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Efficacy of FOLFOX Chemotherapy in Metastatic Enteropancreatic Neuroendocrine Tumors

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Abstract. *Background/Aim: FOLFOX (5-Fluorouracile and oxaliplatin) exhibits promising activity in advanced well-differentiated neuroendocrine tumors (NETs). This retrospective study aimed to analyze the outcome of metastatic enteropancreatic NETs patients treated with FOLFOX. Patients and Methods: We retrospectively identified patients treated with FOLFOX for NETs of enteropancreatic or unknown origin among those referred to our Regional Multidisciplinary Tumor Board. Results: Among 48 patients, most often pancreatic NETs (n=33, 68.8%), the median Ki67 index was 10%. The median number cycle of FOLFOX was 6 and median follow-up was 34.8 months. Disease control rate (DCR) was 83.3%. Median PFS and OS were 12.6 and 29.4 months respectively. Median chemotherapy break was 14.1 months. No significant difference was observed between PFS and the following criteria: Ki67 index, primary tumor site, alkaline phosphatase levels, primary tumor surgery and ^{18}F-FDG PET positivity. Conclusion: FOLFOX exhibits a high DCR and a short duration of treatment with a relative long chemotherapy break in patients with metastatic enteropancreatic NETs.*

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Neuroendocrine neoplasms (NENs) of enteropancreatic origin are often metastatic at diagnosis and their clinical behavior may vary from indolent to aggressive disease (1). The 2017 update of the WHO classification distinguishes between well-differentiated NE tumors (NETs) and poorly differentiated NE carcinomas (NECs) (2). Grading of well-differentiated NETs is based on the Ki67 index (G1 <3%, G2 3-20% and G3 >20%), where G3 NETs usually exhibit a Ki67 index <55%. In advanced disease NETs, somatostatin analogs (SSAs) are used when the disease exhibits a low Ki67 index, a low tumor burden and a slow progression (3, 4).

Numerous therapeutic tools are available in case of disease progression during analogs of somatostatin (SSAs) therapy, such as locoregional treatments like trans-arterial embolization or chemoembolization (TAE or TACE) or local destruction when the disease is mainly confined to the liver (5, 6). Targeted therapeutic agents (everolimus and sunitinib) (7-9) and peptide receptor radionuclide therapy (PRRT) (10) are often used as second or third-line therapies after disease progression with SSAs.

Currently, chemotherapy is indicated in bulky disease with symptomatic patients and rapid tumor progression (11). The role of chemotherapy in NETs has evolved in recent years. The mainstay of treatment has been a streptozotocin (STZ)-based regimen, but this is limited by its toxicity (12, 13). Recently, other regimens have been used such as the combination of capecitabine and temozolomide (CAPTEM), which is mostly used in pancreatic NETs and has promising

response rates and a low toxicity profile (14, 15). However, it is still unclear which treatment option is superior.

More recently, oxaliplatin-based regimens have exhibited promising results as a treatment option with a reported disease control rate (DCR) of 70-80% and acceptable toxicity in patients with advanced NETs irrespective of the primary sites and tumor grade (16-20). Furthermore, this regimen allows for a break from treatment that may improve both safety and quality of life. Unfortunately, no comparative studies have been conducted due to the rarity of the disease and, consequently, the optimal cytotoxic regimen in this setting remains to be determined. Therefore, our multicentric retrospective study aimed to analyze the outcome of patients with metastatic NETs who had received FOLFOX chemotherapy.

Patients and Methods

Patient selection. Patient eligibility criteria for inclusion in our study were: age >18 years; histological diagnosis of well-differentiated neuroendocrine tumor (G1, G2 or G3); primary tumor of intestinal, pancreatic or unknown origin; metastatic disease not amenable to curative treatment and having received at least one line of palliative FOLFOX chemotherapy (any schedule and completion of at least two cycles) as first-line or after progression with a prior systemic or locoregional therapy. Our exclusion criteria consisted of any NEC, non-neuroendocrine histological component and patients with other malignancies. Eligible patients were identified from 2009 to 2018 among those referred to our Regional Multidisciplinary Tumor Board dedicated to NENs (PACA RENATEN Network). Eight French regional centers were participating. All patients that both met the eligibility criteria and were treated between June 1st, 2009 and November 30th, 2018 were considered. The study was authorized by the Institutional Review Board of the Paoli-Calmettes Institute (IPC 2019-042).

