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Visual Morbidity in Patients with Pituitary Adenoma

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Abstract

Visual dysfunction is an important element in the morbidity encountered in patients with pituitary adenoma leading to functional impairment and compromised quality of life. It consists of many parameters (even in the absence of reported symptomatology) as a result of tumour growth in proximity to structures critical for vision (anterior visual pathway, cranial nerves within cavernous sinuses), and as an adverse consequence of therapeutic interventions.

Adenoma resection leads to high rates of visual improvement and possibly continues beyond a year post-surgery but the exact timing of maximum effect requires elucidation. Retinal nerve fibre layer measurement may be a reliable, objective parameter predicting favourable visual outcomes, although its prognostic value when pathological, needs to be confirmed. For compromised vision after pituitary apoplexy, early surgical decompression remains usual practice until evidence-based guidance becomes available. The risk of radiation-induced visual toxicity is mainly influenced by total and per fraction dose of radiation and treatment modality. Careful selection of cases and of radiotherapy technique/planning are of major importance in minimising this risk. Dopamine agonists lead to visual recovery in a considerable number of prolactinoma patients.

Visual morbidity should be considered a vital indicator in the metrics of quality of service/care in pituitary disease making regular, full ophthalmic examination an essential component of modern management of pituitary pathology at all time points of patient pathway. Well-designed studies minimising effects of bias and using tools and scoring systems reliably reflecting visual status will provide robust evidence on valid prognostication and patient stratification guiding clinical decision making.

Introduction

Pituitary adenomas are sellar neoplasms that can cause significant visual impairment as they grow in proximity to structures critical for vision (visual pathways, ocular motor nerves) (1). Compression of these structures by the tumour (primary or recurrent) leads to visual morbidity (2) with subsequent functional impairment and compromised quality of life (3-6), and remains one of the main indications for therapeutic intervention. Moreover, visual function may be adversely affected as a complication of surgery and/or radiotherapy necessitating ongoing neuro-ophthalmology input.

Over the last two decades, there have been significant advances in the assessment and management of pituitary tumours, including neuroimaging, non-invasive ophthalmic imaging [Optical Coherence Tomography (OCT)], surgical techniques and radiotherapy. In this review, we present the contemporary literature on visual outcomes and prognostic factors aiming to provide guidance relevant to clinical practice and to identify areas requiring improvement and further research.

Visual dysfunction at presentation of pituitary adenomas

Optic nerve damage occurs secondary to compression by the adenoma causing direct disruption of axonal conduction, impairment of axonal flow, demyelination and ischaemia. These are initially reversible but over time, they may become permanent (2,7). Following prolonged or intense compression, axonal degeneration and irreversible optic atrophy occur (2). Due to redundancy of ganglion cell fibers in the optic nerve, a degree of atrophy may be observed without compromising subjective visual function, however, advanced atrophy results in permanent visual deficits not amenable to resolution after surgical decompression (2).

The prevalence of visual dysfunction at presentation amongst patients with adenoma varies widely, depending on characteristics of the cohort studied and methods of visual assessment. A recent systematic

review reported visual acuity problems in 14–84%, visual field defects in 28–100% and “unspecified” visual complaints in 15–100% of patients presenting with various types of adenomas (1). Microadenomas do not impact vision (8) and macroadenomas measuring <2 cm are unlikely to cause significant visual impairment (9). Non-functioning adenoma is the most common subtype in patients with visual dysfunction at presentation possibly due to diagnostic delays (10,11). In a series of non-functioning adenomas causing visual dysfunction, the median time from onset of symptoms until diagnosis was 6.5 months (11). In this study, an advanced age of onset of visual symptoms was associated with delayed adenoma detection, as the visual manifestations were initially attributed to other pre-existing ophthalmic pathology (11). The severity of the reported visual dysfunction is variable. Even significant visual defects may be unnoticed by patients. In one series, almost 50% of patients without visual symptoms had visual dysfunction on ophthalmologic evaluation (12) and visual field defects were detected in 5-15% of those with pituitary incidentalomas (13). Conversely, a number of cases come to medical attention due to visual complaints and this is particularly true for non-functioning adenomas (14). Patients may have long-standing visual manifestations (10,11) or present with sudden visual loss or cranial nerve dysfunction in the setting of pituitary apoplexy (2). Reassuringly, the duration of symptoms until adenoma detection has decreased significantly in recent decades, likely reflecting improved recognition of these tumours (15).

