

PITUITARY ADENOMAS

Date Developed: November, 2009

The recommendations contained in this guideline are a consensus of the Alberta Provincial CNS Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

In Canada, it is estimated that there will be 2600 new cases of cancer of the central nervous system (CNS) diagnosed by the end of 2009, and 1750 deaths due to CNS cancer in the same time period.¹ Pituitary adenomas are a diverse group of CNS tumours that arise from the pituitary gland and they account for approximately 6.6 to 9.1 percent of all primary CNS cancers.^{2,3} Pituitary tumours are fairly common in the general population; one important meta-analysis of 10 radiographic and post-mortem studies involving 3577 patients reported an overall prevalence of 16.7 percent.⁴

There is no universally accepted staging system for pituitary adenomas. Historically, they have been classified according to size: microadenomas (<1 cm dimension) and macroadenomas (\geq 1 cm dimension). Further to this, it is useful to classify pituitary adenomas according to their hormonal activity: functioning and non-functioning adenomas.^{5,6} Functioning adenomas are hormonally active, and include:^{2,4,7,8}

- Prolactin (PRL) secreting adenomas – are the most common form of pituitary adenoma, occurring in 40 to 60 percent of cases
- Adrenocorticotropic Hormone (ACTH) secreting adenomas – occur in five to ten percent of pituitary adenomas, but up to 35 percent of pituitary carcinomas; are associated with Cushing disease
- Growth Hormone (GH) secreting adenomas – occur in two to three percent of cases; are associated with acromegaly and gigantism
- Thyroid Stimulating Hormone (TSH) secreting adenomas – occur in less than one percent of cases; are associated with hyperthyroidism
- Mixed adenomas – secrete more than one hormone; occur in approximately ten percent of functioning adenomas

Non-functioning adenomas account for between 25 and 35 percent of pituitary adenomas, are hormonally inactive, and are the most common form of macroadenoma.⁹ Pituitary tumours that produce Follicle Stimulating Hormone (FSH) and/or Luteinizing Hormone (LH) are classified as non-functioning adenomas as well.

GUIDELINE GOALS AND OBJECTIVES

- To outline the management recommendations for adult patients with pituitary adenomas.

GUIDELINE QUESTIONS

- What is the optimal treatment for adult patients with hormonally active (functioning) pituitary adenomas?
- What is the optimal treatment for adult patients with non-functioning pituitary adenomas?

DEVELOPMENT PANEL

This **guideline** was reviewed and endorsed by the Alberta Provincial CNS Tumour Team. Members of the Alberta Provincial CNS Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, neurosurgeons, nurses, neuropathologists, and pharmacists. **Evidence** was selected and reviewed by a working group comprised of members from the Alberta Provincial CNS Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit.

SEARCH STRATEGY

Medical journal articles were searched using the Medline (1950 to August Week 3, 2009), EMBASE (1980 to August Week 3, 2009), the Cochrane Database of Systematic Reviews (3rd Quarter, 2009), and PubMed electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The search terms included: Pituitary Neoplasms [MeSH heading], Prolactinoma [MeSH heading], Pituitary ACTH Hypersecretion [MeSH heading], ACTH-Secreting Pituitary Adenoma [MeSH heading], Acromegaly [MeSH heading], Growth Hormone-Secreting Pituitary Adenoma [MeSH heading], practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. Articles were excluded from the review if they: had a non-English abstract, were not available through the library system, were case studies involving less than 5 patients, or were published prior to the year 2000.

A review of the relevant existing practice guidelines for pituitary adenomas was also conducted by accessing the practice guidelines on the websites of the British Columbia Cancer Agency (BCCA), the National Comprehensive Cancer Network (NCCN), the National Institute for Health and Clinical Excellence (NICE), the International Radiosurgery Association (IRSA), and the National Cancer Institute (NCI).

TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years. Different principles may apply to pediatric patients.

RECOMMENDATIONS

PRL-Secreting Adenomas:

1. The primary treatment is dopamine-agonist therapy, such as bromocriptine or cabergoline.
2. Surgery is recommended for patients with symptomatic progression or with no response or intolerance to the dopamine agonist.
3. Radiotherapy is used occasionally if the dopamine agonist and surgery fail, or if the patient develops intolerance to the dopamine agonist.