The included patients received modified FOLFOX-6 chemotherapy, 85 mg/m^2 oxaliplatin and 100 mg/m^2 leucovorin as a 2 h intravenous infusion on day 1, followed by 5-Fluorouracil (5-FU) as a 400 mg/m^2 bolus and then 2,400 mg/m^2 as a 46-h continuous infusion. The cycles were repeated every two weeks. Complete blood count, serum biochemistry and liver function tests were performed 24-48 h prior to each cycle. The chemotherapy doses were reduced as needed according to standard guidelines.

Data collection. Patients' demographic data, tumor characteristics, treatment modalities and outcomes were collected retrospectively from local medical records. Performance status and clinical symptoms (weight gain, pain, tumor-related symptoms and secretory symptoms) were recorded at each cycle and a meaningful improvement in performance status and/or clinical signs were considered as a clinical benefit. The radiological response to FOLFOX was both assessed *via* conventional imaging (Computed tomography scan and/or magnetic resonance imaging) every three months and classified according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) by each center's dedicated radiologist. After the end of chemotherapy, patients continued to be followed with an evaluation every four months with clinical, biological and imaging tests. Data collection was performed following patient agreement according to the Declaration of Helsinki and it was approved by the Institutional Review Board (IPC 2019-042) of Paoli-Calmettes Institute, Marseille, France.

Statistical analysis. The Disease Control Rate (DCR) was defined as the rate of patients experiencing either a complete response (CR), a partial response (PR) or a stable disease (SD). The Wilson score interval method was performed for this rate, while FDG PET-positive associations were assessed *via* the Fisher's exact test. Progression-free survival (PFS) was defined as the time from the beginning of FOLFOX chemotherapy to the date of radiological/clinical progression or death from any cause. Chemotherapy break was defined as the time from the end of FOLFOX chemotherapy to the beginning of another treatment for progression. Overall survival (OS) was defined as the time from the beginning of FOLFOX chemotherapy to the date of death from any cause. For each of these time-to-event endpoints, patients without an event were right censored as of their last follow-up. Median survivals with associated confidence intervals (CI) and survival curves were estimated *via* the Kaplan–Meier's method and compared using log-rank tests. The length of follow-up was estimated by using the reverse Kaplan–Meier's method. Univariate analysis was used to evaluate the prognostic impact of the following factors on PFS and OS: first-line FOLFOX administration, Ki67 grade (≤5% *vs*. 5%-20% *vs*. >20%), primary tumor site (small intestine *vs*. pancreas), alkaline phosphatase levels (ALP, > Normal *vs*. Normal), primary tumor surgery (yes *vs*. no) and FDG-PET scan (positive *vs*. negative). The prognostic impact of first-line FOLFOX administration on PFS was also evaluated in a multivariate Cox model, adjusting for associated factors identified in univariate analysis with $p<0.20$. Hazard ratios (HR) were estimated with associated Wald confidence intervals and *p*-values for significance. All statistical analyses were performed using the SAS® 9.4 software with a level of $\alpha=0.05$. Frequency distributions were used to summarize categorical variables while medians [min-max] were used for quantitative variables. All tests were two-tailed.

Results

Patient characteristics. Patient and tumor characteristics are summarized in Table I. Forty-eight NETs patients received the FOLFOX regimen, where the median age at the first FOLFOX administration was 63 years (range=20-85 years) and 26 patients (54.2%) had a good performance status (ECOG 0 or 1) upon entry. Tumor-related symptoms and carcinoid syndrome were present in 21 patients (43.8%) and ten patients (20.8%), respectively. The primary tumor site was most often the pancreas (n=33, 68.8%), the small intestine (n=10, 20.8%) or of unknown primary origin (n=5, 10.4%). All patients had well-differentiated NETs and the Ki67 index was available for 47 of the 48 patients: Grade 1 (Ki67 <3%, n=2), Grade 2 (Ki67 3%-20%, n=31) or Grade 3 (Ki67 >20%, n=14) metastatic NETs. The median Ki67 index was ten percent. All the patients had a metastatic disease and 21 patients (43.8%) had more than two metastatic sites. ^{18}F-FDG PET scans were performed in 35 patients (72.9%), with positive results in 24 patients (50% of total population). Primary tumor surgeries were previously