Bitemporal field defects, due to chiasmal compression, are the most common pattern of visual loss, however, pituitary adenomas can cause a broad range of visual complications depending on the nature of contact with the optic pathway (Figure 1) (12,16). Since in most patients the chiasm is located directly above the pituitary fossa, the crossing inferonasal fibres are usually the first to be affected by upward growth of the tumour causing supratemporal field defects, respecting the vertical meridian. Further tumour growth leads to complete bitemporal hemianopia as all of the crossing fibres in the chiasm become affected (17). Patients with a pre-fixed or post-fixed chiasm will not present with this classic picture. When the chiasm is situated posteriorly (post-fixed), the upward tumour expansion will cause compression of one or both optic nerves leading to unilateral or bilateral optic neuropathy or, more rarely,

a junctional scotoma. If the chiasm resides mainly in front of the fossa (a less likely scenario), the optic tract(s) will be compressed leading to a homonymous field defect along with other features of anterior visual pathway compromise (afferent pupil defect, colour vision and visual acuity deficits). Notably, a cadaveric study has estimated that the prevalence of a post-fixed chiasm may be as high as 17% (18). It has also been suggested that most patients have asymmetrical visual field defects and pure bitemporal hemianopia is rare (12,16). Visual acuity, contrast sensitivity and colour vision can also be impaired due to optic nerve compression and atrophy from prolonged compression (1,2,16). Acuity is affected less commonly than visual fields (1) presumably because reduction in visual acuity occurs after prolonged optic nerve compression.

Oculomotor cranial nerve palsies can occur due to compression of nerves III (oculomotor), IV (trochlear) and VI (abducens) due to cavernous sinus invasion by the adenoma or after pituitary apoplexy (2,14,19). This manifests as diplopia, strabismus, ophthalmoplegia and possible ptosis (2,14). Diplopia may also occur with bitemporal hemianopia in the absence of cranial nerve involvement due to 'hemifield slide'. This is attributed to loss of the normal overlap of the temporal field of one eye with the nasal field of the other. This overlap allows fusion of the image and stabilizes the vertical ocular alignment. When this fusion is lost, there is inability to maintain stable alignment of the two retained nasal fields and the images "slide" against each other (2).

Features of chiasmal compression on MRI, while suggestive of visual dysfunction, are not always predictive. Although chiasmal displacement ranging from 4-21 mm has been observed in the majority of patients with visual deterioration, no degree of radiological compression predicts reliably the degree of visual field loss (12). Furthermore, patients may have imaging findings of chiasmal compression, yet normal visual fields (20). These findings could, however, be influenced by differences in measurement techniques between radiologists (21), in keeping with "real-world" practice and underscoring the need for formal neuro-ophthalmologic assessment to guide clinical decision-making. Notably, two recent studies have shown promise in correlating MRI findings with neuro-ophthalmic assessment. Glebauskiene *et al*.(22) demonstrated correlation between retinal nerve fibre layer (RNFL) thickness measured by OCT

and optic chiasm height on coronal T2W/TSE (Turbo Spin Echo) MRI sequence measured by a standardized technique. Furthermore, Rutland *et al*. (23) used 7-T diffusion-weighted MRI to assess microstructural characteristics of the optic pathway in patients and healthy controls, and showed correlation between diffusion indices of the visual pathway and findings of neuro-ophthalmological assessment opening perspectives on potential predictive value of the diffusion indices for visual recovery.

Ophthalmic Evaluation

Full ophthalmic examination is a vital component in the assessment and management of patients with pituitary adenomas (13,24) and consists of assessment of optic nerve structure and function, as well as ocular motility (Table 1).

Evaluation of the optic nerve function comprises of assessment of distance visual acuity (Snellen or LogMAR [Logarithm of the Minimum Angle of Resolution]), visual fields (static or kinetic perimetry), colour vision, the pupils (specifically for relative afferent pupillary defect) and fundoscopy to visualise the optic nerves (2). The assessment of optic nerve structure is performed by OCT. Patients may also have other unrelated visual pathology and the ophthalmic exam should include evaluation for other conditions (refractive status, intra-ocular pressure and slit-lamp examination of the anterior and posterior segment) aiming to define the extent to which visual dysfunction is attributable to adenoma (2,11).

