Università di Foggia

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"MEDICINA TRASLAZIONALE E MANAGEMENT DEI SISTEMI SANITARI "
XXXVI Ciclo

Linac Based STereotactic Arrhythmia Radioablation (STAR) of Atrial fibrillation

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INDEX

1. BACKGOUND

a. Atrial fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia, occurring in 1–2% of the general population. This prevalence is expected to increase due to age of the population.[1,2]

Approximately 70% of AF patients are between 75 and 85 years old.[3] With a 22% projected increase in the elderly population by 2050[4] the numbers of living with AF will similarly arise. Furthermore, the incidence of AF increases in patients with cancer also due to medical oncology treatments. [5]

Patients affected by this arrhythmia have an increased risk of stroke and heart failure, with a significant reduction in functional capacity and quality of life. [6]

A substantial proportion of eligible patients are undertreated with medical therapy and 74.6% of the patients are symptomatic despite ongoing medical therapy. [7, 8] Drugs can also have significant side effects worsening the quality of life in patients with AF. [9]

Five types of AF can be distinguished: first diagnosed, paroxysmal (self-terminating, in most cases within 48 h), persistent, long-standing persistent (continuous AF lasting for ≥1 year), and permanent AF (AF that is accepted by the patient and physician). The European guidelines recommend catheter ablation of AF in symptomatic patients refractory to drugs or with heart failure. [10]

The pathogenesis of AF is complex and several studies reported that pulmonary vein (PV) foci play an important role in both initiation and perpetuation of this arrhythmia. [11]

Pulmonary vein isolation (PVI) remains the cornerstone of all ablation procedures irrespective of patient characteristics.

The appropriate and effective ablation targets beyond the pulmonary veins, particularly in patients with persistent AF, remain poorly defined. Various ablation strategies have been proposed into clinical practice, although scientific evidence from randomized studies was poor. These strategies include ablation of complex fractionated atrial electrograms, linear lesions, ablation of low-voltage areas, ablation of autonomic ganglia, as well as identification and ablation of rotational activities and putative AF trigger sites [12- 13].

A form of ablative energy is delivered through a catheter introduced into the atria via the venous vasculature to create scar and disrupt the postulated underlying arrhythmogenic substrate. Because the currently utilized energy forms (radiofrequency, cryoablation or electroporation) require direct contact with the myocardial target, an invasive approach is required. Procedural complications includes vascular injury, cardiac perforation, phrenic nerve injury, stroke, and most concerning atrioesophageal fistula. One of the novelties in recent years in the AF catheter ablation is pulsed filed (PFA): a non-thermal energy that uses trains of high-voltage, very-short-duration pulses to kill the cells. The mechanism of action of this energy consists of creating pores in the myocardiocyte cell membrane in a highly selective and tissue-specific way; this leads to death of the target cells reducing the risk of damage to surrounding non cardiac tissues. PFA also needs direct contact between catheter and tissue. [14]

Despite a lower risk of AF recurrence with ablation, in the CABANA trial [15] for the primary endpoint of death, disabling stroke, serious bleeding, and cardiac arrest, sub-analysis by age revealed significantly better outcomes with ablation in younger patients (<65 years, OR: 0.52: 0.27–1.0) that trended towards harm with ablation in older patients (>75 years, OR: 1.46: 0.80–2.67). Within this trial, elderly patients >75 years of age made up a minority of participants (14.6%). However, the harm signal in CABANA suggests the need to more comprehensively examine safety and efficacy in elderly patients.

A recent meta-analysis found that AF ablation success rates were similar in both elderly and younger patients. However, older patients experience higher rates of complications (pericardial, vascular, total bleeding, post-procedural mortality. [16]

Moreover in elderly people paroxysmal AF is difficult to treat with drugs since they alternate sinus bradycardia and fast rate AF in the so-called tachy-bradi syndrome, thus PVI is desirable.

Summarizing AF catheter ablation is a reasonably safe and effective procedure but there are well-established risks of complications. As a result, there is ongoing interest in developing improved therapies for AF and a non invasive therapeutic alternatives are warranted.

b. Stereotactic ablative radiation therapy

Stereotactic Ablative Radiation Therapy (SABR) with precise high dose of radiation to a well define targets, potentially guided by previous cardiac diagnostic tools, could become more than an option in the next future.

SABR is an advanced form of radiation therapy that delivers noninvasive, image-guided, precise high dose of radiation to targets reducing dose exposure to adjacent normal tissue and minimizing the treatment toxicity. Rotational arcs, multiple static beams, coplanar or non-coplanar geometries delivering photons or heavy ions can be employed by a variety of available linear accelerator devices to deliver ablative doses. ABR used for ablation of cardiac arrhythmias has been termed StereoTactic Arrhythmia Radioablation **(STAR).**

Historically, the definition of radiosurgery was introduced by Leksell in the 1950 for the treatment of brain cancer, as "a single high dose fraction of radiation, stereotactically directed to an intracranial region of interest". [17]

Considering the ability of radiosurgery to deliver high radiation dose while having a rapid dose gradient falloff beyond the target, quickly the SABR has grown for ablative treatment of cancer in the lung, liver, prostate, pancreas, and other sites [18-20].

Moreover, radiosurgery is applied in non-oncological field, such as trigeminal neuralgia, arteriovenous malformations, seizures, and has been explored for renal artery hypertension, back pain, and cardiac arrhythmias. [21-22]

c. Physiopathologic rational

From a radiobiological point of view, the higher dose of stereotactic radiation may theoretically produce greater biological cell kill respect conventional radiotherapy. Its action mechanism is partly unknown. The tissue damage is probably a multifactorial result, due in part to the double- strand breaks in the DNA, which it leads to apoptosis, but also to vascular damage and consequent ischemic cell death. [23]

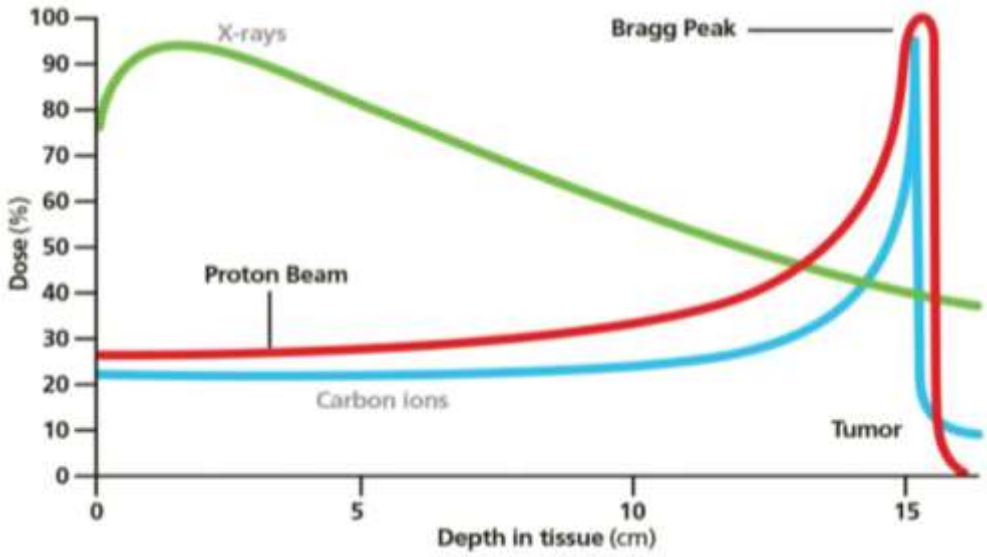
In this context, a relevant issue is represented by dose distribution and dose at organs at risk (OaRs). SABR for cardiac arrhythmia is a challenge due to the position of target near the esophagus, trachea, coronary arteries and other cardiac substructures, considering interfraction movement with breath and heartbeat.

Photons delivered with modern techniques, such as coplanar or not coplanar volumetric modulated arc therapy (VMAT) with 4D CT target motion study, allow to obtain a high quality of dose distribution to target leading a low dose at OaRs[24].

On the other hands, protons due to their favorable physical and radiobiological properties reduce dose at OaRs. The Bragg Peak permits to carefully deliver maximum dose in the target, while photons may achieve a similar conformity using multiple fields [25-26].

However, the greatest advantage of protons is also its greatest limit. Changes in the Bragg Peak position lead to large dose errors, and this is more important for small target in movement [27]. Several methods are being studied to limit movement-related error in proton therapy; however, these studies do not concern heartbeat control [28].

Another issue is the availability of resources. Modern photon therapy techniques and technologies are available and used in most radiotherapy centers, while proton therapy remains a limited resource and, in clinical practice, it requires an accurate cost- effectiveness analysis [29].



Franzetti et al. Frontiers in Cardiovascular Medicine 2022;9:849201

d. Preclinical data

In field of preclinical research applied to radiosurgery and cardiac arrhythmia, to evaluate the feasibility, the dose limiting and the correlation between dose and response, during the last 20 years several studies were conducted in animal models.

The first large animal study that evaluated the feasibility of a noninvasive approach for the cardiac radioablation, was published in 2010 by Sharma A. and colleagues [30].

