COPYRIGHT© 2023 EDIZIONI MINERVA MEDICA

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The creation of derivative works from the Article is not permitted. The production of reprints for personal or commercial use is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.

© 2023 EDIZIONI MINERVA MEDICA
Online version at https://www.minervamedica.it

Minerva Urology and Nephrology 2023 Jun 23
DOI: 10.23736/S2724-6051.23.05322-3

ORIGINAL ARTICLE

Temporary implantable nitinol device for benign prostatic hyperplasia-related lower urinary tract symptoms: over 48-month results

Daniele AMPARORE [1], Sabrina De CILLIS [1] *, Claude SCHULMAN [2], Gregor KADNER [3], Cristian FIORI [1], Francesco PORPIGLIA [1]

[1]Division of Urology, San Luigi Hospital, Orbassano, Turin, Italy; [2]Division of Urology, CHIREC Cancer Institute, University of Brussels, Brussels, Belgium; [3]Division of Urology, Kantonsspital, Frauenfeld, Switzerland

*Corresponding author: Sabrina De Cillis, Division of Urology, Department of Oncology, School of Medicine, San Luigi Hospital, University of Turin, Regione Gonzole 10, 10043 Orbassano, Turin, Italy. E-mail: sabrinatitti.decillis@gmail.com

ABSTRACT

BACKGROUND: This study (MT02) reports >48-month (50-79 months) results of a prospective, single-arm, multicenter study (NCT02145208) of temporary implantable nitinol device (iTind®) in men with benign prostatic hyperplasia (BPH)-related lower urinary tract symptoms (LUTS).

METHODS: Men with symptomatic BPH (International Prostate Symptom Score [IPSS] ≥10, Maximum flow rate [Q_{max}] <12 mL/s, and prostate volume <75 mL) from 9 centers were enrolled from December 2014 to December 2016. Total 50/81 (62%) patients at 3/9 sites (Italy, Switzerland, and Belgium), pursued the study beyond 36 months following iTind® device, per study protocol. Due to COVID-19, follow-up was amended. Each patient was assessed once during 50-79 months postoperatively for IPSS and IPSS-quality of life (IPSS-QoL), change in medication, need for surgical re-treatment and adverse events telephonically.

RESULTS: Post 36 month-follow-up, 5 patients were lost to follow-up and 2 patients died unrelated to iTind® device placement. Two patients (36-48 months follow-up) required surgical re-treatments (1 transurethral resection of prostate, 1 Thulium laser enucleation of prostate). >48 months results were available for 41 patients wherein iTind® device treatment showed significant improvement in symptoms (IPSS: -45.3%, P<0.0001 and IPSS-QoL: -45.1%, P<0.0001) from baseline to 79 months post-procedure; mean±SD of 11.26±7.67 and 2.10±1.41 points, respectively. No complications were recorded between 36 up to 79 months; no patient required additional medication.

CONCLUSIONS: iTind® device provided significant and durable symptom reduction and improved IPSS-QoL for >48 months post treatment. No late postoperative complications were reported beyond 36 months of follow-up. Surgical re-treatment rate for >36 months was 4%.

(*Cite this article as*: Amparore D, De Cillis S, Schulman C, Kadner G, Fiori C, Porpiglia F. Temporary implantable nitinol device for benign prostatic hyperplasia-related lower urinary tract symptoms: over 48-month results. Minerva Urol Nephrol 2023 Jun 23. DOI: 10.23736/S2724-6051.23.05322-3)

KEY WORDS: Prostatic hyperplasia; Lower urinary tract symptoms; Nitinol.

Benign prostatic hyperplasia (BPH), related to the emergence of lower urinary tract symptoms (LUTS), is a common and multifactorial[1] condition among adult males. It affects >50% of the patients before the sixth decade, with an incidence increase associated with aging.[2] A significant number of these patients are candidates for endoscopic surgical treatment such as transurethral resection of the prostate (TURP), which continues to represent the 'gold standard' treatment BPH-related LUTS in patients with prostates smaller than 80 mL, because of its successful and durable outcomes in terms of symptomatic relief.[3] Notwithstanding the association with

COPYRIGHT© 2023 EDIZIONI MINERVA MEDICA

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The creation of derivative works from the Article is not permitted. The production of reprints for personal or commercial use is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.

TURP and postoperative erectile disfunction has been recently been questioned, this surgical approach is still associated with multiple other potential adverse events (AEs) postoperatively in nearly 20% of patients which include morbidities such as: ejaculatory dysfunction (65%) and urethral strictures (7%).[4, 5] Recently, a variety of minimally invasive surgical procedures have been tested aiming to maintain the benefit of oral drugs while decreasing the incidence of invasive surgery-related AEs.[6-8] European Association of Urology (EAU) guidelines cite several of these surgical approaches[9, 10] like water vapor therapy (Rezūm),[11] prostatic artery embolization (PAE),[12] and prostatic urethral lift (PUL).[13] Another surgical option has recently been developed, the temporary implantable nitinol device (Tind), offering symptomatic relief from BPH-related LUTS and a minimally invasive approach.[14] A prospective multicenter study of the second-generation Tind device (iTind, Medi-Tate Ltd®, Israel) has already highlighted the potential benefits of this surgical approach.[15] In fact, iTind device has demonstrated to be effective with no safety concerns, with a stable and significant improvement of symptoms evaluated by International Prostate Symptom Score (IPSS), QoL, and functional results. This study assessed the long-term results at >48 months in patients treated with iTind device.

