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RESEARCH ARTICLE

Enhanced anti-tumor effects of combined electric fields, cabozantinib, and radiation therapy in metastatic renal cell carcinoma

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Abstract

Purpose This study aimed to evaluate the therapeutic potential of combining cabozantinib, electric fields (EFs; also called Tumor Treating Fields [TTFields]), and radiation in the treatment of metastatic renal cell carcinoma (RCC), focusing on overcoming resistance to conventional monotherapeutic regimens.

Methods Human renal cancer cell lines (A498, Caki-1) were treated with cabozantinib (10 μM) for at least 6 h, TTFields (200 kHz, 0.8 V/cm) for 24 h, and radiation (3 Gy), both individually and in combination. Cellular responses, including proliferation, apoptosis, and metastatic potential, were analyzed by flow cytometry and Transwell assays.

Results The combination of cabozantinib, TTFields, and radiation exhibited synergistic effects, significantly reducing cell proliferation, enhancing apoptosis, and suppressing metastatic capacity compared with individual treatments. Triple therapy resulted in marked inhibition of metastasis-related markers and changes in apoptotic profiles compared with the control group.

Conclusion This multimodal therapy demonstrated superior efficacy in reducing the metastatic potential and prolonging the survival of RCC cells, offering a promising approach to overcoming treatment resistance in patients with metastatic RCC.

Keywords Renal cell carcinoma (RCC) · Tumor Treating Fields (TTFields) · Cabozantinib · Radiation · Metastasis · Multimodal therapy

Introduction

Renal cell carcinoma (RCC) is a highly malignant tumor, accounting for approximately 2% of global cancer diagnoses and deaths, with an estimated annual global mortality of approximately 175,000 deaths [1–3]. Approximately 25% of patients are diagnosed with metastatic disease at initial presentation, while another 25% develop metastases after curative surgery [4]. The standard first-line treatment for advanced RCC consists of either dual immune checkpoint inhibition (ICI) or a combination of a tyrosine kinase inhibitor (TKI) with ICI. In contrast, localized RCC is managed with surgical resection or stereotactic body radiation therapy (SBRT), which delivers highly focused radiation in a limited number of sessions [2]. However, achieving complete and durable anti-tumor responses in advanced and metastatic RCC remains a significant challenge due to its strong resistance to traditional chemotherapy and radiotherapy [5, 6].

Recently, targeted therapies such as cabozantinib have emerged as promising treatment options. Cabozantinib exerts its anticancer effects by inhibiting key tyrosine kinase receptors, including VEGFR, MET, and AXL, thereby suppressing tumor growth, angiogenesis, and metastasis [7]. This mechanism is particularly important in metastatic RCC, where tumor progression and invasion represent major therapeutic challenges, and clinical trials with cabozantinib have demonstrated efficacy in improving patient outcomes. The METEOR trial, a phase III study evaluating cabozantinib versus everolimus in patients with advanced RCC who had progressed on prior VEGFR-targeted therapy, demonstrated that cabozantinib significantly extended progression-free survival (median: 7.4 vs. 3.8 months) and overall survival (median: 21.4 vs. 16.5 months) compared to everolimus [8]. Similarly, the CABOSUN trial, a randomized phase II study evaluating cabozantinib versus sunitinib as first-line therapy

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in intermediate- and poor-risk patients with advanced RCC, demonstrated superior progression-free survival with cabozantinib (median 8.6 vs. 5.3 months) [9]. However, similar to radiotherapy and immunosuppressive therapies, targeted treatments such as cabozantinib continue to face the challenge of therapeutic resistance, highlighting the need for ongoing research to develop novel therapeutic strategies [10].

Electric fields (EFs), also called Tumor Treating Fields (TTFields), have been found to affect tumor cell survival and proliferation, altering cancer cell growth and metastasis through pathways such as intracellular signaling, oxidative stress regulation, and cell cycle arrest [11]. Radiation induces oxidative stress in cancer cells, accelerating DNA damage. When combined with TTFields, it inhibits the cellular repair mechanisms necessary for DNA damage recovery, thereby promoting apoptotic pathways [12]. Additionally, the combination of chemotherapy and TTFields not only suppresses cancer cell growth and metastasis but also enhances the sensitization of cancer cells to chemotherapy [22]. For these reasons, the combination of radiation, cabozantinib, and TTFields represents a promising approach for treating metastatic RCC, which frequently exhibits resistance to monotherapy. This multimodal strategy has the potential to overcome the limitations of single-agent treatments, offering stronger anti-cancer effects for patients.

The Von Hippel-Lindau (VHL) gene is frequently mutated in RCC, particularly in clear cell RCC (ccRCC) [13]. This study investigated in vitro effects of cabozantinib, TTFields stimulation, and radiation therapy, administered as monotherapy, dual therapy, or triple combination therapy, in two RCC cell lines: Caki-1 (wild-type VHL) and A498 (mutant VHL). By examining differences in biological responses and treatment sensitivity based on VHL mutation status, we aimed to evaluate whether this multimodal approach could be broadly effective, regardless of genetic mutations. This study lays a critical foundation for advancing RCC treatment strategies and aims to address the inherent limitations of existing therapeutic approaches.