In this experimental work, sixteen swine underwent a single fraction of SABR, using a robotic system with a tracking lesion treatment. The dose range was very huge including a minimum dose of 25 Gy until to a maximum dose of 80 Gy. For each animal, a different target area was identified in cavotricuspid isthmus (CTI), atrial-ventricular (AV) node, pulmonary vein-left atrial junction, or left atrial appendage. After SABR, all animals were monitored with repeat electroanatomic voltage mapping (follow-up range 25–196 days) and subsequently they underwent autoptic and histologic analysis. The results of voltage study showed a variable treatment response based on SABR dose and location of treated area. The histologic evaluation highlighted the transmural loss of myocytes and the increase in fibrin in the target in contrast with the absence of important alterations in untreated heart portions. These findings demonstrated that “Stereotactic robotic radiosurgery can produce CTI

block, AV nodal block, and significant decreased voltage at the pulmonary vein–left atrial junction. No other organ damage was seen. The study findings demonstrate the feasibility of this non- invasive treatment method for creating cardiac lesions."

A second study [31] of dose-escalation evaluated the feasibility of linac-based cardiac SABR and the relationship between treatment dose, voltage and histologic results focused on area located at right superior pulmonary vein (PV) antrum. The treatment was delivered in a single fraction using an approach of 2.5 Gy stepping increase in dose from 17.5 to 35 Gy. To ensure the correct identification and position of the target, respiration-correlated computed tomography (4D- CT) study was developed in each case and the internal target volume (ITV) was delineated according to breath phases and heart cycle. The electrophysiology analysis was performed at 6 months after SABR, followed by the histopathologic examination. The results demonstrated the feasibility of cardiac SABR Linac-based without acute side effects. Moreover, the histopathologic evaluation showed that doses > 32.5 Gy induced a transmural scarring of cardiac irradiated area, although not complete and homogeneous. These data could justify the failure to observe a complete veno- atrial electrical block of the study.

A complete electrical block of the left atrial-PV junction was demonstrated for the first time in the study of Bode F and colleagues [32] using a dose of 40 Gy in a single fraction delivered with a linear accelerator. In this experimental model, a complete circumferential fibrosis of the PV muscle tissue was observed at the dose of 40 Gy according to voltage findings.

Another treatment approach based on the use of heavy ion beams was investigated by Lehmann HI and colleagues [33]. Their paper showed that high doses (40–55 Gy) in single fraction caused slowing and interruption of cardiac impulse propagation between 13 and 17 weeks after radiation treatment and that the extension of target fibrosis was linked with the entity of electrophysiological results. The doses used in the study were 25, 40, and 55 Gy applied in forced-breath-hold to the AV junction, left atrial-PV junction and free wall left ventricle.

The same team published a subsequent article [34] in which a deescalation dose approach was carried out in the treatment of AV junction. The prescription doses were 55, 50, 40 and 25 Gy delivered with

linear accelerator. The relevant aspect of this study was that a complete AV block occurred at dose of 25 Gy and the median time post irradiation to achieve the block was 11.2 ± 0.49 weeks.

The possibility to obtain a complete AV block in a range dose of 35–40 Gy was recently confirmed by Refaat and colleagues. [35] In this work, 5 swine underwent a cardiac SABR in a single fraction using linear accelerator. To ensure the right position of the target, a cone beam computed tomography (CBCT) was performed before treatment and the necessary switches were done based on the comparison and fusion with the images from the treatment planning system, and the same control was performed at the end of SABR. The electrical AV block was achieved in all treated animals. The histopathologic analysis confirmed a presence of fibrosis in the targeted myocardium without collateral damage of the surrounding zone.

Overall, the preclinical research conducted in animal models showed that a safe and efficacy noninvasive treatment approach for cardiac arrhythmias could be represented by SABR with a median time of response around 2–3 months. The technique doesn't condition the results, while the treatment dose plays a crucial role. Furthermore, the position of arrhythmogenic foci is a relevant aspect, considering that in the most studies the AV node would seem more radiosensitive than the other cardiac electric zone. Technological improvements, such as 4D-CT and CBCT imaging studies and gating or tracking treatment delivery, might bring advantages in the clinical realty.

e. Humans' trials of SABR

Almost 10 years after the first study based on experimental model, that described the successfully treatment of target cardiac structure using SABR, there has been significant interest in this nascent field of radiotherapy application and the clinical scenario seems to be in, albeit slowly, promising evolution. To date, there are still few and small case series and case reports conducted on human population. [36-40]

The main characteristics of cardiac SABR humans' studies are summarized in the table 1.

Table 1	***Main characteristics of cardiac SABR humans' studies***							
Author	***N. of patients***	***Cardiac arrhythmia***	***Technology***	***Dose***	***Beam on time***	***Follow-up***	***Toxicity***	***Outcomes***
Cvek[39]	1	VT and PVC	Cyberknife	25 Gy/1 fx (82% isodose line)	114 min	10 days	No side effects	PVC decreased from 9–10 to 1–3% and non-sustained VT diminished
Loo [35]	1	ES and VT VT	Cyberknife	25 Gy/1 fx (75% isodose line)	90 min	9 months	No side effects	Reduction in VT burden of 95% from baseline
Cuculich [34]	5	VT	Linac-based	25 Gy/1 fx	11–18 min	Median 12 months	No side effects	Reduction in VT burden of 99.9% from baseline
Jumeau [36]	1	VT	Cyberknife	25 Gy/1 fx	45 min	4 months	No side effects	No more episodes of sustained VT
Robinson [38]	19	VTand PVC	Linac-based	25 Gy/1 fx	Median 15 min	Median 13 months	1 pericarditis	Reduction of VT/PVC of 94%; 50% reduction and 95% reduction in VT and 24 h PVC burden were achieved in 94% and 61% of patients respectively
Mayinger [41]	1	ES and VT	Hybrid MR- linac	25 Gy/1 fx (85% isodose line)	24 min	3 months	No side effects	No more episodes of sustained VT

VT ventricular tachycardia; *ES* electrical storm; *PVC* premature ventricular contractions

Considering a so restricted number of treated patients, the validation of the efficacy and safety of this treatment approach still need confirmation on a large scale, before it can be considered a standard therapeutic option in patients with cardiac arrhythmias.

The noninvasiveness of the therapy is fundamental in this approach, and the safe delivery treatment requires a multidisciplinary adequate work team. The real nodal point of STAR treatment is linked to the compensation of cardiac target motion that adds complexity in SABR treatment planning and patient positioning prior and during treatment.

Adding the respiratory movements with the myocardial motion, the risk of off target in high dose delivery increases significantly and consequently the risk of treatment toxicity grows.

It is also true that the cardiac motion does not result in significant translational movement, as most of motion occurs in the ventricles and in severe cardiomyopathy overall heart motion is even less due to reduced contractility.

Therefore, respiratory motion resulting in superior-inferior displacement accounts for most of the target motion for intracardiac targets [37].

The respiratory motion can be compensated in different ways such as by respiratory gating systems (the dose is delivered only when the target is in a specific segment of the respiratory cycle), respiratory tracking systems (the radiation beam follows the target throughout the respiratory cycle), respiratory inhibition systems (the respiratory motion is limited by abdominal compression or breath-hold schemes).

Furthermore, to add accuracy in localizing and tracking a moving target, a radio-opaque fiducial marker can be localized near the target region; potentially any radio-opaque structure that moves synchronously with the target can be used as a surrogate for the target position and used to image movement with X-ray or CT imaging.

To maintain the noninvasiveness of the procedure intracardiac or extracardiac structures, naturals (vessels or valvular calcifications) or artificial (mechanical valves, stents, pacemaker or ICD leads) could also be used in place of fiducial markers. On the other hand, to compensate for cardiac and respiratory motion in addition to above-mentioned strategies, an adequate definition of ITV during delineating and planning and short treatment times can be utilized to increase the irradiation accuracy in SABR.

To date in the humans STAR treatment experiences, different delivery devices have been used: Varian Linac System has been used for the first-in-man treatment of ventricular tachycardia (VT) using SABR [34]and Accuray Cyberknife System was used for the first stereotactic radioablation in an experimental model and in some human case reports [35 - 36]. In all cases, patients were treated with a dose of 25 Gy delivered in a single fraction. For all patients, preprocedural imaging was performed to delineate target region with high accuracy.

In Linac experience, patients underwent noninvasive electrocardiographic imaging during induced ventricular tachycardia to precisely map the ventricular tachycardia circuit and other additional cardiac imaging was used to identify regions of anatomical scarring with either resting single-photon emission CT (SPECT) or contrast-enhanced cardiac MRI with the use of standard techniques.

Both electrical and imaging information was combined to build a volumetric target. In Cyberknife experiences, ICD was used as fiducial marker guiding planning and for real-time tracking system. As usual, before RT treatment, patients underwent a planning CT scan, which might include body immobilization with a vacuum-assisted device and acquisition of a respiration-correlated CT scan (four-dimensional CT) to assess the total sum of cardiac and pulmonary motion. A final planning target volume was developed by expanding the target to account for motion, setup uncertainty, and delivery uncertainty. Specific contouring software for delineation and planning was used in Loo's Cyberknife experience, and a temporary pacing wire was fluoroscopically placed as a fiducial marker and tracked with Syncrony system.

