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Research Article

Ultrasound-Elastography for Predicting Response of Hyperfunctional Thyroid Nodules to Radioiodine Therapy: Initial Results

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Abstract

Background: Ultrasound-based real-time elastography (USE) is a useful tool in the diagnosis of suspicious thyroid nodules. This study analysed whether USE can predict the response of hyperfunctional thyroid nodules to Radioiodine Therapy (RIT) and whether USE can be used for individualized optimization of RIT.

Methods: Ninety-three hyperfunctional thyroid nodules (52 unifocal, 14 bifocal, and 27 multifocal) of 72 patients were included in this study. Only nodules without large calcification or cystic areas were included due to the decreased quality and reliability of ultrasound and USE for nodules with those characteristics. The following attributes of the nodules were analysed before RIT: stiffness based on the USE score classification defined by Rago (1 = soft, 2 = medium, 3 = hard); classical ultrasound criteria, such as echogenicity and perfusion; thyroid scintigraphy and serum TSH level. Approximately four months after RIT, the therapy response was evaluated by thyroid scintigraphy and serum TSH level. Therapy response was defined as normalized TSH level and thyroid scintigraphy without hyperfunctional nodules.

Results: RIT was successful in 85 nodules (responders) and unsuccessful in 8 nodules (non-responders). Among the responders, 26 nodules were initially rated as “soft”, 14 as “medium” and 45 as “hard”. Among the non-responders, 5 nodules were initially rated as soft and 3 as hard. There was no statistically significant correlation between USE score and therapy response.

Conclusion: Ultrasound-based real-time elastography (USE) cannot predict whether hyperfunctional thyroid nodules will respond to RIT and, consequently, cannot be used to aid in therapy planning.

Keywords: Elastography; Hyperthyroidism; Thyroid nodule; Radioiodine therapy; Therapy response

Abbreviations

RIT: Radioiodine Therapy; TSH: Thyroidea Stimulating Hormone; USE: Ultrasound-Based Real-Time Elastography

Introduction

Radioiodine Therapy (RIT) is an effective and safe treatment for hyperfunctional thyroid nodules. Individual therapy activity is calculated based on the volume of the targeted thyroid nodule and thyroid uptake, which is measured by the radioactive iodine uptake test [1]. During follow-up, treatment response should be evaluated within 6 months and should include thyroid scintigraphy and measurement of serum thyroid-stimulating hormone (TSH) level [1].

RIT failure is observed in approximately 10% of treated patients for whom the estimated therapy activity was applied [2,3]. It is unclear why some nodules do not respond to RIT. Possible explanations are malfunction of radioiodine absorption resulting in a lower absorbed dose than the calculated one, or a high iodine metabolism of thyroid cells resulting in a shorter retention of iodine in the nodules. Moreover, an inhomogeneous structure of the thyroid nodules could lead to an inhomogeneous distribution of radioiodine with some areas of the nodule remaining untreated or insufficiently treated. To prevent therapy failure and to identify patients at risk for insufficient treatment, a predictive marker of therapy response would be beneficial.

Many studies, including studies by Rago et al. and Vorländer et al., have investigated Ultrasound-Based Real-Time Elastography (USE) for the diagnosis of thyroid nodules [4,5]. The initial results of those studies were promising for the diagnosis of malignant thyroid nodules. USE measures the stiffness of a tissue, and this characterization provides additional information about the nodule, e.g., a hard nodule is suspicious for malignancy. Although recently published studies were not able to reproduce the initial results of USE, we assumed that the stiffness of nodules can indicate nodule homogeneity and might have a predictive value for RIT.

In this study, we investigated whether USE can predict RIT response or identify thyroid nodules that are more likely to have a lower therapy response and, thus, aid in therapy planning.

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Materials and Methods

Patients

In this study, 93 hyperfunctional thyroid nodules (52, 14, and 27 nodules of unifocal, bifocal, and multifocal thyroid autonomies, respectively) of 72 patients (52 women, 20 men; age 62.6 years ±12.2) with hyperthyroidism prior to RIT were included. One of the inclusion criteria was the absence of a large calcification or cystic areas, because these reduce the reliability of USE [6,7]. For the remainder of the manuscript, solitary and bifocal autonomies will be referred to as "focal autonomies". According to the guidelines of the European Association of Nuclear Medicine [8], all patients underwent a pretherapeutic assessment, including thyroid scintigraphy, ultrasound and determination of serum TSH. Additionally, a US-elastography of the target nodules was performed to evaluate elasticity prior to RIT. To assess the success of RIT, a follow-up examination was performed approximately 4 months after RIT and included thyroid scintigraphy and determination of TSH level.

