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# Surgical Use of NanoKnife (Irreversible Electroporation) in Patients with Unresectable Lung Tumors

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## Abstract

Eight patients suffering from unresectable, centrally localized lung tumor were treated with Irreversible Electroporation (IRE) in 2011-2018. A complete remission of the disease was reported in three patients and two patients presented a subcomplete remission. Four patients are without any local recurrence even after several years. The last fifth patient was operated on just two months ago. Three attempts for IRE were unsuccessful at the beginning of our trial due to incorrect indication (tumors were greater than 5 cm or we used low current density) and are not subjects of this report. The longest survival is six years and patient has fully functional preserved lung. All surgeries were performed as an open procedure using posterolateral thoracotomy.

**Keywords:** Irreversible Electroporation; Lung Tumors; Nanoknife

## Introduction

Irreversible Electroporation (IRE) results in cell death within the electrical field among two or more electrodes. High voltage ultrashort electric pulses (μs) induce microscopic defects (320-360 μm) so called "Nano pores" in cellular membranes. Disrupted intracellular homeostasis leads to cellular apoptosis. After its preclinical trials IRE started to be used in human medicine in 2008. This method was alternatively designated for patients with unresectable tumors. It has become the final option to eliminate otherwise unresectable tumor mass. Non-thermic ablation accompanying IRE preserves integrity of vascular structures, bile ducts, ureters, etc. Therefore, no bleeding or leakage from those anatomical structures was recorded. That is a major difference in comparison to the thermic ablation methods and thus IRE presents a mini-invasive method with rapid recovery time and minimum complication rate [1-6]. The greatest hopes and results were expected from IRE use in case of pancreatic, liver, kidney and prostate cancers. Most of the research and trials are conducted within those areas of interest [7-17]. IRE application in pneumo-oncology is however sporadic and the achieved results were mostly negative [18,19]. Contrary of those statements we have recorded several positive responses to IRE method in patients with centrally localized lung tumors. Those results are presented in form of short case reports.

## Methods and Materials

IRE procedure is conducted with the Nano Knife system manufactured by Angiodynamics Inc., USA. The device generates series of very short (70-90μs) high-voltage electric impulses (1500-3000V/cm). Procedures were performed as open procedures using posterolateral thoracotomy under general anesthesia. ECG synchronization device was used during the surgery to automatically disconnect the Nano Knife generator in case of arrhythmia. Tumor mass was dissected after preparation of the hilar structures (Figure 1). Two needle electrodes were collaterally inserted into the tumor mass 1.5-2 cm apart in depth of 1.5 cm so the tips would reach the same depth (Figure 2). After series of 70 to 90 impulses we relocated the electrodes progressively for IRE to completely ablate the tumor mass. The number of series varied according to size of the tumor.

