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Tamoxifen. A treatment for meningioma?

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ABSTRACT

Background: No large-scale study evaluating the usefulness of tamoxifen after meningioma surgery has been undertaken.
Methods: We processed the French Système National des Données de Santé (SNDS) database using an algorithm combining the type of surgical procedure and the International Classification of Diseases to retrieve cases of meningiomas operated between 2007 and 2017. Survival analyses were performed using a matched cohort study.
Results: 251 patients treated by tamoxifen were extracted from a nationwide population-based cohort of 28 924 patients operated on for a meningioma over a 10-year period. 94% were female and median age at meningioma first surgery was 57 years IQR[47–67]. Tamoxifen treatment median duration was 1.4 years IQR[0.4–3.2]. Tamoxifen treatment median cumulative given dose was 11.4 gs, IQR[3.6–24.9]. There was a strong positive correlation between treatment duration and cumulative dose (τ=0.81, p<0.001). 6% of the patient had to be reoperated for a meningioma recurrence and 26.3% had radiotherapy. OS rates at 5 and 10 years were: 92.3%, $_{95\%}$CI[90.3–94.3] and 81.3%, $_{95\%}$CI[75.2–88] respectively. These 251 patients were matched by gender, age at surgery and grade with the same number of subjects within the nationwide cohort. Nor overall (HR=1.46, $_{95\%}$CI [0.86- 2.49], p=0.163) or progression-free survival (HR=1.2, $_{95\%}$CI[0.89- 1.62], p=0.239) were significantly improved by the tamoxifen treatment.
Conclusion: Using this unique database, in the setting of breast cancer, we could not conclude on a favourable effect of tamoxifen to prevent recurrence after meningioma surgery or to increase meningioma-related survival even in case of prolonged treatment duration or high cumulative given dose.

Introduction

Meningiomas are usually non-malignant, slow-growing neoplasms thought to arise from the meningothelial cells of the arachnoid layer. They are the most common intracranial extracerebral tumours accounting for 36.8% in the Central Brain tumor Registry of the United States (CBTRUS) [1]. The 2016 World Health Organisation (WHO) classification of tumours affecting the central nervous system (CNS) recognises three grades of meningiomas [2]. WHO grade I or benign meningiomas have usually a good outcome [3–5]. WHO grade III or malignant meningiomas are rare and aggressive neoplasms with a poor prognosis [6,7]. Behaviour and outcome of atypical - WHO grade II are intermediate [8,9]. Management options include regular monitoring especially for incidental meningioma, symptom control, surgical excision, radiotherapy (RT), and stereotactic radiosurgery (SRS). Complete surgical resection is the treatment of choice for all meningiomas. Further optimal management is difficult to establish; the role of post-operative RT as standard adjuvant treatment remaining controversial apart for malignant meningiomas [7–9]. Most meningiomas show an indolent course after resection but some have an aggressive behaviour not solely related to a high histopathological grade. Those relapsing tumour may required reoperation and / or RT or lead the patient to death when refractory to those treatments.

Almost all meningiomas are sporadic and their incidence in France is

Abbreviations: AMDB, Administrative medical databases; CCAM, Classification Commune des Actes Médicaux; CI, Confidence Interval; CNS, Central Nervous System; ICD, International Classification of Diseases; IQR, Interquartile Range; HR, Hazard Ratio; SKB, Skull Base; SNDS, Système National des Données de Santé; WHO, World Health Organization.

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about 5/100 000 persons per year [3,5]. Ionizing radiation is the only unequivocal risk factor identified although others have been suspected. Evidence suggests the influence of sexual hormones as meningiomas are known to be hormone-sensitive and usually express progesterone receptors but rarely oestrogen receptors. Hormone exposure has been implicated in the development of meningioma as evidenced by a female preponderance or tumour growth during pregnancy [10]. Exposure over one year to high dose of cyproterone acetate which has anti-androgenic, progestagenic and antigonadotropic effect, has been shown to increase the risk of meningioma [11]. Observations also suggest that oestrogen may play a role in the development of meningioma.