Both static threshold perimetry (i.e. Humphrey using either the 24-2 or 30-2 strategy) and kinetic perimetry (such as Goldmann) are commonly used in patients with pituitary tumours. It should be pointed out though that standardized perimetry is susceptible to variability influenced by patient attention and reporting during testing, as well as by physician interpretation (25). Comparison of Humphrey and Goldmann perimetry found no significant difference in the results within the central 30 degrees of the visual field in patients with adenomas (26). Rowe *et al.*, however, reported that kinetic peripheral visual field assessment is superior to static central visual field assessment for detection of peripheral visual field loss which is typically the area first compromised by chiasmal compression in pituitary lesions (25).

OCT is a non-invasive laser-based imaging technique which produces cross-sectional images of the retina and allows direct measurement of the RNFL around the optic disc. It provides a quantitative estimate of the number of ganglion cell axons in the optic nerve and an objective measurement of optic atrophy and its progression (27,28). OCT may also offer information for possible recovery of visual function following pituitary surgery, as a thicker baseline RNFL in patients with visual field defects, prior to tumour removal, suggests more intact retinal ganglion cells (29). Danesh-Meyer *et al.* described improved visual outcomes in patients with pre-operative RNFL thickness above 80 μm (29). Nonetheless, compared with functional methods of assessment (visual fields), OCT RNFL thickness is considered less sensitive for detecting abnormalities in the visual pathway (28).

All patients with adenoma compressing or abutting the visual pathway should undergo baseline ophthalmic assessment (13). A complete neuro-ophthalmic examination including all components listed in Table 1, should be performed at baseline. Follow-up examinations should include optic nerve and ocular motility assessment; OCT may also be of value depending on the clinical scenario. Even if visual function is normal at baseline, there is risk of future visual dysfunction and regular examinations are essential (8,20,30). Surgical intervention is indicated if visual function is impaired but in cases with compromised vision and deferred or contraindicated surgery, regular neuro-ophthalmic evaluation is required, given the possibility of further deterioration (8,20,30). Optimal frequency of visual examinations has not yet been established. Expert consensus suggests review every 1-2 years if chiasmal contact and normal vision, and every 3-4 months if visual dysfunction is present but surgery is deferred (2). The timing of post-operative ophthalmic assessment needs to be individualized, but in general, it should occur within 3 months of surgery with follow-up assessments every 4-6 months until stability is observed (2).

Visual outcomes after management of pituitary adenomas

A. Surgery

i) Visual improvement and factors affecting it

Reports on visual outcomes after transcranial surgery for pituitary adenomas are limited in the recent literature, as the transsphenoidal approach has now been widely adopted. Goel *et al.* (31) in a series of 30 giant adenomas (>5 cm), 29 of which were operated on transcranially, reported visual improvement in one third of them. These findings need to be interpreted in the context of giant tumours which are likely associated with worse visual morbidity at baseline, thereby, impacting post-operative results. Interestingly, Hanizasurana *et al.* (32), in a series of 45 patients with transsphenoidal (n=31) or transcranial surgery (n=14), found no significant difference in the rates of visual acuity or visual field improvement between the two techniques. Visual outcomes following transsphenoidal resection of adenomas are highly variable in the published literature. A meta-analysis on improvement of visual dysfunction after surgery from six studies (n=384) utilizing the microscopic and nine (n=607) the endoscopic transsphenoidal approach reported pooled estimates of the overall proportions 56% for the microscopic and 71% for the endoscopic approach; however, the type of visual improvement was not delineated (33). A more recent systematic review and meta-analysis of 35 case series using the endoscopic approach provided pooled prevalence of post-operative visual improvement of 80.8% for visual fields, 67.5% for visual acuity and 80.9% for non-specific visual defects. The rates of visual improvement across individual case series were highly variable with improvements in visual acuity ranging 27-95% and in visual fields 35-100% (1). Factors explaining these differences include heterogeneity in the components of visual evaluations, the reporting of outcomes and the timing and frequency of assessments. Some authors provide results for both visual acuity and visual fields, others only for visual fields or only for visual acuity, whereas, in some cases, non-specified visual outcomes are presented (1). Other reported parameters include Visual Impairment Score (VIS) [combining visual fields and visual acuity for both eyes, with Findlay *et al.* (34) being the first who proposed this combination in

the evaluation system when assessing visual recovery] (35), assessments of visual fields by gross examination (confrontation) only (36), or various scoring systems developed by individual authors (37). Moreover, some authors only present data on visual improvement, while others distinguish between improvement and recovery (1). The timing of post-operative visual assessment is specified infrequently and most studies clarifying this have relatively short follow-up (<6 months) underestimating long-term rates of visual improvement (1). Exceptions to this are two series with mean follow-up of 37 and 50 months, giving rates of vision improvement 80% and 74%, respectively (38,39).