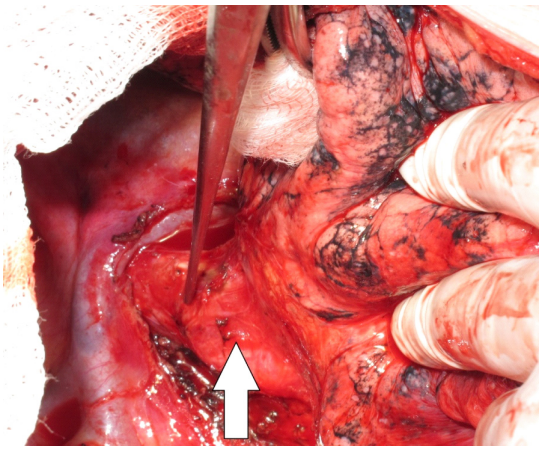

**Figure 1:** Tumor inside the right main stem bronchus prepared for IRE. Area is front of arrow direction.

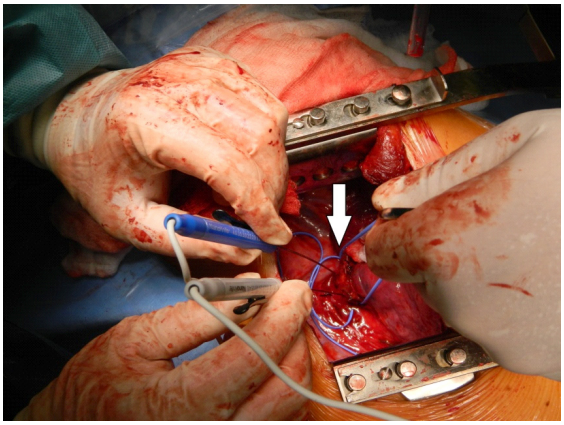

**Figure 2:** IRE probes are inserted into tumor mass.

## Case Report No. 1

A 71- year-old male patient with verified epidermoid carcinoma of the right main stem bronchus staged T3N0M0, stage IIB (Figure 3). Pneumonectomy was contraindicated due to comorbidities (ischemic heart disease, two cardiac versions in 2006 and 2008, arterial hypertension, gastric and duodenum ulcers, hepathomegalia, right-side pneumonia in May 2011, moderate chronic obstructive respiratory disorder, type 2 diabetes). IRE ablation was suggested to the patient as an alternative. Procedure was performed in August 2011. Surgical procedure took 107 minutes with blood loss of 150 ml. Solid fixed tumor was palpated in the main right bronchus obstructing the intermediate bronchus. Lung tissue behind the tumor was atelectatic. Two needle probes were inserted though the membranous portion of the bronchus. Three series each of 70 pulses were applied (pulse length 60 μs and voltage 1700 V). No local bleeding was observed during the procedure or after removal of the needle probes. Bronchoscopy was conducted nine days after surgery due to excessive mucous in the respiratory tract. It detected identical size of the original tumor which could be easily passed through and the mucosal plug was aspirated. Patient was discharged from hospital in good general condition without any dyspnea symptoms on day 12. CT scan performed month after the procedure detected immense regression of the tumor mass by up to 98%. Only slight thickening of membranous wall of the right main stem bronchus.

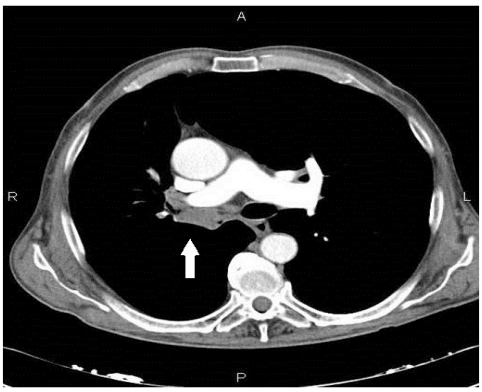


**Figure 3:** Prior the procedure. Pulmonary tumor obstructs the right main stem bronchus.

Biopsy sample taken from this location verified cells of non-small non-differentiated carcinoma with partial necrosis of this sample. Patient was further treated by external radiotherapy at dose of 7400 cGy /37 fraction and four series if outpatient chemotherapy using CDDP/NVR. Complete remission was concluded after six months. CT scans presented tumor free right main stem bronchus, right upper lobar bronchus as well as the other portions of the tracheobronchial tree (Figure 4). Bronchoscopy performed eight months after IRE ablation verified a complete tumor regression in the right upper lobar bronchus without detectable malignant cells in biopsy sample. Patient survived four years after surgery without local recurrence of the tumor and died suddenly due to myocardial infarction.

