Current perspectives on recurrent pituitary adenoma: the role and timing of surgery <mark>versus adjuvant treatment</mark>

Short Title: Recurrent pituitary adenoma

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Summary
The clinical course of pituitary adenoma can be highly variable. Aggressive pituitary tumours may require multimodal therapy with multiple operations. Even standard pituitary adenomas exhibit relatively high long term recurrence rates and delayed intervention is often required. The indications for revision surgery in the endoscopic era are expanding for both functioning and non-functioning tumours, including access to the cavernous sinus and intracranial compartments. Although revision surgery can be challenging, it has been demonstrated to be both safe and effective.   The question of the use of early radiotherapy in pituitary adenoma remains controversial. Our increasing understanding of pituitary tumour biology facilitates individualised treatment and surveillance protocols, with early intervention in high risk adenoma subtypes. In this review we discuss the treatment options for recurring pituitary tumours and focus on the role of revision surgery.
Key words: Pituitary adenoma, surgery, radiotherapy

Introduction

Pituitary adenomas are benign, slow growing neoplasms in the majority of cases, with an incidence of clinically relevant tumours of 4-7 per 100,000 annually [1,2]. Surgery is usually the first line treatment for larger non-functioning adenomas, **where there is compression of the optic apparatus** and the majority of functioning tumours, with the exception of prolactinoma. However, even in the setting of complete surgical resection, there is a high long term recurrence rate of approximately 7 - 12% at 10 years[3,4]. Often a complete resection at first surgery may not be achievable due to anatomical limitations and in these cases progression or recurrence is often inevitable, reported in 53% of those with extrasellar residual tissue at 5 years and over 80% at 10 years[4].

Additionally, there is a subset of histologically aggressive adenomas which display early and multiple recurrences despite multimodal therapy. The prevalence of aggressive pituitary adenoma is not known and furthermore, the exact definition of these tumours in the literature has been variable.

There is currently little international consensus on the management of either recurrent pituitary adenoma or aggressive pituitary adenoma, particularly on the timing of revision surgery versus early or late radiotherapy and the use of chemotherapy, such as temozolomide. Data on the efficacy and safety of revision endoscopic pituitary surgery is emerging but questions remain on the potential impact of radiotherapy in the modern era on long term outcomes, both endocrinological and surgical.

This review aims to highlight the advantages and limitations of revision endoscopic pituitary surgery, identify 'at risk' patients who may require multiple interventions or multimodal therapy and review current guidelines on management, in order to provide an evidence base to guide clinical practice in the multidisciplinary setting.

Identifying patients at risk of recurrence

The overall risk of recurrence after pituitary surgery is reported between 30-50% at 5 to 10 years [5–8]. Complete resection of tumour at first surgery is reported in 69% of patients in endoscopic series and 64.5% in microscopic series**, based on post-operative MR imaging** [9]. Even in the setting of radiologically confirmed complete resection of a pituitary adenoma, there is a recognised risk of long term recurrence. Reddy et al reported recurrence in 6.9% of patients with a complete resection at a mean of 9.1 years. Importantly in this study, 20% of re-growths occurred after 10 years of follow-up. It is clear that in these cases long term and likely lifelong observation alone is the management strategy of choice, with the potential for repeat surgery should recurrence occur. However there are high relapse rates associated with an incomplete resection; these are dependent on the volume of residual disease, with 15% of intrasellar remnant tumours growing within 5 years compared to 51% of extrasellar residual [8]. This has led some centres to adopt routine post-operative radiotherapy where there is residual tumour[8].

