Abstract

Purpose

Percutaneous microwave ablation (MWA) poses a new, minimal-invasive therapeutic approach to thyroid nodules. The goal of this retrospective study is to find out about the prognostic value of different pre-ablative diagnostic results concerning the outcome of benign thyroid nodules treated with MWA at a 3-month follow-up.

Materials and Methods

Twenty-four patients with 26 nodules were treated. Pre-ablative assessment contained different sonographical modalities as well as functional imaging with 99mTc-pertechnetate and 99mTc-MIBI. At a 3-month follow-up, ultrasound examination was performed to assess the nodular volume reduction. Correlation of pre-ablative diagnostic parameters and nodular volume reduction was assessed by calculating Pearson's $r$ and Spearman's rank correlation coefficient $\rho$.

Results

Mean relative nodular volume reduction at follow-up was 50.9 ± 19.8 %. The surveyed diagnostic parameters showed the following results concerning correlation with nodular volume reduction: $r = -0.53$ for baseline volume, $r = -0.40$ and $r = 0.32$ for 99mTc-MIBI-scintigraphy and 99mTc-pertechnetate-scintigraphy, $\rho = 0.21$ for nodular vascularity, $\rho = -0.07$ for stiffness and $\rho = -0.33$ for nodular composition.

Conclusions

Except baseline nodular volume, none of the sonographic findings presented a good correlation with nodular volume reduction. After all, 99mTc-scintigraphy still represents an important tool when dealing with thyroid nodules, although a prognostic significance relating to this procedure could not be validated.

Introduction

Thyroid nodules pose a common clinical issue, ranking amongst the most frequent transformations of the thyroid. The prevalence in Germany, until 2005 representative for a region of relative iodine deficiency [1], is estimated to be up to 68%, depending on age and the way of detection [2,3], with the incidence increasing with continuous improvement of sonographical imaging [4]. Those nodules tend to be benign in most cases; the incidence of thyroid cancer in Europe is reported to be 2.2/100,000 – 12.4/100,000 [5], making it a relatively rare malignant event. Still, benign thyroid nodules may require treatment due to cosmetic issues or subjective symptoms.

In the last years, minimally invasive techniques of treating thyroid nodules have emerged, representing a promising alternative to the well-established methods, i.e. surgical intervention and radioiodine therapy [6]. Amongst these, radiofrequency ablation
(RFA) [7,8], percutaneous ethanol injection [9], ultrasound-guided laser therapy [10,11] as well as high-intensity focused ultrasound (HIFU) [12] are to be mentioned. Percutaneous microwave ablation (MWA) is a thermal ablative technique [13] that has already been successfully put to use in order to treat malignancies in other organs such as the liver [14]. The limited number of clinical and experimental studies dealing with the use of MWA in the treatment of thyroid nodules [15-19] has presented encouraging results featuring a favorable profile of adverse effects [20-23]. In this context, thyroid scintigraphy represents a useful diagnostic tool in terms of assessing the consistency and function of thyroid tissue [24], furthermore allowing a rapid post-ablative prognostic evaluation considering the later outcome [23]. Other diagnostic approaches based on the principle of sonography can be used in pre-ablative examination of thyroid nodules: While duplex ultrasound (DU) poses a widespread and well-known sonographic modality for the detection of blood flow [25], ultrasound elastography (UE), sometimes referred to as a “virtual palpation”, is used to image tissue elasticity [26-28]. The prognostic value of these sonographic modalities in the given context has so far not been explored. With $^{99m}$Tc-scintigraphy being a significant and efficient, yet comparatively wearing (radiation exposure) diagnostic method, the aim of this retrospective study is to find out in what extent findings of pre-ablative sonography and $^{99m}$Tc-scintigraphy correlate with nodular volume reduction at a 3-month follow-up and therefore deliver a prognostic statement about the clinical outcome of MWA of thyroid nodules.

