ORIGINAL ARTICLE

Topoisomerase IIα as a prognostic factor in pituitary tumors

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KEY WORDS

aggressive pituitary tumor, biomarker, topoisomerase IIα

ABSTRACT

INTRODUCTION There is an ongoing search for markers of pituitary tumor proliferation and progression that could facilitate further treatment and patient monitoring.

OBJECTIVES We studied topoisomerase IIα (topo IIα) expression in different types of pituitary adenomas to evaluate its prognostic value.

PATIENTS AND METHODS In a retrospective study of 60 patients (mean age, 46.7 ±17.6 y) who underwent pituitary tumor surgery, expression of topo IIα was assessed by immunohistochemistry and compared with histopathological tumor features, clinical symptoms, magnetic resonance imaging, and postoperative tumor recurrence or progression.

RESULTS Expression of topo IIα was observed in 44 of 60 pituitary adenomas (73%). The highest topo IIα index was observed in adrenocorticotropic hormone (ACTH)-secreting tumors (median, 1.13% [0.37–1.21]), followed by silent-ACTH tumors (0.94% [0.89–1.0]), and hormone immunonegative adenomas (0.8% [0.65–1.55]). There were no differences in topo IIα expression with respect to age or sex. Significant correlations were observed between the topo IIα index and tumor size, its invasiveness, abnormal ocular test results, and postoperative tumor recurrence. In patients with a topo IIα index exceeding 1%, we observed a 3.5-fold higher relative risk of tumor recurrence as compared with patients with a topo IIα index lower than 1% (95% confidence interval: 1.8–6.9; $P < 0.001$). Patients with acromegaly who received somatostatin analogues before the surgery had a lower median topo IIα index compared with untreated patients (0% [0–0.22] vs. 0.71% [0.17–1.0]; $P < 0.05$).

CONCLUSIONS In our study group, the topo IIα index exceeding 1% was found to be a prognostic factor for tumor recurrence or progression, especially in patients with hormonally inactive adenomas, allowing to select patients for intensive postoperative treatment. Use of somatostatin analogues in acromegaly inhibits topo IIα expression, providing molecular evidence for the effectiveness of these analogues.

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INTRODUCTION Following the 2004 World Health Organization (WHO) classification of pituitary tumors,[1-4] which introduced the concept of atypical adenoma, the Ki-67 antigen and p53 immunoreactivity have been among the most frequently evaluated markers in pituitary adenomas. A new prognostic clinicopathological classification of pituitary adenomas, proposed by Trouillas et al.,[5] also uses these markers of the cell cycle for tumor grading.

The Ki-67 antigen, present in all active phases of mitosis, is absent in the G_0 phase. A high Ki-67 index correlates well with tumor invasiveness and its recurrence following surgical treatment[6,7]; however, a low Ki-67 index, comparable with that typical of noninvasive tumors, is quite common in aggressive pituitary adenomas.[8,9]

Despite considerable progress in understanding the pathogenesis of pituitary adenomas, no single marker has been found to independently predict aggressive behavior of pituitary adenomas. Therefore, other specific markers of pituitary adenoma proliferation and angiogenesis, including microRNAs, are being investigated.[10,11]

Topoisomerase IIα (topo IIα) has been established as one of the key enzymes in DNA

TABLE 1 Patient characteristics

general data	age, y	46.7 ±17.6
	sex: female/male	37 (62) / 23 (38)
	overt symptoms/incidentaloma	43 (71.7) / 17 (28.3)
imaging results	largest dimension of tumor, mm	25.1 ±17.6
	microadenoma/macroadenoma	14 (23.3) / 46 (76.7)
	largest dimension of microadenoma, mm	5.9 ±2.2
	largest dimension of macroadenoma, mm	31.0 ±16.0
	patients with destruction of sella turcica	16 (26.7)
	suprasellar invasion	35 (58.3)
	patients with cavernous sinus invasion	36 (60.0)
	patients with optic chiazm compression	36 (60.0)
results of ocular tests	patients with ocular symptoms	32 (53.5)
	patients with fundus abnormalities	9 (15.0)
	patients with visual field defect	31 (51.7)
final classification of pituitary adenomas in the patient group	patients with clinically nonfunctioning adenoma	19 (31.7)
	patients with prolactinoma	13 (21.7)
	patients with acromegaly	16 (26.7)
	patients with Cushing disease	4 (6.7)
	patients with gonadotropinoma	5 (8.3)
	patients with thyrotropinoma	1 (1.7)
	patients with silent-ACTH adenoma	2 (3.4)

Data are presented as mean ± standard deviation or number (percentage).

Abbreviations: ACTH – adrenocorticotropic hormone

replication and cell division,[12] indicating cell proliferation activity in many tumors. It is also a target for several cytostatic drugs.[13,14]

Determination of topo IIα activity enabled to distinguish a group of invasive pituitary adenomas.[15,16] Wolfsberg et al.[17] found a strong correlation between *MIB1* and topo IIα expression in these tumors.

