untersuchungen von komplexen Knoten gab, wurde dieses nur bei soliden Knoten und bei der Gesamtpopulation der Studie analysiert.

3.1.4. Statistische Analyse

Die statistische Analyse wurde mit MedCalc durchgeführt. Die statistische Prüfung war nicht parametrisch, da eine Normalverteilung nicht angenommen werden konnte. Die Unterschiede zwischen dem Volumen vor der Ablation und den Zeitpunkten drei, sechs, neun und zwölf Monate nach der Ablation wurden mit dem Wilcoxon-Signed-Rank-Test verglichen. Ergebnisse mit $p < 0,05$ wurden als signifikant gewertet.

3.2. Ergebnisse

Im Wilcoxon-Signed-Rank-Test ergab sich bei der Gesamtpopulation eine durchschnittliche Volumenreduktion nach drei Monaten von 38,86 % (Spannweite: 4,03 % - 91,16 %, $p < 0,0001$, $n = 25$), nach sechs Monaten von 42,7 % (Spannweite: 7,36 % - 93,2 %, $p < 0,0001$, $n = 18$), nach neun Monaten von 62,21 % (Spannweite: 12,88 % - 93,2 %, $p = 0,0078$, $n = 8$) und nach 12 Monaten von 61,42 % (Spannweite: 39,39 % - 93,2 %, $p > 0,05$, $n = 4$).
Es wurde zum drei-, sechs- und neunmonatigen Follow-up eine signifikante Volumenreduktion mit $p < 0,05$ im Wilcoxon-Signed-Rank-Test festgestellt.

Solide Knoten zeigten nach drei Monaten eine durchschnittliche Volumenreduktion von 49,98 % (Spannweite: 4,03 % - 91,16 %, p = 0,0001, n = 15), 46,40 % nach sechs Monaten (Spannweite: 7,36 % - 93,2 %, p = 0,001, n = 11), 65,77 % nach neun Monaten (Spannweite: 39,39 % - 93,2 %, p = 0,0156, n = 7) und 63,88 % nach zwölf Monaten (Spannweite: 39,39 % - 93,2 %, p > 0,05, n = 2).
Es wurde bei den Patienten mit soliden Knoten eine signifikante Volumenreduktion zum drei-, sechs- und neunmonatigen Follow-up festgestellt (p < 0,05).
Bei soliden Knoten betrug die durchschnittliche Dauer der Energieanwendung 2340 s, d. h. 39 Minuten.

Komplexe Knoten zeigten nach drei Monaten eine durchschnittliche Volumenreduktion von 35,2 % (Spannweite: 5,85 % - 68,63 %, p = 0,002, n = 10), 36,89 % nach sechs Monaten (Spannweite: 12,23 % - 68,63 %, p = 0,0156, n = 7) und 63,64 % nach 12 Monaten (Spannweite: 52,38 % - 73,91 %, p > 0,05, n = 2).
Es wurden zum drei- und sechsmonatigen Follow-up eine signifikante Volumenreduktion festgestellt.
Bei komplexen Knoten betrug die durchschnittliche Dauer der Energieanwendung 3690 s, d. h. 61,5 min.

Drei Patienten hatten nach einer postablativen Volumenreduktion eine erneute Volumenzunahme nach drei Monaten. Kein Knoten erreichte postablativ die präablative Größe.

Die Komplikationsrate betrug 5,2 %. Patienten mit komplexen Knoten hatten keine Komplikationen. Bei den Patienten mit soliden Knoten traten in drei Fällen transiente Komplikationen auf: Drei Patienten hatten eine transiente Lähmung des Nervus laryngeus recurrens.

4. Diskussion

Die vorliegende Studie zeigt, dass HIFU-Echotherapie eine sichere und effektive Methode zu Behandlung von sowohl soliden als auch komplexen benignen Schilddrüsenknoten ist.

Die signifikante Volumenreduktion von 62,1 % nach 9 Monaten in der Gesamtpopulation, ist eine über 50-prozentige Volumenreduktion, die klassischerweise als Therapieerfolg definiert wird.[7] In anderen Studien, mit ähnlichen Ein- und Ausschlusskriterien sowie Therapieabläufen, konnte eine vergleichbare Volumenreduktion beobachtet werden.[14, 15, 20] Die vorliegende Studie bestätigt die aktuelle Studienlage und stärkt die Evidenz von HIFU als effektive Behandlungsalternative bei benignen Schilddrüsenknoten.

Des Weiteren zeigt die vorliegende Studie erstmalig, dass sowohl solide als auch komplexe Knoten eine signifikante Volumenreduktion nach HIFU-Echotherapien haben. In Bezug auf das initiale Volumen hatten solide Knoten mit 49,98 % nach drei Monaten und mit 65,77 % nach neun Monaten eine mehr als 50-prozentige Volumenreduktion. Die Volumenreduktion von komplexen Knoten hingegen lag mit 35,2 % nach 3 Monaten und 36,89 % nach 6 Monaten unter 50 %. HIFU ist bei soliden Knoten im Trend effektiver als bei komplexen Knoten. Diese neue Datenlage ist eine Grundlage, um HIFU weiter zu evaluieren. Die Knotenmorphologie zeigt sich als relevanter Parameter bei der Indikationsstellung für HIFU. Eine mögliche Erklärung für den unterschiedlichen Therapieerfolg bei soliden und komplexen Knoten wird in der vorliegenden Studie aufgezeigt: Die Temperatur, die im Gewebe erzeugt wird, hängt von der Absorption und gleichzeitig von der Temperaturverteilung im Gewebe ab. Komplexe Knoten haben durch ihre inhomogene Struktur mehr Grenzflächen als solide Knoten und absorbieren die Hitze initial besser. Aber die Temperaturverteilung ist in komplexen Knoten größer, so dass die Hitze schneller abtransportiert wird und schlechter zu kontrollieren ist. Dies wird durch die Pennes‘ bioheat equation beschrieben. Diese definiert, dass die Temperaturverteilung umso größer ist, je weniger dicht ein Gewebe ist, je weniger Hitzekapazität es hat, je größer die Wärmeleitfähigkeit ist und je mehr es perfundiert wird.[23-25] Transferiert man dieses Gesetz auf solide und komplexe Knoten, wird deutlich, dass solide Knoten eine geringere Temperaturverteilung

haben. Es können lokal höhere Temperaturen erreicht werden und es kann gezielter therapiert werden.
Die Therapiedauer war bei komplexen Knoten länger als bei soliden Knoten. Trotzdem war die Volumenreduktion bei komplexen Knoten geringer. Die Hitze wird also bei komplexen Knoten schneller abtransportiert und es dauert länger den Knoten zu erhitzen.
Um die Therapie von komplexen Knoten zu optimieren, zeigt die Studie die Möglichkeit auf, nicht nur einen Fokus zu erhitzen, sondern mehrere Foki gleichzeitig. Höhere Temperaturen durch mehr Energie einzusetzen, ist aufgrund der Gefahr von Kavitationsblasen keine Option.[26, 27]

Wie auch in bisher bekannten Studien konnten keine persistenten Komplikationen beobachtet werden.[8, 20, 28] Das Fehlen langfristiger Komplikationen erklärt sich durch die automatisch eingehaltenen Sicherheitsabstände und die konstante Beobachtung durch den behandelnden Arzt. Bei der Therapie solider Knoten trat eine transiente Schädigung des N. laryngeus rekurrens in drei Fällen (8,5 %) auf. Bei anderen thermoablativen Verfahren wie der Mikrowellenablation (MWA) wurde ebenfalls von Nervenschädigungen berichtet.[29]
Da bei soliden Knoten lokal höhere Temperaturen erzeugt werden und mehr Gewebe koaguliert, kann es schneller zu einer Reizung der angrenzenden Nerven kommen.