For the treatment, the patient was placed supine on the treatment table and made comfortable to minimize patient movement for the duration of treatment delivery (the treatment can be inter- rupted if needed and restarted after repositioning). SABR was performed with the use of an image-guided radiotherapy equipped with CBCT system or biplane X-ray imaging cameras system to acquire images of the thorax, which can be directly registered to the planning CT. Ablation target volumes ranged from 17 to 81 cc with a treatment times ranging between 11 and 18 min in Linac experience and the efficacy of the treatment has been demonstrated in all cases, evidencing the reduction or disappearance of the arrhythmia without patients complications and very low toxicity rate (mild inflammatory changes in the adjacent lung tissue resolved after 12 months).

Ablation target volume was 21 cc (no margin was added for planning) in Jumeau et al. and treatment procedure of 45-min. An immediate reduction in VT episodes confirmed the efficacy of the rescue procedure. Importantly, after treatment the patient remains capable of immediately returning to home without acute symptoms.

Remarkable of note is the first prospective study conducted by Robinson and colleagues [38]. This single arm- phase I/II trial of noninvasive cardiac radioablation in adults, named ENCORE-VT trial (electrophysiology-guided non invasive cardiac radioablation for ventricular tachycardia), has shown on a cohort of 19 patients that through cardiac radioablation guided by noninvasive electrophysiology study, a significant reduction in ventricular arrhythmias with modest short-term risks is obtained. Furthermore, the improvement in the clinical conditions allows to reduce the use of antiarrhythmic drugs and to improve the quality of life.

f. STAR treatment in atrial fibrillation

For Atrial fibrillation (AF), the data are sparse [42-46]. AF is the most common cardiac arrhythmia in elderly and due to the population ageing, its prevalence is growing up [47,48]. In the European Union in 2060 the number of patients older than 75 years with AF is estimated to be 13,8 million [49]. In this context, paroxysmal AF is difficult to treat with drugs, due to the frequent AV node conduction or intraventricular conduction delays or due to tachy-brady syndrome. Furthermore, ablation of the atrioventricular node and pacemaker implantation can control ventricular rate when medication fails [47, 50].

Current guidelines recommend catheter ablation targeting pulmonary vein isolation (PVI) to treat paroxysmal AF refractory to antiarrhythmic therapy (AAT) [47, 51, 52]. Nevertheless, catheter ablation is burdened with an increased risk of complication rate in elderly [47, 53, 54].

This prospective phase-II trial was designed to evaluate safety of STAR in elderly patients affected by paroxysmal AF (ClinicalTrials.gov: NCT04575662).

2. METHODS

The trial was approved by the Ethics Committee and all patients signed informed consent. Inclusion criteria were: age > 70 years; symptomatic paroxysmal AF; AAT intolerance or failure. Exclusion criteria were: persistent or permanent AF; previous AF ablation; unstable angina; life expectancy to

<1 year; previous cardiac surgery, myocardial infarction or thromboembolic events; contraindications to oral anticoagulation; active systemic infection. After enrollment, all patients discontinued AAT and they performed 15-days ECG-Holter monitoring, a complete transthoracic echocardiogram and a cardiac computed tomography (CT) before STAR. EQ visual analogue scale (VAS) was used to assess quality of life, administrated before treatment and 12 months after it. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale from 0 (the worst health you can imagine) to 100 (the best health you can imagine) [55].

a. Radiotherapy

STAR procedure was recently published [44-45]: patients underwent to simulation with a 4D CT, with an immobilization system and received a free breathing STAR with a prescription total dose of 25Gy in 1 fraction. A "simultaneous integrated protection" dose was realized to the interface between PVs and critical structures, including esophagus and bronchus, to respect dose constraint value [56-58]. The treatment was generated, optimized and delivered by TrueBeam^{TM} (Varian Medical System, Palo Alto, CA). Image-guided radiotherapy (IGRT) with Cone Beam CT and Surface-Guided RadioTherapy (SGRT) with Align-RT (Vision RT) were used to reduce set-up error and to monitor patients during fraction. Radiotherapy delivery was temporally interrupted in case of deep breaths.

b. Clinical follow up.

All patients were clinically monitored during procedure and for 12 hours after STAR. Follow-up (FU) consisted of clinical evaluation, 15-days ECG-Holter monitoring and transthoracic echocardiogram performed at 1-, 3-, 6-, and 12-months after STAR. Cardiac CT was performed at 6 months from STAR.

c. Study objectives

The primary endpoint was to assess the 1-month post-STAR safety defined as followed: complete STAR delivery, and no acute treatment-related adverse events more than grade 3, assessed according to the Common Terminology Criteria for Adverse Events (version 5.0) [59]. Secondary endpoints were: AF recurrences (episodes ≥30 sec) carried out through ECG or ECG-Holter monitoring, reductions in AAT, quality of life and overall survival.

d. Sample size and statistical analysis

Based on the exploratory nature of study, the planned number of patients was 20 without a formal statistical power calculation. Summary statistics were reported as number of subjects, frequency with percentage for categorical data and median or mean ± standard deviations for continuous variables. The incidence rate ratios (IRR) with 95% confidence interval for the number of AF episodes recorded during ECG-Holter monitoring (pre-treatment and 1-, 3-, 6- and 12-months post-treatment) were calculated using a Poisson regression mixed-model with patient as random effect. A p value of 0.05 or less was considered statistically significant. Wilcoxon matched-pairs signed-rank test was used to compare quality of life 12 months post-treatment than pre-treatment. All analyses were performed using STATA version 16 (StataCorp, College Station, Texas).

3. Results

From May 2021 to July 2022, 20 patients were enrolled on 20 planned (100%). Eighteen patients underwent STAR. One patient withdrew informed consent before treatment and one patient was excluded due to the close relationship between the esophagus and the left PVs (high risk of esophageal toxicity or high risk to performe a no-effective treatment) (figure 1).

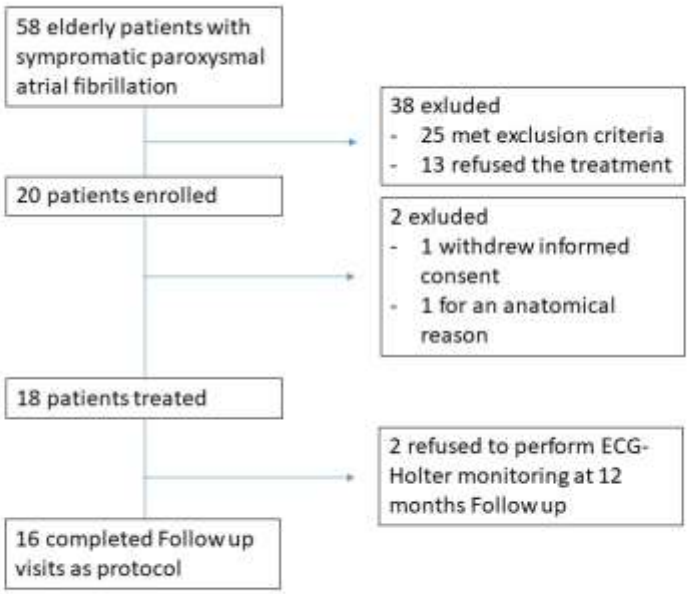


Figure 1

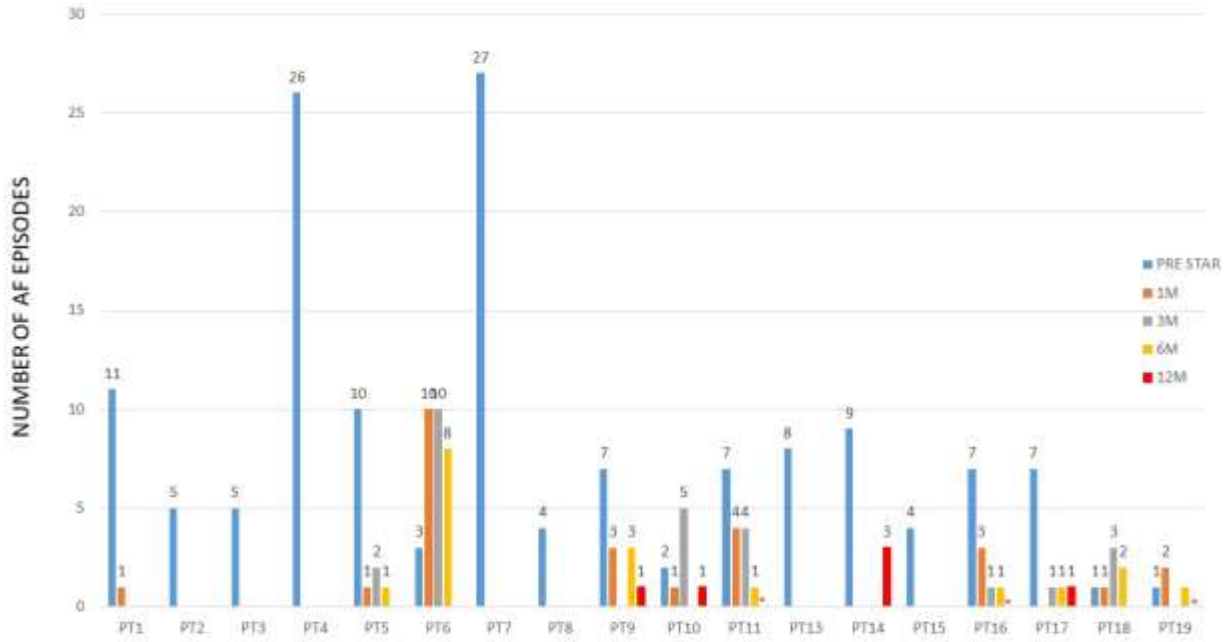
The main clinical characteristics of patients were reported in table 2.

