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RESEARCH ARTICLE

Osimertinib beyond disease progression in T790M *EGFR*-positive NSCLC patients: a multicenter study of clinicians' attitudes

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Abstract

Background In most cases, T790M *EGFR*-positive NSCLC patients receiving osimertinib developed "non-drugable" progression, as the patients with common *EGFR*-sensitizing mutations were treated with first-line osimertinib. In both settings, chemotherapy represents the standard treatment and local ablative treatments (LATs) are potential useful options in the case of oligo-progression.

Methods We conducted a study on "post-progression" (pp) outcomes of T790M *EGFR*-positive NSCLC patients treated with osimertinib, according to the therapeutic strategy applied: osimertinib beyond progression (± LATs), "switched therapies" or best supportive care only (BSC).

Results 144 consecutive patients were evaluated: 53 (36.8%) did not received post-progression treatments (BSC), while 91 (63.2%) patients received at least 1 subsequent treatment; 50 patients (54.9%) received osimertinib beyond disease progression [19 (20.9%) of them with adjunctive LATs] and 41 (45.1%) a switched therapy. Median ppPFS (progression-free survival) and median ppOS (overall survival) of patients who received osimertinib beyond progression vs. switched therapies were 6.4 months vs. 4.7 months, respectively [HR 0.57 (95% CI 0.35–0.92), $p = 0.0239$] and 11.3 months vs 7.8 months, respectively [HR 0.57 (95% CI 0.33–0.98), $p = 0.0446$]. Among patients who received osimertinib beyond progression with and without LATs median ppPFS was 6.4 months and 5.7 months, respectively [HR 0.90 (95% CI 0.68–1.18), $p = 0.4560$], while median ppOS was 20.2 months and 9.9 months, respectively [HR 0.73 (95% CI 0.52–1.03), $p = 0.0748$]. At the univariate analysis, the only factor significantly related to the ppPFS was the therapeutic strategy in favor of osimertinib beyond progression (± LATs). Moreover, the only variable which was significantly related to ppOS at the multivariate analysis was osimertinib beyond progression (± LATs).

Conclusion Our study confirmed that in clinical practice, in case of "non-druggable" disease progression, maintaining osimertinib beyond progression (with adjunctive LATs) is an effective option.

Keywords Osimertinib · *EGFR* · NSCLC · T790M · Progression of disease · Beyond progression

Introduction

First- and second-generation EGFR (epidermal growth factor receptor) tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib and afatinib, have represented the milestones of first-line treatment in non-small cell lung cancer (NSCLC) patients with *EGFR*-sensitizing mutations for years [1], while the other second-generation inhibitor dacomitinib, which proved to be superior over gefitinib, has entered the stage recently [2, 3]. The T790M point mutation is responsible of about a half of acquired resistances to EGFR TKi [4, 5], and can be detected with both tissue and liquid biopsy [6]. T790M-driven progressions, already seemed to be related to better outcomes, compared to non-T790M progression [7], however, after the advent of third-generation EGFR TKIs, the clinical paradigm of these

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patients has radically changed. Considering the significant results of the AURA3 trial [8], osimertinib has become the standard of care for NSCLC patients with T790M-driven progression, after a previous treatment with EGFR TKis (first/second generation), considering, moreover, the controversial results of olmutinib and ASP8273 [9, 10], and that Clovis Inc. has interrupted the development of rociletinib in NSCLC [11]. Actually, osimertinib indication is moving forward to the first-line setting, because it proved to be superior to first-generation EGFR TKIs in untreated NSCLC patients with EGFR-sensitizing mutations [12].

Despite the evolving scenario, at the time of disease progression to osimertinib, the management of patients represents a stumbling block. In most cases, T790M-positive patients receiving osimertinib after a first/second generation TKi develop "non-druggable" progressions, despite the interesting results with targeted treatments, selected according to the molecular resistance pattern [13]. In patients with common *EGFR*-sensitizing mutations, who receive first-line osimertinib, things might be similar: even if potentially "druggable" molecular alterations have been identified in some patients (such as *MET* amplifications and C797S *EGFR* mutation), the most of them develop "non-druggable" progressions, as T790M mutation does not emerge in this setting [14]. Therefore, in clinical practice, there are just two main choices: continuing osimertinib beyond disease progression (with or without local ablative treatments in case of oligo-progression), or switching to another regimen (chemotherapy or immune-checkpoint inhibitors) [13].