Materials and methods

Study design and patient characteristics

This was a single-arm, multicenter, international, prospective study that enrolled patients at 9 centers between December 2014 and December 2016. It was approved by the institutional ethics committee at each center and, according to Good Clinical Practice guidelines, in compliance with the World Health Organization guidelines (NCT02145208). Written informed consent was obtained from all the patients enrolled in the study.

The inclusion criteria were: patients experiencing LUTS with IPSS≥10 and Q_{max}≤12 mL/s, prostate volume <75 mL, normal urinalysis, complete blood count and biochemistry. Exclusion criteria were: post-void residual (PVR) >250 mL, obstructive median lobe, bladder neck sclerosis, previous prostate surgery, prostate or bladder cancer, neurogenic bladder and/or sphincter abnormalities, confounding bladder pathologies, recent cystolithiasis or hematuria, active urinary tract infection, compromised renal function, active antithrombotic or antiplatelet treatment, cardiac disease, including arrhythmias, and uncontrolled diabetes mellitus. Enrolled patients were asked to cease the usage of any oral drugs for BPH-related LUTS before the surgical procedure, 1 month for alpha-blockers and 6 months for 5α-reductase inhibitors. Preoperative data were collected 40 days before the intervention and included medical history, BPH-related drugs, uroflowmetry, IPSS, IPSS-QoL and PVR. Peri- and postoperative data such as operative time, pain (Visual A), complications (modified Clavien-Dindo-Grading System[16]) and AEs were assessed. The functional outcomes, PVR, Q_{max}, IPSS and IPSS-QoL were determined at 1, 3, 6, 12 months and then annually up to 36 months. IPSS and IPSS-QoL were assessed beyond 48 months.

Three out of 9 of the international sites pursued the study beyond the 36 months originally proposed in the protocol. Due to the COVID-19, patients could not be examined in person for objective testing and hence, amendments to the planned follow-up schedule were required. Every patient was evaluated telephonically only once between 50-79 months postoperatively with IPSS and IPSS-QoL questionnaires; information regarding restarting therapeutic drug consumption as well as the presence of AEs were evaluated. Data from these patients were grouped into a single timepoint (>48 months). Furthermore, data regarding the need for a subsequent surgical procedure for recurrent/persistent LUTS during the follow-up timeframe were collected.

Device, mechanism of action and surgical procedure

The iTind device (Medi-Tate Ltd®, Israel) is a temporary implantable device composed of three elongated, intertwined nitinol struts positioned at 12, 5, and 7 o'clock and a leaflet positioned at 6 o'clock to prevent the migration of the device. It measures 50 mm long and has a diameter of 33 mm and can cover the full extension of the prostatic urethra, from the bladder neck to the

COPYRIGHT© 2023 EDIZIONI MINERVA MEDICA

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The creation of derivative works from the Article is not permitted. The production of reprints for personal or commercial use is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.

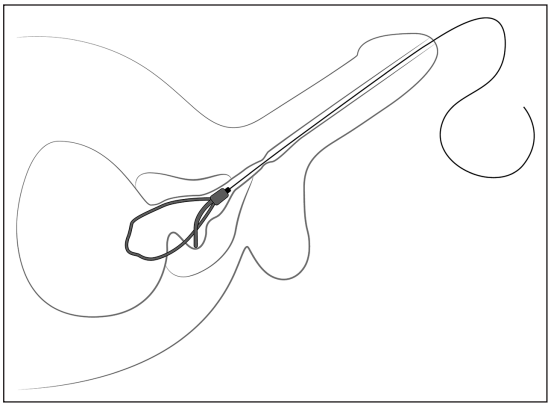

Figure 1.—iTind *in situ*, positioned in the prostatic urethra.

proximal to the external sphincter. The surgical procedure involves the implantation of the device under direct visualization with a rigid or flexible cystoscope. It is kept in situ for 5-7 days, during which time, it exerts a radial force that creates three ischemic incisions with a remodeling of the prostate tissue at the bladder neck and anterior prostatic fossa (Figure 1). The removal of the iTind device is performed either by a rigid cystoscope or an open-ended 22F Foley catheter. Both, implantation and removal can be performed under local, IV, or general anesthesia depending on the preference of the physician and the patient. Catheterization is not necessary after device implantation or removal.

Statistical analysis

Efficacy and safety as well as functional results were evaluated up to 79 months. Retreatment was defined as the requirement for any other surgical procedure for recurrent/persistent LUTS during follow-up requiring symptomatic relief. Data were expressed as median (range) or mean (±SD) for continuous variables due to skewness of the data, and as frequencies and proportion with corresponding confidence interval for categorical variables. For the baseline member characteristic table, we report median (range). For tables that compared the percentage changes from baseline to different follow-up time points, we report the results as mean (±SD) to improve the readability. The Shapiro-Wilk Test was used to check normal distribution of the continuous variables. The comparison between baseline and follow-up clinical variables was performed using Wilcoxon rank test. The analysis up to 79 months of follow-up was performed on intention-to-treat (ITT) basis with and without missing value imputation. To avoid the misleading artifact of the attrition of participants from the study imputation of missing values was done using last observation carried forward (LOCF). P value <0.05 was considered to indicate statistical significance. SAS® (Cary, NC, USA), version 9.4 for Windows was used for all statistical analyses.

