Original Article

Postoperative treatment of clinically nonfunctioning pituitary adenomas with dopamine agonists decreases tumour remnant growth

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Summary

Objective There is no consensus as to the optimal postoperative treatment of patients with clinically nonfunctioning pituitary adenomas (NFPA) in whom total tumour removal has not been achieved. In this study we assessed whether dopamine agonist (DA) treatment can prevent postoperative remnant enlargement in NFPA.

Design and methods Thirty-three patients (25 men/8 women; mean age, 61·7 ± 11·2 years; mean follow-up, 40·6 ± 4·8 months) were treated with DA, and their outcome was compared to that of 47 untreated patients (33 men/14 women; mean age, 59 ± 2 years; mean follow-up, 42·9 ± 4·2 months).

Results Tumour mass decreased or remained stable in 18/20 patients in whom DA treatment was initiated upon detection of residual tumour on postoperative MRI (group I). In 13 subjects (group II), DA therapy was started when remnant growth became evident during the course of routine follow-up. Tumour growth stabilized or decreased in 8/13 (61·5%) of these patients. In contrast, tumour size remained stable in only 38·3% (18/47) of the untreated subjects (P < 0·0001 for comparisons among the three groups) and increased in the remaining 29 patients. Tumour enlargement free mean survival time was 103·7 ± 8·8 months (CI 86·3–121) for group I, 43·9 ± 9·6 months (CI 25·2–62·8) for group II and 36·7 ± 3·8 (CI 29·2–44·2) for the control group (P = 0·0017). Treatment vs. control hazard ratio for tumour enlargement was 0·135 for group I (P = 0·007, 95% CI 0·032–0·577) and 0·892 for group II (P = 0·817; 95% CI 0·34–2·34).

Conclusions Dopamine agonist therapy is associated with a decreased prevalence of residual tumour enlargement in patients with nonfunctioning pituitary adenomas, particularly when treatment is instituted before tumour remnant growth is detected.

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In memoriam.

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There is no consensus as to the optimal postoperative treatment of patients with clinically nonfunctioning pituitary adenomas (NFPA) in whom total tumour removal has not been achieved. Radiation therapy has been traditionally advocated, but its long-term complications reduce the enthusiasm for its use on a routine basis. Preventive postoperative radiotherapy is thus frequently withheld and reserved for patients in whom there is evidence for remnant tumour growth.¹,²

We have recently studied the natural history of patients with NFPA after surgery. Mean actuarial relapse-free survival time was 42·3 ± 2·6 months for patients with a residual mass after surgery, with a 2- and 5-year re-growth rate of 30 and 70%, respectively.³ A ‘wait and see’ approach therefore seems inappropriate for this subgroup of patients, the majority of which will thus require second surgery or radiation.

Medical therapy has been largely unsuccessful in the treatment of NFPA.⁴ Modalities such as somatostatin analogues or GnRH agonists and antagonists have been tried with little success.⁵ Observations that NFPA not only express membrane-bound dopamine receptors,⁶–⁸ but also that these receptors are actually functional, as suggested by the finding that bromocriptine inhibited tumoural secretion of α-subunits both in vitro and in vivo,⁹,¹⁰ prompted hopes that dopamine agonists (DA) might be of value in the treatment of these tumours. Nevertheless, the use of bromocriptine (BRC) in reducing tumour size has been disappointing. Although a significant clinical response has been reported in some patients,¹¹ including important improvement in visual fields, most studies have shown only modest size reduction in a minority of tumours treated with BRC.¹²–¹⁴ Therefore, this therapy has not been used on a routine basis.

Treatment with the nonergot dopamine agonist quinagolide¹⁵,¹⁶ has also been relatively ineffective. Trials using the more potent and specific dopamine agonist cabergoline reported variable results.¹⁶–¹⁸ The heterogeneity of responses to treatment has been attributed to the different pattern and level of expression of dopamine receptor
subtypes in the individual tumours, as well as to possible alterations in the signal transduction pathway.

In the past few years, we have chosen to approach the challenge of treating patients with NFPA from another perspective. If NFPA comprise no threat to the function or integrity of neighbouring structures, attainment of tumour shrinkage may not be an essential treatment goal. Therefore, our aim was to examine whether treatment with DA may prevent enlargement of postoperative residual tumour, thus decreasing the need for radiotherapy and/or repeated surgery.

Subjects and methods

The study was approved by the local institutional ethics committee, and written informed consent was obtained from each participant. All patients, both in the treated and in the control groups, were operated on at the Tel Aviv Sourasky Medical Center by the same neurosurgeon, between 1989 and 2001. The follow-up of 44 of these patients has been reported in a previous paper from our group.

Patients had macroadenoma with suprasellar extension before surgery and remained with a significant tumour remnant after surgery, as detailed in Table 1.

The entire cohort of patients with NFPA with postoperative tumour remnant undergoing follow-up in our Institution is outlined as defined in Table 1, which also shows the source of the various subgroups included in this study. As shown, patients in the treatment group were under routine follow-up at the Endocrine Department at our institution. Treatment group I consisted of 20 patients in whom medical treatment was initiated upon detection of significant residual tumour on postoperative MRI as a preventative measure, as there was no evidence for mass growth at that time point (Fig. 1). Treatment group II consisted of 13 patients who likewise had residual masses on postoperative MRI and initially declined medical therapy. These patients, however, consented to medical treatment once growth was detected on subsequent MRI studies. The 13 patients comprising treatment group II were selected (based on their interest to receive treatment upon tumour expansion) from a larger group of 20 patients showing evidence of residual tumour growth (Fig. 1).

In yet 18 other patients (out of the 38 subjects (47%) who initially declined medical treatment) no growth of the tumour remnant was recorded and they continued to be followed conservatively.

For comparison with this treated cohort, we used a database of 76 subjects who were under surveillance at the institutional neurosurgery clinic during the study period, but received endocrine follow-up outside the hospital. At the time of analysis, patients in the control group were matched to the treatment groups according to age, sex, preoperative tumour size, and size of postoperative tumour remnant. The matched control group consisted of 47 patients. None of the patients received radiation therapy. Minimal required follow-up time for inclusion in the analysis was 12 months.

### Treatment protocol

All patients were initially treated with BRC. The dosage was gradually increased with the aim of reaching 10 mg daily. If significant side-effects developed at this dose, patients received the highest tolerable dosage, with a minimal dose of 5 mg/day. If significant side-effects persisted even at the lower dosage, patients were switched to quinagolide (up to 300 mg daily) or to cabergoline (up to 1·5 mg per week).

### Imaging protocol

MRI was performed 3–6 and 12 months after surgery as well as yearly thereafter in all patients. All treated subjects (groups I and II) were referred for MRI, 3–6 and 12 months following initiation of medical therapy and yearly thereafter. Visual field examinations were performed at the same time points.

Tumour size and growth characteristics were determined by MRI and direct surgical inspection, using a modification of Wilson and Hardy’s classifications, developed by one of us (G.O.). Briefly, grades I, II, III and IV indicate microadenoma, noninvasive macroadenoma, invasive microadenoma and invasive macroadenoma, respectively. Stages A, B and C indicate increasing degrees of suprasellar extension. Stages a, b and c indicate increasing extent of infrasellar extension. Stage E indicates cavernous sinus invasion. 0 indicates absent extra-sellar extension.

<table>
<thead>
<tr>
<th>Grade and stage</th>
<th>Control group</th>
<th>Treatment group</th>
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<tbody>
<tr>
<td>Grade</td>
<td></td>
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</tr>
<tr>
<td>I</td>
<td>6 (12·8%)</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>13 (27·7%)</td>
<td>11 (33·3%)</td>
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<tr>
<td>III</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>IV</td>
<td>28 (59·5%)</td>
<td>21 (63·6%)</td>
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<tr>
<td>Supra</td>
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<td></td>
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<tr>
<td>0</td>
<td>17 (36·2%)</td>
<td>11 (33·3%)</td>
</tr>
<tr>
<td>A</td>
<td>22 (46·8%)</td>
<td>17 (51·5%)</td>
</tr>
<tr>
<td>B</td>
<td>7 (14·9%)</td>
<td>5 (15·2%)</td>
</tr>
<tr>
<td>C</td>
<td>1 (2·1%)</td>
<td>0</td>
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<tr>
<td>Infra</td>
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</tr>
<tr>
<td>0</td>
<td>19 (40·4%)</td>
<td>15 (45·5%)</td>
</tr>
<tr>
<td>a</td>
<td>11 (23·4%)</td>
<td>5 (15·2%)</td>
</tr>
<tr>
<td>b</td>
<td>15 (31·9%)</td>
<td>9 (27·3%)</td>
</tr>
<tr>
<td>c</td>
<td>2 (4·3%)</td>
<td>4 (12·1%)</td>
</tr>
<tr>
<td>Cavernous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27 (57·4%)</td>
<td>16 (48·5%)</td>
</tr>
<tr>
<td>E</td>
<td>20 (42·6%)</td>
<td>17 (51·5%)</td>
</tr>
</tbody>
</table>

Grades I, II, III and IV indicate microadenoma, noninvasive macroadenoma, invasive microadenoma and invasive macroadenoma, respectively. Stages A, B and C indicate increasing degrees of suprasellar extension. Stages a, b and c indicate increasing extent of infrasellar extension. Stage E indicates cavernous sinus invasion. 0 indicates absent extra-sellar extension.
Two independent neuroradiologists who were blinded to the assigned treatment group examined MRI studies. A change in tumour size was considered significant and recorded as such only if a difference of at least 2 mm in diameter was observed and confirmed in a subsequent report.

**Hormone measurements**

TRH stimulation test was performed in both patients and controls as previously outlined, between 8 and 9 a.m. Blood samples for β-FSH and β-LH were collected immediately prior and 30, 45, 60 and 90 min after the intravenous injection of 400 µg of TRH. An increase in circulating β-subunits was considered significant when levels rose by 50% or more over the basal concentration.

β-FSH and β-LH were measured by fluoroimmunoassays developed in our laboratory, as described previously. Cross-reactivity with LH, FSH, HCG, β-hCG, β-LH or β-FSH, α-subunits and TSH was less than 0.1%. Assay sensitivity was 0.1 µg/l. Intra-assay coefficient of variation was 7% for β-FSH and 8% for β-LH. Interassay coefficient of variation was 8% for β-FSH and 10% for β-LH.

**Immunohistochemistry**

Immunohistochemistry was performed using an avidin-biotin complex method with reagents provided by Dako Corporation (Carpentaria, CA, USA). The polyclonal antisera detected only intact human pituitary hormones and not subunits. Silent corticotroph and silent somatotroph adenomas were excluded from the study.

**Statistical analysis**

The association between tumour characteristics and changes in tumour size and according to treatment group were examined using Fisher’s exact test for categorical variables. The rank-sum (Mann–Whitney) test and the Student’s t-test were used for between-group comparisons for numerical variables. Results are expressed as the mean ± SEM. The Cox Proportional-Hazards model was utilized to assess the independent association of different variables with tumour enlargement. All variables that were associated with tumour enlargement with a significance level of < 0.1 were included in the multiple logistic regression analysis. The time to detection of tumour enlargement and the median recurrence-free survival time were estimated using the Kaplan–Meier method.

**Results**

Thirty-three patients received DA treatment (25 men/8 women; mean age, 61.7 ± 1.9 years (range: 30–75), and 47 subjects comprised the matched control group (33 men/14 women; mean age, 59.3 ± 1.8 years (range: 24–79). Twenty patients (15 men/5 women) started medical treatment upon detection of significant tumour remnant in postoperative MRI (treatment group I), whereas in 13 patients (10 men/3 women) treatment was initiated only once tumour remnant growth had been detected on MRI during routine follow-up (treatment group II). Follow-up was 40.6 ± 4.8 months (range: 12–122) in the treatment groups and 42.9 ± 4.2 (range: 12–146) in the control group (P = ns).
All patients in the control group and in both treatment groups had macroadenomas with suprasellar extension before surgery. There were no significant differences in tumour characteristics between the groups after operation, as detailed in Table 1.

Mean preoperative prolactin levels were 25 ± 2·9 µg/l (47–81 µg/l) in the control group and 24·8 ± 2·4 µg/l (5·6–56 µg/l) in the treatment group (P = ns) (conversion factor of 21·2 for mU/l). Immunostaining pattern was similar in the study population. Positive immunostaining for FSH and/or LH was detected in 64% of tumours from the control group and in 60% of tumours in the treatment group. There were 22·2% and 32% null tumours in the control and treatment groups, respectively. Prolactin staining in a few cells was detected in three tumours from the control group and in one tumour from the treatment group. Focal staining for TSH or ACTH was detected in five tumours from the control group and in one tumour from the treatment group. There was no correlation between tumour staining characteristics and the occurrence of tumour growth during follow-up or in response to medical treatment.

Results from gonadotropin subunit response to TRH stimulation were available in 29/33 patients from the treatment group. This information was available in only 10/47 patients in the control group, restricting the value of any further analysis. This reflects the fact that only the neurosurgical team and community endocrinologists were following patients from this group. In 27/29 tested patients from the treatment group, TRH induced a significant elevation in β-FSH (31%), β-LH (17%) or both subunits (45%). Among the latter, serum FSH levels were elevated in four subjects, one of whom also had elevated serum LH levels. There was no correlation between the gonadotropin β-subunit response to TRH and treatment outcome.

Twenty-three patients tolerated the initial treatment well. The mean bromocriptine dosage was 8 ± 0·7 mg/day. The remaining 10 subjects were switched to another dopamine agonist: five patients were treated with quinagolide at a mean dose of 225 mg/day and five received cabergoline at a mean dose of 1·2 mg/week.

Reduction of tumour size in the DA-treated group was discernible on MRI between 3 and 12 months of treatment initiation. In four of eight patients with visual field defects after surgery, DA treatment was accompanied with an improvement in vision. Tumour growth despite treatment occurred between 7 and 37 months from initiation of treatment (mean 15 ± 3·8 months).

Altogether, DA treatment was associated with tumour control in 26 of 33 patients (78·8%), Fig. 2(a). In treatment group I tumour size decreased in nine patients (45%), and did not change in nine (45%), thus achieving an overall control rate of 90% (Fig. 2b). Tumour growth occurred in only two patients (10%) despite treatment. In treatment group II DA treatment halted tumour growth in six patients (46·1%) and caused tumour shrinkage in two patients (15·4%), but tumour growth persisted in five patients (38·5%) despite therapy, with an overall control rate of 61·5% (Fig. 2). In contrast, tumour size remained stable in only 38·3% of the untreated control patients (18/47) while tumour growth was recorded in 29 subjects (61·7%). Moreover, in the control group there was not a single case of spontaneous mass shrinkage (P < 0·0001 for comparisons among the three response patterns, stable, growing and shrinking). Mean decrease in height in the treatment groups was 6·3 ± 1·1 mm (range: 3–14 mm). In one patient from treatment group I who initially responded with a significant reduction in tumour size, escape from therapy occurred after 30 months and she underwent a second operation.

Patients in whom tumour enlargement occurred were younger than those in whom the tumour remained stable in the cohort as a whole (57·4 ± 11·3 vs. 62·6 ± 12·4 years, P = 0·05) and in the treatment groups (52·1 ± 11·9 vs. 64·2 ± 9·6 years, P = 0·009). Sex, serum prolactin and gonadotropin subunit levels and immunostaining characteristics did not correlate with the response to treatment.

The Cox Proportional-Hazards model was used to examine the effect of treatment on occurrence of tumour enlargement. The parameters entered into the model were treatment group, age, sex and presence of extra-sellar extension. Hazards ratio for growth in the treatment group vs. control was 0·347 (C.I. 0·147–0·821; P = 0·016). Importantly, when the analysis was performed looking at treatment subgroups, DA treatment vs. control hazard ratio for tumour enlargement was 0·135 for group I (P = 0·007, 95% CI 0·032–0·577) and 0·892 for group II (P = 0·017; 95% CI 0·34–2·34).

Tumour enlargement-free mean survival was 103·7 ± 8·8 months (CI 86·3–121) for group I, 43·9 ± 9·6 months (CI 25·2–62·8) for
The use of DA has been previously explored as a treatment alternative for NFPA. Our study is unique in that we have treated a large group of patients for a mean period of more than 3 years with an appropriate control group, whereas previous reports were uncontrolled and had a short follow-up time.

Furthermore and in contrast to previous trials, we chose to approach the treatment of patients with NFPA from another perspective. Because NFPA causes morbidity predominantly through a mass effect, we postulated that size reduction of residual tumours not compressing surrounding vital tissues is not essential and that prevention of tumour progression is a reasonable goal. We were able to show that DA treatment is effective in preventing residual tumour growth in almost 80% of patients with NFPA. Importantly, when treatment was initiated before evidence for mass enlargement existed, control rate reached 90%. Control rate was lower (61-5%) if DA treatment was instituted later in the disease course (group II), but still higher than that in the untreated group (38-3%). The lower response rate in group II could reflect variation in the expression of dopamine 2-receptor 2 (D2R) in the individual tumours. Recently, Pivonello et al. showed significant tumour shrinkage in five of nine patients treated with cabergoline for 12 months. The more prominent response was attained in patients whose tumours expressed the D2R short isoform. This observation is in line with work published by Renner et al., which showed the importance of the short isoform of D2R in the inhibition of cell proliferation by BRC treatment in vitro. The possible influence of D2R pattern of expression on outcome remains entirely hypothetical in our study, as we have not characterized D2R in the removed tissue. Finally, it is possible that the treatment is less effective if initiated when tumours are already in a phase of exponential growth.

An inherent limitation to a MRI-based study of NFPA following surgery is that occasionally it can be difficult to distinguish between tumour tissue and postoperative changes. While this comprises a true confounding factor in this field, we took measures to minimize its effects on our observations. First, the initial imaging in the database was recorded 3 months following surgery, at which time most acute postoperative tissue responses are known to have regressed. Second, the diagnosis of tumour remnant was accepted only if established independently by two experts in pituitary imaging. Lastly, treated and untreated patients were matched for tumour size both before and after surgery, such that chances for erroneous inclusion of individuals with no real tumour remnants would appear reasonably equal for the two groups.

In conclusion, our results support the routine use of DA to prevent residual mass expansion after surgery. Nonetheless, double blind, randomized placebo-controlled trials are needed to confirm these results.

References
