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Magnetic resonance imaging in the management of prolactinomas; a review of the evidence

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Abstract

Purpose This review aimed to evaluate data on the use of magnetic resonance imaging in the management of prolactinomas.
Methods Recent literature about prolactinoma behavior and magnetic resonance imaging in the management of prolactinomas is reviewed.
Results A review of evidence regarding prolactinoma pituitary MRI follow-up; techniques and sequences, recent data on possible gadolinium retention, the role and a review of T2-weighted images in the identification of prolactinomas and frequently encountered clinical scenarios, as well as MRI correlation with prolactin secretion, tumor growth and prediction of response to medical therapy are presented.
Conclusion The underlying decision to perform serial imaging in prolactinoma patients should be individualized on a case-by-case basis. Future studies should focus on alternative imaging methods and/or contract agents.

Keywords Prolactinoma · Magnetic resonance imaging · T2-weighted · Gadolinium · Lactotroph adenoma

Introduction

Prolactinomas (lactotroph adenomas) are the most prevalent pituitary tumor type, [1] and magnetic resonance imaging (MRI) has become the method of choice for pituitary gland and perisellar structures examination [2]. While macroprolactinomas may be easily visible on non-contrast enhanced MRI, gadolinium contrast may be necessary to identify some microprolactinomas and has become part of the standard protocol for pituitary imaging in many centers [1, 3]. Gadolinium based contrast agents (GBCAs) were initially thought to not diffuse through plasma membranes, not cross the intact blood–brain barrier, and be efficiently excreted unchanged by the kidney [4]. However, gadolinium deposits have been noted in post-mortem human brain as well as bone, skin, and other tissues even in patients with intact kidney function [4]. Although macrocyclic agents (gadoteridol, gadobutrol, gadoterate) are more stable than linear agents (gadopentetate, gadobenate, gadodiamide, gadoversetamide) and have less potential for accumulation, tissue deposits of macrocyclic agents have been also observed [4–6].

Prolactinoma treatments are currently very effective at normalizing prolactin levels and shrinking tumors, however, repeat MRIs are performed on a regular basis for continued monitoring in many patients [3]. This can create a cost burden for patients and healthcare systems, and coupled with the recent data on possible gadolinium retention, determining the optimal frequency to perform follow-up MRI to safely assess an individual's prolactinoma response to treatment has increased in importance [1].

Reductions in the number of gadolinium MRIs is desired, although evidence-based guidelines on the frequency of follow-up MRIs are lacking [7]. The search for alternative non-contrast enhanced MRI sequences for detection [8], prognosis on response to treatment [9] and follow up for prolactinomas has focused on T2-weighted images and ancillary imaging signs [8].

We have conducted a review of evidence regarding prolactinoma follow-up pituitary MRI, in different clinical scenarios. MRI techniques and sequences and the role of

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T2-weigthed images in the identification of prolactinomas as well as prediction of response to medical therapy are presented.

MRI monitoring and dopamine agonist therapy

Currently, there is no clear consensus on a precise timeline regarding follow-up MRIs for prolactinoma patients. The Endocrine Society (ES) Clinical Practice Guidelines provide a general recommendation of repeating a MRI in 1 year for micro- and in 3 months for macroprolactinomas after dopamine agonist (DA) initiation, or if prolactin levels rise despite treatment, or if a patient develops new visual disturbances, headaches, galactorrhea or evidence of a new hormonal dysfunction [3]. However, there is no recommendation regarding any additional follow-up imaging and frequency. A decision to perform follow-up serial imaging remains dependent on the specific clinical situation and determined on a case-by-case basis.

Observational studies have demonstrated that adenoma size correlates with prolactin level, in most patients [10, 11]. Decreasing prolactin levels while taking a DA is usually accompanied by considerable tumor shrinkage [12], and effects, including improvement in visual fields (VFs), which may be notable as early as 1 month after DA initiation [12]. However, discordant results are observed for some prolactinomas, either normalization of prolactin level without substantial tumor shrinkage [13] (Fig. 1), or excellent tumor shrinkage without complete prolactin normalization (albeit a major reduction) [13]. Although prolactin usually normalizes within the first 6 months and significant tumor size reduction also occurs during this time frame [14], many prolactinomas continue to slowly decrease in size during the first 4 years [15–17].

Tumor enlargement while on DA therapy may occur in resistant prolactinomas, but is typically accompanied by persistently *elevated* or *rising* prolactin (Fig. 2). However, rare tumor growth with *stable or decreasing prolactin* levels has been described, albeit limited to case reports [18].

