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Tumour fibrosis in dopamine agonist-exposed prolactinomas is a diminishing concern

We applaud the Pituitary Society on the latest prolactinoma Consensus Statement (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]), which highlights rare but serious dopamine agonist-related toxicities, such as impulse control disorders, as we demonstrated in a large cross-sectional study[2]. Accordingly, we support the increasing use of operative management in surgically accessible prolactinomas and have previously advocated for a low surgical threshold approach for prolactinomas[3].

We question, however, the recommendation to routinely offer primary surgery to all patients with a microprolactinoma or a well-circumscribed macroprolactinoma (Knosp grade 0 or 1) before attempting cabergoline therapy. Although surgery can provide a definitive cure, a large subset of patients can be successfully treated by cabergoline without exposure to potentially permanent operative complications like hypopituitarism and meningitis[3]. Noting that dopamine agonist-induced toxicity is almost always reversible[4], the recommendation for primary surgery before any attempt at cabergoline therapy seems to relate largely to concerns around the potential risk of dopamine agonist-induced tumour fibrosis.

The initial evidence for tumour fibrosis was related to the historic use of bromocriptine[5] rather than cabergoline, which is the preferred drug in the modern management of prolactinomas[1]. More recent data show that the operative finding of tumour fibrosis is no more common in cabergoline-treated prolactinomas than in dopamine agonist-naive prolactinomas[6,7]. If fibrosis is a function of the tumour itself rather than a consequence of cabergoline therapy, we do not see cabergoline pretreatment as an impediment to later surgery.

Even if fibrosis is histologically present in dopamine agonist-exposed prolactinomas as we have previously documented[8], this finding does not equate to poor surgical outcomes. From the neurosurgical perspective, the presence of tumour fibrosis tends to obscure the pseudocapsule. This tendency makes complete resection more challenging for large prolactinomas and increases the risk of complications. However, the microprolactinomas and small macroprolactinomas in question here might not present the same challenges, particularly when managed with modern endoscopic techniques by a specialised skull base team.

Prospective randomised data are required to determine whether primary surgical management yields better outcomes than a low surgical threshold approach, where surgery is used after at least a short trial of cabergoline. The evidence supporting the Pituitary Society's recommendation for primary surgery for patients with a microprolactinoma or a well-circumscribed macroprolactinoma[1] was data from a meta-analysis looking at postoperative remission rates in prolactinomas of any diameter. This meta-analysis found that studies with more frequent preoperative dopamine agonist use had lower surgical remission rates than studies with less preoperative dopamine agonist use[9]. However, as all studies were purely observational, the dopamine agonist-exposed study populations were likely enriched with larger, more invasive prolactinomas requiring medical pretreatment as well as prolactinomas with dopamine agonist resistance necessitating a switch to surgical management, both of which would expectedly yield worse operative outcomes. Data were inadequate to determine the effect of preoperative dopamine agonist use as a dichotomous variable on surgical remission rates[9].

We eagerly await results from the ongoing PRolaCT studies involving randomisation of patients with non-invasive prolactinomas to either primary surgery or surgery after defined durations of dopamine agonist therapy[10]. Until then, we hold caution in routinely offering primary surgery for microprolactinomas and encased macroprolactinomas, which poses a risk of permanent operative complications. Albeit low in the eminent retrospective surgical series published to date, this risk could rise if the capacity of expert pituitary neurosurgeons is outstripped by increased referral numbers, beyond the typical 10–20% of patients with prolactinomas who have dopamine agonist intolerance or resistance.

There is a reply to this letter by Petersenn, S. et al. *Nat. Rev. Endocrinol.* https://doi.org/10.1038/s41574-024-00978-w (2024).

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Competing interests

The authors declare no competing interests.