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Application of irreversible electroporation ablation in oncology - a narrative review

PIECUCH Dawid[1*], HAŃCZYK Edyta[2], SOBOTA Weronika[3], PISKORZ Przemysław[4]

[1*] Faculty *of Medicine, Kazimierz Pułaski University of Radom: Radom, Poland*
dawsid1999@gmail.com
https://orcid.org/0009-0006-8074-0122
[2] *Faculty of Medicine, Kazimierz Pułaski University of Radom: Radom, Poland*
edyta.hanczyk25@gmail.com
https://orcid.org/0009-0003-2769-943X
[3] Faculty *of Medicine, Kazimierz Pułaski University of Radom: Radom, Poland*
werasobota@gmail.com
https://orcid.org/0009-0000-7778-7030
[4] Faculty *of Medicine, Kazimierz Pułaski University of Radom: Radom, Poland*
przemekpiskorz95@o2.pl
https://orcid.org/0009-0000-9812-2230

***correspondence: dawsid1999@gmail.com**

Abstract

Irreversible electroporation-IRE is an innovative cancer treatment method that can selectively destroy cancer cells without damaging surrounding tissues. It is a safe and effective alternative to traditional methods, with the patient faster recover potential and spare critical body structures such as blood vessels and nerves.In surgical oncology, the IRE treatment technique is used especially in cases where other methods are not possible or have limited effectiveness. The method is proving to be seen as an effective local treatment with good clinical results and limited side effects in prostate, biliary, pancreatic, kidney and liver cancers.

Keywords

Irreversible electroporation-IRE, literature review, prostate cancer (PCa), Perihinal bile tract cancer, Pancreatic cancer, Kidney tumors, Liver cancer, Glioblastoma multiforme

Introduction

Electroporation is an innovative treatment technique based on the creation of "nanopores" in the cell membrane, increasing its permeability and disturbing the homeostatic balance. This technique can be reversible (“RE”) or lead to cell death (irreversible electroporation “IRE”). Among the available methods (standard electroporation, irreversible electroporation [IRE], calcium electroporation, vascular endothelial growth factor electrochemotherapy [VEG-ECT] and gene electrotransfer [GET]), in patients with large and deep soft tissue tumors, an alternative treatment to standard electroporation became VEG-ECT. However, due to the ease of performance, safety and clinical results, reversible electroporation remains the most popular treatment technique among the above-mentioned [1]. It has been used in electrogenotherapy and electrochemotherapy. However, IRE has been used in oncology due to the selective destruction of cancer cells, without generating a significant increase in temperature, which results in minimizing damage to the tissues surrounding the treated area [2-3]. It is a non-thermal and minimally invasive ablation that uses short, ultra-fast and strong electrical impulses [4]. It allows you to spare nearby blood vessels and nerves that are sensitive to heat and damage, which distinguishes this method of thermal techniques. Moreover, the treatment effect is not dependent on blood perfusion within the treated area. Treatment with IRE results in faster recovery [5]. IRE is a promising new technique for the local treatment of tumors that do not qualify for surgical resection or thermal ablation, such as: liver, kidney, pancreas, prostate and others [3,6-8]. The effectiveness of cancer cell treatment is also largely due to the retention of tumor-specific antigens after IRE, which determine a strong immune response of patients while improving therapeutic results [6]. Clinical trials have also been ongoing for several years on the use of irreversible pulsed field electroporation ablation (PAF). It is an innovative, non-thermal method of treating atrial fibrillation (AF). PFA exhibits tissue selectivity, where the myocardium may have a lower threshold field intensity to induce

necrosis compared to other tissues such as blood vessels or nerve fibers [2,5,9-10]. Due to the assumptions, this review article discusses current research on the clinical application of irreversible electroporation in oncology.

Methods

A literature review was performed in the PubMed database. The search was performed on August 25, 2024. Limited to the last 10 years The following search terms were used: "electroporation ablation" OR "IRE". Only articles with full free access, such as clinical trials and randomized clinical trials in oncology, were included in the review [Fig1].