performed in 15 patients (nine for pancreatic NETs and six for small intestine NETs). Patients had progressive disease on radiological follow-up, based upon response evaluation criteria in solid tumors (RECIST 1.1) or were treatment naïve with high volume disease. Of the 48 patients, 28 [58.3%, mainly pancreatic NETs (n=20)] received FOLFOX as first-line chemotherapy, 7 of whom received SSA before. Twenty patients received others therapeutic lines (except SSA) before FOLFOX including: STZ-based regimen, platinum-etoposide, targeted therapy or TACE. Three patients (11.1%) received PRRT before FOLFOX. The median time between diagnosis and the first FOLFOX cycle was seven months [0-184]. The median number of FOLFOX cycles administered was six [2-12], which was equivalent to three months of treatment. The median chemotherapy break, median interval from the end of FOLFOX until the beginning of another systemic or loco-regional treatment for progression, was 14.1 months (range=9.9-18.4 months) in the total population.

Response and survival endpoints. The median follow-up was 34.8 months (95%CI=19.1-58.6) with a partial response in 13 patients (27.1%, 11 pancreatic NETs, one small intestine NET and one NET of unknown primary origin) and a stable disease in 27 patients (56.3%, 16 pancreatic NETs, eight small intestine NETs, and three NETs of unknown primary origin). The DCR of the entire population was 83.3% (95%CI=70.4-91.3; small intestine NETs: 90%, pancreatic NETs: 81.8% and NETs of unknown primary origin: 80%), while the DCR of first-line FOLFOX was similar to that of pretreated patients, 85.7% and 80%, respectively. Eight patients (16.7%) had disease progression (six pancreatic NETs, one small intestine NET and one NET of unknown primary origin), all of whom presented a high tumor burden while four received first-line FOLFOX and only two patients were able to receive another therapy after FOLFOX. After FOLFOX administration, 33 patients (68.7%) demonstrated clinical benefit (weight gain, reduction of tumor related symptoms and carcinoid syndrome, PS improvement).

In order to assess the prognostic impact of the Ki67 proliferation index, patients were divided into three groups of comparable size: Ki67 ≤5% (n=14, 29.2%), Ki67 between 5% to 20% (n=19, 39.6%) and Ki67 >20% (n=14, 29.2%). Favorable responses (PR, SD) were not significantly different between these three groups (78.5%, 85.7% and 84.2%, respectively). ^{18}F-FDG PET positivity was not found to be associated with favorable responses to FOLFOX chemotherapy (p=1). The median PFS was 12.6 months (range=10.6-16.3 months) in the total population (Figure 1). Univariate analysis did not reveal any statistically significant association between PFS and the following potential prognostic factors: Ki67 score (Figure 2), primary tumor site (p=0.87), ALP levels (p=0.75), primary tumor surgery (p=0.84) and ^{18}F-FDG PET positivity (p=0.37). Patients receiving FOLFOX as first-line treatment (n=28) had a median PFS of 15.2 months (range=10.68-17.74 months) compared to 9.7 months (range=6.70-13.57 months) in pretreated patients, though this was not statistically significant [p=0.27, HR=0.69 (0.35-1.34)]. Multivariate analysis confirmed these results with a trend towards improved PFS for chemo-naive patients [p=0.22, HR=0.65 (0.32-1.30)] and for patients with Ki67 5%-20% compared to those with Ki67 >20% [p=0.11, HR=0.49 (0.20-1.18)],

Table I. *Patient characteristics*.

