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The Rationale for performing MR Imaging before Surgery for Primary Hyperparathyroidism

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Abstract. *Objective :* The purpose of this study was to evaluate prospectively Magnetic Resonance Imaging (MRI) for the preoperative localization of hyperfunctioning parathyroid glands.
Design : Prospective study of 58 consecutive patients with biochemically confirmed primary hyperparathyroidism who underwent preoperative MRI.
Setting : The setting is a referral centre.
Patients : Fifty-six of the 58 consecutive patients (41 women, 17men) were studied by both preoperative MRI and ^{99m}TC MIBI scintigraphy, and two by MRI alone. The same surgeon, using the information from both MRI and ^{99m}TC MIBI, performed surgery in 58 patients, including 19 with a history of neck surgery. Initial interpretation of each MR study was done independently by one radiologist and the surgeon and then results were compared. At surgery, the operative duration, the precise anatomical location, weight, and dimensions as well as complete histopathological evaluations of all excised glands were recorded.
Main outcome measure : In addition to the prospective assessment of MRI, this study compared performance of MRI with double-phase ^{99m}TC MIBI scintigraphy for preoperative localization of hyperfunctioning parathyroid glands.
Results : All patients became normocalcaemic after surgery. MRI and ^{99m}TC MIBI imaging revealed 53 of 58 (91%) and 47 of 56 (84%) of abnormal glands, respectively. Sensitivities of MRI and ^{99m}TC MIBI were respectively 94.3 and 88.0. Positive predictive values were 96.15 and 93.60. When MRI and ^{99m}TC MIBI were interpreted together, the sensitivity and positive predictive values both raised to 98.10. Median operative duration was 30 minutes (ranges 20-300 minutes, mean 65).
Conclusion : MRI has better sensitivity and positive predictive value than ^{99m}TC MIBI scintigraphy for the detection of hyperfunctioning parathyroid glands. The combination of the two studies provides an additional increase in sensitivity and positive predictive value leading to a more precise anatomical localization of the abnormal parathyroid glands reducing both the extent of the surgical dissection and the operative duration.

Recommended therapy for patients with primary hyperparathyroidism is parathyroidectomy. Much more often than in the past, diagnosis of primary hyperparathyroidism is made incidentally or very early in asymptomatic patient based on biochemical tests. As a direct consequence, surgeons are faced with the challenge to remove smaller parathyroid lesions and thus with the difficulties to localize them. Depending on the surgeon's understanding of the developmental relationship of the parathyroid glands to the thyroid and the thymus, which is fundamental in the delineation of the embryologic origin of the parathyroid glands (1), and on the surgeon's skill, success rate can be rather different. This is particularly true for patients with prior history of neck surgery (2-4), mainly thyroid or parathyroid surgery (including patients with MEN 2 having been operated before for asynchronous thyroid medullary carcinoma). Moreover, taking into account the fact that the risks of surgical complications are higher at reoperation, any test allowing precise anatomical localization of the abnormal parathyroid glands that could lead to a first try successful operation can be worth considering (5-7). Furthermore, for elderly patients and/or high surgical risks patients, because of associated medical diseases, improved methods for precise preoperative localization may also decrease perioperative morbidity by reducing operating time and obviating extensive and prolonged surgical neck dissection.

In this prospective study, we sought to investigate whether the advances in Magnetic Resonance Imaging (MRI) might improve the accuracy and feasibility in localizing abnormal parathyroid glands in patients presenting with primary hyperparathyroidism.

We also wished to compare the accuracy of MRI with double-phase technetium-99m-sestamibi scintigraphy (^{99m}TC MIBI) for preoperative localization of hyperfunctioning parathyroid glands (8-10). As a functional technique, ^{99m}TC MIBI has the advantage of broad anatomic coverage, but the disadvantage of showing just persistent activity and increased tracer uptake in a relatively wide anatomical area (eg. upper mediastinum, right or left inferior or superior thyroid poles) compared with the more descriptive and topographic MRI localization. In other words, the surgeon who makes the efforts to familiarize himself with the basics of MRI technology and who get used to confront his interpretation of MR imaging with radiologist (both prospectively and retrospectively) will soon feel at home with *MRI surgical anatomy of parathyroid glands*.

Materials and methods

Patients

Fifty-eight consecutive patients (41 female and 17 males patients ; age 60 ± 14 years, range 27-83 years, median 62) with biochemical evidence of primary hyperparathyroidism were prospectively investigated with MRI prior to surgery between June 2005 and June 2011 at our institution.

There was a history of previous neck surgery in 19 patients (33%) : thyroid surgery 17, cervical arthrodesis 2. Furthermore, 10 patients presented with multinodular goitre (17%)

The presence of hyperparathyroidism was documented by demonstrating a serum calcium value greater than 10.5 mg/dl calculated according to the formula :

calcium corrected = calcium measured + 0.8 (4 – albumine [g/dl]),

as well as elevated level of parathyroid hormones (PTH) or in the upper half of the normal range. PTH was measured by a two-site assay. PTH value greater than 90 pg/ml was considered abnormal. Alkaline phosphatase and 24-hour urine calcium were also measured (Fig. 1).

Both MRI and ^{99m}TC MIBI scintigraphy were performed during the course of the clinical investigation for primary hyperparathyroidism in all 58 patients for MRI and in 56 for ^{99m}TC MIBI.

Surgical and histopathologic confirmation of abnormal parathyroid tissue were obtained in all patients. Intraoperative assay (11, 12) for PTH (IOPTH) as well as postoperative PTH and calcium levels at 3, 6 and 12 months were routinely requested.

MR Imaging

All examinations were performed on a 1.5T MR imaging system (Symphony Tim, Siemens Medical solutions) with neck and body coils.

The protocol included 4-mm-thick transverse images through the neck from the hyoid bone down to the aortic arch with a TSE T1-weighted sequence (9/585-591 [echo time msec/repetition time msec], matrix size 320 × 320 to 384 × 384), a TSE T2-weighted sequence (92-98/4540-4780, matrix 384 × 384 to 512 × 408), a short tau inversion recovery (STIR) sequence (26-58/3210-7570, matrix size 320 × 320 to 512 × 392) and a fat-suppressed T1-weighted sequence (9/459-591, matrix size 320 × 320) after administration of 0.2 ml/kg of gadoterate meglumine (Dotarem Laboratoire, guerbet, Aulnay sous-bois, France). When the fat suppression of the fat-suppressed T1-weighted sequence was too inhomogeneous, the T1-weighted sequence was repeated after the gadolinium injection.