Considering this background, we conducted a study on "post-progression" outcomes of T790M *EGFR*-positive NSCLC patients, who received osimertinib after a first/second-generation EGFR TKi in clinical practice.

Patients and methods

Patient eligibility

In this study, we enrolled consecutive patients with confirmed stage IV T790M *EGFR*-positive NSCLC, who experienced disease progression while receiving osimertinib, at 16 Italian centers, between October 2015 and February 2019. All patients were previously treated with first/second-generation EGFR TKi.

Study design

This is a "real-life" multicenter retrospective observational study of stage IV, T790M *EGFR*-positive NSCLC patients. The aim of this study was to describe post-progression clinical outcomes of patients receiving osimertinib in clinical practice. Measured clinical outcomes were: post-progression progression-free survival (ppPFS) and post-progression overall survival (ppOS). PpPFS was defined as the length of time between the first occurrence of progressive disease during osimertinib treatment and the further disease progression or death (resulting from any cause), or to the last contact; ppOS was defined as the length of time between the first occurrence of progressive disease during osimertinib and death, or to last contact. Clinical outcomes were also evaluated according to the therapeutic strategies chosen by clinicians at the moment of disease progression: patients who received osimertinib beyond disease progression, with or without local ablative treatments (LATs), and patients who received other post-progression treatments (switched therapy).

Patients who did not receive a further treatment line (due to early death/poor clinical conditions) were excluded from the analysis of clinical outcomes. Baseline patients' characteristics were reported with descriptive statistic. The following covariates were analyzed in the univariate/multivariate analyses: sex (male vs female), Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (0–1 vs ≥ 2), age (< 70 vs ≥ 70 years) [15], SNC metastases (yes vs no) and best response to osimertinib (partial/complete response vs stable/progressive disease).

Responses were evaluated with RECIST criteria (version 1.1), according to the local clinical practice of the participating centers and to the respective investigators' evaluation [16]. Median ppPFS and median ppOS were evaluated using the Kaplan–Meier method [17]. Patients who had not progressed/not died at data cutoff were censored at the time of the last clinical visit. Median follow-up was calculated according to the reverse Kaplan–Meier method [18]. Cox proportional hazards model [19] was used to evaluate predictor variables in univariate and multivariate analyses for ppPFS and ppOS. The data cutoff period was May 2019. All statistical analyses were performed using MedCalc Statistical Software version 19.0.4 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019).

EGFR mutational analysis

EGFR (exons 18, 19, 20, 21) genetic analysis was performed on paraffin-embedded tissue blocks from the primary tumor and/or metastases using direct sequencing, pyrosequencing, and real-time PCR techniques (Cobas® Z480 analyzer, Easy® EGFR Diatech Pharmacogenetics, Myriapod® Lung status, Therascreen® EGFR RGQ real-time PCR assay), according to the local clinical practice of the participating centers. T790M analysis was performed either on paraffin-embedded tissue blocks from tissue re-biopsy and/or through "liquid-biopsy" from circulating free tumor DNA, with real-time PCR techniques (Cobas® Z480 analyzer, Easy® EGFR Diatech Pharmacogenetics, Therascreen® EGFR RGQ

real-time PCR assay) according to the local clinical practice of the participating centers.

Results

Patients' characteristics

Patients' characteristics are summarized in Table 1; 144 consecutive patients were evaluated. Among them, 53 (36.8%) did not received post-progression treatments, while 91 (63.2%) patients received at least one subsequent treatment line. 50 patients (54.9%) received osimertinib beyond disease progression; 19 (20.9%) of them with adjunctive LATs. One of them received adrenal thermoablative therapy, while 18 received radiation therapy (RT): 6 (33.3%) to the SNC, 4 (22.2%) to the bone, 10 (55.5%) to the lung/mediastinal lymph nodes, and 2 (11.1%) to the liver. 3 patients received LATs to more than one site. 41 patients (45.1%) received a switched therapy: 31 (75.6%) received a platinum-based doublet chemotherapy, 3 (7.3%) patients received anti-PD-1 checkpoint inhibitors, 3 (7.3%) patients received single-agent chemotherapy, 1 (2.5%) patient received a first-generation TKi, and 3 (7.3%) patients were enrolled in a clinical trial. Among the 91 patients who received a post-progression treatment line, 44 PR/CR were reported as best response to the previous osimertinib 48.3% (95% CI 35.1–64.9).

