Response to Reviewers:

Reviewer #1

Comment: Dear author, Thank you for this opportunity. However, this article needs more information about the methods of data collection. It is not clear, where the study is being conducted? who has done the review and so on. The type of articles included; the data included for the review. In my assessment, the article needs to be present in the proper format for review analysis. Regards

Response: Thankyou for your comments. This is a review article. No study was conducted as such.

Reviewer #2:

Comment: Manuscript NO: 82638 Title: Multi-modality Parathyroid Imaging: A shifting paradigm Some specific concerns: In the 'Abstract': The goal of imaging in hyperparathyroidism is not diagnosis, ----◊ The goal of parathyroid imaging in hyperparathyroidism is not diagnosis.

Response: The change has been made.

Comment: In the 'Imaging': Tc99 sestamibi ---◊ Tc99m sestamibi In the 'Anatomy', There are four parathyroid glands, 2 superior and 2 inferior.-----◊ Please rephrase it, for the usual number of parathyroid glands is four, but this can vary. Some persons have more than four parathyroid glands.

Response: The change has been made.

Comment: Linear array transducer with 10 MHz or higher frequency with grey scale and colour doppler settings is used for imaging of the parathyroid glands. ----------should be: duplex ultrasound with a linear array transducer with 10 MHz or higher frequency is used for imaging of the parathyroid glands. ----------or multi-parameter ultrasound with a linear array transducer with 10 MHz or higher frequency is used for imaging of the parathyroid glands

Response: The change has been made.

Comment: doppler----------should be Doppler, throughout the manuscript, including figure legends, tables.

Response: The change has been made.

Comment: ‘The most common cause of primary hyperparathyroidism is a single parathyroid adenoma (85-90%) followed by parathyroid hyperplasia (6%), double adenomas (4%) and parathyroid carcinoma (~1%).[3] ’need to be replaced with updated data. Reference 3 is out of date.

Response: The references have been changed.

Comment: Colour doppler provides additional information and demonstrates a peripheral arc of vascularity encircling 90 to 270 degrees of the lesion circumference.[12,13] ----------should be: Colour Doppler provides associate information of the origin and course of feeding artery of the parathyroid adenoma.[12,13]

Response: The change has been made.

Comment: Spectral doppler shows a low resistance waveform. ---------- should be: Spectral Doppler can determine the blood flow velocity of the feeding artery and get information of a low resistance index.

Response: The change has been made.

Comment: In ‘Four Dimensional CT (4D CT):’ t has a sensitivity of 70% which was significantly higher when compared to 33% for sestamibi scan and 29 % for high resolution ultrasound.[22]----------◊ they are not accurate, e.g., ‘29 % for high resolution ultrasound’, please check and use different references, such as (1) reference 19; (2)Lane et al. Use of color and power Doppler sonography to identify feeding arteries associated with parathyroid adenomas. AJR Am J Roentgenol. 1998;171(3):819-23; (3) others.

Response: The references have been changed.

Comment: 4D MRI is a novel method which has been explored in the imaging of parathyroid adenomas.----------◊ ‘The sensitivity of the 4D MRI was 90% and after optimization, 100%. Specificity was 100%.’ Should be added, please refer to reference 30.

Response: The change has been made.

Comment: ‘Contrast-Enhanced Ultrasound (CEUS):’ should be next to the ‘High resolution ultrasonography:’.

Response: The change has been made.

Comment: Elastography for the parathyroid gland should also be added to the review(including the conclusions), please referred to ‘Isidori et al. Multiparametric ultrasonography and ultrasound elastography in the

differentiation of parathyroid lesions from ectopic thyroid lesions or lymphadenopathies. Endocrine. 2017;57(2):335-343. ‘ and ‘Azizi et al. Shear wave elastography and parathyroid adenoma: A new tool for diagnosing parathyroid adenomas. Eur J Radiol. 2016;85(9):1586-93.

Response: Shear wave elastography has been added.

Comment: Reference styles of 41 and 43 are different while they are some journal, so do in some other references, please make consistence.

Response: The change has been made.