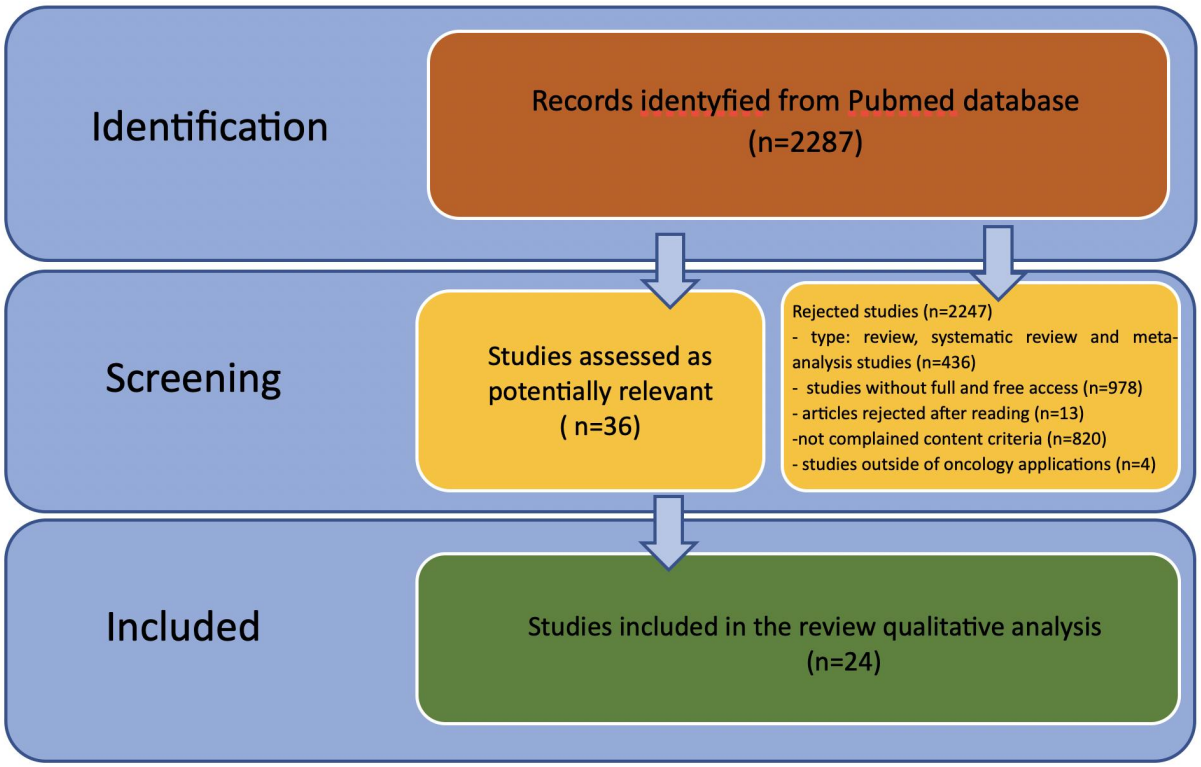

Figure 1. Scheme for including studies in a literature review.

Results

This systematic review included 24 studies. Table 1 presents the included studies with their brief description and division according to the treated organ and the year in which the study was conducted.

	Study	Year	Brief description of the methods and results of studies
Prostate cancer	Haifenga Wanga	2022	Controlled Clinical Trial about High-Frequency Irreversible Electroporation
	Massimo Valerio	2017	Nanoknife Electroporation Ablation Trial
	Shoulong Dong	2018	First Human Trial of High-Frequency Irreversible Electroporation Therapy
	Matthijs JV Scheltema	2016	Randomized Controlled Trial - Focal vs extended ablation Clinical
	Kai Zhang	2023	trial Focal vs Extended Irreversible Electroporation
	Jean de la Rosette	2022	Randomized Controlled Trial about patients quality of life
Glioblastoma multiforme	Melvin F. Lorenzo	2017	Descriptive study about Irreversible Electroporation and High-Frequency Irreversible Electroporation
	John Rossmeisl	2017	Retrospective study about treatment
Perihinal bile tract cancer	Lotte C Franken	2022	A Prospective Pilot Study
Liver cancer	Yumei Yang	2019	Randomized Controlled Trial about Electroporation and Clinical trial - Allogenic Natural Killer Cell
	Laura Coletti	2017	Clinical trial about colorectal liver metastases treatment
	Hester J Scheffer	2015	Trial about efficacy of irreversible electroporation
	K Nielsen	2014	Clinical trial - Anaesthetic management
Pancreatic cancer	Katsutoshi Sugimoto	2018	evaluation of irreversible electroporation
	Laurien G P H Vroomen	2017	Clinical trial about MR and CT imaging after IRE
	Maria Paola Belfiore	2015	Clinical trial - IRE and neoadjuvant chemiotherapy
	Yang-Yang Ma	2020	Gemcitabine plus IRE vs gemcitabine alone
	Mao Lin	2020	Randomized Controlled Trial about IRE plus allogenic Vγ9Vδ2 T cells
Kidney tumors	Mara Buijs	2021	Clinical trial-MRI and CT in the follow-up after IRE
	Peter G K Wagstaff	2015	A a prospective trial - The efficacy and safety of IRE
Soft tissue tumours	Andrea Simioni	2020	Clinical trial-long needle variable electrode-geometry electrochemotherapy

Table 1. Brief characteristics of all studies included in the review.

Prostate cancer

Treatment of prostate cancer (PCa) with radiotherapy and radical prostatectomy is associated with numerous complications. A new way to destroy cancer cells while sparing healthy tissues close to the prostate is IRE. The IRE technique may induce muscle spasms that reduce the therapeutic effectiveness of ablation. In order to spare functional structures exposed during IRE, Shoulong Dong et al. conducted the first trial of PCa treatment using high-frequency pulse electroporation (H-FIRE). Very quick post-operative recovery was noted, and after half a year the clinical condition of the patients was assessed, stating 100% preservation of sexual functions, micturition control, NVB sparing and no urethral disruption. This technique allows for reducing the doses of muscle relaxants during the procedure [5]. The same technique was used by Haifeng Wang et al. in a two-year study. Investigators demonstrated significantly lower rates of PCa after H-FIRE and fewer side effects compared

to historical controls of patients treated with other energy platforms. Half a year after H-FIRE, only 7 of 109 patients had clinically significant PCa. The collected biopsies revealed PCa in 13% of patients (Gleason 7 - 2%, Gleason 6 - 11%). Researchers observed a median (IQR) reduction in prostate-specific antigen (PSA) levels of 7.9, the International Prostate Symptom Score (IPSS) was 0.57 at baseline, and only 10 patients experienced erectile dysfunction as measured by the International Index of Erectile Function 5 (IIEF-5) [2]. This method is associated with low aggressiveness towards the tissues surrounding the prostate and is a promising treatment alternative. High safety and minor urogenital complications after irreversible electroporation in the treatment of localized prostate cancer were demonstrated by Valerio et al. One year after IRE treatment, researchers noted that the percentage of patients with an erection enabling sexual intercourse decreased by only 6%, and taking into account changes in UCLA-EPIC (UCLA Expanded Prostate Cancer Index Composite) and I-PSS (International Prostate Symptom Score) reported improved urinary tract function. In as many as 69% of patients, no remnants of PCa were detected and a significant reduction in PSA was noted [11]. Similarly, Matthijs JV Scheltema et al. indicate satisfactory short-term oncological effects in patients with unilateral PCa [12]. Kai Zhang et al., who assessed oncological patients with low- and intermediate-risk PCa at the time of treatment, an average of 2.5 years after focal and extended irreversible electroporation. At the time of follow-up, as many as 85% of patients were not diagnosed with clinically important prostate cancer, and the oncological effects in both groups of patients were comparable. Only 5 people in each group had PCa ≥3 + 4 on the Gleason scale in the area where focal and extended IRE was used [13]. Based on the above study by Kai Zhang et al., Jana de la Rosette et al. assessed side effects and quality of life in patients undergoing focal and extended IRE. After 13 weeks, the number of side effects was comparable, and taking into account IIEF-5 and EPIC, less erectile dysfunction was found in patients undergoing focal IRE. Other components of quality of life were comparable. Both techniques bring comparable therapeutic effects, and focal electroporation translates into a better quality of intercourse for patients during the convalescence period [14].

Perihinal bile tract cancer

Lotte C. Franken et al. conducted studies showing the safe effectiveness of open or percutaneous IRE in patients with unresectable perihilar cholangiocarcinoma (PHC). Survival after 3 months after the procedure was 100%, and adverse events occurred in half of the treated patients. . The researchers point out that the procedure was carried out without any problems and was not associated with any equipment problems or intraoperative events. Mortality one year after treatment was also determined and was 25%, with the age of patients at the time of qualification ranging from 51-75 years [15]. The study confirms the feasibility of the procedure, but indicates the validity of conducting research examining the effectiveness of IRE in PHC. There is a need for further research taking into account patients from a wider age group.

Pancreatic cancer

In patients with locally advanced pancreatic cancer (LAPC) who cannot undergo radical tumor resection, a new method of IRE has been introduced into the treatment in the last 10 years. Researchers indicate that this is a promising and minimally invasive method that does not damage nerves and blood vessels, as well as the closely located bile, pancreatic and common ducts, as well as the walls of the stomach and duodenum.

Sugimoto K et al. conducted a small study of 8 patients with LAPC ≤ 5 cm subjected to IRE to evaluate its effectiveness. Open (4 patients) and percutaneous (4 patients) approaches were used. The study took into account the primary endpoints, i.e. the occurrence of complications within 90 days, and the secondary endpoints: overall survival (OS) and time to local progression. All patients recovered completely and none of them died within 90 days. There were 5 minor complications in 3 patients and 4 major complications in 3 patients [16]. Laurien G P H Vroomen et al. focused on the assessment of characteristic imaging features after percutaneous IRE in patients with LAPC (after ceMRI and ceCT). 25 patients underwent IRE, and 28% of them experienced complications. The investigators observed: pancreatitis (n = 1), duodenal wall ulceration (n = 1), new-onset biliary obstruction (n = 3), cholangitis with infected biloma (n = 1), and partial occlusion of the superior mesenteric artery (n = 1). After 6 months, tumor recurrence and local growth were assessed. Early local recurrence and an increase in the CA 19.9 marker occurred in 20% of patients. In post-IRE examination using diffusion-weighted imaging (DWI)-b800, an overall reduction in signal intensity was observed in all cases. The volume of the ablation zone increased early after the procedure, reaching a maximum after 6 weeks, and then decreased. In patients with tumor recurrence, a hyperintense spot was observed on DWI-b800 images, preceding a clear recurrence confirmed by ceCT [17]. In a small study by Maria Paola Belfiore et al., patients were treated with IRE followed by chemotherapy. No serious complications were noticed after the procedure. Two patients developed a mild increase in amylase and mild ascites without the need for drainage. After 6 months of follow-up, 90% of patients achieved local control, 3 patients underwent surgery after treatment with R0 resection, and 18 patients had no tumor progression. Investigators concluded that neoadjuvant percutaneous IRE ablation and gemcitabine-oxaliplatin-based chemotherapy in patients with LAPC is safe and effective in providing short-term local control of LAPC, with a possible downstaging effect [18]. Yang-Yang Ma et al also conducted a study evaluating the treatment effects of 33 LAPC patients with Gemcatybine (GEM) in combination with IRE compared with 35 patients who received chemotherapy alone. The technical success rate for IRE ablation was 100%. The main adverse events reported after IRE were pancreatitis (n=2) and bleeding from a duodenal ulcer (n=1). The symptoms disappeared within two weeks. The researchers concluded that the use of IRE + GEM is a feasible and safe therapeutic method. Combination therapy reduced tumor progression twice (82.5% of patients after chemotherapy, 45.4% after combined treatment with GEM + IRE). Despite the small number of subjects studied, researchers suggest that Gemcitabine combined with concurrent IRE is an effective treatment for patients with LAPC [19]. Lin M et al. assessed the effectiveness of combining IRE with immune cell therapy in patients with pancreatic adenocarcinoma. 30 patients underwent combined IRE and T-cell treatment, while 32 patients underwent ablation only. They suggest that IRE in combination with γδ T cells ensures longer survival for patients and enhances the anti-cancer effect. This may be a new treatment strategy for LAPC patients [20]. Percutaneous IRE in the treatment of pancreatic cancer is associated with greater pain compared to the same procedure in patients with kidney, liver and pelvic cancer [9].

Kidney tumors

In the group of patients with small renal masses (SRM), an alternative treatment to partial nephrectomy is focal IRE ablation, which is associated with minor renal insufficiency. The best candidates for IRE are patients with kidney tumors < 4 cm in diameter; larger tumors may reduce the effectiveness of the procedure [21]. Mara Buijs

et al. used MRI and CT imaging to study the effectiveness of IRE in patients with SRM (80% - clear cell carcinoma, 10% - papillary carcinoma, 10% - non-diagnostic biopsy). One week and 3 months after the procedure, an increase in the ablation zone (AZV) was observed, and from the 6th month, its reduction was observed compared to the intraoperative AZV. Researchers attribute the initial increase in AZV mainly to postoperative tissue swelling. One of the subjects, whose tumor initially had the largest dimensions among those examined (56.3 cm3), had residual disease - clear cell carcinoma. Planned volumes (NCV) were slightly higher on CT imaging than MRI. The few post-procedure complications included: pyelonephritis, hematuria visible to the naked eye, dysuria and renal hematoma. In all subjects, renal function returned to its pre-operative state [4]. In K. Nielsen's studies, the only complication in patients with renal tumors was hematuria and it occurred only in 1 of the subjects [9]. It is therefore important to carefully select candidates for the procedure, taking into account the potential risks and benefits of IRE ablation, especially when tumors are > 4 cm in diameter. Due to the small cohort of subjects, there is a need to conduct more extensive clinical trials confirming the safety and feasibility of this modern treatment technique. Hematuria is the most frequently reported complication.

Liver cancer

IRE is a modern alternative to local treatment for tumors located in the liver that do not qualify for resection and thermal ablation [1,9,22]. Yumei Yang et al. demonstrated that IRE combined with allogeneic NK cell immunotherapy in the treatment of primary liver cancer (PLC) is associated with greater effectiveness and safety compared to IRE alone. For combined therapy, the average progression-free survival (PFS) was higher by 4.5 months and the clinical response rate after 3 months was higher by 20.7%. Dual therapy compared to IRE alone was characterized by lower values of circulating tumor cells (CTC) and serum α-fetoprotein (AFP), CA 19-9 values did not change in both groups [6]. Combination therapy brings satisfactory therapeutic effects, however, the assessment of patient response was short-term and included only 40 patients, therefore there is a need to conduct longer clinical trials. IRE has potential application in the treatment of centrally located liver metastases (CRLM) of colorectal cancer, which are unresectable and cannot be treated with thermal ablation [1]. Research conducted by Laura Coletti et al. confirms the feasibility and effectiveness of combined treatment with electrochemotherapy combining electroporation with bleomecin in patients with multifocal liver metastases of colorectal cancer. One month after the procedure, a response to treatment was observed using MRI in as many as 5/9 lesions, and 4/9 lesions remained as at the time of treatment. Ultimately, after 6 months, one third of the cancer lesions responded fully to treatment, 1 lesion was stable, and in one patient, as many as 5 metastases progressed. No complications were recorded during or after surgery [22]. The use of open surgical intervention on the liver combined with electrochemotherapy can guarantee the effectiveness and preservation of organ tissues in patients with unresectable liver metastases. In studies on anesthetic management, K. Nielsen et al. drew attention to few complications related to the IRE procedure. Among the 28 patients included in the study, as many as 46% were patients with liver cancer. The treatment was not associated with life-threatening complications. Pneumothorax occurred in 15% of patients with liver cancer, and additional ventricular contractions were also observed during open IRE on the liver near the left diaphragm [9]. Treatment with IRE is associated with minor intraoperative and postoperative complications.

