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Real world study on efficacy and safety of surufatinib in advanced solid tumors evaluation

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Surufatinib is a novel, China-developed small-molecule tyrosine kinase inhibitor that demonstrates high selectivity for VEGFR, FGFR1, and CSF1R. Surufatinib has been approved for the treatment of neuroendcrine tumors, including pancreatic neuroendocrine tumors (PNEN) and non-pancreatic neuroendocrine tumors (N-pNEN). The purpose of this retrospective study is to assess Surufatinib's safety and effectiveness in patients with various advanced solid malignancies. The general clinical statistics and follow-up data of patients treated with Surufatinib for advanced solid tumors at Zhejiang Provincial People's Hospital between January 2021 and April 2024 were gathered. Enhanced CT was used to assess the effectiveness during that time, and cases side effects were gathered. Survival rates of different diseases were analyzed using the Kaplan-Meier method. A total of 28 eligible patients were enrolled in this study. At the end of follow-up, treatment with Surufatinib resulted in the following outcomes: Complete response (CR) in 0 cases (0.0%), Partial response (PR) in 5 cases (17.9%), Stable disease (SD) in 7 cases (25.0%), and Progressive disease (PD) in 16 cases (57.1%). Objective response rate (ORR) and Disease control rate (DCR) were 17.9% and 42.9%, respectively. In the PNEN group, ORR was 33.3%, DCR was 66.7%, median progression-free survival (mPFS) was 11 months, while median overall survival (mOS) was 17 months. In the N-pNEN group, ORR was 14.3%, DCR was 42.3%, mPFS was 6 months and mOS was 7 months. ORR was 8.3%, DCR was 25%, mPFS was 2 months, and mOS was 2 months. The most common adverse reactions included hypoproteinemia, proteinuria, bone marrow suppression and gastrointestinal toxicity, and which of them were grade 1 to grade 2. In advanced solid tumors beyond PNEN, Surufatinib demonstrates clinically meaningful survival benefits for patients refractory to standard therapies, with a generally manageable safety profile.

Keywords Surufatinib, Solid tumor, Vascular endothelial growth factor receptor, Pancreatic neuroendocrine tumor, Non-pancreatic neuroendocrine tumor

Cancer remains a global public health priority and represents a leading cause of morbidity and mortality worldwide. China bears the highest cancer burden globally, with malignant tumor mortality constituting the primary cause of death among urban residents and individuals aged < 65 years in China[1]. Advances in clinical medicine have led to the emergence of numerous targeted therapies, which now represent a promising treatment option for patients with advanced malignancies. Notably, anti-angiogenic agents have achieved substantial breakthroughs in oncology, with clinical trials demonstrating their significant efficacy in prolonging overall survival[2,3]. Angiogenesis is a tightly regulated biological process orchestrated by the dynamic balance between pro-angiogenic and anti-angiogenic factors, which is essential for physiological tissue development and homeostasis[4]. Dysregulated cellular proliferation constitutes a defining characteristic of malignant transformation, wherein vascular endothelial growth factor (VEGF) functions as a principal modulator of tumor angiogenesis, playing an indispensable role in oncogenic progression[5,6].

The primary medications that block the VEGF pathway are fuquitinib, bevacizumab, and anlotinib hydrochloride, among others[7–10]. Each medication differs from the others in terms of its indications, effectiveness, frequency of use, adverse effects, etc[11]. Among these, Surufatinib is a brand-new oral small-molecule tyrosine kinase inhibitor (TKI) of the receptors for vascular endothelial cell growth factor receptor (VEGFR), fibroblast

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growth factor receptor 1 (FGFR1) and colony stimulating factor-1 receptor (CSF-1R). By preventing tumor angiogenesis, it can stop the growth of tumor cells[12]. Overall survival was considerably increased by using surufatinib as a third-line or postline treatment for pancreatic (pNEN) and non-pancreatic neuroendocrine tumors (N-pNEN), according to the findings of the randomized, double-blind, placebo-controlled Phase 3 SANET-p and SANET-ep trials in Chinese patients. When compared to the placebo group, the median progression-free survival of individuals receiving surufatinib improved noticeably[13,14]. Based on these studies, Surufatinib was approved by the US FDA in April 2020 as the first anti-angiogenic agent for the treatment of neuroendocrine tumors, and in China in December 2020 for the treatment of N-pNEN, changing the landscape of neuroendocrine tumor treatment strategies.