Given the delays in the diagnosis of visual deterioration in elderly patients (11), post-operative visual outcomes in this group are of particular interest. Chinezu *et al.* (40), in a series of non-functioning adenoma patients undergoing endoscopic transsphenoidal surgery, found improvement of visual status in 80% of those aged >80 and 35% of those aged 65-75 years which was statistically significant. This finding may be partially explained by the baseline difference between the two groups with a higher degree of initial visual impairment present in the very elderly patients (93% *vs* 69%). In this series, visual deterioration was observed in only 1.5% of the total group and the authors suggested that visual deficits should not result in very elderly patients being denied surgery (40). Review of seven further studies on post-operative visual outcomes in patients aged from $\geq$ 65 to $\geq$ 80 years showed improvement in 34-92%, stability in 3-63% and deterioration in 0-8%, and comparison with various control groups (ranging in age from 18 to <80 years) demonstrated no difference in visual improvement rates (39-45).

Visual outcomes after transsphenoidal surgery of regrown/recurrent adenomas have been assessed in a systematic review and metanalysis by Esquenazi *et al.* (46) which reported a 73% cumulative rate for visual improvement. A series of 268 patients, comparing outcomes after primary and repeat endoscopic transsphenoidal surgery, showed higher rates of visual improvement in the primary surgery group; nonetheless, this group had higher rate of visual field impairment at baseline (47% *vs* 30%), and after adjusting for this factor, the difference did not remain significant (43).

The impact of surgical technique (endoscopic *vs* microscopic) has been addressed in a systematic review and meta-analysis which found no difference in the post-operative visual field improvement between the

two approaches (47). However, the small number of patients and limited follow-up in the endoscopic group may have resulted in underestimation of the visual improvement (47). Furthermore, retrospective data on this topic are inherently biased, as endoscopic surgery has become favoured in an era where fewer patients have visual dysfunction at presentation (15). In fact, visual outcomes for adenoma patients appear to have improved overall since the introduction of endoscopic surgery (15). This may not be attributable to the surgical technique alone, as it may also reflect improvements in diagnosis and timing of intervention.

Studies assessing the impact of the experience of the pituitary surgeon on visual outcomes have yielded discrepant results. Two retrospective single surgeon series of 79 and 80 patients did not demonstrate a difference in the rates of visual field improvement in the later cohorts (48,49). On the other hand, a larger series of 331 patients suggested improved visual outcomes after operating on >100 cases, although potential differences in baseline visual characteristics were not provided (35). That a clear advantage of surgeon experience has not been demonstrated may suggest that a higher volume of cases is required for these effects to be identified. Alternatively, this may illustrate the limitations of surgical experience alone in specifically achieving improvement of vision, as other parameters like endocrinological remission, gross total resection and length of hospital stay have all improved with increased surgeon experience, even when visual outcomes were unchanged (48,49).

ii) Timing, mechanisms and predictors of visual improvement after surgery

Visual recovery after transsphenoidal surgery occurs in various phases. Initial improvement may be rapid within minutes to a few days (7,50,51) but additional significant changes may continue over a longer time frame (months) (7,29,51,52). The majority of studies are retrospective chart reviews where arbitrary time points were chosen for analysis. Anik *et al.* (51) assessed visual recovery (visual fields and acuity) following transsphenoidal surgery in 200 patients. The percentage with full recovery of vision increased by 7% between 48 hours and 6 months, by 17% between 6 months and one year and by 2% beyond one year. Kerrison *et al.* (7) in a series of 62 patients showed that improvement in visual fields and acuity

could be detected between surgery and one week, from one to 4 months and from 6 months to 3 years; the most significant degree of visual recovery occurred up to 4 months. Danesh-Myer *et al.* (29) in a series of 107 patients showed that the greatest visual fields improvements in patients with thin RNFL pre-operatively were identified in assessments taking place between 6-10 weeks and 9-15 months post-surgery; in those with normal RNFL pre-operatively, the greatest improvement occurred within the first 6-10 weeks. Kerrison *et al.* (7) has proposed that the early recovery phase is due to restoration of signal conduction along ganglion cell axons following decompression, whereas the later improvement is due to remyelination of axons. Interestingly, Danesh-Myer *et al.* (29), showed that the greatest increases to RNFL thickness were observed by the 9 to 15 month follow-up in patients with the thinnest RNFL correlating with the most marked improvements to visual fields. It is evident that ongoing improvement to vision is possible beyond one year but the timing of the maximum effect, the longest interval during which further visual correction continues and the most appropriate time points for review of visual function and retinal structure are yet to be determined.