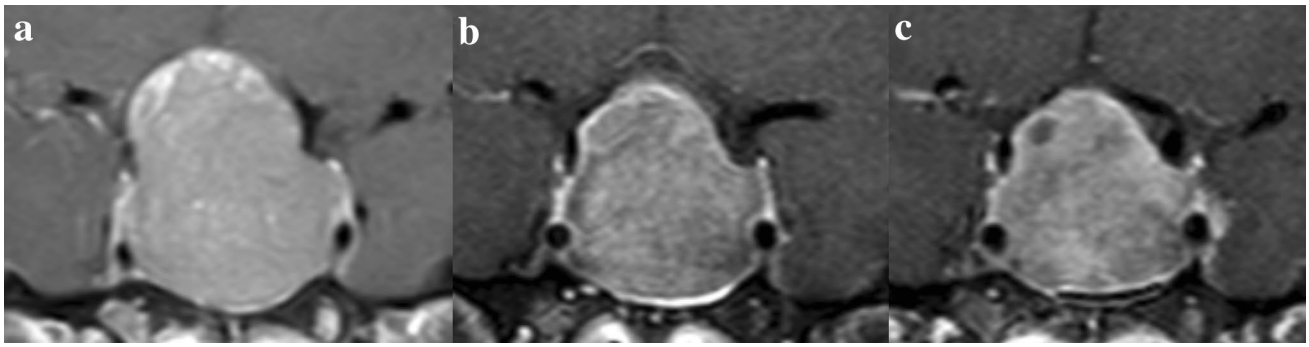

Fig. 1 27-year-old male with macroprolactinoma treated with cabergoline 0.5 mg twice weekly. Coronal T1, contrast enhanced MRI. **a** At diagnosis; prolactin > 4700 ng/mL **b** 3 months follow up; prolactin 1232.6 ng/mL; mild initial tumor shrinkage, and **c** 6 month follow up; prolactin 6.7 ng/mL; minimal further tumor shrinkage despite normalization of prolactin

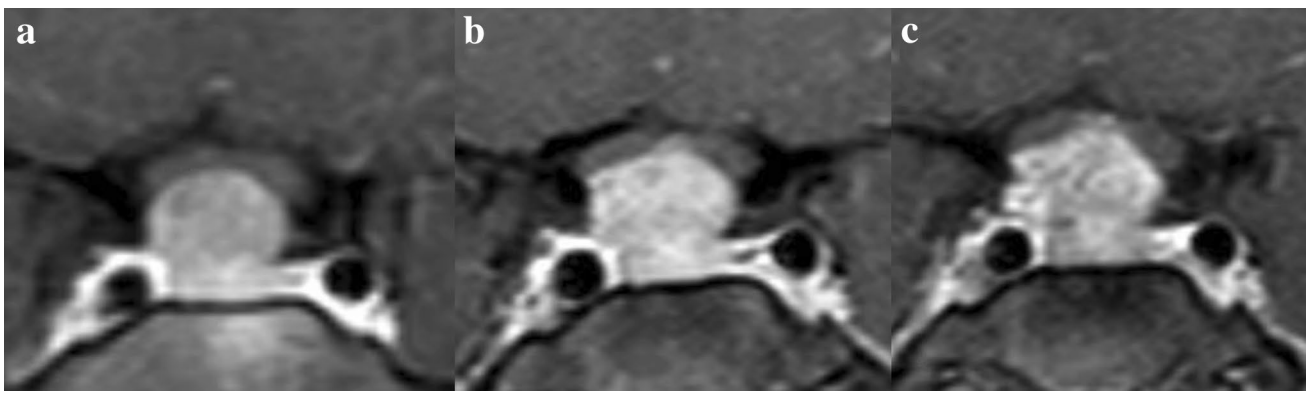

Fig. 2 Macroprolactinoma in a 13-year-old female. MRI, Coronal T1, contrast enhanced. Progressive increase in size of the tumor is accompanied by persistently elevated and rising prolactin level. **a** At diagnosis, prolactin 310 ng/mL, **b** 5 month follow up, prolactin 95 ng/mL; cabergoline 1 mg/week, and **c** 14 month follow up, prolactin 165 ng/mL; cabergoline 1.5 mg/week

Kupersmith et al., described 4 cases of macroprolactinoma enlargement despite reduction of prolactin levels with bromocriptine. Two of the four patients had surgery twice and while the first surgical specimen was consistent with prolactinoma, a second specimen (tumor resurrence) was negative for prolactin. The authors could not completely rule out medication non-adherence and/or a nonfunctioning adenoma with stalk effect [19]. Saeki et al., reported a case of a 41 mm prolactinoma that initially responded with prolactin reduction from 9200 to 105 ng/ml (normal < 30 ng/ml) and size reduction to 28 mm but with subsequent regrowth to 36 mm despite further decrease of prolactin to 47.6 ng/ml. There was no evidence of bleeding and surgical pathology was negative for prolactin and other hormones suggesting regrowth of the non-functioning part of the tumor [20]. In a study of 69 patients with micro- and macroadenomas with stable/reduced prolactin for a median of 2.8 years (0.3−9.5 years), only 2 patients with macroadenomas experienced tumor enlargement, and in both cases this was attributed to asymptomatic pituitary hemorrhage [18]. There was no microprolactinoma enlargement in the patient cohort, nor were any cases of micropolactinoma enlargement while on DA therapy in the literature the authors reviewed [18]. This finding, as well as observation by others has led some experts to recommend not performing follow-up MRI for microadenomas unless prolactin rises significantly (e.g., > 250 ng/mL), or if compressive symptoms (headache, visual loss) develop [21, 22].