Administrative medical databases (AMDB) are massive repositories of collected healthcare data for various purposes. AMDB provide a variety of already stored data with a constant and often increasing ongoing collection process [12]. They encompass very large population and frequently the whole nation, ensuring high statistical power without biases related to the representativity of a sample. AMDB can be used to conduct epidemiological studies and evaluate medical practices. Use of these databases is less expensive than conducting specific surveys in dedicated populations by providing rapid access to data gathered in a standardised format [13].

In that respect, the recent access opening of French nationwide health record database or SNDS (Système National des Données de Santé) is a great opportunity to carry out comprehensive health studies at the country level. The SNDS includes many information such as demographic data, medical and surgical procedure with linked and associated diagnoses or date of death [13]. The database representativeness is nearly perfect, since it includes the whole country's population of nearly 68 millions of inhabitants [13].

For aggressive meningioma, despite combined surgery and radiotherapy progression-free and overall survival are both impaired [14]. These outcomes have upheld the need for additional treatment such as chemotherapy. Only some candidates were promising in a small case series and high volume studies to solidify efficacy and safety profiles are still lacking [15].

Tamoxifen has been widely used to treat patients with oestrogen receptor-positive breast cancer. Tamoxifen acts as a selective oestrogen receptor modulator or as a partial agonist of the oestrogen receptors. It has mixed oestrogenic and antioestrogenic activity, with its profile of effects differing by tissue. Two studies suggest that tamoxifen may prevent the development of meningioma [16,17].

Ji et al. evaluated the association of tamoxifen with meningioma in a Swedish population of 227 535 breast cancer patients between 1961 and 2010. For women without tamoxifen exposure, the risk of meningioma was significantly increased, with an standardized incidence ratios of 1.54, $_{95\%}$CI[1.30–1.81] *vs.* 1.06, $_{95\%}$CI[0.84–1.32] for those with tamoxifen exposure suggesting that tamoxifen may prevent the development of meningioma [17]. Sun et al. found a trend of decreased risk of meningioma development amongst Taiwanese breast cancer survivors treated with tamoxifen, especially for those with a long duration or a high dosage of tamoxifen therapy [16]. Although this could be explained partially by the hormone factor, they advised further research and confirmatory evidence before any recommendations could be made. Following conclusions made by these two studies, we aimed at assess the usefulness of tamoxifen after meningioma surgery in the setting of breast cancer using this unique SNDS database, as to date, such a research has never been achieved in France where around 3 000 patients are operated on for a meningioma each year.

Objective

The aim of this study was to investigate progression-free (PFS) and overall survival (OS) of patients treated by tamoxifen and operated on for a meningioma using population-based cohort of patients and matched controls, drawn from the French National Healthcare (SNDS) database.

Material and methods

We performed a nationwide descriptive observational and analytic retrospective study using a matched cohort design. Incidental meningiomas never operated were not considered in this study; only surgically treated tumours were taken into account. Data were extracted from the Système National des Données de Santé (SNDS), the national French medico-administrative database. The age and sex of individuals included in the database, are representative of the French population, enabling selection of population-based controls. The high quality of SNDS diagnostic and prescription information has been reported elsewhere [13]. All patients who underwent the surgical resection of a meningioma between 2007 and 2017 were included. Direct identification of patients who underwent a surgery for meningioma is not possible. Therefore, we used an algorithm combining two variables: the type of the surgical procedure identified by the Common Classification of Medical Acts (CCAM) and the primary diagnosis according to the International Classification of Diseases (ICD-10) as described previously [3,18,19]. Meningioma were categorised into 7 anatomical locations according their dural base insertion after further categorisation of the 40 CCAM codes which aimed at described intracranial extracerebral tumour resection. Benign meningiomas were considered as corresponding to the D32 ICD-10 codes, atypical to D42 and malignant to C70. The patients who had tamoxifen treatment were identified using dedicated CIP codes which full list is available here: http://www.codage.ext.cnamts.fr/codif/bdm_it//fiche/index_lis_medisoc.php?p_code_cip=&p_nom_commercial=TAMOXIFEN&p_nb=33&p_site=AMELI&p_homol_ass=ass&p_homol_coll=coll}. We defined the first recorded date of meningioma surgery as the index date. Patients below 18 years were excluded. Progression was defined as any new treatment for meningioma recurrence *e.g.* redo surgery, radiotherapy or stereotactic radiosurgery. Causes of death ascertained from the death certificate were available for the years 2008 to 2016.