Characteristics	Statistics
Gender	
Male	26 (54.2%)
Female	22 (45.8%)
Age at diagnosis	
Median [Min-Max]	61 [20-85]
Age at first FOLFOX	
Median [Min-Max]	63 [20-85]
Site of primary tumor	
Pancreas	33 (68.8%)
Small intestine	10 (20.8%)
Unknown origin	5 (10.4%)
Performance status at first FOLFOX	
0-1	26 (54.2%)
2-3	14 (29.2%)
Unknown	8 (16.6%)
No. of metastatic sites	
1	12 (25%)
2	15 (31.2%)
>2	21 (43.8%)
Syndrome	
Carcinoid	10 (20.8%)
Tumor-related symptoms	21 (43.8%)
None	17 (33.4%)
Ki67 index	
≤5%	14 (29.2%)
5%-20%	19 (39.6%)
>20%	14 (29.2%)
Unknown	1 (2%)
Previous treatment lines	
≤2	40 (83.3%)
>2	8 (16.7%)
ALP levels	
Normal	11 (22.9%)
>Normal	21 (43.8%)
Untested	16 (33.3%)
Primary tumor surgery (yes)	15 (31.2%)
FDG-PET	
Positive	24 (50%)
Negative	11 (22.9%)
Not Done	13 (27.1%)
FOLFOX first-line*	28 (58.3%)

*Prior somatostatin analog therapy included. Min: Minimum; Max: maximum; ALP: alkaline phosphatase; FDG-PET: fluorodeoxyglucose-positron emission tomography.