Unlike microprolactinomas, potential growth in macroprolactinomas is more concerning. A retrospective study investigated long-term macroprolactinoma behavior in 115 patients treated with DA for a mean of 9.7 years who maintained normal prolactin levels [1]; 102 (88.7%) patients experienced tumor shrinkage and 11 (9.5%) had no change in tumor size, while 2 patients had tumor enlargement due to asymptomatic hemorrhage, which subsequently decreased on the same DA dose [1]. The authors concluded that follow-up MRI in macroprolactinomas may not be necessary as long as prolactin level is normal on DA therapy. They further suggested that the small risk of asymptomatic hemorrhage should not be regarded as basis for serial repeat MRIs [1]. This study, however, excluded patients with optic chiasm contact or compression and giant prolactinomas.

Repeat MRI is clearly warranted in patients with prolactinomas causing optic chiasm compression and abnormal VFs who are started on DA. At our center, we perform MRI at approximately 3 months after initiation of DA in these patients; we repeat VFs 2–4 weeks after DA initiation. Absence of shrinkage should prompt consideration for dose escalation; and worsening VFs for pituitary surgery.

Although micro- and macroprolactinomas without optic chiasm contact and with excellent biochemical response to DA may be regarded as "low-risk" for tumor progression, the decision to repeat MRI should be based on a specific clinical scenario. Factors such as absolute adenoma size, invasiveness, prior treatment, rate of prolactin decline and tumor shrinkage, sex, estrogen state, as well as adherence to the medication may influence the decision about repeat MRI frequency. Additionally, when assessing the change in the tumor size overtime, it is important to review the entire series of available MRIs because subtle changes may not be observed when a comparison is limited to just two consecutive studies.

Several frequently encountered clinical situations are discussed below.

MRI prior to dopamine agonist withdrawal

One of the factors determining the success of DA withdrawal is the absence of tumor remnant or significant reduction in tumor size as determined by MRI [23]. Therefore, a decision to withdraw DA necessitates repeat imaging. The ES Clinical Practice Guidelines recommend that patients be treated for a minimum of 2 years, have normal prolactin level and no visible tumor on MRI to maximize the chance of remission [3]. This means that a significant number of patients may undergo serial repeat MRIs starting at least 2 years after DA initiation in patients for whom taper or DA discontinuation is planned. In a 12-month prospective study, tumor was not visible in 29% of microadenomas and 17% of macroadenomas treated with cabergoline [24]. In another study, long-term follow-up of patients with macroprolactinoma (median 54 months) showed no visible tumor in 38% [25]. Thus, many patients, especially those with macroadenomas, will remain on long-term DA treatment without attempting withdrawal. However, in some cases withdrawal can be attempted even if tumor remnant is present. In one study, although patients with MRI visible tumor remnant had higher rates of recurrence, 59% of patients with microadenoma remnant and 23% of those with small macroadenoma remnant maintained normoprolactinemia after stopping cabergoline. This suggests that pituitary lesions visible on MRI could represent scar tissue or other non-functioning lesions [26]. Interestingly, in another study, patients with and without visible tumor remnant had a similar frequency of hyperprolactinemia recurrence (50% vs. 53.8%) after a median of 4.5 years of cabergoline; although larger size of the tumor remnant did predict recurrences [23].

Some have suggested not to use MRI prior to DA withdrawal in microadenomas such as in a study by Biswas et al. [27] where 89 patients with microadenomas (84 women) received DA for a mean of 3 years. The recurrence was 64% within 1 year, which was higher than in the studies that required tumor shrinkage/disappearance proir to DA withdrawal (31–52%) [23, 26], but somewhat similar to

others that did not use MRI to determine withdrawal criteria (74.2–77.8%) [27-29].

Initial tumor size, baseline prolactin levels and duration of therapy have also been correlated with remission [27]. Therefore, we consider that tumors with "favorable" withdrawal profile (small size, mild baseline prolactin elevatation and longer duration of therapy) may be considered for DA discontinuation without pre-withdrawal MRI, which seems both a safe and cost-effective strategy.