ACTH-Secreting Adenomas:

4. The primary treatment is surgery, usually with a transsphenoidal approach.
5. Repeat surgery or radiotherapy with a steroidogenesis inhibitor may be recommended for incomplete resection or for persistent disease.

GH- and TSH-Secreting Adenomas:

6. Standard treatment options include surgery (usually a transsphenoidal approach), bromocriptine, somatostatin analogue (e.g. octreotide), growth-hormone antagonist, or surgery plus postoperative radiotherapy. Maximal reductions in growth-hormone levels may not be seen for years after institution of radiotherapy, during which time medical therapy may continue to be required.

Non-Functioning Adenomas:

7. Surgical resection (usually a transsphenoidal approach) is indicated for patients with enlarging tumours or visual changes.
8. Radiotherapy or continued observation is recommended for incompletely resected tumours.

Radiation Therapy Principles:

9. In general, radiotherapy for pituitary adenomas is delivered at a dose of 45 to 50.4 Gy in 1.8 to 2.0 Gy per fraction, taking care to observe tolerance of the optic pathway to radiation. The maximum dose to the optic structures should be limited to 8 Gy in a single fraction treatment, if used.
10. Stereotactic radiosurgery presents as potential alternative radiotherapy approach in selective cases.

DISCUSSION**PRL-Secreting Adenomas**

PRL-secreting adenomas, also referred to as prolactinomas, are more common in women, and have a peak incidence during childbearing years. In premenopausal women, the symptoms most often associated with prolactinoma include: oligomenorrhea or amenorrhea, infertility, and galactorrhea; postmenopausal women most often present with headache or visual field deficits.^{10,11} In men, the most common symptoms are impotence, infertility, and decreased libido.^{10,11} The primary goal of therapy in patients with micro-prolactinomas is to restore gonadal and sexual functioning by normalizing PRL levels; in macro-prolactinomas, control and reduction of tumour size are of additional importance.¹⁰ As stated in recommendation #1, the primary therapy for prolactinomas is treatment with dopaminergic agonists such as bromocriptine and cabergoline. These drugs normalize PRL levels and significantly reduce tumour size in the majority of patients.¹⁰ Several large studies comparing cabergoline and bromocriptine have reported that cabergoline has a more satisfactory side-effect profile than bromocriptine, and cabergoline therapy is recommended for patients whose tumours are resistant to bromocriptine therapy, or who cannot tolerate bromocriptine.^{10,12,13} The guidelines for the treatment of pituitary adenomas published by the Pituitary Society recommend that therapy with bromocriptine be initiated at a dose of 0.625 mg to 1.25 mg daily, and increased by 1.25 mg weekly until a dose of 2.5 mg twice or three-times daily is reached.¹⁰ For cabergoline, the Pituitary Society recommends a dose of 0.25 to 0.5 mg once- or twice-weekly, and an increase in the dose monthly until prolactin secretion normalizes.¹⁰

The Alberta Provincial CNS Tumour Team recommends the use of surgery be reserved for patients with prolactinoma who have symptomatic progression, or for those who cannot tolerate dopamine agonists (recommendation #2). Success rates of surgery and disease-free survival rates for patients with prolactinomas have been reported to be quite high for cases involving smaller tumours.^{10,14} In a thorough review of 50 surgical studies of patients with prolactinomas, *Gillam et al.* found that remission rates averaged 74.7 percent (range 38.5-100%) for micro-adenomas and 33.9 percent (range 6.7-80%) for macro-adenomas, suggesting that this approach is acceptable as a second-line therapy for select patients who do not respond to dopaminergic agents.¹⁵

Radiotherapy is used only occasionally in the treatment of prolactinomas, in cases where both treatment with dopamine agonists and surgery fail, if the patient develops an intolerance to the dopamine agonist, or in the very rare cases of malignant prolactinoma (recommendation #3).¹⁰