Table 1 Patients' characteristics

	Screened patients	Patients who received post-progression therapy	Patients who did not received post-progression therapy
	144 (%)	91 (%)	53 (%)
Age (years)			
Median	65	63	67
Range	30–88	31–83	42–88
Elderly (≥ 70)	42 (29.2)	21 (23.1)	21 (39.6)
Sex			
Male	63 (43.7)	34 (37.4)	29 (54.7)
Female	81 (56.3)	57 (62.6)	24 (45.3)
ECOG PS			
0–1	124 (86.1)	85 (93.4)	39 (73.6)
≥ 2	20 (13.9)	6 (6.6)	14 (26.4)
EGFR primary mutation			
Exon 19 deletions	107 (74.3)	70 (76.9)	37 (69.8)
L858R point mutation	35 (24.3)	20 (21.9)	15 (28.3)
Synchronous L858R/T790M	1 (0.7)	1 (1.2)	–
Synchronous exon 19 deletion/T790M	1 (0.7)	–	1 (1.9)
T790M diagnosis			
Tissue re-biopsy/cytology	62 (43.1)	41 (45.1)	21 (39.6)
"Liquid" biopsy	90 (62.5)	53 (58.2)	37 (69.8)
Smoking status			
Yes	55 (38.2)	35 (38.5)	20 (37.7)
No	89 (61.8)	56 (61.5)	33 (62.3)
SNC metastases			
Yes	61 (42.4)	36 (39.6)	25 (47.2)
No	83 (57.6)	55 (60.4)	28 (52.8)
Osimertinib treatment line			
Second	121 (84)	72 (79.1)	49 (92.4)
Third	23 (16)	18 (20.9)	5 (74.6)
Therapeutic strategy			
Osimertinib beyond progression		31 (34)	
Osimertinib beyond progression + LAT	–	19 (20.9)	–
Switched post-progression therapy		41 (45.1)	

Among patients who received a switched therapy and osimertinib beyond progression, 5 (10%) and 11 (26.8%) received a further treatment line, respectively.

Efficacy analysis

Among patients who received at least one post-progression treatment, the (post-progression) median follow-up was 14.5 months. Median ppPFS was 5.7 months (95% CI 4.7–6.7; 69 progression events), while median ppOS was 8.1 months (95% CI 7.2–12.2; 37 censored patients). Median ppPFS of patients who received osimertinib beyond progression was 6.4 months (95% CI 4.8–7.9; 35 progression events), while median ppPFS of patients who received a switched therapy was 4.7 months (95% CI 2.9–6.7; 34 progression events), with a statistically significant difference [HR 0.57 (95% CI 0.35–0.92), $p = 0.0239$] (Fig. 1). Among patients who received osimertinib beyond progression median ppOS was 11.3 months (95% CI 7.2–17; 24 censored patients), while among patients who received a switched therapy was 7.8 months (95% CI 5.3–11.7; 13 censored patients), with a statistically significant difference [HR 0.57 (95% CI 0.33–0.98), $p = 0.0446$] (Fig. 1).

Among patients who received osimertinib beyond progression with and without LATs median ppPFS was 6.4 months (95% CI 4.8–10.9; 13 progression events) and 5.7 months (95% CI 3.8–9.9; 21 progression events), respectively [HR 0.90 (95% CI 0.68–1.18), $p = 0.4560$], while median ppOS was 20.2 months (95% CI 7.2–20.2; 11 censored patients) and 9.9 months (95% CI 5.4–14.9; 13 censored patients), respectively [HR 0.73 (95% CI 0.52–1.03), $p = 0.0748$] (Fig. 1). Table 2 reported the univariate analysis of ppPFS; in the study population, the only factor significantly related to the ppPFS was the therapeutic strategy. Patients who received switch therapies had a shorter ppPFS when compared to patients who received osimertinib beyond progression overall, and when compared to patients who received osimertinib beyond progression with adjunctive LATs. Table 3 reported the univariate and multivariate analyses of ppOS; in the study population the only factor significantly related to the ppOS was the therapeutic strategy. Osimertinib beyond progression, and osimertinib beyond progression with adjunctive LATs (respectively, compared to switch therapies) were confirmed independent predictors of a significantly longer ppOS.

