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The Relationship Between Total Lesion Activity on ^{18}F Choline Positron Emission Tomography-Computed Tomography and Clinical Outcome in Patients with Castration-Resistant Prostate Cancer Bone Metastases Treated with ^{223}Radium

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Abstract

The aim of the study was to assess the correlation between metabolic response measured through positron emission tomography-computed tomography (PET-CT) with ^{18}F choline (^{18}F FCH) and overall survival (OS) in patients affected by bone lesions from metastatic castration-resistant prostate cancer treated with ^{223}Ra dichloride. Eleven subjects were subjected to PET-CT with ^{18}F FCH before and 1 month after ^{223}Ra treatment. Reduction in total lesion activity (ΔTLA) between pretreatment and post-treatment scan was determined and patients were divided into responders (ΔTLA >50%) and nonresponders (ΔTLA <50%). The OS of the entire cohort was 12.7 ± 3.8 months. Kaplan–Meier analysis showed that responders presented a significantly longer survival than nonresponders (16.5 ± 1.9 months vs. 10.5 ± 0.9 months, $p < 0.05$). Reduction in TLA after ^{223}Ra treatment seems to be correlated with a trend toward a longer survival.

Keywords: ^{18}F coline, metastatic castration-resistant prostate cancer, PET-CT, ^{223}Radium dichloride, targeted α therapy, total lesion activity

Introduction

^{223}Radium dichloride (^{223}Ra dichloride) has been recently introduced as α-particle emitting radiopharmaceutical approved for the treatment of symptomatic skeletal lesions from metastatic castration-resistant prostate cancer (mCRPC).

Which is the most appropriate imaging approach for monitoring the response to ^{223}Ra treatment is still a debated issue. Conventional radiological imaging (both computed tomography and magnetic resonance imaging) presents some limitations.[1] ^{18}F fluorodeoxyglucose (^{18}F FDG), the most commonly used radiopharmaceutical for positron emission tomography (PET), proved not sufficiently accurate for prostate cancer (PC). Therefore, other tracers have been introduced to overcome these drawbacks. In particular, ^{18}F choline (^{18}F FCH), a surrogate biomarker of phospholipids' synthesis, has been successfully applied for the detection of PC recurrence and metastases. However, few studies addressed the role of positron emission tomography-computed tomography (PET-CT) with ^{18}F FCH for the assessment of the response to treatment in mCRPC, especially as concerns ^{223}Ra dichloride. In a previously published report on 2 subjects affected by mCRPC treated with ^{223}Ra dicloride, the changes in bone metastatic activity, calculated as a reduction of at least 30% of the total lesion activity (TLA) between baseline ^{18}F FCH PET-CT scan and that performed after the third ^{223}Ra cycle, were found to have predictive value on patients' final outcome.[2]

The aim of this article was to further investigate the correlation between metabolic response, assessed through ^{18}F FCH PET-CT, and the final outcome in mCRPC patients subjected to therapy with ^{223}Ra dichloride.

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Materials and Methods

Patients

Clinical records of 11 patients (median age: 64.7 ± 10.5 years) affected by bone lesions from mCRPC and treated with ^{223}Ra dichloride at the Nuclear Medicine Department of ''Santa Maria Goretti'' Hospital between January 2016 and December 2018 were retrospectively evaluated. The inclusion criteria were (1) age >18 years; (2) an initial histopathology diagnosis of PC; (3) fulfillment of clinical criteria for CRPC according to the international guidelines;[3] (4) at least six symptomatic bone metastases and no known visceral metastases, except for malignant lymphadenopathy with <3 cm in the short-axis diameter, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0–2 and adequate hematological, liver, and renal function; and (5) PET-CT with ^{18}F FCH performed at baseline and within 1 month after the conclusion of ^{223}Ra treatment. This retrospective study was carried out according to the guidelines of the institutional ethic committee. The research was conducted according to the principles of the Declaration of Helsinki.

Treatment with ^{223}Ra dichloride

All the subjects included in the analysis were subjected to therapy with ^{223}Ra dichloride (Xofigo®), which consisted of 6 intravenous injections of the radiopharmaceutical at a standard dose of 55 kBq/kg at 4-week intervals until unacceptable toxicity or worsening of the overall PS. The use of androgen deprivation therapy continued during radionuclide treatment. Concomitant treatment with abiraterone and enzalutamide was not allowed. Patients were also receiving the best standard of care, including glucocorticoids and analgesics.