This study was conducted according to the rules and regulations of the local ethics committee. All patients gave their informed consent to participate in the study.

Sonography and US-Elastography

Sonography and USE were performed with an IU22 (Philips Deutschland GmbH, Germany) equipped with a L12-5 transducer (linear, 5-12 MHz). This device is equipped with a strain-based technology that uses breathing or artery pulsation to assess the elasticity of tissues. An experienced physician performed sonography and USE. Each nodule was evaluated using the established sonographic criteria, including nodule size in three dimensions, echogenicity and vascularization. Moreover, the volume of each nodule was measured (length x width x height x ½) by ultrasound. USE was performed in the same session. Approximately 200-300 images per nodule were recorded in the sagittal and axial orientation of the whole nodule and the surrounding thyroid tissue. All acquired images were saved for subsequent analysis.

Image analysis

Two experienced physicians viewed the saved images on an Osirix Workstation (Pixmeo SARL, Switzerland, version 5.8.5) and classified the nodules by consensus. The quality of USE for each image is displayed on a scale. Only images with a quality of 66% or higher were analysed to ensure good reliability. A representative image of the nodule that showed the typical feature of the nodule (without cystic areas and calcifications) was selected by consensus. According to the established scoring system of Rago et al., the elasticity of each nodule was classified as soft (Rago 1), medium (Rago 2) or hard (Rago 3) [4].

Thyroid scintigraphy

The scintigraphy scans were performed according to the German guidelines [9]. Briefly, 20 minutes after intravenous injection of approximately 60 MBq ^{99m}Tc pertechnetate (TcO_4), a planar image was acquired using a dedicated gamma camera (MiniCam 250, INTER MEDICAL Medizintechnik GmbH, Germany). The acquisition period lasted for either 10 minutes or 100,000 counts, whichever was accomplished first. Each detected hyperfunctional nodule was correlated with sonography and USE.

Radioiodine therapy

Radioiodine Therapy (RIT) was performed according to the German and EANM guidelines [1,10]. The therapy activity was calculated from the results of the radioiodine test (aim: unifocal and bifocal: 400 Gy, multifocal: 200 Gy), and the therapeutically achieved dose was measured by serial uptake measurements [10].

Statistics

Statistical analyses were performed with Prism 6 (GraphPad Software Inc., version 6.05). For differences between responders and non-responders, unpaired t-tests (two-tailed) were performed with a significance level of $p<0.05$. For differences between the Rago groups (1-3), the chi-square test was performed with a significance level of $p<0.05$. The descriptive statistical results are expressed as means (median±SD).

Results

The results are presented based on two groups: "responders" and "non-responders" to RIT.

Therapy responders

At follow-up, 85 thyroid nodules of 65 patients showed a therapy response: hyperthyreosis was eliminated in all 65 patients (Figure 1). However, 31 of the 65 patients had a higher serum TSH level and, thus, were given L-thyroxin substitution treatment at follow-up, and 34 of the 65 patients had a euthyroid serum TSH level and, thus, did not receive L-thyroxin substitution treatment. At follow-up, no hyperfunctional nodules were found by thyroid scintigraphy in any of these 65 patients (Figure 2).

Before RIT, the ^{99m}Tc uptake of the thyroid nodules was 1.5% (1.2±1.3) in the focal autonomies group and 1.4% (1.3±0.8) in the multifocal autonomies group. The average volumes of the thyroid and of the thyroid nodules were 23.7ml (20±10.1) and 6.3ml (4.4±6.5) for the focal autonomies group and 23.5ml (19±9.4) and 3.3ml (1.2±5.6) for the multifocal autonomies group, respectively. The mean administered activity of radioiodine and the absorbed dose of radioiodine were 554.7 MBq (475±273.3) and 332.5 Gy (325±145.5) in the focal autonomies group and 597.3 MBq ^{131}I (575±193.9) and 225.4 Gy (230±62.3) in the multifocal autonomies group, respectively. Before RIT, the mean serum TSH level was 0.18mU/l (0.05±0.33)