Drei Patienten hatte in der vorliegenden Studie nach einer initialen postablativen Volumenreduktion ein erneutes Knotenwachstum. Ob es Prädiktoren gibt, die ein postablatives Knotenwachstum begünstigen, ist eine relevante Fragestellung und sollte systematisch untersucht werden. Auch bei anderen thermoablativen Verfahren wie der Radiofrequenzablation (RFA) wurde ein erneutes Wachstum der Knoten beobachtet.[30] Bei RFA wurde das erneute Wachstum auf eine zu große Restmenge von vitalem Gewebe zurückgeführt.[30]
Verglichen mit anderen thermoablativen Verfahren ist HIFU eine effektive Behandlungsalternative. Bei MWA und RFA wurde nach 3 Monaten eine signifikante Volumenreduktion von 32,01 - 53,54 % und. 51,21 % beobachtet.[29, 31] HIFU ist mit 38,86 % nach 3 Monaten und 62,21 % nach 9 Monaten ähnlich

effektiv. Vorteile der HIFU-Echotherapie gegenüber RFA und MWA sind jedoch, dass sie nicht hautpenetrierend ist und somit kein Risiko für Hämatome oder Infektionen besteht. Auch bei anderen thermoablativen Verfahren wie der MWA und RFA wurde beobachtet, dass die Knotenmorphologie den Therapieerfolg beeinflusst. In der vorliegenden Studie wird festgestellt, dass bei komplexen Knoten RFA mit 56 - 93 % und MWA mit 72 % Volumenreduktion effektiver ist als HIFU mit einer Volumenreduktion von 36,89 % nach sechs Monaten. Bei soliden Knoten hingegen ist HIFU mit einer 65,77 % Volumenreduktion nach neun Monaten effektiver als MWA mit 27 % und RFA mit 49 %.[32- 36]

Im Vergleich zu herkömmlichen Verfahren wie der Schilddrüsenchirurgie und der RIT, ist HIFU eine nebenwirkungsärmere und effektive Behandlungsalternative. Bei HIFU wird der Knoten im Gegensatz zur Schilddrüsenchirurgie jedoch nicht komplett entfernt und es kann keine postinterventionelle histologische Untersuchung des Gewebes stattfinden. Eine Malignität des Knotens wird jedoch bereits präablativ durch eine Feinnadelaspirationsbiopsie (FNAB) ausgeschlossen. Nur Patienten mit einem benignen FNAB-Befund werden einer HIFU-Echotherapie zugeführt. HIFU ist somit eine sichere Methode um nachgewiesen benigne Knoten nicht-invasiv und ohne die möglichen Nebenwirkungen einer Operation, wie beispielsweise Blutungen und Thyreotoxikose, zu therapieren.[2, 3, 4]

5. Limitationen

Die Volumenreduktion der Knoten war sowohl bei soliden als auch bei komplexen Knoten signifikant. Zusätzlich zeigte die vorliegende Studie erstmalig den Trend, dass solide Knoten besser auf HIFU-Echotherapie ansprechen als komplexe Knoten. Sie wurde jedoch dadurch limitiert, dass das Patientenkollektiv zu gering war, um einen signifikanten Gruppenvergleich durchzuführen. Für weitere Arbeiten wäre es attraktiv, ein größeres Patientenkollektiv hinsichtlich der Knotenmorphologie auszuwerten, um den neu erkannten Trend zu bestätigen.

Des Weiteren wurde die Studie durch die zu geringe Studienpopulation nach 9 und 12 Monaten limitiert. Dies war der Fall, da viele Patienten für die Therapie von extern anreisten und nach 6 Monaten die von uns empfohlene Nachsorge wieder extern stattfand. Um mögliche Komplikationen oder eine erneut

auftretende Symptomatik zu verfolgen, blieben die Studienautoren mit allen Patienten in Kontakt.

6. Schlussfolgerung

Die vorliegende Studie generiert weitere Evidenz für HIFU als sichere und effektive Behandlungsalternative von benignen Schilddrüsenknoten. Zudem werden signifikante und neue Erkenntnisse zum Einfluss der Knotenmorphologie auf den Therapieerfolg von HIFU gewonnen. Dadurch ist es möglich die verschiedenen thermoablativen Verfahren hinsichtlich ihrer Effektivität in Bezug auf die Knotenmorphologie zu vergleichen und die Therapieindikation noch differenzierter zu stellen.
Die Tatsache, dass der Therapieerfolg von HIFU durch die Knotenmorphologie beeinflusst wird, ist eine wegweisende neue Erkenntnis und kann somit ein wichtiger Beitrag zur Forschung sein.

Weitere Ergebnisse der Arbeitsgruppe

Zusätzlich zu der vorliegenden Studie wurden weitere Ergebnisse erzielt und veröffentlicht.

Initial wurden Unterschiede bezüglich der Volumenreduktion in den zwei Zentren statistisch analysiert. Dabei zeigte sich, dass in den Daten aus dem Universitätsklinikum Frankfurt nach 3 Monaten mit 36,02 % (Spannweite 4,03 % - 68,63 %, n = 17, $p \leq 0{,}0001$) eine geringere Volumenreduktion der behandelten Schilddrüsenknoten erreicht wurde als in den Daten aus dem Bürgerhospital mit 48,09 % (Spannweite 13,64 % - 91,16 %, n = 19, $p \leq 0{,}0001$). In beiden Behandlungszentren wurde das gleiche Gerät verwendet und in beiden Zentren wurde die Behandlung vom selben Arzt durchgeführt. Im Universitätsklinikum wurde jedoch vorwiegend unter Lokalanästhesie und im Bürgerhospital vorwiegend unter Propofolnarkose behandelt. Ein statistischer Vergleich zum Einfluss von Propofolnarkose und Lokalanästhesie auf das therapeutische Outcome von HIFU zeigte, dass unter Propofolnarkose die Volumenreduktion größer ist (n = 30, $p = 0{,}033$ im Mann-Whitney Test) und weniger Energie verwendet werden muss (n = 30, $p < 0{,}0001$ im Mann-Whitney Test). Der Unterschied der Volumenreduktion wurde auf weniger Bewegungsartefakte während der Propofolnarkose im Vergleich zur Lokalanästhesie zurückgeführt. Die Ergebnisse wurden im „World Journal of Surgery“ veröffentlicht.[15]

In einer weiteren im „Endocrine“ veröffentlichten Arbeit wurde der Einfluss der initialen Knotengröße auf den Therapieerfolg von HIFU bei benignen Schilddrüsenknoten und der Einfluss von HIFU auf die hormonelle Schilddrüsenfunktion analysiert. Ein Vergleich der Knoten mit initial < 3 ml und > 3 ml wurde durchgeführt. Die Volumenreduktion der Knoten > 3 ml und die der Knoten < 3 ml unterschieden sich nicht signifikant (n = 72, $p > 0{,}05$ im Mann-Whitney Test). Die initiale Knotengröße beeinflusste den Therapieerfolg nicht. Auch die präablativen und postablativen TSH-Serumwerte der Patienten unterschieden sich nicht signifikant (n= 46, $p > 0{,}05$ im Wilcoxon-signed-rank Test). Die hormonelle Schilddrüsenfunktion wurde durch HIFU-Echotherapie nicht beeinträchtigt.[14]

Beitrag zur Beantwortung der Fragestellung

HIFU-Echotherapie benigner Schilddrüsenknoten ist eine vielversprechende Methode zur Behandlung benigner Schilddrüsenknoten, da sie im Vergleich zu herkömmlichen Methoden nebenwirkungsärmer ist und mehr Patientenkomfort bietet. Hierzu sind bereits Studien aus der Arbeitsgruppe von Prof. Dr. Dr. Korkusuz und Dr. Vorländer erschienen. Die Methode nimmt in den letzten Jahren einen immer größeren Stellenwert ein und die Analyse von HIFU-Daten sind von großer Aktualität. Dies wird auch daran deutlich, dass in den aktuellen Leitlinien mehr Evidenz zu HIFU-Echotherapie gefordert wird, um die Methode als Behandlungsalternative empfehlen zu können.[16, 17]

Die vorgestellte Studie wertet als erste wissenschaftliche Studie den Einfluss der Knotenmorphologie auf die Effektivität der HIFU-Echotherapie benigner Schilddrüsenknoten in einer bizentrischen Langzeitstudie aus. Für den Erfolg der HIFU-Echotherapie ist die Volumenreduktion nach Therapie der entscheidende Parameter für die Symptombesserung des Patienten und ist somit ein Indikator für den Therapieerfolg. Es konnte gezeigt werden, dass durch die HIFU-Echotherapie sowohl in der Gesamtpopulation als auch bei soliden und komplexen Knoten eine signifikante Volumenreduktion erreicht werden konnte. Es wurden Komplikationen bei der Therapie solider Knoten beobachtet. Diese waren jedoch alle transient. Die Erkenntnisse der Studie leisten einen wichtigen Beitrag zur weiteren Evaluation von HIFU-Echotherapie und stützen HIFU-Echotherapie als sichere und effektive Behandlungsalternative benigner Schilddrüsenknoten.

Um die HIFU-Echotherapie zu optimieren, ist es notwendig den Einfluss verschiedener Knotencharakteristika statistisch zu untersuchen. Die vorliegende Studie analysierte, ob die Knotenmorphologie die Effektivität der HIFU-Echotherapie beeinflusst und somit bei der Indikationsstellung der Therapie beachtet werden sollte. Dabei konnte ein Trend gezeigt werden, dass solide Knoten besser auf HIFU-Echotherapie ansprechen als komplexe Knoten. Dies ist ein wichtiger Hinweis, der eine differenziertere Indikationsstellung und die Abwägung der HIFU-Echotherapie gegen Alternativen wie RFA und MWA erlaubt. Trotz der vielversprechenden Ergebnisse ist mehr Evidenz weiterer

großangelegter Langzeitstudien notwendig, um den gezeigten Trend statistisch im Gruppenvergleich bestätigen zu können.

Die Daten der vorliegenden bizentrischen Studie mit 12-monatigem Follow-up stützen HIFU als effektive Behandlungsalternative in der Therapie benigner Schilddrüsenknoten. Sie ermöglichen eine differenzierte Indikationsstellung in Bezug auf die Knotenmorphologie. Der Trend, dass solide Knoten besser auf HIFU ansprechen als komplexe, tritt in der vorliegenden Studie deutlich hervor.