PET imaging with ^{18}F FCH

All subjects fasted at least 4 h before tracer administration and underwent PET-CT scan 60 min after the intravenous administration of 3.7 kBq/kg of ^{18}F FCH (^{18}fluoromethylcholine/Cholscan®). PET-CT device and the protocol of reconstruction have been described elsewhere.[4] The reconstructed data were transmitted to a nuclear medicine database, fused and displayed using a dedicated software (Advantage 4.7; GE Healthcare).

PET-derived parameters calculation

Metabolic active tumor volume (MATV) was defined on the pretreatment PET-CT scan using a dedicated software (PET VCAR; GE Healthcare). Every lesion was segmented with a threshold of 42% of the maximum standardized uptake value (SUV) within the bounding box of the lesion. TLA was calculated as the product of $MATV \times SUV_{mean}$. All the lesions were countered and the TLA considered was the sum of the TLA of each lesion. Change in TLA between pretreatment and post-treatment PET scans was calculated according to the following formula: [(pretreatment TLA−post-treatment TLA)/pretreatment TLA] × 100. Metabolic response was defined as a 50% or greater reduction in TLA between pretreatment and post-treatment PET scans.

Clinical and imaging follow-up post ^{223}Ra dichloride

After treatment, patients underwent monthly follow-up through clinical examination and laboratory tests and imaging follow-up by contrast-enhanced Computed Tomography (ceCT) and/or ^{18}F FCH PET-CT examination every 3 months. All patients were monitored until death. A biochemical (alkaline phosphatase [ALP] and prostate specific antigen [PSA]) response was defined as a reduction of ≥30% from the baseline values to the end of ^{223}Ra treatment.[5]

Statistical analysis

Overall survival (OS) was calculated by the Kaplan–Meier method, measured from the date of the first procedure to the death of the patients. Significance was established at $p < 0.05$.

Results

Clinical characteristics and treatments of the enrolled patients are summarized in Table 1. Among the 11 examined subjects, 7 completed all the scheduled 6 cycles, the remaining 4 subjects stopped the treatment before the completion of the scheduled cycles due to biochemical progression ($n = 3$) or worsening of the overall PS ($n = 1$).

The mean interval between baseline ^{18}F FCH PET-CT and the start of the treatment with ^{223}Ra dichloride was 12.4 ± 2.5 d, whereas the mean interval between the post-treatment PET-CT and the end of ^{223}Ra therapy was 15 ± 3.7 d.

At the pretreatment scan, all patients presented ^{18}F FCH avid lesions in the appendicular/axial skeleton without evidence of visceral involvement. The average pretreatment TLA was 425.1 ± 268.3 g and the average post-treatment TLA was 1573.3 ± 2772.7 g. According to metabolic response criteria, four patients (i.e., 36.4%) were responders: 3 of whom were with partial response and 1 was with complete metabolic response (Fig. 1).

The remaining 7 were nonresponders (i.e., 66.6%). Among them, at post-treatment PET-CT, 4 subjects presented exclusive skeletal progression (Fig. 2), 2 patients showed both skeletal progression and extraosseous localizations ($n = 1$ in adrenal gland and lymph nodes, $n = 1$ in spinal cord), and 1 showed partial response of the skeletal lesions but developed a painful muscular paraspinal metastasis and a gross abdominal lymphadenopathy (Fig. 3).

The OS of the entire cohort was 12.7 ± 1.1 months. When stratified according to metabolic response, Kaplan–Meier analysis showed that responders presented a significantly longer survival (16.5 ± 1.1 months, 95% CI: 14–19) than nonresponders (10.5 ± 0.9 months, 95% CI: 8–15), as shown in Figure 4. A perfect agreement was found between metabolic and biochemical response (i.e., PSA decline).

Discussion

To the best of the authors' knowledge, this report is the first to specifically focus on the role of PET-CT with ^{18}F FCH for assessing the response to ^{223}Ra treatment in mCRPC.