Predicting which patients are likely to have favourable visual outcomes is of major importance, as this could aid decision-making about the benefits of surgical intervention. Multiple reports have demonstrated that age and tumour size/volume are not significant predictors in multivariate analyses (11,52-54). In a series of 19 patients, Jacob *et al.* (55) demonstrated that, independent of age and symptom duration, both mean and inferior quadrant greater RNFL thickness significantly increased the probability of complete post-operative visual recovery; this was especially robust for the inferior quadrant measurement. Yoneoka *et al.* (56) in a study of 35 patients showed that preserved RNFL thickness pre-operatively independently predicted full or nearly full recovery of vision post-operatively. Lee *et al.* (57) in a series of 57 patients also demonstrated that pre-operative inferior RNFL thinning was significantly predictive of impaired visual recovery. Furthermore, pre-operative RNFL thickness has been shown to predict both early (6-10 weeks) and late (9-15 months) visual results (29). On the other hand, evidence on the role of pre-operative visual function has been conflicting, with some (52,57) but not others (53,55) showing significant prognostic value in multivariate analyses. These discrepancies may be influenced by differences in the

methodology of visual assessment or by differences in the criteria for exclusion of patients with potentially confounding visual pathology. Analysis of symptom duration has also yielded discrepant results, however, the methods of assessing this parameter were highly variable; some authors reporting duration of systemic symptoms including both visual and endocrine (52,53), others assessing visual symptoms only (11) and others not specifying the symptoms assessed (54,57). A further limitation for this factor is the lack of objectivity, as it relies on self-reported symptoms which may be inaccurate, particularly in the presence of other ocular morbidity or when visual deficits are very mild. Given the uncertainty of this parameter in predicting recovery, patients with visual deficits at presentation should be offered prompt intervention regardless of symptom duration. Exception to this point represent prolactinomas in which, as discussed later, medical treatment can gradually improve visual deficits.

iii) Deterioration of vision after surgery

Visual deterioration occurs rarely following transsphenoidal resection of adenoma. A systematic review and meta-analysis estimated the prevalence of visual deterioration at 2.3% (1). The optic apparatus can be damaged by surgical manipulation secondary to direct trauma, vascular compromise, haemorrhage or swelling (32,58). Direct trauma may occur from curette or suction during resection of suprasellar tumours, while removal of adherent tumour from the optic apparatus can cause devascularisation and subsequent infarction (32). Patients undergoing transsphenoidal surgery after a previous transcranial approach may be particularly vulnerable; adhesions may develop between residual sellar contents and the optic apparatus, predisposing to traction injury, contusion or vascular insufficiency (58). The optic nerve may be also compressed following surgery due to haematoma formation or by overpacking the sella with fat (32,58).

Cranial nerves within the cavernous sinus are also vulnerable to direct trauma or post-operative haemorrhage (59).

Late visual deterioration may occur months or years post-operatively due to traction of the optic chiasm into an empty sella (58).

iv) Pituitary tumour apoplexy

Pituitary tumour apoplexy is a rare clinical syndrome precipitated by acute haemorrhage and/or infarction in a pituitary tumour. Clinical manifestations include sudden-onset severe headache, nausea, vomiting and visual impairment (60,61). Visual impairment occurs due to adenoma expansion causing rapid compression of optic nerves/chiasm or extension into the cavernous sinus(es) (60) and manifests as visual field defects (36-71%), impaired visual acuity (39-56%), blindness (up to 30%) and oculomotor nerve palsies (40-78%) (60). Cranial nerve III is the most frequently affected due to close anatomical relationship with the sella, although multiple and bilateral palsies may also occur (60,61).