Statistical methods

We analysed data that were fully anonymised. Continuous variables are reported as medians and interquartile ranges (IQR); categorical variables are reported as frequencies and proportions. To compute the PFS, redo surgery, RT, SRS or death were treated as event and the time between the first surgery and this event was measured. Overall survival (OS) was measured from the date at meningioma first surgery to the date of last follow-up or death [20]. We used a time-to-event framework with Kaplan–Meier method to estimate the PFS and OS and the Mantel Cox log-rank test to compare survival curves. We censored records at the end of a participant's registration, the last date of SNDS data collection, or death. Cox proportional hazards regression was implemented to identify predictors of death and, to estimate Hazard Ratio (HR) with 95% Confidence Intervals [$_{95\%}$CI] [21]. We obtained matched controls for comparison from the nationwide population-based cohort of 28 673 patients who underwent meningioma resection and did not had tamoxifen treatment. We matched controls for gender, index age, tumour location and grade using the optimal matching method without replacement using the MatchIt package [22,23]. All tests were 2-sided and statistical significance was defined with an alpha level of 0.05 ($p < 0.05$). Analysis was performed with both the SAS Enterprise the R programming language and software environment for statistical computing and graphics (R version 4.0.3 (2020–10–10)) and the survival package amongst others [24,25]. The statistical programme and workflow was written in R Markdown v2 with RStudio® for dynamic and reproducible research [26].

Compliance with ethical standards

This study was conducted according to the ethical guidelines for epidemiological research in accordance with the ethical standards of the

Helsinki Declaration (2008), to the French data protection authority (CNIL) an independent national ethical committee, authorisation number: 2,008,538; to the RECORD guidelines for studies conducted using routinely-collected health data and, according to the SAMPL Guidelines [27–29]. Informed consent was not required due to the retrospective nature of the study. The SNDS encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers.

Results

Population description

251 patients treated by tamoxifen were extracted from a nationwide population-based cohort of 28 924 patients operated on for a meningioma over a 10-year period. 94% were female and median age at meningioma first surgery was 57 years IQR [47 - 67]. Tamoxifen treatment median duration was 1.4 years IQR[0.4 - 3.2]. Tamoxifen treatment median cumulative given dose was 11.4 gs, IQR[3.6 - 24.9]. There was a strong positive correlation between treatment duration and cumulative dose (Kendall correlation coefficient $\tau = 0.81$, $p < 0.001$). Only 4.8% of the patients of our cohort took tamoxifen for 5 years or more. Characteristics of the tamoxifen treatment duration and cumulative given dose related to the date of meningioma surgery are given in table 1. Cranial convexity (22.7%) and middle skull base (24.7%) were the most common locations. 93.6% of the tumours were benign and 3.2% malignant. 6% of the patient had to be reoperated for a meningioma recurrence and 26.3% had radiotherapy. Characteristics of the tamoxifen cohort and controls are given in Table 2. Cranial convexity was the most common (22.3%) location followed by posterior skull base (11.2%). Spinal tumours accounted for 8.2%. Benign meningioma represented 94%, atypical 2.8% and malignant 3.2%. 5.6% of the patients underwent two or more surgeries and 7% had two or more meningioma locations *e. g.* spine, posterior skull base (SKB) then anterior SKB. Median follow-up was 6.2 years $_{95\%}$CI[5.6 - 6.8].