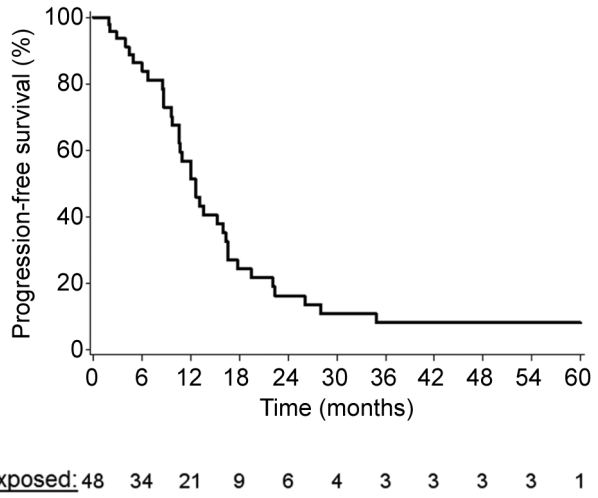

Figure 1. *Progression-free survival in the total population.*

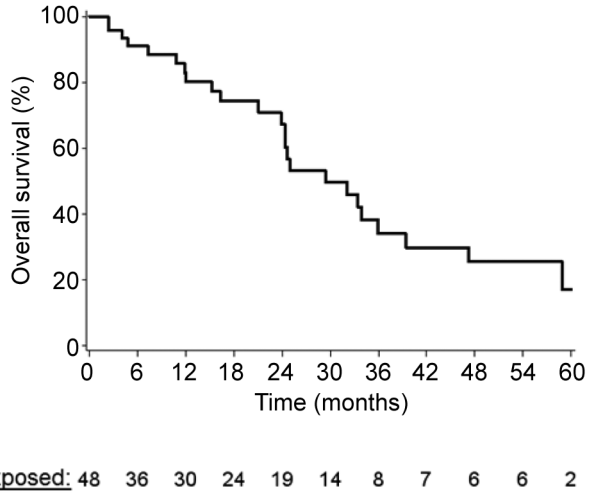

Figure 3. *Overall survival in the total population.*

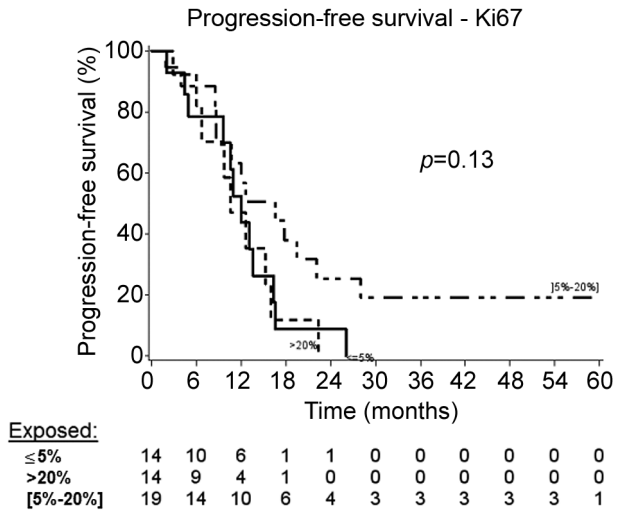

Figure 2. *Progression-free survival according to Ki67 index.*

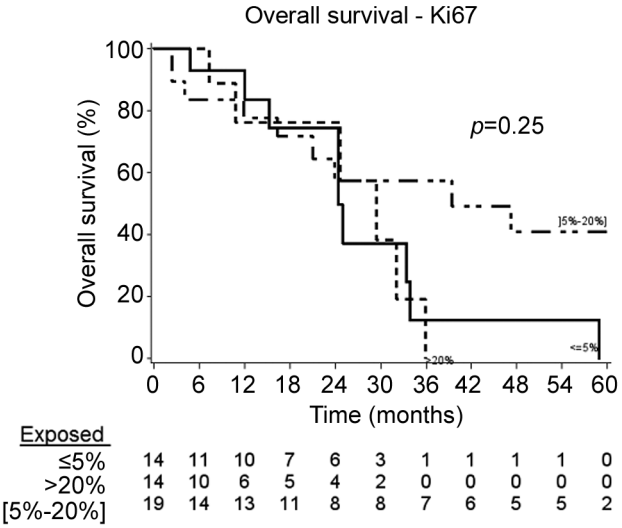

Figure 4. *Overall survival according to Ki67 index.*

though this did not reach statistical significance as shown in Table II. The median OS was 29.4 months (range=23.9-39.4 months) in the total population (Figure 3). Although the differences were not statistically significant, median OS was greater with first-line FOLFOX administration: 47.2 months *vs.* 24.9 months [p=0.10, HR=0.51 (0.22-1.16)]. Median OS was also greater but not significant (log rank test p=0.25) in Ki67 5%-20% patients (39.4 months) compared to patients with Ki67 ≤5% (24.4 months) and Ki67 >20% (29.4 months) (Figure 4), and was also greater in patients with normal ALP levels *vs.* greater than normal levels (33 months *vs.* 24.4 months, respectively, p=0.3).

Among the 12 patients who received a second FOLFOX regimen due to further progression, after a break from chemotherapy, three had a stable disease and eight had disease progression, mainly within the first three months. Three out of four patients with a long interval, 12 to 26 months, between the end of the first FOLFOX administration and the beginning of the second, experienced disease progression. One patient had severe immuno-allergic toxicity

Table II. *Progression-free survival in univariate and multivariate analysis.*

Contrast	Univariate analysis		Multivariate analysis	
	HR [95%CI]	*p*-Value	HR [95%CI]	*p*-Value
First-line FOLFOX administration	0.69 [0.35-1.34]	0.27	0.65 [0.32-1.30]	0.22
Ki67 grade ≤5% *vs*. >20%	0.94 [0.40-2.25]	0.90	0.93 [0.39-2.22]	0.87
Ki67 grade 5%-20% *vs*. >20%	0.46 [0.19-1.12]	0.09	0.49 [0.20-1.18]	0.11
Small intestine *vs*. Pancreas	0.93 [0.42-2.10]	0.87		
>Normal *vs*. Normal ALP	1.16 [0.45-2.99]	0.75		
Primary tumor surgery	0.93 [0.46-1.87]	0.84		
FDG-PET: Positive *vs*. Negative	1.47 [0.64-3.42]	0.37		

ALP: Alkaline phosphatase; FDG-PET: FDG-PET: fluorodeoxyglucose-positron emission tomography.

that occurred during the first oxaliplatin re-administration and prevented the evaluation of the response. Seven patients were able to receive another systemic treatment after the second FOLFOX regimen.