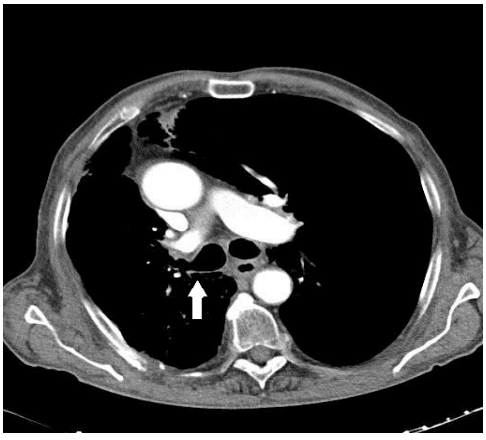

**Figure 4:** CT scan 6 months after IRE. Tumor diminished completely, the main stem bronchus is clear.

## Case Report No. 2

A 63-year-old male patient with verified typical carcinoid (chromogranin positive) without any symptoms of the carcinoid syndrome. CT scan presented the tumor in the right main stem bronchus sized 13 x 11 mm infiltrating the bronchial wall by another 17 x 14 mm. Azygos vein adhered to the tumor which was located 15 mm from carina and the right main stem bronchus was stenotic to 4 mm. Lymph node sized 9 x 8 mm was located in the right pulmonary hilum (Figure 5).

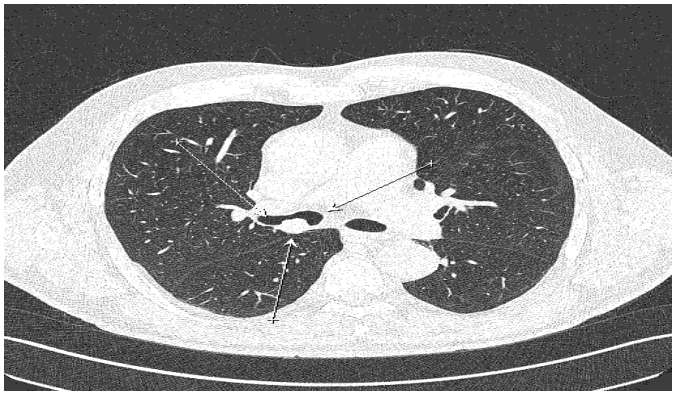

**Figure 5:** Pulmonary CT scan before IRE procedure.

Patient agreed to surgical procedure but preferred lung preserving surgery. Surgical procedure was performed in June 2018 and took 98 minutes with blood loss of 150 ml. After thoracotomy we detected collapsed pink lung parenchyma which was soft on palpation and without any tumor in the parenchyma. Carcinoid tumor sized 2 cm was palpated in the right main stem bronchus close to carina. The lymph node adhering to the right tracheal wall was removed and verified preoperatively as tumor-free. The right main stem bronchus was dissected and two IRE needle probes were inserted through the membranous portion of the right main stem bronchus into the tumor mass. Five series of IRE ablation conducted as follows:

- pulse length 80 µs, number of pulses 70, 2100 V – current density 25 A/cm$^2$.
- pulse length 90 µs, number of pulses 70, 2280 V – current density 30A/cm$^2$.
- pulse length 90 µs, number of pulses 70, 2250 V – current density 25 A/cm$^2$.
- pulse length 90 µs, number of pulses 70, 2450 V – current density 30 A/cm$^2$.
- pulse length 90 µs, number of pulses 70, 2150 V – current density 25 A/cm$^2$.

Surgical procedure was without any complications. We used Tachosil 3x2 cm to prevent air leak after repeated insertions of needle probes in the bronchus. Hemostasis and air leak absence were complete. Chest tube was extracted three days after the procedure and patient was discharged from the hospital five days after surgery. Patient reported a severe cough attack two weeks after the surgery when he expectorated peculiar dark mass sized 2 cm. He disposed this mass and after this attack there was no cough or expectoration anymore. CT scan presented no signs of carcinoid and completely patent airways one month after IRE procedure (Figure 6). Patient is still surviving even six years after the procedure. CT scan and bronchoscopy follow-ups show no recurrence of the tumor. Chromogranin levels were within the normal range in 2018.

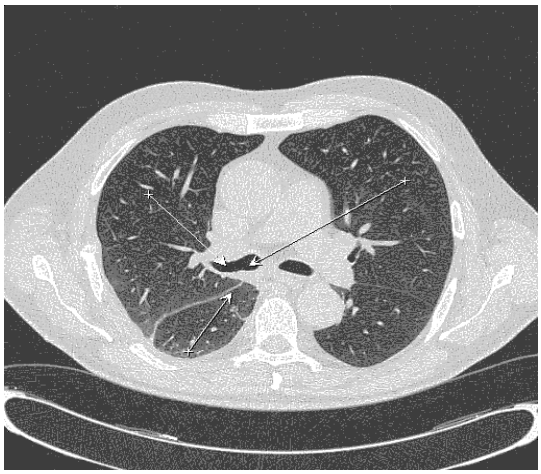

**Figure 6:** Pulmonary CT scan one month after IRE. Carcinoid "diminished."

## Case Report No. 3

A 70-year-old female patient with epidermoid tumor of the left lung staged T3N0M0. Due to multiple comorbidities and spirometry results only lobectomy could have been performed. Nano Knife device was stand by in case of resection failure. Surgical procedure in November 2013 took 115 minutes with blood loss of 500 ml (pulmonary artery was injured during dissection of the hilar structure and required its suture). Tumor sized 5 cm was located in the lower lobe however infiltrated upper lobe and mediastinum. Difficult lower lobectomy with lymph nodes dissection was performed. The residual unresectable tumor mass was ablated using IRE in two series:

- Number of pulses 70, pulse length 90 µs, voltage 2800 V
- Number of pulses 60, pulse length 90 µs, voltage 2800 V.

Nano Knife device interrupted its activity due to tachycardia exceeding 140 beats per minute at the end of the second series. Surgical procedure was terminated and chest tubes were inserted. Definite biopsy presented G1 squamous cell carcinoma infiltrating pleura and resection margin of the transected bronchus. All hilar lymph nodes were tumor-free. The surgical procedure was evaluated

as R1 resection. Subsequent chemotherapy followed and patient is still surviving without local recurrence after five years.

## Case Report No. 4

A 68-year-old female patient with a neuroendocrine tumor (malignant atypical carcinoid located centrally in the right main stem bronchus). Chromogranin level was strongly positive. Patient refused pneumonectomy and insisted on a lung preserving method. Surgical procedure was performed in July 2017 lasting 101 minutes with blood loss of 200 ml. Tumor mass was located just behind the division of the right upper lobar bronchus from the right main stem bronchus. Size of the tumor was 3-4 cm and it infiltrated the lung parenchyma. Seven series of IRE were applied, each with 70 pulses and pulse length 90 µs. Voltage and current density: 1) 2750 V, 22 A/cm$^2$; 2) 2750 V, 26 A/cm$^2$; 3) 2400 V, 22 A/cm$^2$; 4) 2400 V, 35 Acm$^2$; 5) 2850 V, 39 A/cm$^2$; 6) 2850 V, 41 A/cm$^2$; 7) 2850 V, 40 A/cm$^2$.

There were no postoperative complications and patient was discharged from hospital on postoperative day 9. Bronchoscopy detected no recurrence of the tumor and all biopsy samples were negative one year after the surgery. CT scan presented great reduction of tumor mass (by 95%) one year after IRE procedure with local calcified string residuum (it could be also changes after IRE procedure). Patient feels well and performs all kinds of sport activities. She lives a full active life 17 months after surgery.

## Case Report No. 5

A 50-year-old female patient with atypical carcinoid of the right lung verified 5 years ago. Right upper lobectomy was performed then and recurrence was detected during follow-up visit this year. Patient was eligible for resection due to unsatisfactory spirometry tests. Therefore, IRE procedure was indicated. Surgical procedure was performed in October 2018 lasting 113 minutes with blood loss of 200 ml. After re-thoracotomy and deliberation of the middle and lower lobe from adhesions, the pulmonary hilum was dissected. Spherical tumor sized 3 cm was detected adhering to the middle lobe from which the tumor mass infiltrated fissure as well as arterial and venous branches for the middle and lower lobes. The spherical tumor was removed but the infiltration was left in situ. The residual tumor mass was ablated by three series of IRE. Each series contained 70 impulses with pulse length 90 µs. Voltage in individual sequences: 2550 V, 2680 V, 2880 V, 2890 V. Current density varied from 25 to 30 A/cm$^2$. There were no postoperative complications, chest tube was removed on postoperative day 3 and patient was discharged from hospital on postoperative day 5. Follow up CT scan presented no residual tumor and reduction of the tumor infiltration by 1 cm. Next follow up CT scan is scheduled in four months.