Data availability

The data associated with the paper are not publicly available but can be made available from the sponsor to individual requestors upon reasonable request.

Results

Total 81 patients with median (range) age of 65 (45.5-84.5) years, prostate volume 39.5 (16-70) mL, IPSS -22.0 (11-35) points, Q_{max} 7.0 (3-14) mL/s, and IPSS-QoL score of 4 (2-5) points were enrolled in the study (Table I). All the device implantations were successful and well-tolerated by the patients with median (range) Visual Analogue Scale (VAS) pain score of 4 (0-10). No intraoperative complications were recorded. All patients were discharged on the same day of the procedure and no post-procedural catheterization was required. The removal of the devices was carried out at a mean±SD of 5.7±0.9 days, the removals were uneventful, with a median (range) VAS pain score of 2 (0-10).

All perioperative AEs were Grade I or II based on the Clavien-Dindo system, with hematuria (12.3%), micturition urgency (11.1%), pain (9.9%), dysuria (7.4%), and UTI (6.2%), recorded shortly after the procedure (54.7% ≤7 days, 30.2% 8-20 days; and 15.1% 20-30 days). Total 8/81 (9.9%) patients experienced urinary retention (N.=5 patients, with iTind device in place and N.=3 patients after device retrieval).[15]

At 36 months follow-up, data were available for 50/81 (62%) patients (Figure 2). The iTind device efficacy demonstrated stability during the study period with recorded improvements from preoperative data as % change of -58.2% for

COPYRIGHT© 2023 EDIZIONI MINERVA MEDICA

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The creation of derivative works from the Article is not permitted. The production of reprints for personal or commercial use is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.

TABLE I.—*Baseline and perioperative parameters in ITT populations.*

	Enrollment baseline values	36-months follow-up baseline values	>48-months follow-up baseline values
	N.=81	N.=50	N.=41
Age (median, range, years)	65 (45.5-84.5)	64.2 (45.5-83.7)	62.5 (45.5-77.8)
BMI (median, range, kg/m²)	26.1 (18.5-35.1)	26.1 (18.5-35.1)	26.1 (18.6-35.1)
PSA level (median, range, ng/mL)	1.4 (0.2-8.2)	1.2 (0.3-4.7)	1.2 (0.3-3.2)
Prostate volume (median, range, mL)	39.5 (16-70)	37 (16-65)	37 (16-65)
PVR (mean, SD, mL)	63.0 (0-240)	68.8±39.1 60(0-196)	60.0 (0-196)
Q_{max} (mean, SD, mL/sec)	7.3±2.6 7.0 (3-14)	8.0 (4-14)	-7.0 (4-11)
IPSS Score (mean, SD, pt)	22.0 (11-35)	-20.0 (13-34)	20 (15-34)
IPSS-QoL Score (median, range, pt)	4 (2-5)	4 (2-5)	4 (2-5)
Capable of performing sex (erectile function), N. (%)	74 (91.3)	49 (98.0)	41 (100)
Ejaculate upon orgasm, N. (%)	72 (88.9)	49 (98.0)	41(100)
Median lobe, N. (%)	10 (12.3)	0 (0)	0 (0)

IPSS: international prostate symptom score; PSA: prostate-specific antigen; pt: points; PVR: post-void residual; Q_{max}: maximum flow rate; QoL: quality of life; SD: standard deviation.

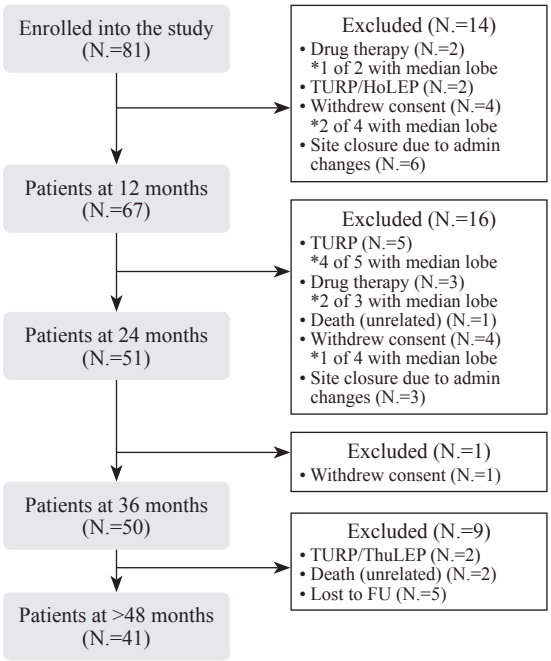

Figure 2.—Study enrollment flowchart: From enrollment to >48-month follow-up.
FU: follow-up; HoLEP: holmium laser enucleation of the prostate; ThuLEP: thulium laser enucleation of the prostate; TURP: transurethral resection of the prostate.

IPSS, -55.6% for IPSS-QoL, +114.7% for Q_{max}, and -85.4% for PVR (Table II). A significant difference from preoperative values (P<0.0001) was recorded for all these variables.