Materials and Methods

Patients

This study evaluates data collected from 24 patients with a total of 26 nodules who were treated with MWA (11 men, 13 women; mean age 52.4 years; median age 54 years; range 31 – 75 years). Patients met the criteria for treatment if there were (a) cosmetic problems, (b) symptomatic nodules (e.g. swallowing problems, hoarseness, distress) or (c) refusal of surgery or contraindications against it, respectively. Exclusion criteria for treatment were (a) excessive thyroid volume with retrosternal growth, (b) lack of symptoms, (c) histological evidence for follicular proliferation in terms of a malignant dysplasia or (d) critical position of adjacent structures such as vessels or nerves.

Patients were treated on a compassionate use basis; written informed consent, clarifying possible risks and the experimental nature of the treatment, was obtained from all patients. Local ethics committee approved the study protocol and the retrospective evaluation of gathered data, respectively.

Equipment

The microwave system used in this study (Avecure MWG881, MedWaves, Inc., San Diego, CA) works in a frequency range of 902–928 MHz generating maximum temperatures of approximately 140°C. According to individual needs and the
size of the area to be ablated, three different probes (uncooled tip, 14–16 G) with diverging ablation radii are available. The field size varies from 1 – 4 cm, all probes feature integrated temperature sensors. The target temperature was 60–95°C with an output of 24–36 W. The device was operated in power control mode with the microwave generator periodically delivering pre-adjusted peak energy.

All sonographic examinations were performed using a SonixTOUCH Ultrasound system (Ultrasonix Medical Corporation, Richmond, BC, Canada), ran in 2D/B-Mode for regular ultrasound imaging of the thyroid, in Power Color Doppler mode in order to display nodular vascularity and in Elastography mode, respectively. A linear transducer was used for all sonographic modalities.

Pre-ablative assessment

Before ablation all patients underwent ultrasound examination, laboratory tests and scintigraphic thyroid imaging. Ultrasound examination was performed in order to evaluate volume, number and composition of the nodules. Volume was calculated using the following equation:

\[
\text{Volume} [cm^3] = \frac{\text{height} [cm] \times \text{width} [cm] \times \text{depth} [cm]}{2}
\]

Duplex ultrasound examination [Figure 1] and ultrasound elastography [Figure 2] were performed in order to determine vascularity and stiffness of each nodule. Vascularity was graduated as following: 1 – no blood flow; 2 – minimal blood flow; 3 – marked blood flow. Nodular stiffness was graduated in the following way: 1 – soft; 2 – rather soft; 3 – rather
hard; 4 – hard. Additionally, nodules were classified by their composition, as imaged by sonography, depending on their relation of solid and cystic portion: 1 – cystic; 2 – rather cystic; 3 – equally cystic and solid; 4 – rather solid; 5 – solid. The type of vagus nerve location [29] was identified in order to avoid irritation or lesion of the vagus nerve during ablation. Laboratory tests included a complete thyroid hormone status, blood count, coagulation diagnostic, C-reactive protein and blood glucose.

Patients with known “hot” or “indifferent” nodules, according to earlier scintigraphy, received a thyroid scan with averagely 75 MBq 99mTc-pertechnetate [Figure 3a]. Patients presenting “cold” nodules in earlier scintigraphic examinations underwent a thyroid scintigraphy with 500 – 557 MBq 99mTc-MIBI [Figure 4a] and additionally fine needle aspiration biopsy (FNAB), which has proven to be a safe method of excluding malignancy, especially when combined [30]. In patients with both “cold” and “indifferent” thyroid nodules both of the mentioned scintigraphy modalities were performed. Acquisition was conducted 20 minutes after administration of 99mTc-pertechnetate or, in case of 99mTc-MIBI scans, 10 and 60 minutes after, respectively. For this purpose a scintillation camera (Nuclide TH/22, Mediso Medical Imaging Systems, Budapest, Hungary) equipped with a low energy collimator was used.

