Is Strain Elastography Really a Good Adjunct for Prediction of Malignancy in Soft Tissue Tumours?

Dear Editor,
With great interest we have studied the recent publication by Riishede et al. (Riishede et al. Ultraschall in Med 2015; 36: 369 – 374) concerning the role of sonoelastography (SE) as an adjunct diagnostic mean in the differentiation of soft tissue tumours. SE is certainly a new method on the rise as can be concluded from the increasing number of publications. However, its clinical adaptation seems to lag behind scientific propositions and is still mainly confined to hepatic, breast, thyroid and prostate applications (Dudea S. Med Ultrason 2014; 16: 87 – 88). To our opinion not without reason, with strong operator-dependency and sometimes erratic inter-observer agreement (Carlsen JF et al. Diagnostics 2013; 3: 117 – 125). Regardless of the slow acceptance in clinical routine, numerous papers continue to be published examining the use of SE in various other settings, even in the assessment of intrapulmonary nodules (Adamietz B et al. Ultraschall in Med 2013; 35: 33 – 37). One of such is the recent article by Riishede et al. which proposes SE as a viable addition in the diagnosis of soft tissue tumours. However, we believe that the proposition is poorly substantiated and that the actual information presented should rather lead to an opposite conclusion.
Strain SE does not yield absolute values for elasticity such as SI-based Pascal, but rather returns relative compressibility given as false-colour overlays. Thus strain ratios between regions of interest (ROIs) are usually calculated to compare target tissue with surrounding reference tissue – preferably at the same depth as the primary ROI (Carlsen JF et al. Diagnostics 2013; 3: 117 – 125). Obviously the tissue elasticity within the reference ROI influences the strain ratio and should be chosen with care. In contrast to rather homogeneous organs such as the liver or breast, the surrounding tissue in musculoskeletal lesions varies widely and can range from bone, muscles or tendons to subcutaneous fat. This is not properly accounted for in the study and not mentioned in the discussion.
The figures and quantitative analyses presented in the paper show several inconsistencies. Visual scoring – which is commonly used to grade tissue elasticity (Pedersen M et al. Ultraschall in Med 2012; 33: 441 – 446) – was demonstrated to be non-diagnostic. The ratio of malignant to benign soft tissue tumours was roughly the same across SE groups (modified from Tsukuba (Itoh et al. Radiology 2006; 239: 341 – 350)) with about 40 %; only the second group scored a bit higher with 56 %, but due to the relatively small number of cases this is not surprising (data from figure 6c: resp. 3 vs. 8, 9 vs. 16, 4 vs. 10, 3 vs. 8). Curiously the (ancient) schwannoma in Fig. 3 is presented as an exemplary benign tumour, while the deeper cystic-like area is deeply blue in the elastogram. In our view this does not make much sense, since schwannomas can often be identified due to central cystic areas (as is the case here) and neural contact. All in all, this undermines one of the authors' main statements that visual grading does not allow for tumour classification and – from a practical standpoint – only serves to demonstrate that SE carries no information beyond the obvious in this case.
Strain ratio on the other hand apparently demonstrated a significant difference between the groups; the authors report $p = 0.043$. However, totally contradictory to this result, the presented confidence intervals of the mean strain ratios of the two groups would lead us to the conclusion that there is no statistical significance at a two-sided < 0.05 level (1.94 [95 % CI 0.37 to 10.21] and 1.35 [95 % CI 0.32 to 5.63]). The p-value will be less than 0.05 only when the 95 % confidence interval does not contain the other mean strain ratio (see § 8.8.1 in: "Practical statistics for medical research" (Altman DG. Chapman and Hall, 1991)). This condition is not fulfilled here. In addition, the comparison between box plots for benign and malignant tumours (all 61) in figure 6a does not give reason to believe there is a relevant difference.
The authors furthermore report an increase in difference of mean strain ratios for benign and malignant lesions when excluding fat-containing tumours. As fat-containing lesions are the largest group of musculoskeletal tumours, usually present as tender masses and frequently prove difficult to diagnose as certainly benign or malignant, the motivation behind their exclusion is not clear. On the other hand, cases of osteosarcoma and chondrosarcoma were included, which are typical 'hard' lesions containing osteoid or chondroid matrix and are often readily diagnosed using CT and MRI.
Overall there is no clear support for the purported usefulness of SE in soft tissue tumours as the data presented by Riishede et al. do not demonstrate significance for either visual grading, histogram analysis or strain ratios. Shear-wave SE may prove better suited for such an application, but until further evidence-based research is presented there is no incentive to use SE in the diagnosis of soft tissue tumours.

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Response

We have read the comments to our recent article [1] and appreciate the interest in our work.

Before we commence our answer to the specific questions put forth, we should like to stress two key points: 1) Soft tissue tumors are a morphologically heterogeneous entity located in a variety of anatomical locations, which makes the diagnoses challenging. 2) The diagnostic work-up for soft tissue tumors varies between different hospitals, but in our article we adhere to the Scandinavian guidelines on said topic. Other institutions follow other guidelines, and naturally any new diagnostic method,

should be considered in the light of the current diagnostic guidelines used.

As emphasized in the title of our article, the results are preliminary. We have not investigated the impact on daily clinical practice, but have evaluated whether strain elastography used independently could be used to distinguish benign from malignant soft tissue tumors. This is mentioned in the manuscript. Our conclusions are therefore cautious and we consider the study hypothesis-generating. We propose, that strain ratios may at a point be used as an adjunct in the diagnosis of soft tissue tumors. Similar conclusions have been proposed for breast tumors and thyroid nodules previously [2, 3]. Our post-hoc power analysis gave a power of 60 %, which speaks to the limited data available.

We agree that musculoskeletal tissue is inhomogeneous and that ROIs should be chosen with care. This is mentioned in the discussion – all ROIs were chosen to cover as much tissue as possible to ensure that both the tumor and reference ROI were representative, despite the heterogeneity of the tissues. In practice, this also meant that we tried to find identical adjacent underlying structures for both ROIs.

We are unsure what is meant by "inconsistencies in the figures and quantitative analyses". Regarding the visual score, we only evaluated the elastogram and not the corresponding B-mode image. Therefore no B-mode characteristics of the Schwannoma were taken into account. In the clinical guidelines adhered to in this study, B-mode imaging is not part of the routine diagnostic evaluation, but is only used as a tool for tumor biopsy. The article mentions that no validated system for visual scoring in musculoskeletal ultrasound is available and that we used a modification of the Tsukuba score [4].

In the beginning of our discussion we state that the 95 % confidence intervals are overlapping. Confidence intervals can overlap, even when there is statistical difference between the two groups [5]. As the strain ratio data were skewed, the statistical calculations were carried out on log-transformed data. The strain ratio confidence levels and means presented are back-transformed from the log-transformed data, which makes the interpretation of the data less direct. We concede that this particularity could have been emphasized in the article.

The reason fat containing lesions were excluded for a subgroup analysis, was that they were readily distinguishable on MRI, and because malignant and benign fat containing tumors were elastographically similar. Further, we did not include many simple lipomas, due to the highly selected patient group in our clinic. Only very few osteoid and chondroid sarcomas (N = 2) were included in the study, and as we wanted to assess the overall ability of strain elastography to discern benign from malignant tumors these were not excluded. We agree, that in later studies, it may be a good idea, to exclude these tumors from the analysis, as the diagnostic gain from elastography probably is limited.

Finally, our conclusion is conservative as previously stated. Future studies are needed to discover the full range and the application of elastography in daily clinical practice for musculoskeletal applications.

References

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