For the 3 centers which agreed to continue the follow-up > 48 months, out of the 50 patients enrolled, 5 patients were lost to follow-up and 2 patients died unrelated to the iTind device. Further, 2 patients required surgical re-treatment (N.=1 TURP, N.=1 Thulium laser enucleation of prostate [ThuLEP]). As a result, >48 months outcomes were registered for 41 patients with follow-up time a mean±SD of 60.2 (±7.9) months (Figure 2). IPSS demonstrated a small increase (+2.7 points) over the 36-month follow-up values, with a mean±SD of 11.26±7.67 and an improvement from baseline of -45.3%. IPSS-QoL mirrored these findings with a mean±SD of 2.10±1.41 points at >48 months follow-up, with an improvement from baseline of -45.1% (Table II). For all these variables a significant difference was recorded from preoperative levels (P<0.0001). Figure 3, 4 show the values of IPSS and IPSS-QoL at each timepoint from baseline up to >48 months.

In the ITT-LOCF imputation analysis set (Table III), the >48-month results demonstrated significant improvements from baseline for IPSS (-37.68%) and IPSS-QoL (-36.65%) (P<0.0001; both).

From baseline to 36 months, 5/81 (6.2%) patients required oral medication for BPH, and 7/81 (8.6%) patients underwent surgical retreatment. After 36 months but prior to the >48-month time point, 2/50 (4%) of patients underwent surgical treatment (in total 2/81 [2.5%]); 1 treated with TURP, 1 with ThuLEP. This leads to an overall 11.1% rate of retreatments from baseline to >48 months. No patient restarted oral medications. No late AEs were recorded beyond 48 months of follow-up.

COPYRIGHT© 2023 EDIZIONI MINERVA MEDICA

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The creation of derivative works from the Article is not permitted. The production of reprints for personal or commercial use is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.

TABLE II.—*Outcome measures after iTind: 4 weeks to >48 months (ITT Analysis Set).*

		4 weeks	6 months	12 months	24 months	36 months	>48 months
IPSS (points)	N.	72	69	64	49	49	41
	Baseline	22.22±5.62	21.99±5.48	21.70±5.56	20.71±4.56	20.69±4.58	20.56±4.42
	Follow-up	11.72±7.99	9.75±7.10	8.78±6.41	8.86±5.34	8.55±6.38	11.26±7.67
	Change	-10.50± 8.32	-12.23± 6.79	-12.92±6.92	-11.86± 6.20	-12.14±6.95	-9.29±7.63
	% Change	-46.9±33.0	-56.4±27.5	-59.1±26.3	-56.7±25.6	-58.2±32.1	-45.3±35.6
	(95% CI)	(-54.7%, -39.2%)	(-63.0%, -49.8%)	(-65.7%, -52.5%)	(-64.1%, -49.4%)	(-67.4%, -49.0%)	(-56.5%, -34.1%)
	P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
IPSS-QoL (points)	N.	72	69	64	51	49	41
	Baseline	4.00±0.84	3.97±0.84	3.97±0.87	3.96±0.87	3.98±0.88	4.00±0.89
	Follow up	2.08±1.35	1.81±1.30	1.59±1.29	1.76±1.32	1.76±1.33	2.10±1.41
	Change	-1.92±1.50	-2.16±1.44	-2.38±1.60	-2.20±1.46	-2.22±1.36	-1.90±1.59
	% Change	-46.4±34.2	-53.3±32.5	-56.9±38.5	-54.0±38.5	-55.6±37.0	-45.1±39.5
	(95% CI)	(-54.5%, -38.4%)	(-61.1%, -45.5%)	(-66.5%, -47.3%)	(-64.8%, -43.2%)	(-66.2%, -45.0%)	(-57.6%, -32.7%)
	P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Q_{max} (mL/sec)	N.	75	69	62	50	48	
	Baseline	7.28±2.49	7.58±2.43	7.61±2.25	7.62±2.25	7.71±2.26	
	Follow up	11.23±5.66	13.69±6.26	14.91±8.06	16.00±7.43	15.20±6.59	
	Change	3.94±5.22	6.12±6.22	7.30±8.20	8.38±7.93	7.49±6.86	
	% Change	65.0±112.3	95.6±106.5	111.7± 147.1	130.8±132.2	114.7± 108.5	
	(95% CI)	(39.2%, 90.9%)	(70.1%, 121.2%)	(74.3%, 149.0%)	(93.3%, 168.4%)	(83.2%, 146.2%)	
	P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Post-void residual urine (mL)	N.	76	70	63	50	48	
	Baseline	76.17±55.52	78.70±56.11	73.54±49.54	65.84±38.46	68.58±39.53	
	Follow up	49.84±57.27	48.84±47.59	34.03±54.13	14.26±24.05	9.38±17.43	
	Change	-26.33± 57.59	-29.86± 60.89	-39.51± 57.46	-51.58± 36.68	-59.21± 37.75	
	% Change	-28.2±60.1	-13.8±105.9	-47.8±72.5	-75.7±45.1	-85.4±30.7	
	(95% CI)	(-42.5%, -13.8%)	(-39.9%, 12.2%)	(-66.7%, -28.9%)	(-88.9%, -62.4%)	(-94.6%, -76.3%)	
	P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	

All values for baseline and change from baseline are represented as Mean±SD. Missing values were not imputed. For IPSS, QoL, Q_{max} and PVR, change from baseline was evaluated.
CI: confidence interval; IPSS: international prostate symptom score; PVR: post-void residual; Q_{max}: maximum flow rate; QoL: quality of life; SD: standard deviation.