Materials and methods

Cell culture and drug/radiation treatment

Human renal cancer cell lines, A498 and Caki-1, were obtained from the Korean Cell Line Bank and maintained in DMEM supplemented with 10% fetal bovine serum (FBS) at 37°C in a humidified atmosphere containing 5% CO_2. The cells were subcultured once or twice per week and plated in 30 mm, 60 mm, or 100 mm dishes, depending on the experimental requirements. Cabozantinib (Sigma-Aldrich Japan, Tokyo, Japan) was dissolved in DMSO according to the manufacturer's instructions and administered to cells at a final concentration of 10 μM for a minimum of 6 hours. For radiation treatment, cells were irradiated using an IBL 437C type H irradiator. To ensure uniform exposure, culture dishes were placed at the center of the irradiator's canister, and cells received a radiation dose of 3 Gy.

Setting experiments for TTFields

Electric signals were generated using a function generator (AFG-2112, Good Will Instrument Co., Ltd., New Taipei City, Taiwan) and amplified using an amplifier (A303, A. A. Lab Systems Ltd., Ramat-Gan, Israel). The amplified electric fields were applied to cells cultured in 100 mm dishes via sterilized insulated wires. TTFields were tested under various conditions, and the optimal parameters for inducing renal cancer cell death were identified as an intensity of 0.8 V/cm and a frequency of 200 kHz.

Cell proliferation and viability assay

To evaluate cell viability, renal cancer cells were exposed to cabozantinib, TTFields, and radiation therapy as monotherapy or in combination. Following exposure, 2,000–5,000 cells per well were seeded into 96-well plates and allowed to adhere. The cells were then incubated with WST-8 reagent (QM2500, BIOMAX) for over one hour, and absorbance was measured at 450 nm using a microplate reader (PHOmo, Autobio Labtec Instruments). Additionally, live cell counts were quantified using a hemocytometer (DHC-N01-5, Incyto) and a microscope after trypan blue staining of the cell suspension. For long-term proliferation analysis, cells were seeded at low density, and after one week, colony formation was assessed via crystal violet staining.

Invasion and migration assays using Transwell chamber systems

Metastatic potential was assessed using invasion and migration assays with Transwell chamber systems. Briefly, 4,000 cells suspended in 200 μL of serum-free DMEM were seeded onto the membrane of each upper chamber, which had been precoated with Matrigel or gelatin. The lower chamber was filled with DMEM supplemented with FBS. Following 48 h of incubation, cells that had traversed the membrane were stained with crystal violet and examined under a microscope.

Apoptosis detection by flow cytometry

Apoptosis assays were conducted according to the manufacturer's protocol (K201-100, BioVision; Milpitas, CA, USA). Apoptosis was induced in experimental cell cultures, while

control cultures were maintained without induction. A total of 1×10^5 cells were harvested by centrifugation, resuspended in 500 µL of 1X Binding Buffer, and labeled with 5 µL of Annexin V-FITC and 1 µL of SYTOX Green dye. The samples were incubated at room temperature for 5–10 min in the dark to prevent photobleaching. Stained cells were analyzed using flow cytometry, with excitation at 488 nm and emission detection at 530 nm. Live cells exhibited minimal fluorescence, apoptotic cells displayed moderate green fluorescence, and necrotic cells showed high-intensity green fluorescence.

Western blotting

The target cells were lysed in lysis buffer, and protein concentrations were quantified using a bicinchoninic acid (BCA) assay. Protein samples were then normalized to the appropriate concentrations and separated by sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE), followed by transfer onto polyvinylidene fluoride (PVDF) membranes. To minimize non-specific binding, the membranes were blocked with 5% bovine serum albumin (BSA) before incubation with primary antibodies specific to the target proteins for over 4 h. After washing with TBST to remove unbound antibodies, the membranes were incubated with secondary antibodies recognizing the primary antibodies. Following additional washes, protein signals were detected using an enhanced chemiluminescence (ECL) method, and the relative expression levels of target proteins were normalized to β-actin as a housekeeping control.

Statistical analysis

Means were compared using Student's t-tests, with p-values < 0.05 defined as statistically significant.

Results

Effects of TTFields alone on RCC cell proliferation

TTFields at intensities of 0.4, 0.8, and 1.2 V/cm for 24 h inhibited RCC cell proliferation in a dose-dependent manner compared to untreated control cells, with significant reductions observed at 0.8 and 1.2 V/cm (Fig. 1A). Similar inhibitory effects were observed in colony formation assays, as determined by crystal violet staining (Fig. 1B). Evaluation of the effects of different TTFields frequencies (150 kHz and 200 kHz) on cell proliferation revealed that 200 kHz exerted a more pronounced inhibitory effect on cell growth than 150 kHz (Fig. 1C). Under optimized conditions (200 kHz frequency and 0.8 V/cm intensity), TTFields significantly suppressed the growth of RCC cell lines A498 and Caki-1 compared to controls, and this inhibitory effect persisted for 24 to 48 h post-treatment (Fig. 1D).