Table 2. CLINICAL CHARACTERISTICS OF THE 20 STUDY PATIENTS

Male sex, n (%)	8 (40)
Mean age (years)	77±6
CHA2DS2-VASc, n (%) 0 1 2 3 4	 0 (0) 1 (5) 1 (5) 12 (60) 6 (30)
EHRA SCORE, n (%) 2 A 2 B 3 4	 - - 16 (80) 4 (20)
Diabetes mellitus, n (%)	1 (5)
Hypertension, n (%)	16 (80)

Family history of coronary artery disease, n (%)	15 (75)
Hypercholesterolemia, n (%)	11 (55)
Hypertriglyceridemia, n (%)	9 (45)
Active smoking, n (%)	6 (30)
Body mass index (Kg/m^2)	26±3
Heart failure (EF<35%), n (%)	0 (0)
Coronary artery disease, n (%)	1 (5)
Previous ischemic stroke, n (%)	1 (5)
Transient ischemic attack, n (%)	1 (5)
Chronic renal failure, n (%)	7 (33)
Dysthyroidysm, n (%)	7 (35)
Chronic lung disease, n (%)	4 (20)
Medical therapy, n (%)	
Beta blockers, n (%)	15 (75)
Flecainide, n (%)	7 (35)
Propafenon, n (%)	1 (5)
Amiodaron, n (%)	5 (25)
Sotalol, n (%)	2 (10)
Direct oral anticoagulant, n (%)	20 (100)

Before treatment, all patients performed 15 days-ECG-Holter monitoring, reporting a median of 8 AF episodes (range 1-27) (Figure 2).



Patient 12 and 20 did not perform STAR treatment. Patients 11, 16 and 19 had persistent atrial fibrillation after 6 months from STAR treatment (*). Patients 5 and 18 did not performed ECG Holter monitoring at 12 months FU

Figure 2

Furthermore, frequent premature atrial beats (>1000/24h) without episodes of bradycardia or ventricular arrhythmias were recorded. Data regarding the T0-echocardiography were reported in table 3.

Table 3. BASELINE ECHOCARDIOGRAPHIC DATA (20 PATIENTS)	
Left ventricle Ejection Fraction (%)	55±5
Left ventricle hypertrophy (septum diameter >12mm), n (%)	13 (65)
Right ventricle dysfunction, n (%) (defined as TAPSE<16mm and S'<10cm/s)	-
Mean left atrial anterior-posterior diameter (mm)	44±5
Mean left atrial area (cm2)	22±4
Right atrium enlargement, n (%) (2D right atrial volume >30 mL/m2)	5(25)

Mitral valve regurgitation, n (%) Mild Moderate Moderate-severe Severe	 11 (55) 3(15) 1(5) -
Mitral valve stenosis, n (%)	-
Aortic valve regurgitation, n (%) Mild Moderate Moderate-severe Severe	 5(25) 1(5) - -
Aortic valve stenosis, n (%)	-
Tricuspid valve regurgitation, n (%) Mild Moderate Moderate-severe Severe	 12(60) 3(15) 1(5) -
Tricuspid valve stenosis, n (%)	-
Pericardial Effusion, n (%)	-

TAPSE: Tricuspid annular plane systolic excursion.

No significant findings were documented at the baseline chest/cardiac CT.

In terms of RT data, regarding dose constraints, average heart and left anterior descending artery (LAD) mean dose were 3.9 and 6.3Gy, respectively; while mean maximum dose for LAD, spinal cord, left and right bronchus and esophagus were 11.2, 7.5, 14.3, 12.4 and 13.6Gy respectively.

From geometrical point of view, STAR plan was delivered using 3 no-coplanar arcs with 10MV-FFF (flattening Filter Free). The median delivering Treatment Time was of 3 minutes. All patients receive a total dose of 25Gy in single fraction on PVs.

a. Primary Endpoint

With a median FU time of 16 months (range 12-23), no acute toxicity more than grade 3, surely related with irradiation, were reported. All adverse events were reported in table 4.

Table 4. Adverse events classification	**Grade 1**				**Grade 2**			
	unrelated	unlikely	possible	probable	Unrelated	unlikely	possible	probable
Cardiac disorder								
Sustained VT								
Pericarditis				8				
Coronary embolism								
AV block								
GI disorder								
Esophagitis				6				
	Grade 3				**Grade 4**			
	unrelated	unlikely	possible	probable	Unrelated	unlikely	possible	probable
Cardiac disorder								
Sustained VT							1	
Pericarditis			1					
Coronary embolism					1			
AV block					1			
GI disorder								
Esophagitis								

Five patients (27.7%) had a mild esophagitis (grade 1) 24 hours after STAR, the symptoms resolved after 1 week using proton pump inhibitors and sucralfate. Five months after STAR, 1 patient (5.5%) had epigastric pain unresponsive to pharmacological treatment using proton inhibitors and sucralfate. The patient underwent chest CT and endoscopy not documenting esophageal damage. After discharge, the patient developed herpes zoster infection at the site of pain symptoms.

Furthermore, 8 patients (44.5%) experienced an asymptomatic mild (grade 1) pericardial effusion (max 2 mm): 2 patients after 1 month from STAR and their pericardial effusion completely resolved in 3 months; 6 patients after 6 months from STAR and 1 out 6 had a complete resolution while the other 5 patients had a stable asymptomatic mild pericardial effusion at 1-year FU.

Only 1 patient (5.5%) had a symptomatic (grade 3) pericardial effusion (about 5 mm) documented after 6 months from STAR; the pericardial effusion completely resolved in 2 months using pharmacological treatment with corticosteroids. No other significant alterations were found at echocardiograms performed during the FU visits.

One patient had a clinically significant acute event after STAR: after 1 hour from treatment patient n. 13 had a torsade de pointes treated effectively by electrical cardioversion and subsequent cardiac ICD implantation.

Two adverse events were not related to STAR. In particular, 1 patient had a coronary artery embolism after electrical cardioversion for AF performed 4 months after STAR. The patient did not perform exams to exclude atrial thrombus because anticoagulant therapy had been taken, without interruption, for more than 3 weeks before electrical cardioversion. Moreover, 1 patient had a dual-chamber pacemaker implanted 13 months after STAR for a sinus node disease progression. An asymptomatic mild sinus node dysfunction was documented before enrollment for which beta-blocker therapy was discontinued.

No significant alterations were documented on the chest CT scan performed 6 months after STAR.

b. Secondary endpoint

Frequent atrial ectopies (>1000/24h) and atrial tachycardias episodes were documented in all patients during the first 2 months after STAR. Most patients had a significant reduction in AF episodes during FU (figure 2). Compared to pre-treatment number of AF episodes (8 per patient over 15 days), the risk was significantly lower at each post-baseline time point with IRRs indicating a reduction greater than 80% (1-, 3-, 6-, 12-months) (table 5).

Table 5. Incidence rate of atrial fibrillation episodes by time since STAR treatment and risk of atrial fibrillation for time at risk after thereafter.

	Events per 15 days	Incidence Rate Ratios	p
Pre-treatment	8.00 (6.80-9.42)	1.00	
1-month	1.44 (0.98-2.12)	0.18 (0.12-0.27)	<0.001
3-month	1.44 (0.98-2.12)	0.18 (0.12-0.27)	<0.001
6-month	1.00 (0.63-1.59)	0.13 (0.08-0.20)	<0.001
12-month	0.56 (0.29-1.08)	0.07 (0.04-0.14)	<0.001

The median value of maximal AF duration was 10 hours (range 1 to 36). Seven patients were arrhythmia free during FU (figure 2). Three patients (16.6%) developed persistent AF after 6 months from STAR (patient 11, 16 and 19). In particular, patient 11 had a pericardial effusion, patients 16 and 19 had a significant valve disease (moderate-severe mitral and tricuspid regurgitation).

Patients 1 and 3 had a symptomatic atypical atrial flutter at 6 months post STAR while patient 13 had an episode of atypical atrial flutter after 12 months. No other significant arrhythmias were documented.

All the patients with arrhythmia recurrences resumed AAT with beta-blockers; 1 patient started flecainide 6 months from STAR and 2 patients started amiodarone after 3 and 12 months from STAR. All patients with recurrent arrhythmias were offered to undergo an electrophysiological study (ES) but most of them refused due to a significant improvement in symptoms. Five patients performed ES

(patients 1, 3 and 13 presenting an atypical atrial flutter and patients 5 and 9 with paroxysmal AF). In these patients, the atrial mapping using CARTO system and Pentaray or Octaray mapping catheters (Biosense Webster, Ca, USA) were performed and no PV stenosis or phrenic nerve damage were documented.

Electrophysiological study performed after 6 months from STAR:

- Patient 1, PVI was documented; high-rate atrial stimulation induced the clinical atrial flutter whose critical isthmus was ablated in a low-voltage area in the anterior wall (this area was far from targeted areas of STAR) (figure 3).