Although impairment of visual fields or visual acuity has necessitated urgent decompressive surgery in most series (60), the optimal management strategy is still controversial. Potential approaches include immediate (within days) or delayed (within weeks) surgery or conservative management (60-66). The safety of delayed surgical intervention remains uncertain. Randeva *et al.* (66) in a report of 35 patients demonstrated that immediate surgery (within 8 days) resulted in greater improvement in visual acuity compared with delayed operation (within 9-35 days) but subsequent studies have not corroborated these findings. Singh *et al.* (62) in a series of 87 patients [61 with immediate surgery (median 5 days), 8 delayed surgery and 18 managed conservatively], demonstrated that at mean follow-up of 44 months, all had resolution or improvement of pre-operative visual deficits, with the exception of two cases in the early surgery group. Bujawansa *et al.* (63) in a series of 55 patients [23 had immediate surgery (within 7 days), 10 delayed surgery and 22 managed conservatively], showed rates of improvement to visual field defects and cranial nerve palsies 60-80% and 92-100% respectively, with no significant differences between treatment strategies. Giritharan *et al.* (64) reported on 31 patients [11 had emergency surgery (within 7 days), 9 delayed surgery and 11 conservative management]; all patients, except one in the conservatively managed group, had improvement or resolution of visual defects, while complete resolution was seen in 70%, 75% and 71% of the immediate surgery, delayed surgery and conservatively managed patients, respectively. Selection bias must be considered when interpreting these data, as cases

with milder symptoms at presentation are more often managed with delayed surgery or conservatively (60-63,65). Interestingly, a small case series described by Muthukumar *et al.* (67) illustrated that recovery is more limited with delayed surgery for cases presenting with severe visual compromise. In this report of 4 patients with unilateral or bilateral blindness, only one underwent immediate surgery and the other 3 initially declined or were medically unfit for surgical intervention. The patient with immediate surgery (blind in both eyes) had improvement in visual acuity to 6/9 and 6/12. However, the remaining three (all with unilateral blindness) who underwent surgery at 2 weeks, 3 weeks and 2 months after presentation demonstrated poorer visual recovery with improvements to 6/60, 6/60, and 1/60 in their initially blind eyes (67). Current practice in the management of apoplexy is individualised and overall resolution or improvement of pre-operative visual deficits is observed in the majority of patients, ranging from 57-95% for visual fields and 86-93% for visual acuity (60,62-64,68). Prospective, randomised-controlled studies are needed to provide evidence-based guidance on this controversial issue.

Prognosis for oculomotor nerve palsies following apoplexy is particularly favourable and may respond well even to conservative management (60,62,63). In the Singh *et al.* series (62), 54% of patients had cranial nerve involvement at presentation which resolved or substantially improved in 100% at last follow-up; in this report, the patients were managed conservatively or by surgery (acute or delayed). Bujawansa *et al.* (63) reported 47% prevalence of cranial nerve palsies at presentation and this resolved completely or near completely in 100%, 92% and 100% in the conservatively managed, the immediate surgery or delayed surgery groups, respectively. In a series of 41 surgically managed patients by Kim *et al.* (68), 68% had cranial nerve palsies at presentation and in 96% complete resolution was observed.

B. Radiotherapy

Radiotherapy is an established second line management option for residual or recurrent adenomas following surgery (69,70). Optic nerves, optic chiasm and cranial nerves within the cavernous sinuses are all susceptible to radiation-induced damage (69,71).

Radiation induced optic neuropathy (RION) typically presents with sudden, painless, monocular vision loss preceded in some instances by weeks of transient monocular or binocular vision loss; further deterioration progresses over weeks and second eye involvement may also occur. Loss of visual acuity is variable; blindness occurs in up to 45%, and up to 85% of the cases have deterioration to acuities of 6/60 or worse. Visual field defects of any pattern related to optic nerve or chiasmal damage can occur (72). Acute enhancement of optic nerves and/or chiasm following gadolinium on T1-weighted MRI is suggestive of RION, although only if seen in the appropriate clinical context, as these findings are non-specific and indistinguishable from other causes of optic neuropathy (72). Tumour recurrence as an alternative cause of visual deterioration needs also to be excluded (72,73). Cavernous sinus cranial nerve dysfunction may also be observed but these nerves are less radiation sensitive compared with the optic nerve (71).