Effects of cabozantinib on RCC cell growth

The effects of cabozantinib on RCC cell growth in vitro were assessed by evaluating cellular responses to various cabozantinib concentrations. A498 and Caki-1 cells were incubated with tenfold serial dilutions of cabozantinib, ranging from 10 µM to 1 nM, for 24, 48, and 72 h. Both cell lines exhibited growth inhibition at a cabozantinib concentration of 10 µM, regardless of treatment duration. This inhibitory effect became more pronounced over time, with prolonged exposure leading to a gradual increase in efficacy (Fig. 2A). To determine the critical time points for growth inhibition within 24 h, A498 and Caki-1 cells were treated with cabozantinib for 0, 0.5, 1, 3, and 6 h, followed by measurement of phosphorylated STAT3 levels, a key regulator of cell growth. Treatment for 0.5 h was sufficient to suppress growth-related protein expression in both cell lines. In Caki-1 cells, phosphorylated STAT3 levels progressively decreased over time, whereas in A498 cells, STAT3 levels transiently increased between 0.5 and 3 h before declining at 6 h. These findings suggest that a minimum treatment duration of 6 h is required to achieve significant growth inhibition (Fig. 2B). Finally, the individual and combined effects of TTFields and cabozantinib on cell proliferation were evaluated in comparison to untreated cells. Both TTFields and cabozantinib, whether administered alone or in combination, suppressed cell proliferation (Fig. 2C).

Effect of radiation treatment on RCC cell survival

To evaluate the effects of radiation treatment on RCC cell survival, A498 and Caki-1 cells were exposed to 0, 3, 6, and 12 Gy of radiation and subsequently incubated for 48 to 96 h. At 48 h, the lowest radiation dose (3 Gy) significantly reduced cell survival compared to untreated controls, with survival rates decreasing in a dose-dependent manner. In Caki-1 cells, survival rates continued to decline progressively from 48 to 96 h. In contrast, A498 cells exhibited a reduction in survival rates up to 48 h, followed by a subsequent increase at 96 h (Fig. 3A). Treatment with TTFields and radiation, either individually or in combination, significantly decreased cell survival rates (Fig. 3B). The combination of TTFields and radiation resulted in lower survival rates than radiation alone, with a more pronounced effect observed in Caki-1 cells. Whereas A498 cells exhibited only a marginal additional reduction in survival with combination treatment compared to radiation alone, Caki-1 cells showed a statistically significant dose-dependent decrease in survival rates (Fig. 3C). These findings suggest that the combination