Anatomical limitations to complete resection

The ability to achieve a complete resection of tumour is dependent upon several factors, including tumour consistency and invasiveness. Many radiological features are markers of poor surgical outcome, such as multi-lobulated giant adenoma, bony invasion and cavernous sinus involvement. The modified Knosp grade is a useful tool to predict tumour resection rates for both functioning and non-functioning adenoma (Table1, Figure 1)[10]. It depicts the relationship of the adenoma to the carotid artery and was first described by Knosp et al in 1993 [11]. This was updated in 2015 to include endoscopic evaluation of the extent of true cavernous sinus invasion and correlated to resection rates, Micko et al demonstrated that a radiological grade 3A adenoma extending into the superior compartment of the cavernous sinus was associated with true breach of the cavernous sinus wall in only 26.5% and a complete resection was achieved in 85% [10]. In contrast, grade 3B adenomas involve the inferior compartment of the cavernous sinus and are truly invasive with breach of the cavernous sinus wall in 70%, and a significantly lower complete resection rate of 64%. However, grade 4 adenomas completely encase the internal carotid artery and cavernous sinus structures and complete resection of these tumours was 0% in this series (Figure 1). Additionally, radiologically higher grade adenomas tended to display a higher proliferation index (MIB-1 or Ki-67) on histology than lower grade tumours, indicating that radiological extension is a function of potentially aggressive tumour biology.

Aggressive pituitary adenoma

As demonstrated, the majority of pituitary adenomas display benign characteristics with a slow relapse rate over many years and anatomical limitations to surgical resection govern the natural history.   However, there are subtypes of adenoma that demonstrate rapid recurrence and resistance to treatment. The World Health Organisation classification of pituitary tumours was updated in 2017, with adenoma classification now based on cell lineage from immunohistochemistry and pituitary transcription factors[12]. A major change has been to abandon the term 'atypical adenoma'. Previously an atypical adenoma was defined as an adenoma with a Ki-67 **(or MIB-1)** index greater than 3%, with features of invasive growth and denoted a tumour with a propensity for early recurrence. Atypical adenomas were reported to account for 3-15% of cases [13,14]. However, the term has been used variably in the literature with the cut-off values for Ki-67 varying among different centres, hence the reported behaviour of so-called atypical adenoma is difficult to interpret. Additionally, using a Ki-67 threshold of 3% meant that evidence for aggressive behaviour was conflicting, with little difference seen in recurrence rates [15]. Many centres consider a Ki-67 of 7-10% more clinically relevant for prediction of aggressive behaviour [16]. In the current classification, whilst Ki-67 remains an important marker of aggressive behaviour, no threshold value is defined and additional evidence of tumour invasion (cavernous sinus or clival invasion) should also be considered as a marker of clinically aggressive behaviour **(Table 2)**.

Importantly, several adenoma variants are noted to have more aggressive clinical behaviour, including the sparsely granulated somatotroph adenoma, silent corticotroph adenoma and the new entity of the plurihormonal PIT-1 positive adenoma, previously silent subtype 3 adenoma **(Table 3)**.

The role of revision surgery

The role of repeat surgery in recurrent adenoma is not well studied. The widespread adoption of the endoscopic approach has recently increased focus on the potential to maximise tumour resection, due to the improved field of view, better illumination, improvement of identification of critical neurovascular structures and normal pituitary gland, plus the ability to access the cavernous sinus using angled endoscopes. A factor associated with a high rate of residual adenoma after microscopic approaches is the limited sphenoid and sellar bony exposure, with poor access to the sellar and suprasellar region [17] . With an endoscopic approach there is wide resection of the sellar floor, exposure of the cavernous sinus walls and with an expanded approach, excellent visualisation of the suprasellar cistern and optic apparatus. However, revision pituitary surgery is challenging. The anatomy can be distorted by scar tissue, particularly after prior endoscopic approaches. Anatomical planes and landmarks tend to be better preserved after a prior microscopic approach and some authors have demonstrated better outcomes in revision surgery after a prior microscopic approach [18,19].

Prior radiotherapy can de-vascularise local tissue leading to limited options for skull base reconstruction to prevent post-operative CSF leak[2021]. It may also contribute to optic nerve tethering, which is frequently seen after prior resection of large non-functioning adenomas, with a higher risk of post-operative visual decline after revision surgery in our experience. Additionally, tumour residuum is often in unfavourable anatomical locations, but in experienced pituitary centres many such adenomas can be resected surgically using an expanded endoscopic approach prior to considering other treatment options. This highlights the need for tertiary pituitary centres of excellence with dedicated pituitary surgeons [22]. The indications for revision surgery are outlined in Table 4.

