Peer Review File

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Reviewer comments

Comment 1: This retrospective review reports the outcomes and appropriateness if investigation of incidentally discovered thyroid nodules referred for ultrasound examination over a 5 year period at a single UK centre. This is a subject of key importance, with a well recognised problem in the over diagnosis and over treatment of very low risk thyroid cancers.
Response 1: We thank the reviewer for their comments.

Comment 2: The abstract provides a clear and helpful summary of the aims of the study, the key findings and conclusions.
Response 2: We thank the reviewer for their comments.

Comment 3: Whilst the introduction gives some useful background information, it would be helpful to elaborate on some of the key clinical circumstances when incidental thyroid lesions might be found on imaging- e.g., on FDG PET during the investigation of other cancers, on MRI spine, on neck ultrasound requested to investigate other problems. This would help to give some clinical context, and also illustrate situations (e.g., patients with advanced incurable lung cancer) where further investigation may be totally inappropriate. It would also be helpful to cite relevant literature reporting the incidence (First line of discussion) of these findings (eg on FDG PET).
Response 3: We agree with the reviewer, and as such have included some examples in the introduction. We have also included references on FDG PET in the discussion.
Changes in the text: Lines 77-89; Lines 218-235.

Comment 4: I am not entirely sure that I agree with the interpretation of the BTA guidelines regarding the investigation of incidental thyroid nodules. My reading is that their advice is-
'ii Incidentally detected nodules by CT should undergo clinical evaluation. In the majority of cases, no further assessment/investigation will be required. However if there are suspicious findings on CT (extra-capsular extension, tracheal invasion, associated suspicious lymphadenopathy), or the patient belongs to a high-risk group or if there is significant clinical
concern, US assessment is recommended (4, D). iii Nodules detected by PET-CT with focal FDG activity should be investigated with ultrasound and FNAC, unless disseminated disease is identified and the prognosis from an alternative malignancy would preclude further investigation (1++, A).'
So there is actually no recommendation here specifically about size.
Response 4: We agree with the reviewer. We were using subcentimtre nodules as an easy way to capture nodules because BTA guidelines states that these can be managed by primary care in absence of risk factors. In our unit, our clinical practice was using incidental nodules >1cm as significant clinical concern so for the purpose of this study we used this as our cut-off. We do however agree that all of these do not need investigated per the guidelines. We agree that this means we may be

underestimating the number of incidental nodules and have updated this in the text. We agree going forward as a unit that more consideration based on risk factors, imaging reports and clinical evaluation before requesting ultrasound +- FNA.
Changes in the text: 155-174; 192-195; 201-207

Comment 5: My understanding of the guideline's recommendation about nodules <1cm is that careful thought should be given to whether or not FNAC should be undertaken, rather than the initial decision about whether an ultrasound should be done- 'The high sensitivity of US for the detection of papillary carcinoma can result in the finding of small (<1 cm) nodules that are suspicious for thyroid malignancy. In such cases extra thyroidal extension and associated metastatic lymphadenopathy will influence the decision as to whether or not to perform FNAC. When there is no evidence of extra thyroidal disease, or no associated high risk clinical history, the decision whether or not to perform FNAC will depend on the clinical picture, and the responsible clinician needs to make an appropriate judgment (supported by the MDT) about pursuing cytological confirmation, in order to avoid over treatment of clinically insignificant micro-papillary thyroid carcinomas (microPTCs)'.
Response 5: We were using BTA guidelines "3.2 Patients with thyroid nodules who may be managed in primary care: "Patients with a non-palpable asymptomatic nodule <1 cm in diameter discovered incidentally on neck ultrasound (US) USS / CT /MRI without other worrying features". We however very much agree that if a patient has had US performed then extra thyroidal extension and risk factors should dictate whether FNA should be performed and have included a paragraph to reflect this.
Changes in the text: 207-212

Comment 6: It would be helpful if more detail could be given in the methods about the criteria used to define an incidental nodule- were these nodules that were purely picked up on imaging? Did they have to be clinically impalpable?
Response 6: We have updated more information in the methods. We assessed any nodule that was picked up purely on imaging -and patients had no prior thyroid complaints. We then assessed the notes after the fact to see if it was palpable.
Changes in the text: 101-105

Comment 7: Whilst the results are clearly presented, in view of comments above, I'm not sure that they fully reflect the number of inappropriate investigations. For example, per BTA guidelines, there may have been CT identified nodules >1cm that had purely benign features and did not warrant USS, and there may have been incidental nodules on FDG PET in patients with life-limiting illnesses where USS would also have been inappropriate. I think more thought needs to be given to the definition of what was an inappropriate investigation.
Response 7: We have included additional information in the introduction regarding inappropriate in palliative patients . And we refer back to the new paragraph stating we may be under reporting the number inappropriately investigated.
Changes in the text: 84-89, 164-174, 238-244

Comment 8: It would also be interesting to understand what proportion of the incidental nodules

went on to have FNAC, and what proportion had surgery, as these are potentially more harmful interventions than merely having an ultrasound.
Response 8: I have updated Figure 1 to reflect this
Changes in the text: See figure 1. 214-222

Comment 9: Some helpful suggestions are made in the discussion regarding radiology reporting of small lesions with no risk factors to advise that no further investigation is required which I am sure would be very helpful. I am less sure of the advice that for larger lesions the radiologist should directly arrange an FNA. I think this is missing a step where a discussion is required with the patient about the potential implications of further investigations, and it is probably not reasonable to expect a radiologist to undertake this discussion.
Response 9: We agree and have removed that radiologist to undertake this, and that referral to ENT clinic for evaluation should happen.
Changes in the text: 195-207

Comment 10: Comparison with ACR guidelines is helpful- for clarity it might be useful to tabulate the number of unnecessary investigations undertaken if BTA or ACR guidelines were followed?
Response 10: We have made a table for this; Table 1
Changes in the text: See table 1. Lines 192-193.

Comment 11: In summary, whilst the study addresses an important issue, further thought needs to be given to the exact definition of an incidental thyroid nodule, to the interpretation of BTA and other guidelines, and to what actually constitutes an unnecessary investigation, which is probably wider than just nodules <1cm.
Response 11: Thanks for your comments. I think they have been excellent. I think the changes overall reflect <1cm is not the only factor to be considered. We think this has been reflected in all of the comments above. Many thanks.

Editorial Comments

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Response: We have included this attachment.

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Response: We have attached these as requested.

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Response: All figures/tables/videos are original.

e. If available, please update your reference list by including related literature published within a year. Some of the references are outdated.
Response: We have updated 2 references (5+6).