The STIR sequence was used because of its low sensitivity to magnetic field heterogeneities that often cause problems with spectral fat saturation in the neck.

The combined reading of all the sequences was used for the evaluation of the anatomy and detection of parathyroid lesions (Fig. 2).

99mTC MIBI Scintigraphy

Double-phase ^{99m}TC MIBI scintigraphy was performed according to well described sequential acquisition of ^{123}I and ^{99m}TC MIBI followed by images realignment and image substraction. This technique can differentiate an abnormal parathyroid from the thyroid gland, only the latter taking up both tracers (13).

A double-phase study was considered positive for abnormal parathyroid tissue if a focal area of tracer activity seen on immediate images persisted on delayed images while tracer activity in the thyroid tissue washed out.

Images Analysis

A four steps protocol was followed for images analysis. MR images were reviewed prospectively by a senior radiologist and by the same operating surgeon independently from the radiologist (*step 1*). At this stage, both observers interpreted MR images without knowledge of the results from the ^{99m}TC MIBI study. The agreement between the radiologist and the surgeon was determined by the Kappa statistic (14, 15). Prior to surgery, both the radiologist and the surgeon confronted the results of their reading and ultimately reached a consensus (*step 2*). Then, the same surgeon, using the information from both the MRI consensus reading and the ^{99m}TC MIBI study, performed surgery in all 58 patients (*step 3*). After operation, the surgical findings such as the exact anatomical location, lesion size, ectopic glands, relation to adjacent structures (ie. within the thymus, intrathyroidal), as well as the false positive or false negative MRI diagnoses, were thoroughly discussed by the surgeon and the radiologist in order to enhance the performance of both the radiologist and surgeon regarding MR anatomy and MR images analysis, but also to improve the effectiveness of subsequent parathyroid MRI exams for the benefit of new patients (*step 4*).

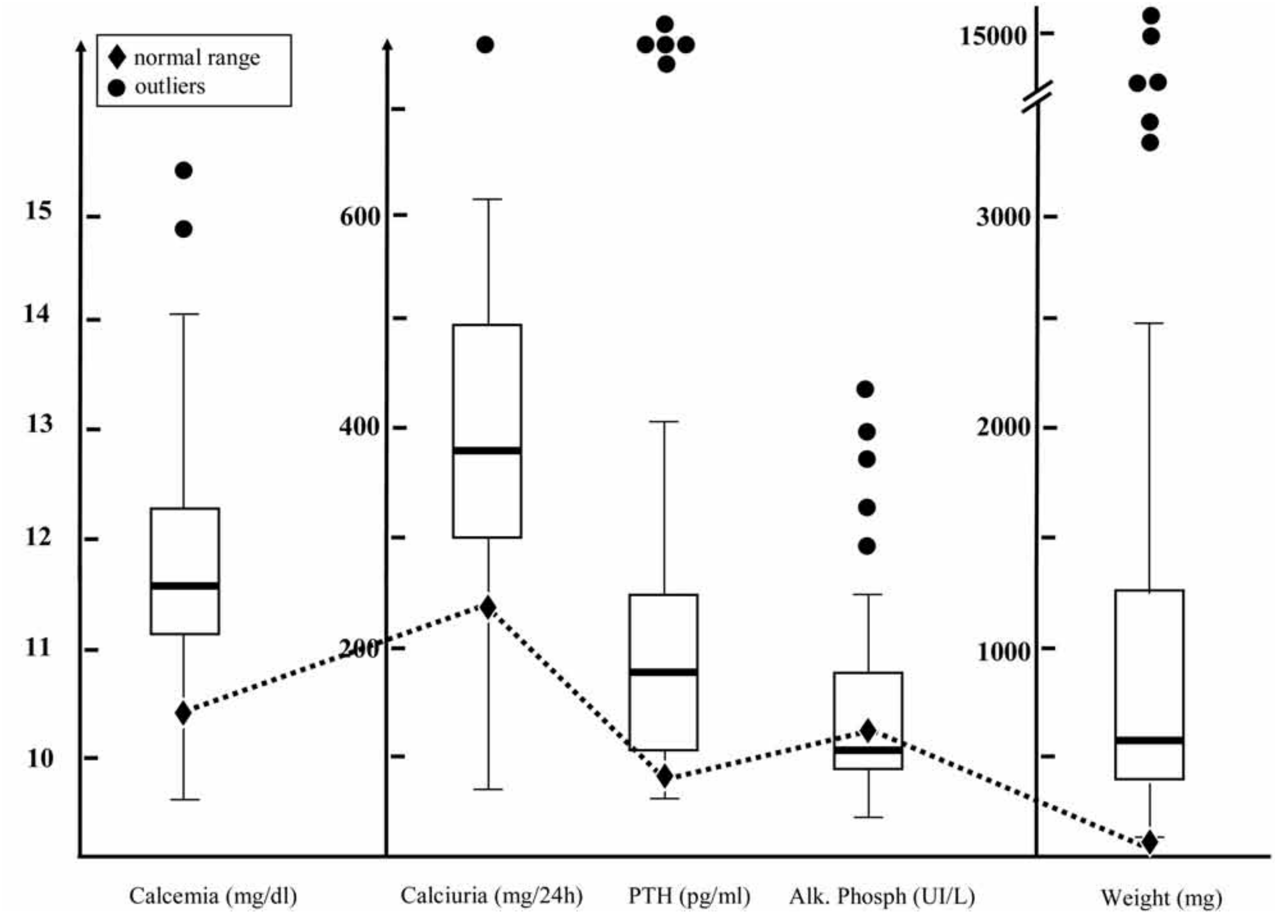


Fig. 1
Biochemical parameters confirming primary hyperparathyroidism in 58 patients (normal values range below the dotted line ; major outliers are represented by the dark circles ; weight in mg of parathyroid lesions).

Correlation of Surgical and Histopathological Findings

The number of abnormal glands identified at surgery and their location were recorded by the same surgeon. All histopathologic specimens were removed in one piece carefully avoiding fragmentation. The true-positive rates for the detection of abnormal parathyroid glands by both MRI and ^{99m}TC MIBI scintigraphy were noted and compared.

Statistical Analysis

The respective sensitivity and positive predictive values of MRI and ^{99m}TC MIBI scintigraphy were calculated. Because the 58 patients had biochemically confirmed hyperparathyroidism, each one was expected to have at least one abnormal gland. Therefore, a true-negative test was considered impossible ; thus, specificity and negative predictive value could not be calculated.

