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REVIEW ARTICLE

Irreversible electroporation and sarcomas: where do we stand?

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Summary

Sarcomas arise from uncontrolled cell growth in tissues of mesodermal origins, such as connective tissue, bone, cartilage, fat or muscle. Surgical resection is still considered the cornerstone in the treatment of sarcomas. However, in many cases where tumor is adjacent to vital structures like major vessels, other treatment modalities may be implemented. Irreversible electroporation (IRE), a new form of ablative technique has been introduced lately in the treatment of several types of sarcomas. Irreversible electroporation has shown promising results and survival improvement in primarily inoperable solid tumors and locally advanced cancers, including prostate, kidney, liver, bone and pancreatic cancers in close proximity to important structures. The aim of this review was to sum up the current knowledge and the future perspectives of the usage of IRE in the management of sarcomas. Our study indicates that IRE could possibly represent a potential therapeutic option in patients with advanced or metastatic sarcoma, when surgery is not indicated.

Key words: *ablation, irreversible electroporation, irreversible electroporation, sarcoma, soft tissue tumor*

Introduction

Sarcoma is a type of malignancy that arises from uncontrolled cell growth in tissues of mesodermal origins, such as connective tissue, bone, cartilage, fat or muscle. There are around 100 different subtypes of sarcoma that can be classified into three broad groups: soft tissue sarcoma, primary bone sarcoma, and gastro-intestinal stromal tumors. Surgery is considered the cornerstone in the treatment of sarcomas.

However, in a significant amount of cases, the close proximity of the tumor to important vital structures limits the treatment options as far as surgical treatment is concerned [1]. In such complicated cases, various different modalities have been tested in order to find the best treatment option. Radiofrequency ablation (RFA) is implemented in many cases, especially in colorectal liver metastases and other liver malignant lesions, as well as in cases of sarcomas. However, the heat dissipation that is generated by RFA adjacent to important vital structures (e.g. organs, blood vessels, nerves, bile ducts) limits its use [2]. Irreversible electroporation (IRE), a new form of ablative technique, has been introduced lately in the treatment of several types of sarcomas. IRE is a non-thermal ablation technique, based on the transmission of short direct current pulses through the tumor via needles, leading to apoptosis due to irreversible change in cell membrane integrity. IRE has shown promising results and survival improvement in primarily inoperable solid tumors and locally advanced cancers, including prostate, kidney, liver, bone and pancreatic cancers in close proximity to important structures [3,4].

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IRE has not been established yet as an ablative technique for the management of sarcomas and the majority of the reports in the literature consist of case reports and experimental trials in animals. The aim of this review was to sum up the current knowledge and the future perspectives of the usage of IRE in the management of sarcomas.

Principles of IRE

IRE is based on electric pulses that create defects in cell membrane (nano-pores) that are spread to the whole plasma membrane, disrupting the cell homeostasis and causing programmed cell death [5]. To achieve this effect, adjustable needle electrodes (18G) are placed around the targeted tumor, usually using ultrasound (US) or computed tomography (CT). The transmembrane potential is altered by microsecond electrical fields generated by those electrodes. Irreversible ablation depends on the proper setting of parameters such as the modifiable altitude, shape, duration, number and frequency of applied pulses [6]. Probes need to be placed in parallel, with the same depth, 1.7-1.8 cm apart to have the maximum ablative efficacy. Duration depends on the number of the probes that are used and treatment duration between each pair of probes takes approximately 5-10 min. 4-5 probes are recommended for tumors up to 3 cm and more probes for larger lesions. A limitation of the procedure is the requirement of sinus rhythm since the device could not synchronise with the heart rate, it will not function [7].

The main advantages of IRE is, firstly, the characteristic of being nearly non-thermal, not affecting the blood flow, the efficacy contiguous to blood vessels through the "heat sink effect" [8] and the fact that not it does not prohibit the application near heat-sensitive structures such as bile ducts, nerves or intestinal loops [7]. Secondly, as being a locoregional therapy, IRE achieves precise ablation of the tumor with a peritumoral safety margin, preserving the healthy surrounding, vital structures and minimizing the treatment related complications [7,9]. The major tissue vasculature is preserved while the treated regions exhibit lesion resolution leaving the extracellular matrix and structures available for regeneration of the region with healthy cells and tissue [10]. The affected areas are determined by the electric field produced by the pulses to which the tissue is exposed and can be predicted through numerical modeling [11].