Overall the rates of gross total resection (GTR) after revision surgery are lower than primary surgery regardless of the approach, with reported rates of 46.6%-53.5% in revision surgery compared to 69-71% in primary surgery [23]. The current experience on outcomes for revision surgery using the endoscopic approach is summarized in Table 5. Do et al reported 61 patients who underwent revision endoscopic surgery [19]. GTR was achieved in 51.7% of cases. The cavernous sinus was involved in 38%. In those with Knosp grade 0-2 the GTR rate was 70.3% and for those Knosp grade 3-4, the GTR rate was 21.7%. CSF leak occurred in 4.9% and 2 patients (3.2%) had a post-operative haematoma with visual deterioration. However, pre-operative visual defects improved or stabilized in 95%. New anterior hypopituitarism occurred in 14.7% and Diabetes Insipidus (DI) in 4.9%. When compared to primary endoscopic surgery, a meta-analysis of post operative complications in revision endoscopic transsphenoidal surgery demonstrated a CSF leak rate of 7%, vascular complications in 1.5%, DI in 2.31% and anterior hypopituitarism in 8.5% [9]. In a comprehensive analysis of morbidity in repeat transsphenoidal surgery, Jahangiri et al reported outcomes in 108 revision procedures, compared to 907 primary procedures [21]. There was no significant difference in length of stay (2.5 days in primary procedures vs 2.3 days), new onset hypopituitarism (19% vs 7%) or post-operative hyponatremia. However, DI occurred in 35% of revision procedures compared to 13% of primary procedures and CSF leak occurred in 9% of revision cases versus 0.3% of primary cases [21]. Although it is felt that prior radiotherapy may contribute to increased morbidity, there was no difference in complications rates with prior radiotherapy in this series [21].

Most reports in the literature on repeat transsphenoidal surgery focus on non-functioning adenoma resection rates and complications. There are few data on biochemical remission rates for functioning adenomas after revision surgery. Do et al reported biochemical remission in 75% of 12 patients (7 GH secreting, 3 ACTH-secreting, 1 TSH-secreting and 1 prolactin-secreting), but did not use strict criteria of remission [19]. Moreover, Almeida et al reported biochemical remission in revision surgery for growth-hormone secreting adenoma in 63.6% using strict criteria of remission (80% in microadenomas and 50% for macroadenomas), in 11 reoperations [24]. These results compare favourably to remission rates in first time surgery. Almeida et al reported biochemical remission in acromegaly in 71.4% in first time surgery [24]; however, meta-analysis of the published literature for functioning adenoma remission rates show an overall biochemical remission rate of 66% [25]. Similarly, for Cushing's disease, Patil et al reported outcomes in 36 patients with Cushing's disease undergoing repeat surgery, with 61% achieving remission [26].

Improving pre-operative localisation of residual tumour

The accurate identification of the functioning tumour target in recurrent disease is paramount to successful surgery. Standard imaging can be misleading in recurrent disease due to scar tissue and packing material used in prior operations. Therefore, functional imaging such as positron emission tomography (PET) is an attractive modality to accurately localise functioning tissue. By combining ^{11}C-methionine PET-CT with co-registered MRI, Koulouri et al found tracer uptake in 25 of 26 patients with persistent acromegaly [27]. 14 patients subsequently underwent repeat surgery, with confirmed GH secreting adenoma found at the corresponding site in 12 cases. Similar results have been demonstrated in ACTH-secreting adenoma [28]. It is likely that PET-MRI will form the basis of decision-making in recurrent functioning adenoma in the future, reducing the need for blind fractionated radiotherapy to the whole sellar and parasellar region. However, routine access to ^{11}C-Methionine PET imaging remains limited, but is rapidly increasing.

Although the morbidity of repeat surgery is slightly higher than primary surgery, there is still substantial benefit in a significant proportion of patients with both functioning and non-functioning adenoma. It is therefore our philosophy in the event of either tumour or biochemical recurrence to offer repeat surgery as the first option, unless the patient is unfit for surgery or there are anatomical reasons limiting the likelihood of success.

What to do with the cavernous sinus?