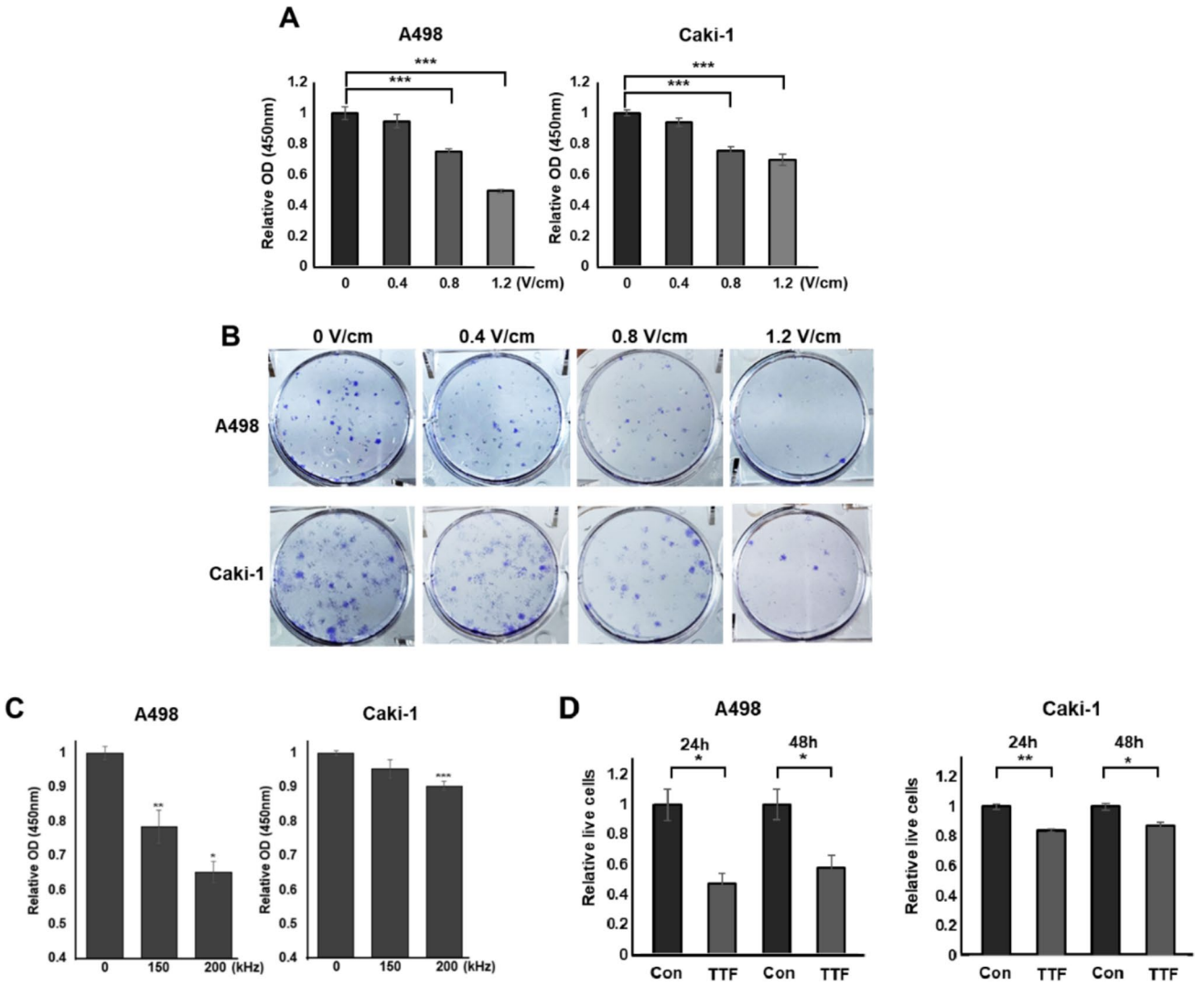

Fig. 1 Effects of TTFields on the A498 and Caki-1 renal cancer cell lines. **A** Effects of TTFields dose on renal cancer cell proliferation, showing that TTFields inhibited cell growth in a dose-dependent manner after 24 h, with significant effects at ≥ 0.8 V/cm. **B** Colony-forming assays, showing that long-term TTFields treatment inhibited cell growth. **C** Frequency-dependent effects of TTFields on cell growth, with 200 kHz showing stronger than 150 kHz. **D** Effects of optimal TTFields conditions (200 kHz, 0.8 V/cm) on cell growth from 24 to 48 h. $*p < 0.05$, $***p < 0.01$, compared with control

of TTFields and radiation therapy may enhance the therapeutic efficacy of radiation in RCC cell lines.

Effects of cabozantinib, radiation, and TTFields, singly or together, on RCC cell survival

Under the established experimental conditions, A498 and Caki-1 cells were treated with various combinations of cabozantinib (10 μM), radiation (3 Gy), and TTFields (200 kHz, 0.8 V/cm). Compared to untreated control cells, these treatments significantly inhibited cell proliferation, following patterns consistent with previous findings (Fig. 4). The combination treatments exhibited synergistic effects, with the degree of growth inhibition varying depending on the specific treatment combinations. Notably, the concurrent application of all three treatments—cabozantinib, radiation, and TTFields—produced the most potent growth-inhibitory effect, highlighting their potential as an integrated therapeutic strategy.

Effects of combination therapy on cell apoptosis and metastasis

Western blot analysis revealed that the expression of the metastasis-associated marker vimentin was lower in cells treated with cabozantinib, radiation, and TTFields compared to untreated control cells. The levels of cleaved PARP, a marker of cancer cell death, were higher in cells receiving the triple

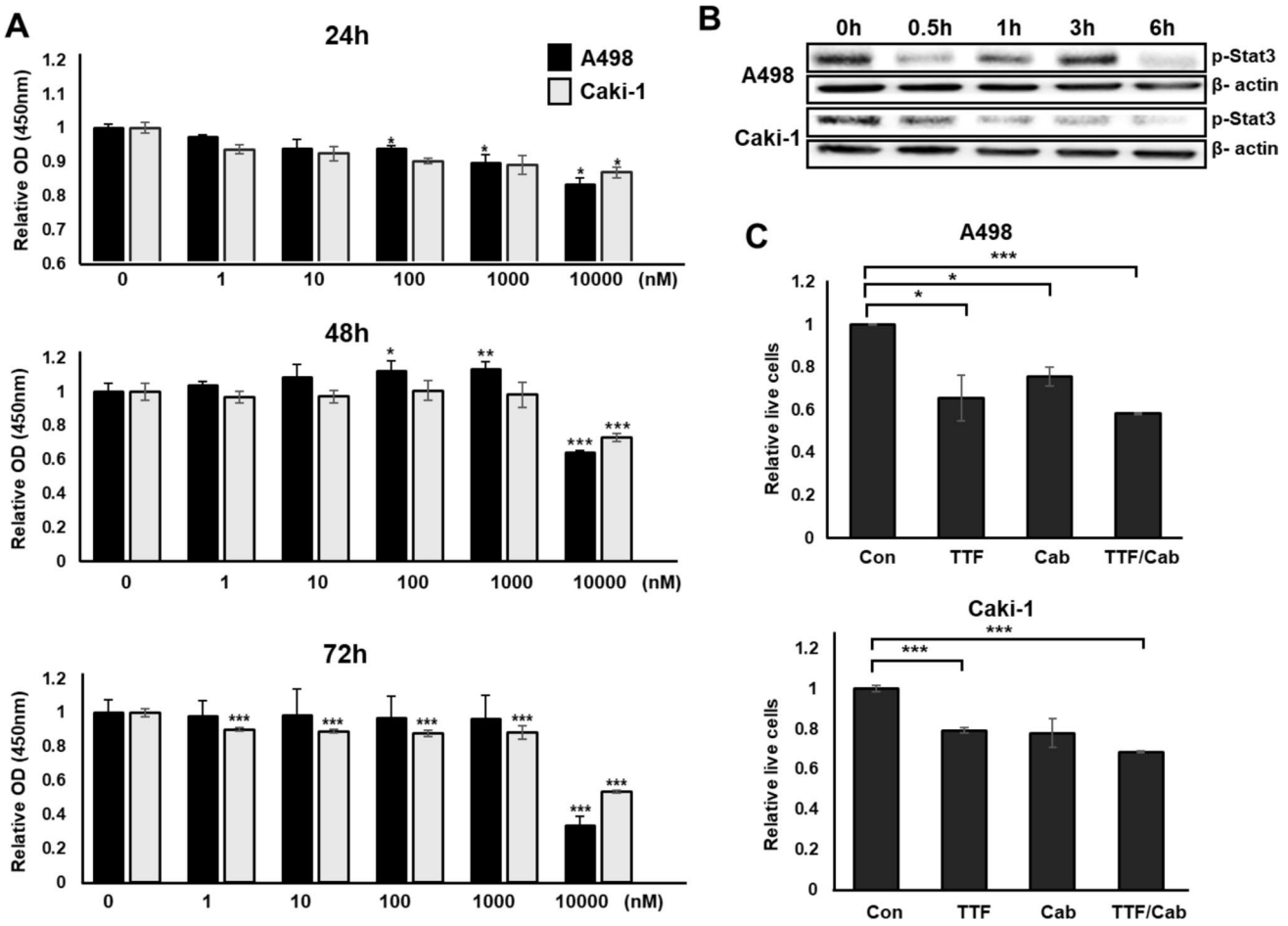

Fig. 2 Effects of cabozantinib on the A498 and Caki-1 renal cancer cell lines. **A** Cabozantinib inhibited cell proliferation in a dose- and time-dependent manner, with significant effects at ≥ 10 μM regardless of treatment duration, and a greater inhibitory effect over time (24, 48, 72 h). **B** Effects of cabozantinib treatment for 0, 0.5, 1, 3, 6 h on phosphorylated STAT3 levels in A498 and Caki-1 cells, showing that growth-related protein expression was suppressed after 0.5 h in both cell lines. In Caki-1 cells, STAT3 levels decreased steadily, whereas A498 cells showed a transient increase before reduction at 6 h. **C** Effects of TTFields and cabozantinib, individually or in combination, on cell proliferation compared with untreated controls. $*p < 0.05$, $***p < 0.01$, compared with control

combination treatment than in control cells. However, neither marker exhibited significant differences in expression between cells treated with the triple combination and those administered conventional treatments (Fig. 5A). In contrast, apoptosis assays using PI/Annexin V staining and FACS analysis demonstrated that the triple combination induced the most potent apoptotic effect (Fig. 5B). Furthermore, assessment of the metastatic potential and cell death capacity of RCC cell lines using Transwell assays indicated that the triple combination therapy significantly suppressed metastatic capacity compared to cells treated with each individual agent or dual-agent combinations (Fig. 5C).

Discussion

Metastatic renal cell carcinoma (mRCC) is frequently diagnosed at an advanced stage, and metastasis significantly affects patient survival [21]. Although targeted therapies and immunotherapies have demonstrated clinical efficacy, their therapeutic potential is limited by low complete response rates and the emergence of drug resistance. For instance, sunitinib has reported an objective response rate(ORR) of only 33%, with resistance continuing to be a major hurdle [13]. However, recent advancements

