Aggressive pituitary tumours: a challenge to predict and treat

The pituitary gland is a pea-sized gland located at the base of the brain. Affectionately regarded as the “master gland” or “leader of the endocrine orchestra”, the pituitary secretes a number of hormones instrumental in the function of many other glands in the body. Pituitary tumours account for up to 25% of brain tumours. Approximately 1 in every 1000 persons has a clinically significant pituitary tumour. Pituitary tumours cause problems due to hormone hypersecretion (e.g. acromegaly, Cushing’s syndrome), lack of hormone production or compression of surrounding vital brain structures such as nerves to the eyes. There is a range of clinical manifestations associated with pituitary tumours, including infertility, diabetes mellitus, osteoporosis, osteoarthritis, headaches and visual loss. The majority of pituitary tumours occur sporadically, but around 5-10% occur in the context of an underlying familial predisposition towards pituitary tumours and other endocrine tumours.

Most pituitary tumours are considered benign, that is, they don’t possess the biological capabilities to spread outside the pituitary gland. However, up to one third of pituitary tumours may behave in an aggressive manner. Clinicians refer to "aggressive" pituitary tumours as those that continue to grow or recur, usually despite multiple modes of therapy, and also invade surrounding structures of the brain. The most aggressive pituitary tumours are true pituitary cancers, defined as tumours which begin in the pituitary but ultimately spread elsewhere in the body, but these are rare (0.2% of all pituitary tumours). Aggressive pituitary tumours cause serious morbidity. Patients often have significant symptoms related to the tumour mass, such as headache or visual disturbance, and may have further symptoms if the tumour is secreting an excess of hormone. Patients with these tumours often prove resistant to standard medical therapies, require multiple operations and often radiotherapy in an attempt to control tumour growth and excess hormone production. These treatments can also have complications which may compound the patients’ symptoms. There is an increased mortality rate (2-3 times the general population) amongst patients with pituitary tumours. At the extreme end, patients with pituitary carcinomas usually die within 1 year of diagnosis.

It is currently very difficult to predict with any degree of certainty which patients are harbouring tumours which could become more aggressive. There may be some clues provided by the pathologist when they review the tumour specimen following surgery but such clues may not be present in some aggressive tumours and furthermore some non-aggressive tumours may exhibit such clues. Better predictors are clearly required. Particular genetic changes in tumour tissue are likely to provide better markers of tumour aggressiveness. If patients with potentially aggressive tumours could be determined earlier in the course of their disease, then perhaps more aggressive surgery would be attempted, radiotherapy offered earlier or even chemotherapy offered to the patient.

The ability to recognise patients with a familial predisposition to pituitary tumours is also very important. These patients typically have very aggressive tumours, which present at a much younger age. Genetic screening of family members holds the key to early identification of mutation carriers and detection of pituitary tumours before they become incurable.

At the present time, surgery remains the first line treatment for aggressive pituitary tumours, the aim being to reduce the bulk of the disease and decrease symptoms. These tumours, which are normally very large, are unlikely to be cured by surgery however. Newer surgical techniques, such as use of an endoscope, may aid a surgeon's field of view and make resection of a tumour more complete, but often these large tumours are best approached via a large incision at the front of the skull rather than through the back of the nose.

As these tumours are often resistant to standard medical therapies, such as cabergoline or octreotide, radiotherapy is often used following surgery (or if surgery is not possible) and can slow tumour growth, although the effect from radiotherapy is slow and can take months or years. Radiotherapy techniques nowadays are quite sophisticated and the technology can deliver radiotherapy accurately to a tumour, minimising delivery of radiotherapy to surrounding normal structures. Depending on the tumour location and size, one single high strength dose of radiotherapy can be delivered on just one occasion (called radiosurgery). Despite these advances, patients with large aggressive pituitary tumours still may require conventional radiotherapy delivered more gently over several procedures.

There are some new medical therapies on the horizon, which are essentially variations of currently available drugs (e.g. pasireotide), however these are unlikely to offer much additional benefit to patients with aggressive disease. Historically, several different chemotherapeutic agents have been tried in the treatment of aggressive pituitary tumours but none have proven particularly effective. Over the past few years, temozolomide, an oral chemotherapeutic agent used as standard treatment for glioblastomas, has been found to be very efficacious in the management of aggressive pituitary tumours. Frequently, the response is quite sustained even after cessation of the drug. Side effects reported are generally mild and include fatigue, nausea and a drop in white blood cell count. Current research in this area is focussed on determining whether a particular genetic change is present in a tumour which may predict whether the patient will respond to temozolomide therapy. Whilst temozolomide represents a significant advance in the management of aggressive pituitary tumours, there is a great need to discover other agents, which could be used in the management of these difficult tumours.

A glimpse into the future would reveal a new dimension in the management of aggressive pituitary tumours. It is hoped that we may be able to offer patients undergoing surgery for a pituitary tumour genetic testing of their tumour sample. This would reveal if a particular tumour contained genetic changes forecasting a more aggressive course of disease. Genetic analysis would also be able to tell treating doctors which medical therapies, including chemotherapeutic agents if required, would be most effective in treating the tumour. However, without much needed support for pituitary research, these goals will not be realised.