The cavernous sinus can be explored from a medial approach, viewing and entering the medial cavernous sinus wall endoscopically from within the sella (Figure 2). Adenomas of Knosp grade 2-3 can be completely resected in a significant proportion of cases [10]. The question of surgery for adenoma within the lateral compartment of the cavernous sinus is controversial. As discussed, meaningful resection rates for Knosp grade 4 adenoma are poor [10].   It is possible to expose the lateral compartment, lateral to the carotid artery, from within the sphenoid sinus using an endoscopic approach. However the lateral compartment contains the 6th cranial nerve free within the cavity and the 3rd, 4th and first division of the trigeminal nerve in the lateral wall. Therefore surgery within this compartment carries significant risk of cranial nerve injury in addition to carotid injury. The Pittsburgh group, who have the largest experience with expanded endoscopic surgery, have recently published their experience with cavernous sinus surgery for pituitary adenoma [29]. In this series the rate of gross total and near total resection of adenoma from the lateral compartment

of the cavernous sinus was only 21%, with a complication rate of 6%, including 6th nerve palsy, post-operative haematoma and a carotid injury. Other centres report rates of 0% GTR with lateral cavernous sinus invasion [10,30] and 0% biochemical remission rates [30]. With such low rates of meaningful resection of tumour and the potential for long term cranial neuropathy, many centres consider alternative treatment options for residual disease in the lateral cavernous sinus, such as radiosurgery as first line.

The effect of radiotherapy

Radiotherapy is commonly used as second line treatment in functioning and non-functioning adenomas, for both tumour control and to achieve biochemical remission. All types of radiotherapy aim to deliver an effective treatment dose to gross tumour volume (residual or recurrent tumour) whilst limiting dose to surrounding normal tissues/structures.

Radiotherapy techniques

The radiation dose is usually delivered over 5 to 6 weeks in conventional radiotherapy (CRT) or over fewer fractions, (3 to 5) in hypo fractionated radiotherapy (HFRT) or single fraction, in stereotactic radiosurgery (SRS). HFRT and SRS can be delivered using a variety of platforms (Gamma Knife, Cyber knife or Linear Accelerator). CRT usually delivers a total dose of 45-50.4Gy in 1.8 Gy per fraction and SRS delivers treatment dose (13-16Gy for non-functioning adenoma or 21-25Gy in the case of secreting adenomas) in a single fraction.

The linear accelerator based treatment planning involves acquisition of a dedicated CT scan acquired with thermoplastic shell head immobilization. The diagnostic MRI or planning MRI scan is fused with the CT scan to localise gross tumour volume. Modern radiation delivery techniques such as intensity modulated radiotherapy conforms treatment dose to target volumes better than CRT. HFRT and SRS uses planning techniques to deliver high dose to target volume with sharp dose fall to surrounding normal structures, thereby reduce the volume of brain tissue irradiated to high radiation doses compared to CRT[31].

High energy proton beam therapy (PBT) due to its physical properties is able to spare more normal tissue compared to conventional x rays. Pituitary adenoma was one of first indications for PBT. Most reported series used passive scattering technique and a recent systematic review of PBT for intra cranial benign tumours in adults found it to be safe and effective in treating pituitary adenomas and could be used as an alternative to HFRT or SRS[32]. PBT is becoming more widely available and carries the theoretical advantage of better dose distribution and normal tissue sparing, as yet there are limited data in pituitary adenoma and no evidence to suggest an advantage over conventional x rays [31]. PBT is currently recommended for suitable patients under age of 25 in the UK.

The toxicity and dose to surrounding organs at risk (in particular normal pituitary gland and the optic apparatus) is dependent on tumour volume and its proximity to critical structures, which limits the use of SRS in clinical practice to smaller tumours that are at least 2 to 5mm away from optic apparatus. For instance, to minimise the risk of radiation-induced visual decline, the tumour should be at least 2-5mm from the optic apparatus and the dose limited to 8 to 10 Gy.

Radiotherapy Outcomes

Radiotherapy is an effective treatment for non-functioning pituitary adenoma with reported overall rates of long-term tumour control between 80-97% [33–35]. Traditionally, CRT has been used for large volume residual adenoma after surgery. Minitti et al reported 5 and 10 year tumour control rates of 97% and 91%, in a series of 68 patients with large residual tumours over 3cm [36]. When compared to post-operative observation alone, radiotherapy significantly improves tumour control from 68% for observation alone at 5 years to 93% [37].