Table 2 Univariate analysis of post-progression progression-free survival

Variable (comparator)	Post-progression progression-free survival Univariate analysis HR (95% CI); *p* value
Therapeutic strategy	
BPO vs switched therapy	0.57 (0.35–0.92); $p = 0.0239$
Therapeutic strategy (switched therapy)	
BPO alone	0.64 (0.37–1.09); $p = 0.0981$
BPO + LAT	0.49 (0.26–0.95); $p = 0.0344$
Sex	
Female vs male	0.91 (0.55–1.49); $p = 0.7018$
SNC metastases	
Yes vs no	1.55 (0.95–2.54); $p = 0.0791$
Age	
Elderly vs non-elderly	0.95 (0.53–1.69); $p = 0.9517$
Best response to osimertinib	
SD/PD vs PR/CR	1.12 (0.69–1.82); $p = 0.6255$
ECOG PS	
≥2 vs 0–1	1.24 (0.53–2.93); $p = 0.6107$

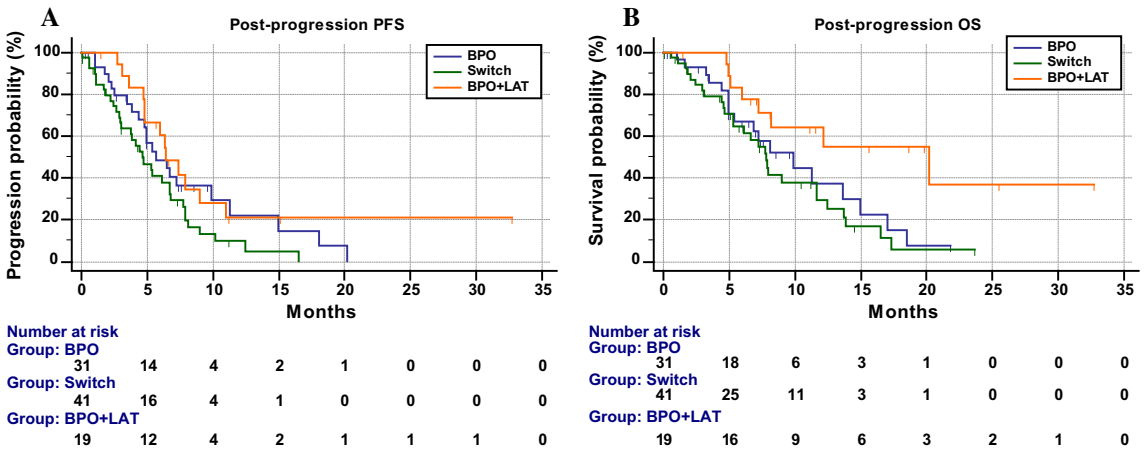

Fig. 1 Kaplan–Meier survival curves according to post-progression therapeutic strategy. **a** Progression-free survival. **b** Overall survival. *BPO* osimertinib beyond progression (alone), *switch* switched therapy, *LAT* local ablative therapy

Table 3 Univariate and multivariate analyses of post-progression overall survival