Übersicht der Publikationen

A. Fischer, H. Korkusuz, C. Vorländer
Effectiveness of High-intensity Focused Ultrasound (HIFU) Therapy of Solid and Complex Benign Thyroid Nodules - A Long-term Follow up Two-center Study.
Exp Clin Endocrinol Diabetes. 2022; 130:374 - 380. doi: 10.1055/a-1719-4441.

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World J Surg. 2022 Jan 24. doi: 10.1007/s00268-022-06447-7. Epub ahead of print. PMID: 35072745.

C. Vorländer, **A. Fischer**, H. Korkusuz
High intensity focused ultrasound in the therapy of benign thyroid nodules - first German bicentric study with long-term follow-up.
Endocrine. 2022 Apr 27. doi: 10.1007/s12020-022-03058-z. Epub ahead of print. PMID: 35476180.

Wissenschaftliche Vorträge

A. Fischer
„HIFU in Lokalanästhesie und unter Narkose – Unterschiede“ 10. Frankfurter Symposium für Endokrine Chirurgie und 2. Internationaler Kongress für Thermoablation, Samstag 25. Juni 2022

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Thieme

Effectiveness of High-intensity Focused Ultrasound (HIFU) Therapy of Solid and Complex Benign Thyroid Nodules – A Long-term Follow up Two-center Study

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ABSTRACT

Purpose To investigate the effectiveness of high-intensity focused ultrasound (HIFU) of solid and complex benign thyroid nodules.

Methods Fifty-eight patients with benign thyroid nodules were treated with HIFU at two centers from 2014–2019. The device, EchoPulse (Teraclion, Malakoff, France), heats the nodes to 80–90 °C. Nodal volumes were measured by ultrasound at regular intervals before and up to 12 months after therapy. In a retrospective long-term two-center study, average volume reductions in relation to baseline volume were statistically analyzed by the Wilcoxon signed-rank test. Side effects were documented.

Results In solid nodules, the average percent volume reductions at the 3, 6, 9, and 12-months follow-up were 49.98 %, 46.40 %, 65.77 %, and 63.88 %, respectively. The results were significant with $p < 0.05$ in the Wilcoxon signed-rank test at the 3, 6, and 9-months follow-up. In complex nodules, the average percent volume reduction was 35.2 % at 3 months, 36.89 % at 6 months, and 63.64 % at twelve months follow up. The results were significant with $p < 0.05$ in the Wilcoxon signed-rank test at the 3- and 6-months follow-up. The complication rate was 5.2 %. All complications occurred in patients with solid nodules.

Conclusion The study showed that HIFU is an effective treatment method for both solid and complex nodules. The complication rate is relatively high at 5.2 %. No long-term complications occurred. The solid nodules responded better to HIFU than complex nodules.

Introduction

Thyroid nodules are very common in our population and are therefore of great scientific interest. About 50 % of women and 30 % of men have thyroid nodules [1]. Benign nodules (80–95 % of the thyroid nodules) are classified as cystic, complex, and solid nodules according to their nodule morphology [2–4]. Most benign nodules do not cause any symptoms, although, they are nowadays easily diagnosed by ultrasound.

The nodules only need to be treated if they cause symptoms (feeling of pressure, difficulty swallowing, dyspnea) or cosmetic impairments [5, 6]. The treatments include radioiodine therapy or surgical removal; despite their advantages, these therapy options have several side effects and are therefore not accepted by patients. For example, bleeding, laryngeal recurrent nerve paralysis, hypothyroidism, or infections may occur. Pregnant women or women who wish to have children in the next few months cannot undergo radioiodine therapy [7–9]. Therefore, minimally invasive thermoablative procedures such as HIFU, radiofrequency ablation (RFA), microwave ablation (MWA), and laser are other alternatives and have been assessed intensively over the past years [5, 10–14]. Among the alternative thermoablative procedures, HIFU is the least invasive and most precise [15]. In HIFU, ultrasound rays are focused by a concave ultrasound probe to heat the tissue to 85 °C. This irreversibly causes coagulation necrosis and nodule atrophy

[5, 11, 13, 14]. HIFU is not skin penetrating and therefore much more comfortable for the patient. There is no risk of infection. HIFU is used not only for the treatment of thyroid nodules, but also for prostate cancer, uterine myomas, and liver or bone metastases [16–18]. To make the structures react even more sensitively to ultrasound, research is underway on so-called sonosentizers, for instance, for the liver and kidney [19, 20].

HIFU is found to be a safe and effective method to treat benign thyroid nodules [10–14, 21]. It is currently mentioned as an alternative treatment option for solid and complex nodules, but with the caveat that further studies are needed [1]. This study investigated whether the morphology of the nodule influences the therapeutic effect. Nodule volume is the crucial assessment parameter of both treatment success and patient comfort, therefore, the primary criteria of judgment was volume evaluation.

This study aimed to investigate volume reduction of solid nodules and complex nodules in the treatment of benign thyroid nodules with HIFU and to determine the complication rate in a long-term follow-up two-center study.

Material and methods

Study design

The study was a retrospective analysis of data in an open-label, baseline controlled, two-center study. The study complied with the institutional review board, ethic committees, informed consent regulation, the Declaration of Helsinki, and local regulations.

Patients

Fifty-eight patients (50 female, 8 male) from two-centers were enrolled in the study from 2014 to 2019. Twenty-three patients were recruited from Centrum 1 (University Hospital Frankfurt) and 35 patients were from Centrum 2 (Buergerhospital Frankfurt). The median solid nodules volume was 4.7 mL (range 0.2–23.1 mL, n = 35) and the median complex nodule volume was 4.3 mL (range 0.13–17 mL, n = 23). Twenty-four nodules were located in the left thyroid lobe, 32 nodules in the right thyroid lobe, and two nodules in the isthmus.

All patients were over 18 years of age. Patients were included in the study if they had proven nonmalignant nodules, symptomatic thyroid nodules (thyrotoxicosis, swallowing problems, pain, or hoarseness), cosmetic concerns, and refused surgery or had proven contraindications to it. No patient was known to have had previous therapy or thermoablative procedures. None of the patients received RIT or surgery. The indication for HIFU was thyroid autonomy in 26 patients and pressure symptoms in 32 patients.

Treatment procedure and equipment

The HIFU therapy was performed at both centers using the EchoPulse (Teraclion, Malakoff, France) system. The device uses a concave ultrasound head (3 MHz) to heat a 2 × 9 mm focus to 80–90 °C. The therapeutic head generates 87.6–320.3 J per sonication at the focus, in which heat is generated by absorbing the acoustic energy and converting it to thermal energy. To heat 1 mL of the nodule, the device needs 10 seconds.

The system automatically selects the following safety margins: 0.5 cm to the skin, 0.3 cm to the trachea, and 0.2 cm to the carotid. Furthermore, endangered structures are protected by a physical process – the "heat sink". The vessels surrounding the major nerve and vascular tracts (from 4 mm) transpose the heat generated and thus protect the nerves and vessels from heat-induced necrosis [11].

The exact point of the nodule treatment was defined by the doctor on the device using a so-called voxel map. The tissue was divided into voxels by 10–20 sagittal and transverse layers.

A cooling kit was installed before any therapy. The nodule volume was measured by the Echopulse system. This was followed by either local anesthesia with Mecain1 % or general anesthesia. Then the ultrasound probe was positioned on the hyperextended neck, with the patient in a supine position. The sonication was performed by the device in a screw pattern and the energy level was adjusted after each sonication.

The device uses a laser to detect deviations between the planned focus and the actual position of the probe. If the pattern shifted, the device automatically stopped the current sonication and the adjustment was made. At the same time, the doctor observed the therapy process with the diagnostic ultrasound probe. The presence of deviations or heat bubbles indicated too high a temperature, and the doctor had to intervene manually at any time and correct the process [5, 10–14, 22, 23].

Baseline assessment

In all patients, a pre-ablative assessment was done. Malignancy was excluded by cytological examination based on fine-needle aspiration biopsy (FNAB) [24]. In addition, laboratory blood tests, 99Tc MIBI scan, and calcitonin measurement were performed. Two pathologists were involved in the study. The 2017 Bethesda-System was used as the pathological classification system [25]. There were no biopsies due to insufficient material.

All nodules were also examined for the position, volume, and echogenicity by B-mode ultrasound (Sonix Touch Ultrasound System, Ultrasonix Medical Corporation, Richmond Canada) before and at regular intervals after therapy. Ultrasound measurements were performed by three examiners as three-dimensional measurements [26]. Nodules with a liquid portion > 50 % but ≤ 90 % of the nodule volume were defined as a complex nodule [27, 28].

The volume reduction is the crucial parameter for the patient's symptom improvement and thus for the success of the therapy. Studies have shown significant volume reduction of the nodules up to 12 months after therapy [12]. Therefore, volume reduction of the nodules at three, six, nine, and 12 months after therapy was observed. There were few examinations of the complex nodules at nine months follow-up. Therefore, the nine-month follow-up was only performed for the solid nodules and the overall study population.