Procedure

The intervention was performed during local anesthesia and under aseptic conditions. If realizable an access via transisthmic approach was chosen, hereby permitting the display of the microwave probe in its entire length and its current location in reference to vascular or neuronal structures via ultrasound imaging. If transisthmic approach was not accomplishable, a craniocaudal access path was chosen. After correct identification of vagus and recurrent laryngeal nerve the probe was placed in the nodule under sonographical guidance [Figure 5]. If nodules were found to be mainly cystic, fluid contents were aspirated before ablation in order to minimize the pre-procedural ablation volume and to exclude possible heat-sink effects resulting from cystic fluids [31].

During ablation the operating physician had to pay attention to the occurrence of so-called “microbubbles” and hypoechoic areas, sonographical signs indicating the direct effects of heat development in the ablation area [32]. If required, the probe was repositioned and other parts of the nodule were treated equally.

Twenty-four hours after intervention each patient underwent another ultrasound examination of the ablation site in order to evaluate post-ablative nodular volume reduction. No patients were re-treated.

Statistical analysis

Statistical results were obtained using “BIAS.”, version 10.04 (epsilon Verlag, 1989 – 2013). Values were tested for normality of distribution and t-tests as well as Wilcoxon-matched-pairs-test were performed to evaluate nodular volume and functional imaging findings. Pearson’s $r$ was calculated in order to find a possible correlation between nodular volume reduction and pre-ablative nodular volume and 99mTc-uptake, respectively. Additionally, Spearman’s rank correlation coefficient $\rho$ was determined to correlate nodular volume reduction with nodules’ vascularity, stiffness and composition, respectively. All data are reported as mean ± standard deviation.

Results

MWA

Mean pre-ablative nodular volume was 35.2 ± 45.4 ml, post-ablative volume was 21.9 ± 34.7 ml. This equals a mean absolute volume reduction of 13.3 ± 14.7 ml and a relative reduction of 50.9 ± 19.8 % ($p < 0.001$). Duplex ultrasound examination showed 1 nodule with no relevant blood flow, 12 with minimal and 13 nodules with marked blood flow. Ultrasound elastography imaged 2 nodule of soft, 14 of rather soft, 7 of rather hard and 3 of hard consistency. Furthermore, regarding nodular composition, 3 nodules presented as rather cystic, 12 as equally cystic and solid, 4 as rather solid and 7 as solid. Mean pre-ablative nodular 99mTc-MIBI-uptake was 18.3 ± 10.0 % ($^{99m}$Tc-MIBI) and 16.7 ± 13.0 % ($^{99m}$Tc-pertechnetate).

Correlating relative volume reduction with nodular baseline volume and 99mTc-uptake, Pearson’s $r$ was found to be $0.53$ ($p = 0.005$) for baseline volume and $0.40$ ($p = 0.088$) and $0.32$ ($p = 0.532$) for nodules imaged with 99mTc-MIBI and 99mTc-pertechnetate, respectively. One nodule, rather forming a conglomerate of 4 single nodules imaged partly with 99mTc-MIBI and 99mTc-pertechnetate, could not be separately distinguished by sonographic means and therefore was not taken into consideration in terms of correlating volume reduction and 99mTc-uptake. Correlating nodular volume reduction with the other pre-ablative findings, the calculation of Spearman’s rank correlation coefficient showed the following results: $\rho = 0.21$ ($p = 0.293$) for vascularity, as displayed with DU, $\rho = -0.07$ ($p = 0.718$) for stiffness, as found by UE, and $\rho = -0.33$ ($p = 0.097$) for nodular composition.

Complications

Slight pain and a feeling of pressure during the ablation were reported by all patients, yet the pain could be easily decreased by just reducing the temperature. No further
treatment was required; the pain rapidly vanished after ablation. All patients developed first-degree skin burns at the puncture site which did not require any specific treatment either and disappeared within days. One patient developed a cervical hematoma, yet an active hemorrhage could be ruled out by color duplex sonography. Three patients reported dragging pain towards the mandibular angle and ear during the treatment. No swallowing difficulties, vagal reactions or voice changes were observed.

Serious complications like secondary hemorrhage, infections, nodule ruptures, deep hematomas or injuries of nerval structures did not occur. In one patient a slight hyperthyreosis with a T4 level of 207 nmol/l (normal range: 55 – 170 nmol/l) without elevated T3 was discovered after ablation, yet the thyroid function normalized within one week without occurrence of any further complications. Another patient with known diabetes mellitus presented a slightly increased blood glucose level of 118 mg/dl. All other patients presented a proper thyroid function after ablation. In the post-procedural observation period one patient who had received radioiodine therapy in addition to MWA developed Graves’ disease. Although self-limiting immunogenic hyperthyreosis is known to rarely occur in patients after radioiodine therapy it is not possible to definitely exclude MWA as a potential (co-) factor.

Discussion

The goal of this study was to explore whether there are sufficient ultrasound-based alternatives to 99mTc-scintigraphy in the prognostic evaluation of thyroid nodules treated with MWA. For this purpose nodular volume reduction at a 3-month follow-up, which was averagely 50.9 ± 19.8 % (p < 0.001), was correlated with pre-ablative diagnostic parameters.

Considering the mean pre-ablative nodular volume, an appreciable correlation could be found, with r = - 0.53 (p = 0.005), which strongly indicates a better effect of MWA on smaller nodules [Figure 6a]. Yue et al. [21] propose that the final clinical outcome considerably depends on nodular baseline volume, with a significant inverse correlation between baseline volume and volume reduction ratio. The results of this study support this thesis, even presenting a stronger correlation, as Yue et al. found that the correlation was r = - 0.24, which might actually be considered as rather weak. A significant prognostic value of the baseline nodular volume might be deduced from these findings; hence smaller nodules might be expected to respond to the treatment better as bigger ones. This circumstance might be based on the overall difficulty of delivering an adequate dose of microwave energy to the entire node if the microwave probe needs to be relocated due to the nodule’s size [33]. In this case overlapping microwave fields are thinkable as well as the deficient covering of marginal areas by MWA, both leading to a less desirable outcome than in nodules requiring only a single shot ablation.

Pre-ablative sonographic examinations also included the rating of nodular vascularity by duplex ultrasound and stiffness of nodular tissue by qualitative ultrasound elastography. No strong correlation of nodular volume reduction and nodular blood flow could be discovered, with Spearman’s ρ = 0.21 (p = 0.293) tending to indicate better results in well perfused nodules. While the diagnostic advantages of DU are hardly deniable in various medical fields, one may attribute a rather negligible role to DU in terms of this particular context. Apart from the lacking diagnostic value there was no apparent therapeutic consequence for the treatment with MWA coming from DU findings, as Happel et al. [24] pointed out that DU cannot replace scintigraphy in the diagnosis of functional thyroid autonomy, while Algin et al. [34] interpreted DU as not useful for distinguishing malignant from benign thyroid nodules. Nodular stiffness, as detected by UE, showed a correlation of ρ = - 0.07 (ρ = 0.718), hence not indicating a prognostic advantage of soft nodules over nodules of rather hard structure or vice versa. These findings do not support UE as a potential replacement for scintigraphy in the detection or evaluation of thyroid nodules. Etzel et al. [35] concluded that UE might deliver additional information about nodular consistency compared to manual palpation, yet that it could not replace scintigraphy in diagnostic terms. As for DU, there were no therapeutic consequences for MWA coming from UE findings, for the important question of malignancy cannot be clarified by UE alone [36]. After all, neither DU or UE seem to deliver reliable predications in the field of thermal ablation of thyroid nodules [37]. This, as well as the lacking therapeutic consequence of DU and UE findings, respectively, does not allow assessing these sonographic modalities as useful tools in the field of MWA of thyroid nodules.