MRI after withdrawal of dopamine agonist therapy or in patients not treated with dopamine agonists

Monitoring for tumor regrowth after DA withdrawal includes periodic measurement of prolactin levels and MRI. The ES Clinical Practice Guidelines recommend to repeat MRI if prolactin levels become abnormal [3]. Studies examining recurrence of hyperprolactinemia showed that patients who experienced a recurrence had no evidence of tumor progression or regrowth after they were treated with DA for median of 42–48 months prior to DA withdrawal [23, 26, 29]. However, short term use and early discontinuation of DA may result is tumor regrowth [30-–32]. Therefore, the decision to repeat MRI may rely on the degree of prolactin elevation, duration of treatment, initial tumor size and other factors.

Several studies have demonstrated that microprolactinomas rarely increase in size to become clinically significant [33, 34]. Although a change in prolactin level typically correlates with change in tumor size and furthermore, precedes tumor growth, discrepances may occur and some clinicians recommend routine MRI follow up in patients not taking a DA, such as once a year for the first 3 years followed by less frequent imaging if the patient's condition remains stable [21, 35], while others repeat imaging only if a significant increase in prolactin levels occurs [21]. We suggest that MRI in untreated patients with *microprolactinomas* and *stable* prolactin levels be performed on a case-by-case basis, such as if there is evidence of new pituitary dysfunction, new or change in severity of headaches or peripheral vision changes.

MRI monitoring in patients on estrogen therapy

Patients with microprolactinomas who are treated with oral estrogen-progesterone containing contraceptives for amenorrhea are at a theoretical risk of adenoma enlargement due to stimulation of lactrotrophs by exogenous estrogen. However, studies have shown that tumor enlargement in patients followed for 2−6 years does not occur. In fact, some tumors regress in size and prolactin levels remain unchanged [36, 37]. However, the data are limited by small number of patients and studies with relatively short follow-up period.

MRI in postmenopausal women

Discontinuation of DA upon reaching menopause is considered a reasonable approach in women given that menopause is a natural state of low estrogen and galactorrhea is very rare. Cases of spontaneous hyperprolactinemia resolution after menopause have been described, however tumor behavior in menopause is not well studied. The ES Clinical Practice Guidelines recommend surveillance for increasing size of the pituitary tumor on a periodic basis [3].

A recent retrospective analysis included women who were taken off DA after menopause (all had normal prolactin and 17/28 had visible adenoma prior to discontinuation of DA) and followed for 3 years; prolactin increased in 15%, decreased in 33% and remained normal in 52% of the women. Tumor regrowth was found in 2/27 (7%) of patients measuring 2 and 4 mm at 4 and 6 years after DA discontinuation, respectively. In both cases, prolactin levels progressively increased doubling and trippling in value [38]; thus we suggest that persistent hyperprolactinemia should be regularly monitored and MRI performed when tumor growth is suspected based on rising prolactin levels or clinical signs of new headaches or vision changes.

Resistant prolactinomas

Monitoring of resistant prolactinomas is performed on a case-by-case basis due to various degrees of resistance and various response to treatment. The length of time after which tumor can be classified as resistant, usually ranges between 3 and 6 months. The ES Clinical Practice Guidelines define prolactinoma resistance as failure to normalize prolactin on maximally tolerated doses of DA and a failure to achieve at least 50% tumor size reduction [3]. Rapidity of dose escalation can also influence the final prolactin level and the tumor size at any follow-up time point, which in turn determines how the tumor will be classified [39]. Additionally, how tumor shrinkage is assessed also can influence the outcome classification.

In terms of tumor size reduction, up to 30% of macroprolactinomas do not respond with significant shrinkage to cabergoline [39] and up to 36% are resistant to bromocriptine [13]. Predictors of resistance include larger tumor size, higher prolactin levels, invasiveness, being male, very young age, cystic tumors, and MEN 1 mutation [16, 39]. These factors should be taken into consideration when determining follow-up. Resistance in microadenomas is less common [3].

The World Health Organization now recognizes that prolactinomas in men are more aggressive independent of hystologic subtype [40]. Men present with macroadenomas more commonly than with microadenomas [41, 42]. Some have suggested that prolactinomas in men have higher proliferative activity and are more resistant to DA therapy [43–45]. A

study comparing "resistant" with "sensitive" tumors, found a higher percentage of men in the resistant group (69% vs. 33%) [45]. However, prospective and retrospective studies have demonstrated that prolactinomas in men can be effectively treated with DA monotherapy. In a prospective cohort of 51 men (41 with macroadenomas; 17 with visual field defects), 24 months of therapy with cabergoline resulted in 76% normalization of prolactin in macro- and 80% in microadenomas with > 30% tumor reduction in all macroadenomas and an average of 73.7% reduction of maximal diameter suggesting an overall treatment response similar to women [46]. Furthermore, none of the treatment resistant patients experienced tumor enlargement while on cabergoline. In other series of men treated with DA, prolactin normalization in 73−83% of micro- and 65−79% of macroademonas, and tumor shrinkage in 17−60% micro- and 33−76% of macroprolactinoma patients, was demonstrated [41, 42, 47]. These data suggest that MRI frequency in men with small and responsive microadenomas may not need to be more frequent than in women.