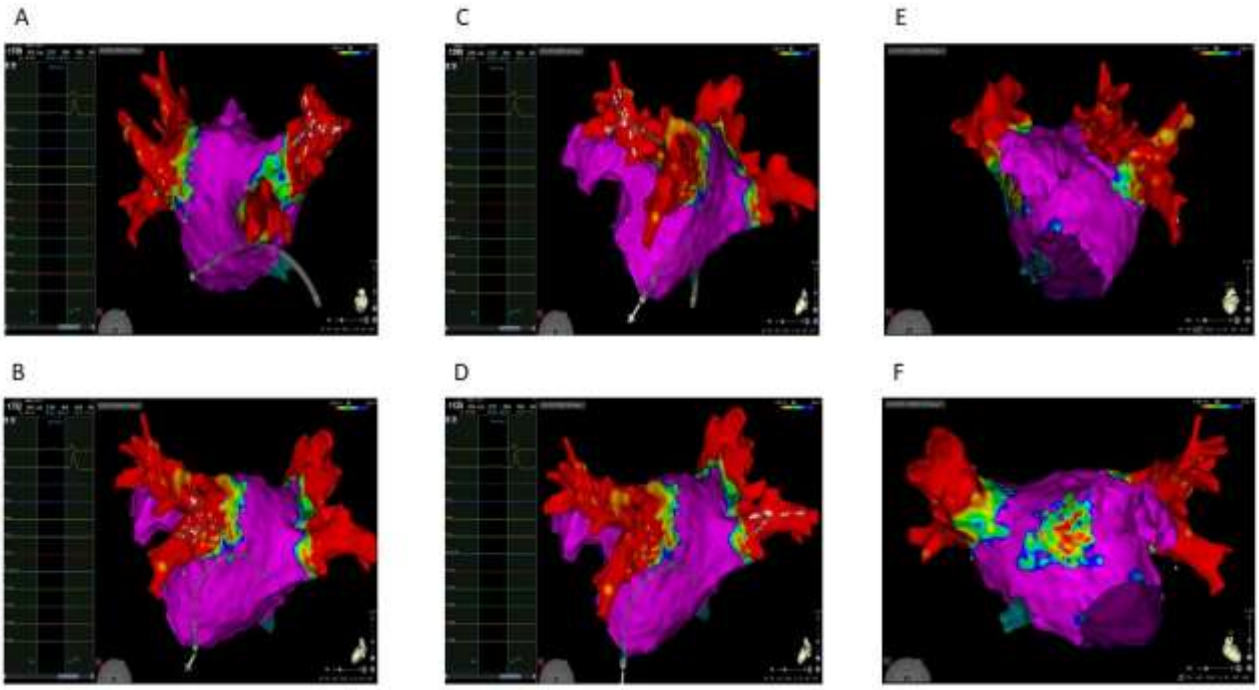


Figure 3. Electroanatomic mapping of left atrium using CARTO System and Pentaray catheter. *Panel A*: Pentaray catheter inserted into the right superior pulmonary vein documenting the absence of electrical potentials. *Panel B*: Pentaray catheter inserted into the left inferior pulmonary vein documenting the absence of electrical potentials. *Panel C*: Pentaray catheter inserted into the left superior pulmonary vein documenting the absence of electrical potentials. *Panel D:* Pentaray catheter inserted into the right inferior pulmonary vein documenting the absence of electrical potentials. *Panel E*: left lateral view of left atrium. *Panel F* Anterior view documenting a low-voltage area on the roof of left atrium. This area was the site of atrial tachycardia.

- Patient 3, ES documented PVI, absence of low voltage areas in both atria. Programmed and high-rate atrial stimulation was not able to induce any arrhythmia (figure 4).

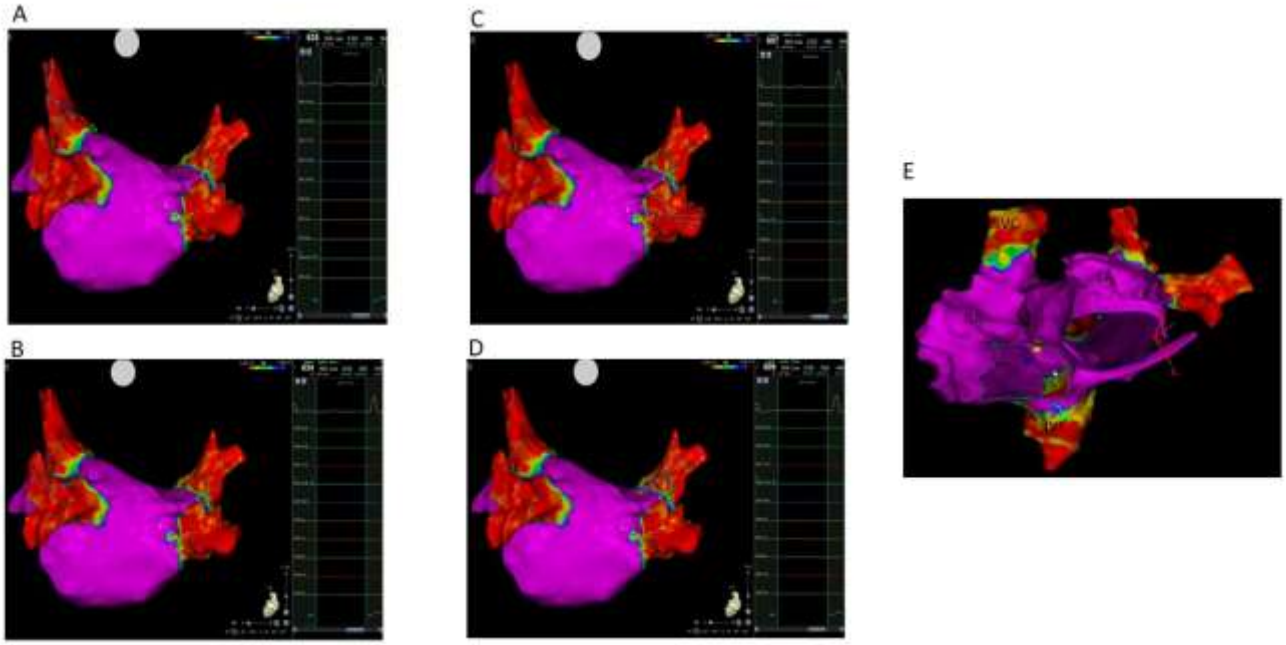


Figure 4. Electroanatomic mapping of left atrium using CARTO System and Pentaray catheter. *Panel A*: Pentaray catheter inserted into the left superior pulmonary vein documenting the absence of electrical potentials. *Panel B*: Pentaray catheter inserted into the left inferior pulmonary vein documenting the absence of electrical potentials. *Panel C*: Pentaray catheter inserted into the right inferior pulmonary vein documenting the absence of electrical potentials. *Panel D:* Pentaray catheter inserted into the right superior pulmonary vein documenting the absence of electrical potentials. *Panel E*: right and left atrial electroanatomic mapping.

Electrophysiological study performed after 12 months from STAR:

- Patient 9 documented PVI with lesions performed distally in the superior veins (figure 5). In this patient, esophagus and left bronchus were located close to the superior PV ostia and the STAR was planned deeper in the veins to avoid their damage. In this patient, antral electrical activity on the superior PVs was ablated.

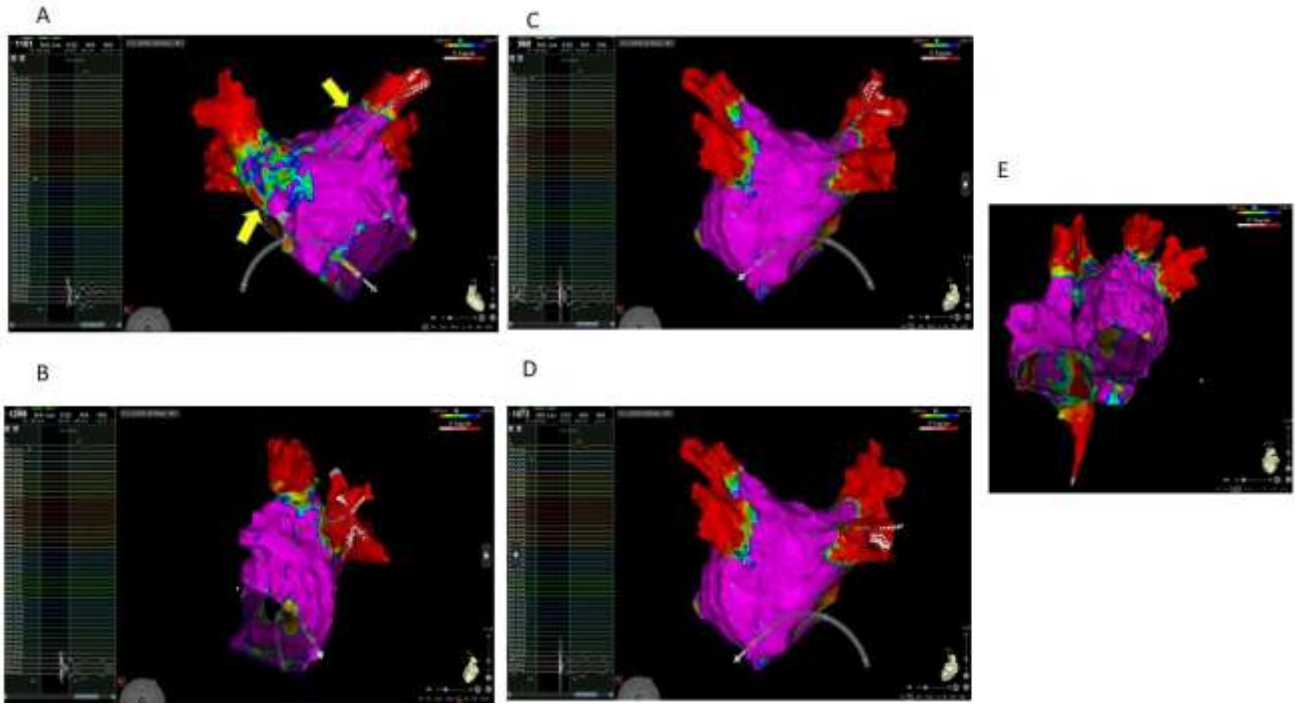


Figure 5. Electroanatomic mapping of left and right atrium using CARTO System and Octaray catheter. *Panel A*: Octaray catheter inserted into the left superior pulmonary vein documenting the absence of electrical potentials. Yellow arrows represent the areas close to esophagus and left bronchus. *Panel B*: Octaray catheter inserted into the left inferior pulmonary vein documenting the absence of electrical potentials. *Panel C*: Octaray catheter inserted into the right superior pulmonary vein documenting the absence of electrical potentials. *Panel D:* Octaray catheter inserted into the right inferior pulmonary vein documenting the absence of electrical potentials. *Panel E*: right and left atrial electroanatomic mapping.

