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The shift of therapeutic strategy for prolactinomas: surgery as the first-line option

Recently, *Nature Reviews Endocrinology* published a Consensus Statement by Petersenn et al. on the diagnosis and management of prolactin-secreting pituitary adenomas, endorsed by the Pituitary Society (Petersenn, S. et al. Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement. *Nat. Rev. Endocrinol.* **19**, 722–740 (2023)[1]). The biggest change from the previous versions of these recommendations[2,3] is that surgery should be considered as the first-line option in some patients, such as patients with microprolactinomas and well-circumscribed macroprolactinomas (Knosp grade 0 and 1), and especially in young women.

The two previous consensus guidelines, published in 2006 and 2011[2,3], stated that medical therapy with a dopamine agonist represented the first-line option for almost all patients with prolactinomas; surgery as a second-line treatment was only applicable in the cases of dopamine agonist resistance or intolerance, dopamine agonist-induced tumour apoplexy or cerebrospinal fluid leakage, or dopamine agonist contraindications owing to psychiatric symptoms.

Comparing these consensus documents[1–3], we find a gradual change in the perception of what treatment is appropriate. The fundamental cause is the advancement of neuroendoscopic technology accompanied with the improvement of biochemical remission rate after surgery in the past few decades. Transsphenoidal surgery (TSS) by experienced neurosurgeons using neuroendoscopy can achieve normalization of circulating levels of prolactin in up to 93% of patients with microadenomas and 75% of patients with selected macroadenomas, with low incidence rates of perioperative and postoperative complications (1–4%) and 0% mortality[4]. Also, extra-pseudocapsule resection can improve the endocrine remission rate. More than 75% of microadenomas (>4 mm) and well-defined macroprolactinomas have a pseudocapsule[5]. Through a search of 13 publications from 2011 to 2022, we found that in 2,088 patients, the biochemical remission rate of extra-pseudocapsule resection was about 87% (Supplementary Table 1). Dopamine agonists, especially cabergoline, achieve about 90% effectiveness in the treatment of prolactinomas. However, dopamine agonist usage faces two potential problems: the adverse effects and the difficulty of drug withdrawal. Considering the similarity in the effectiveness of medical treatment and surgery, with the fact that the recurrence rate is 80% versus 20% for medical treatment after dopamine agonist withdrawal versus surgery[1], it is reasonable to consider surgery as the first-line option for some specific subgroups of patients with prolactinomas.

However, there are two issues that I would like to discuss. First, the current consensus proposed surgery as the first-line treatment for patients with prolactinoma of Knosp grade 0 or 1, but patients with Knosp grade 2 or above should be treated with dopamine agonists. The consensus of the Italian Association of Clinical Endocrinologists also recommends that TSS be presented as a viable option to any patient with a readily resectable adenoma (microadenoma or enclosed macroprolactinoma)[6]. The enclosed macroprolactinoma (which is enclosed by a pseudocapsule) usually includes adenomas of Knosp grade 1 and 2. The majority of Knosp grade 2 tumours are pushing the medial wall of the cavernous sinus but do not invade the cavernous sinus. Therefore, patients with this type of tumour will have a high chance of biochemical remission after a surgery with extra-pseudocapsule resection. Randomized clinical trials to directly compare dopamine agonist treatment with TSS could provide clear, evidence-based conclusions. Second, the technical expertise of TSS is not the same around the world. A Pituitary Tumour Center of Excellence with a multidisciplinary team, including an excellent transsphenoidal neurosurgeon, is critical.

There is a reply to this letter by Petersenn, S. et al. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-024-00954-4 (2024).

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Competing interests

The author declares no competing interests.

Additional information

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