Whether men have worse surgical outcomes compared to women remains controversial. Tumor size and invasion, which are commonly observed in men, have been associated with poor surgery outcomes, however, it is unclear if sex per se influences outcomes [48]. In a study of 87 men who underwent surgery for a prolactinoma (17% due to resistance to DA), overall remission was 53% [48]. On the other hand, a study of 31 men who had surgery (58% due to lack of tumor shrinkage) demostrated that 93% had a tumor remnant on post-operative MRI, 24% underwent additional pituitary surgery and 19% required radiation therapy [49]. Thus men with resistant prolactinomas may undergo more frequent imaging.

Although traditionally considered resistant to DA, cystic prolactinomas have been shown to be treated effectively with DA (Fig. 3). Faje et al., showed that prolactin normalized in 18/22 patients and cyst volume decreased in 20/22 patients by a median of 83.5% over median of 3 years [50]. Cyst reduction occured at a median of 24 weeks, however, was detected as early as 3 weeks. None of the patients (majority women) experienced tumor growth while on treatment, thus a cystic component on MRI does not seem to be a predictive factor for DA response and therefore does not necessarily warrant more frequent imaging compared with same clinical scneario patient, but without cystic tumor.

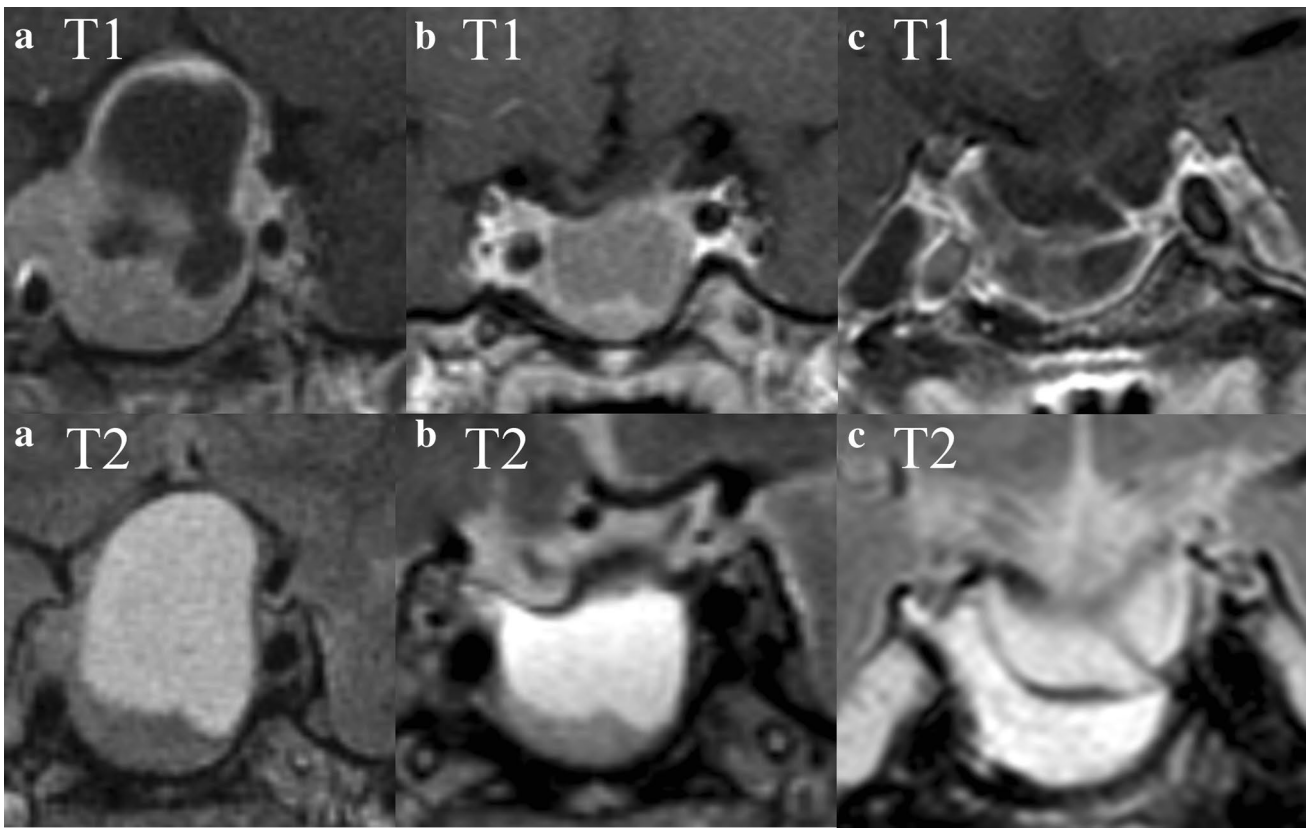

Fig. 3 35-year-old male with macroprolactinoma with cystic change treated with standard dose cabergoline. Serial coronal T1, contrast enhanced, and T2 sequences show progressive decrease in size of the cystic adenoma. **a** At diagnosis; prolactin 1400 ng/mL, **b** 5 months follow up; prolactin 65 ng/m; cabergoline 1 mg/week, and **c** 3 year follow up; prolactin 5 ng/mL; 1.25 mg/week