Risk factors relate to the individual patient, tumour characteristics, treatment modality and radiation dose (72). Younger patients are at higher risk (74), however, this may be due to their longer survival, as increasing age increases the risk of RION (72). Damage to visual pathway by previous radiation or from compression of optic nerves/chiasm also enhances susceptibility to RION (72,74,75). The risk of visual toxicity (RION and dysfunction of cavernous sinus cranial nerves) is influenced by both total and per fraction radiation dose. Interestingly, the relationship between time-dose fractionation and radiation-induced loss of vision was reported as early as 1977 by Aristizabal *et al.* (76). Reported prevalence differs based on the modality of radiotherapy. With conventional radiotherapy, rates of visual toxicity range 0-6% after cumulative doses of <54 Gy, however, the follow-up across different series varies from 7 to 108 months (69). For stereotactic radiosurgery (SRS), rates of late visual toxicity range 0-15% across studies with follow-up of 23-204 months (71). In a study of 512 patients offered SRS (mean dose 16 Gy, mean follow-up 48 months), 9.3% prevalence of visual toxicity was reported (74). With SRS, the maximum tolerated point dose to the chiasm is 8-10 Gy; rates of optic neuropathy of <2% have been reported in this setting (71). With fractionated stereotactic radiotherapy (FSRT), rates of optic neuropathy range 0-7% in series with mean follow-up 30-80 months and are <2% when total doses <50 Gy are delivered in fractions

of <1.8 Gy (69). Data on visual toxicity following proton beam therapy in pituitary adenomas is limited. Ronson *et al.* (77) reported visual outcomes in 43 patients after proton therapy and 9% had objective evidence of visual deterioration.

Studies focusing on rates of post-radiotherapy cavernous sinus cranial nerve dysfunction are very limited. In a series of 217 patients, Cifarelli *et al.* (78) found 3% rate of cranial nerve III, IV and VI dysfunction following gamma knife surgery (median peripheral dose 23 Gy, median follow-up 30 months); all but one resolved within the study period. Sheehan *et al.* (74) in a series of 479 patients following gamma knife surgery (median dose 16 Gy to tumour margin, median follow-up 36 months) reported overall prevalence of cavernous sinus cranial nerve dysfunction 3%.

It should be noted that lack of adequate follow-up in most studies to exclude late development of visual toxicity (which can occur at 8 years or longer) may have led to underestimation of the reported post-radiotherapy visual toxicity (69).

Improvement in visual function after radiotherapy has been previously described (79-81); the majority of patients had surgery before irradiation and, therefore, these findings may simply reflect late post-surgical improvement.

C. **Medical treatment – Prolactinomas**

The value of DA treatment in patients with prolactinoma is well established (82, 83). Macroprolactinomas present with visual compromise in 40%-85% of cases with higher rates in large or giant (>4 cm) adenomas (84-86). The 2011 Endocrine Society clinical practice guideline on diagnosis and treatment of hyperprolactinemia reported cumulative rate of visual field defect resolution with DA therapy of 67% (range 33-100%) (83). This benefit can be seen even in giant prolactinomas (92). Visual improvement has been confirmed as early as 24-72 hours after DA initiation (87) and the timing of maximum visual field recovery ranges between 0.5 and 6 months (94). Failure to improve vision may be due to lack of tumour shrinkage following treatment or due to long-standing optic nerve compression/ischemia (86,88).

The optimal treatment regimen for impacting vision has not been established. A systematic review and meta-analysis demonstrated no difference between cabergoline and bromocriptine in improving visual field defects (82). A prospective study of 150 prolactinoma patients (57 macroprolactinomas) evaluated the efficacy of a high dose regimen of cabergoline (starting dose 0.25-0.5mg twice weekly, up-titrated every 2-4 weeks until amelioration of hyperprolactinemia) (89). All patients with documented visual defects at presentation normalized within 1-3 months. Although randomised studies confirming the superiority of a high DA dose as initial treatment regime in improving vision are lacking, this option could be considered in patients with visual deterioration (provided the DA is well tolerated).

Secondary deterioration of visual fields following DA treatment has been described illustrating the significance of regular ophthalmologic evaluation. In a study of 28 patients with macroprolactinomas, Raverot *et a*l. (84) reported further visual deterioration associated with chiasmal herniation on MRI in three patients treated with cabergoline; one case was detected around two months after treatment initiation, whereas the others were identified after over two years of treatment. Visual improvement was seen in all three cases after cabergoline withdrawal.

D. Conservative Management - Non-functioning pituitary adenomas

Patients with non-functioning pituitary macroadenomas may be managed conservatively in cases without associated visual involvement, presence of co-morbidities preventing surgery or patient's preference. Their visual outcomes have been reviewed in a few series and demonstrate deterioration or improvement coinciding with tumour size changes.