For small volume residual or tumour progression, SRS provides a more attractive alternative for patients, as it is usually a single day case treatment. In a large series, Losa et al demonstrated a recurrence rate of 9.6% for recurrent non-functioning adenoma treated with SRS at a median of 78 months [38]. In a retrospective study comparing the use of early SRS for residual tumour following surgery compared to delayed SRS (>6 months following surgery)[39], delayed SRS was associated with a higher risk of long term tumour recurrence (6.3% in the early group versus 28.1% in the delayed group, p=0.043). Additionally, new onset endocrinopathy was demonstrated in 17% of the early SRS group versus 64% in the late cohort. However, most of the new endocrinopathy in the delayed cohort occurred prior to SRS and was attributed to interval tumour progression, leading the authors to conclude that early SRS is superior.

For functioning adenoma, both CRT and SRS may be used after failed surgery, with the aim of achieving biochemical remission. However, remission rates after radiotherapy are much lower than radiological tumour control rates and are highly variable. Remission rates for SRS in GH-secreting adenoma range from 35-100%. However, using current stringent criteria of cure, the average remission rate at 5 years is 48% [40]. Similarly, the biochemical remission rate for Cushing's disease across 15 studies including 465 patients was 64% [40]. Despite the higher marginal doses used in secreting tumours, new onset hypopituitarism and optic nerve dysfunction are comparable to non-functioning adenoma.

The decision between CRT and SRS depends largely on the residual tumour volume and the distance from the optic apparatus. A recent meta-analysis demonstrated no difference in biochemical remission rates between CRT and SRS [41]. Some authors suggest a faster rate of hormone normalisation after SRS [42,43]. However, many studies have demonstrated median times to normalisation between 30-66 months, similar to CRT, and show that time to normalisation is related to pre-irradiation hormone levels, not the method of radiation [44].

Repeat irradiation for pituitary adenoma can be considered, for example using focal SRS where prior CRT has failed. However, careful attention must be paid to the dose distribution to the temporal lobes as temporal lobe necrosis has been described following re-irradiation with both repeat CRT [45] and SRS [46]. Additionally there is a risk of radiation induced optic neuropathy that may be higher than in primary radiotherapy[46].

Early and late side-effects of pituitary radiotherapy – should early radiotherapy be avoided?

For any technique, the use of adjuvant radiotherapy must be carefully balanced against the risks. In a large multicentre study of Gamma Knife radiosurgery for non-functioning pituitary adenoma, 6.6% of patients developed new or worsened optic nerve dysfunction whilst new or worsened hypopituitarism occurred in 21% [47]. Therefore, the use of early radiotherapy to prevent future tumour recurrence or growth is controversial. It is also important to remember that early post-

operative imaging can be misleading, with operative packing material or normal gland being interpreted as residual tumour.

The risk of optic neuropathy varies from 1-5% with conventional RT and 1-4% in SRS, when the dose to the optic nerve is limited to <10Gy [48]. Other cranial neuropathies are rare but there is a risk of brain necrosis in SRS when doses >20Gy are used [40].

Hypopituitarism is a well-known complication of conventional RT for pituitary disease, reported to occur in 80% over 10 years [35]. **Different pituitary axes exhibit different radiosensitivity with GH deficiency occurring in 45-100%, followed by gonadotroph deficiency (30%), TSH deficiency (25%) and ACTH deficiency (22%)**[49]. Modern radiotherapy techniques aimed at sparing normal tissue (either IMRT or SRS) seem to be associated with lower rates of hypopituitarism between 10-40%. However, longer term follow up studies are lacking for newer techniques. Hypopituitarism itself is associated with a two-fold increase in mortality rate, predominantly due to cerebrovascular events [50]. Additionally, radiotherapy is associated with an increased risk of cerebrovascular events and cognitive decline [51]. Ischaemic stroke has not been reported as a complication of SRS [52], but longer follow up data is needed.

RT also carries a risk of inducing a second intracranial tumour including glioma, sarcoma or meningioma. Minniti et al report a cumulative risk of a second brain tumour of 2.4% at 20 years [53]. However, the risk of inducing second tumours appears to be significantly less with SRS[54] and PBT[32].