Sodium ^{18}F fluoride (^{18}F NaF), an imaging biomarker of osteometabolic turnover, has been applied in a cohort of 10 patients with bone lesion from mCRPC.[6] All subjects were subjected to PET-CT with ^{18}F NaF at baseline and after 6 cycles; furthermore 6 of them also underwent a PET evaluation after the first ^{223}Ra cycle. The authors applied PET

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Table 1. Patients' Clinical Features

Patients	*Age*	*Gleason*	*Previous treatments*	*PSA_{pre}*	*ALP*	*ECOG*	*METS*	*TLA_{pre}*	*Cycles completion*	*Post-treatment PET findings*	*TLA_{post}*	*Metabolic response*	*PSA_{post}*	*OS*
1	76	7 (4+3)	ADT+RT +ABI	54.4 ng/mL	<200 U/L	0	9	412.3 g	Y	Bone progression	987.3 g	NR	312 ng/mL	13 months
2	73	8 (4+4)	ADT+ABI +Biph	70.1 ng/mL	<200 U/L	0	14	731.4 g	N	Bone progression	5634.3 g	NR	320 ng/mL	8 months
3	77	7 (4+3)	ADT+ABI	30 ng/mL	<200 U/L	0	7	783 g	Y	Bone lesions regressed in number and uptake	99.8 g	R	5 ng/mL	19 months
4	71	7 (4+3)	ADT+ABI +Biph	40.7 ng/mL	<200 U/L	1	11	654 g	N	Bone and extraosseous progression	6484 g	NR	218 ng/mL	8 months
5	82	9 (5+4)	ADT+AB +Biph	130.6 ng/mL	236 U/L	1	9	370.6 g	N	Extraosseous progression	317 g	NR	256 ng/mL	9 months
6	81	8 (4+4)	ADT	74.6 ng/mL	<200 U/L	0	5	159.8 g	Y	Bone lesions regressed in number and uptake	0 g	R	7.4 ng/mL	14 months
7	74	9 (5+4)	ADT+RT	17.3 ng/mL	<200 U/L	0	10	93.7 g	Y	Bone lesions regressed in number and uptake	30.2 g	R	8.2 ng/mL	15 months
8	71	8 (4+4)	ADT+Biph +ABI+Deno	70.1 ng/mL	<200 U/L	0	31	773.2 g	Y	Bone and extraosseous progression	3206.6 g	NR	251 ng/mL	11 months
9	71	8 (4+4)	ADT+Enz+CT	53.9 ng/mL	<200 U/L	0	9	249.3 g	N	Bone progression	705.6 g	NR	98.8 ng/mL	10 months
10	81	7 (4+3)	ADT+ABI +Biph	15.7 ng/mL	<200 U/L	0	12	91.5 g	Y	Bone progression	78.4 g	NR	88.3 ng/mL	15 months
11	74	7 (4+3)	ADT+ABI	65.1 ng/mL	<200 U/L	0	6	357.5 g	Y	Bone lesions regressed in number and uptake	35.2 g	R	6.3 ng/mL	18 months

ABI, abiraterone acetate; ADT, adrogenic total deprivation; Biph, biphosphonates; CT, chemotherapy; Deno, denosumab; ECOG, Eastern Cooperative Oncology Group; Enz, enzalutamide; METS, number of metastases; N, not completion of the scheduled cycles; NR, nonresponder; OS, overall survival; PET, positron emission tomography; PSA_{pre}, pretreatment PSA; PSA_{post}, post-treatment PSA; R, responder; RT, radiotherapy; TLApre, pretreatment total lesion activity; Y, completion of the scheduled cycles.

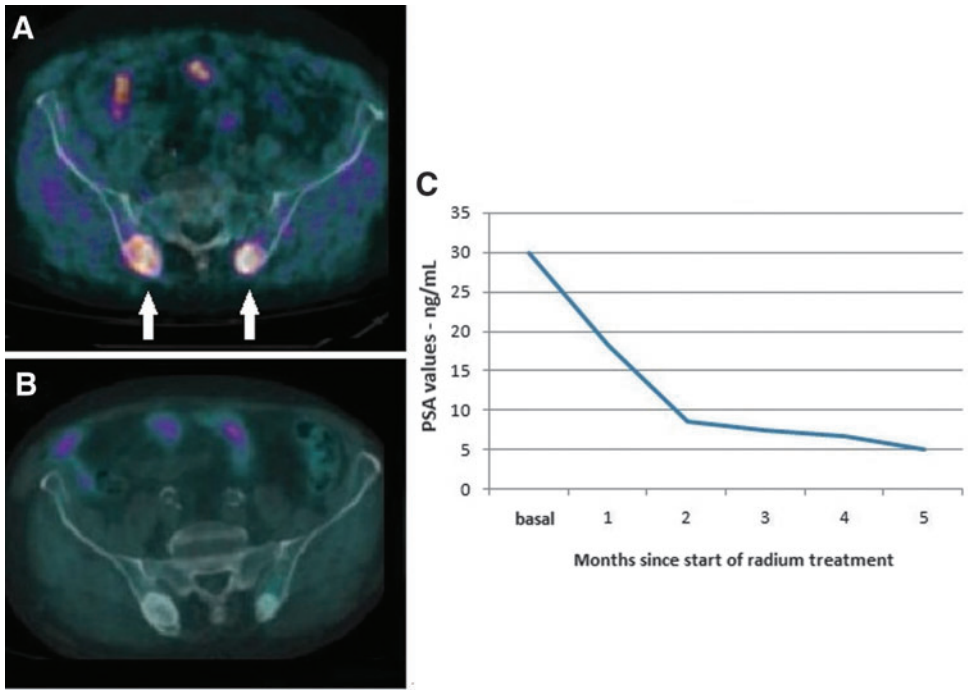

FIG. 1. A 77-year-old patient with mCRPC bone lesions subjected to 6 cycles of ^{223}Ra treatment. **(A)** Corresponding fused PET-CT axial slices acquired before therapy showed intense ^{18}F FCH uptake in the posterior iliac bones (*white arrows*). **(B)** Post-treatment PET-CT demonstrated complete metabolic response. **(C)** Graphic representation of PSA trend during the 6 cycles. Initial TLA was 783 g, final TLA was 0 (complete response). ^{18}F FCH, ^{18}F choline; mCRPC, metastatic castration-resistant prostate cancer; PET-CT, positron emission tomography-computed tomography; TLA, total lesion activity.

response critera in solid tumors (PERCIST) for defining the response to treatment with a good correlation between imaging findings and PSA decline. However, it has to be pointed out that PET-CT with ^{18}F NaF, although it is very accurate in assessing skeletal metabolic changes induced by therapy, is unable to provide information regarding possible extraosseous progression. Of note, in this study, one of the nonresponders interrupted ^{223}Ra treatment after the fifth cycle due to the onset of intense lumbar pain and worsening of the overall PS. This subject was restaged with ^{18}F FCH PET-CT that revealed, despite partial regression of the bone lesions, a metastasis in paraspinal muscular tissue and a gross abdominal lymphadenopathy. In such a case, PET-CT with ^{18}F NaF would have correctly identified skeletal response without disclosing the visceral localizations. These results suggest that, in mCRPC subjected to ^{223}Ra therapy, in case of worsening of the overall status or PSA progression, cycles should be stopped and the patient should be promptly subjected to restaging with ^{18}F FCH PET-CT. Furthermore, it is worth mentioning that in this