Survival analysis

At data collection, 33 patients were dead (13.1%) and median age at death was 64.1 years, IQR[54.3 - 74.2]. Analysis of death causes found 3 patient (1.2%) with a meningioma-related death in the tamoxifen group *vs.* 1 patients (0.4%) in the control group (Fisher $p = 0.623$). For the tamoxifen cohort, OS rates at 5 and 10 years were: 92.3%, $_{95\%}$CI[90.3 - 94.3] and 81.3%, $_{95\%}$CI[75.2 - 88] respectively (Fig. 1). amongst this cohort of 251 patients treated by tamoxifen, nor a long treatment duration after the meningioma surgery or a high cumulative given dose, did improve PFS or OS. Nor overall (HR= 1.46, $_{95\%}$CI[0.86 - 2.49], $p = 0.163$) or progression-free survival (HR= 1.2, $_{95\%}$CI[0.89 - 1.62], $p = 0.239$) were significantly influence by the tamoxifen treatment in the matched data analyse (Fig. 2). Neither a treatment prolonged over 1.4 years nor a tamoxifen cumulative given dose greater than 11.4 gs did influence PFS or OS.

Table 1
Characteristics of the tamoxifen treatment received by the 251 patients, for the whole cohort and according the periods before and after the surgery.

Characteristics	*n* or median	% or IQR[1]
Whole cohort		
n=	251	0.9%
Duration	1.4 years	[0.4 - 3.2]
Cumulative dose	11.4 gs	[3.6 - 24.9]
Treatment given before the surgery		
n=	150	0.6%
Duration	1.7 years	[0.5 - 3.6]
Cumulative dose	14.4 gs	[3.7 - 29.2]
Treatment given after the meningioma surgery		
n=	146	0.6%
Duration	1.5 years	[0.7 - 3.5]
Cumulative dose	13.2 gs	[4.9 - 26.9]
Time of treatment initiation following meningioma resection	2.6 years	[0.4 - 1.7]
Treatment before and after the surgery		
n=	45	0.2%
Duration	3.5 years	[1.9 - 4.9]
Cumulative dose	26.4 gs	[16.2 - 36]

[1] IQR: Inter Quartile Range

Table 2
Characteristics comparison of the 251 patients treated by tamoxifen *vs.* 251 matched controls after propensity score matching of selected variable.

Characteristics	Treatment by tamoxifen n= 251		No tamoxifen (Matched data) n= 251		*p*-value
	n or median	% or IQR[1]	*n* or median	% or IQR	
Gender female	236	94%	242	96.4%	Matched
Median age at surgery[2]	57 years	IQR[47 - 66]	56 years	IQR[49 - 66]	Matched
Age at surgery[2]					
• <50 years	92	36.7%	78	31.1%	-
• > 50 years - < 59 years	56	22.3%	74	29.5%	-
• > 60 years - < 69 years	64	25.5%	64	25.5%	-
• > 70 years	39	15.5%	35	13.9%	Matched
Count of surgeries for meningioma					
Solely one	237	94.4%	235	93.6%	-
Two or more	14	5.6%	16	6.4%	0.85
Count of different location					
Solely one	233	92.8%	233	92.8%	-
Two or more	18	7.2%	18	7.2%	1
Location[2]					
• Cranial convexity	57	22.7%	53	21.1%	-
• Middle skull base	62	24.7%	66	26.3%	-
• Anterior skull base	33	13.1%	32	12.7%	-
• Posterior skull base	24	9.6%	27	10.8%	-
• Parasagittal	31	12.4%	25	10%	-
• Falx cerebri	25	10%	21	8.4%	-
• Spine	18	7.2%	25	10%	0.86
Venous sinus invasion	33	13.1%	27	10.8%	0.49
Pre-operative embolisation	11	4.4%	9	3.6%	0.82
Dura mater reconstruction	49	19.5%	61	24.3%	0.24
Cranioplasty	23	9.2%	14	5.6%	0.17
CSF shunt	4	1.6%	3	1.2%	1
Tumour grading					
• Benign	235	93.6%	237	94.4%	-
• Atypical	8	3.2%	7	2.8%	-
• Malignant	8	3.2%	7	2.8%	Matched
Redo surgery for recurrence	15	6%	18	7.2%	0.72
RT	66	26.3%	49	19.5%	0.089
SRS	7	2.8%	6	2.4%	1
Neoplasm					
• Breast	232	92.4%	245	97.6%	-
• Colon	16	6.4%	6	2.4%	-
Death	33	13.1%	19	7.6%	0.057
Meningioma-related death	3	1.2%	1	0.4%	0.62