Statistical analysis

The statistical analysis was done with MedCalc. Normal distribution could not be assumed thus, statistical testing was nonparametric. Differences between the pre-ablation volume and the time points three, six, nine, and 12 months were compared by the Wilcoxon signed-rank test. The results were significant with $p < 0.05$.

Results

As shown in ▶ **Fig 1**, at three months-follow up the overall study population had an average volume reduction of 38.86 % (range: 4.03 %–91.16 %, p < 0.0001 in the Wilcoxon test, n = 25), at six months-follow-up of 42.7 % (range: 7.36 %–93.2 %, p < 0.0001, n = 18), at nine months-follow-up of 62.21 % (range: 12.88 %-93.2 %, p = 0.0078, n = 8), and at 12 months-follow-up of 61.42 % (range of 39.39 %–93.2 %, p > 0.05, n = 4) Thus, significant differences between pre-ablative volume reduction and volume reduction with p < 0.05 in the Wilcoxon-signed-rank-test were found at the three, six, and nine month follow-up. The percentage volume reduction of the nodules showed large ranges.

As shown in ▶ **Fig 2** and ▶ **3**, at the study population with solid nodules had an average volume reduction of 49.98 % at three months (range: 4.03–91.16 %, p = 0.0001 in the Wilcoxon test, n = 15), 46.40 % at six months (range: 7.36–93.2 %, p = 0.001, n = 11), 65.77 % at nine months (range of 39.39–93.2 %, p = 0.0156, n = 7) and 63.88 % at 12 months (range of 39.39–93.2 %, p > 0.05, n = 2) follow up. Thus, significant differences between pre-ablative volume reduction and volume reduction with p < 0.05 in the Wilcoxon-signed-rank-test were found at three-, six-, and nine-month follow-ups.

As shown in ▶ **Fig 3** and ▶ **4**, the study population with complex nodules had an average volume reduction of 35.2 % at three months (range: 5.85–68.63 %, p = 0.002 in the Wilcoxon test, n = 10), 36.89 % at six months (range of 12.23–68.63 %, p = 0.0156, n = 7) and 63.64 % at 12 months (range of 52,38–73.91 %, p > 0.05, n = 2) of follow up. Thus, significant differences between pre-ablative volume reduction and volume reduction with p < 0.05 in the Wilcoxon-signed-rank-test were found at the three- and six-month follow-up.

In solid nodules, the average applied energy duration was 2340 s i. e. 39 min. In complex nodules it was 3690 s i. e. 61.5 min.

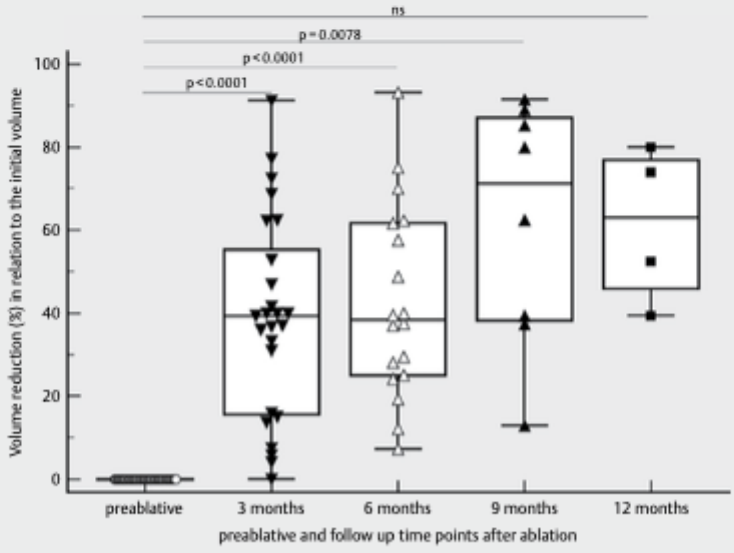
Postinterventional nodal re-growth occurred in three patients. All three patients showed initial volume reduction in the first three months and renewed volume growth after three months. In none of the patients did the nodules increase to the pre-interventional size with the renewed volume increase.

The complication rate was 5.2 %. No complications occurred in patients with complex nodules. In the group of patients with solid nodules, three patients had short-term complications. Two patients had laryngeal recurrent nerve paralysis, which was reversible after speech therapy. One patient complained of a vocal cord weakness three months after therapy. No long-term complications occurred.

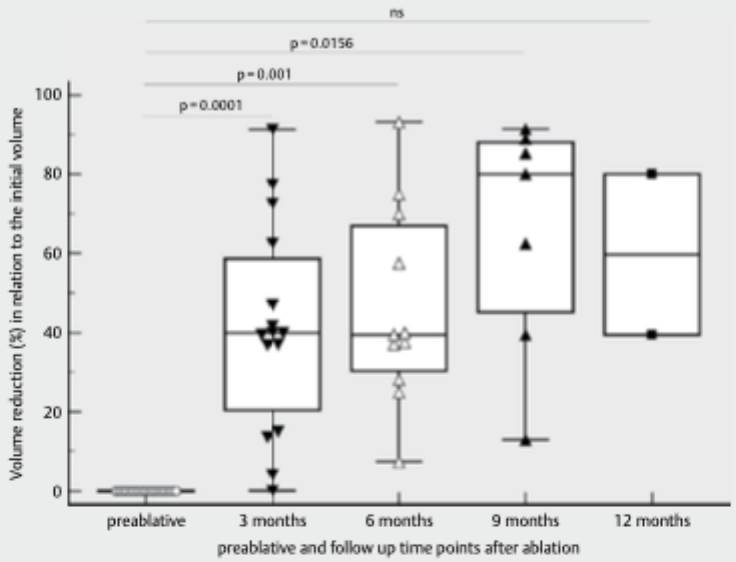
Discussion

In our study, the overall population showed a significant volume reduction and therefore a response to HIFU therapy. Both solid and complex nodules responded with a significant volume reduction to the therapy. The solid nodule group had a higher percent volume reduction in relation to baseline volume at three months and six months. These are further important data to strengthen the evidence for HIFU therapy of benign thyroid nodules in clinical routine.

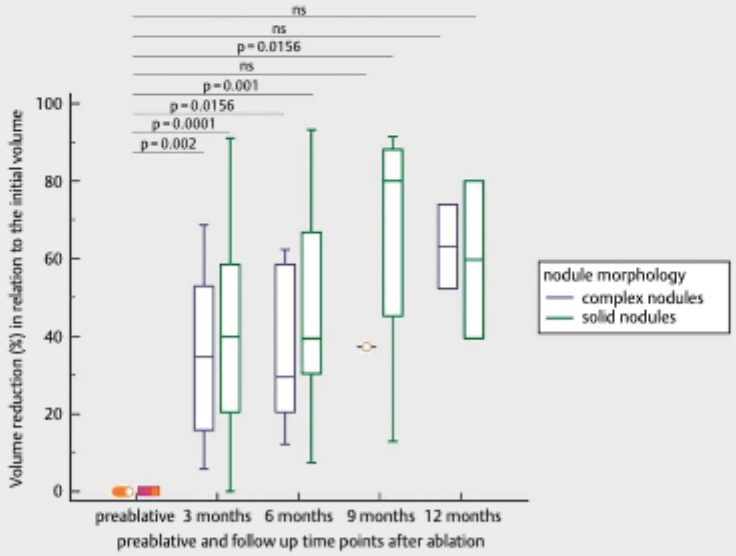
The volume reduction of 62.21 % percent achieved after nine months in the total study population, could effectively improve the patient's symptoms such as the feeling of pressure and problems with swallowing. It confirms the statistically significant results of other studies on HIFU therapy of benign thyroid nodules, which often defined a volume reduction of 50 % as a therapeutic success



▶ **Fig. 1** Percentage volume reduction in benign thyroid nodules after HIFU therapy in relation to the baseline volume at the follow-up of three, six, nine, and twelve months.



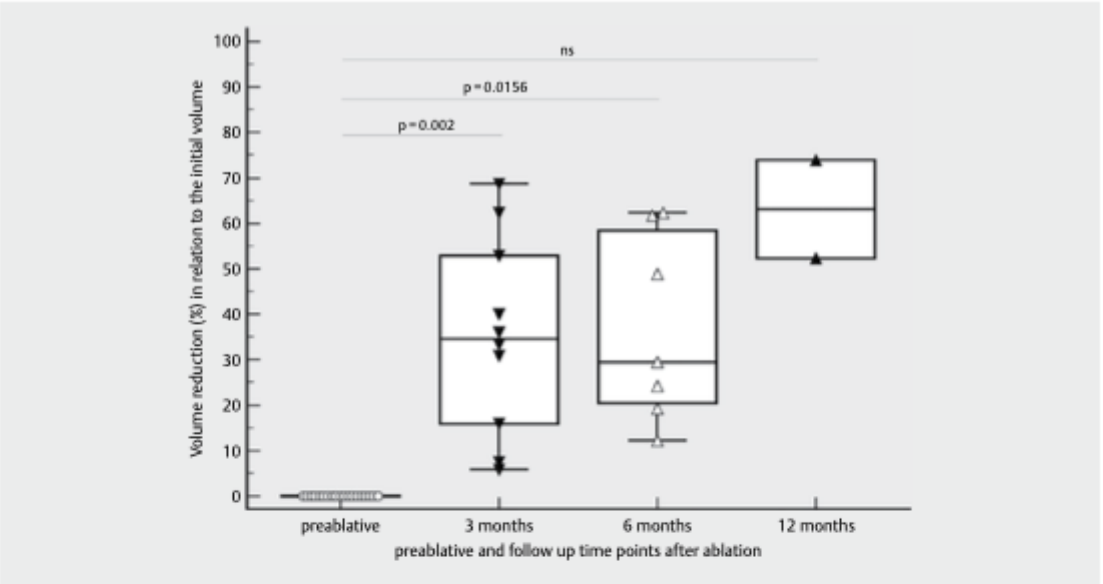
▶ **Fig. 2** Percentage volume reduction in solid thyroid nodules after HIFU therapy in relation to the baseline volume at the follow-up of three, six, nine, and twelve months.



▶ **Fig 3** The boxplots show the average percent volume reduction of benign thyroid nodules after HIFU therapy at the time points of three, six, nine, and twelve months follow-up divided into groups of complex and solid nodules.

[15]. Since residual tissue remains after HIFU, it was necessary to exclude malignancy in all nodules with FNAB before treatment [24].

In solid nodules, 49.98 % volume reduction was observed after three months and a 65.77 % volume reduction after nine months. Thus, solid nodules achieved a volume reduction of 50 %, which was



▶ **Fig. 4** Percentage volume reduction of complex thyroid nodules after HIFU therapy in relation to the baseline volume at the follow-up of three, six, nine, and twelve months.

usually defined as therapeutic success [15]. Complex nodules in our study achieved a volume reduction of only 35.2 % after three months and 36.89 % after six months. They exhibited less than 50 % volume reduction. In the present study, the therapy was overall more effective in solid nodules. In the group comparison, no statistically significant difference could be detected due to insufficient sample size. More studies are needed to perform a group comparison.

Since complex nodules are more inhomogeneous and have more interfaces, they would respond better to therapy if absorption is the decisive factor for the response to therapy [29–31]. Therefore, it seems that not absorption, but possibly another factor, such as the removal of heat is crucial for the success of therapy. The therapeutic effect, i. e. the heating of the tissue, depends not only on the initial process of heating but also on the removal of heat. If the heat is removed quickly, the therapeutic effect is less. The distribution or conduction of temperature in tissues is described by Pennes heat transfer. According to this, the greater the temperature distribution, the less dense tissue is, the less specific heat capacity a tissue has, the greater are thermal conductivity and the more the blood perfusion [29, 32, 33]. Transferring these aspects to cystic, complex, and solid nodules, it becomes clear that solid nodules have the least heat distribution. The heat exerted on them has a very local effect. This means that more targeted therapy can be performed and endangered structures can be avoided. Cystic nodules are the other extreme. These have a very high-temperature distribution so that the energy applied is quickly distributed or evaporates and is not so easy to control. With HIFU, only areas the size of a grain of rice are heated. If only such a small area is heated in several mL of the cyst, the temperature is quickly distributed and the overall temperature of the cyst rises only slightly. A complex nodule has cystic and solid areas so that in some areas the effect of temperature is significant and local and in other areas, the temperature is distributed quickly and the target area is heated less. Therefore solid nodules should respond better to HIFU than complex ones.

A limitation of this study was that the data at the 12-months follow-up were not significant. This was due to insufficient sample size at 12 months. Further data would be needed to significantly assess different trends in volume reduction of solid and complex nodules beyond six months. Another weakness of the study was the retrospective data analysis and the small number of patients in the nine- and twelve-month groups.

In some patients, we observed a renewed volume increase after the initial volume reduction after therapy. What causes recurrences after therapy? It is known that 15 % of benign thyroid nodules have a size progression without therapy [6]. After therapy, however, these usually do not grow any more despite the remaining tissue. The larger the nodule is, the more nodules a patient has; the younger a patient is and the higher the BMI of a patient is, the higher is the probability that the nodule will grow without therapy [6]. In the patients in our study with the grown nodule, none of the above-listed criteria applied. It would be necessary to clarify which factors correlate with a renewed increase in nodule volume after therapy.

In this study, the duration of therapy of complex nodules was significantly longer, although the patients initially had a similar median volume as the solid nodules. Despite the longer therapy duration, they had a relatively small volume reduction. This may be because the heat is removed too quickly in complex nodules as described above. This could only be compensated by even higher

temperatures. However, this is not possible, because otherwise heat bubbles are created by cavitation, which would cause complications [22, 31]. Therefore, the same energy is used for a longer time, but this cannot compensate for the larger heat distribution, besides, the therapeutic effect is smaller. One solution would be to heat not only a small area but several areas simultaneously next to each other so that relatively less heat is dissipated.

The fact that in our study side effects only occurred in solid nodules and none in complex nodules underlines the hypothesis that complex nodules did not develop such high temperatures as solid ones. Less tissue was damaged.

In other thermo-ablative procedures such as MWA and RFA, a dependence of the therapeutic outcome on the nodule morphology has already been observed.

In MWA and RFA, cystic or complex nodules respond better to therapy than solid nodules. In one report, MWA, volume reduction of complex nodules was 72 % and of solid nodules was 27 % [34]. In RFA, cystic nodules showed 87–93 % volume reduction while that in solid nodules was 49 % [34–37]. Therefore, in complex nodules, RFA or MWA should be considered more likely, since HIFU, with 36.89 % volume reduction, was significantly worse than MWA and RFA. Nonetheless, for small solid nodules, the HIFU would be preferable to MWA and RFA, because it is more effective with a 46.40 % volume reduction after six months in solid nodules.

Conclusion

To conclude, HIFU is an effective method to treat benign solid and complex thyroid nodules. Overall, solid nodules had more volume reduction than complex nodules through this method. The complication rate was relatively high at 5.2 % and no long-term complications occurred. All complications occurred in patients with solid nodules.

Based on these results, the treatment alternatives of solid and complex nodules can be evaluated better and strategies for the optimization of HIFU therapy of complex nodules can be discussed.

Conflicts of Interest

The authors declare that they had no conflict of interest.

One sentence summary In the investigation of volume reduction of solid and complex benign thyroid nodules after HIFU therapy a trend was shown that solid nodules respond better to HIFU and thus nodule morphology influences the effectiveness of HIFU.

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Notice

This article was changed according to the following Erratum on February 9th 2022.

Erratum

In the above-mentioned article, the order of the authors' names was corrected and Affiliations 2 and 3 were added.

Darstellung des eigenen Anteils an der Publikation

Der Anteil von mir, Anne Fischer (geboren in Mannheim), an der Publikation „Effectiveness of High-intensity Focused Ultrasound (HIFU) Therapy of Solid and Complex Benign Thyroid Nodules – A Long-term Follow up Two-center Study“ veröffentlicht im Journal „Experimental and Clinical Endocrinology & Diabetes“, welche die Grundlage für die vorliegende Dissertation ist, setzt sich aus den folgenden Tätigkeiten zusammen:

Zu Beginn des Projekts führte ich über mehrere Monate eine ausführliche Literaturrecherche durch, wählte die relevante Literatur aus und strukturierte diese. Ich erarbeitete die Fragestellung der Doktorarbeit und formulierte eine Arbeitshypothese. Nach Erhalt des positiven Ethikvotums sichtete, strukturierte und vervollständigte ich die von Prof. Korkusuz bereitgestellten Daten im Studiensekretariat für ein halbes Jahr. Ich erhob relevante Parameter wie die Knotenmorphologie, die Laborwerte der Patienten und die während der Therapie aufgewendete Energie aus den Patientenakten und erstellte eine Übersicht der relevanten Ablationsdaten. Nach Abschluss der Datenerhebung arbeitete ich mich in das Gebiet der Statistik zur Datenauswertung ein. Ich analysierte die erhobenen Daten eigenständig mittels MedCalc, überprüfte die Arbeitshypothesen und fasste die Erkenntnisse zusammen. Daraufhin stellte ich die Ergebnisse Prof. Dr. Dr. Korkusuz, Leiter des DZTA - Deutsches Zentrum für Thermoablation e.V. und Dr. Vorländer, Chefarzt der Klinik für Endokrine Chirurgie des Bürgerhospitals Frankfurt, vor. Nach Diskussion der Ergebnisse erstellte ich das Manuskript. Das Manuskript wurde von Prof. Dr. Dr. Korkusuz und Dr. Vorländer gegengelesen. Nach mehrmaligen Diskussionen übernahm ich die Korrekturvorschläge und überarbeitet das Manuskript mehrmals. Das Manuskript wurde bei jeder Änderung mit dem aktuellen Stand der Wissenschaft überprüft. Aufgrund der umfassenden Ergebnisse entschieden wir uns mehrere Publikationen zu dem Themenkomplex zu veröffentlichen. Ich habe das Manuskript meines Papers selbstständig im Journal „Experimental and Clinical Endocrinology & Diabetes" eingereicht. Im Rewiew-Prozess war ich die Ansprechpartnerin für das Editorial Office. Das Paper durchlief das Peer-Review Verfahren und ich setzte die Ergänzungen und Nachbesserungen, die durch das

Editorial Office angemerkt wurden, um. Daraufhin wurde das hier vorliegende Manuskript am 06.12.2021 im Journal „Experimental and Clinical Endocrinology & Diabetes“ akzeptiert und am 11.01.2022 publiziert.
Die erarbeiteten Ergebnisse der zwei weiteren Themenkomplexe wurden ebenfalls publiziert: Der Artikel „Effects of Regional and General Anesthesia on the Therapeutic Outcome of Benign Thyroid Nodules Treated with High Intensity Focused Ultrasound (HIFU)” wurde am 24.01.2022 im „World Journal of Surgery“ publiziert. Die Veröffentlichung des Artikels „High intensity focused ultrasound in the therapy of benign thyroid nodules - first German bicentric study with long-term follow-up” erfolgte am 27.04.2022 im Journal “Endocrine”.

Den restlichen Anteil der Dissertationsschrift wurde von mir allein anhand der Richtlinien des Promotionsbüros des Fachbereiches 16 der Johann Wolfgang Goethe-Universität Frankfurt am Main verfasst.

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Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann Wolfgang Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

„Thermoablation von Schilddrüsenknoten”

in dem Deutschen Zentrum für Thermoablation e.V. unter Betreuung und Anleitung von Prof. Dr. Dr. Hüdayi Korkusuz ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht*. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

Vorliegende Ergebnisse der Arbeit wurden in folgendem Publikationsorgan veröffentlicht:
A. Fischer, H. Korkusuz, C. Vorländer. Effectiveness of High-intensity Focused Ultrasound (HIFU) Therapy of Solid and Complex Benign Thyroid Nodules - A Long-term Follow up Two-center Study. Exp Clin Endocrinol Diabetes. 2022; 130:374 - 380. doi: 10.1055/a-1719-4441.

Teile der Doktorarbeit wurden in anderen Arbeiten mitpubliziert:
C. Vorländer, A. Fischer, H. Korkusuz
Effects of Regional and General Anesthesia on the Therapeutic Outcome of Benign Thyroid Nodules Treated with High Intensity Focused Ultrasound (HIFU).
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Vorländer C, Fischer A, Korkusuz H.

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

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Frankfurt a.M., 13.02.2024

(Ort, Datum)

(Unterschrift)

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Publikation: Effects of Regional and General Anesthesia on the Therapeutic Outcome of Benign Thyroid Nodules Treated with High Intensity Focused Ultrasound (HIFU)

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ORIGINAL SCIENTIFIC REPORT

Effects of Regional and General Anesthesia on the Therapeutic Outcome of Benign Thyroid Nodules Treated with High Intensity Focused Ultrasound (HIFU)

Christian Vorländer[1] · Anne Fischer[2] · Hüdayi Korkusuz[3]

Accepted: 26 December 2021

Abstract

Background The study investigated whether anesthesia performed during high-intensity-focused-ultrasound treatment (HIFU) of benign thyroid nodules influenced the therapy outcome, based on volume reduction and the amount of energy delivered.

Methods Thirty patients with benign thyroid nodules were treated with HIFU under general or regional anesthesia at two centers from 2014 to 2019. During HIFU, a therapeutic ultrasound probe, EchoPulse (Teraclion, Malakoff, France), heats the focus to 80–90 degrees Celsius. Nodal volumes were measured by ultrasound before and 3 months after therapy. For statistical analysis, the total population was divided into two groups according to the anesthesia performed. In a retrospective long-term multicenter study, volume reduction and the energy delivered were analyzed using the Wilcoxon signed-rank test and the Mann–Whitney test.

Results At three months follow-up, the total study population had an average volume reduction of 39.26% (range 4.03–91.16%, $p < 0.001$, $n = 30$), the general anesthesia group of 47.46% (range 13.64–91.16%, $p = 0.001$, n = 15) and the regional anesthesia group of 31.06% (range 4.03—68.63%, $p = 0.001$, $n = 15$). Under regional anesthesia a median energy of 3.16 kJ/cm^3 (range: 0.96 – 8.2 kJ/cm^3) and under general anesthesia a median energy of 0.88 kJ/cm^3 (range: 0.18 – 1.63 kJ/cm^3) were delivered. All results were significant with $p < 0.05$. The complication rate was 6.67%.

Conclusion HIFU is an effective method to treat benign thyroid nodules. Comparing anesthesia methods, volume reduction is higher in patients treated under general anesthesia and less energy has to be delivered under general anesthesia.

Trial registration number 2020–1728-evBO.

Agency Ethik-Kommission bei der Landesäztekammer Hessen.

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Introduction

There is a high prevalence of thyroid nodules, 50% in females and 30% in males. [1, 2]. Most benign nodules do not cause symptoms and can be easily diagnosed by ultrasound [3–5].

Therapy is performed when symptoms (sensation of pressure, dyspnea, thyrotoxicosis) or cosmetic impairment occur. Typically, nodules are treated by surgical excision or radioiodine therapy (RIT) [3, 5]. Potential side effects of these therapies are hypothyroidism, infection, hemorrhage, injury to the parathyroid gland and recurrent laryngeal nerve due to surgical removal of the nodules, and hypothyroidism due to RIT [6, 7]. RIT cannot be performed on pregnant females or on females with a desire to have children in the next few months [8]. Minimally invasive thermal ablation such as microwave ablation (MWA), radiofrequency ablation (RFA), laser and HIFU offer an alternative to surgical excision and RIT and are already used clinically. Among the minimally invasive thermal ablation procedures, HIFU is the least invasive and most precise [9]. In HIFU, a concave ultrasound probe is used to focus the ultrasound beams. The tissue is heated up to 85 degrees Celsius. The heat irreversibly causes coagulation necrosis and the nodule atrophies [5, 9–12]. Since HIFU does not penetrate the skin, it is more comfortable than traditional thyroid surgery and there is no risk of infection. It is not only used in thyroid nodule therapy, but also in prostate cancer, uterine fibroids, liver metastases, and bone metastases. [13–15] Studies have shown that HIFU is a safe and effective procedure to treat benign thyroid nodules [5, 9–12, 16, 17]. However, more evidence is needed [1].

In the present study, the effects of two anesthetic procedures on nodule volume reduction and on required energy delivery during HIFU were investigated in a multicenter study. The aim of the study is to compare volume reduction under regional anesthesia and general anesthesia in the treatment of benign thyroid nodules with HIFU and to assess whether one of the anesthesia methods is preferable during HIFU.

Materials and methods

Study design

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

Patients and baseline assessment

For patient characteristics see Table 1. Patients with symptomatic benign thyroid nodules causing thyrotoxicosis, swallowing problems, pain, or hoarseness and non-symptomatic benign thyroid nodules causing cosmetic impairment were included in the study. Only patients who refused surgery or RIT of the nodules or had contraindications to the same were included. Only proven nonmalignant nodules were included.

Patients with asymptomatic nodules, malignant nodules, nodules with retrosternal growth, and nodules in proximity to sensitive structures such as the trachea, esophagus, the recurrent laryngeal nerve and the carotid artery were excluded from the study. Patients with nerve anomalies were excluded from the study.

Patients were assigned to anesthesia methods based on the in-house guidelines of the center and patients' preferences. Patients were treated with regional anesthesia at Center 1 and predominantly under general anesthesia at Center 2. There were no volume cut-offs of the nodules that influenced group selection.

All patients underwent a pre-interventional calcitonin measurement and thyroid hormone measurement. If necessary, a fine-needle aspiration biopsy (FNAB) was done to exclude malignancy. All nodules were also examined for position, volume, and echogenicity by B-mode ultrasound (Sonix Touch Ultrasound System, Ultrasonix Medical Corporation, Richmond Canada) before and at regular intervals after therapy.

A follow-up of the symptoms by means of a symptom score was not performed due to too high subjectivity. Since the volume reduction of the nodules is decisive for the improvement of the patient's symptoms and thus for the success of the therapy, it was chosen as an objective follow-up parameter. [9, 17, 18]. Previous studies have shown that the greatest volume reduction occurs in the first 3 months after therapy [17]. Therefore, a follow-up period of 3 months was chosen in the study. Furthermore, it was investigated whether the amount of energy delivered per cubic volume of the nodule differed at regional and general anesthesia.

Treatment procedure and equipment

The nodules were treated with the EchoPulse device (Teraclion, Malakoff, France). The device consists of two ultrasound systems, a concave therapeutic head with 3 MHz and a diagnostic head with 7.5 – 12 MHz. The approximately 4 s long pulse produces heat by the absorption of acoustic energy and by converting it to thermal energy. The focal point is heated to 80 – 90 degrees Celsius and irreversible coagulation necrosis

Table 1 Baseline characteristics

	General anesthesia	Regional anesthesia
Number of patients	15	15
Average age of patients	50 years (range 26–73)	60 years (range 38–82)
Median nodule volume	6.65 ml (range 0.61–53 ml)	3.76 ml (range 0.8–7.76 ml)
Sex of patients		
Female	14	11
Male	1	4
Nodule morphology		
Solid	10	5
Complex	5	10
Indication for therapy		
Pressure symptoms	8	11
Autonomy	7	4

occurs, which is cleared by the immune system. The focal point is about 2 × 9 ml in size. A total of 10 s are required to heat 1 ml of the nodule [9–12].

The vessels supplying the nodule up to 3 mm are coagulated. The large vessels surrounding the nerves and vascular tracts remain intact and dissipate the heat generated. This is called a "heat sink" and protects vulnerable structures.

A cooling kit is installed before therapy. Nodal volume is measured by the Echopulse system. For regional anesthesia, 5 – 10 ml of Mecain 1% was applied subcutaneously to pericapsularly before therapy. General anesthesia was performed with Propofol. Initially, a dosage of approximately 1 mg/kgbw dependent on patient characteristics was given intravenously as a bolus over 1 – 5 min. Sedation was maintained with continuous administration at approximately 4.5 mg/kgbw/h dependent on patient characteristics.

The ultrasound probe is positioned on the hyperextended neck of the patient lying on his back. The device automatically creates a map of the tissue to be treated and the sensitive structures to be protected. The map is created by 10–20 sagittal and transverse layers, called voxels. The exact ablation zone of the nodule is determined by the treating doctor based on the voxel map. The device automatically selects a safety distance of 0.5 cm to the skin, 0.3 cm to the trachea and 0.2 cm to the carotid artery. In addition, the attending doctor monitors the therapy process with a diagnostic ultrasound head. Thus, the doctor can intervene manually and readjust the device at any time if he detects deviations or so-called heat bubbles which are an indicator for too high a temperature.

Statistical analysis

Because normal distribution of the data could not be assumed, statistical analysis was performed with nonparametric tests. Median pre-ablative volume reduction and median volume reduction of the total population and of both groups at three months were compared using the Wilcoxon signed-rank test. The difference in volume reduction at 3 months between the regional anesthesia group and the general anesthesia group was compared using the Mann–Whitney test. The amount of energy delivered per cubic volume of the nodule during regional and general anesthesia was compared using the Mann–Whitney test. The results were considered significant with $p < 0.05$.

Results

From 2014—2019, 30 patients (24 female and 6 male) were included in the study. Fifteen patients were treated in center 1 from 2014 to 2017, and 15 patients were treated in center 2 from 2016 to 2019. The average age of the patients was 55 years (26 to 82 years). Fifteen patients were treated with general anesthesia (0 in center 1 and 15 in center 2). Fifteen patients received regional anesthesia (15 in center 1 and 0 in center 2).

The median nodule volume before therapy was 4.2 ml (range 0.61–53 ml). In patients under general anesthesia, the median volume was 6.65 ml (range 0.61–53 ml). In patients under regional anesthesia, the median volume was 3.76 ml (range 0.8–7.76 ml).

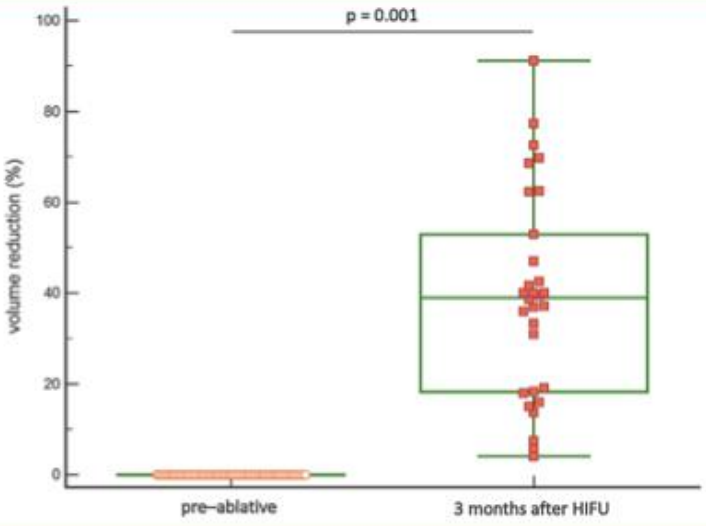

Fig. 1 Comparison of volume reduction of benign thyroid nodules before and three months after HIFU performed with the Wilcoxon signed-rank test. The total study population had an average volume reduction of 39.26% (range 4.03–91.16%, $p < 0.001$, $n = 30$) at three months follow-up

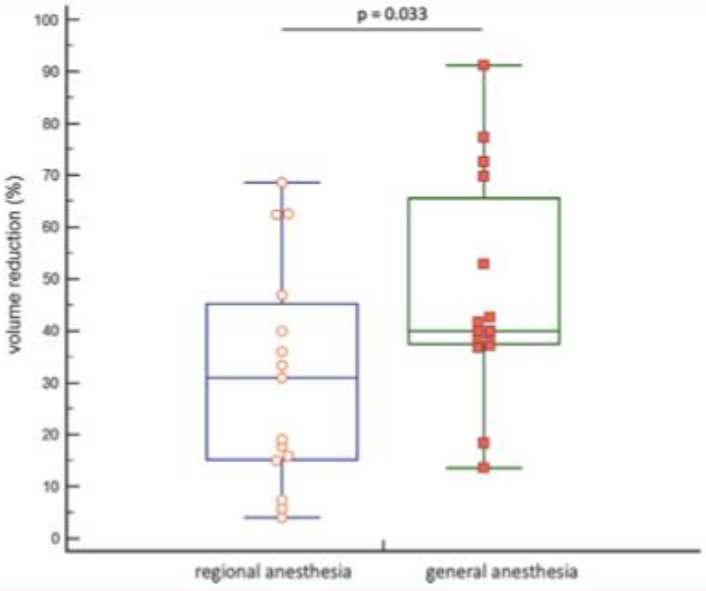

Fig. 2 Comparison of significant volume reduction of benign thyroid nodules 3 months after HIFU between regional and general anesthesia using the Mann–Whitney test. With $p = 0.033$, the volume reduction of the group treated under regional anesthesia was significantly higher

As shown in Fig. 1, the total study population had an average volume reduction of 39.26% (range 4.03–91.16%, $p < 0.001$, $n = 30$) at three months follow-up.

The group treated with regional anesthesia had an average volume reduction of 31.06% (range 4.03–68.63%, $p = 0.001$, $n = 15$) at three months follow-up. The group treated under general anesthesia had an average volume reduction of 47.46% (range 13.64—91.16%, $p = 0.001$, $n = 15$) at three months follow-up. Significant volume

reduction was found with $p < 0.05$ in the Wilcoxon signed-rank test in all three groups.

As shown in Fig. 2, the volume reduction after 3 months of the group treated under regional anesthesia was significantly different compared to the group treated under general anesthesia with $p = 0.033$ in the Mann–Whitney test.

Under regional anesthesia a median energy of 3,16 kJ/cm^3 (range: 0.96 – 8.2 kJ/cm^3) was delivered. Under general anesthesia, a median energy of 0.88 kJ/cm^3 (range: 0.18–1.63 kJ/cm^3) was delivered. The difference in energy delivery per cubic volume of the nodule in general and local anesthesia was significant with $p < 0.0001$ in the Mann–Whitney test.

The overall complication rate was 6.67%. No complications occurred in patients treated with regional anesthesia. Two patients treated with general anesthesia experienced reversible complications. Two patients suffered from recurrent laryngeal nerve paresis after therapy. In both patients, the vocal cords were freely movable again after 2 months with speech therapy. No patient suffered from an irreversible complication. The nodule sizes in these two patients were 6.65 ml and 11 ml, and the amount of energy delivered during therapy was 1.04 and 0.32 kJ/cm^3.

Discussion

The study showed that volume reduction in the group of patients treated under regional anesthesia differed significantly from the group of patients treated under general anesthesia. The average volume reduction was higher and less energy had to be delivered under general anesthesia than under regional anesthesia.

Different parameters during the intervention could explain why volume reduction was higher under general anesthesia despite less energy delivered during therapy.

During the therapeutic procedure, it is important to keep the focal point stable at the ablation zone. If the grid shifts due to movement, the device automatically stops the intervention and only partially treated lesions with a small ablation zone result. [19, 20] Due to the small ablation zone, it is very difficult to accurately target and heat the previous lesions again. If the patient is only locally anesthetized with regional anesthesia and moves, more incompletely heated lesions occur. Under general anesthesia, the patient does not move and therefore the intervention is less interrupted. Each ablation zone is heated completely. As a result, the volume reduction after therapy is greater in patients under general anesthesia and less energy is used due to the shorter treatment time. Research is already being conducted in relation to other organs to develop motion compensation techniques. [19–21]

The study indicates that in some cases, the intervention was interrupted and readjusted due to pain or deviations on the voxel map. However, no therapy was terminated early. Suboptimal placed regional anesthesia may have an impact on the patient's pain tolerance and thus on therapy tolerance. The longer heat is applied, the larger the ablation zone becomes. [12] If therapy is interrupted more frequently due to pain, more incompletely heated lesions result, and the ablation zone becomes smaller.

Whether the procedure can be performed under general anesthesia has to be evaluated individually for each patient. If regional anesthesia is chosen, it is important to minimize movements. It may be helpful to position the patient as comfortably as possible and to create a pleasant atmosphere so that the patient tolerates prolonged immobilization.

The group difference in pre-interventional nodal volume originates from the fact that, for large nodules, general anesthesia is more likely to be chosen than regional anesthesia. Since large nodules take longer to treat, the patient would not be able to lie still long enough under regional anesthesia.

More complications were observed in patients treated under general anesthesia. Recurrent laryngeal nerve paresis occurred but was reversible after speech therapy. Irreversible complications did not occur. The fact that more complications occurred under general anesthesia may be due to the patients' inability to provide feedback about pain or discomfort. With regional anesthesia, the patient can alert the doctor and the doctor can stop and readjust the procedure. Complications primarily involved the recurrent laryngeal nerve rather than the other vulnerable structures, such as the carotid artery and jugular vein. These structures, unlike the recurrent nerve, have a higher heat sink and are therefore better protected [12]. In the recurrent nerve, heat is not dissipated as well, causing it to be damaged more quickly. The complications occurred in large nodules, but not with greater amount of energy. Since the nodules were large nodules, it is likely that they were located near the nerve. Consideration should be given to neuromonitoring of the recurrent nerve under general anesthesia.

Other nodal characteristics that may have an impact on the therapeutic outcome of HIFU is nodal morphology [22, 23]. How nodal morphology affects volume reduction after HIFU has to be systematically investigated.

The advantage of HIFU over other thermoablative procedures is that it does not penetrate the skin. Therefore, there is no risk of infection and no scars are created. It does not require puncturing the thyroid capsule, and there is no risk of bleeding.

It was observed that patients complained of pain during therapy of superficial nodules with MWA and RFA. [8, 10]

In addition, HIFU can be used to treat small nodules more precisely due to the small focus (approximately 2 by 9 mm) and less surrounding tissue is damaged. The procedure is also better suited to be repeated several times, for example, in the case of large nodules.

Therefore, HIFU is an attractive alternative for benign thyroid nodules.

Conclusion

When comparing the types of anesthesia, the study showed that patients under general anesthesia had a higher volume reduction than patients under regional anesthesia. In addition, less energy was delivered under general anesthesia than under regional anesthesia. Therefore, after consideration of individual patient factors, general anesthesia is advantageous for HIFU of benign thyroid nodules. In the follow-up, it is particularly important to observe the recurrent laryngeal nerve.

Declarations

Conflict of interest The authors declare that they had no conflict of interest.

Ethical standards The study has been approved by the ethics committees and complies with the Declaration of Helsinki and local regulations.

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

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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.

Trial registraftion number 2020-1728-evBO. **Date of registration:** 16.06.2020. **Agency:** Ethik-Kommission bei der Landesäztekammer Hessen

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 thermo-ablative 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 pre-interventionally 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 ($p > 0.05$)

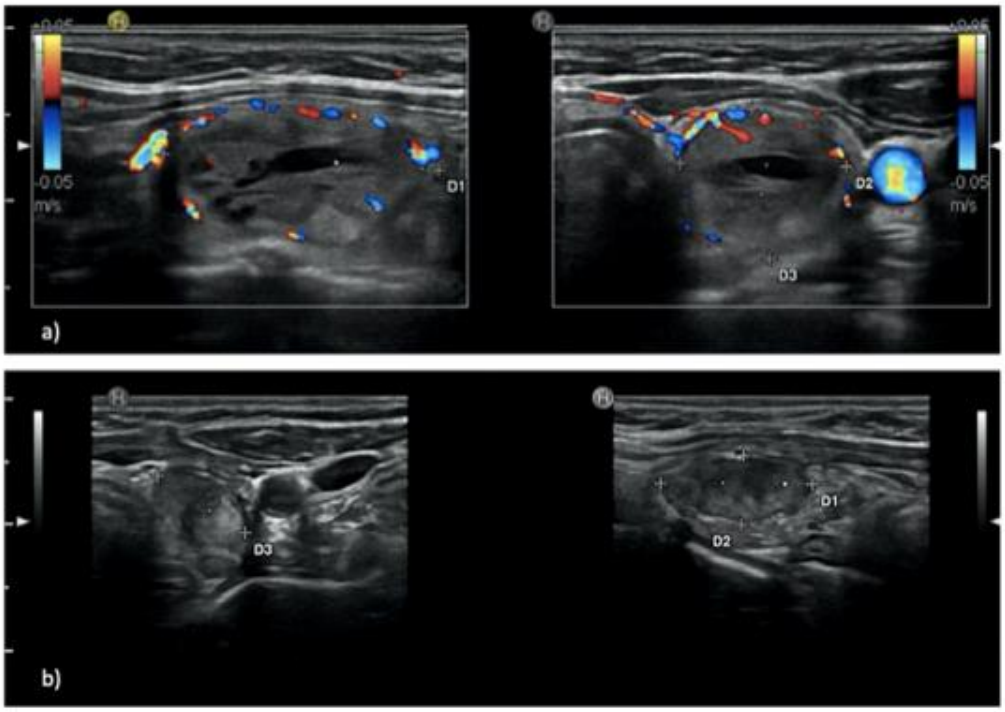

Fig. 1 **a** Screen capture of ultrasound examination before HIFU therapy (Diameter 1 [D1]: 31.8 mm, D2 19.1 mm, D3 17.4 mm, nodule volume: 5.55 ml). **b** Screen capture of ultrasound examination after HIFU therapy (D1: 24.1 mm, D2 11.1 mm, D3 16.6 mm, nodule volume: 2.32 ml)

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

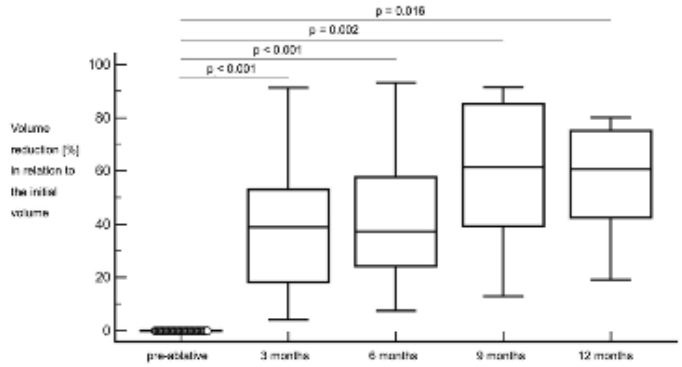

Fig. 2 Median volume reduction of benign thyroid nodules compared to initial volume 3, 6, 9 and 12 months after therapy. A volume reduction with $p < 0.05$ in the Wilcoxon-signed-rank test was considered significant

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

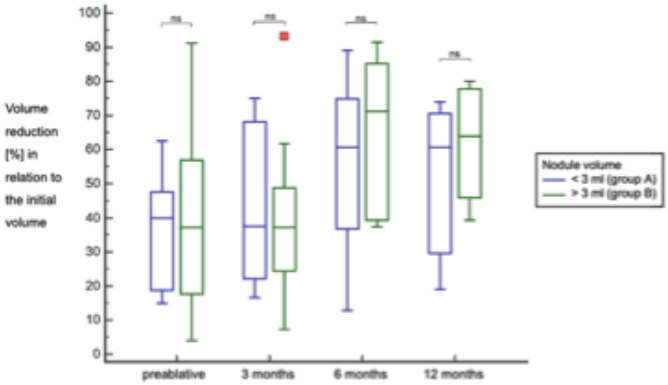

Fig. 3 Comparison of median volume reduction between benign thyroid nodules with an initial nodule volume <3 ml and >3 ml preablatively and at the time points 3, 6, and 12 months after therapy. $P < 0.05$ by Mann–Whitney test was considered significant. There was no significant difference in volume reductions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

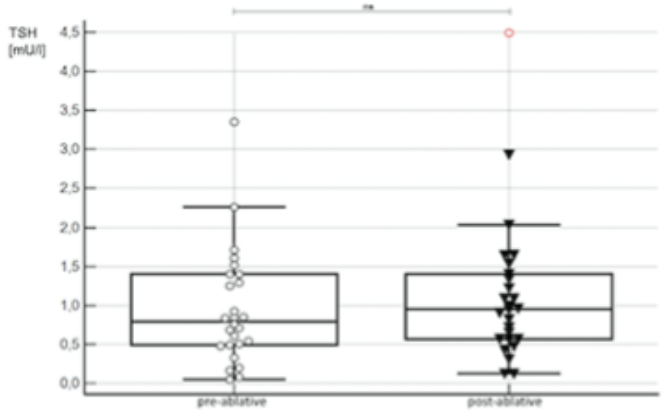

Fig. 4 Effects of HIFU of benign thyroid nodules on hormonal-thyroid-function. Preablative and postinterventional serum TSH levels compared with Wilcoxon-sign-rank test. With $p > 0.05$, no significant change is presented

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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