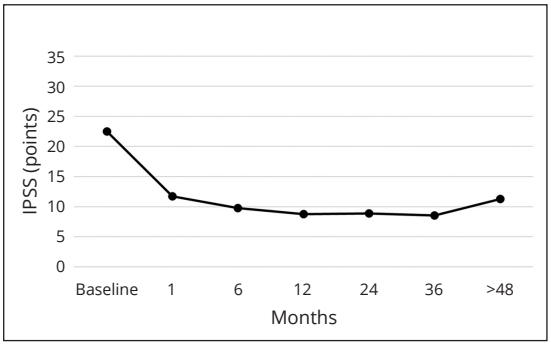

Figure 3.—Improvement of IPSS over time from baseline to >48-month follow-up, ITT analysis set.
IPSS: international prostate symptom score; ITT: intent-to-treat.

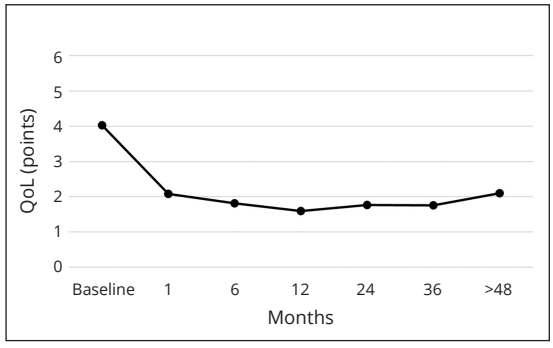

Figure 4.—Improvement of IPSS-QoL over time from baseline to >48-month follow-up, ITT analysis set.
IPSS-QoL: international prostate symptom score-quality of life; ITT: intent-to-treat.

Discussion

The results of this prospective, single arm, multicenter study demonstrate that the treatment of BPH-related LUTS with the implantation of second-generation iTind device is effective with no safety concerns for extended time periods, showing a prompt (4 weeks; IPSS -46.9% and patients' quality of life (IPSS-QoL -46.4%) and sustained improvement (% change) in symptoms (IPSS -45.3%) and (IPSS-QoL -45.1%) for >48 months after the procedure. As previously published,

COPYRIGHT© 2023 EDIZIONI MINERVA MEDICA

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The creation of derivative works from the Article is not permitted. The production of reprints for personal or commercial use is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.

TABLE III.—*Outcome measures after iTind -4 weeks to >48 months (ITT - LOCF Imputation Analysis Set).*

		4 weeks	6 months	12 months	24 months	36 months	>48 months
IPSS (points)	N.	81	81	81	81	81	81
	Baseline	22.47±5.65	22.47±5.65	22.47±5.65	22.47±5.65	22.47±5.65	22.47±5.65
	Follow up	13.14±8.73	11.26±7.87	11.14±7.84	12.19±7.65	12.02±8.17	13.90 ± 8.23
	Change	-9.33±8.52	-11.21± 7.38	-11.33± 7.61	-10.28± 7.29	-10.44± 7.72	-8.57 ± 8.04
	% Change	-41.7±34.4	-50.8±30.4	-50.8±30.6	-46.1±30.2	-46.9±33.9	-37.68 ± 35.02
	(95% CI)	(-49.3%, -34.1%)	(-57.5%, -44.1%)	(-57.5%, -44.0%)	(-52.8%, -39.4%)	(-54.4%, -39.4%)	(-45.42%, -29.94%)
	P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
IPSS-QoL (points)	N.	81	81	81	81	81	81
	Baseline	4.02±0.82	4.02±0.82	4.02±0.82	4.02±0.82	4.02±0.82	4.02±0.82
	Follow up	2.32±1.46	2.07±1.40	1.94±1.43	2.23±1.43	2.22±1.45	2.47 ± 1.41
	Change	-1.70±1.54	-1.95±1.48	-2.09±1.61	-1.79±1.55	-1.80±1.50	-1.56 ± 1.53
	% Change	-41.3±35.4	-47.7±33.9	-49.8±38.8	-42.7±39.5	-43.9±39.0	-36.65 ± 37.72
	(95% CI)	(-49.1%, -33.5%)	(-55.2%, -40.2%)	(-58.3%, -41.2%)	(-51.4%, -34.0%)	(-52.5%, -35.2%)	(-44.99%, -28.31%)
	P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Q_{max} (mL/sec)	N.	80	80	80	80	80	
	Baseline	7.28±2.56	7.28±2.56	7.28±2.56	7.28±2.56	7.28±2.56	
	Follow up	10.90±5.67	12.59±6.50	13.29±8.01	14.16±9.00	13.47±8.45	
	Change	3.62±5.24	5.32±6.21	6.02±7.91	6.88±9.15	6.20±8.45	
	% Change	60.3±110.4	85.0±104.8	97.2±143.0	113.7±163.9	102.0±151.0	
	(95% CI)	(35.7%, 84.9%)	(61.7%, 108.3%)	(65.3%, 129.0%)	(77.3%, 150.2%)	(68.4%, 135.6%)	
	P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	
Post-void residual urine (mL)	N.	80	80	80	80	80	
	Baseline	77.25±55.17	77.25±55.17	77.25±55.17	77.25±55.17	77.25±55.17	
	Follow up	54.11±63.02	54.29±54.20	48.06±64.31	42.83±65.76	39.54±65.91	
	Change	-23.14±59.65	-22.96±63.38	-29.19± 68.01	-34.43±67.10	-37.71± 68.53	
	% Change	-25.3±60.5	-9.4±103.9	-30.0±91.3	-44.2±85.8	-50.3±84.3	
	(95% CI)	(-39.3%, -11.3%)	(-33.5%, 14.7%)	(-51.2%, -8.9%)	(-64.1%, -24.3%)	(-69.8%, -30.7%)	
	P value	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	