Comment: Figure legends and tables are required to revision and edit, with help of radiologists in different imaging fields.

Response: The change has been made.

Comment: Figure 1: Diagrammatic representation of location of eutopic (yellow) and ectopic (red) parathyroid adenomas.----------should be ‘Figure 1: Diagrammatic representation of location of eutopic (yellow) and ectopic (red) parathyroid glands.’ Figure 2: (b) Colour Doppler shows a hypertrophied feeding vessel, likely from the inferior thyroid artery (arrow) supplying the lesion with a vascular peripheral rim. ------◊had better be ‘(b) Colour Doppler shows a big feeding vessel, likely from the inferior thyroid artery (arrow) supplying the lesion. ’ Figure 3: In a known case of MEN-1 syndrome, (a-f) ultrasound neck images show multiple (3) parathyroid adenoma in the right superior and left superior and inferior parathyroid glands respectively. ------◊ should be ‘Figure 3: In a patient with MEN-1 syndrome, (a-f) cervical and parathyroid ultrasound shows multiple (3) parathyroid adenomas in the right superior and left superior and inferior parathyroid glands, respectively.’ Figure 5: Left Inferior Parathyroid Adenoma: In a patient with raised PTH levels (290 IU) grey scale ultrasound (a) and colour doppler (b,c) showed a hypodense lesion just below the left lobe of the thyroid gland which showed peripheral arc of vascularity. 4 D CT showed the lesion to be hypodense on NCCT (d), hyperenhancing with central necrosis on arterial phase (e) and washout on the venous phase (f). Coronal image (g) better demonstrates the lesion. ------◊ should be Figure 5: Left Inferior Parathyroid Adenoma: In a patient with raised PTH levels (290 IU) grey scale ultrasound (a) and colour Doppler flow imaging (b,c) showed a hypoechoic lesion with vascularities just below the left lobe of the thyroid gland. 4 D CT showed the lesion to be hypodense on NCCT (d), hyperenhancing with central necrosis on arterial phase (e) and washout on the

venous phase (f). Coronal image (g) better demonstrates the lesion. Figure 8: Ectopic Parathyroid Adenoma in the Supraclavicular fossa: Ultrasound of the neck carried out on a 49-year-old male patient, who came with history of bilateral stones with elevated PTH levels show a hypoechoic lesion (a) in right supraclavicular location with internal vascularity on colour doppler (b). 4 D CT showed a hypodense lesion on non-contrast scan (not shown) with arterial enhancement (c) and washout on the venous phase (d). Coronal reformatted image (e) better depicts the ectopic parathyroid adenoma in the right supraclavicular fossa. ------◊ should be Figure 8: Ectopic Parathyroid Adenoma in the Supraclavicular fossa: on colour Doppler ultrasound of the neck on a 49-year-old male patient with history of bilateral renal stones and elevated PTH levels, a hypoechoic lesion (a) in right supraclavicular region with internal vascularities (b) was detected. 4 D CT showed a hypodense lesion on non-contrast scan (not shown) with arterial enhancement (c) and washout on the venous phase (d). Coronal reformatted image (e) better depicts the ectopic parathyroid adenoma in the right supraclavicular fossa. Figure 9: Intrathyroidal Parathyroid Adenoma: In a patient with raised PTH (208 IU) (a) Ultrasound of the neck showed a well circumscribed solid hypoechoic lesion within the left lobe of thyroid gland. 4D CT revealed the lesion to be hypodense as compared to thyroid tissue on non-contrast (b), showed intense arterial hyperenhancement (c) and washout on the venous phase (d), consistent with diagnosis of intra-thyroid parathyroid adenoma. Coronal (e) and sagittal MIP (f) images better depict the lesions with vascular pedicle (black arrow) seen supplying the lesion. (g) SPECT MIBI image showing a thyroid nodule which is mildly tracer avid. (h) Left hemithyroidectomy was done and the cut open section confirmed the presence of the adenoma. ------◊ had better be Figure 9: Intrathyroidal Parathyroid Adenoma: In a patient with raised PTH (208 IU) (a) Color Doppler ultrasound of the neck showed a circumscribed solid hypoechoic lesion with blood vessels within the left lobe of thyroid gland. 4D CT revealed the lesion to be hypodense as compared to thyroid tissue on non-contrast (b), showed intense arterial hyperenhancement (c) and washout on the venous phase (d), consistent with diagnosis of intra-thyroid parathyroid adenoma. Coronal (e) and sagittal MIP (f) images better depict the lesions with vascular pedicle (black arrow) seen supplying the lesion. (g) SPECT MIBI image showing a thyroid nodule which is mildly tracer avid. (h) Left hemithyroidectomy was done and the cut open section confirmed the presence of the tumor. Figure 10: Right Superior parathyroid adenoma: A 50-year-old female with raised PTH levels (96 IU), underwent high resolution sonography of the neck. (a) Grey scale image in the transverse and longitudinal plane showed a well circumscribed lesion posterior to the right lobe of thyroid gland and separated from it by a clear fat plane. (b)