The sensitivity of the combination of MRI and ^{99m}TC MIBI scintigraphy for the detection of abnormal parathyroid tissue was also calculated on a per-patient basis. A true-positive result was recorded when either MRI or ^{99m}TC MIBI scintigraphy helped correctly identify a surgically proven abnormal parathyroid gland.
The agreement between the radiologist and the surgeon (part of step 1) was measured by the Kappa statistic (14-15).

Results

Identification of Abnormal Glands

MRI versus ^{99m}TC MIBI scintigraphy

MRI was used successfully to identify abnormal glands in 53 of 58 patients (91% - 2FP, 3 FN) whereas ^{99m}TC MIBI scintigraphy was used to correctly identify 47 of

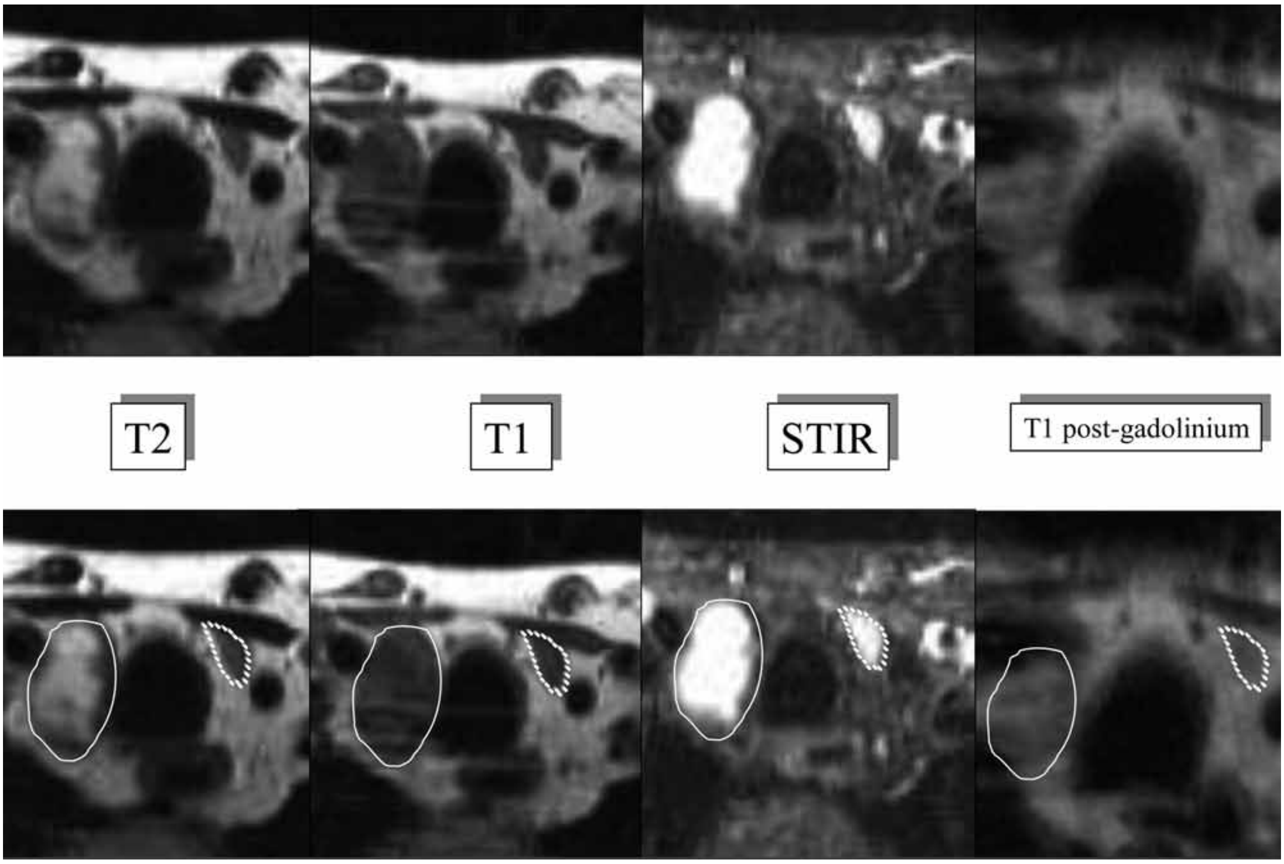


Fig. 2
61-year-old woman presenting a big nodule in the inferior portion of the right lobe of the thyroid (solid line) and an adenoma (320 mg) of the left inferior parathyroid (dotted line).

56 (83% - 3FP, 7 FN). The described four steps protocol followed for images analysis did not demonstrate a learning curve evolution as in fact the joined performance of the surgeon-radiologist duo was quite satisfactory from the beginning.

MR Imaging

In most cases, abnormal parathyroid tissue demonstrated isointense to low signal intensity relative to muscle on T1-weighted images, with increased signal intensity present on T2-weighted images (Fig. 3). However, because of the surrounding fat, abnormal parathyroid tissue was hypointense in T1- and T2-weighted sequences relative to fat, while STIR sequences could demonstrate increased T2 signal intensity in most of the abnormal parathyroid tissue without the interference of surrounding fat.

Some enhancement was frequently observed on T1-weighted sequence after intravenous administration of gadolinium chelate (Fig. 4).

No specific histopathologic correlate (adenoma versus hyperplasia) for the signal intensities was noted. However, in 10 patients with associated multinodular goitre (17%), thyroid nodules appeared isotense in T1 without enhancement after gadolinium while parathyroid adenomas did (Fig. 5a-b). In those 10 cases, signal intensity was also higher in STIR sequences (Fig. 5c) both for thyroid nodules and parathyroid adenoma.

Histopathologic Correlation in False-Positive or False-Negative MR Imaging and ^{99m}TC MIBI Scintigraphic Studies

Although correlation of the imaging findings with the weight and size of the resected gland was expected, this was not the case because many histopathological specimens were actually smaller than expected at least ex vivo. In contrast, a direct correlation was found between PTH level and weight of parathyroid lesion (Pearson $r = 0.627$, $p < 0.0001$; Spearman $r_s = 0.287$, $p = 0.0336$).

Surgical Results and Improvements of the Operative Approach

Surgical location of the 58 parathyroid lesions are summarized in Figure 6 (B). Ten of them were found in the mediastinum (Fig. 6A) among which four (Fig. 7) were located in the thymus (16).