All values for baseline and change from baseline are represented as Mean±SD. Imputation of missing values was done using last observation carried forward (LOCF).
CI: confidence interval; IPSS: international prostate symptom score; PVR: post-void residual; Q_{max}: maximum flow rate; QoL: quality of life; SD: standard deviation.

iTind device has proven to be a low-impact procedure for the patient.[17] All implantations and removals that were conducted in an outpatient setting, with the patient returning home on the same day the surgery was performed, could be completed without intraoperative complications and with an excellent patient tolerability profile (median VAS pain score of 4 (0-10) and 2 (0-1), respectively). The iTind device demonstrated a low rate of postoperative complications and AEs and these complications occurred within 30 days post-surgery, most being low-grade (Clavien-Dindo <3) and self-resolving; none were long-term. The iTind device did not show any effect on erectile or ejaculatory function,[18] a factor that holds great appeal for patients with BPH-related LUTS as the impact on these functions is often a reason for discontinuation or rejection of therapy. Moreover, an acceptable total cumulative surgical retreatment rate of 9/81 (11.1%) patients at up to 79 months was reported in the entirety of the original study cohort.

Within the guidelines of the European Association of Urology (EAU), iTind device is currently cited as a non-ablative technique under investigation for the surgical treatment of BPH.[9] Given the minimally invasive nature of the procedure, it is appropriate to discuss the results obtained in this study by comparing them with those of other minimally invasive techniques mentioned in EAU guidelines with comparable longer-term follow-up, in particular with other non-ablative techniques such as PUL as well as an ablative technique under investigation, the water vapor therapy Rezūm.

When comparing long-term results between clinical studies, special attention must be paid to the percentage of patients available for follow-up in order to prevent misleading considerations. In our study, 41 (50.6%) of the originally enrolled

COPYRIGHT© 2023 EDIZIONI MINERVA MEDICA

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The creation of derivative works from the Article is not permitted. The production of reprints for personal or commercial use is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.

81 patients were available for the 50 to 79 months follow-up period. In the 5-years outcomes of the L.I.F.T. Study,[19] a prospective, multicenter, randomized, blinded control study of the PUL *versus* sham procedure. 62.5% of the originally PUL group patients were available for the 5-year follow-up and IPSS, IPSS-QoL and Q_{max} improvements of 36%, 50% and 44% respectively were reported. In the present study, iTind device showed a greater improvement in IPSS (45.3% *vs*. 36%) and comparable improvement in IPSS-QoL (45.1% *vs*. 50%) compared with PUL. Considering other ablative techniques under investigation, the long-term results of a multicenter, randomized, sham-controlled study of patients who underwent Rezūm,[20] 77/135 patients (57%) were available for the 60-month follow-up. Patients demonstrated a reduction of IPSS of 48% and an increase of IPSS-QoL of 45% from baseline, the findings corroborated that of the study for iTind device.

Postoperative AEs related to iTind device implantation were 6.2% UTI *versus* up to 12.5% PUL[21] and 21.5% Rezum,[22] 12.3% hematuria *versus* up to 41% PUL[23] and 13.8% Rezūm;[22] and 9.9% reports of postoperative pain *versus* up to 17.9% PUL[24] and 17% Rezūm.[22] No AEs were noted with iTind device treatment after the 30-day postoperative period, unlike Rezūm and PUL. The low rate of postoperative AEs and the absence of late complications can probably be attributed to the non-ablative nature of the technique and the non-permanent placement of the device. The iTind device placement causes low complications in the patients, does not lead to significant changes in the serum level of prostate specific antigen (PSA) and does not interfere with any subsequent imaging procedures that may be required like multiparametric resonance imaging of the prostate (mp-MRI).

In addition to symptom reduction and improved functional outcomes over time, the duration of effectiveness of surgical interventions for BPH is often assessed by the reintervention rate for recurrent or persistent LUTS. In this study we report a total cumulative surgical reintervention rate of 11.1% up to 79 months after iTind device implantation (13.6% PUL and 4.4% Rezūm 5-years surgical reintervention rate).[19, 20] Considering that the reintervention rate presented in this study includes patients with obstructive median lobe, which has been identified as a predictor of treatment failure in a previous report,[25] the appropriate selection of patients is a key element for the effectiveness and durability of the iTind device implant. As the current 'gold standard' surgical treatment TURP for BPH-related LUTS has shown retreatment rates of 5.8-9.7% at 5 years,[26, 27] it may seem inaccurate to define these events as true treatment failures. Reconsidering these events in terms of treatment durability, iTind device can be viewed as a potential 'bridge treatment' for BPH, a minimally invasive treatment that allows an immediate and significant improvement in symptoms and functional parameters, without affecting the patient's sexual function. This improvement, often maintained over years, can be re-gained with a standard surgical treatment or proposing another minimally invasive option in those cases in which iTind device implantation did not offer a long-term resolution of urinary symptoms. The 'non-negligible' proportion of patients (5-35%) undergoing TURP who require postoperative medical therapy for persistent or de novo LUTS[28] may be because the patients seek surgical options too late in the disease progression due to concern of surgical risks. Thus, a 'bridge treatment' offers the patient a low-risk, minimally invasive procedure that does not involve changes in sexual function and that allows the benign prostatic obstruction (BPO) to be relieved before it causes irreversible bladder dysfunction.[29]