To further examine the safety and effectiveness of Surufatinib in treating several advanced solid tumors, we carried out a real-world study, creating new therapy options for solid tumors.

Materials and methods

Cases selection criteria

Study enrollment is restricted to patients meeting all inclusion criteria specified below: (1) With histologically or cytologically confirmed advanced solid tumors; (2) Clinical stage IV with measurable target lesions; (3) The patient was treated with Surufatinib for more than one 28-day cycle during systemic therapy; (4) Eligible participants aged 18–75 years, regardless of sex, with body weight ≥ 40 kg; (5) Expected survival ≥ 3 months; (6) Availability of complete clinical data with documented informed consent obtained from all participants.

Cases exclusion criteria

Patients meeting any of the following exclusion criteria were ineligible for study participation: (1) Multiple primary tumors or pathology was unclear; (2) Incomplete, missing or difficult to obtain clinical data; (3) Cases were excluded for either inadequate Surufatinib exposure (< 1 treatment cycle) or unwillingness to participate in survival follow-up.

Treatment method

For a treatment cycle, the standard dosage of surufatinib (made by Hutchison Whampoa Pharma Shanghai Co, LTD) is 300 mg once daily, every four weeks. The dosage is changed based on the individual circumstances of enrolled patients and is combined with other anti-tumor therapies (chemotherapy, vaccination, etc.) until the disease progresses, the patient dies, has intolerable side effects, or refuses to continue treatment. Enhanced CT scans were performed every 8 weeks to monitor changes in target lesions, with treatment response evaluated according to Response Evaluation Criteria in Solid Tumors RECIST 1.1.

Evaluation of therapeutic effect and observation index

Objective efficacy evaluations

Target lesion responses were categorized according to Response Evaluation Criteria in Solid Tumors RECIST 1.1 based on contrast-enhanced CT findings, with the following classifications: (1) Complete response (CR): complete response was achieved, with disappearance of all target lesions (confirmed on subsequent imaging), no emergence of new lesions, and normalization of tumor markers sustained for ≥ 4 weeks; (2) Partial response (PR): The target lesions' overall longest diameters decreased by at least 30% and remained that way for at least a week as compared to the baseline sum of the longest diameters; (3) Stable disease (SD): tumor measurements that neither shrank sufficiently to qualify for complete response nor grew sufficiently to constitute progressive disease (maintained for ≥ 6 weeks), with the reference value being the smallest sum of the longest diameters recorded since treatment initiation; (4) Progressing disease (PD): an increase of at least 20% in the total length and diameter of baseline lesions or the appearance of new lesions.

Objective response rate (ORR) and disease control rate (DCR), which are determined using the formulas Objective response rate = (CR + PR)/total cases ×100% and Disease control rate = (CR + PR + SD)/total cases ×100%, are included in the short-term efficacy evaluation.

Survival assessments

They comprised median overall survival (mOS) and median progression-free survival (mPFS). OS referred to the time interval between the first dose and the date of death from any cause, with the last known date of survival used as the deletion date for subjects who did not report death as of the time of analysis. PFS was defined as the time interval between the first dose and objective PD or death (no progression, death from any cause).

Statistical analysis

Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff value, which was typically selected by maximizing Youden's index. Youden's index was calculated as: sensitivity – (1 - specificity), with the maximum value corresponding to the optimal cutoff threshold[15] (Supplementary Fig. 1).

Statistical analyses were performed using SPSS 25.0 software (IBM Corp.). Fisher's exact test was employed to compare differences in CR, PR, SD, PD, ORR, and DCR among patients with different clinical characteristics. Survival analysis was conducted using the Kaplan-Meier method to estimate OS and PFS. Cox proportional hazards regression models were utilized for survival and prognostic analysis. In the univariate Cox regression analysis, variables with $P < 0.1$ were subsequently incorporated into the multivariate Cox regression model.

Projects	Variables	No.of patients	%
Sex	Men	18	64.3
	Women	10	35.7
Age (years)	< 65	18	64.3
	≥ 65	10	35.7
ECOG PS	0–1	21	75
	2–5	7	25
Type of tumor	Pancreatic neuroendocrine tumor	9	32.1
	Non-pancreatic neuroendocrine tumor	7	25
	Other tumors	12	42.9
Lines of therapy at surufatinib	First-line	6	21.4
	Second-line	13	46.5
	Third-line or later	9	32.1
Site of metastasis	Less than 3	21	75
	3 or above	7	25
Dose tolerated	Less than 300 mg/day	22	78.6
	300 mg/day	6	21.4

Table 1. All baseline parameters of patients at the beginning of Surufatinib.ECOG PS, Eastern cooperative oncology group performance status.

Type of tumor	No. Of patients(*n*)	CR	PR	SD	PD	ORR(%)	DCR(%)
Pancreatic neuroendocrine tumor	9	0	3	3	3	33.3	66.7
Non-pancreatic neuroendocrine tumor	7	0	1	2	4	14.3	42.3
Other tumors	12	0	1	2	9	8.3	25.0

Table 2. Best response of Surufatinib in different solid tumors. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Results

Clinical factors of the patients

A total of 28 patients with advanced solid tumors meeting the eligibility criteria were enrolled from Zhejiang Provincial People's Hospital and treated with surufatinib. The cohort comprised 9 PNEN patients, 7 N-pNEN patients, and 12 patients with other tumor types. Baseline characteristics of all patients (Table 1).

Objective efficacy evaluations

The number of patients with the objective efficacy evaluation of CR, PR, SD, and PD following Surufatinib treatment was 0 (0.0%), 5 (17.9%), 7 (25.0%), and 16 (57.1%), in that order. DCR was 42.9%, and ORR was 17.9%. The table of objective efficacy evaluations for various tumor species was displayed (Table 2).

Curative effect

According to Kaplan-Meier analysis of tumor patients from different sources showed that mPFS for PNEN patients were 11 months(95%CI,6.3–24.0 months) and mOS for 17 months (95%CI, 9.7–37.2 months), which was basically similar to the results of SANET-p study. mPFS for N-pNEN patients was 6 months (95%CI, 3.2-1 months), lower than 9.2 months in previous studies. mOS was 7 months (95%CI, 3.7–17.4 months), mPFS was 2 months (95%CI, 0.3–3.7 months) and mOS was 2 months (95%CI, 0.3–3.7 months) for patients with other tumors. Subsequent investigation revealed that PNEN, N-pNEN, and other tumor patients' mPFS and mOS did not differ statistically significantly ($p = 0.091$; $p = 0.088$) (Fig. 1).

Analysis of prognostic factors

Cox proportional hazards modeling and Kaplan-Meier survival analysis in neuroendocrine tumor patients treated with Surufatinib identified the following independent prognostic factors: for OS, fewer than 3 metastatic sites (Fig. 2A), Eastern Cooperative Oncology Group performance status (ECOG PS; Fig. 2B), and baseline free fatty acid (FFA) levels > 635.5 μmol/L (Fig. 2C); for PFS, fewer than 3 metastatic sites (Fig. 2D; Supplementary Table 1). Multivariate Cox regression analysis revealed no independent prognostic factors in other tumor types treated with Surufatinib (Supplementary Table 2).

Adverse reactions

The most common AEs in this study included hypoalbuminemia (38.5%), proteinuria (25%), myelosuppression (14.3%), gastrointestinal reactions (14.3%), hypertriglyceridemia (14.3%), and hyperbilirubinemia (14.3%) (Table 3). Grade ≥ 3 AEs consisted of proteinuria (7.1%) and gastrointestinal reactions (7.1%), all of which

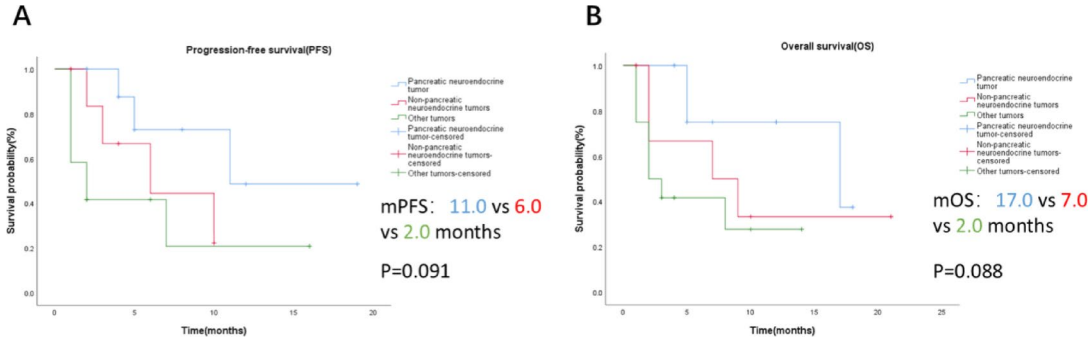

Fig. 1. Kaplan-Meier survival curves of PFS and OS in these three groups of tumor patients. (**A**) PFS in patients with pancreatic neuroendocrine tumors, non-pancreatic neuroendocrine tumors, and other tumors. (**B**) OS in patients with pancreatic neuroendocrine tumors, non-pancreatic neuroendocrine tumors, and other tumors. PFS, progression-free survival; OS, overall survival; mPFS, median progression-free survival; mOS, median overall survival.

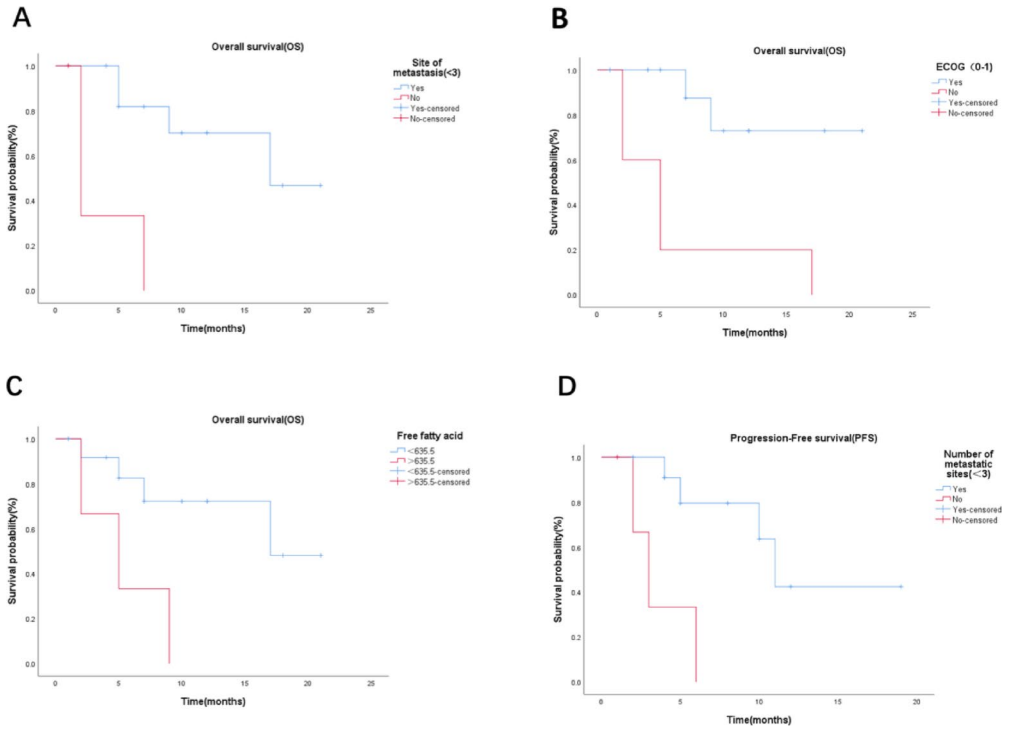

Fig. 2. Based on the important factors of survival and progression-free survival of patients with neuroendocrine tumors treated with solvatinib. (**A**) Patients with a number of metastatic sites < 3 had longer OS than patients with a number of metastatic sites > 3. (**B**) Patients with an ECOG score of 0–1 had a longer OS than patients with an ECOG score of > 0–1. Patients with FFA > 635.5μmol/L had longer PFS than those with less than 3 OS(D) metastatic sites. OS, overall survival; PFS, progression-free; ECOG PS, Eastern Cooperative Oncology Group Performance status. FFA, free fatty acid.

resolved rapidly following symptomatic treatment or drug discontinuation. No grade 4 or higher AEs were observed in the study population.

Figure 2. Based on the important factors of survival and progression-free survival of patients with neuroendocrine tumors treated with solvatinib, (A) Patients with a number of metastatic sites < 3 had longer OS than patients with a number of metastatic sites > 3. (B) Patients with an ECOG PS of 0–1 had a longer OS than patients with an ECOG score of > 0–1. Patients with FFA > 635.5μmol/L had longer PFS than those with less than 3 OS(D) metastatic sites.OS, total lifetime; PFS, progression-free ; ECOG PS, Eastern Cooperative Oncology Group Performance status. FFA, free fatty acid.

Adverse events	Number of patients (%)		Management strategy	
	All levels	Level 3–4	Level 1–2	Level 3–4
Blood system				
Anemia	3(10.7)	0	Supplement iron, vitamin B12, folic acid and other drugs, Surufatinib reduction treatment	Red blood cells were transfused. Surufatinib therapy was suspended
Thrombocytopenia	1(3.6)	0	Recombinant human thrombopoietin and other drugs were used to increase platelets and Surufatinib was reduced	Emergency platelet transfusion. Surufatinib treatment suspended
Metabolic and endocrine systems				
Hypoproteinemia	10(38.5)	0	Increase the intake of high-quality protein, oral nutritional supplements, etc., Surufatinib reduction treatment	Intravenous administration of human albumin, correction of electrolyte disturbance, suspension of Surufatinib therapy
Triglycerides increase	4(14.3)	0	Low fat diet, reduced intake of efinedsugar, etc., Surufatinib reduction treatment	Use lipidlowering agents and stop Surufatinib treatment if necessary
Uric acid increase	1(3.6)	0	Limit high-purine foods, drink more water, and reduce treatment	The drug inhibits the rise of uric acid, and Surufatinib therapy is suspended
Thyroid Stimulating hormone increase	2(7.1)	0	Combined with thyroid function assessment, it can be observed	Endocrinologyconsultation, according to the results of the consultation comprehensive consideration of the next treatment plan
Digestive system				
Bilirubin increase	4(14.3)	0	Liver drug, Surufatinib reduction therapy	Drug intervention, Surufatinib on hold
Aminotransferase increase	3(10.7)	0	Liver drug, Surufatinib reduction therapy	Drug intervention, Surufatinib on hold
Celialgia	2(7.1)	2(7.1)	Dietary adjustment, drug intervention and lifestyle management are the main factors	Emergency drug intervention, screening for serious complications, suspension of Surufatinib treatment
Constipation	1(3.6)	0	Increase dietary fiber and use laxatives	Enema or mechanical defecation, suspension of Surufatinib treatment
Vomiting	1(3.6)	0	Antiemetic therapy	Tube feeding or parenteral nutrition is required and Surufatinib therapy is discontinued
Urinary system				
Proteinuria	7(25)	2(7.1)	Routine hydration, diuresis and 24-h urine volume were measured. Review the urine routine to monitor whether the indicators are normal	Drug intervention, close monitoring of renal function indicators, suspension of Surufatinib treatment
Creatinine increase	3(10.7)	0	Routine hydration, diuresis and 24-h urine volume were measured. Review the urine routine to monitor whether the indicators are normal	Drug intervention, close monitoring of renal function indicators, suspension of Surufatinib treatment
Cardiovascular system				
Hypertension	1(3.6)	0	Low salt diet, blood pressure medication	Antihypertensive medication, suspension of Surufatinib, evaluation of cardiac function
Pericardial effusion	2(7.1)	0	Close monitoring, conservative treatment, Surufatinib reduction treatment	Pericardial puncture and drainage should be performed, and tumor metastasis should be investigated (combined with imaging evaluation), and Surufatinib therapy should be suspended
Other				
Fatigued	1(3.6)	0	Lifestyle intervention, combined with nutrition and psychological support	Drug intervention and multidisciplinary combination therapy

Table 3. Surnfantinib treatment-related adverse reactions.

Discussion

Targeted medicines are particularly noteworthy when the precision medicine age dawns. In order to suppress particular proteins linked to the development of malignant tumors, promote tumor cell apoptosis, and have a potent anti-tumor effect, targeted therapies examine or sequence the DNA or RNA of tumor cells and create medications based on the pertinent mutation sites. Additionally, it can lessen the harmful side effects on healthy cells. Small-molecule kinase inhibitors and macromolecular antibodies are the two primary forms of targeted therapy for malignancies. Small-molecule kinase inhibitors function by blocking the catalytic activity of kinases, such as gefitinib, which inhibits the epidermal growth factor (EGFR) of cancer cells and is authorized for the treatment of non-small cell lung cancer (NSCLC); macromolecular antibody drugs have an anti-tumor effect by blocking the binding of signaling molecules and antibodies[3,16,17].

Both Surufatinib and fruquintinib are small-molecule, multi-target tyrosine kinase inhibitors (TKIs) independently developed by Hutchison Whampoa Pharma[2]. While fruquintinib primarily targets VEGFR-1, -2, and − 3, Surufatinib demonstrates broader kinase inhibition, additionally targeting FGFR1 and CSF-1R beyond the VEGFR family, resulting in a more extensive target profile compared to fruquintinib[18]. The elimination half-life (t1/2) of 300 mg of Surufatinib was comparable in tumor patients and healthy volunteers, with the mean t1/2 following a single oral dosage of the drug being 17.1 h. The geometric mean plasma peak concentration (Cmax) of surufatinib in tumor patients was 674 ng/mL. However, in advanced cancer patients, the mean Cmax of a single 5 mg oral dose of fruquintinib capsule is 195 ng/Ml. When administered at single doses ranging from 2 mg to 6 mg, the mean t1/2 of fruquintinib is 35.2 to 48.5 h. It can be concluded that the Cmax of Surufatinib is higher than that of fruquintinib, while the t1/2 of Surufatinib is the shortest. Due to its faster clearance in

humans, Surufatinib thereby reduces the risk of drug toxicity accumulation in the body[19–21]. (Supplementary Fig. 2; Supplementary Table 3).

Surufatinib has been licensed for the treatment of advanced nonfunctional, well-differentiated (G1, G2), locally or metastatic, non-surgically resectable PNEN and N-pNEN. It also exhibits antitumor angiogenesis and prolongs OS and PFS in patients with neuroendocrine tumors.
[13,14]. Although previous studies by Mizuno Y et al. demonstrated that the anti-angiogenesis target kinase inhibitor TKI could treat PNEN, the efficacy in N-pNEN was unclear[22]. In this study, the survival data for PNEN (11 months) were generally consistent with previous findings from the SANET-p study (10.9 months). However, mPFS for N-pNEN patients was 6 months, which was lower than the 9.2 months observed in SANET-ep. Given the limited sample size of this real-world study, particularly in the N-pNEN subgroup (n = 7), these results should be considered exploratory and not directly comparable with data from large-scale clinical trials. Larger investigations are necessary to confirm the preliminary findings, which indicates that the prognosis of N-pNEN may be substantially worse than that of PNEN.

Patients with neuroendocrine tumors with fewer than three metastases, ECOG PS, and a baseline FFA level below 635.5 mmol/L were shown to have a longer OS based on the results of prognostic survival analysis of various tumor types based on baseline values of metabolic markers. Longer PFS is possible if there are fewer than three metastases. Prior research has demonstrated that a poor prognosis for neuroendocrine tumors is linked to increased levels of lactate dehydrogenase and platelets as well as the number of metastatic locations[23,24]. The findings of this study differ from previous reports, which may be attributed to the limited sample size. While these results require further validation, they provide promising preliminary evidence that warrants confirmation in larger-scale studies.

Despite Surufatinib's current indication being restricted to neuroendocrine tumors, clinical trials have been carried out to treat thyroid and biliary tract cancers (BTC) due to its broad spectrum anti-VEGFR activity[25,26]. For BTC, clinical trial results of Surufatinib monotherapy in patients who failed first-line treatment showed: a 16-week progression-free survival rate of 46.33% (95% CI, 24.38–65.73), median PFS of 3.7 months, and median OS of 6.9 months. These findings indicate that Surufatinib demonstrates clinically meaningful activity in BTC treatment, with safety and tolerability profiles consistent with expectations. Furthermore, the comparative study of Surufatinib monotherapy versus capecitabine chemotherapy in BTC remains ongoing[25]. Given that only 4 BTC patients were included in the current study, survival analysis was not feasible. Therefore, we recommend further investigation with larger real-world datasets to validate these findings.

The optimal dosing strategy of Surufatinib for this tumor type requires further exploration. Real-world evidence indicates that merely 21.4% of patients maintained the standard 300 mg dose, with dose reductions primarily attributed to treatment-related adverse events or clinicians' therapeutic choices when used in combination regimens. Since 100 mg of Surufatinib produced PR efficacy in one patient with pancreatic cancer, it is debatable if all patients require a dose of 300 mg. The number of cases in this study is small, and more cases are expected to be further explored. Our analysis revealed distinct efficacy patterns between dose cohorts: patients receiving the standard 300 mg dose of surufatinib achieved an ORR of 50.0% and DCR of 66.7%, whereas the reduced-dose group (< 300 mg) demonstrated significantly lower response rates (ORR: 9.1%; DCR: 36.4%). Notably, while the standard-dose group showed clinically meaningful improvements in both endpoints, the intergroup differences lacked statistical significance (Supplementary Table 4).

The adverse event profile of Surufatinib reflected characteristic anti-VEGFR class effects, with the most common treatment emergent adverse events being hypoalbuminemia, proteinuria, gastrointestinal toxicity, and elevated bilirubin a pattern consistent with the safety data reported in the pivotal SANET-ep study. The incidence of skin reactions such as hand-foot syndrome is lower than that of other similar drugs, which may be related to the difference in the past chemotherapy of selected cases. Compared to published literature, the incidence of grade 3/4 adverse events was decreased, and most adverse events were grade 1/2 in severity overall.

Surufatinib has been approved for the treatment of PNEN and N-pNEN patients and has demonstrated some success in advanced solid tumors that have not responded to conventional regimens. It has also been proven to enhance survival in these patients[27–30]. The following restrictions have an impact on the study's findings: Because this is a single-center real-world retrospective study, the sample size is small, and there aren't enough outcome events in some subgroups, which could skew the data'stability. To further confirm Surufatinib's effectiveness in various tumor species, multicenter, prospective, large-sample cohort studies with a predetermined sample size and adequate statistical power are therefore desperately needed.

Conclusion

Surufatinib and fuquitinib work through separate mechanisms. While the latter can prevent tumor growth by selectively inhibiting the EGFR pathway, the former can achieve an anti-tumor impact by inhibiting VEGFR 1 and many targets of 2, 3, FGFR 1, and CSF-1R. With a generally manageable toxicity profile, Surufatinib has demonstrated comparable effectiveness trends in patients with PNEN and N-pNEN as well as some therapeutic promise in other advanced solid malignancies. As a result, patients with advanced solid tumors now have a new therapy option with Surufatinib.

Data availability

The data sets generated and analyzed during this period are not publicly available because the study data involves basic patient information. However, areavailable from the corresponding author on reasonable request.

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Author contributions

Z.C. and K.C. made contribution to conception and design. H.Y. analyzed and interpreted the data. H.Y., H.Z., A.Q., X.C. performed the data collection. H.Y. and H.Z. prepared the final draft. F.Y. contributed extensively to the subsequent revisions of the manuscript, including critical data analysis and substantial improvements to the content. All authors contributed to the article and approved the submitted version.

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Declarations

Competing interests

The authors declare no competing interests.

Informed consent

Confirms that informed consent was obtained from all participants and their legal guardians.

Institutional review board

This study was approved by the Ethics Committee of Zhejiang Provincial People's Hospital. Confirms that all experiments were performed in accordance with relevant named guidelines and regulations.

Additional information

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