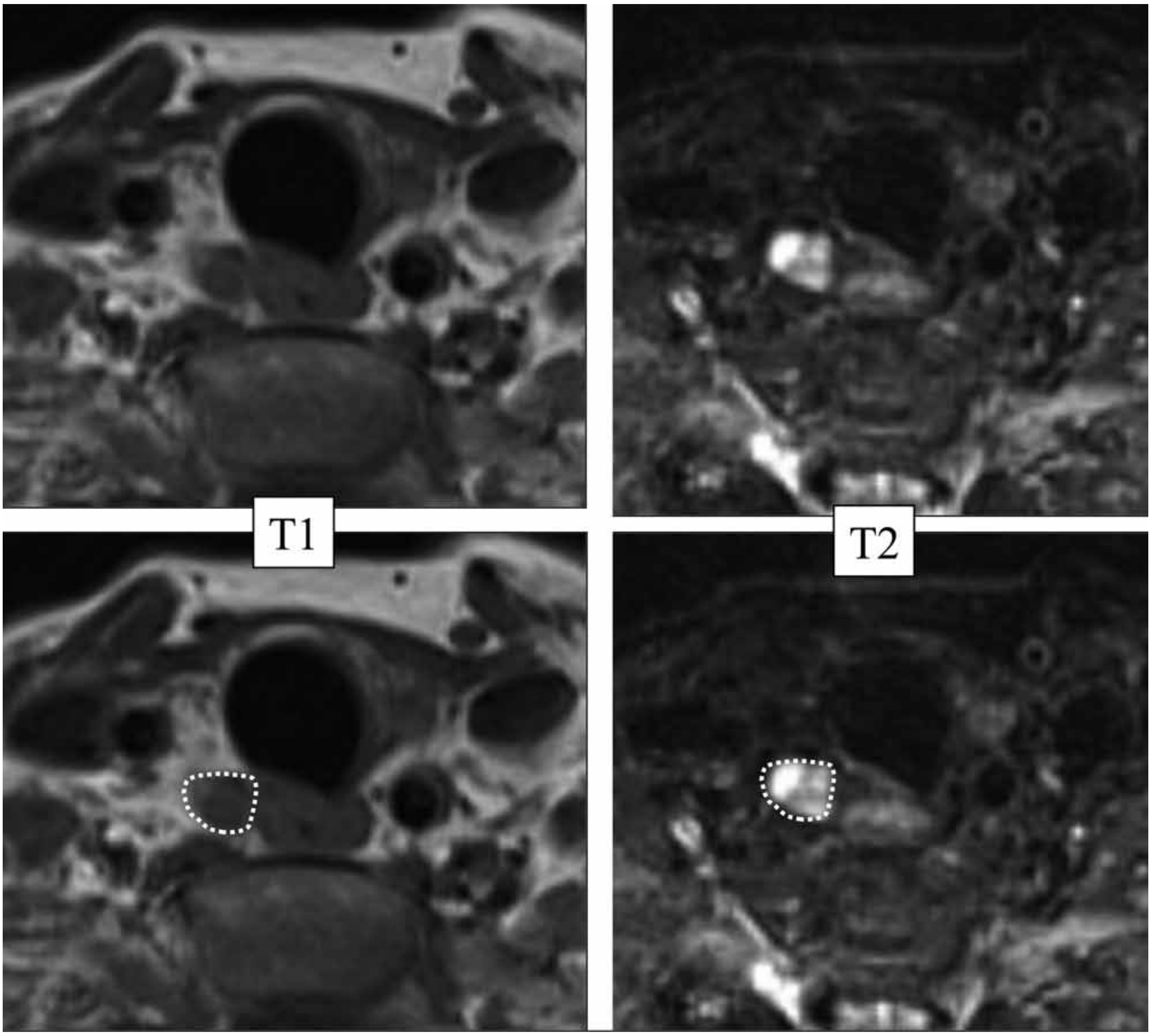
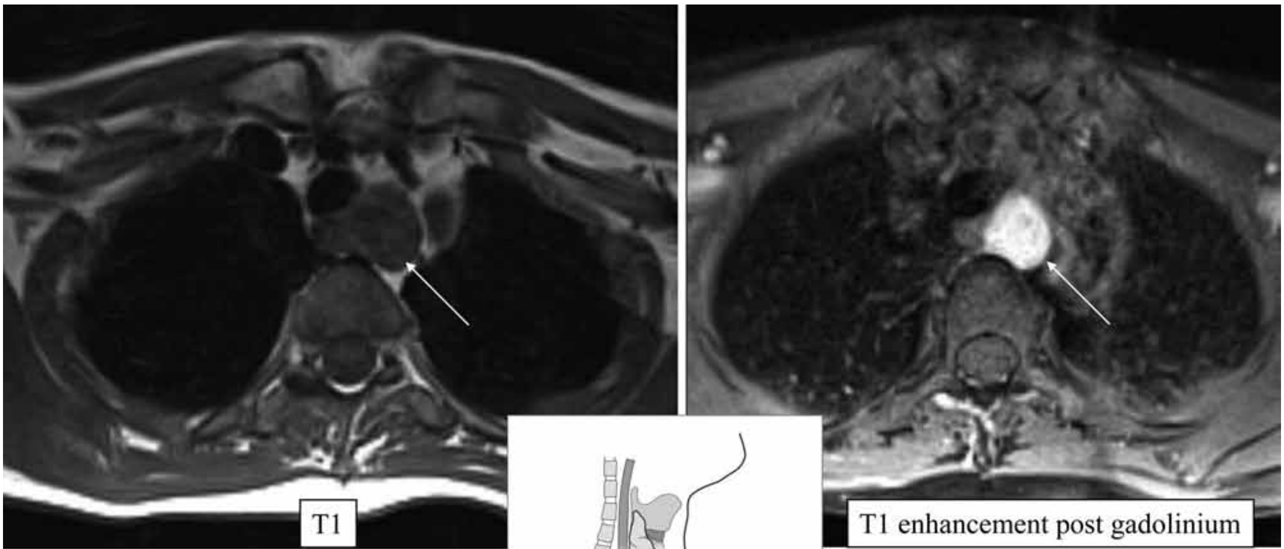


Fig. 3
Right inferior parathyroid adenoma (600 mg) demonstrating isointense signal relative to muscle on T1-weighted images, with increased signal intensity on T2-weighted images.

IOPTH demonstrated a decrease in PTH by > 50% and within the normal range 20 minutes after gland resection (11, 12). All 58 patients were eucalcaemic at last follow-up.