Ryu *et al.* (20) in a study of 6 patients with adenomas contacting optic chiasm at presentation reported worsening visual function in two over mean period of 41 months. A study by Karavitaki *et al.* (8) including 24 conservatively managed non-functioning macroadenomas, illustrated that over mean follow-up of 43 months, 50% showed enlargement with 67% (of this group) having new or worsened visual field defects. Most of these patients went on to have transsphenoidal surgery but final visual outcomes were

not described (8). In a series of 28 macroadenomas by Dekkers *et al.* (30) with mean follow-up 85 months, 50% of the patients with adenoma growth had increased visual field defects likely caused by tumour mass; when surgery was offered, visual improvement was reported but not its extent (30). In a systematic review and meta-analysis of observational studies of pituitary incidentalomas, the risk of visual field deterioration was higher in tumour growth of >3.5 mm (64.3%/100 patient-years) (90).

Of particular interest is the dilemma of timing of surgery in patients presenting without visual compromise. Some authors advocate earlier intervention to prevent visual complications before they occur (91), while others argue it is safe to monitor vision and intervene once deterioration develops (20). Data to support either approach are limited. A review of 76 patients with non-functioning adenomas demonstrated better post-operative visual outcomes for those with normal vision at baseline compared with patients with visual dysfunction pre-operatively (91). Long-term visual prognosis of patients with adenoma presenting with normal visual function and managed conservatively, with surgical intervention in the event of visual dysfunction, is unknown. Extrapolation from both Jacob (55) and Danesh-Meyer (29) would suggest that if RNFL is of a normal thickness, it would be reasonable to await evidence of chiasmopathy prior to undertaking surgery.

Series of conservatively managed macroadenomas have also demonstrated decrease in tumour size in 12% of cases during variable follow-up periods (92,93), possibly attributed to cystic component reduction or tumour infarction; however, there are few reports of spontaneous visual improvement in this setting. Thus, resolution of a unilateral superotemporal defect was observed in one patient in the series by Ryu *et al.* (20), while Dekkers *et al.* (30) reported visual improvement in two patients, both of which had previous apoplexy.

Conclusions and Future Perspectives

Visual manifestations are an important element in the morbidity encountered in patients with pituitary adenoma and can be present at all stages of their journey. Visual dysfunction consists of many parameters

(even in the absence of reported symptomatology) as result of tumour growth in proximity to structures critical for vision and as adverse consequence of therapeutic interventions. It has negative impact on daily activities and overall on quality of life and should be considered a vital indicator in the metrics of quality of service/care in pituitary disease. Objective assessment of the visual function and the structural integrity of the anterior visual pathway is an essential component of modern management of pituitary pathology.

Surgical resection of adenoma improves visual dysfunction in the majority of cases, whereas deterioration, as surgical complication, occurs at very low rate. Ongoing improvement to vision is possible beyond a year post-surgery but the exact timing of maximum effect requires further elucidation. Amongst a number of factors assessed, RNFL measurement may be a reliable and objective clinical parameter for predicting favourable visual outcomes, although its predictive value when pathological, needs to be confirmed. In cases with compromised vision and deferred or contraindicated surgery, regular ophthalmic evaluation should be performed. Optimal approach for patients with apoplexy and visual dysfunction has not been determined; nonetheless, early surgical decompression remains the usual current practice until evidence-based guidance becomes available. The risk of radiation-induced visual toxicity is mainly influenced by total and per fraction dose of radiation and treatment modality. Careful selection of cases and of radiotherapy technique/planning are of major importance. Long-term follow-up with reporting of visual outcomes in series of patients treated with SRS, FSRT and proton therapy will be more informative in the future.

Prospective well-designed studies minimising the effects of bias and using tools and scoring systems reliably reflecting visual status will provide robust evidence on outcomes after various treatments, effective patient stratification and valid prognostication. These will undoubtedly improve the care of patients with pituitary disease and are eagerly awaited.

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Figure 1. Pattern of visual field defects based on anatomic localisation of the pituitary adenoma.

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774 **Table 1.** Ophthalmic assessment of the patient with pituitary adenoma.

Optic nerve assessment	Visual acuity Pupil assessment (relative afferent pupillary defect) Visual fields Colour vision Fundoscopy
Ocular motility assessment	Double vision Smooth pursuit Saccades
Slit lamp examination	Anterior and posterior segment Intraocular pressure
Optical coherence tomography (OCT)	Retinal nerve fibre layer (RNFL) and ganglion cell complex (GCC)

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