[1] IQR: Inter Quartile Range.
[2] Of the first surgery.

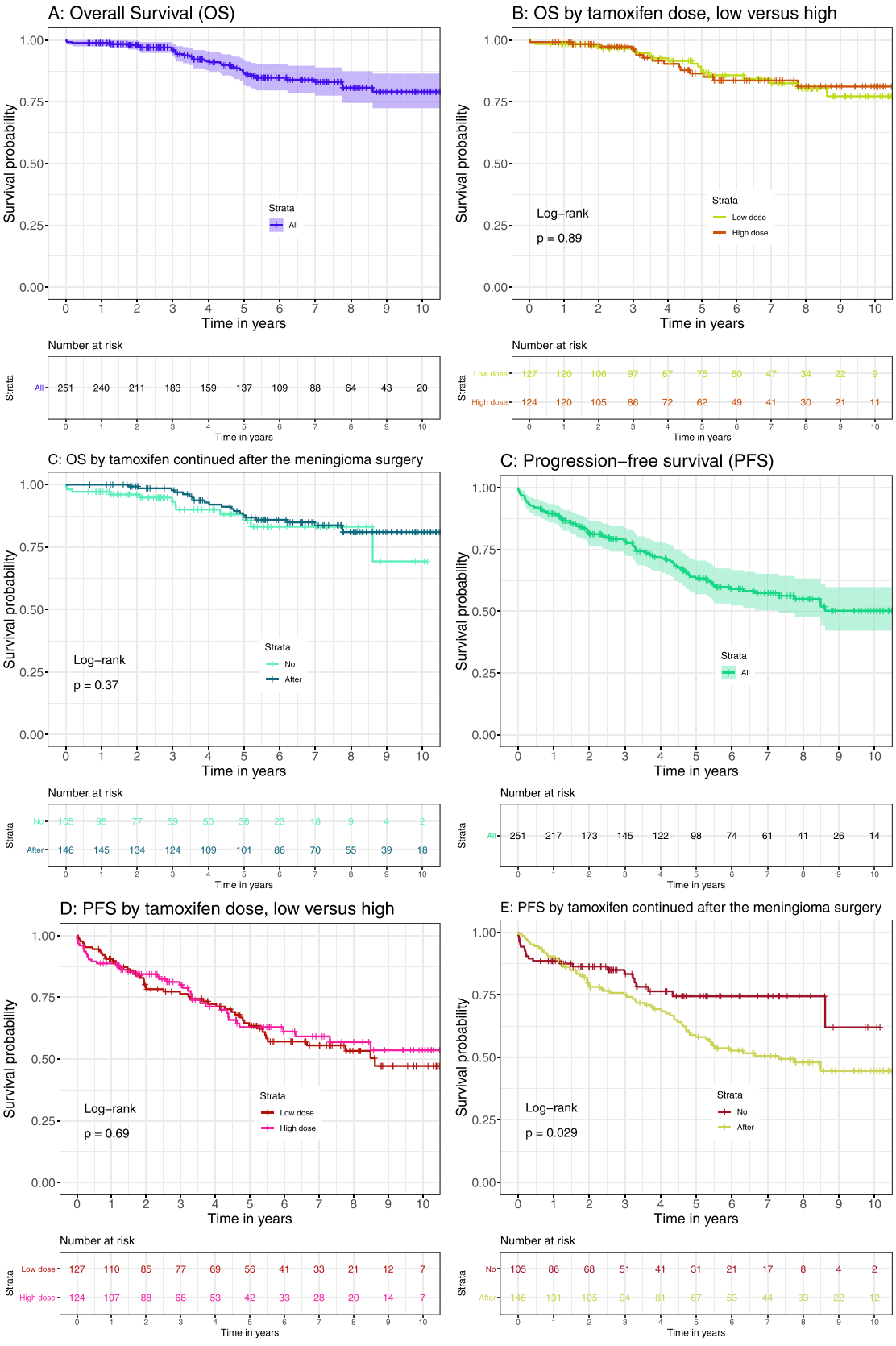

Fig. 1. Kaplan-Meier overall and progression-free survival curves comparison for the 251 patients treated by tamoxifen.