Variable (comparator)	Post-progression overall survival		
	Univariate analysis	Multivariate analysis	
	HR (95% CI); *p* value	HR (95% CI); *p* value	
Therapeutic strategy			
Switched therapy vs BPO	0.57 (0.33–0.98); $p=0.0446$	0.67 (0.39–1.17); $p=0.1684$	–
Therapeutic strategy (switched therapy)			
BPO alone	0.81 (0.45–1.46); $p=0.4837$	–	0.87 (0.47–1.59); $p=0.6615$
BPO + LAT	0.33 (0.15–0.75); $p=0.0081$		0.43 (0.18–0.97); $p=0.0431$
Sex			
Female vs male	0.98 (0.55–1.71); $p=0.9347$	–	–
SNC metastases			
Yes vs no	1.54 (0.91–2.64); $p=0.1115$	–	–
Age			
Elderly vs non-elderly	2.21 (1.19–4.08); $p=0.0113$	1.83 (0.94–3.54); $p=0.0713$	1.84 (0.95–3.55); $p=0.0663$
Best response to osimertinib			
SD/PD vs PR/CR	2.02 (1.15–3.53); $p=0.0132$	1.84 (1.03–3.27); $p=0.0375$	1.74 (0.98–3.09); $p=0.0556$
ECOG PS			
≥ 2 vs 0–1	2.46 (1.04–5.79); $p=0.0395$	1.74 (0.67–4.51); $p=0.2471$	1.57 (0.61–4.01); $p=0.3459$

Discussion

The results of the AURA3 and FLAURA studies [8, 12] established osimertinib as the new milestone in the treatment algorithm of *EGFR*-positive NSCLC patients, in both the second- (for T790M-positive patients) and the first-line setting. Anyway, being a target therapy, clonal selection and subsequent clinical progression are inevitable, regardless of the treatment line.

Few "real-life" studies have focused the attention on post-progression clinical outcomes in T790M EGFR-positive patients, although continuing osimertinib beyond progression already seemed to be the preferred option within clinical trial populations. Indeed, in the AURA3 trial, 129 patients in the osimertinib group were still alive after radiological progression, and among them, 82 (64%) continued osimertinib beyond progression, with a median treatment duration of 4.1 months [8]. A recent pooled analysis, with an updated follow-up, of the AURA and AURA2 trials, revealed that of the 301 patients who progressed according to investigator assessment, 73% continued osimertinib beyond progression, with a median treatment duration of 4.4 months [20].

Our first result is the rate of patients who did not receive a post-progression treatment (36.8%), which is most than what we expected. In a similar case series, among the 65 patients who experienced disease progression during osimertinib, only 9 (12.3%) did not received a post-progression treatment [21]. On the other hand, even looking to the ppPFS and ppOS of patients who received post-progression treatments overall, they seem lower than what reported in the same study [21], but aligned to what reported by Le et al. in their case series [22]. In the study by Mu et al. [21], 60% of the patients who received a post-progression treatment, received osimertinib beyond progression (± adjunctive LATs) with a median duration of the treatment of 4.1 months. Despite that, they did not find significant differences in ppOS between patient treated with osimertinib beyond progression and those who received chemotherapy [21]. In the study by Le et al. [22], 47 out of 76 patients (62%) received osimertinib beyond progression, with a median ppPFS of 12.6 months. 21 of them also received adjunctive LATs with a ppPFS of 15.5 months. Moreover, it was the only study that reported a significantly prolonged ppOS for patients treated with osimertinib beyond progression, compared to patients who discontinued osimertinib (11.2 vs 6.1 months, $p=0.02$) [22]. These data are aligned to our findings of a significantly longer ppOS with osimertinib beyond progression compared to switched therapies, with an even lower HR considering those who received adjunctive LATs.

In our cohort, post-progression therapeutic strategy seems to be the most important factor in determining post-progression clinical outcomes. Indeed, osimertinib beyond progression overall, and with adjunctive LATs, are the only factors significantly related to ppPFS at the univariate analysis, and to ppOS at the multivariate analysis. These evidences are related to either biological or clinical factors, such as pattern of progression. Mu et al. have categorized disease progression patterns as "local" (23.1%), "gradual" (44.6%) and "dramatic" (21%) [21]. Among the local/gradual progressed

patients, a higher percentage (65.9%) received osimertinib beyond progression, with a longer ppPFS (6.9 months) [21]. In addition, Schmid et al. [23] reported a trend of developing "oligoprogressive disease" during osimertinib (73%), with a median duration of osimertinib beyond progression of 6.7 months on those patients.