The major practical contribution of the preoperative MR imaging in primary hyperparathyroidism is the fact that a *precise anatomical localization* of the lesion can be obtained. From the surgeon's viewpoint, this is important as it will help to plan the operative approach and/or strategy. For instance, Figure 8 illustrates a case of mediastinal parathyroid adenoma situated in front of the right brachiocephalic artery and on the inner side of the innominate vein that was removed by a straightforward retrosternal dissection performed through a cervical approach leading to a short duration operation (30 minutes). Figure 9 refers to a mediastinal parathyroid adenoma of 16 g visualized on transverse and coronal MR images, that was easily removed through the left upper thoracic outlet again by a simple cervical approach.

Regarding *operation duration*, the median duration was 65 minutes (ranges 45-240 ; mean 90) for 50 patients operated between June 2001and May 2005 in the pre-MRI era. Since we routinely used MRI for preoperative localization of abnormal parathyroid, the



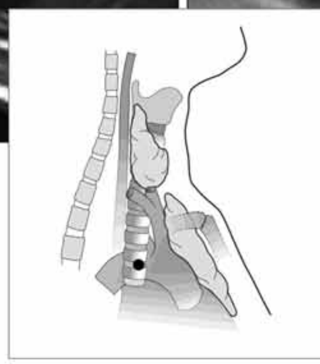
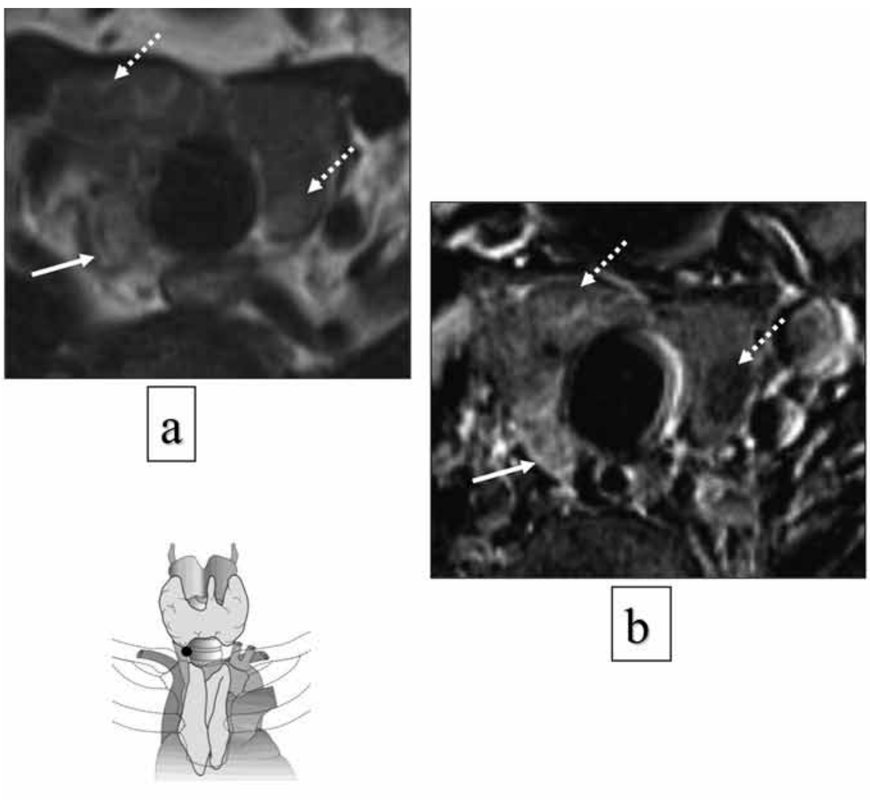


Fig. 4
Left inferior adenoma (4900 mg – 240 × 20 × 15 mm) demonstrating signal enhancement on T1-weighted sequence after intravenous administration of gadolinium.



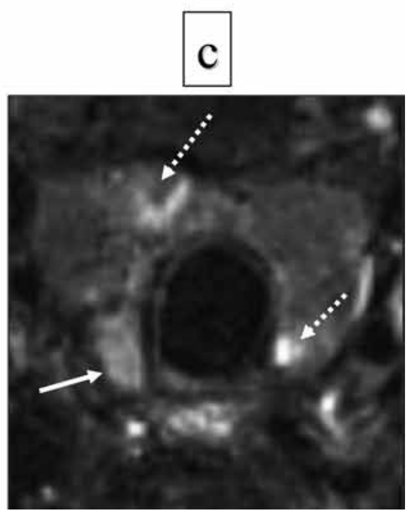


Fig. 5
Thyroid nodules (broken arrows) appearing isotense in T1 (a), without enhancement after gadolinium (b) while the parathyroid adenoma (solid arrows) did. Signal intensity was also higher in STIR sequences (c) both for thyroid nodules and parathyroid adenoma.