Giant pituitary adenomas are significantly more common in men (9:1 male to female ratio) [51] and usually present with symptoms of mass effect on the optic chiasm and headaches [52]. In a summary of 13 series, giant pituitary adenomas seem to respond well to DA; 60% of patients normalizing prolactin while taking DA and 74% having tumor shrinkage (30% decrease in tumor diameter, or > 65% reduction in tumor volume) after a mean follow up of 37 months [53].

Giant prolactinomas in women are rare with a peak incidence in the 5th decade of life [51]. Interestingly, a literature review on giant prolactinomas in women shows frequent biochemical resistance; prolactin normalized in approximately 50% of women and more than half required higher than standard doses of DA. Tumor shrinkage (> 30%) occurred in 11/14 patients [54]. In a series of 14 patients who had surgery as first line treatment for giant prolactinomas (4 for pituitary apoplexy and 10 for personal preference), mean degree of resection was 69.2 ± 6.7% (range 24.7−95.2%) by postoperative MRI, followed by bromocriptine. Two patients experienced tumor regrowth after 3 and 5 months and required re-operation [55]. These examples emphasize that despite overall success in treatment of giant adenomas, they often require more close monitoring with imaging.

MRI monitoring after surgery

Surgery, either complete or partial resection (debulking) of a tumor is the second line treatment modality and is performed in patients with resistant prolactinomas, DA intolerance, and in a rare case of cerebrospinal fluid leak as a result of DA therapy. Remission rates range between 30−93%, with invasive adenomas exhibiting lower remission [56]. Recurrence of hyperprolactinemia is relatively common, ranging between 5 and 58% [56–58]. Interestingly, a metanalysis of 30 studies examining surgical outcomes of prolactinomas showed that age, sex, and tumor invasion did not influence recurrence rates while basal low postoperative prolactin levels were predictive of permanent cure [59]. Studies reporting surgical outcomes did not focus on the rate of tumor regrowth after complete resection or tumor enlargement after incomplete resection. Some studies reported no tumor regrowth on computed tomography and x-ray polytomography in patients with recurrent hyperprolactinemia [60], however, these techniques are not sensitive enough to detect tumor recurrence or remnant enlargement.

We recommend that MRI should be performed at least once approximately 3 months after surgery to assess for residual tumor and to establish a new baseline for follow up imaging. Following that, we suggest that non-resistant microprolactinomas with complete gross resection be followed in a similar manner to microprolactinomas without surgical resection. Resistant, large and incompletely resected prolactinomas should be followed more closely with MRI frequency on an individualized basis.

MRI monitoring after radiation

Radiation therapy is reserved for prolactinomas resistant to medical therapy as well as aggressive or malignant types. Gamma knife radiosurgery (GKRS) has been shown to be 89–92% effective in tumor control, while prolactin normalization is only achieved in 26–52% of patients [61–63]. One study showed that no tumor characteristics were significantly associated with imaging outcomes, and DA continued use throughout follow-up did not affect imaging outcomes either [62]. As 11% of patients had tumor enlargement of at least 20% despite being on bromocriptine after GKRS [62] and patients who had radiation had more aggressive tumors initially, there is a need for continued monitoring with MRI after radiation in most patients for at least a few years.

MRI monitoring during pregnancy and lactation

Dopamine agonists are typically discontinued once pregnancy is confirmed to minimize fetal exposure and theoretical negative effects on the fetus [3]. Discontinuation of DA and stimulatory effects of estrogen can lead to enlargement of prolactinoma in pregnancy. While 4.5−5% of women with microadenomas experience enlargement, the risk of significant microadenoma enlargement with compressive symptoms is 2−3% [64, 65], similar to macroadenomas previously treated with surgery or radiation [66]. One study showed that as many as 46% of microadenomas > 5 mm enlarge during pregnancy [65, 67]. The risk of some macroadenoma enlargement is 65% and of symptomatic enlargement is 30% [65, 67]. It is reasonable to perform MRI prior to conception to confirm efficacy of DA treatment and to establish a baseline and attempt to assess the potential risk enlargement during pregnancy.

The ES Clinical Practice Guidelines recommend no routine MRI during pregnancy, however, endorses clinical examination for patients with each trimester in micro- and formal VFs in macroprolactinomas [3]. New or worsening headaches or vision changes should prompt an MRI without contrast. Furthermore, some authors recommend routine coronal T1- and T2-weighted MRI sequences without contrast between weeks 28 and 32 in women with a macroadenoma at the onset of their pregnancy [68, 69], however, there is no current evidence that this practice leads to improved outcomes in asymptomatic patients. In our practice we do not perform MRIs in pregnancy unless there is concerning symptomatology.

Breastfeeding has not been shown to induce tumor growth in women and DA treatment is withheld in asymptomatic women who did not take DA during pregnancy [70, 71].

Routine MRI surveillance during breastfeeding is not needed in most patients and there is no guidance when pituitary MRI should be performed after delivery [70].

Role of T2 WI MRI sequences in pituitary adenomas

Three basic MRI sequences (1) T1-weighted (T1 WI) (2) T2-weighted (T2 WI) and (3) gadolinium contrast-enhanced T1-weighted images (CE T1 WI) are often adequate to evaluate pituitary tumors. In some cases, dynamic T1 sequences with gadolinium are helpful to identify some microadenomas that are not readily recognized on standard sequences [72]. Pituitary adenomas are usually mildly hypointense or isointense on T1WI and have variable intensity on T2 WI [73]. T2 sequences can help recognize pituitary hemorrhage which usually results in T2 hypointensity in acute and chronic stage, while cystic component may be hypo- or hyperintense on T2 [74].

Recently, T2 intensity of pituitary adenomas has been shown to correlate with histological subtype and clinical behavior of some adenomas [73]. In particular, T2 WI signal intensity correlates with granulation pattern and predicts response to somatostatin receptor ligands in somatotroph adenomas [75–80]. Furthermore, T2 hyperintense corticotropinomas have been found to be larger and more sparsely granulated, although no difference in baseline adrenocorticotropic hormone or cortisol levels and no difference in remission and recurrence rate has been found [81]. Studies of the use of T2 in prolactinomas are limited, although it has also become of more interest in recognition of resistant prolactinomas and in prediction of response to therapy.

The underlying histologic and structural characteristics determining intensity of the T2 are poorly understood. Fibrous tissue, iron deposits and amyloid have been found in hypointense adenomas in some studies, however, similar amounts of amyloid have been seen in hyperintense adenomas as well [73, 82]. Likewise, consistency of pituitary tumors, which may depend on the collagen content, has not always been correlated with T2 intensity [82, 83]. Machine learning-based T2 WI histogram analysis may have better performance than traditional T2 signal intensity ratio for this purpose [84]. Additionally, some data suggest that diffusion-WI may be superior to T2 WI in predicting tumor-collagen content [85].

T2 WI was shown to be useful in visualization of the contours of residual tumors after surgical resection, in particular, the borders between the tumor and normal pituitary gland or the cavernous sinus [2]. T2 signal of tumor remnants at 3 months and beyond are usually hyperintense compared with normal pituitary tissue, except in some somatotroph adenomas [86].

Finally, coronal T2 WI seems to be the preferred sequence to measure transverse and craniocaudal dimensions to detect early tumor shrinkage after radiation therapy [86]. Demonstration of a heterogeneous T2 hyperintensity of the adenoma usually precedes shrinkage and has been postulated to be linked to the onset of treatment action [86].

Use of T2 WI in prolactinomas

Prolactinomas in general are usually hypointense on T1 and mildly hyperintense relative to normal pituitary tissue and temporal lobe gray matter on T2, however, sex-related T2 differences have been observed (Fig. 4). In addition to larger tumor size and higher prolactin levels [9], prolactinomas in men are often heterogeneous, with areas of focal necrosis or old hemorrhage [86]. One retrospective study examined T2 signal intensity relative to gray matter in 41 men and 41 women and found that hypointense adenomas were more commonly encountered in men than in women (15% vs. 3%). Although clinical significance of this finding is unknown, the authors speculated that these tumors may contain amyloid deposits, as previously reported in a radiology-pathology correlation study [87], and can potentially be more resistant to treatment [88]. Another study on 48 women and 30 men with prolactinomas found that 19% were hypointense in women and 17% were hypointense in men; interestingly, T2 hypointensity correlated with DA resistance only in women, while T2 hyperintensity correlated with smaller adenoma size [81]. On the other hand, in a retrospective study of 70 prolactinomas, T2 intensity (hypo- or hyper-) did not predict DA response, however, T2 heterogeneity correlated with poorer response to DA. It remains unclear whether resistant