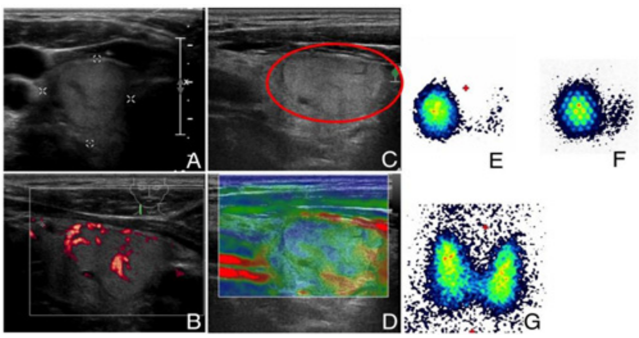

Figure 1: Thyroid nodule right lobe (unifocal autonomy): A: Axial; B: sagittal; C: sonography showing increased perfusion; D: sagittal sonography corresponding to the elastography (nodule marked in red), the elasticity is predominantly soft. E: The scintigraphies show the focal autonomies before radioiodine therapy; F: during radioiodine therapy; and G: At follow-up, the scintigraphy shows a thyroid without focal autonomy.

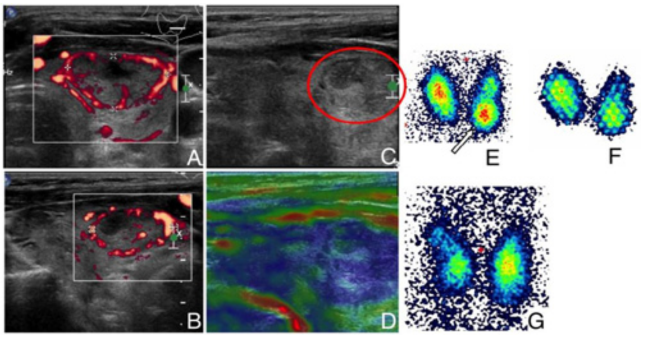

Figure 2: Thyroid nodule lower left lobe (multifocal autonomy): A: Axial; B: sagittal; C: sonography showing increased perfusion; D: sagittal sonography corresponding to the elastography (nodule marked in red), the elasticity is hard. E: The scintigraphies show the multifocal autonomies (arrow point at the mentioned nodule) before radioiodine therapy; F: during radioiodine therapy; G: At follow-up, the scintigraphy shows a thyroid without the previous multifocal autonomies.

in the focal autonomies group and 0.15mU/l (0.08±0.19) in the multifocal autonomies group.

Therapy non-responder

Eight thyroid nodules of 7 patients presented with serum TSH levels of < 0.3mU/l at follow-up, indicating that they did not respond to RIT. The thyroid scintigraphies of these nodules at follow-up showed that they were still hyperfunctional. Table 1 presents some details of these nodules.

Before RIT, the ^{99m}Tc uptake of the thyroid nodules was 3.2% (3.3±2.0). The average volume of the thyroid was 38.8 ml (26.5±32.6), and the average volume of the thyroid nodules was 8.2ml (2.0±12.6). The mean administered activity of radioiodine was 643.8 MBq (525.0±385.9), and the mean absorbed dose was 290.0 Gy (220.0±114.14). The mean serum TSH level before RIT was 0.30mU/l (0.16±0.33).

Because of the small number of non-responders, the statistical analysis was performed without dividing them by type of autonomy, i.e., unifocal *vs.* multifocal. The non-responders had a statistically significantly higher thyroid volume before RIT than the responders (p = 0.0026). There were no statistically significant differences between responders and non-responders regarding the following attributes: age (p = 0.72); ^{99m}Tc uptake (p =0.76); thyroid nodule volume (p = 0.29); TSH (p = 0.24); therapy activity (p = 0.44); and absorbed dose

Table 1: Sonography, Elastography and Radioiodine Therapy of the 8 Non-responding Thyroid Nodules.