Discussion

Metastatic well-differentiated enteropancreatic NETs display a very heterogeneous behavior ranging from indolent to rapidly progressive disease. Various therapies available in this setting include somatostatin analogs, targeted therapies, TACE or TAE and PRRT. When a patient progresses under SSA therapy, has a high tumor burden or exhibits symptomatic or aggressive features, cytotoxic chemotherapy should be considered as the first-line treatment of choice. Streptozotocin was one of the first agents to demonstrate clinical effectiveness in metastatic pancreatic NETs, but it has been difficult to compare the response rates obtained by other agents to those of STZ-based regimens as efficacy in previous studies was not based on standardized radiological response criteria (12, 13). One such example is a remarkable response rate of greater than 60% obtained *via* a combination of doxorubicin and streptozotocin, previously published by Moertel *et al*. (13), which is now considered to be overestimated. Furthermore, the combination of 5-FU/STZ has been prospectively compared to 5-FU/ doxorubicin in the phase II/III ECOG study (21), which reported a modest response rate of approximately 16% in the two arms with a trend towards improved survival in the 5-FU/STZ group. The 5-FU/STZ combination is recommended as standard treatment for metastatic pancreatic NETs in European guidelines.

Our study indicates that FOLFOX chemotherapy exhibits promising activity in well-differentiated metastatic digestive NETs with a high disease control rate (DCR: 83%), median PFS and OS of 12.6 months and 29.4 months, respectively, and a median follow-up of 34.8 months. Our results are consistent with those of other studies involving oxaliplatin in advanced well-differentiated NETs (16-20). In a prospective phase II study of XELOX chemotherapy, Bajetta *et al*. reported a high DCR (78%) and a median PFS and OS of 20 and 40 months, respectively, in a population of well-differentiated chemo-naive digestive and pulmonary NETs (n=27) that had progressed after SSA therapy (16). Kunz *et al*. described similar DCRs in two different oxaliplatin-based regimens (94% and 75%, FOLFOX *vs*. XELOX, respectively) combined with bevacizumab in pretreated advanced neuroendocrine tumors (20), where PFS was 21 months and 17 months and OS was 31 and 42 months in the FOLFOX-bevacizumab and XELOX-bevacizumab arms, respectively. However, interpreting the contribution of bevacizumab is a delicate matter in the absence of a therapeutic control arm and without an anti-angiogenic agent. Several retrospective studies have also reported a high DCR in pretreated populations. Dussol *et al*. described a DCR of 83%, a PFS of eight months and an OS of 32 months after a GEMOX-based regimen in a pretreated population of well-differentiated NETs (18), while our overall DCR (80%) matched that reported by Spada *et al*. in their retrospective study of several oxaliplatin-based regimens (XELOX, GEMOX and FOLFOX) in heavily pretreated patients with NETs (mostly of gastroenteropancreatic origin) with a PFS of eight months and an OS of 32 months (22). Additionally, while the majority of patients from Faure *et al*. study of a FOLFOX-based regimen in well-differentiated G1 or G2 NETs (mainly of digestive origin) are already included in our study, the authors have previously reported a DCR of 70% and a PFS of 14 months (19). These data suggest that oxaliplatin based regimens are active even in pretreated NET population.

In recent years, the oral alkylating agent temozolomide has emerged as promising treatment in metastatic pancreatic NETs and the CAPTEM protocol is now widely used as a standard of care in well-differentiated metastatic pancreatic NETs. In clinical studies, CAPTEM has been associated with significant tumor response in either chemotherapy-naive or heavily pretreated patients with mainly pancreatic NETs. A

DCR of 97% and an overall response rate of 70% in a population of 30 chemo-naive patients with low or intermediate grade pancreatic NETs with a median treatment duration of eight months and a median PFS of 18 months has been previously published (15). Chatzellis *et al*. recently reported one of the largest retrospective studies of CAPTEM-treated NET patients including gastroenteropancreatic and lung/thymic NETs (n=79), which had mostly been pretreated. The DCR was 59.5% with a median PFS of 10.1 months, a median OS of 103 months and a median treatment duration of 12.1 months (14). Despite a shorter duration of treatment (3 months), the DCR and PFS of our study were both greater than these results. To our knowledge, there have not been any previous prospective data comparing the efficacy of the CAPTEM regimen with oxaliplatin-based chemotherapy in NET patients. Furthermore, there is no current consensus concerning the use of a fixed number of CAPTEM cycles *versus* treatment until progression.