ACTH-Secreting Adenomas

ACTH-secreting adenomas are the second most common type of pituitary adenoma, accounting for five to ten percent of hormone-secreting pituitary adenomas, and up to 35 percent of pituitary carcinomas.^{4,16} ACTH-secreting adenomas cause Cushing disease, which is most often a micro-adenoma, affects men three times more often than women, and is associated with symptoms such as central obesity, neuropsychiatric symptoms, striae, easy bruising, skin thinning, hirsutism, osteopenia, and proximal

myopathy.¹¹ The primary therapy for ACTH-secreting adenomas is transsphenoidal surgery (recommendation #4). High rates of gross total resection of the pituitary tumour have been reported with both microscopic and endoscopic surgery techniques, and the remission rates associated with transsphenoidal surgery have been reported to be approximately 78 percent for microscopic surgery,¹⁷ and between 67 and 81 percent for endoscopic surgery.^{14,17,18} In an analysis of recently published surgical series involving 50 or more patients, *Platta et al.* reported that recurrence rates for patients who had been treated with transsphenoidal surgery for ACTH-secreting pituitary adenomas ranged from 3.9 to 15 percent.¹⁹

For patients with either an incomplete tumour resection or persistent disease, repeat surgery or radiotherapy is recommended by the Alberta Provincial CNS Tumour Team (recommendation #5). In their comprehensive review, *Platta et al.* analyzed studies conducted between 1957 and 1993 which involved the use of primary conventional radiotherapy for the treatment of Cushing disease.¹⁹ Tumour control rates ranged between 44 and 100 percent in this analysis. In the postoperative setting, doses of conventional radiotherapy have been reported to range from 20 to 50 Gy, with remission rates ranging from 46 to 84 percent.²⁰⁻²⁴

GH- and TSH-Secreting Adenomas

Growth hormone (GH) secreting adenomas account for approximately two to three percent of pituitary adenomas, and cause gigantism in younger patients and acromegaly in older patients.¹¹ Excess GH stimulates hepatic secretion of insulin-like growth factor-1 (IGF-1), which causes most of the clinical manifestations of acromegaly, including growth of hands and feet, coarsening of facial features, carpal tunnel syndrome, obstructive sleep apnea, jaw growth, osteoarthritis, excessive sweating, and visual field deficits.¹¹ In addition, increased rates of cardiovascular complications, hypertension, diabetes mellitus, and colon cancer have all been associated with adults with acromegaly.¹⁹ Thyroid Stimulating Hormone (TSH) secreting adenomas are quite rare, accounting for less than one percent of pituitary adenomas. These adenomas are characterized by hyperthyroidism *without* TSH suppression, thus antithyroid treatment is inappropriate and may lead to further growth of these tumours.¹¹

As stated in recommendation #6, the standard treatment options for both GH- and TSH-secreting adenomas involves transsphenoidal surgical resection as first-line therapy and medical treatment with a dopamine agonist such as bromocriptine, a somatostatin analogue such as octreotide, or a GH antagonist as second-line therapy. Combined modality therapy with surgery and adjuvant radiotherapy has also shown promising results in long-term follow-up studies.

Surgical resection using a transsphenoidal approach has yielded similar results for GH- and TSH-secreting adenomas as with other pituitary adenomas, and the majority of studies report higher success rates with micro-adenomas compared to macro-adenomas.^{14,19,25,26} In an analysis of 86 patients with GH-secreting adenomas, *Laws et al.* reported remission rates of 87 percent for micro-adenomas, and 51 percent for macro-adenomas.²⁵ Similarly, *Nomikos et al.* published the results of 506 patients who received primary transsphenoidal surgery for acromegaly, and reported higher remission rates for patients with micro-adenomas (75%) versus patients with macro-adenomas (50%).²⁶ However, in a recent study involving only endoscopic transsphenoidal surgery, *Dehdashti et al.* reported almost identical remission rates for GH-secreting micro- and macro-adenomas (83 and 82%, respectively), but they noted that the patients who did not achieve remission following surgery all had macro-adenomas with cavernous involvement.¹⁷

For second-line treatment, the somatostatin analogue octreotide has been reported to be successful in controlling hormone levels in between 50 and 79 percent of patients with GH-secreting adenomas, and up to 95 percent in TSH-secreting adenomas.^{19,27,28} Additionally, the dopamine agonist bromocriptine has shown favourable results in stabilizing GH and TSH levels in limited published studies.^{29,30} Recent preliminary data involving the use of the GH receptor antagonist pegvisomant suggest that this is an effective treatment for GH-secreting adenomas, effectively controlling IGF-1 levels in as many as 90 percent of patients.³¹⁻³³ However, pegvisomant does not appear to have an effect on the tumour itself, long-term safety data have yet to be made available, and the cost of the drug is limiting in many situations.