- Patient 5 had PVI with high grade of left atrial fibrosis (figure 6). No rotational or focal activity was detected by CARTO Finder software (Biosense Webster, Ca, USA) posterior wall isolation was performed.

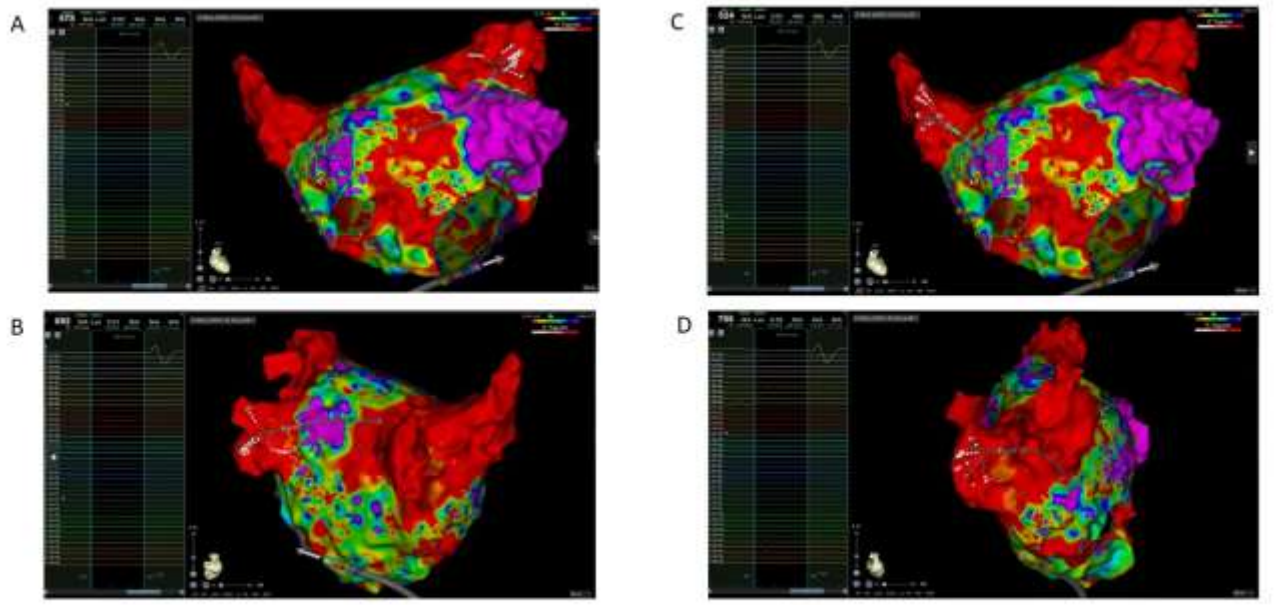


Figure 6

Figure 6. Electroanatomic mapping of left atrium using CARTO System and Octaray catheter. *Panel A*: Octaray catheter inserted into the left superior pulmonary vein documenting the absence of electrical potentials. *Panel B*: Octaray catheter inserted into the left inferior pulmonary vein documenting the absence of electrical potentials. *Panel C*: Octaray catheter inserted into the right superior pulmonary vein documenting the absence of electrical potentials. *Panel D:* Octaray catheter inserted into the right inferior pulmonary vein documenting the absence of electrical potentials.

- Patient 13 had PVI and left atrial posterior wall didn't show any electrical activity (figure 7); critical isthmus of left atrial flutter was ablated on the left atrial roof.

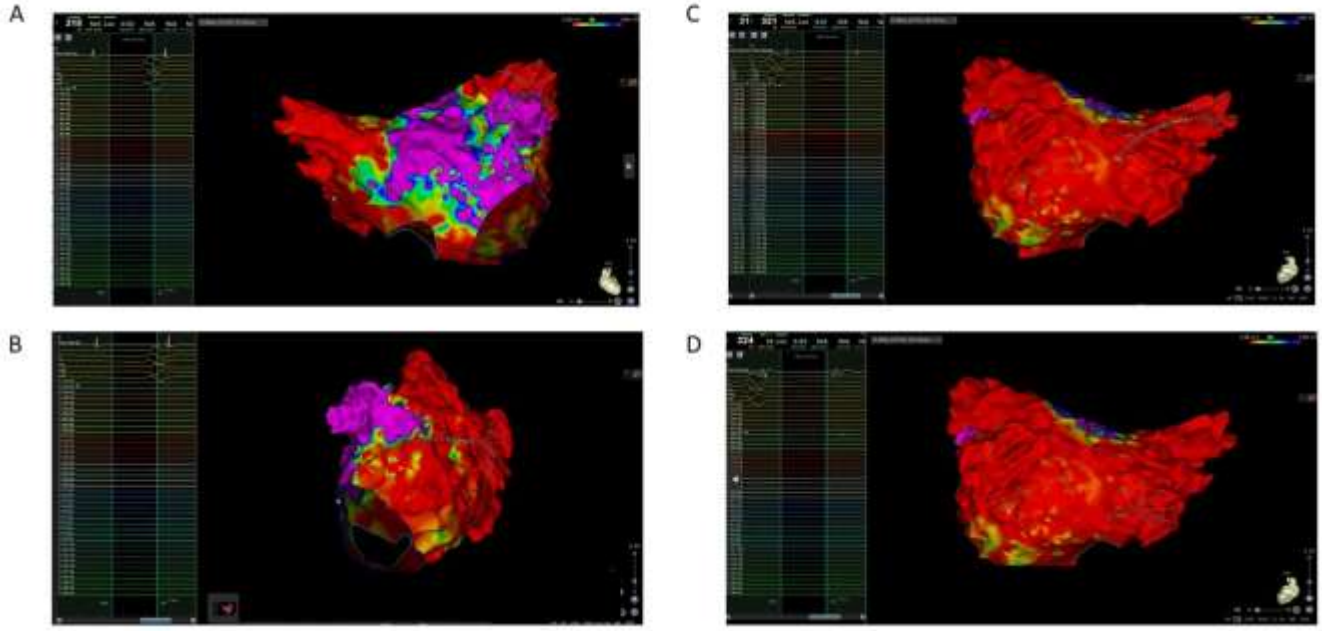


Figure 7. Electroanatomic mapping of left atrium using CARTO System and Pentaray catheter. Panel A: Octaray catheter inserted into the left superior pulmonary vein documenting the absence of electrical potentials. Panel B: Octaray catheter inserted into the left inferior pulmonary vein documenting the absence of electrical potentials. Panel C: Octaray catheter inserted into the right superior pulmonary vein documenting the absence of electrical potentials. Panel D: Octaray catheter inserted into the right inferior pulmonary vein documenting the absence of electrical potentials.

A significant improvement of quality of life was documented after STAR (48±15 at enrollment vs 75±15 at 12 months FU; $p<0.001$). No patient died.

4. Discussion

AF is the most common cardiac arrhythmia with an increased risk of complications especially if a proper anticoagulation or a proper rhythm and rate control are lacking [47-54].

PV isolation remains the cornerstone of AF ablations [51]. In elderly, this procedure is often not performed due to the higher risk of procedural complications: vascular injury, cardiac perforation, phrenic nerve injury, stroke, and most concerning, atrio-esophageal fistula, with high mortality rate [51-54]. For these reasons, in the clinical practice it is preferred to use pharmacological treatment rather than interventional procedures. However, AAT can lead to serious side effects or it is contraindicated due to sinus bradycardia or conduction disorders [47]. The ablation of the atrioventricular node and pacemaker implantation can control ventricular rate when medication fails, however exposing the patient to the risk of device malfunction and infection [47, 50]. Moreover, many of patients enrolled in this study refused interventional therapies.

As a result, there is ongoing interest in developing improved therapies for AF and non-invasive therapeutic alternatives are warranted. The STAR study was born from the desire to obtain PVI using a non-invasive method, suitable for older patients or those who cannot have or not desire an invasive procedure. The outpatient care setting allows for the treatment of a large number of patients without occupying hospital beds. This aspect is of great importance considering the large number of patients eligible for the procedure as opposed to the progressive reduction of hospital beds.

The present phase-II LINAC-STAR trial is the first worldwide study designed to evaluate the safety of this treatment. In terms of safety endpoint, the adverse events with a possible correlation to STAR were mild esophagitis and mild pericardial effusion among which only one required pharmacological therapy.

Esophagitis is essentially due to the anatomical proximity of the esophagus and the PVs and we documented mild esophagitis without the onset of fistulas in a longer follow-up. We performed a "simultaneous integrated protection" dose for esophagus and bronchus, for reducing the risk of side effect. Moreover, STAR was delivered using IGRT and SGRT to increase precision of target position

and organs at risk and the delivering treatment time was very short (3 minutes instead of 45-90 minutes for other technologies), reducing the risk of esophagus displacement during a longer treatment [46]. Prophylactic treatment to prevent esophagitis should be considered in the future.

The patient's anatomy is essential for structuring an optimal treatment plan and some unfavourable anatomies (mainly esophagus, PVs and left bronchus very close together) may not allow it. In our series, 1 patient was excluded due to the esophagus located behind the left PVs and in 1 patient esophagus and left bronchus were located so close to the superior PV ostia that the STAR treatment was planned deeper in the veins to avoid their damage. In the last case, the ES after STAR documented a suboptimal PV isolation since the PV antral electrical activity was widely recorded.

Finally, we highlighted mild pericarditis and asymptomatic effusions during follow-up. It is necessary to monitor these events over a long time for potential development of chronic pericarditis and, in addition, to understand a possible correlation with arrhythmic recurrences.

For the “torsade de pointes”, it is not possible to determine if this event was due to STAR or to a chance because in the patient's clinical history there are factors that can be associated with this type of event. In particular, the patient had a syncope about 5 years ago, mild prolonged QT interval on ECG (corrected QTc 480 msec) and was suffering from hypertensive heart disease (ventricular septum diameter 15 mm). His treating physician decided to resume the flecainide therapy seven days before STAR due to daily symptomatic AF episodes. After 1 hour from STAR, the patient had a torsade de pointes treated effectively by electrical cardioversion and he was admitted to the Cardiology department. Coronary angiography, echocardiogram, serum electrolytes and troponin were normal. The patient underwent cardiac ICD implantation. During his follow-up visits, very early ventricular ectopies (minimum coupling interval 290 msec) were documented and the ICD recorded only 1 atypical atrial flutter after 1 year from STAR. The patient is in good general condition with a significant improvement in the quality of life.

Regarding the secondary endpoints, the efficacy data have several limits (small number of patients, the analysis of recurrences carried out only through ECG and 15 days ECG-Holter monitoring, and

the absence of a control group). However, our data report a trend towards a strong reduction in arrhythmic events, a reduction in the intake of AAT and an improvement in the patients' quality of life. According to recent data [54], atrial arrhythmias free survival rate after AF ablation are variable, ranging from 70 to 86% in elderly patients (data comparable with our results). This is a pilot study with a limited sample size, further studies are needed to compare efficacy and safety of STAR with catheter ablation or "ablate and pace" strategy in elderly patients.

Three patients developed a form of persistent AF and refused the catheter ablation. These patients had a cardiac valvulopathy that predisposed them to an atrial arrhythmic substrate worsening, even if catheter ablation was performed [47, 51, 60].

In terms of ES, we have demonstrated for the first time that STAR is effective in performing PVI even 12 months after treatment. Regarding pathophysiological mechanisms, previous studies reported that myocardial inflammation and structural changes can be induced within a month after STAR while fibrosis develops after several months. Later physiological changes are mainly fibrosis, the maturation of which takes several months to complete. The PVI demonstrated 6 and 12 months after STAR is probably the result of a combination of these mechanisms but mainly tissue fibrosis.

In terms of treatment dosimetry, our treatment plan has been performed to minimize the radiation dose to heart and close organs, conforming dose to PVs. However, despite dose to healthy organs (including heart, lungs, bronchus, esophagus and all body) respected the radiation dose constrains, as previously reported [44,45], long-term FU will be important to assess possible adverse events due to radiation exposure even for AF and ventricular tachycardia. In absence of data for the latter procedure in arrhythmias, in this study we enrolled elderly people to reduce the long side effect risk in a population with lower life expectancy respect to younger.

The main limitations of our treatment concern the anatomical characteristics of patients and the absence of a pre-treatment arrhythmic substrate analysis.

Furthermore, due to a non-invasiveness design of the present trial, an electroanatomical map to analyse the arrhythmic substrate was not performed. However, the ablative target in patients with

paroxysmal AF is PVI that was achieved with STAR [46, 51]. Elderly patients with paroxysmal AF may have fibrosis located in areas other than PVs but there are currently no studies demonstrating an antiarrhythmic advantage in ablation of these areas and, therefore, PVI remains the main ablation target [51, 54]. In the future, studies supported by non-invasive cardiac mapping will allow us to improve this treatment.

5. Conclusions

The present phase II trial demonstrated the feasibility of STAR in AF elderly patients, reporting also promising data in terms of safety, outcomes and quality of life. This new non-invasive and outpatient therapeutic approach can represent a valid alternative for a rapidly growing category of patients.

Close collaboration between radiation oncologists, cardiac electrophysiologists and medical physics is paramount for this technique, to minimize patient risk and achieve highest levels of ablation accuracy. Further data are needed to confirm our results and to assess possible long- term side effects.

6. REFERENCES

1. Krijthe BP, Kunst A, Benjamin EJ, Lip GYH, Franco OH, Hofman A, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J.* (2013) 34:2746–51. doi: 10.1093/eurheartj/eht280
2. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol.* (2009) 104:1534–9. doi: 10.1016/j.amjcard.2009.07.022
3. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med. 1995;155(5): 469-473.
4. Newgard CB, Sharpless NE. Coming of age: molecular drivers of aging and therapeutic opportunities. J Clin Invest. 2013;123(3): 946-950.
5. Jakobsen CB, Lamberts M, Carlson N, Lock-Hansen M, Torp-Pedersen C, Gislason GH, et al. Incidence of atrial fibrillation in different major cancer subtypes: a nationwide population-based 12 year follow up study. *BMC Cancer.* (2019) 19:1105. doi: 10.1186/s12885- 019- 6314- 9
6. Wolf PA, Abbott RD, Kannel WB. Original contributions atrial fibrillation as an independent risk factor for stroke: the Framingham study. Stroke. (1991) 22:983–8. doi: 10.1161/01.str.22.8.983
7. Zoni-Berisso M, Filippi A, Landolina M, Brignoli O, D'Ambrosio G, Maglia G, et al. Frequency, patient characteristics, treatment strategies, and resource usage of atrial fibrillation (from the Italian survey of atrial fibrillation management [ISAF] study). *Am J Cardiol.* (2013) 111:705–11. doi: 10.1016/ j.amjcard.2012.11.026
8. Ha Marzec LN, Wang J, Shah ND, Chan PS, Ting HH, Gosch KL, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. *J Am Coll Cardiol.* (2017) 69:2475–84. doi: 10.1016/j.jacc.2017.03.540
9. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation(ATRIA) Study. *JAMA.* (2001) 285:2370–5. doi: 10.1001/ jama.285.18.2370
10. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for European Association for Cardio – Thoracic Surgery (EACTRS). Eur Heart J. 2021 Feb 1;42(5):373-498. doi: 10.1093/eurheartj/ehaa612
11. Haissaguerre, M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, J Clémenty. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659-66.
12. Calkins, H.; Hindricks, G.; Cappato, R.; Kim, Y.H.; Saad, E.B.; Aguinaga, L.; Akar, J.G.; Badhwar, V.; Brugada, J.; Camm, J.; et al. 2017 HRS/EHRA/EACS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace 2018, 20, 157–208.
13. Pelargonio, G.; Di Monaco, A.; Guida, P.; Pellegrino, P.L.; Vergara, P.; Grimaldi, M.; Narducci, M.L.; Tritto, M. AIAC Task Force AF Ablation. Atrial fibrillation ablation: Is common practice far from guidelines' world? The Italian experience from a national survey. J. Interv. Card. Electrophysiol. 2022, 63, 125–132.
14. A. Di Monaco, N. Vitulano, F. Troisi, M. Grimaldi Pulsed Field Ablation to Treat Atrial Fibrillation: A Review of the Literature , J. Cardiovasc. Dev. Dis. **2022**, 9, 94. https://doi.org/10.3390/jcdd9040094
15. Packer DL, Mark DB, Robb RA, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. JAMA. 2019;321(13):1261-1274.