Other tumors in the pelvic area

In a study by K Nielsen et al., 28 patients with pancreatic cancer, biliary tract cancer, hepatic adenoma, renal cell carcinoma, presacral carcinoma-colorectal cancer metastasis, and colorectal liver metastasis (CRLM) were treated with IRE for 30 sessions. Thirteen patients were treated at laparotomy for CRLM, the remaining 15 patients were treated percutaneously. During the procedure, patients noticed increased systolic and diastolic blood pressure, which was easy to control. Minor cardiac arrhythmias were noted in two patients and were self-limited. Apart from these cardiac arrhythmias, no major complications were noticed after the procedure. By assessing muscle contractions during IRE, the researchers suggested that local contractions were more profound during percutaneous procedures, especially when the electrodes were inserted through large muscles. During IRE in the pelvis and pancreas, isolated muscle spasms concerned: the gluteus maximus and the rectus abdominis muscle. No electrolyte disturbances were noted in laboratory tests. Percutaneous IRE of the liver, kidneys and pelvis did not cause much discomfort. The study, although conducted on a small group of people, shows that IRE ablation is safe and complications resulting mainly from muscle cell contractions are easy to manage [9]. Scheffer HJ et al. also point to the potential use of IRE in CRLM, suggesting that it may be a palliative treatment that prolongs life in patients with unresectable tumors [24].

Glioblastoma multiforme

Glioblastoma multiforme is a very aggressive and poorly prognostic cancer, therefore research is being conducted on the use and effectiveness of treatment with IRE and H-FIRE [23]. Both methods temporarily disrupt the blood-brain barrier, which can be used to deliver therapeutic substances to the tissue surrounding the tumor [7]. The use of H-FIRE offers the opportunity to spare major blood vessels and nerves, selectivity towards malignant cells, more predictable ablation geometry due to the mitigation of impedance changes and the absence of muscle spasms [23]. H-FIRE is an innovative method enabling non-thermal tissue ablation without the need to use neuroparalyzing agents. Studies in dogs with brain tumors have confirmed the safety and effectiveness of both methods, with improved radiological outcomes and function after IRE treatment of gliomas. Both techniques are being considered for use in intracranial surgery, particularly in the treatment of brain cancer [7].

Conclusion

This review focuses on the application of the modern IRE technique in the treatment of cancers of the prostate, biliary tract, pancreas, kidney, liver, pelvis and glioblastoma multiforme. This method is used for cancers that do not qualify for other treatments. IRE is a precise and accurate technique that increases the chances of a complete cure or long-term inhibition of tumor growth. Additionally, it can reduce the risk of disease recurrence after treatment. The present study demonstrates the safety and absence of significant complications associated with the procedure and in the postoperative period. The high selectivity and low invasiveness of IRE against target tissues spares the structures surrounding the treated area, resulting in faster patient recovery. In prostate cancer, high protection of genitourinary organs and preservation of erectile function are observed after H-FIRE treatment.The method has also proven effective in LAPC patients, as it is not associated with serious

postoperative complications.It can ensure longer survival for patients.In qualifying potential candidates for IRE as an alternative to partial nephrectomy, the diameter of SRM tumors is important. The larger the tumor, the less effective the therapy. Association of IRE with NK cells guarantees PFS in patients with primary liver cancer. Electrochemotherapy with cytostatic treatment improves the efficacy of IRE in patients with multifocal colorectal cancer metastases to the liver and LAPC. Further clinical trials on the use of IRE for PHC and pelvic cancers and H-FIRE in patients with glioblastoma multiforme are warranted.

Limitations of the review

Limitations of this review paper include the scant availability of sources related to a modern treatment technique such as IRE. Difficulties in synthesizing and comparing the collected information are due to the lack of international treatment standards and differences in the application of the technique itself in novel studies. Due to the modernity of research on the use of IRE in oncology medicine, there is no complete view of the effectiveness and possible side effects of this technique.

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