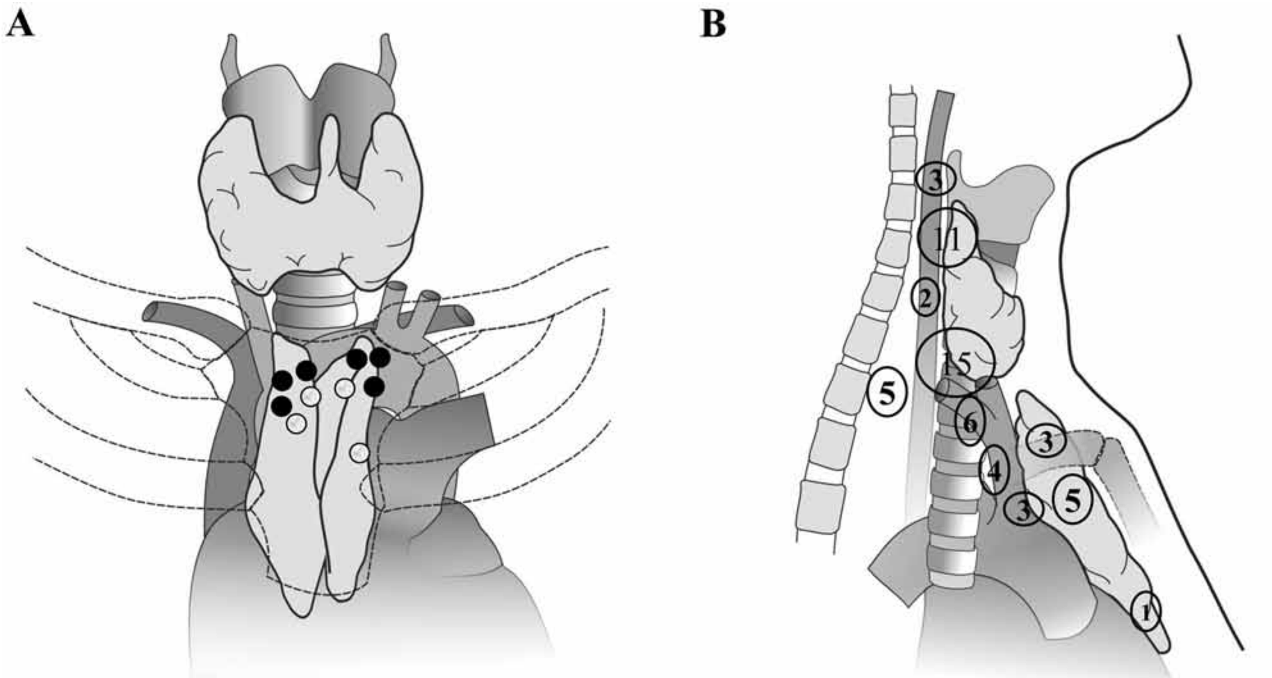


Fig. 6
Distribution of 10 mediastinal parathyroids (A) ; The site of the 58 parathyroid lesions (B)
(open dots = intrathymic parathyroid lesions)

median duration has decreased to 30 minutes (ranges 20-300 ; mean 60). Considering that our surgical population's mean age is relatively high (mean 60 ± 14 ; range 27-83 ; median 61), such a decrease of duration represents a direct benefit for elderly patients often presenting numerous additional risk factors.

Discussion

Imaging studies have no role in the diagnosis of primary hyperparathyroidism which has to be based on biochemical tests. However, parathyroid imaging is performed in the setting of primary hyperparathyroidism with intent to localize adenomatous parathyroid tissue before minimally invasive surgery. Available imaging options currently consist in ultrasound, radionuclide scanning, computed tomography, SPECT scan, and MRI (5-11). Various combinations of these modalities are used based primarily on institutional bias, and although highly successful in localizing the common single adenoma, they are less effective when there is multiglandular disease, glandular ectopia (2, 16), associated multinodular goitre (17), and/or a history of previous neck surgery. Nevertheless, according to the results of our ongoing study, it is possible to list precisely the negative and positive arguments in favour of preoperative parathyroid MRI.

The Pros, the Cons and the Payoff

The ***Pros*** are rather convincing : (a) MRI provides a useful noninvasive imaging modality to localize abnormal parathyroid tissue and does not require iodinate contrast or exposure to ionizing radiation (13) to the patient ; (b) the anatomical informations provided by MRI, either on transversal images or on coronal images, are close to surgical anatomy ; (c) those anatomical informations lead to a direct surgical approach of the parathyroid lesion allowing to reduce the operative duration and the area of surgical dissection ; (d) the combined interpretation of different MR sequences (T1, T2, STIR) is helpful to localize parathyroid lesion in patients with thyroid nodules (Fig. 2 & 5), considering that the sensitivity of ultrasound and sestamibi scintigraphy is reduced in patients with thyroid nodules (17) ; (e) ultrasound are not effective for the localization of mediastinal or intrathoracic parathyroid lesions (16). In our series 10 out of 58 patients (17%) had mediastinal parathyroid lesions ; all were correctly localized by MRI. Last but not least : ultrasound results are examiner dependent ; (f) for reoperative surgery in the neck, MRI can also provide a useful noninvasive imaging modality to localize abnormal parathyroid tissue years after total thyroidectomy for Grave's disease (Fig. 10).

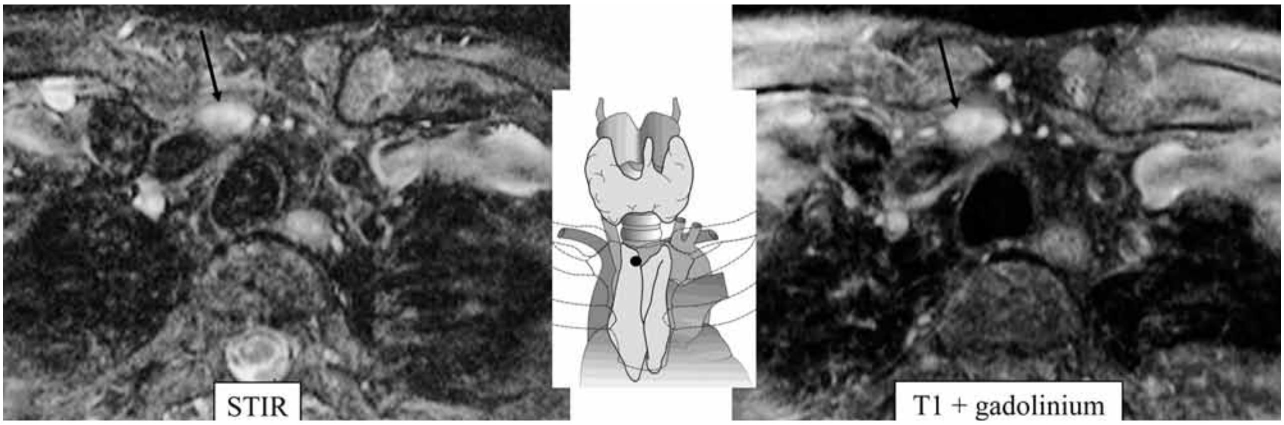


Fig. 7
Right intra-thymic parathyroid adenoma (2480 mg – 20 × 15 × 10 mm)