The long-term effects of IRE in a large animal model demonstrated that mathematical modeling of electrical and thermal fields is critical in designing IRE ablation, thermal effects are not induced even though the electrical parameters used are above those used in reversible electroporation, and also that through IRE ablation only the cell membrane is affected and connective tissues are spared [12]. Especially as far as sarcomas are concerned, Al-Sakere et al. [13] studied the immune cell recruitment by immunohistochemistry during their treatment with IRE. They reported that no infiltration of immune cells was found, probably because of the destruction of infiltration routes. The immune response is not instrumental in IRE efficacy and, as there is no increase in the immune cells during IRE ablation, the immune system is not needed for the tumor ablation with this technique. Other factors such as the patient's reaction to the procedure itself have to be considered, but IRE is a viable option to consider within the choice of treatments for immunosuppressed cancer patients [13].

IRE & bone sarcomas

Ewing's sarcoma

Ewing's sarcoma is the second most common bone cancer with a higher incidence in the second decade of life, most commonly presented on long bones and the pelvis. Frequent metastases involve lung and liver [14]. Of the patients, 25% present with upfront clinical metastatic disease, while subclinical microscopic widespread disease at the time of diagnosis is present in 80-90% of the patients [15]. Local control of the tumor is the standard therapy which can be achieved by induction of chemotherapy followed by surgery, radiation or both. Resection of the tumor is usually performed, if possible, in relation of the tumor location and the ability to obtain negative surgical margins. Radiotherapy is indicated for patients where surgery would cause excess morbidity or positive surgical margins [16]. If the location of the tumor is near vital blood vessels, nerve plexuses or other vital structures, surgery or radiation may not be indicated. Steinbrecher et al. [17] proposed IRE ablation for those patients as a feasible option for local control. In fact, they used IRE to ablate a recurrent sacral Ewing's sarcoma lesion that was surgically unresectable and proton irradiation of the pelvis was considered too risky. The patient was 9-year-old in whom the proximity of the lesion with the sacral nerve plexus would increase the risk of paralysis with any other treatment option. After 4 cycles of chemotherapy with no tumor response the patient successfully underwent IRE following the fifth cycle of chemotherapy with five 1.1-gauge coaxial trans-osseous needles, that were placed under CT guidance into the target area. No complications were reported during and after the procedure. Follow-up imaging showed a complete radiologic response, the patient was able to proceed with autologous stem cell cell transplantation and three years later, the patient remained in complete clinical remission [17].

Osteosarcoma

Osteosarcoma is the most common bone tumor with the lung being the most common site of metastasis. Approximately 20% of the patients have metastatic disease at the time of diagnosis [18]. Therapeutic strategies include chemotherapy (doxorubicin, cisplatin) and surgical resection of both primary and metastatic lesions with a 5-year overall survival of nonmetastatic disease reaching 75% and of lung metastatic disease reaching 50% [19]. The standard treatment of lung metastasectomy with or without chemotherapy is associated with short and long-term morbidity including pain immediately after the operation, chronic pain, decreased lung function and inferior quality of life, highlighting the need of introducing new less invasive techniques for the management of metastatic osteosarcomas [20]. Harris et al. [20] used IRE to ablate *ex vivo* a lung metastasis from femur osteosarcoma in a 12-year-old patient. They found that the optimal voltage to achieve an effective ablation was higher than normal due to the aeration of the lung parenchyma (2200kV with the default voltage being 1800 kV). The probes were placed 1.2 cm apart on either side of the lesion and a total of 100 pulses with a pulse width of 90 ms were delivered. Areas of fibrosis and evidence of edema and intra-alveolar hemorrhage both within the tumor cells and the surrounding lung parenchyma were found. They concluded that IRE in unresectable metastatic osteosarcomas of the lung may be feasible and effective in non-bulky tumors, using greater voltage to achieve appropriate current draw due to the aeration of the lungs and the penetration through osteoid material, with maintenance of bronchovascular architecture, despite the risk of pneumothorax associated with percutaneous ablation [20].

Histiocytic sarcoma

A novel and pioneering case report by Neal et al. in 2011 [21] introduced and encouraged the use of IRE ablation in soft-tissue malignancies. More specifically, a 7-year-old female canine patient underwent IRE ablation for the treatment of a focal histiocytic sarcoma of the coxofemoral joint, encompassing bone, muscle, femoral arteries and the sciatic nerve. This was achieved by: 1) tumor and electrodes reconstruction with a creation of a three-dimensional geometric representation of the tumor and the electrodes within a software for representation of their size relative to the tumor for deciding the appropriate depth and angle before treatment; 2) numerical modeling for deciding the electric field distribution by solving the Laplace equation; 3) neuromuscular paralytic to prevent depolarization of the muscles and insertion of the 3 electrodes according to the treatment plan with their placement checked by CT-guidance; 4) pulse application using 80 pulses, each 80 μs long at a rate of 90 pulses per min; 5) electrode withdrawal technique for the final treatment plan with pulses applied at a new depth. Withdrawal technique has the benefit of reducing the number of electrode insertions and killing cancer cells preventing seeding along the needle tracks. Contrast-enhanced CT and histopathology showed complete tumor ablation after 6 months. This result suggested that IRE ablation was feasible and safe for soft-tissue sarcoma.