Of course, pattern of disease progression could be related to clinicians' attitudes in maintaining osimertinib beyond progression, and to post-progression survival itself. In the case of indolent progression, localized to a single organ, and without new symptoms, clinicians rightly tend to continue the same treatment (which is also well tolerated), eventually adding a LAT for the "oligoprogressive" site. On the other hand, in case of a widely disseminated progression, with symptoms development, a radical change of the systemic therapy is required. The biggest bias of our study is the lack of data availability regarding radiological pattern of disease progression (e.g., oligoprogressions), because it certainly affected ppPFS and ppOS. Among the limits, we must also cite the retrospective design, which is related to selection biases and the lack of centralized data review.

In case of prolonged clinical benefit, maintaining the same agent has already become common clinical practice in *EGFR*-positive NSCLC patients treated with first-generation EGFR TKi [24]. Moreover, adjunctive radiation therapy (mainly stereotactic radiation treatments), in case of oligoprogressive disease, is now a clear goal in the multidisciplinary management of oncogene addicted patients at the moment of disease progression [25–27]. Our results, with the highest clinical benefit with osimertinib beyond progression with adjunctive LATs, seem to confirm that also in the setting of disease progression during osimertinib.

As previously stated, current possibilities after osimertinib are limited, despite the interesting results reported with targeted treatments in both first- and second-line setting [13, 14]. Therefore, in selected cases, treatment beyond progression might be a reliable therapeutic option also for patients who develop disease progression during first-line osimertinib. Some limited clinical experiences are reported with the addition of chemotherapy to osimertinib beyond progression [28], and with osimertinib rechallenge after a middle chemotherapy [29]. An emerging treatment option, which might be offered to the patients without "druggable" resistance, is chemo-immunotherapy combination. Indeed, the subgroup analysis of pre-treated *EGFR*-positive patients of the phase III trial comparing bevacizumab/atezolizumab plus chemotherapy (carboplatin/paclitaxel), and atezolizumab plus chemotherapy, with bevacizumab plus chemotherapy, revealed a prolonged PFS and OS for the bevacizumab/atezolizumab combination arm, compared to the control one (bevacizumab/chemotherapy) [30].

Regarding the study population, our opinion is that in a metastatic disease, after two (or more) lines of therapy, the goal of a disease-oriented treatment should be to relieve symptoms and to improve quality of life, as well as prolonging survival. This awareness is crucial for an appropriate decision-making process and to properly weigh expected outcomes and risk/benefit ratio at the moment of disease progression. When clinical/radiological pattern of progression allows, maintaining a well-tolerated treatment such as osimertinib, evaluating adjunctive LATs indication with a multidisciplinary team, should always be taken into account.

Conclusions

Our study confirmed that in clinical practice, in case of "non-druggable" disease progression, and when clinical/radiological pattern of progression allows, maintaining osimertinib beyond progression is an effective therapeutic option. A multidisciplinary assessment with a radiation oncologist, to evaluate adjunctive LATs, should always be taken into account.

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Compliance with ethical standards

Conflict of interest Dr Alessio Cortellini received grants as speaker/medical writer by MSD, Astra-Zeneca, Roche, Ipsen and Astellas, grant consultancies/advisory by BMS, Roche, Novartis, Istituto Gentili; Dr. Marcello Tiseo received grant for advisory boards and speakers' fee by Astra-Zeneca, Pfizer, Eli-Lilly, BMS, Novartis, Roche, MSD, Boehringer Ingelheim, Otsuka, Takeda, Pierre Fabre. Dr. Marcello Tiseo received research grants by Astra-Zeneca, Boehringer-Ingelheim; Dr. Diego Cortinovis received speakers' fee and advisory grant by Roche, BMS, MSD, Boehringer-Ingelheim, Astra-Zeneca, and Amgen; Dr. Emilio Bria received speakers' and travels' fee from MSD, Astra-Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis and Roche. Dr. Emilio Bria received consultant's fee from Roche, Pfizer and institutional research grants from Astra-Zeneca and Roche; Dr. Elisa Sala received grants as medical writer by Eisai.

Ethical approval All patients provided written, informed consent to the treatment. The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. The study was approved by the respective local ethical committees on human experimentation of each institution, after previous approval by the coordinating center (University of L'Aquila, Internal Review Board protocol number 26654, approved on May 21th, 2019).

Informed consent Not applicable.

Availability of data and materials The datasets used during the present study are available from the corresponding author upon reasonable request.

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