In our study, median OS reached 29.4 months in the whole population and was consistent with published data of oxaliplatin-based regimens used in pretreated NET patients (23 to 42 months) (17, 18, 20, 22). Median OS of 47.2 months was reached in first-line treatment of chemo-naive patients, which is consistent with published OS data of 40 months for patients receiving XELOX as first-line (16). Even though the small sample size of our study limits the prognostic power of any analyses, we were unable to identify a subgroup of patients with a significant difference in survival outcome after FOLFOX, suggesting that this regimen may broadly apply to this entire population with similar efficacy.

It is important to note that our survival data, as in the literature, should be weighed in accordance with the duration of chemotherapy treatment. In our study, patients received a median of three months of the FOLFOX regimen, which is shorter than in other studies and allowed for a relative long break from therapy (14.1 months) before additional therapies were performed for disease progression. This break from treatment may be of particular interest in terms of quality of life, avoiding prolonged exposure to cytotoxic agents and consequent hematological toxicity in the context of a chronic disease where the cumulative toxicity of chemotherapy is a major concern.

We also observed that FOLFOX appears to be effective regardless of Ki67 index as the DCR was comparable across groups, from 78% (Ki67 <5%) to 86% (Ki67 >20%) with 12 and 16.6 months of PFS, respectively. It is interesting to note that populations with a low proliferation rate responded similarly, though non-significantly, to more aggressive populations. Dussol *et al*. also did not report a significant difference in GEMOX treatment efficacy according to the Ki67 index, much like Faure *et al*. who did not demonstrate a statistical difference regarding PFS and OS between Ki67 subgroups (<5% and 5-20%) (18, 19).

In addition, ^{18}F-FDG PET positivity appears to be a poor prognostic factor with a median OS of 25 months compared to a median OS that was not reached in ^{18}F-FDG PET-negative patients. These data are consistent with the literature concerning the prognostic value of ^{18}F-FDG PET in well-differentiated NETs even with a low Ki67 index score. Binderup *et al*. reported a strong prognostic value of ^{18}F-FDG PET in NETs that actually exceeds the prognostic value of the Ki67 index (23). Bahri *et al*. demonstrated that 25% of Somatostatin-Receptor-Scintigraphy-positive patients and 21% of patients with a low proliferation rate (Ki67 <2%) were also ^{18}F-FDG PET-positive and had a poor prognosis (24). In our study, the response was not affected by ^{18}F-FDG PET positivity (DCR 83% *vs*. 91% if negative), indicating that this was not a predictor of chemotherapy efficacy in the population of well-differentiated tumors. A FOLFOX regimen may be effective in NETs with low proliferation rate and this approach should be considered in metastatic NET patients with a low Ki67 index score and FDG-PET negativity.

Though the sample size of our study is limited, it is interesting to note the high disease control rate (DCR: 90%) achieved in almost all of the small intestine NETs (n=10). Spada *et al*. also described a 63% DCR in a gastrointestinal population, the majority of which originated from the small intestine (22). As therapeutic options are limited in this setting, FOLFOX could be a suitable option in case of progressive disseminated disease with a large tumor burden. Additional studies are required in order to understand the role of FOLFOX in the therapeutic arsenal with regard to PRRT or everolimus.

In conclusion, our real-world study confirms the activity of FOLFOX chemotherapy in the treatment of well-differentiated metastatic enteropancreatic NETs with a high disease control rate regardless of grade and line of treatment. A FOLFOX regimen may be considered as a valid option in first-line therapy, allowing for a short duration of treatment and a relatively long break from chemotherapy which may be relevant in terms of both quality of life and toxicity profile compared with more lengthy regimens.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Study conception and design: Oziel-Taieb S, Zemmour C, Raoul JL, Niccoli P; Acquisition of data: Oziel-Taieb S, Raoul JL, Mineur L, Poizat F, Charrier N, Piana G, Cavaglione G, Niccoli P; Analysis and interpretation of data: Oziel-Taieb S, Zemmour C, Raoul JL, Niccoli P; Drafting of manuscript: Oziel-Taieb S, Zemmour C, Raoul JL, Niccoli P; Critical revision: Raoul JL, Mineur L, Niccoli P. All Authors read and approved the final version submitted.

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