ID	autonomy	Rago	echogenicity	vascularization	absorbed dose [Gy]	nodule volume [ml]
1	unifocal	3	isoechoic	hyper	510	19
2	unifocal	1	isoechoic	normal	210	1
3	unifocal	1	isoechoic	peripher	250	4
4	unifocal	3	isoechoic	peripher	350	2
5	unifocal	3	isoechoic	peripher	410	3
6	multifocal	1	isoechoic	peripher	220	14
7*	multifocal	1	isoechoic	hyper	220	2
8*	multifocal	1	isoechoic	hyper	220	0.5

Table 2: Elastography of the Thyroid Nodules Classified by Rago Score and Divided into Responders and Non-Responders after Radioiodine Therapy.

	all	responder		non-responder
		uni- / bifocal	multifocal	
Rago 1	31	19	7	5
Rago 2	14	10	4	0
Rago 3	48	32	13	3

(p = 0.81).

For evaluation of the influence of the elastographic results, the nodules were divided into three groups: “soft” (Rago 1), “medium” (Rago 2) and “hard” (Rago 3). Table 2 presents an overview of the elastographic results. Thirty-one thyroid nodules were rated as soft, 14 as medium and 48 as hard. In the responders group, 26 nodules were rated soft, 14 as medium and 45 as hard. In the non-responders group, 5 nodules were rated as soft, 0 as medium and 3 as hard. Differences between the groups of responders and non-responders in regards to the Rago classification of the nodules were not significant (p = 0.143).

Discussion

Although radioiodine therapy of hyperfunctional thyroid nodules is an established and well-proven therapy, approximately ten percent of patients show insufficient results after the first treatment [2,3]. To date, there are no predictive factors for assessing response to RIT. We hypothesized that the stiffness of nodules reflects their composition, e.g., heterogeneity, vascularization and colloidal structure, and therefore, may be a predictive factor for the effectiveness of RIT. Information about the stiffness of hyperfunctional thyroid nodules could potentially be used for therapy planning or to minimize therapy failure.

In recent years, USE has gained increasing interest for the characterization of thyroid nodules. Initial studies in this field showed encouraging results. For the assessment of malignancy in thyroid nodules, Rago et al. and Vorländer et al. found a high sensitivity and specificity of USE and a high negative predictive value of USE, respectively [4,5]. More recent studies questioned the results of the initial studies. For example, Rivo-Vázquez et al. reported a lower sensitivity and specificity [11] of USE than did the original studies, and Unlütürk et al. stated that USE is not superior to ultrasound [12]. In summary, the benefit of USE in the diagnosis of malignant thyroid nodules is unclear.

The aim of this study was to assess the benefit of USE in predicting response to RIT and in optimizing treatment planning and patient management for patients with hyperfunctional thyroid nodules.

In this study the hyperfunctional nodules of about the half of all responders to RIT were categorized as hard nodules. The authors of the initially published literature on USE for the diagnosis of malignant thyroid nodules argued, that the transformation of thyroid cells occurs in conjunction with an increase of tissue stiffness, which reflects the loss of the characteristics of the thyroid cell itself. If that is the case, most of the hard nodules in our study should have shown decreased radioiodine uptake resulting in an insufficient treatment response; however, that outcome was not observed in this study.

Another assumption was that highly vascularized thyroid nodule might be categorized as soft rather than hard; thus, soft nodules might show a better response to RIT. This assumption seems to be invalid, too. These results suggest that USE is not able to predict the RIT response of hyperfunctional thyroid nodules.

The main limitation of this study is the small number of non-responders in our cohort, which limited the strength of the results of the statistical analysis. However, these numbers mirror the clinical situation, as non-responders in this setting are rare, approximately 10% [2,3]. Another limitation is that we included patients with bifocal and multifocal hyperfunctional nodules. To analyse the predictive value of USE, it would have been preferable to include only solitary hyperfunctional nodules. This issue should be addressed in future studies. An additional limitation of our study is the clinical setting itself. The applied activities could have been overestimated. Even if structural changes to nodular tissues cause decreased radioiodine uptake, an overestimation of the required dose would make this activity difficult to observe. However, we cannot determine whether the required dose was overestimated in our study.

To our knowledge, this is the first study to analyse the predictive value of USE for RIT of hyperfunctional thyroid nodules. Our results indicate that the stiffness of thyroid nodules is not a reliable indicator of therapy response and has no consequences for patient management. Further studies with a larger group of non-responders are needed to confirm or refute our results.

Conclusion

In our clinical setting ultrasound-based real-time elastography was not able to predict whether hyperfunctional thyroid nodules will respond to RIT and, consequently, cannot be used to aid in therapy planning.

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