Limitations of the study

The lack of a control arm limits the capacity to make a direct comparison between iTind device and other procedures or shams. Nevertheless, 1-year follow-up results of a multicenter, randomized, controlled study with iTind device compared to sham[30] have confirmed the findings of the present study. Only 50.6% of study population was available for the >48 months follow-up, and this may weaken the results of the study. To overcome this issue, the ITT-LOCF analysis was performed in addition, showing comparable results. Due to the outbreak of COVID-19 pandemic, at the >48 months timepoint, only patient reported information regarding IPSS, IPSS-QoL

COPYRIGHT© 2023 EDIZIONI MINERVA MEDICA

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The creation of derivative works from the Article is not permitted. The production of reprints for personal or commercial use is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.

and need for reintervention or drug therapy re-administration, were recorded leaving other functional variables such as Q_{max} and PVR unexplored. It was fortuitous that despite the adverse scenario that scientific research has experienced in the COVID-affected years, the protocol of this study could be adapted to generate valuable information about long-term symptoms' relief, QoL improvement, and need for treatment after iTind device implant.

Conclusions

The iTind® device treatment provided a significant and durable reduction of symptoms and improvement of patients' QoL for >48 months and up to 79 months postoperatively. No late postoperative complications were reported. Surgical re-treatment rate for >36 months was 4%, the total cumulative re-treatment rate up to 79 months was 11.1%, highlighting the importance assumed by patient selection. The long-term follow-up data reported in this study has provided evidence that the iTind® device implant demonstrates clinical durability and may be considered a reliable surgical modality for the relief of BPH-related LUTS, even in a setting of 'bridge treatment'.

References

1. DE Nunzio C, Giglio S, Baldassarri V, Cirombella R, Mallel G, Nacchia A, *et al.* Impairment of autophagy may represent the molecular mechanism behind the relationship between obesity and inflammation in patients with BPH and LUTS. Minerva Urol Nephrol 2021;73:631–7.

2. Lim KB. Epidemiology of clinical benign prostatic hyperplasia. Asian J Urol 2017;4:148–51.

3. Xie CY, Zhu GB, Wang XH, Liu XB. Five-year follow-up results of a randomized controlled trial comparing bipolar plasmakinetic and monopolar transurethral resection of the prostate. Yonsei Med J 2012;53:734–41.

4. Cornu JN, Ahyai S, Bachmann A, de la Rosette J, Gilling P, Gratzke C, *et al.* A Systematic Review and Meta-analysis of Functional Outcomes and Complications Following Transurethral Procedures for Lower Urinary Tract Symptoms Resulting from Benign Prostatic Obstruction: an Update. Eur Urol 2015;67:1066–96.

5. Rassweiler J, Teber D, Kuntz R, Hofmann R. Complications of transurethral resection of the prostate (TURP)—incidence, management, and prevention. Eur Urol 2006;50:969–79, discussion 980.

6. Fiori C, Checcucci E, Gilling P, Amparore D, Volpi G, De Cillis S, *et al.*; ESUT Lower Tract Group. All you need to know about "Aquablation" procedure for treatment of benign prostatic obstruction. Minerva Urol Nefrol 2020;72:152–61.

7. Manfredi C, Arcaniolo D, Spatafora P, Crocerossa F, Fusco F, Verze P, *et al.* Emerging minimally invasive transurethral treatments for benign prostatic hyperplasia: a systematic review with meta-analysis of functional outcomes and description of complications. Minerva Urol Nephrol 2022;74:389–99.

8. Fuschi A, Al Salhi Y, Velotti G, Capone L, Martoccia A, Suraci PP, *et al.* Holmium laser enucleation of prostate versus minimally invasive simple prostatectomy for large volume (≥120 mL) prostate glands: a prospective multicenter randomized study. Minerva Urol Nephrol 2021;73:638–48.

9. Gravas S, Gacci M, Gratzke C, Herrmann T, Mamoulakis C, Rieken M, *et al.* EAU guidelines on non neurogenic male LUTs including benign prostatic obstruction; 2022 [Internet]. Available from: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Non-Neurogenic-Male-LUTS-2022.pdf [cited 2023, Jun 13].

10. Checcucci E, Veccia A, De Cillis S, Piramide F, Volpi G, Amparore D, *et al.*; Uro-technology and SoMe Working Group of the Young Academic Urologists Working Party of the European Association of Urology and of the Lower Tract and Research Group of the European Section of Uro-technology. New Ultra-minimally Invasive Surgical Treatment for Benign Prostatic Hyperplasia: A Systematic Review and Analysis of Comparative Outcomes. Eur Urol Open Sci 2021;33:28–41.