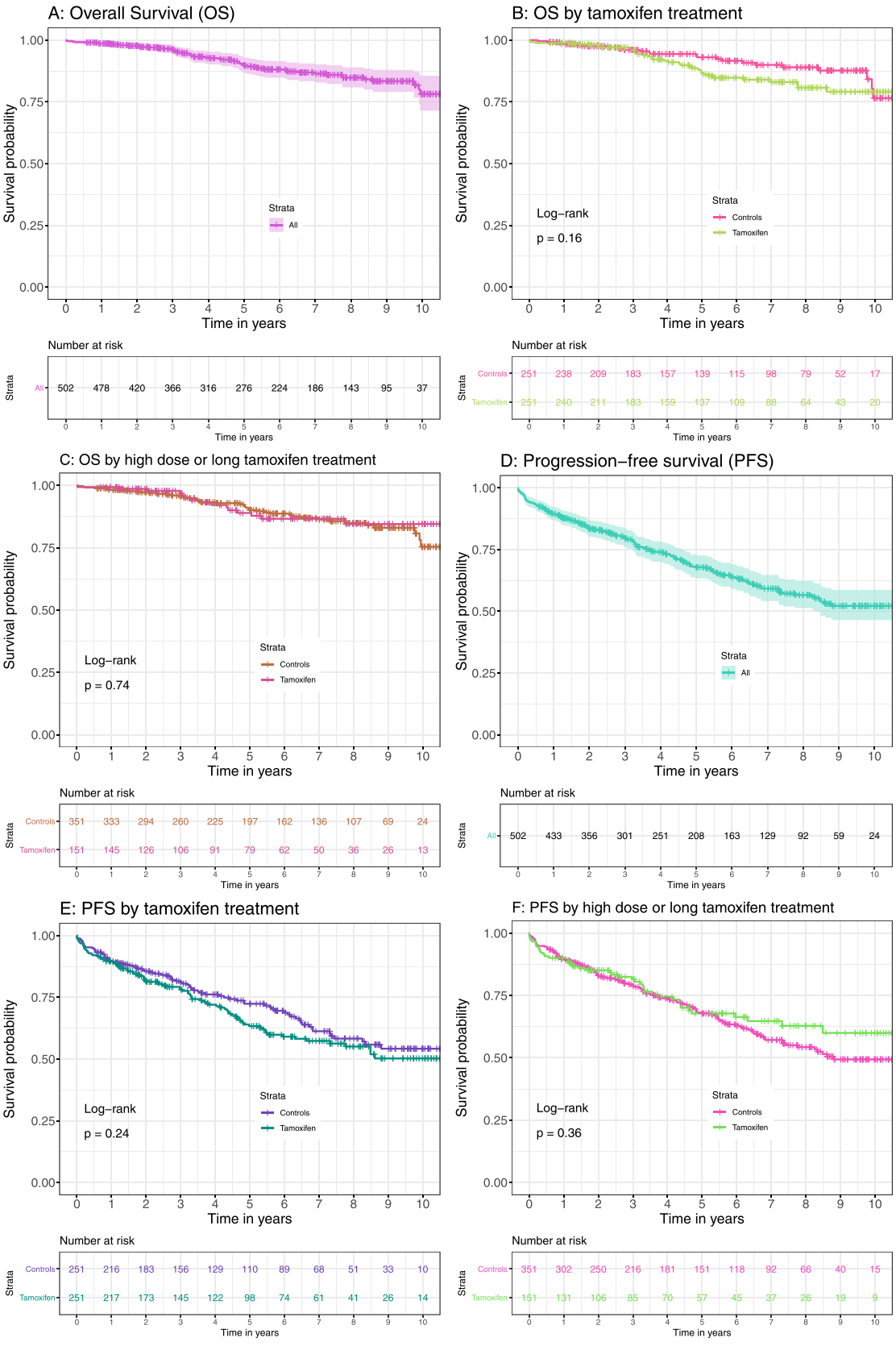

Fig. 2. Kaplan-Meier overall and progression-free survival curves comparison of the 251 patients who received tamoxifen *versus* the 251 matched controls patients.

Discussion

In this large population-based cohort of patients treated by tamoxifen for breast cancer who underwent meningioma surgery, the risk of recurrence and death was not reduced compared with controls patients who did not received tamoxifen. Our report is the first large-scale pragmatic study to assess the effect of tamoxifen on outcome after meningioma resection in the context of usual care settings. Studies relying on AMDB are useful for evaluating treatment strategies as they offer another insight compared to results of selected retrospective data. AMDB allow inclusion of large patients' groups that may be ineligible for trials due to older age and co-morbidities.

Strengths and limitations

Studies bases on AMDB are made of what is available in themselves, sometimes limiting the potential to explore interesting associations. However, for the variables included, it is possible to collect large amounts of data in a population-based setting. The strengths of the SNDS reside both in the high number of patients and in the exhaustive data available from every hospital in France. The SNDS which covers 97.2% of the French population is one of the largest AMDB in the world [13]. Moreover, important variables such as the quality of resection are not recorded [30]. Despite some limitations, the SNDS is an invaluable tool to evaluate tumour outcome and offers incomparable means to explore associations with other pathology, medication or combined surgical treatment which has and could not be assessed otherwise. The retrospective nature of this study, together with the lack of clarity regarding treatment rationales and non-homogeneous management strategies without random assignment, needs to be considered when evaluating the results.