Multimodal therapy in aggressive pituitary tumours

Where standard interventions fail, medical therapy or **systemic** chemotherapy is considered. Cabergoline has been used in non-functioning adenoma as treatment for post-operative residual tumour. In a retrospective observational study, Greenman et al, reported 55 patients treated with cabergoline as preventative treatment following surgery; tumour control was achieved in 87% at 8 years compared to 53% of controls [55]. Additionally, 42% of the control group required further surgery, compared to 13% of those treated with cabergoline. However, randomised trials are lacking. Pasireotide has also been reported to be effective in some aggressive functioning tumours, including ACTH carcinomas, resistant somatotroph adenomas and prolactinoma [56–59], although experience is still minimal and the expense of treatment is likely to limit its use to only very selected cases.

Temozolamide (TMZ) , an oral alkylating chemotherapy agent, has become widely used in clinically aggressive pituitary tumours and carcinomas, and is now recommended as first-line therapy after failure of conventional therapy [60]. First reported in 2006 [61], subsequent reports with increasing numbers of patients have demonstrated a consistent response rate of approximately 69% in carcinomas and 60% in aggressive adenomas [62]. A survey of European Society of Endocrinology members reported 166 patients treated with TMZ [63], of which 69% were functioning tumours (45% corticotroph adenomas). After a median of 9 cycles, treatment response, including disease stability, was observed in 70%. Patients with clinically functioning tumours and who received concomitant radiotherapy showed a better response. However, of those with a partial response or stable

disease, progression was seen in 40% and 48% respectively at a median of 12 months following treatment, reflecting the underlying tumour biology of these difficult-to-treat tumours[63]. **However, current guidance is based on small cohort studies and to date no randomized control trial has been undertaken. Additionally all decisions regarding the use of TMZ should be undertaken with an oncologist in the setting of a multidisciplinary team (MDT).**

It is currently uncertain at which stage in the disease process TMZ should be considered and for what duration of treatment, particularly as concomitant radiotherapy appears beneficial. In patients who progress after initial response to 6 months of TMZ, a further challenge with TMZ is recommended [60]. **TMZ is generally well tolerated, fatigue is frequently reported and haematological toxicity may require drug withdrawal[64].**

Current guidelines

There are evidence based guidelines for the management of recurrent pituitary adenoma and aggressive adenoma produced by North American and European groups [60,65]. Common to both is the recommendation that these tumours are managed by an MDT with dedicated pituitary surgeons **(Table 6).**

The Congress of Neurological Surgeons' guidelines are based on level 2 and 3 evidence and recommend early radiotherapy for post-operative residuum (either CRT or SRS), to reduce the risk of future progression. However they acknowledge that this recommendation is based on limited evidence and state that the timing of radiation treatment after resection warrants further investigation. They also recommend repeat resection as the primary intervention for recurrent or residual adenoma, reserving CRT or SRS for cases where the risk of surgery is deemed high.

The European Society of Endocrinology guidelines for the management of aggressive pituitary tumours also recommend repeat surgery by an expert pituitary surgeon prior to consideration of other treatment options, but suggest adjuvant RT for initial post-operative residuum only where there are clinical indicators of aggressive behaviour, such as tumour invasion or high ki-67 [60]. Temozolomide chemotherapy is recommended for aggressive pituitary tumours or pituitary carcinomas, where there is documented tumour growth, although this is based on low quality evidence. There is also no recommendation of the stage in the course of the disease that TMZ should be considered. **Although both guidelines are based on low quality evidence, they provide a framework for current practice.**

Conclusion

Aggressive pituitary tumours should be recognised early and a tailored treatment plan outlined. It is our preference to consider early repeat surgery in most cases where possible, with the aim of maximal safe resection of tumour for long-term visual protection in non-functioning adenoma and biochemical remission in functioning adenoma. Where possible, the aim is to preserve normal pituitary function and avoid radiotherapy, in order to reduce the incidence of long term hypopituitarism and reduce exposure to radiation. Revision surgery is often better tolerated by patients than conventional fractionated radiotherapy. In the majority of non-functioning adenomas,

recurrence rates are low and the interval to recurrence relatively long, allowing for initial observation followed by repeat surgery for significant relapse.