Colour doppler images showed a feeding vessel and peripheral arc of vascularity. Corroborative MRI axial images show a subcentimetric lesion (arrows) posterior to the middle third of the right lobe of thyroid gland which is (c) T1 hypointense and (d) T2 hyperintense. (e) Coronal T2 image better demonstrates the lesion. (f) Correlative SPECT component of MIBI scan showing tracer avid lesion at the superior pole of the right lobe of thyroid. (g) Post-operative image of the same adenoma measuring 1.05 g. ------◊ had better be Figure 10: Right Superior parathyroid adenoma: A 50-year-old female with raised PTH levels (96 IU) was examined using duplex ultrasound for the parathyroid glands. (a) On grey scale sonographies in the transverse and longitudinal plane showed a circumscribed lesion posterior to the right lobe of thyroid gland and separated by a clear fat plane. (b) On images of colour Doppler flow imaging, a feeding vessel and its branches were visualized. Corroborative MRI axial images showed a subcentimetric lesion (arrows) posterior to the middle third of the right lobe of thyroid gland which is (c) T1 hypointense and (d) T2 hyperintense. (e) Coronal T2 image better demonstrated the lesion. (f) Correlative SPECT component of MIBI scan showed tracer avid lesion at the superior pole of the right lobe of thyroid. (g) Image of the resected tumor weighing1.05 g. Figure 11: CEUS in Parathyroid adenoma (a-c): In a 33-year-old female with raised PTH levels (87 IU), contrast enhanced ultrasound performed immediately after infection of Sonovue demonstrated a well circumscribed lesion at the lower pole of the left lobe of thyroid gland demonstrated early peripheral enhancement with central washout consistent with a diagnosis of parathyroid adenoma. ------◊ had better be Figure 11: CEUS in Parathyroid adenoma (a-c): A 33-year-old female with raised PTH levels (87 IU) was assessed using SonoVue contrast enhanced ultrasound. A circumscribed lesion at the lower pole of the left lobe of thyroid gland was found consistent with parathyroid adenoma, demonstrating early peripheral enhancement with central washout. Table 1 was not adequate and accurate, changed as below: Table 1: Differentiating features of parathyroid adenoma from lymph nodes and thyroid nodules on imaging Modality Features Parathyroid adenoma Thyroid nodule Lymph node Colour Doppler ultrasound Echogenicity Homogenously marked hypoechoic Homo/heterogenously hypo/isoechoic Central echogenic hilum Vascularity Peripheral polar vessel sign present Absence/ a few/abundant Central/ hilar vascularity Calcification Less common Common +/- Cystic changes Less common More common +/- CT Non contrast Hypodense Hyperdense Hypodense Arterial Intense arterial enhancement Enhancement in arterial phase but less than parathyroid adenomas No enhance in the arterial phase Venous Washout Persistent enhancement Progressive enhancement in venous phase MRI Morphology Cleavage plane

with thyroid gland No cleavage plane Cleavage plane present Diffusion weighted Image High SI High SI PET Choline Uptake Present Absent Absent

Response: The suggested changes have been made in the legends and tables.