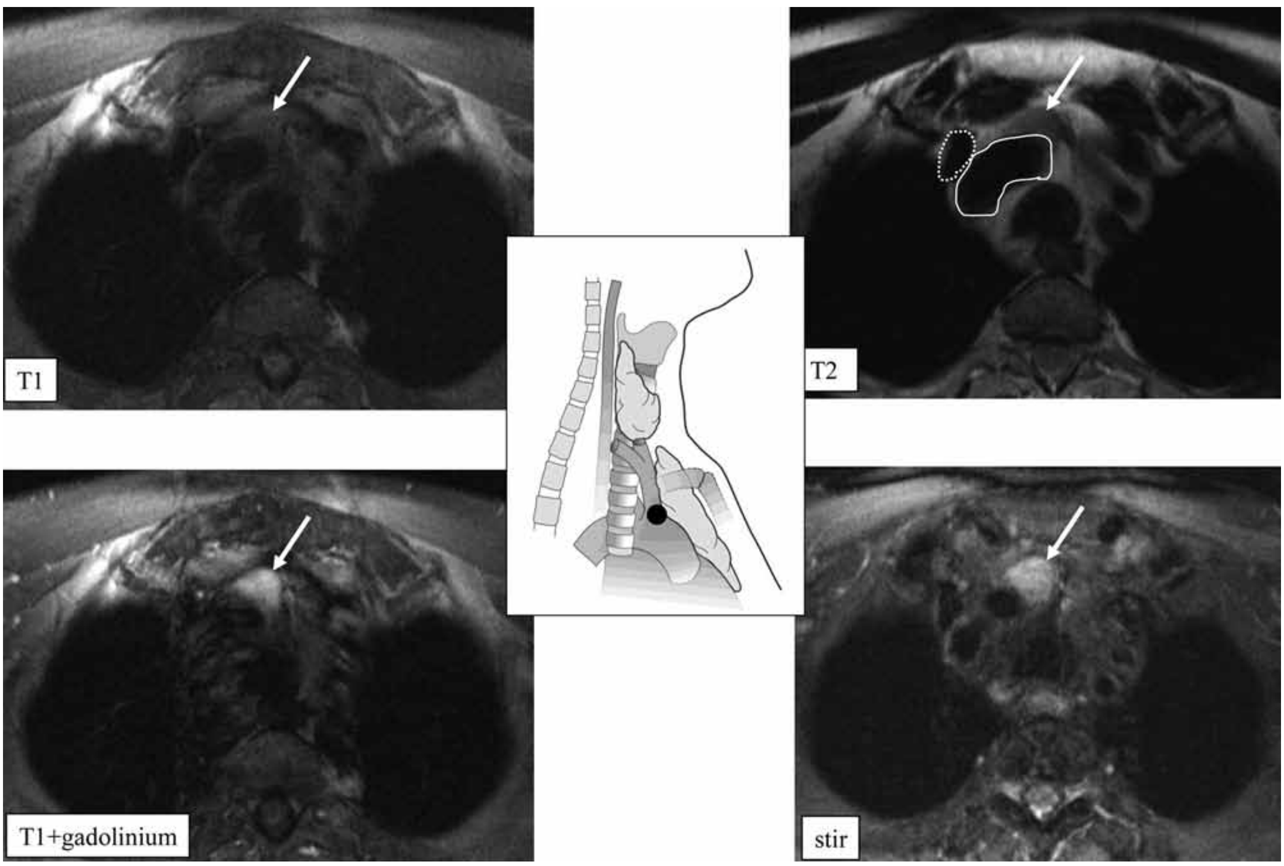


Fig. 8
Mediastinal parathyroid adenoma (solid arrows) in front of the right brachiocephalic artery (solid line) and on the inner side of the right innominate vein (broken line).

The ***Cons*** are essentially represented by the difficulties to make a precise and accurate differential diagnosis between parathyroid adenoma and lymphatic nodes. Indeed, parathyroid adenoma characteristics on MRI include intermediate to low signal intensity on T1 sequence and high density on T2 sequence. Cervical nodes can also have similar imaging characteristics, which limits the accuracy of MRI.

So far, the ***payoff*** from our experience lies in the fact that good transdisciplinary collaboration between

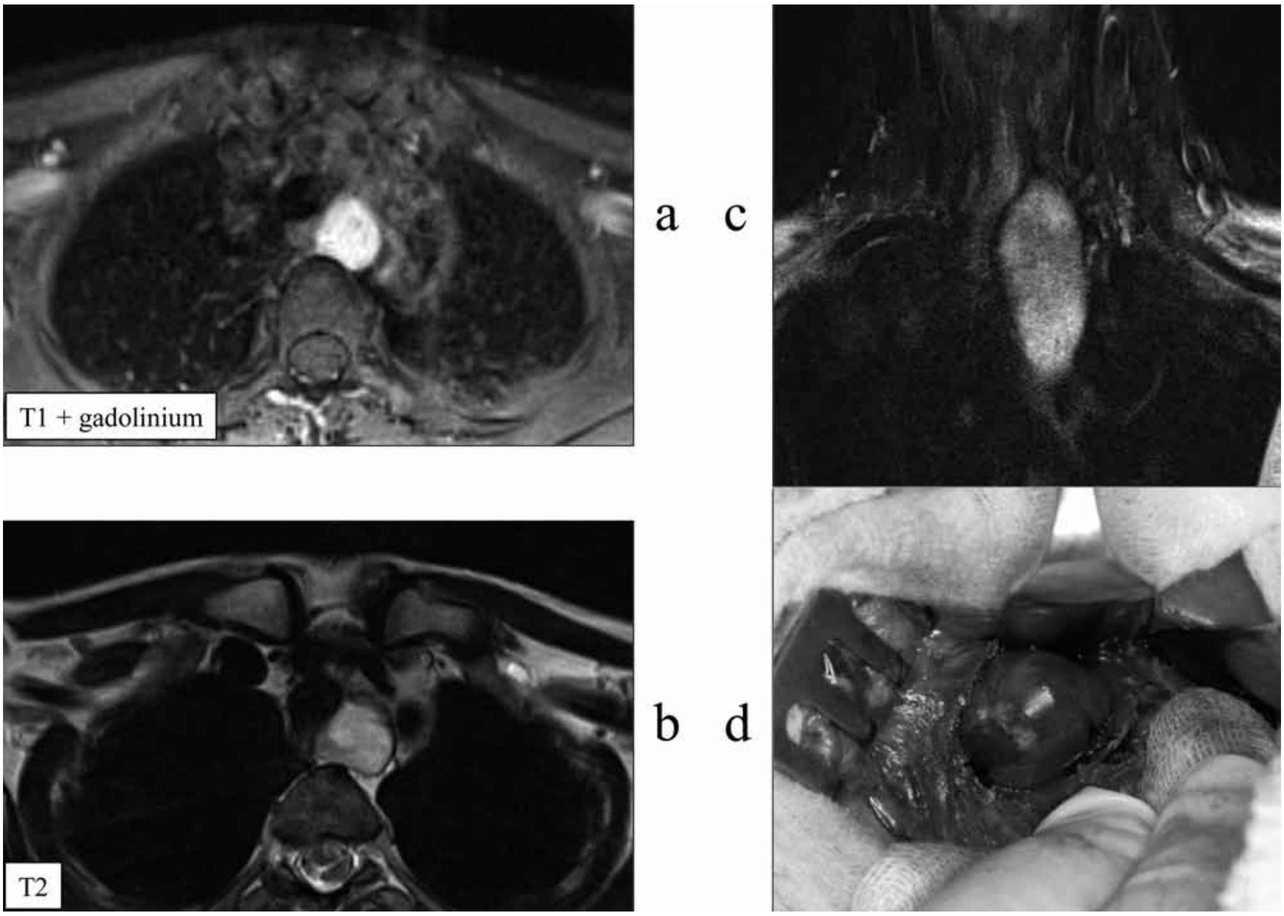


Fig. 9
Mediastinal parathyroid adenoma of 16 g visualized on transverse (a, b) and coronal (c) images, that was removed through the upper thoracic outlet by a cervical approach (d).

dedicated endocrine surgeons and dedicated radiologists brought MRI to the forefront of the armamentarium of preoperative tests available for the detection of abnormal parathyroid responsible of primary hyperparathyroidism. The sensitivity of MRI in the current study (94%) compares favourably with the reported sensitivity of MRI for abnormal parathyroid tissue ranging from 40 to 85 percent (8-10).