The aim of our study was to investigate whether topo IIα expression, assessed by immunohistochemical staining, could be used as a prognostic factor in the treatment of patients with pituitary adenomas. We investigated the correlation of the topo IIα labeling index with the demographic, clinical, and imaging data of those patients.

PATIENTS AND METHODS This was a retrospective study including 60 patients with pituitary adenomas who underwent pituitary surgery and were admitted to the Department of Endocrinology of the Jagiellonian University Medical College, Kraków, Poland, between the years 2003 and 2006. Each patient was followed up for 48 months after the surgery. All patients were operated by the same team of neurosurgeons. Tumors were removed by transsphenoidal resection. The final diagnosis of the patients was based on demographic and clinical data, results of postsurgical specimen histopathology, and evaluation of magnetic resonance imaging (MRI) retrieved retrospectively from their medical records. The same group of patients was also studied with respect to cyclooxygenase-2 (COX-2) expression in pituitary adenomas.[18] The characteristics of the patients are presented in TABLE 1. The study was approved by the ethics committee of the Jagiellonian University Medical College.

Fundus abnormalities and visual field defects were assessed retrospectively from patients' medical records. Tumor size, defined as its largest dimension, sella turcica destruction, cavernous or sphenoid sinus invasion, and optic chiasm compression (TABLE 1) were evaluated from 1.5 T magnetic resonance images obtained at baseline and at 3 to 6, 12, 24, 36, and 48 months after the surgery. Routine T_1-weighted spin-echo sequences were obtained before and after the administration of gadolinium chelate (0.1 mmol). All images were evaluated by the same radiologist.

Tumor invasiveness was assessed on the basis of the radiological criteria of Knosp et al.[19] and Zada et al.[20] and patient surgical records. Tumor recurrence or progression was defined as regrowth (enlargement) of residual pituitary adenoma after the surgery.

Patients with prolactinoma who required pharmacological treatment (6 of 13 patients) received a dopamine agonist (bromocriptine) for 3 to 6 months. Patients with acromegaly (8 of 16 patients) were treated with a somatostatin analogue (octreotide long-acting release [LAR]) 6 to 12 months before the surgery. Patients with pituitary insufficiency received appropriate hormone replacement therapy. Before the surgery, no patient was diagnosed with diabetes insipidus. Recurrence of hormonal secretion was considered in

TABLE 2 Topoisomerase IIα expression as an independent predictor of tumor recurrence or progression, confirmed by magnetic resonance imaging (Cox multiple regression analysis)

Parameter	RR	95% CI	*P* value
topoisomerase IIα expression >1%	4.56	1.80–11.51	0.001
compression of optic chiasm	2.13	0.67–6.77	0.199
no hormone expression	1.61	0.64–4.07	0.314

Abbreviations: CI – confidence interval, RR – relative risk

patients who did not fulfill the generally accepted criteria for cure after surgery.[21-24]

Surgically obtained specimens of pituitary adenomas were stained with hematoxylin and eosin. The following specific primary antibodies against pituitary hormones were used: adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin (PRL), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) (Dako, Glostrup, Denmark). All samples were evaluated by the same pathologist. Tumors with atypical morphological features such as increased pleomorphism and elevated mitotic activity, suggestive of invasive growth, were defined as "more aggressive". Pituitary adenoma specimens were classified according to the WHO criteria. Tumors with no expression of ACTH, GH, PRL, TSH, LH or FSH were classified as hormone immunonegative adenomas.[1]

Immunohistochemical staining for topo IIα with monoclonal immunoglobulin G-class antibodies directed against C-terminal domain of human topoisomerase (NCL-TOPOIIA, Novocastra, Novocastra Laboratories Ltd, New Castle upon Tyne, United Kingdom) was performed in optimum dilution (1:30). The antigen was retrieved by microwave treatment at 95°C in citrate buffer (pH = 6.0). Overnight incubation with primary antiserum (NCL-TOPOIIA) at refrigerator temperature was followed by incubation with a secondary biotinylated antibody for 30 minutes. Next, avidin–biotin complex horseradish peroxidase (30 minutes) with diaminobenzidine tetrahydrochloride as chromogen was applied for up to 8 minutes using microscopy, followed by counterstaining with hematoxylin (Mayer's Hematoxylin, Life Technologies, United Kingdom).

Control of specificity of the primary antibody and positive and negative control tests were performed according to the manufacturer's instructions. Sections of anaplastic gastric cancer served as positive control. Substitution of the primary antibody with phosphate buffered saline (pH = 7.4) served as negative control. Tumor sections were immunostained for topo IIα and evaluated by optical microscopy (NIKON OPTISHOT-2, Nikon, Tokyo, Japan) at ×400 magnification. The topo IIα labeling index was evaluated as the percentage of positively stained cells with respect to the total of at least 2000 cells viewed in each section.

Basic statistical and comparative analyses appropriate to the distributions of data points were performed. The Kolmogorov–Smirnov, Mann–Whitney, Kruskal–Wallis, analysis of variance, and Fischer exact tests were used as appropriate. Relative risk (RR) and odds ratio (OR) were calculated based on χ^2 frequency tables. Linear regression was applied to evaluate the degree of correlation of normally distributed variables (n ≥30). Otherwise, the nonparametric Spearman rank correlation test was used.

In Kaplan–Meier graphs, time to incidence was plotted, with 48 months as the last follow-up point. For Kaplan–Meier and receiver operating characteristic (ROC) plots, statistic tests were generated using GraphPad Prism version 5.03 for Windows (GraphPad Software, San Diego California, United States).

To establish predictors of recurrence and pituitary tumor advancement, Cox multiple regression and logistic regression were generated using the Statsdirect version 2.0 for Windows (Statsdirect Ltd., Cheshire, United Kingdom). A *P* value of 0.05 or less was considered statistically significant.

RESULTS Positive staining for pituitary hormones was established in 41 patients (68.3%) on the basis of immunohistochemistry records. Of 60 tumors, 19 showed no expression of ACTH, GH, PRL, TSH, LH, or FSH, and were classified as hormone immunonegative adenomas.[1]

Of 60 patients, 35 (58.3%) had functioning tumors and 25 (41.7%) had nonfunctioning tumors, of which 4 cases of gonadotropin-positive adenomas and 2 ACTH-positive tumors were found on histopathology.

Prolactinoma was observed in 13 patients (21.7%); acromegaly, in 16 (26.7%); Cushing disease, in 4 (6.7%); gonadotropinoma, in 5 (8.3%); thyrotropinoma, in 1 (1.7%); and silent-ACTH adenoma, in 2 (3.4%). In some adenomas, expression of more than 1 hormone was observed (TABLE 1).

In 6 cases (10%) of adenomas, the polymorphism of cell nuclei and presence of mitotic figures was demonstrated, suggesting an aggressive course and more invasive growth.[1]

Between the 3rd and 48th month of postoperative follow-up, a recurrence or progression of pituitary tumor (diagnosed by MRI or hormonal tests) was reported in 22 of 60 patients (36.7%).

Expression of topo IIα was reported in 44 of 60 cases (73%) of pituitary adenoma. Topo IIα immunoreactivity was present in cell nuclei additionally stained with hematoxylin (FIGURE 1). The values of the topo IIα labeling index ranged from 0% to

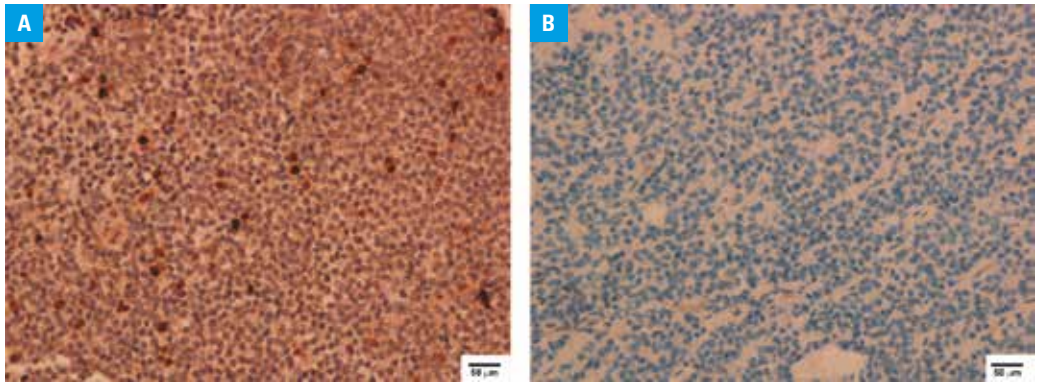


FIGURE 1 Topoisomerase IIα (topo IIα) expression in pituitary adenomas (optical microscopy, magnification ×200); **A** – a 65-year-old man; gonadotropinoma; topo IIα index, 0%; **B** – a 47-year-old woman; hormone immunonegative adenoma; topo IIα index, 3.5%

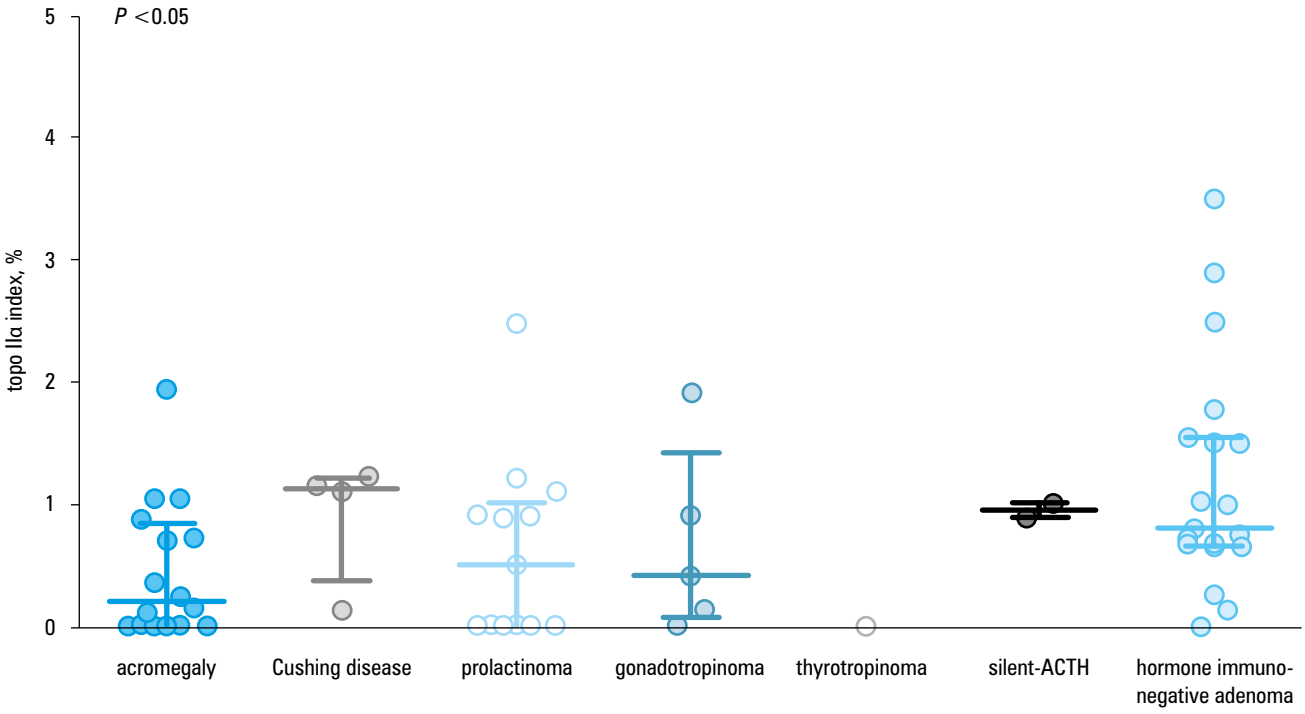
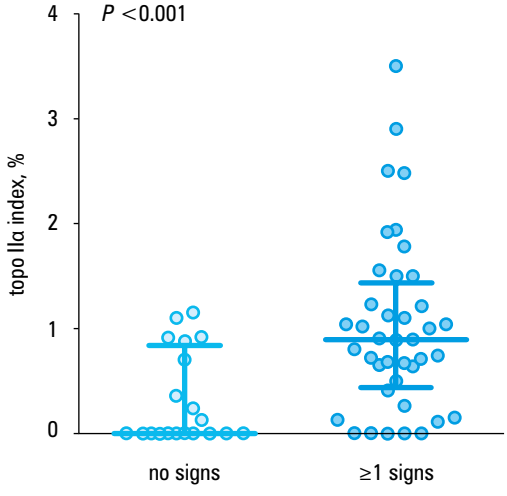


FIGURE 2 Topoisomerase IIα (topo IIα) expression in patients with pituitary adenomas classified according to their final diagnosis; the median values and interquartile ranges (IQR) of the topo IIα index are as follows: acromegaly, 0.19% (IQR, 0.0–0.84); Cushing disease, 1.13% (IQR, 0.37–1.21); prolactinoma, 0.50% (IQR, 0.0–1.01); gonadotropinoma, 0.41% (IQR, 0.07–1.42); thyrotropinoma, 0.0% (IQR, 0.0); silent-ACTH hormone, 0.95% (IQR, 0.89–1.0); hormone immunonegative adenomas, 0.8% (IQR, 0.65–1.55) (analysis of variance)

FIGURE 3 Topoisomerase IIα (topo IIα) expression in patients with no signs or 1 or more signs of tumor invasiveness on magnetic resonance imaging (n = 60) (Mann–Whitney test)



3.5%, with a median value of 0.71% [0.0–1.1]. No differences in topo IIα expression with respect to patient age or sex (female, 0.71% [0.0–1.18] vs. male, 0.67% [0.13–1.04], $P > 0.05$) were observed.

The highest median values of the topo IIα index (1.13% [0.37–1.21]) were observed in ACTH-secreting pituitary tumors leading to Cushing disease, followed by silent-ACTH tumors (0.94% [0.89–1.0]), and hormone immunonegative adenomas (0.8% [0.65–1.55]). There were no significant differences in the median values of the topo IIα index between the different types of tumors (FIGURE 2). In patients with hormone immunonegative adenomas, the median value of the topo IIα index was significantly higher than that in those with hormone-secreting tumors (0.8% [0.65–1.55] vs. 0.41% [0.0–1.04]; $P < 0.05$).

In 32 of the 60 patients (53.3%) with documented visual defects, the median value of the topo IIα labeling index was higher compared with patients

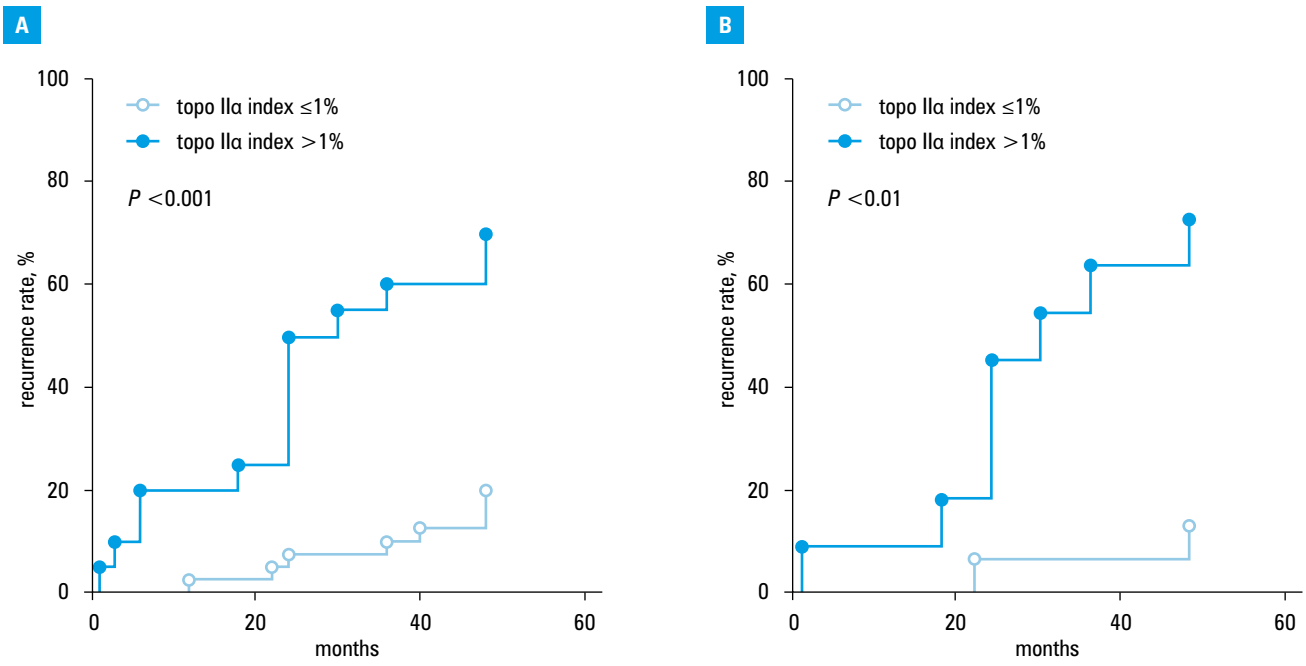


FIGURE 4 Kaplan–Meier plots of correlation between the recurrence or progression of pituitary adenoma on magnetic resonance imaging and the topo IIα index in patients classified according to the values of the topo IIα index; **A** – all patients: topo IIα index >1% (14 of 20 patients; recurrence of 70.0%); topo IIα index ≤1% (8 of 40 patients; recurrence of 20.0%); **B** – patients with hormone immunonegative adenomas: topo IIα index >1% (6 of 8 patients; recurrence of 75%); topo IIα index ≤1% (2 of 11 patients; recurrence of 18.2%)

without such symptoms (0.89% [0.18–1.54] vs. 0.43% [0.0–0.92], P <0.05).

In patients with visual field defect, the median value of the topo IIα index was higher than that in patients with normal visual field (0.89% [0.15–1.55] vs. 0.5% [0.0–0.97]; P <0.05).

The mean value of the largest tumor dimension was 25.1 ±17.6 mm (TABLE 1). In pituitary adenomas, the value of the topo IIα index correlated with tumor size (r = 0.31; P <0.05). Higher values of the topo IIα index were observed in macroadenomas as compared with microadenomas (0.73% [0.13–1.2] vs. 0.19% [0.0–0.97]; P <0.05).

Significant differences were found between the median topo IIα index in patients with invasive tumors (TABLE 1) compared with patients without such tumors (0.89% [0.43–1.43] vs. 0.0% [0.0–0.84]; P <0.001; FIGURE 3).

The logistic regression model showed that a topo IIα labeling index exceeding 1% in hormone immunonegative adenomas was associated with the highest risk of developing adenomas invading the cavernous sinus (OR, 0.23; 95% Cl: 0.07–0.80; P <0.02).

Expression of topo IIα in patients with local tumor recurrence or with regrowth of the postsurgical adenoma residue, as shown by MRI, was significantly higher compared with other patients (1.12% [0.7–1.8] vs. 0.38% [0.0–0.88]; P <0.001).

The Kaplan–Meier plots showed a significantly higher recurrence rate for MRI-confirmed tumors in the group with the topo IIα index exceeding 1% compared with that with a topo IIα index of 1% or lower (P <0.001; FIGURE 4A). The same finding was observed in patients with hormone immunonegative adenomas (P <0.01; FIGURE 4B).

The RR of tumor recurrence in patients with topo IIα expression was not statistically significant. However, in patients with topo IIα expression exceeding 1%, an RR was 3.5 (95% CI, 1.8–6.9; P <0.001), ie, the RR of tumor recurrence was 3.5-fold higher.

In Cox multiple regression analysis, only topo IIα expression exceeding 1% remained an independent predictor of tumor recurrence or progression on MRI (TABLE 2).

At the cut-off level of a topo IIα index of 1%, topo IIα expression showed 63.6% sensitivity and 86.8% specificity in predicting tumor recurrence or progression. A large area under the ROC curve (AUC, 0.76; 95% CI, 0.62–0.90; P <0.001) indicated high significance of topo IIα expression in predicting tumor recurrence or progression (FIGURE 5).

Expression of topo IIα was not significantly higher in patients with hormone secretion recurrence compared with other patients (1.04% [0.0–1.21] vs. 0.65% [0.0–1.01], P >0.05). topo IIα expression was not related with the risk of hormone secretion recurrence (RR, 1.0; 95% CI, 0.4–2.7; P >0.05), also in patients with the topo IIα index exceeding 1% (RR, 2.3; 95% CI, 0.9–5.4; P >0.05).

In patients with acromegaly treated with octreotide LAR before the surgery, the mean topo IIα index was significantly lower (0.0% [0.0–0.22]) than that in patients who did not receive such treatment (0.71% [0.17–1.0], P<0.05).

In patients with prolactinoma, higher values of the topo IIα index (but not significantly) were observed in patients not treated with bromocriptine before the surgery compared with patients pretreated with this dopamine agonist (0.9% [0.0–1.21] vs. 0.0% [0.0–0.91]).

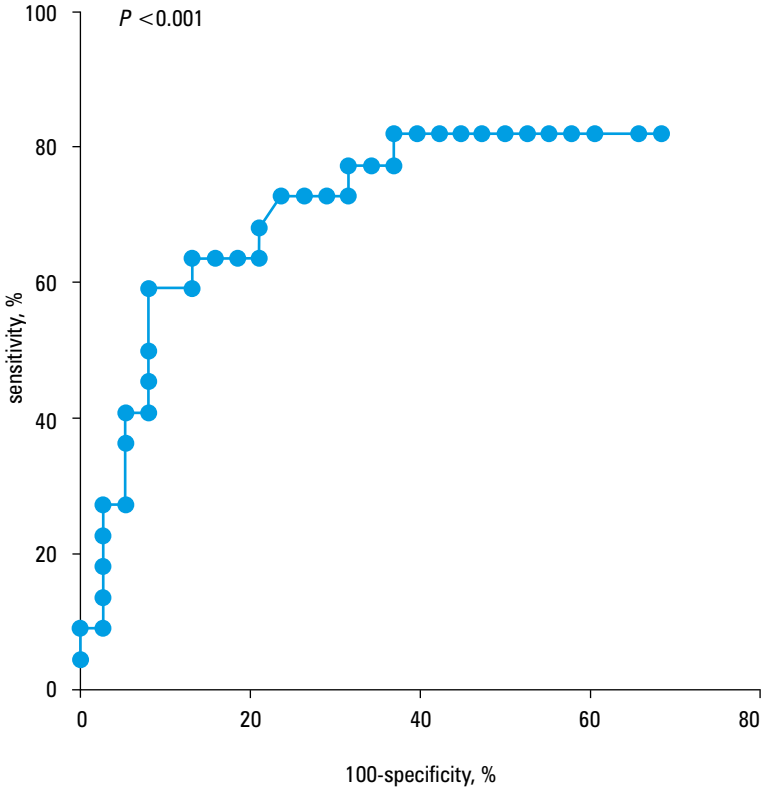


FIGURE 5 Receiver characteristic operating curve for topoisomerase IIα expression as predictor of tumor recurrence or progression, confirmed by magnetic resonance imaging

DISCUSSION In our study, we investigated topo IIα expression as a proliferation marker of pituitary tumors in patients who underwent neurosurgery. We evaluated a relationship between the topo IIα labeling index and demographic data of patients as well as tumor features to establish the prognostic value of topo IIα in predicting tumor invasiveness. We examined topo IIα expression in the context of tumor progression or recurrence and indication for reoperation or radiotherapy. We also analyzed the effect of preoperative treatment with somatostatin analogues on the topo IIα index in patients with acromegaly, and with dopaminergic agonists in patients with prolactinoma. So far, no prognostic advantage of topo IIα over Ki-67 has been shown.[16,17,25]

Pituitary tumors are usually benign and slowly growing and present no clinical manifestations, as evidenced by the discrepancy between the number of symptomatic adenomas and the number established on autopsy.[26] Local invasion and infiltration of the adjacent structures as well as postoperative regrowth or maintanance of hormonal function are potential indicators of aggressiveness.[27-30] In order to treat patients more effectively, rather than wait to confirm tumor recurrence by MRI, new markers of invasiveness and proliferation of pituitary adenomas are being sought to identify patients with atypical pituitary adenomas. In our group of 60 patients, 73% expressed topo IIα compared with 76% of the patients reported by Vidal et al.[16]

In agreement with Suzuki et al.[15] and Wolfsberger et al.,[17] we found that topo IIα expression did not depend on patient age. However, Wolfsberger et al.[17] found that female sex is significantly associated with a higher topo IIα index. Vidal et al.[16] reported a negative correlation between topo IIα expression and patient age. However, our study group differed from those in the above studies in the number of patients and the spectrum of adenomas analyzed.

In our study, topo IIα expression was higher in macroadenomas and correlated with tumor size, in agreement with the results reported by Suzuki et al.[15] Wolfsberger et al.[17] observed no correlation between topo IIα expression and tumor size, while Vidal et al.[16] suggested a negative correlation.

In hormone immunonegative adenomas, topo IIα expression was higher compared with that in other tumors. In particular, we observed a high topo IIα index in large adenomas compressing the optic chiasm and penetrating the cavernous sinus. On the basis of MRI findings and hormonal test results, it may be concluded that high topo IIα index values may be observed predominantly in nonfunctioning macroadenomas.

Our results concur with those of Saeger et al.[25] who evaluated the expression of Ki-67, topo IIα, and cyclin D_3 as proliferation markers in hormonally inactive pituitary adenomas.

In studies by Vidal et al.[16] and Wolfsberger et al.,[17] which involved larger groups of patients, the highest topo IIα expression levels were observed in pituitary carcinomas, silent-ACTH adenomas, prolactinomas, somatotropinomas, and silent subtype 3 adenomas. The results of our study were slightly different. A large dispersion in topo IIα index values observed in our relatively small group of patients with diverse types of pituitary adenomas and no pituitary carcinoma may have affected the results of our statistical analysis.

We found the evaluation of visual field to be a significant clinical indicator of pituitary tumor invasiveness that correlates with topo IIα expression. Visual field impairment was observed in 65% of our patients with macroadenomas, which was consistent with the correlation between topo IIα expression and tumor size. Visual field impairment in up to 74% of adenoma patients was reported by Thomas et al.[31]

Tumor recurrence or progression in patients undergoing transsphenoidal surgery was observed in 30.8%[6] to 46%[28] of the cases. Over a 4-year follow-up, we observed tumor recurrence or progression in 36.7% of the cases, as shown by MRI, which was most likely due to a large tumor size and nonradical surgery.

We found significantly higher topo IIα expression in patients with tumor recurrence or progression, indicating that the predictive factor of tumor regrowth is represented by a high value of the topo IIα index rather than by topo IIα expression itself. While no markers of an increased risk of recurrence have been established so far, our novel finding is that the topo IIα labeling index exceeding 1% predicts pituitary adenoma regrowth. The multiple regression analysis showed that the topo IIα index exceeding 1%

is an independent predictor of MRI-confirmed tumor recurrence or progression. Therefore, our study suggests that patients with the topo IIα index exceeding 1% are at a higher risk of tumor recurrence, and should thus be monitored more frequently and referred for radiotherapy early.

In line with the results reported by Suzuki et al.[15] and Vidal et al.,[16] we showed higher topo IIα index values in tumors that compressed or infiltrated the sella turcica and cavernous sinus compared with tumors without such features.

Preoperative treatment with somatostatin analogues in patients with acromegaly results in a significant decrease in topo IIα expression. Somatostatin receptors are not expressed exclusively in the pituitary cells. They are targeted in diagnosis and therapy in numerous diseases.[32,33] The use of somatostatin analogues, apart from achieving tumor shrinkage and better metabolic balance, also improves the efficiency of neurosurgery.[34-36] Low topo IIα index values in our patients treated with octreotide LAR provide evidence of their effectiveness, at the molecular level, in controlling GH-producing adenomas. Vidal et al.[16] drew similar conclusions concerning topo IIα expression in patients who received preoperative treatment with somatostatin analogues.

High topo IIα expression may be helpful in identifying adenohypophyseal tumors responsive to antiproliferative therapy. The possibility exists to introduce agents inhibiting the expression of topo IIα in hormone immunonegative adenomas where pharmacotherapy is currently limited.[37-39] In our study, these tumors showed the highest topo IIα expression levels and a high recurrence rate.

It is worth noting that somatostatin analogues and dopamine agonists have been shown to be efficient in about 12% and 27.6% of the patients, respectively, in nonfunctioning pituitary adenomas, as reported by Colao et al.[40] We have shown this treatment to effectively decrease topo IIα expression. However, there are currently insufficient evidence-based data to clearly recommend somatostatin analogues and dopamine agonists for treatment of nonfunctioning pituitary adenomas.

The analysis of immunocytochemistry results and better understanding of the subcellular mechanism that underlies pituitary tumor development will allow to establish new markers of tumor aggression and novel targeted therapies.

In conclusion, the topo IIα labeling index exceeding 1% may be used as a prognostic factor for the recurrence or progression of pituitary tumors, especially in hormonally inactive adenomas. topo IIα expression correlates with tumor size and degree of tumor invasiveness or with compression of anatomical structures around the sella turcica. Topo IIα may constitute a marker that enables to select patients with potentially aggressive pituitary adenomas for further therapy. Use of somatostatin analogues in patients with acromegaly inhibits topo IIα expression, providing molecular evidence for the effectiveness of these analogues.

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Contribution statement MT-M and AHD conceived the idea of the study. MT-M coordinated fundingfor the project. MT-M, AB-W, GS, and FG contributed to the design of the research. All authors were involved in data collection. GS, AB-W, and FG prepared statistical analysis and presentation of the data. AB-W prepared the manuscript, references, and edited the final version of the manuscript. All authors approved the final version of the manuscript.

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ARTYKUŁ ORYGINALNY

Topoizomeraza IIα jako czynnik prognostyczny w guzach przysadki

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SŁOWA KLUCZOWE

agresywny guz przysadki, biomarker, topoizomeraza IIα

STRESZCZENIE

WPROWADZENIE W guzach przysadki poszukuje się markerów proliferacji i progresji guza, które miałyby znaczenie dla planowania dalszego leczenia i monitorowania.

CELE Badano ekspresję topoizomerazy IIα (topo IIα) w różnych gruczolakach przysadki, aby ocenić jej przydatność jako czynnika prognostycznego.

PACJENCI I METODY W badaniu retrospektywnym wzięło udział 60 pacjentów (średnia wieku 46,7 ±17,6 roku) poddanych operacji guza przysadki. Oceniono immunohistochemicznie ekspresję topo IIα i porównano z cechami guza w badaniu histopatologicznym, objawami klinicznymi, obrazem MR i pooperacyjnym nawrotem lub progresją guza.

WYNIKI Ekspresję topo IIα stwierdzono w 44 z 60 (73%) badanych gruczolaków przysadki. Najwyższe wartości indeksu topo IIα obserwowano w guzach wydzielających hormon adrenokortykotropowy (*adrenocorticotropic hormone* – ACTH; mediana 1,13% [0,37–1,21], następnie w guzach „silent-ACTH" (0,94% [0,89–1,0]) oraz w gruczolakach niebarwiących się immunohistochemicznie na obecność hormonów przysadki (0,8% [0,65–1,55]). Nie stwierdzono różnicy w ekspresji topo IIα w zależności od wieku lub płci pacjentów. Stwierdzono znamienne zależności między wartością indeksu topo IIα a wielkością guza, jego inwazyjnością, nieprawidłowym badaniem okulistycznym i nawrotem guza w dalszej obserwacji po operacji. U pacjentów z indeksem topo IIα większym niż 1% stwierdzono 3,5-krotnie większe ryzyko względne nawrotu guza w porównaniu z pacjentami z indeksem topo IIα poniżej 1% (95% CI: 1,8–6,9; p <0,001). W grupie pacjentów z akromegalią leczonych analogami somatostatyny przed operacją obserwowano mniejszą medianę wartości indeksu topo IIα niż u pacjentów nieleczonych (odpowiednio 0,0% [0,0–0,22] *vs* 0,71% [0,17–1,0]; p <0,05).

WNIOSKI W badanej grupie pacjentów indeks topo IIα powyżej 1% był czynnikiem prognostycznym nawrotu lub progresji guza, szczególnie w grupie pacjentów z gruczolakami niewydzielającymi. Wskazuje to pacjentów, którzy powinni być zakwalifikowani do intensywnego leczenia pooperacyjnego. Zastosowanie analogów somatostatyny w akromegalii hamuje ekspresję topo IIα, co jest molekularnym dowodem skuteczności tych analogów.

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