## Results

- Case report No. 1: Procedure performed in 2011. Adjuvant radiation therapy and chemotherapy followed. Patient survived four years after the procedure and died of myocardial infarction without any recurrence of the tumor.
- Case report No.2: Procedure performed in 2012. No other adjuvant therapy after IRE procedure. Patient is still alive without local recurrence of the tumor.
- Case report No. 3: Procedure performed in 2013 followed by chemotherapy. Patient has been without local recurrence for 5 years.
- Case report No. 4: Procedure was performed in 2017. Patient only followed up after IRE without adjuvant therapy. She has been without recurrence for 1,5 years.
- Case report No. 5: Procedure was performed in 2018. Patient presented regression of the tumor.

| Case | IRE performed in | Adjuvant radio / chemotherapy | Recurrence | Survival period | Cause of death |
|---|---|---|---|---|---|
| 71-year old male patient | 11-Aug | Yes | None | 4 years | Myocardial infarction |
| 63-year-old male patient | 12-Jun | No | None | 6 years | Alive |
| 70-year-old female patient | 13-Nov | Yes | None | 5 years | Alive |
| 68-year-old female patient | 17-Jun | No | None | 17 months | Alive |
| 50-year-old female patient | 18-Oct | No | ?, short time after IRE | 2 months | Alive |

**Table 1:** Diagnosis: central lung tumor. Results after IRE procedures.

## Discussion

IRE can be performed either mini-invasively as CT navigated procedure or as an open thoracotomy or thoracoscopic procedure. Two electrodes are sufficient to activate IRE device. However, up to six NanoKnife probes inserted around the tumor can lead to completion of IRE

procedure in single pulse sequence Our department uses two needle probes which are subsequently re-arranged around the tumor due to economical reasons. This procedure is less expensive. However, it requires repeated sequential IRE ablation. We prefer open type of procedure in centrally located lung tumors as we believe to achieve more precise probes placement and preservation of their position to create sufficient homogenous density of the electric field around the tumor. As we insert the needle probes directly into the tumor, there is no interlayer between the tumor and NanoKnife probes such as lung parenchyma which could reduce tissue conductivity. IRE ablation is targeted directly into the solid tumor mass.

We assume that absolute precise positioning and stabilization of the probes during the complete procedure is difficult during CT navigated procedure (restricted intercostal space limits conditions for ablation). This can be one of the reasons why IRE is unsuccessful in peripheral tumors [17,18]. Besides the peripheral tumors can be ablated more easily by Cyber Knife, RF ablation, microwave ablation or resected as wedge. IRE loses its significance in those indications and it is also the most expensive method from the above mentioned options. Variables such as number of pulses in a series, pulse length, pulse voltage, distance and position of the probes affect the final effect of IRE procedure-cellular apoptosis. Apoptosis was achieved using the current density between 25-30 A/cm$^2$. Presuming cytoreduction plays an important role in treatment of tumors, IRE or combination of IRE and resection procedure can favorably affect the results of the complex treatment of malignancies.

## Conclusion

We confirm a successful use of IRE in several patients with centrally localized tumor sized 2-5 cm. We predict the positive effects of IRE accompany current densities around 25-30 A/cm$^2$. Tumor diminished within 4-6 weeks accruing to CT scans. Local recurrence has not been detected eve after several years follow up. Single use of IRE but also combining IRE and surgical lung resection can conveniently complete the complex oncological therapy. According to our experience indications for IRE procedure can be especially found in centrally located lung tumors.

It is worth mentioning that besides destruction and elimination of the tumor, IRE preserves patient's functional lung parenchyma. Those patients would probably require pneumonectomy. We would not suggest using IRE for peripheral lung tumors but other alternatives such as RF ablation, Cyber Knife or microwave ablation. Conclusions based on this small sample population cannot be generalized but positive effect of IRE in some patients with centrally located lung tumor encourages our team to continue research in this field.

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