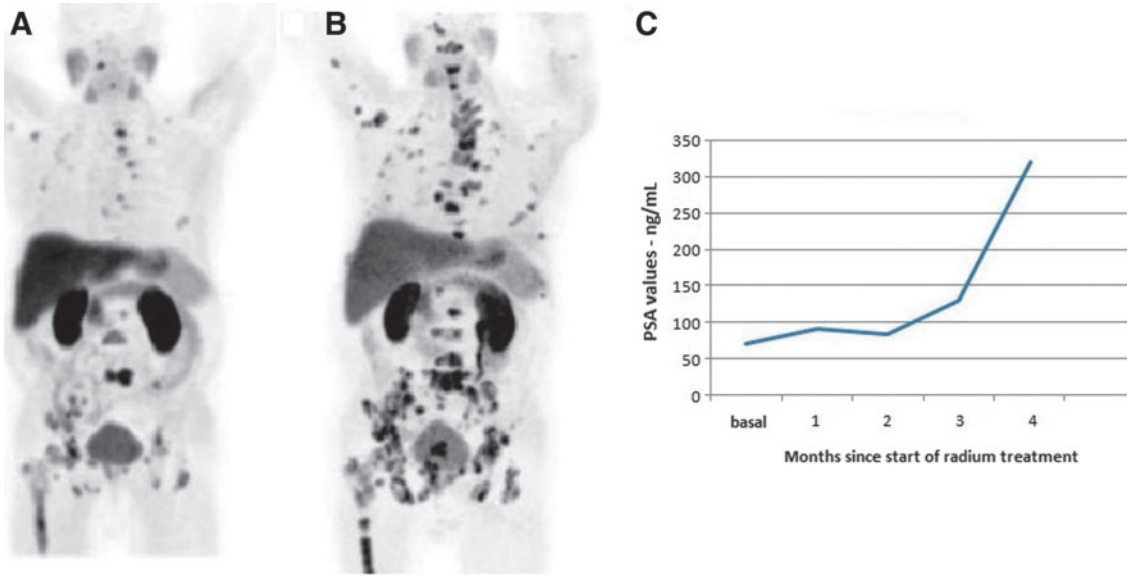

FIG. 2. A 73-year-old male patient with mCRPC bone lesions subjected to ^{223}Ra treatment. **(A)** ^{18}F FCH PET-CT maximum intensity projection (MIP) acquired at baseline demonstrated multiple skeletal lesions. **(B)** Owing to PSA progression, after the 5th cycle, the patient was subjected to restaging with PET-CT, which demonstrated impressive skeletal progression, as shown by MIP. **(C)** Graphic representation of PSA trend during the five cycles. Initial TLA was 731.4 g, final TLA was 5634.3 g.

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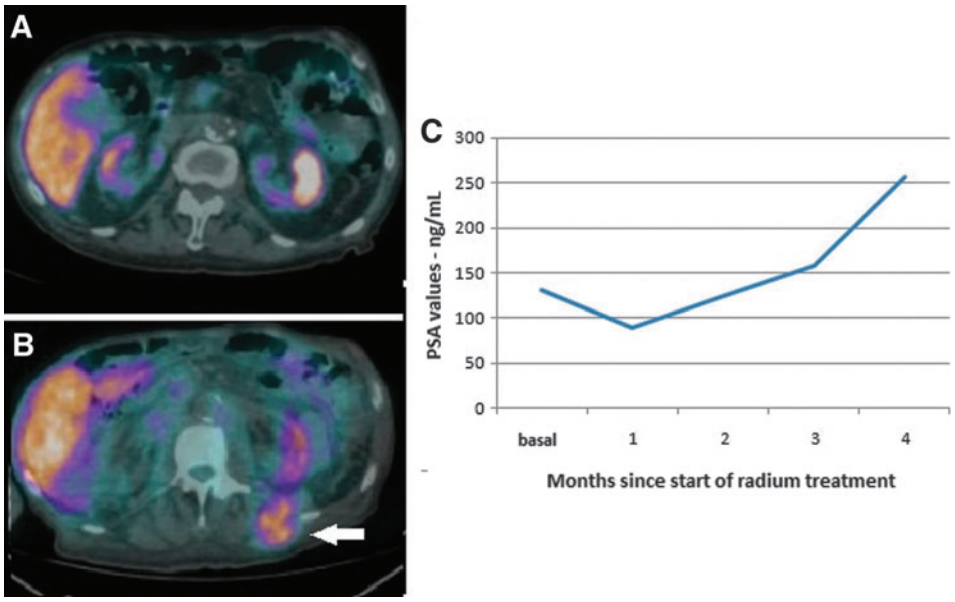

FIG. 3. A 82-year-old patient with mCRPC bone lesions subjected to ^{223}Ra treatment. **(A)** Corresponding fused PET-CT axial slices acquired before therapy. **(B)** Owing to the onset of intense pain in the lumbar region, after the fifth cycle, the patient was subjected to restaging with PET-CT, which demonstrated focal ^{18}F FCH uptake in a right paraspinal muscular metastasis (*white arrow*). ^{223}Ra therapy was stopped and the patient underwent antalgic radiotherapy. **(C)** Graphic representation of PSA trend during the five cycles. Initial TLA was 370.6 g, final TLA was 317 g.

cohort, a strong correlation was found between PSA and metabolic response. As a matter of fact, PSA dosage is routinely performed during treatment with ^{223}Ra dichloride for monitoring patients' biochemical response. However, PSA in itself is unable to provide information regarding the site of disease progression, which are essential data to readily switch patients to more effective treatments (i.e., antalgic radiotherapy or chemotherapy).