As another aspect of ultrasound-based diagnostic nodules were classified by their composition in terms of the relation of cystic and solid portion. Compared to the results of DU and UE, there was a better, yet still mediocre, correlation with nodular volume reduction detectable, with ρ = - 0.33 (ρ = 0.997) hinting at cystic nodules to have a better prognosis than solid ones. Feng et al. [20] and Yue et al. [21] both found a significant better outcome of MWA treated nodules, which were of predominantly cystic composition compared to mixed or solid nodules. In this context, the role of a more homogenous conduction of heat and removal of cystic components were discussed as possible explanations for the more effective nodular volume reduction. Lim et al. [38] declared a similar correlation in the radiofrequency ablation of thyroid nodules at a 4-year follow-up. Bearing in mind, that there were no nodules of mainly cystic composition in this collective and that the overall distribution of different compositional types was fairly homogenous, with the majority of treated nodules...
being of mixed solid-cystic composition, nodular composition cannot explicitly negated as a prognostic factor for the morphological outcome. Yet, it remains unclear whether the assumed better response to MWA comes only from the pre-ablative aspiration of the cystic portion, resulting in a more or less striking loss of volume itself, or if there are further factors, which may lead to an improvement of prognosis.

Correlating relative volume reduction with pre-ablative $^{99m}$Tc-uptake, Pearson’s $r$ was found to be -0.40 ($p = 0.088$) [Figure 6b] and 0.32 ($p = 0.532$) [Figure 6c] for nodules imaged with $^{99m}$Tc-MIBI and $^{99m}$Tc-pertechnetate, respectively. Korkusuz et al. [23], using a center specific functional imaging score (CSFIS), found a significant decrease of nodular $^{99m}$Tc-uptake 24 hours after ablation for both scintigraphic modalities, suggesting a statistical correlation of $^{99m}$Tc-uptake reduction and nodular volume reduction. Viewing at the results of this study, single pre-ablative scintigraphy with $^{99m}$Tc-MIBI presented a good and significant correlation with nodular volume reduction at a 3-month follow-up. Here, the negative correlation ($r = -0.40$) indicates a better prognosis for nodules with rather little $^{99m}$Tc-MIBI-uptake. This circumstance seems to be not transferable to $^{99m}$Tc-pertechnetate-scintigraphy ($r = 0.32$), with the positive correlation indicating a contrary interpretation compared to the findings of $^{99m}$Tc-MIBI-scintigraphy, thus nodules with high $^{99m}$Tc-pertechnetate-uptake potentially showing rather appreciable results. The reason for this circumstance is not apparent and requires further analyses, with higher case numbers possibly allowing a more comprehensive interpretation.

The comparatively small number of examined cases surely poses a major limitation to this retrospective study, as well as its retrospective nature itself, with higher case numbers maybe allowing a more reliable statement about the prognostic value of the different diagnostic tools in the context of microwave ablation of thyroid nodules. Future endeavors should imply prospective randomized studies to define the role of MWA in the field of minimal-invasive treatment of thyroid nodules.

Conclusions

MWA appears to be a sufficient minimal-invasive approach to benign nodules of the thyroid, with a mean nodular volume reduction of 50.9 ± 19.8 % at a 3-month follow-up. Neither ultrasound elastography ($p = 0.07$) or duplex ultrasound ($p = 0.21$) seem to bear the potential of delivering a reliable statement about the final morphological and thereby clinical outcome. Although the correlation of nodular composition and nodular volume reduction ($p = -0.33$) could not be explicitly confirmed, based on the collective of nodules examined, it might serve as a prognostic factor with a negative correlation. Nodular baseline volume occurred to be of appreciable prognostic value ($r = -0.53$), with smaller nodules presenting a more favorable outcome than bigger ones. Single pre-ablative $^{99m}$Tc-scintigraphy ($r = -0.40$ for $^{99m}$Tc-MIBI; $r = 0.32$ for $^{99m}$Tc-pertechnetate) might potentially obviate a second post-ablative scan, considering the prognostic value. Yet, the results appear somewhat dubious, since scintigraphy with $^{99m}$Tc-MIBI suggests a negative correlation in contrast to the positive correlation of nodular volume reduction and $^{99m}$Tc-pertechnetate-scintigraphy. After all, $^{99m}$Tc-scintigraphy still remains an important diagnostic tool in the field of the treatment of thyroid nodules, for example with MWA, that may be sufficiently complemented by sonographic tools.

References