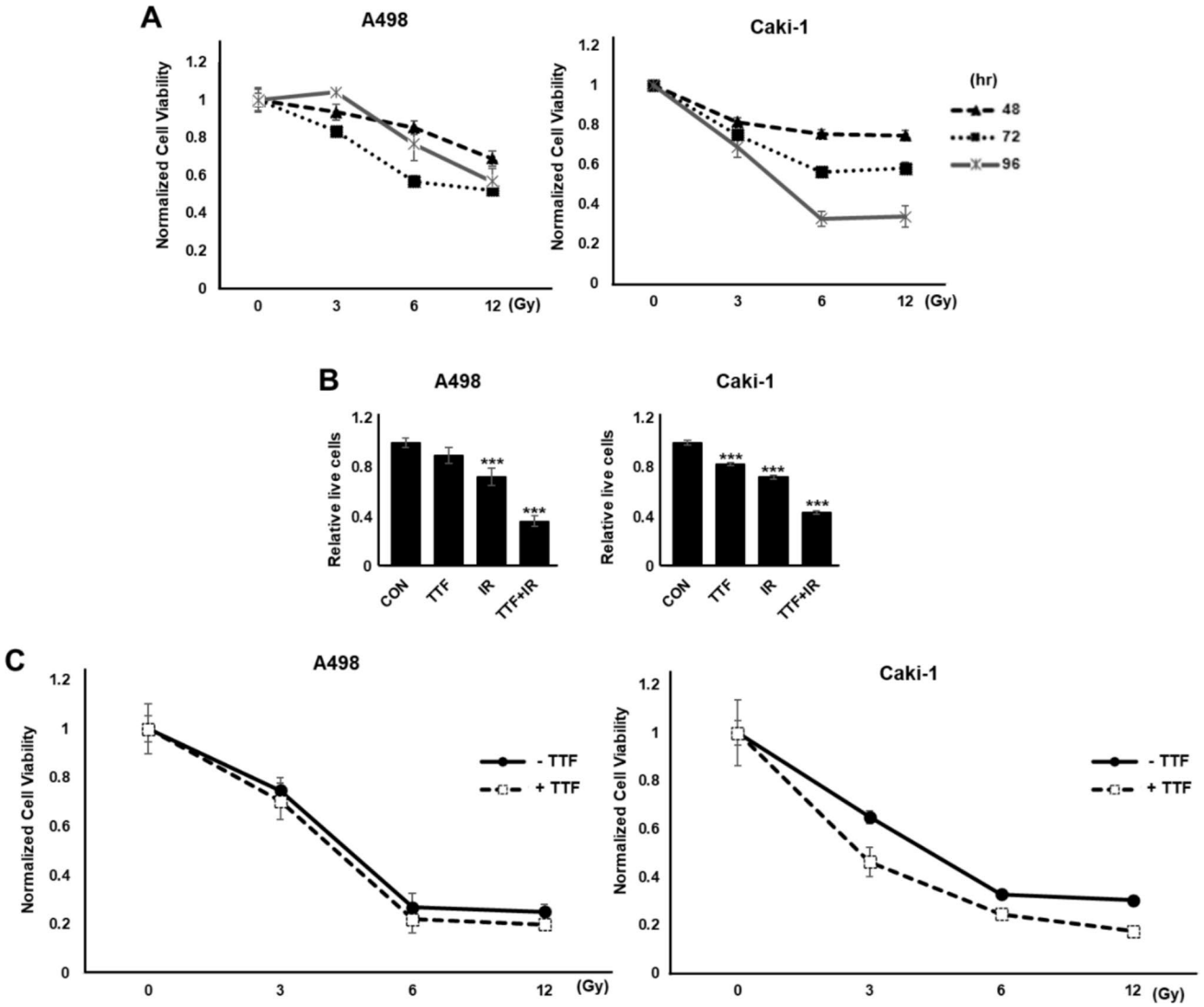

Fig. 3 Effects of radiation treatment on the A498 and Caki-1 renal cancer cell lines. **A** Dose-dependent effects of radiation treatment (3, 6, 12 Gy) on cell survival rates. Caki-1 cells showed continuous reductions in survival from 48 to 96 h, whereas A498 cells exhibited recovery at 96 h after an initial reduction. **B** Effects of TTFields and radiation, alone or in combination, on cell survival rates compared with untreated controls. **C** Effects of combined TTFields and radiation, compared with individual treatments, on cell survival rates. Caki-1 cells showed a more pronounced effect, with a dose-dependent reduction, whereas A498 cells showed only slight additional reductions with combination treatment. $^{*}p < 0.05$, $^{***}p < 0.01$, compared with control

have redefined the therapeutic paradigm, resulting in the approval of cabozantinib plus nivolumab as a first-line treatment for mRCC and a subsequent-line option [14]. Importantly, cabozantinib has demonstrated improved efficacy as an adjunct therapy in patients previously treated with radiation. Additionally, cabozantinib is approved for hepatocellular carcinoma and medullary thyroid carcinoma. Despite these clinical benefits, dose optimization is essential due to the high incidence of adverse effects such as fatigue, dermatologic reactions, and nausea. Therefore, careful consideration of these adverse effects is necessary when determining optimal treatment strategies [7, 15, 16].

TTFields have demonstrated efficacy across various cancers, including glioma, non-small cell lung cancer, and pancreatic cancer [17, 18]. Notably, TTFields are known to enhance anticancer treatment outcomes by increasing DNA damage and drug sensitivity when combined with radiation therapy and chemotherapy [11]. However, previous studies have primarily reported a strong synergistic effect of TTFields in combination with cytotoxic chemotherapeutic agents, such as paclitaxel, doxorubicin, and cisplatin, whereas its combinatorial effects with targeted therapies remain relatively underexplored. Cabozantinib, a targeted anticancer agent, exerts its therapeutic effects by inhibiting

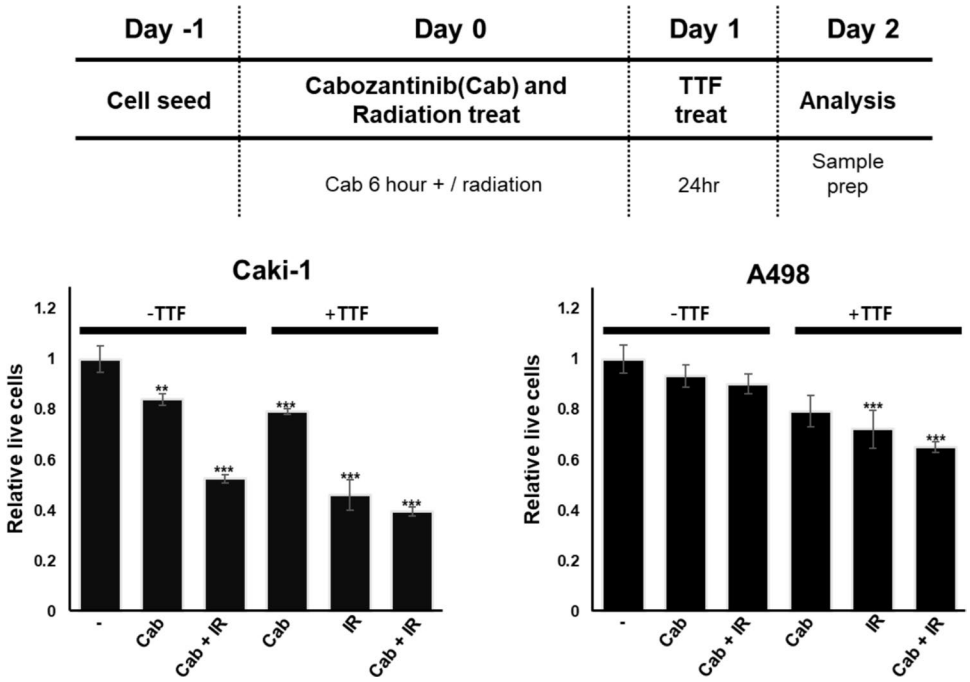

Fig. 4 Effects of cabozantinib (10 μM), radiation (3 Gy), and TTFields (200 kHz, 0.8 V/cm), individually or in combination, on the growth of A498 and Caki-1 cells, with growth inhibition being consistent with previous findings. Combination treatments demonstrated synergistic effects, with varying levels of growth inhibition depending on the specific combination. The triple combination of cabozantinib, radiation, and TTFields exhibited the strongest growth-inhibitory effect, highlighting its potential as a comprehensive therapeutic strategy. *$p < 0.05$, ***$p < 0.01$, compared with control

VEGFR, MET, and AXL, thereby disrupting the endothelial-mesenchymal transition (EMT). Additionally, cabozantinib has been shown to suppress STAT3 phosphorylation—a key regulator of EMT—as well as the activation of metastasis-associated transcription factors, such as vimentin, in renal cell carcinoma (RCC) cells [19]. Therefore, the combination of cabozantinib with TTFields and radiotherapy in RCC cell lines represents a promising anticancer strategy, offering potential therapeutic benefits while reducing the adverse effects associated with cytotoxic chemotherapy.

Our study is the first to apply cabozantinib in combination with radiotherapy and TTFields to renal cancer cells. As a result, we observed not only a substantial reduction in the number of renal cancer cells but also an increase in cleaved PARP protein levels and elevated PI/Annexin V staining, indicating the induction of cell proliferation inhibition and apoptosis. Additionally, vimentin expression was reduced at the protein level, and Transwell assay results demonstrated a significant attenuation of cell migration and invasion compared to the untreated group. These findings particularly highlight the ability of the TTFields-based combination therapy to suppress cancer cell survival and epithelial-mesenchymal transition (EMT). When treated with the triple combination therapy, cell viability was significantly reduced in both RCC cell lines, with a notably higher sensitivity observed in Caki-1 cells. In fact, simultaneous treatment with TTFields and cabozantinib for 24 h resulted in complete cell death in Caki-1 cells, regardless of radiotherapy administration (data not shown). This discovery suggests a potential correlation with the VHL gene status; however, further studies are required to precisely validate this hypothesis. Moreover, since the in vitro model used in this study does not fully replicate the complexity of the in vivo tumor microenvironment, additional research is necessary to assess the feasibility and efficacy of this approach in preclinical and clinical settings.

In conclusion, this study introduces a novel therapeutic strategy that effectively targets and inhibits the survival and metastasis of RCC cells by combining cabozantinib and radiotherapy with TTFields. This approach holds significant potential to overcome cancer cell resistance observed in monotherapies and allows for the use of lower doses of cabozantinib and radiotherapy, thereby reducing systemic toxicity and side effects. Furthermore, similar to previous findings demonstrating synthetic lethality when hyperthermia is combined with TTFields in lung cancer cell lines [20], our study suggests that the combination of cabozantinib, radiotherapy, and TTFields may also induce synthetic lethality by suppressing phosphorylated STAT3 and PARP. Future research should focus on optimizing the parameters of the electric field to enhance its therapeutic efficacy and exploring its broader applicability across various types of cancer. Additionally, further efforts are needed to expand clinical trials aimed at evaluating the effectiveness of the combined treatment approach involving cabozantinib, TTFields, and radiotherapy, ensuring a comprehensive assessment of its potential benefits and safety in diverse cancer models.

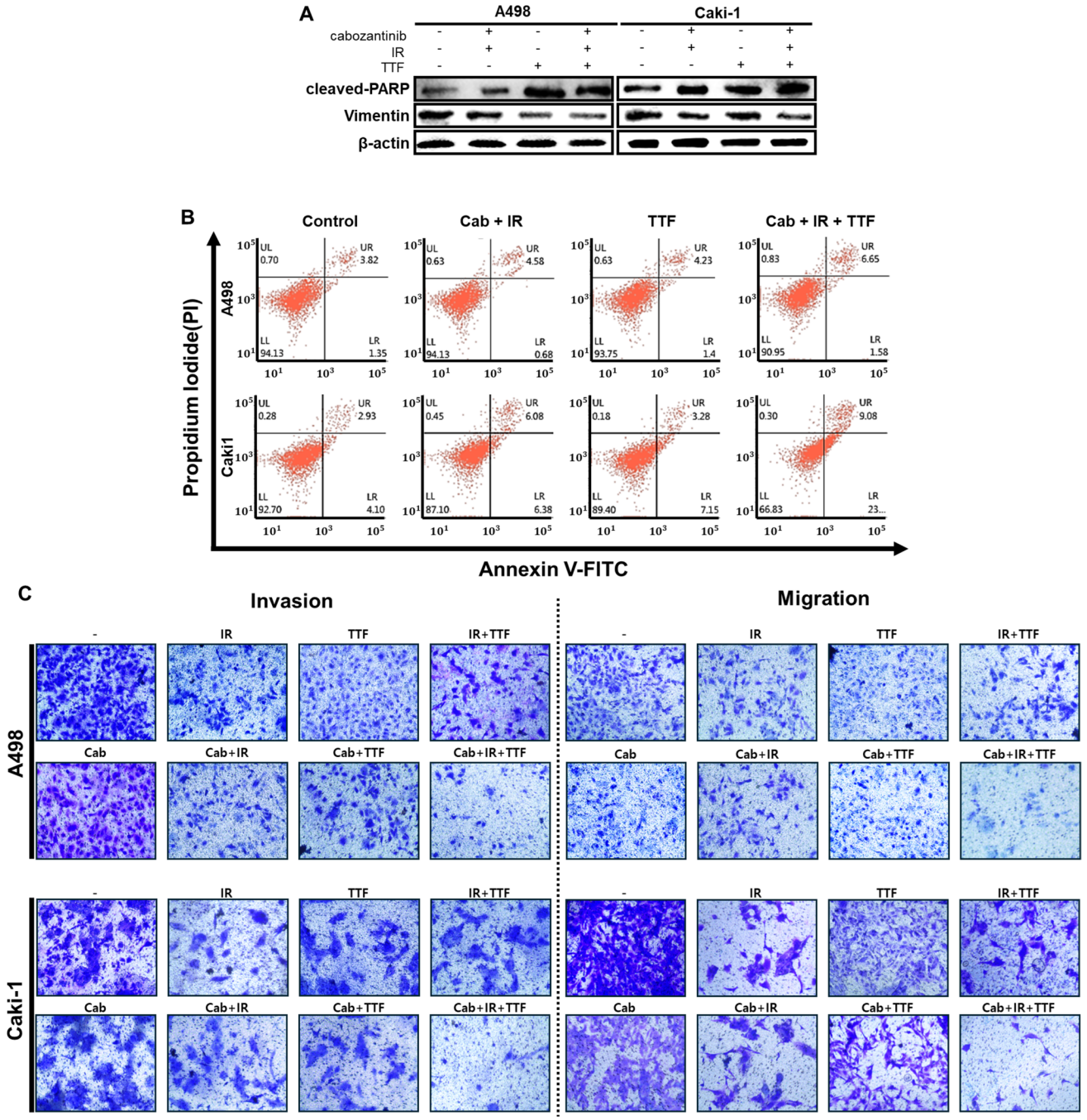

Fig. 5 Effects of cabozantinib (10 μM), radiation (3 Gy), and TTFields (200 kHz, 0.8 V/cm), individually or in combination, on the properties of A498 and Caki-1 cells. **A** Western blot analysis, showing that treatment reduced the expression of the metastasis-specific marker vimentin, while increasing the expression of the cell death marker cleaved PARP, compared with control cells. **B** Apoptosis assays using PI/Annexin V staining and FACS analysis, confirming that apoptosis was more pronounced in cells receiving triple combination therapy than in those receiving other combinations. **C** Transwell assays showing that the triple combination therapy significantly reduced the invasive and migratory capacities of renal cancer cell lines compared with single or dual treatments

Conclusion

This study underscores the synergistic therapeutic potential of combining cabozantinib, TTFields, and radiation therapy to overcome the limitations of monotherapy in metastatic renal cell carcinoma. By concurrently targeting proliferation, apoptosis, and metastasis-associated pathways, this multimodal strategy exhibited enhanced efficacy, presenting a promising approach for mitigating treatment resistance and improving patient outcomes. Future clinical investigations

are essential to refine this strategy and facilitate its translation into a standardized and accessible treatment paradigm for RCC and other refractory malignancies.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jin-ju Heo. The first draft of the manuscript was written by Jin-ju Heo and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval This manuscript does not involve any studies conducted by the authors with human participants or animals; therefore, ethical approval and informed consent are not applicable.

Informed consent For this type of study formal consent is not required.

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