However, the endocrine surgeon's learning curve depends on her/his ability to cope with a combined reading of all the sequences of the MR exam in order to accurately locate the parathyroid lesion. Indeed, it is the combined reading of images provided by different sequences of the MR exam (i.e., T1 with and without gadolinium, T2 and STIR) that will ultimately provide integrated information about the anatomy, localization, differentiation and detection of organs and tissues (Fig. 2).

Practically, the radiologist and the surgeon must analyze preoperatively the MR imaging separately and then together, confront their results with the scintigraphy results if available, make progress by re-checking together the MR images after the operation in the light of the intra-operative findings. Such a systematic confrontation of surgical and MR results is particularly useful to improve the accuracy of the differential diagnosis between parathyroid glands and cervical lymph nodes. In the current study, surgeon and radiologist reached a fair agreement (Kappa coefficient of 0.276) both in terms of precision and accuracy (14, 15). Nevertheless, MR images interpretation by the radiologist reading with the attending endocrine surgeon resulted in improved accuracy of gland localization. Such improvement may be due to increased awareness of clinical factors and head-and-neck anatomy details shared between the radiologist and the surgeon.

Conclusions

MRI is a non invasive test easy to perform if dedicated radiologists are available.

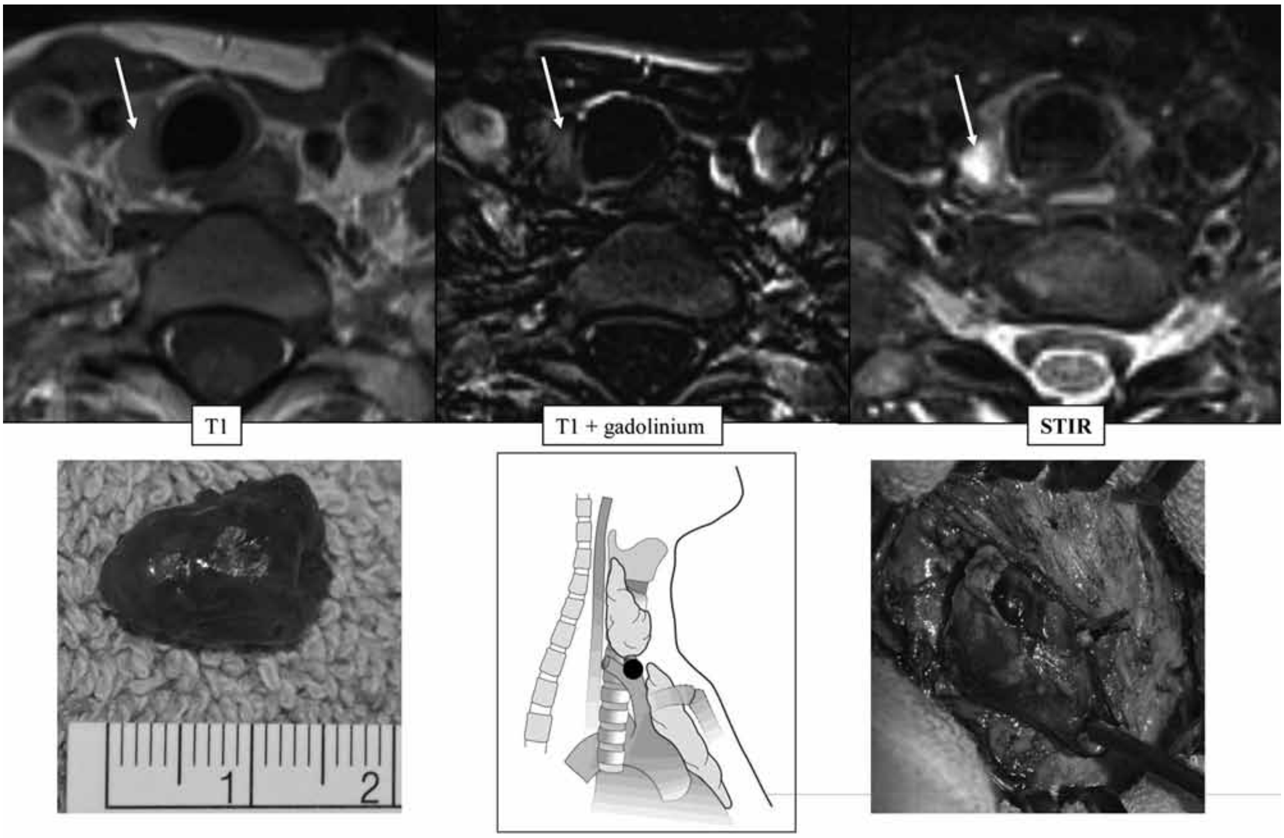


Fig. 10
36-year-old woman operated for Grave's disease 13 years before. Right superior parathyroid adenoma (600 mg - 12 × 10 × 10 mm) isointense on T1 with a discrete enhancement after gadolinium administration. The signal intensity is markedly increased in STIR sequence.

MRI does not administrate additional ionizing radiation, which is in the line of the ALARA principle (*As Low As Reasonably Achievable*) regarding the safety-involved systems in the field of Radiation Protection (13) in order to reduce the residual risk as low as reasonably practicable.

MR images close to surgical anatomy are helpful in reducing operative time duration, which represents a significant benefit for elderly and/or high risk patients.

MRI study should precede scintigraphy study. Only for difficult cases, the association of both should be considered. In fact, the superior anatomical resolution achieved with MR imaging combined with the physiological information gained from ^{99m}TC MIBI scintigraphy can then improve the sensitivity and positive predictive value to localize parathyroid lesions in difficult cases.

MRI efficient and effective interpretation imposes constructive interaction between surgeon and radiologist before and after surgery. In our experience, such a transdisciplinary collaboration has led to a fair interobserver agreement between endocrine surgeon and senior radiologist. More studies are needed to confirm and further improve those promising results with such a non invasive technology.

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