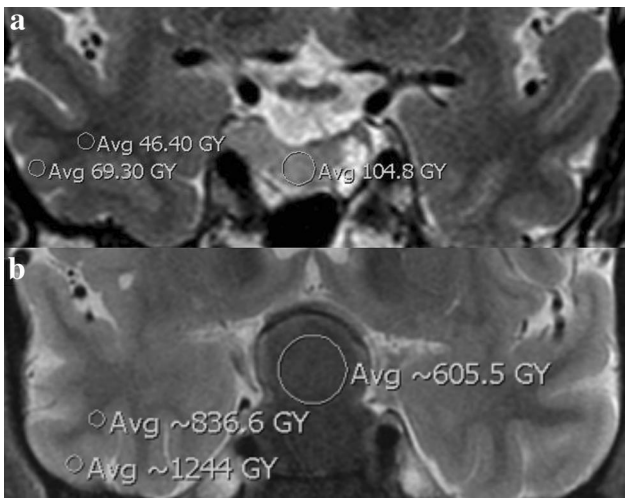

Fig. 4 Example of T2 signal intensity measurement (as described by Hagiwara et al. [73]). **a** Hyperintense prolactinoma; T2 intensity is higher than that of the gray matter, and **b** hypointense prolactinoma; T2 intensity is lower than that of the white matter. Isointense adenoma (not shown); T2 intensity is higher than that of the white matter and lower than that of the gray matter

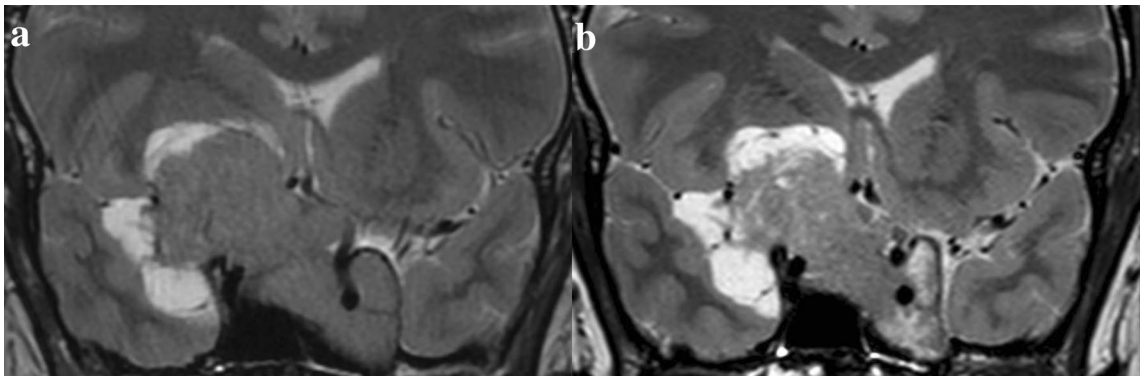

Fig. 5 Treatment effect of cabergoline on giant prolactinoma. Coronal T2 MRI. **a** Before treatment, prolactin 11,940 ng/mL, and **b** after 3 months of treatment with cabergoline. Increase in hyperintensity of T2; minimal tumor shrinkage, prolactin 4108 ng/mL

prolactinomas can be identified based on certain T2 characteristics. In a retrospective study that assessed radiologic and pathologic characteristics of prolactinomas in men who required surgery, more than half of whom were DA resistant, a majority of the prolactinomas were isointense (75%), followed by hyperintense 19%, and finally by hypointense tumors (6%) [49].

Tumor shrinkage post DA can be accompanied by change in the MRI signal, the most common change is accentuation of T2-signal hyperintensity, although hemorrhagic and markedly hyperintense prolactinomas do not exhibit change in MRI signal (Fig. 5) [86].

T2 signal can be also of some interest in women with prolactinomas who desire pregnancy as it has been postulated that T2-hypointense prolactinomas seem to be more prone to grow during pregnancy than the most commonly encountered hyperintense ones [86], however more research is needed. Whether or not these T2-hypointense prolactinomas should actually be followed by MRI in the third trimester is not yet known [86].

Conclusion

For most patients with prolactinomas, prolactin and/or visual fields can be used as a monitoring mechanism, but MRI is still needed in the long-term management of prolactinoma patients, especially in aggressive cases. A decision to perform serial imaging should be individualized on a case-by-case basis considering a variety of factors such as adenoma size, invasiveness, resistance, sex, estrogen state and prior treatment. Small tumors with mild baseline hyperprolactinemia and longer duration of therapy may be considered for DA discontinuation without pre-withdrawal MRI. Possible retention of gadolinium-based contrast agents even in patients with normal kidney function and increasing MRI costs have brought more attention to non-contrast imaging options. Few studies have evaluated T2 WI signal intensity in prolactinomas as a possible predictor to therapy response. Further examination of alternative imaging methods and/or agents is needed.

Compliance with ethical standards

Conflict of interest All the authors declared that they have no conflict of interest.

Research involving human participants or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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