Various hormone therapies have been investigated for the treatment of meningiomas based on the finding that these tumours commonly express progesterone and sometimes oestrogen receptors. However, none has shown a significant effect so far such as for Mifepristone, a progesterone receptor antagonist, whose initial therapeutic benefit was suspected in small-scale studies. However, this was not confirmed in multicentre randomised phase III clinical trial in which 180 patients were enroled.

Tamoxifen and meningioma

Tumour relapse represents a significant challenge in the management of meningioma in which the risk of recurrence increases with the histopathological grade. Surgery and/or RT remain the mainstay, but each has their limitations and despite advancement in surgical and irradiation techniques, aggressive meningiomas do usually not respond to these treatments. The search for effective systemic therapy continues as all of the initially promising molecules have failed to produce sustained and successful results. The link between breast cancer and meningioma remains controversial: several studies have detected an association which was otherwise not confirmed by others. A potential connection is likely related to common aetiological factors such as genetic predisposition, endogenous and / or exogenous hormones exposure. It has been shown that hormonal factors may be involved in meningioma growth with hormone replacement therapy increasing the risk of meningioma [10,11,31]. Previous studies have found that meningioma tend to express frequently progesterone receptors but less commonly oestrogen ones suggesting that receptors antagonists may therefore inhibit tumour growth [16]. Following encouraging in-vitro studies, anti progesterone / oestrogen therapy has been proposed to treat aggressive meningioma.

Tamoxifen is usually prescribed in breast cancer patients with a daily dose of 20 mg for several years. All consensus statements from US, UK and European societies have recommended at least 5 years of tamoxifen for premenopausal and up to 5–10 years for postmenopausal women following breast cancer treatment. Sun et al. found that breast cancer patients receiving more than 1 500 days or a cumulative given dose greater than 26.32 gs of tamoxifen exhibited significantly decreased meningioma risk compared with breast cancer patients who had not received tamoxifen treatment (HR= 0.42, $_{95\%}$CI [0.19–0.91]/ HR= 0.44; $_{95\%}$CI [0.22–0.88]) [16]. Unfortunately, we could not demonstrate any favourable effect of tamoxifen on meningioma patients neither amongst the cohort of 251 patients nor after patients matching. However, the median tamoxifen treatment duration is much shorter in our study with 1.4 years, IQR[0.4 - 3.2] despite a median follow-up of 6.2 years, $_{95\%}$CI [5.6 - 6.8]. To verify our method, a test between the total cumulative given dose taken and the treatment duration found a strong positive correlation (Kendall correlation coefficient $\tau = 0.81, p < 0.001$) asserting that the low treatment duration found is indeed a correct finding. We do not have a clear explanation for this but one may be the interruption or the discontinuation of the tamoxifen treatment around the postoperative period. A significant number of patients took tamoxifen for only a short period, likely following treatment intolerance. Our cohort were treated by tamoxifen during a median time of 528 years, IQR[136.5 - 1170] which represents solely 35.2% of the 1 500 days, threshold found by Sun et al. above which breast cancer patients exhibited significantly decreased meningioma risk. Alike, the median cumulative given dose of 11.4 gs, IQR[3.6–24.9] received by our cohort reaches 43.3% of the 26.32 gs of tamoxifen, cumulative dose above which breast cancer patients exhibited also significantly decreased meningioma risk. By doing this propensity score matching study we wanted to analyse an observational data mimicking some of the characteristics of a RCT. If our results would have favoured a positive effect of tamoxifen on OS for meningioma patients, we may have set up a RCT to assert this finding. Ji et al. evaluated the association of tamoxifen with meningioma in the Swedish population and reported that women with breast cancer who did not use tamoxifen had increased meningioma incidence, whereas in breast cancer patients treated with tamoxifen, the incidence was nearly the same as that of the general population, which suggests that tamoxifen likely plays in preventing meningioma development [17]. However, no threshold treatment duration or cumulative given dose are given. In the light of these two studies, we decided to investigate on a large scale a potential effect of tamoxifen on meningioma using the SNDS database. Despite the fair number of patients enlisted, we failed to demonstrate a beneficial effect, including at high cumulative given dose. Compared to Sun et al. findings, only 15.5% of our patients had a treatment course above 1 500 days or a cumulative tamoxifen given dose over 26.32 gs (23.9%). In our study, those who were treated by tamoxifen for more than 528 days or with a cumulative dose of 11.4 gs did not show either a prolong PFS or OS.

Solely two small studies previously assessed tamoxifen on inoperable and/or recurrent meningioma [32,33]. Tamoxifen did not demonstrate efficacy amongst patients with ongoing meningioma disease progression: in a phase II study including 19 patients, only 3 showed a partial or minor response [33]. In another study included six patients, no significant improvement in tumour growth was noted under tamoxifen [32]. Considering our findings and previous results we can assert that tamoxifen is unlikely a effective treatment for meningioma. Recently, new distinct oncogenic pathways have been identified, laying the foundations for targeted therapies. Several drugs trials targeting key mechanisms of oncogenesis such as cell replication, hormonal mechanisms, aberrant cell signalling or angiogenesis have produced mixed result. As treatment of aggressive unresectable meningiomas remains unsolved, the development of effective therapy is necessary for such untreatable tumours which have often a poor outcome.

Conclusion

Using this unique database, in the setting of breast cancer, we could not conclude on a favourable effect of tamoxifen after meningioma surgery to prevent recurrence or to increase survival even in case of

prolonged treatment duration or high cumulative given dose.

Availability of data and material

Restricted

Code availability

On demand

Conflict of interest

None

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