16. N. Prasitlumkum, N. Tokavanich, A. Trongtorsak, Wisit Cheungpasitporn, Jakrin Kewcharoen, Ronpichai Chokesuwattanaskul Catheter ablation for atrial fibrillation in the elderly >75 years old: Systematic review and meta-analysis, DOI: 10.1111/jce.15549 J Cardiovasc Electrophysiol. 2022;33:1435–1449.
17. Leksell L (1951) The stereotactic method and radiosurgery of the brain. Acta Chir Scand 102:316–319
18. Mazzola R, Fersino S, Alongi P et al (2018) Stereotactic body radi- ation therapy for liver oligometastases: predictive factors of local response by ^{18}F-FDG-PET/CT. Br J Radiol 91(1088):20180058
19. Mazzola R, Fersino S, Aiello D et al (2018) Linac-based stereotac- tic body radiation therapy for unresectable locally advanced pan- creatic cancer: risk-adapted dose prescription and image-guided delivery. Strahlenther Onkol 194(9):835–842
20. Alongi F, Mazzola R, Fiorentino A et al (2019) Phase II study of accelerated Linac-based SBRT in five consecutive fractions for localized prostate cancer. Strahlenther Onkol 195(2):113–120
21. Franco P, De Bari B, Ciammella P (2014) The role of stereotactic ablative radiotherapy in oncological and non-oncological clinical settings: highlights from the 7th meeting of AIRO–Young Mem- bers Working Group (AIRO Giovani). Tumori 100(6):214–219
22. Graeff C, Bert C (2018) Noninvasive cardiac arrhythmia ablation with particle beams. Med Phys 45(11):e1024–e1035
23. Song CW, Cho LC, Yuan J et al (2013) Radiobiology of stereo- tactic body radiation therapy/stereotactic radiosurgery and the linear-quadratic model. Int J Radiat Oncol Biol Phys 87(1):18–19
24. Shimohigashi Y, Doi Y, Kouno Y et al (2019) Image quality evaluation of in-treatment four-dimensional cone-beam computed tomography in volumetric-modulated arc therapy for stereotactic body radiation therapy. Phys Med 68:10–16
25. Constantinescu A, Lehmann H, Packer D, Bert C, Durante M, Graeff C (2016) Treatment planning studies in patient data with scanned carbon ion beams for catheter-free ablation of atrial fibril- lation. J Cardiovasc Electrophysiol 27:335–344
26. Bert C, Durante M (2011) Motion in radiotherapy: particle ther- apy. Phys Med Biol 56:R113–R144
27. Verma V, Mishra MV, Mehta MP (2016) A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. Cancer 122(10):1483–1501
28. Sharma A, Wong D, Weidlich G et al (2010) Noninvasive stereo- tactic radiosurgery (CyberHeart) for creation of ablation lesions in the atrium. Heart Rhythm 7(6):802–810
29. Blanck O, Bode F, Gebhard M et al (2014) Dose-escalation study for cardiac radiosurgery in a porcine model. Int J Radiat Oncol Biol Phys 89(3):590–598
30. Bode F, Blanck O, Gebhard M et al (2015) Pulmonary vein isola- tion by radiosurgery: implications for non-invasive treatment of atrial fibrillation. Europace 17(12):1868–1874
31. Lehmann HI, Richter D, Prokesch H et al (2015) Atrioventricu- lar node ablation in Langendorff-perfused porcine hearts using carbon ion particle therapy: methods and an in vivo feasibility investigation for catheter-free ablation of cardiac arrhythmias. Circ Arrhythm Electrophysiol 8:429–438
32. Lehmann HI, Deisher AJ, Takami M et al (2017) External arrhyth- mia ablation using photon beams: ablation of the atrioventricular junction in an intact animal model. Circ Arrhythm Electrophysiol 10:e004304
33. Refaat MM, Ballout JA, Zakka P et al (2017) Swine atrioven- tricular node ablation using stereotactic radiosurgery: methods and in vivo feasibility investigation for catheter-free ablation of cardiac arrhythmias. J Am Heart Assoc 6(11):e007193
34. Cuculich PS, Schill MR, Kashani R et al (2017) Noninvasive car- diac radiation for ablation of ventricular tachycardia. N Engl J Med 377(24):2325–2336

35. Loo BW Jr, Soltys SG, Wang L et al (2015) Stereotactic ablative radiotherapy for the treatment of refractory cardiac ventricular arrhythmia. Circ Arrhythm Electrophysiol 8:748–750
36. Jumeau R, Ozsahin M, Schwitter J et al (2018) Rescue procedure for an electrical storm using robotic non-invasive cardiac radio- ablation. Radiother Oncol 128(2):189–191
37. Stöhr EJ, Shave RE, Baggish AL, Weiner RB (2016) Left ven- tricular twist mechanics in the context of normal physiology and cardiovascular disease: a review of studies using speckle tracking echocardiography. Am J Physiol Heart Circ Physiol 311(3):H633–H644
38. Robinson CG, Samson PP, Moore KMS et al (2019) Phase I/II trial of electrophysiology-guided noninvasive cardiac radioabla- tion for ventricular tachycardia. Circulation 139:313–321
39. Cvek J, Neuwirth R, Knybel L et al (2014) Cardiac radiosurgery for malignant ventricular tachycardia. Cureus 6:e190
40. Zei PC, Mak R (2019) Noninvasive stereotactic radioablation for ventricular tachycardia ENCORE-VT (EP-guided noninvasive cardiac radioablation): is the sequel as good as the original? Cir- culation 139:322–324
41. Mayinger M, Kovacs B, Tanadini-Lang S et al (2020) First magnetic resonance imaging-guided cardiac radioablation of sustained ventricular tachycardia. Radiother Oncol. https://doi. org/10.1016/j.radonc.2020.01.008
42. Monroy E, Azpiri J, De La Pena C, Cardona C, Hinojosa M, Zamarripa R et al. Late Gadolinium Enhancement Cardiac Magnetic Resonance Imaging Post-robotic Radiosurgical Pulmonary Vein Isolation (RRPVI): First Case in the World. Cureus 2016;8:e738
43. Qian PC, Azpiri JR, Assad J, Gonzales Aceves EN, Cardona Ibarra CE, de la Pena C et al. Noninvasive stereotactic radioablation for the treatment of atrial fibrillation: First-in-man experience. J Arrhyth 2020;36:67-74.
44. Di Monaco A, Gregucci F, Bonaparte I, Troisi F, Surgo A, Di Molfetta D et al. Paroxysmal Atrial Fibrillation in Elderly: Worldwide Preliminary Data of LINAC-Based Stereotactic Arrhythmia Radioablation Prospective Phase II Trial. Front Cardiovasc Med. 2022 Mar 2;9:832446.
45. Bonaparte I, Gregucci F, Di Monaco A, Troisi F, Surgo A, Ludovico E et al. Phase II Trial of LINAC-Based STereotactic Arrhythmia Radioablation (STAR) for Paroxysmal Atrial Fibrillation in Elderly: Planning and Dosimetric Point of View, J Pers Med 2023;13:596.
46. Di Monaco A, Gregucci F, Bonaparte I, Troisi F, Surgo A, Di Molfetta D et al. First Pulmonary Vein Isolation Using LINAC-Based STAR. Circ Arrhythm Electrophysiol 2022;15:e010880,
47. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373-498.
48. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial fibrillation: epidemiology, pathophysiology, and clinical outcomes. Circ Res 2017;120:1501-1517
49. Krijthe BP, Kunst A, Benjamin EJ, Lip G YH, Franco OH, Hofman A et al. Projections on the number of individuals with atrial fbrillation in the European Union, from 2000 to 2060. Eur Heart J 2013;34:2746– 2751.
50. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC): With the special contribution of the European Heart Rhythm Association (EHRA). Europace 2022;24:71–164
51. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace. 2018;20:e1-e160

52. Tilz RR, Dagres N, Arbelo E, Blomström-Lundqvist C, Crijns HJ, Kirchhof P et al. Which patients with atrial fibrillation undergo an ablation procedure today in Europe? A report from the ESC-EHRA-EORP Atrial Fibrillation Ablation Long-Term and Atrial Fibrillation General Pilot Registries. Europace 2020;22:250-258
53. Kennedy R, Oral H. Catheter ablation of atrial fibrillation in the elderly: does the benefit outweigh the risk? Expert Rev Cardiovasc Ther 2013;11:697-704.
54. Prasitlumkum N, Tokavanich N, Trongtorsak A, Cheungpasitporn W, Kewcharoen J, Chokesuwattanaskul R et al. Catheter ablation for atrial fibrillation in the elderly >75 years old: Systematic review and meta-analysis. J Cardiovasc Electrophysiol 2022;33:1435-1449.
55. Cheng LJ, Tan RL, Luo N. Measurement Properties of the EQ VAS Around the Globe: A Systematic Review and Meta-Regression Analysis. Value Health 2021;24:1223-1233
56. Kong FM, Ritter T, Quint DJ, Senan S, Gaspar LE, Komaki RU et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: Atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int. J. Radiat. Oncol. Biol. Phys. 2011;81:1442–1457
57. Boda-Heggemann J, Blanck O, Mehrhof F, Ernst F, Buergy D, Fleckenstein J et al. Interdisciplinary Clinical Target Volume Generation for Cardiac Radioablation: Multicenter Benchmarking for the RAdiosurgery for VENtricular TAchycardia (RAVENTA) Trial. Int. J. Radiat. Oncol. Biol. Phys. 2021; 110:745–756,
58. Cox BW, Jackson A, Hunt M, Bilsky M, Yamada Y. Esophageal toxicity from high-dose, single-fraction paraspinal stereotactic radiosurgery. Int. J. Radiat. Oncol. Biol. Phys. 2012;83:e661–e667.
59. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. Actas Dermosifiliogr (Engl Ed) 2021;112:90-92.
60. Zhao D, Zhang F, Liu X, Li M, Zhang L, Hu J et al. Efficacy of catheter ablation for atrial fibrillation in patients with significant functional mitral regurgitation. Medicine (Baltimore) 2023;102:e33231