IRE & Soft-tissue sarcomas

In 2012, Usman et al. [22] reported a case of IRE of lung metastatic lesion of synovial cell sarcoma in a young male patient. Particularly, seven years after surgical treatment of synovial cell sarcoma of the thigh, the patient presented with pulmonary metastases for which cryoablation was performed. However, one of the lesions was located close to the right hilum, precluding the use of ablation, due its close proximity to important structures. Subsequently, the patient underwent CT-guided IRE of the metastatic lesion, using three IRE probes in a triangular pattern in 1.5 and 2.0 cm of distance. Ninety pulses were delivered with 2800 volts of maximum voltage. The procedure was uneventful, however, in six-month follow-up, the lesion showed progression.

In 2017, Qin et al. [23] reported the use of IRE for recurrence of retroperitoneal fibrous sarcoma of a 7.5 cm in maximum diameter mass in a 74-year-old woman. Preoperative CT scan showed that the mass was located near to inferior vena cava, portal triad, head of the pancreas and the left hepatic lobe. The authors decided to perform a 4-target strategy in order to limit the number of electrodes being used. In the first target section, under CT and ultrasound-guidance, two probes of 15 cm in length with 2 cm of active length were placed in a 2 cm distance. The voltage-to-distance ratio was 1500V/cm with delivery of 90 pulses. In the end, using 1300V/cm voltage they performed overlapping ablation, by pulling back 1 cm each electrode. Likewise, placing the two electrodes in a 2 cm-distance to the right, the second target section was then followed. In addition to the first section, the overlapping ablation was performed by pulling back 1.2 cm the electrodes without further information. Consequently, the third and fourth target sections were performed, using the same parameters. Immediately postoperatively, a CT scan was performed, showing a hypodense ablation zone containing gas bubbles, with no evidence of procedure-related complications. The recovery was uneventful, and the patient was discharged from the hospital on the fourth postoperative day (POD). On the 2-month follow-up, CT scan indicated complete response of the tumor with the size of the mass reduced to 5.2 cm in maximum diameter.

Discussion

Sarcomas can be classified into three types based on their origin: soft tissue sarcomas, primary bone sarcomas and gastro-intestinal stromal tumors.

Bone sarcomas are usually classified according to the type of matrix production; osteoid-producing sarcomas are classified as osteosarcomas, while chondoid-producing sarcomas are classified as chondrosarcomas. Each of these malignant diseases has unique features and characteristics regarding prognosis, biological behavior and treatment. Multidisciplinary approach of sarcomas is necessary, as single-treatment of any kind, including chemotherapy, radiotherapy or immunotherapy, is linked with increased recurrence rate [24].

Soft tissue sarcomas (STS) are rare types of cancer of mesenchymal origin that constitute 1-2% of all solid tumors. The reported incidence rates range from 1.8-5 cases per 100,000 population per year. STS represent a wide spectrum of tumors of various biologic behaviors, posing a real challenge to surgeons nowadays. Approximately 40% of STS occur in the extremities, 10% in the trunk, 16% in the retroperitoneum/abdominal cavity, 22% in the viscera, and 12% in other sites, including the head and neck [25].

Surgery is the main treatment option in the management of sarcomas. R0 resection is considered the gold-standard for the appropriate management of these tumors. Chemotherapy, radiotherapy or both along with surgical resection can be used for the local and systemic control of the disease [16,19]. With the exception of surgical resection, current adjuvant therapies such as chemotherapy, radiotherapy and immunotherapy are accompanied with high rate of recurrence. While surgery remains the gold standard of treatment for STS and bone sarcomas, in a significant percent of cases the close proximity of the tumor to important vital structures precludes the possibility of surgical resection. Therefore, as an alternative to surgery, new therapeutic less invasive strategies have been developed.

Lately, RFA has been used as an ablative technique in sarcoma cases. Few recent studies included small cohorts of patients with metastatic sarcoma, establishing the safety and feasibility of RFA in metastatic lesions [26-29]. In addition, two small series were published outlining the outcomes and survival rates for patients with lung metastases from sarcoma [30,31]. Nakamura et al. [30] reported their experience with RFA ablation of lung metastases from musculoskeletal sarcomas in 20 patients, while Palussiere et al. [31] published the results in a single-center study in 29 patients with sarcoma lung metastases treated with percutaneous RFA ablation. RFA offered a complete tumor necrosis to 59-91% of the tumors [26,29] with

Table 1. IRE in sarcoma cases

First author [REF]	*Year*	*Sarcoma*	*Initial treatment*	*Guidance*	*Overlapping ablation*	*Complications*	*Long-term results*
Neal et al. [21]	2010	Focal histiocytic sarcoma	IRE	CT	yes	no	6 months disease free
Usman et al. [22]	2012	Lung metastatic lesion of synovial cell sarcoma	Resection	CT	N/A	no	recurrence after 6 months
Steinbrecher et al. [17]	2016	Ewing's sarcoma	Chemotherapy	CT	N/A	no	3 years disease free
Harris et al. [20]	2016	Lung metastasis of femur osteosarcoma	Resection	Ex vivo	N/A	-	8 months disease free
Qin et al. [23]	2017	Retroperitoneal fibrous sarcoma	Resection	CT	yes	no	2 months disease free

an overall complication rate of 76% [29] involving pneumothorax (68-100%) [28,31], chest tube impulsion (17-38%) [28,30], pleural effusions (15-17%) [27,28] and lung abscess and hemothorax (1.9%) [29]. Of the tumors, 25-64% enlarged during the first month follow-up [5,6], while 1- and 3- year survival rates were 58-92% and 29-65% respectively [30,31].

As far as IRE is concerned, since there are not many patients with sarcomas who have been treated with IRE, a safe conclusion cannot be reached but the results are promising, regarding remission [17,21,32,33] and complications. Table 1 summarizes the current available data. More patients treated with IRE are needed so that rates of survival, remission and complications could safely be evaluated , but current data suggest that IRE is a safe and effective way to manage sarcomas in selected patients so far.

Conclusion

Owing to the complexity and variability of sarcomas, a multidisciplinary approach is imperative in order to develop an appropriate treatment plan for such tumors. The median overall survival for patients with advanced or metastatic sarcoma is approximately 12 months and has remained unchanged during the last 20 years. IRE could possibly represent a potential therapeutic option in patients with advanced or metastatic sarcoma, when surgery is not indicated. In the absence of any randomized trial, our review of reported outcomes sums up the current knowledge of the usage of IRE in the management of sarcomas.

Conflict of interests

The authors declare no conflict of interests.

References

1. Honore C, Meeus P, Stoeckle E,Bonvalot S. Soft tissue sarcoma in France in 2015: Epidemiology, classification and organization of clinical care. J Visc Surg 2015;152:223-30.
2. Lencioni R, Crocetti L. Local-regional treatment of hepatocellular carcinoma. Radiology 2012;262:43-58.
3. Tartaglia E, Fabozzi M, Rizzuto A et al. Irreversible electroporation for locally advanced pancreatic cancer through a minimally invasive surgery supported by laparoscopic ultrasound. Int J Surg Case Rep 2018;42:290-4.
4. Ansari D, Kristoffersson S, Andersson R, Bergenfeldt M. The role of irreversible electroporation (IRE) for locally advanced pancreatic cancer: a systematic review of safety and efficacy. Scand J Gastroenterol 2017;52:1165-71.
5. Wagstaff PG, de Bruin DM, Zondervan PJ et al. The efficacy and safety of irreversible electroporation for the ablation of renal masses: a prospective, human, in-vivo study protocol. BMC Cancer 2015;15:165.
6. Savic LJ, Chapiro J, Hamm B, Gebauer B, Collettini F. Irreversible Electroporation in Interventional Oncology: Where We Stand and Where We Go. Rofo 2016;188:735-45.
7. Van den Bos W, de Bruin DM, Jurhil RR et al. The correlation between the electrode configuration and histopathology of irreversible electroporation ablations in prostate cancer patients. World J Urol 2016;34:657-64.
8. Faroja M, Ahmed M, Appelbaum L et al. Irreversible electroporation ablation: is all the damage nonthermal? Radiology 2013;266:462-70.
9. Maor E, Ivorra A, Leor J, Rubinsky B. The effect of irreversible electroporation on blood vessels. Technol Cancer Res Treat 2007;6:307-12.
10. Onik G, Mikus P, Rubinsky B. Irreversible electroporation: implications for prostate ablation. Technol Cancer Res Treat 2007;6:295-300.
11. Davalos RV, Mir LM, Rubinsky B. Tissue Ablation with Irreversible Electroporation. Ann Biomed Eng 2005;33:223-31.
12. Rubinsky B, Onik G. Mikus P. Irreversible electroporation: a new ablation modality-clinical implications. Technol Cancer Res Treat 2007;6:37-48.
13. Al-Sakere B, Bernat C, Andre F et al. A study of the immunological response to tumor ablation with irreversible electroporation. Technol Cancer Res Treat 2007;6:301-6.
14. Kaatsch P. Epidemiology of childhood cancer. Cancer Treat Rev 2010;36:277-85.
15. Khanna N, Pandey A, Bajpai J. Metastatic Ewing's Sarcoma: Revisiting the "Evidence on the Fence". Indian J Med Paediatr Oncol 2017;38:173-81.
16. Reed DR, Hayashi M, Wagner L et al. Treatment pathway of bone sarcoma in children, adolescents, and young adults. Cancer 2017;123:2206-18.
17. Steinbrecher K, Arslan B, Nassin ML, Kent P. Irreversible electroporation in the curative treatment of Ewing's sarcoma. BMJ Case Rep 2016;2016.
18. Daw NC, Chou AJ, Jaffe N et al. Recurrent osteosarcoma with a single pulmonary metastasis: a multi-institutional review. Br J Cancer 2015;112:278-82.
19. Arndt CA, Rose PS, Folpe AL, Laack NN. Common musculoskeletal tumors of childhood and adolescence. Mayo Clin Proc 2012;87:475-87.
20. Harris JC, Chen A, Macias V, Mahon B, Chiu B, Pillai S. Irreversible Electroporation as an Effective Technique for Ablating Human Metastatic Osteosarcoma. J Pediatr Hematol Oncol 2016;38:182-6.