In a case series of 3 patients with bone lesions from mCRPC, García Vicente and coworkers demonstrated the usefulness of PET-CT with ^{18}F FCH for monitoring the response to ^{223}Ra treatment.[7] Nevertheless, in the previously cited article, PET-CT scans were only visually evaluated, without the support of any semiquantitative parameters. However, in a recently published article by Caroli et al. analyzing the prognostic impact of ^{18}F FCH and PET-derived parameters in mCRPC patients subjected to treatment with abiraterone or enzalutamide,[8] the sum of TLA of each lesion was found to present a significant prognostic impact on progression-free survival and OS. In agreement with the data reported by Caroli et al., the results of this study suggest that TLA changes after therapy, providing information on both tumor volume and uptake, might play an important role in mCRPC treated with targeted α therapy.

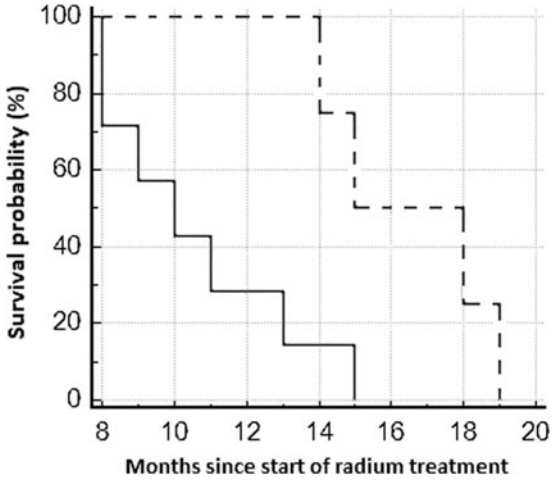

FIG. 4. Kaplan–Meier survival analysis as function of ΔTLA. Patients with ΔTLA <50% (*solid line*) had significantly lower ($p < 0.05$) survival than those having ΔTLA >50% (*dashed line*).

A further consideration should be made regarding the recently introduced radiopharmaceutical ^{68}Ga-prostate–specific membrane antigen (^{68}Ga-PSMA), a ligand binding to a glycosylated type-II transmembrane protein highly expressed in PC cells. PET-CT with ^{68}Ga-PSMA might have a role in assessing the response to treatment in mCRPC. However, the relatively short half-life of the radionuclide ^{68}Ga requires the need of on-site generator, whereas ^{18}F FCH may be produced and delivered to clinical centers located far from the production site. Furthermore, it has to be pointed out that in a recently published meta-analysis by Treglia et al., a significant difference in detection rate between PET-CT with ^{68}Ga-PSMA and that with radiolabeled choline was found only in case of PSA <1 ng/mL.[9] Therefore, more studies, particularly focusing on the cost-effectiveness analysis, are warranted to define the role of these two radiopharmaceuticals in the specific clinical setting of mCRPC treated with ^{223}Ra dichloride.

The main limitations of this study are represented by its retrospective nature and the limited number of patients. Further studies with larger series are needed to better define the role of PET-CT with ^{18}F FCH in this field.

Conclusions

The findings suggest the potential usefulness of PET-CT with ^{18}F FCH for monitoring mCRPC patients treated with targeted α therapy. In particular, a decrease of at least 50% in TLA between baseline and post-treatment measurement was found to be correlated with a more favorable outcome after ^{223}Ra treatment.

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Ethical Approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Authors' Contributions

All the authors jointly designed the retrospective study, performed the statistical analyses, and interpreted the data. L.F. drafted the article and O.S. critically revised it for important intellectual content. All the authors have approved the final version of this article.

Disclosure Statement

No competing financial interests exist.

Funding Information

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