Maximal reductions in growth-hormone levels may not be seen for years after institution of radiotherapy, during which time medical therapy may continue to be required. *Platta et al.* recently summarized the results of eight studies conducted since the year 2000 investigating the use of conventional radiotherapy in the treatment of 1374 patients with acromegaly.¹⁹ Their analysis showed that remission rates increased with the amount of time elapsing since receiving radiotherapy, with remission rates as high as 84 percent demonstrated at 15 years post-radiotherapy. The authors concluded that radiotherapy confers the additive benefit of significant growth control, and that adjuvant radiotherapy plays a key role in the management of patients with GH-secreting pituitary adenomas.¹⁹

Non-Functioning Adenomas

Non-functioning adenomas account for 25 to 35 percent of all pituitary adenomas. Clinically non-functioning *micro*-adenomas do not cause any signs or symptoms, and are often found incidentally during radiologic imaging for other indications.³⁴ On the other hand, clinically non-functioning *macro*-adenomas are the most common type of pituitary macro-adenoma, and present with symptoms such as headache, hypopituitarism, decreases in visual acuity, and visual field defects associated with compression of the optic chiasm.^{19,34} Transsphenoidal surgical resection is the mainstay of treatment for patients with enlarging tumours or visual changes associated with non-functioning pituitary macro-adenomas (recommendation #7). However, although surgery is effective for immediate debulking of the tumour and resolves visual symptoms immediately, a growing body of literature suggests that long-term control of tumour growth is best managed by post-operative radiotherapy.^{19,34} *Dekkers et al.* recently summarized the results of twelve published studies involving 922 patients with non-functioning pituitary macro-adenomas who were treated with transsphenoidal surgery and post-operative radiotherapy, and they concluded that post-operative radiotherapy offered a benefit for long-term tumour control.³⁴ On the basis of these findings, the Alberta Provincial CNS Tumour Team recommends close observation and post-operative radiotherapy for patients with incompletely resected tumours (recommendation #8).

Radiation Therapy Principles

In the cases of pituitary adenomas where post-operative radiation is indicated, the Alberta Provincial CNS Tumour Team recommends that conventional radiotherapy be delivered at a dose of 45 to 50.4 Gy in 1.8 to 2.0 Gy per fraction, taking care to observe tolerance of the optic pathway to radiation (recommendation #9). The maximum dose to the optic structures should be limited to 8 Gy in a single fraction treatment, if used.

In select cases, stereotactic radiosurgery (SRS) presents a potential alternative to conventional radiotherapy for patients with pituitary adenomas (recommendation #10). The Alberta Provincial CNS Tumour Team has adopted the recommendations of the International RadioSurgery Association (IRSA), which state that the selection of patients for SRS is dependent on: prior treatment history, the age of the

patient, existing co-morbidities, anatomic location of the tumour, and clinical history.³⁵ Furthermore, the IRSA recommends that single-session SRS, which is a minimally-invasive, closed-skull treatment strategy, may be especially suitable for patients of advanced age, those with excessive co-morbidities, and those with adenomas involving the cavernous sinus.³⁵

GLOSSARY OF ABBREVIATIONS

Acronym	Description
ACTH	adrenocorticotrophic hormone
CNS	central nervous system
FSH	follicle-stimulating hormone
GH	growth hormone
IGF-1	insulin-like growth factor-1
IRSA	International RadioSurgery Association
LH	luteinizing hormone
PRL	prolactin
SRS	stereotactic radiosurgery
TSH	thyroid-stimulating hormone

IMPLEMENTATION STRATEGY

- Present the guideline in the tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.

EVALUATION STRATEGY

A formal review will be conducted in 2010, however if new evidence is brought forward before that time, the guideline will be changed accordingly.

DECLARATION OF CONFLICT OF INTEREST

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

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