11. Cindolo L, Ferrari R, Rabito S, Siena G, Spatafora P, Ferrari G. Rezum procedure with Exime® stent: a step forward to micro-invasiveness. Minerva Urol Nephrol 2021;73:273–5.

12. Pisco JM, Bilhim T, Costa NV, Torres D, Pisco J, Pinheiro LC, *et al.* Randomised Clinical Trial of Prostatic Artery Embolisation Versus a Sham Procedure for Benign Prostatic Hyperplasia. Eur Urol 2020;77:354–62.

13. Denisenko A, Somani B, Agrawal V. Recent advances in UroLift: A comprehensive overview. Turk J Urol 2022;48:11–6.

14. Porpiglia F, Fiori C, Bertolo R, Giordano A, Checcucci E, Garrou D, *et al.* 3-Year follow-up of temporary implantable nitinol device implantation for the treatment of benign prostatic obstruction. BJU Int 2018;122:106–12.

15. Amparore D, Fiori C, Valerio M, Schulman C, Giannakis I, De Cillis S, *et al.* 3-Year results following treatment with the second generation of the temporary implantable nitinol device in men with LUTS secondary to benign prostatic obstruction. Prostate Cancer Prostatic Dis 2021;24:349–57.

16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.

17. Porpiglia F, Fiori C, Amparore D, Kadner G, Manit A, Valerio M, *et al.* Second-generation of temporary implantable nitinol device for the relief of lower urinary tract symptoms due to benign prostatic hyperplasia: results of a prospective, multicentre study at 1 year of follow-up. BJU Int 2019;123:1061–9.

18. Elterman D, Alshak MN, Martinez Diaz S, Shore N, Gittleman M, Motola J, *et al.* An Evaluation of Sexual Function in the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia in Men Treated with the Temporarily Implanted Nitinol Device. J Endourol 2023;37:74–9.

19. Roehrborn CG, Barkin J, Gange SN, Shore ND, Giddens JL, Bolton DM, *et al.* Five year results of the prospective randomized controlled prostatic urethral L.I.F.T. study. Can J Urol 2017;24:8802–13.

20. McVary KT, Gittelman MC, Goldberg KA, Patel K, Shore ND, Levin RM, *et al.* Final 5-Year Outcomes of the

COPYRIGHT© 2023 EDIZIONI MINERVA MEDICA

Multicenter Randomized Sham-Controlled Trial of a Water Vapor Thermal Therapy for Treatment of Moderate to Severe Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. J Urol 2021;206:715–24.

21. Sønksen J, Barber NJ, Speakman MJ, Berges R, Wetterauer U, Greene D, *et al.* Prospective, randomized, multinational study of prostatic urethral lift versus transurethral resection of the prostate: 12-month results from the BPH6 study. Eur Urol 2015;68:643–52.

22. Dixon C, Cedano ER, Pacik D, Vit V, Varga G, Wagrell L, *et al.* Efficacy and Safety of Rezūm System Water Vapor Treatment for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. Urology 2015;86:1042–7.

23. Chin PT, Bolton DM, Jack G, Rashid P, Thavaseelan J, Yu RJ, *et al.* Prostatic urethral lift: two-year results after treatment for lower urinary tract symptoms secondary to benign prostatic hyperplasia. Urology 2012;79:5–11.

24. Roehrborn CG, Rukstalis DB, Barkin J, Gange SN, Shore ND, Giddens JL, *et al.* Three year results of the prostatic urethral L.I.F.T. study. Can J Urol 2015;22:7772–82.

25. Kadner G, Valerio M, Giannakis I, Manit A, Lumen N, Ho BS, *et al.* Second generation of temporary implantable nitinol device (iTind) in men with LUTS: 2 year results of the MT-02-study. World J Urol 2020;38:3235–44.

26. Madersbacher S, Lackner J, Brössner C, Röhlich M, Stancik I, Willinger M, *et al.*; Prostate Study Group of the Austrian Society of Urology. Reoperation, myocardial infarction and mortality after transurethral and open prostatectomy: a nation-wide, long-term analysis of 23,123 cases. Eur Urol 2005;47:499–504.

27. Gilfrich C, Leicht H, Fahlenbrach C, Jeschke E, Popken G, Stolzenburg JU, *et al.* Morbidity and mortality after surgery for lower urinary tract symptoms: a study of 95 577 cases from a nationwide German health insurance database. Prostate Cancer Prostatic Dis 2016;19:406–11.

28. Nitti VW, Kim Y, Combs AJ. Voiding dysfunction following transurethral resection of the prostate: symptoms and urodynamic findings. J Urol 1997;157:600–3.

29. Creta M, Collà Ruvolo C, Longo N, Mangiapia F, Arcaniolo D, DE Sio M, *et al.* Detrusor overactivity and underactivity: implication for lower urinary tract symptoms related to benign prostate hyperplasia diagnosis and treatment. Minerva Urol Nephrol 2021;73:59–71.

30. Chughtai B, Elterman D, Shore N, Gittleman M, Motola J, Pike S, *et al.* The iTind Temporarily Implanted Nitinol Device for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Multicenter, Randomized, Controlled Trial. