

Treatment of clinically nonfunctioning pituitary adenomas with dopamine agonists

Y Greenman^{1,5}, O Cooper⁶, I Yaish¹, E Robenshtok^{4,5}, N Sagiv¹, T Jonas-Kimchi^{3,5}, X Yuan⁷, A Gertych⁷, I Shimon^{4,5}, Z Ram^{2,5}, S Melmed⁶ and N Stern^{1,5}

¹Institute of Endocrinology, Metabolism and Hypertension, ²Department of Neurosurgery, ³Neuroradiology Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, ⁴Institute of Endocrinology and Metabolism, Rabin Medical Center, Petah Tikva, Israel, ⁵Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, ⁶Pituitary Center and ⁷Department of Pathology, Cedars Sinai Medical Center, Los Angeles, California, USA

Correspondence should be addressed to Y Greenman

Email
yonagr@tlvmc.gov.il

Abstract

Objective: Clinically nonfunctioning pituitary adenoma (NFPA) remains the only pituitary tumor subtype for which no effective medical therapy is available or recommended. We evaluated dopamine agonist (DA) therapy for preventing growth of postsurgical pituitary tumor remnants.

Design: The study design included historical cohort analysis of clinical results at two pituitary referral centers with different standard practices for postoperative NFPA management: DA therapy or conservative follow-up.

Methods: Seventy-nine patients followed for 8.8 ± 6.5 years were treated with DA, initiated upon residual tumor detection on postoperative MRI (preventive treatment (PT) group, $n=55$), or when tumor growth was subsequently detected during follow-up (remedial treatment (RT) group, $n=24$). The control group ($n=60$) received no medication. Tumoral dopamine and estrogen receptor expression assessed by quantitative RT-PCR and immunostaining were correlated with response to treatment.

Results: Tumor mass decreased, remained stable, or enlarged, respectively, in 38, 49, and 13% of patients in the PT group, and in 0, 53, and 47% of control subjects; shrinkage or stabilization was achieved in 58% of enlarging tumors in the RT group, $P < 0.0001$.

Fifteen-year progression-free survival rate was 0.805, 0.24, and 0.04, respectively, for PT, RT, and control groups ($P < 0.001$). About 42% of patients in the control group required additional surgery or radiotherapy, compared with 38 and 13% subjects in the RT and PT groups, respectively ($P=0.002$). Outcome measures were not related to NFPA D2R abundance.

Conclusions: Dopamine agonist therapy in patients with NFPA is associated with decreased prevalence of residual tumor enlargement after transsphenoidal surgical resection.

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Introduction

Nonfunctioning pituitary adenomas (NFPAs) are defined by the absence of elevated circulating pituitary hormones, as well as features secondary to tumor-related hormone hypersecretion. They mostly synthesize but rarely secrete gonadotropins or gonadotropin hormone subunits. Hence, NFPA remains clinically silent until significant mass expansion has already occurred. They are typically large at diagnosis, often

compressing critical neighboring structures, causing hypopituitarism, visual compromise, and cranial nerve palsy (1). Transsphenoidal resection is the preferred treatment, allowing decompression and rapid symptom amelioration in most cases (2). Nevertheless, as these tumors are mostly invasive macroadenomas, a complete resection is challenging. Most patients harbor residual postoperative tumor tissue, which, if left untreated, is

associated with progression rates of over 40% in 5–10 years (3, 4, 5). Radiation therapy may be effective in preventing residual tumor growth (6), but is associated with a high rate of complications, thus limiting routine use (7, 8). Reoperation for tumor recurrences is often necessary, particularly when there is risk for compromised optic function. Although major surgical complications are infrequent, they are not negligible and include new onset hypopituitarism, cerebrospinal fluid leak, meningitis, cranial nerve injury, and visual compromise, with a mortality rate of 0.3–0.5% (9).

NFPA comprises the most common form of pituitary macroadenomas that require surgical intervention, yet they remain the only pituitary tumor subtype for which no medications are effective. This contrasts with effective drugs available (10, 11) for the treatment of hormone-secreting pituitary tumors.

Most NFPA express dopamine receptors, predominantly dopamine receptor 2 (D2R) (12, 13). Thus, dopamine agonists (DA) reduce gonadotropin secretion (14) and inhibit thymidine incorporation *in vitro* (15), providing a potential therapeutic target for NFPA. However, dopaminergic binding sites (16) as well as D2R mRNA isoforms (17) are less abundant in NFPA than in prolactinomas, perhaps accounting for the modest rate of tumor shrinkage attained by DAs (18). Small studies, including a report from our own group (19), suggested that DA may retard NFPA growth (20, 21, 22, 23, 24), but to date, this potential therapeutic modality has not been broadly practiced.

We sought to determine the impact of routine DA treatment on progression of postoperative tumor remnants. We hypothesized that such treatment would reduce the need for subsequent interventions such as radiotherapy and repeat surgery with associated risk of added complications. We therefore retrospectively analyzed prospectively collected data derived from two separate NFPA patient cohorts from similar metropolitan population bases: in one center, DA are routinely administered after surgery, whereas in another, standard practice for postoperative NFPA care is a conservative follow-up. We also assessed the abundance of tumoral dopamine and estrogen receptor expression as determinants of treatment response.

Subjects and methods

Patients

The study included NFPA patients from two pituitary referral centers in central Israel distanced less than 9 km from each other. Eligible adults (>18 years of age) had residual tumor visible in the first postoperative MRI, with a minimum 1-year follow-up. Exclusion criteria included silent corticotroph and silent somatotroph tumors, and previous history of radiation therapy.

The study included two patient populations (Fig. 1):

1. Treatment group: patients followed at Tel Aviv-Sourasky Medical Center between 1989 and 2013. A total of 114 patients were initially identified and

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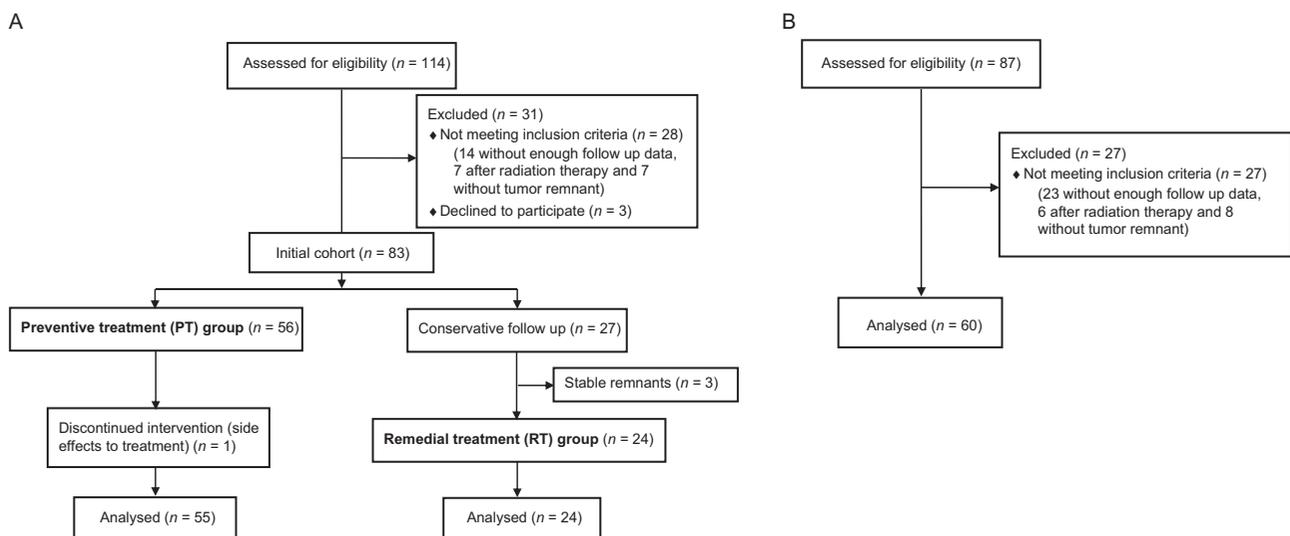


Figure 1 Assessment for eligibility and enrollment in the treatment (A) and control (B) groups.

79 were available for final analysis. Initial follow-up of 33 of these patients has been reported (19).

- Control group: patients followed at Rabin Medical Center between 1995 and 2012. A total of 87 patients were initially identified and 60 were available for analysis. Characteristics of this cohort have been described (25).

The study was approved by the respective independent institutional ethics committees and complied with the Declaration of Helsinki. Written informed consent was obtained before surgery from patients whose tumor samples were subsequently analyzed. A waiver of written consent was approved for retrospective data extraction from clinical records.

Treatment protocol

Preventive treatment (PT) group

Patients in whom a clear tumor remnant was evident in the first postoperative MRI were offered the option to undergo DA treatment for the prevention of subsequent tumor progression. Patients who declined medical therapy were followed conservatively, i.e. no active therapy. During 1989–2001, bromocriptine was administered, and since 2002, cabergoline was used in all but two patients. Dosages were gradually increased, according to tolerability, with the aim of reaching 10 mg qd of bromocriptine (mean 6.8 ± 2.6 mg, range 2.5–10 mg) and 2 mg of cabergoline weekly (mean 1.5 ± 0.7 mg, range 0.5–3.5 mg). Twenty-one out of 55 evaluable patients in the PT group were initially treated with bromocriptine and 14 subsequently switched to cabergoline after a mean period of 4.6 ± 3.2 years (three due to tumor growth while receiving bromocriptine and eleven for patient convenience). The mean time from surgery to medical treatment initiation was 0.8 ± 0.85 years.

Remedial treatment (RT) group

This group comprised patients who likewise had residual masses on postoperative MRI, initially declined medical therapy, but consented once tumor progression was detected on subsequent MRI studies. Medical treatment was as described for the PT group, reaching a mean daily bromocriptine dose of 7.5 ± 2.8 mg (range 2.5–10 mg) and a mean weekly cabergoline dose of 1.4 ± 0.7 mg (range 0.5–3.5 mg). Twelve out of 24 patients in the RT group were initially treated with bromocriptine and

6 subsequently switched to cabergoline after a mean period of 3.34 ± 3.3 years (two due to tumor growth while receiving bromocriptine and four for convenience). The mean time from surgery to medical treatment initiation was 4.2 ± 3.2 years.

Endpoints and assessments

The primary endpoint was prevention of tumor progression. Secondary end points were tumor shrinkage and the number of clinically required additional interventions (surgery and radiotherapy) during follow-up.

Imaging protocol

MRI was performed 3–6 months after surgery and yearly thereafter in all patients. Subjects in treatment groups also underwent MRI 6 months following medical therapy. MRI scans were performed with gadolinium contrast, and evaluated by two experienced neuroradiologists at each institution. Maximal tumor diameters in each plane were used for comparison between MRI scans. Comparisons were performed with the most recent previous images, and also with antecedent available scans. A change in tumor size was considered significant and recorded as such if a difference of at least 2 mm in diameter was observed.

Patients underwent pituitary function and neuro-ophthalmologic assessment including visual fields before and 4–6 weeks after surgery. Follow-up was conducted every 3 months during the first year and twice yearly thereafter, or at the discretion of the treating physician. At each visit, vital signs and physical condition were assessed, and re-evaluation of pituitary function and vision were performed as per standard clinical practice. Pituitary hormone deficiencies were treated with hormone replacement therapy, except for growth hormone deficiency that was not routinely evaluated or treated. Decisions regarding indication for surgery and/or radiotherapy for patients in whom tumor progression occurred during follow-up were determined by the treating physician at each institution according to standard clinical practice.

Immunohistochemistry

Immunostaining for intact pituitary hormone expression and Ki-67 proliferative index was performed in the respective clinical pathology laboratories. D2R and estrogen receptors (ER α (ESR1)) and ER β (ESR2) were

immunostained, digitized, and quantified at the Cedars-Sinai Translational Research Core in 53 tumor samples of DA-treated subjects. The percentage of positive cells and staining intensity was recorded for each slide using the immunoreactivity scoring system (IRS) (26) and the (QUICKScore) technique (27) (Supplementary Methods, see section on supplementary data given at the end of this article).

Quantitative RT-PCR

Quantification of *D2R* (long and short isoforms) as well as *ERα* and *ERβ* mRNA levels (Supplementary Table 1 and Supplementary methods) was performed in 18 tumor samples of DA-treated patients (14 from PT and 4 from RT groups), for whom frozen tissue was available for analysis in the institutional tumor bank.

Statistical analysis

The association between tumor characteristics and changes in tumor size by treatment group was examined using the Fisher’s exact test for categorical variables. The rank-sum (Mann–Whitney) test and analysis of variance (ANOVA) were used for between-group comparisons for numerical variables as appropriate. Results are presented as mean ± s.d. The Cox proportional hazards model was used to assess independent associations of different parameters with tumor enlargement. Variables associated with tumor enlargement with a significance level of <0.1, in addition to age and sex, were included in the multivariate Cox proportional hazard models. Schwarz Bayesian information criteria were used for the selection of the best-fit interaction model. Time for detection of tumor enlargement and median recurrence-free survival times were estimated using the Kaplan–Meier method. Tumor progression-free survival was measured from the date of surgery until tumor growth detection in control and PT groups, and from DA treatment initiation until tumor growth detection in the RT group. Data were censored at the date of the last follow-up visit. The log-rank test with Bonferroni adjustment for multiple comparisons was used to compare progression-free survival curves. Pearson correlation analysis was performed to study correlations between receptor expression levels. *P* values of less than 0.05 were considered to indicate statistical significance. Data analysis was performed with SAS 9.3 software (SAS Institute Inc, Cary, NC, USA.).

Results

Patient characteristics

All patients had pituitary macroadenomas before surgery, with a mean (range) maximal diameter of 26.2 mm (10–55), 27.7 mm (13–47), and 28.8 mm (12–90) in the control, remedial (RT), and preventive treatment (PT) groups, respectively (Table 1). No significant differences were evident in other tumor features, such as presence of invasiveness or hormone immunostaining pattern (Table 1). Baseline characteristics including age, gender, presence of hyperprolactinemia, and visual field defects were similar in all groups, but hypopituitarism was more common in the treatment groups (*P*=0.037; *P*=0.042 for RT vs control group, *P*=0.053 for PT vs control group) possibly reflecting different thresholds for hypopituitarism diagnosis between the two medical centers and the longer follow-up time in the RT group (*P*<0.0001; Table 1).

Table 1 Baseline demographic and clinical characteristics of the study population. Data are presented as mean (S.D.) or as number (%).

	Control (n=60)	Remedial treatment (n=24)	Preventive treatment (n=55)
Age (years)	57.3 (14.5)	56.6 (13.7)	58.3 (13.4)
Sex (female)	21 (35%)	7 (29.2%)	26 (47.3%)
F/U time (years) ^a	6.3 (5.2)	13.3 (6.3)	6.7 (5.6)
F/U time after DA initiation		6.7 (4.7)	
Maximal pre-operative tumor diameter (mm)	26.2 (10.9)	27.7 (9.5)	28.8 (12.3)
Invasiveness ^b	35 (58.3%)	13 (54.2%)	32 (58.2%)
Visual field defect	35 (58.3%)	12 (54.5%)	27 (50.9%)
<i>n</i>	60	22	53
Hyperprolactinemia	14 (31.8%)	7 (33.3%)	15 (34.9%)
<i>n</i>	44	21	43
Hypopituitarism ^c	22 (40%)	15 (68.2%)	31 (52.7%)
<i>n</i>	55	22	52
Immunostaining			
Gonadotropinoma	15 (31.9%)	12 (54.5%)	16 (31.4%)
Null cell adenoma	27 (57.4%)	10 (45.5%)	27 (52.9%)
Other/plurihormonal	5 (10.6%)	0	8 (15.7%)
Total <i>n</i>	47	22	51
Remnant size ^d			
<10 mm	16 (36.4%)	6 (25%)	6 (11.8%)
>10 mm	28 (63.6%)	18 (75%)	45 (88.2%)
Total <i>n</i>	44	24	51

^a*P*<0.0001; ^bDefined as invasion of cavernous sinus detected in MRI and quantified over grade 2 in the Knosp classification (28); ^cPresence of dysfunction in one or more pituitary axes; *P*=0.037; *P*=0.042 for the comparison between RT and control groups; *P*=0.053 for the comparison between PT and control groups; ^d*P*=0.016.
F/U, Follow-up

Although follow-up time in the RT group (13.3±6.3 lyers) was longer than in the PT (6.7±5.6 years) and the control groups (6.3±5.2 years), follow-up after treatment initiation in the RT group (6.7±4.7 years) was similar to that in the other groups (Table 1). Tumor remnants larger than 10 mm were more prevalent in the PT group (88.2%), compared with the RT (75%) and control (63.6%) groups, $P=0.016$; PT vs control, $P=0.0068$ (Table 1).

Primary endpoint: prevention of tumor remnant progression

Tumor control was achieved in 87.3% of the PT group (tumor shrinkage in 38.2% and tumor stabilization in 49.1% of patients), but only in 46.7% of the control group ($P<0.0001$, Table 2).

In the RT group, in which clear evidence of tumor growth had already been documented in all patients before initiation of DA, tumor control was still achieved in 58.4% of them (shrinkage in 29.2% and stabilization in 29.2%), despite the unfavorable preselection (Table 2). Escape from therapy was encountered in two patients who initially exhibited tumor shrinkage in the PT group, 30 months and 20 years after treatment initiation, respectively.

Patients who experienced tumor growth during follow-up, both in the treated and untreated groups, were younger than subjects whose tumors remained stable (54.3±14.1 years, range 27–55, vs 59.4±13.5, range 27–88, respectively; $P=0.03$). In patients receiving preventive treatment, preoperative maximal tumor diameter was significantly larger (37±35 mm) in the progressing tumors than in the controlled tumors (27.5±9 mm), $P=0.047$. The presence of hyperprolactinemia, hypopituitarism, remnant size, and immunostaining characteristics was not related to outcome.

Tumor progression-free median survival was 6 years (95% CI: 5–7) for the control group, 8.5 years (95% CI: 3.1 – not computable) for the RT group, and could not

be estimated in the PT group since after 24 follow-up years, the rate of tumor progression was less than 50% ($P<0.0001$; Fig. 2). Actuarial tumor progression-free survival at 5 years was 0.69, 0.88, and 0.6 in the control, PT, and RT groups, respectively ($P=0.052$; $P=0.04$ (PT vs RT)). Ten-year progression-free survival rate was 0.81, 0.48, and 0.12 for PT, RT, and control groups, respectively ($P=0.0002$; $P=0.0001$ (PT vs control), $P=0.06$ (RT vs control) and $P=0.02$ (PT vs RT)). Fifteen-year progression-free survival rate was 0.81, 0.24, and 0.04 for PT, RT, and control groups, respectively ($P<0.0001$; $P<0.0001$ (PT vs control), $P=0.04$ (RT vs control), and $P=0.0053$ (PT vs RT)).

The Cox proportional hazards model was used to examine the treatment effect on the occurrence of tumor enlargement. Parameters entered into the model were treatment group, age, sex, as well as tumor size and invasiveness before surgery and postoperative remnant size. Hazards ratio for growth in treatment vs control groups was 0.3 (95% CI: 0.16–0.56; $P=0.0002$), after

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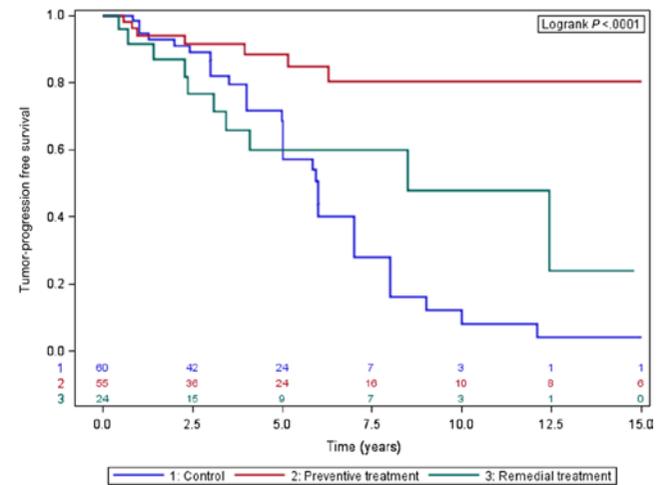


Figure 2

Actuarial tumor progression-free survival in patients with postoperative tumor remnants according to treatment group: preventive treatment group (PT) – treatment was initiated upon residual tumor detection on postoperative MRI; remedial treatment group (RT) – treatment was initiated upon tumor growth detection during follow-up; control group – untreated. At 5 years: log-rank test $P=0.052$; PT vs RT $P=0.045$; $n=NS$ for other comparisons. At 10 years: log-rank test $P=0.0002$; control vs PT $P=0.0001$; control vs RT $P=0.06$; PT vs RT $P=0.019$. At 15 years: log-rank test $P<0.0001$; control vs PT $P<0.0001$; control vs RT $P=0.039$; PT vs RT $P=0.0053$.

A full colour version of this figure is available at <http://dx.doi.org/10.1530/EJE-16-0206>.

Table 2 Effect of treatment on residual tumor progression.

	Control (n=60)	Remedial treatment (n=24)	Preventive treatment (n=55)
Tumor growth	32 (53.3%)	10 (41.6%)	7 (12.7%)
Tumor stabilization	28 (46.7%)	7 (29.2%)	27 (49.1%)
Tumor shrinkage	0	7 (29.2%)	21 (38.2%)
Overall tumor control (shrinkage+stabilization)	28 (46.7%)	14 (58.4%)	48 (87.3%)

$P<0.0001$.

adjustment for gender (HR for male vs female gender 2.2; 95% CI: 1.18–4.09; $P=0.012$) and age (HR for each increasing year 0.96; 95% CI: 0.94–0.98, $P=0.001$). Within the treatment arm, the hazards ratio for tumor progression in PT vs RT groups was 0.273 (95% CI: 0.1–0.74, $P=0.011$) after adjustment for preoperative maximal tumor diameter (in mm) (HR 1.049, 95% CI: 1.008–1.09; $P=0.02$), age (HR 0.96, 95% CI: 0.93–0.99, $P=0.02$), and sex (HR 2.17 for male gender, 95% CI: 0.586–8).

Secondary endpoints

Clinical events

Twenty-five patients (41.7%) in the control group, compared with 9 (37.5%) and 7 (12.7%) in the RT and PT groups, respectively, required additional surgery and/or radiotherapy ($P=0.002$), with a total event rate of 46.7, 50, and 16.4%, respectively ($P=0.0008$, Table 3). One of three patients in the PT group and one of two patients in the RT group who experienced tumor progression while receiving bromocriptine treatment had stabilized tumor growth after switching to treatment with cabergoline. One patient in the PT group developed nausea and dizziness shortly after initiation of DA therapy, leading to drop him out of the study (Fig. 1). After reaching the maximal tolerated DA dose, no adverse events attributable to DA therapy were identified during long-term follow-up.

Correlation between clinical outcome and tumor D2R expression

Tissue was available for immunostaining in 53 of 79 patients in the treatment groups (36 and 17 in the PT and RT groups, respectively). D2R staining was positive in the majority of cells (>75%) in 53% of tumor samples. However, only 15% of samples exhibited scarce D2R staining (<25% of cells). The IRS score, which integrates the percentage of positively stained cells with the intensity of staining, was high (upper quartile) in 77% of tumor

Table 3 Clinical outcomes.

	Control (n=60)	Remedial treatment (n=24)	Preventive treatment (n=55)
Radiation therapy	12 (20%)	4 (16.7%)	3 (5.5%)
Additional surgery	16 (26.7%)	8 (33.3%)	6 (10.9)
Total events ^{a,b}	28 (46.7%)	12 (50%)	9 (16.4%)

^aThree, three, and two patients in the control, RT, and PT groups had both additional surgery and radiation therapy; ^b $P=0.0008$.

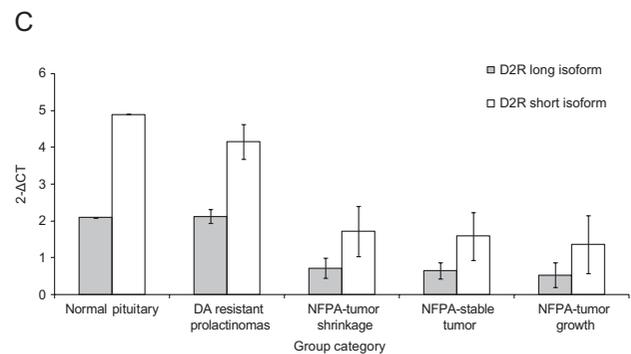


Figure 3

(A) Strong (IRS12) and (B) weak (IRS3) immunostaining for D2R. Both tumors remained stable under DA therapy. Magnifications 4x and 10x. IRS, immunoreactivity score. (C) D2R isoform mRNA expression in normal pituitary, DA-resistant prolactinoma (n=3), and NFPA tumors according to response to treatment: tumor shrinkage (n=6), stable tumor (n=8), and tumor growth (n=3). $P<0.001$ for the comparison between prolactinoma and NFPA groups for both isoforms. A full colour version of this figure is available at <http://dx.doi.org/10.1530/EJE-16-0206>.

samples (Supplementary Table 2). Primary or secondary outcome measures were not related to D2R tumor abundance (Fig. 3A and B; Supplementary Tables 2 and 3), or to D2R mRNA isoform expression levels (Fig. 3C). Interestingly, expression of D2R mRNA isoform was higher in DA-resistant prolactinomas (2.1 ± 0.2 and 4.2 ± 0.5 $1/2 \Delta Cr$ for long and short isoforms, respectively) than in DA-responsive NFPA (0.7 ± 0.3 and 1.6 ± 0.7 $1/2 \Delta Cr$ for long and short isoforms, respectively), $P < 0.001$, (Fig. 3C).

ER α staining was undetectable in 47% of tumor samples. Only three samples stained positively for ER α in 25–75% of tumor cells. By contrast, ER β was expressed in 90% of samples, half of which expressed the receptor in all cells (100%). ER α and ER β staining scores (Supplementary Tables 2 and 3), and mRNA levels (Supplementary Fig. 1) as well as Ki-67 immunopositivity (Supplementary Table 2) in tumor remnants did not differ according to their response to DA treatment.

There was a significant and strong positive correlation between mRNA expression levels of the long and short D2R isoforms ($r = 0.941$; 95% CI: 0.847–0.978; $P < 0.0001$) and between mRNA expression levels of ER α and ER β ($r = 0.57$; 95% CI: 0.15–0.82; $P = 0.012$). This uniformity in D2R isoform and ER expression in NFPA samples supports the finding that the possible preponderant expression of one isoform over the other may not be an important determinant of tumoral response to DA therapy, as suggested previously.

Discussion

Faced with a tumor remnant after incomplete surgical resection of NFPA, the current consensus guidance for practice is expectant follow-up and the use of radiotherapy or repeat surgery if required (1, 29, 30). This ‘wait and see’ strategy reflects the often unacceptable rate of long-term complications of radiation therapy as well as the usual indolent course of the disease. However, tumor progression in untreated patients occurs commonly and is often unpredictable (31) with variably delayed recurrence and most importantly, not consequence-free. Secondary interventions such as repeated surgery and radiotherapy are then implemented, not always under clinically optimal circumstances, and carry the risk of concurrent associated morbidity.

In this study, we demonstrated the efficacy of DA therapy in this clinical setting, and as compared with untreated patients, preventive treatment with DA reduced the occurrence of tumor progression by 76%. Furthermore,

even when treatment was administered to patients in whom there was already evidence for active tumor growth, it still lowered the incidence of tumor progression, and induced tumor shrinkage or stabilization in over 58% of patients subjected to delayed rather than preventive DA therapy. Response to treatment was prolonged, with a very low rate of escape (1.6%) during a long-term follow-up. Importantly, the requirement for additional surgery and radiation during follow-up decreased from 46.7 to 16.4% with preventive treatment, indicating that the observed DA treatment-related decline in tumor progression translated to clinically significant benefits. This reduction in the need for additional interventions is of particular importance in view of the recently reported association between multiple surgeries or surgery combined with RT, with elevated standardized mortality ratios (2.67) reported in patients with NFPA (32). Our results lead us to propose that currently practiced expectant follow-up in subjects with NFPA with residual postoperative remnant, even in the absence of evident mass effects on vital structures, is less beneficial than preventive treatment with DA.

The use of DA for the treatment of NFPA has been explored for over 30 years, but results are derived from case reports and small series, including heterogeneous patient populations, with follow-up times usually shorter than 1 year, using different dosages of medication, mostly bromocriptine. Colao and coworkers (18) analyzed 24 studies published between 1981 and 2005, encompassing 199 patients, and report stabilization of over 90% of NFPA masses in patients treated with DA. Five studies (20, 21, 22, 23, 24) encompassing 54 patients used cabergoline (mean dose 1–3 mg/week) for the treatment of NFPA (primary treatment or postsurgical remnants) with mean follow-up times between 6 and 12 months. Pooled results indicate that tumor stabilization occurred in 85% of patients (Supplementary Table 4). Albeit encouraging, the lack of untreated control groups in most published studies, the possibility of selection bias, and the small number of patients in each series do not allow for firm conclusions as to treatment effectiveness or tumor characteristics that may influence response to treatment.

Although our study is also limited in its design and a double blind, randomized placebo-controlled study (RCT) would have been preferable, under “real-world” circumstances, the design of our study should be weighed against the practical alternatives. First, the probability that such a study with generic DA will be performed is low due to the lack of commercial incentive. Second, our report is based on a long-term study, overall encompassing 20 years. Given the slow growing nature of these tumors

and the lack of serum markers to reflect treatment effectiveness, even if a publicly funded RCT is initiated, it would require a protracted follow-up time. We minimized patient selection bias using a design in which the studied patient populations were derived from two different medical centers within a similar geographical, ethnic, and cultural area, which to the best of our judgment differ only with respect to the different management protocols which are the subject of the present report. Of note, the use of radiation therapy in the postoperative management of NFPA was also never studied in an RCT, and a similar design as in our study was utilized to investigate its effectiveness in this clinical context (6).

In contrast to the low D2R expression characteristic of prolactinomas resistant to DA therapy (33), we found no correlation between clinical response to DA treatment and D2R expression, as evaluated at the protein level by immunocytochemistry and, in a smaller number of cases, at the mRNA level. These results are in accordance with a previous report in which dopamine D2R imaging using [¹²³I]-epidepride had limited clinical usefulness for predicting the efficacy of DA treatment in NFPA (22). Discordant studies reported the association of dopamine resistance in prolactinomas with low expression levels of the short (34) or long (35) isoforms of D2R. In NFPA, an association between the (qualitative) expression of the D2R short isoform with response to DA *in vitro* (36) and *in vivo* (21) has been suggested. We did not find an association between either the isoform type or expression levels with clinical response to medical treatment in NFPA. Possibly, a larger number of clinical and tumor correlates could shed more light on this question. At this point, we cannot explain the lack of correlation between dopamine receptor expression levels and response to DA treatment in NFPA. Additional factors potentially associated with clinical response to DA treatment in prolactinomas such as D2R polymorphisms, nerve growth factor receptor expression, and alterations in cellular signaling factors down-stream of D2R such as decreased levels of G_{ai} inhibitory G protein subunit (33) have yet to be analyzed.

Another important limitation of this study is the inherent variability in imaging interpretation at the two centers. Nevertheless, such variability would not account for the large differences in the requirement for repeated surgery and radiation observed between the groups, which can derive only from clear-cut and clinically relevant tumor enlargement. Finally, the possible safety concern regarding high-dose cabergoline-induced valvular heart disease (37) has not been reported with lower doses such

as those used in our study, and in pituitary disorders in general (38), and therefore appears not to weaken the significance of our report.

In conclusion, dopamine agonist therapy was associated with decreased incidence of postoperative residual tumor enlargement in patients with NFPA. We propose that this treatment modality be considered for management of these patients.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-16-0206>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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