Given the low cure rates associated with non-surgical treatment of functioning adenoma (with the exception of prolactinoma), repeat surgery offers the best chance of endocrine remission. Residual tumour should be sought on both thin slice MRI and (functional) PET imaging to identify a surgical target, and expanded approaches used where necessary in an attempt to achieve remission. SRS can then be considered if repeat surgery fails or there is no evidence of residual tumour on imaging.

Aggressive pituitary tumours often require multimodal therapy and repeat salvage interventions. The use of temozolomide is likely to increase, with earlier use in the course of the disease. However, surgery plays a key role to minimise tumour burden and preserve neurological function, although repeat pituitary surgery remains challenging.

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Tables

Table 1: Modified Knosp grade of pituitary adenoma[10]. (CS, cavernous sinus)

Knosp Grade	Tumour Extension
0	No extension beyond medial border of carotid artery. CS not involved
1	Extends to but not beyond intercarotid line
2	Extends to lateral border of carotid
3A	Extends beyond carotid in superior CS compartment
3B	Extends beyond carotid into inferior CS compartment
4	Total encasement of the intracavernous carotid artery

Table 2: Imaging markers of aggressive pituitary adenoma

Imaging Markers of Aggressive Pituitary Adenoma
Cavernous sinus invasion (Knosp Grade 3B or 4)
Clival bone invasion
Sphenoid bone invasion
T2 hyperintensity (sparsely granulated somatotroph)
Early recurrence

Table 3: Probability of recurrence of pituitary tumours [12]

Low probability of recurrence	High probability of recurrence	Malignant
Pituitary adenoma	Adenoma with elevated Ki 67	Pituitary carcinoma
	Sparsely granulated somatotroph adenoma	
	Lactotroph adenoma in men	
	Silent corticotroph adenoma	
	Crooke cell adenoma	
	Plurihormonal PIT-1 positive adenoma	

Table 4: Indications for revision surgery

Indications for revision pituitary surgery
Prior subtotal resection with ongoing mass effect on optic apparatus
Persistent elevated hormone level after failed pituitary surgery with tumour evident on MRI or **11-C Met PET imaging**
Recurrent tumour approaching optic apparatus
Regrowth after prior radiotherapy
Adenoma reduction to facilitate effective radiotherapy/radiosurgery

Table 5: Current literature on endoscopic revision surgery for recurrent or residual adenoma, radiological outcomes and complications (GTR, gross total resection; DI, diabetes insipidus)

Reference	Total patients	GTR (%)	New hypopituitarism (%)	New DI (%)	CSF leak (%)	Major complications
[19]	61	51.7	14.7	4.9	4.9	3% haematoma
[66]	41	58.5	9.8	4.9	2.4	2.4% haematoma
[67]	27	63	3.7	7.4	0	3.7% abducens palsy
[21]	48	-	7	35	9	0
[18]	59	62.7	6.8	5	1.6	1.7% haematoma
[68]	39	46	0	0	2.6	2.6% haematoma

Table 6: Summary of current guidelines for management of recurrent pituitary adenoma from Congress of Neurological Surgeons (CNS) and European Society of Endocrinology (ESE)[60,65]

Current management guidelines for recurrent adenoma
Dedicated pituitary surgeon opinion on revision surgery prior to adjuvant therapies
Patients should be managed in the setting of an MDT
Repeat resection for symptomatic recurrent or residual tumour
SRS or CRT recommended for residual tumour (USA – upfront, Europe growing residual)
Serial imaging after complete or near total resection
Adjuvant radiotherapy should be considered for tumour remnant with biological features of aggression such as high proliferative index, aggressive tumour subtype

Figure Legends

Figure 1: Modified Knosp grade depicted on coronal MR imaging (a)Grade 0, white lines depict the medial and lateral aspect of the internal carotid artery (b) Grade 1 (c) Grade 2 (d) Grade 3A (e) Grade 3B (f) Grade 4

Figure 2: Medial cavernous sinus wall defect after tumour resection, viewed with a zero degree endoscopic transsphenoidal approach.