21. Neal RE, Garcia PA, Rossmeisl JH, Davalos RV. A study using irreversible electroporation to treat large, irregular tumors in a canine patient. Conf Proc IEEE Eng Med Biol Soc 2010;2010:2747-50.
22. Usman M, Moore W, Talati R, Watkins K, Bilfinger TV. Irreversible electroporation of lung neoplasm: A case series. Med Sci Monit 2012;18:CS43-7.
23. Qin Z, Jianying Z, Guifeng L et al. Irreversible Electroporation Ablation of an Unresectable Fibrous Sarcoma With 2 Electrodes: A Case Report. Technol Cancer Res Treat 2017;16:964-8.
24. Doyle LA. Sarcoma Classification: An update based on the 2013 World Health Organization Classification Of tumors of Soft Tissue and Bone. Cancer 2014;120:1763-74.
25. Brennan MF, Antonescu CR, Moraco N, Singer S. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. Ann Surg 2014;260:416-22.
26. Akeboshi M, Yamakado K, Nakatsuka A et al. Percutaneous radiofrequency ablation of lung neoplasms: initial therapeutic response. J Vasc Interv Radiol 2004;15:463-70.
27. Bojarski JD, Dupuy DE, Mayo-Smith WW. CT imaging findings of pulmonary neoplasms after treatment with radiofrequency ablation: results in 32 tumors. AJR Am J Roentgenol 2005;185:466-71.
28. Suh RD, Wallace AB, Sheehan RE, Heinze SB, Goldin JG. Unresectable pulmonary malignancies: CT-guided percutaneous radiofrequency ablation-preliminary results. Radiology 2003;229:821-9.
29. Yasui K, Kanazawa S, Sano Y et al. Thoracic tumors treated with CT-guided radiofrequency ablation: initial experience. Radiology 2004;231:850-7.
30. Nakamura T, Matsumine A, Yamakado K et al. Lung radiofrequency ablation in patients with pulmonary metastases from musculoskeletal sarcomas [corrected]. Cancer 2009;115:3774-81.
31. Palussiere J, Italiano A, Descat E et al. Sarcoma lung metastases reated with percutaneous radiofrequency ablation: results from 29 patients. Ann Surg Oncol 2011;18:3771-7.
32. Papalampros A, Vailas MG, Deladetsima I et al. Irreversible electroporation in a case of pancreatic leiomyosarcoma: a novel weapon versus a rare malignancy? World J Surg Oncol 2019;17:6.
33. Kourounis G, Paul Tabet P, Moris D et al. Irreversible electroporation (nanoknife® treatment) in the field of hepatobiliary surgery: Current status and future perspectives. JBUON 2017;22:141-9.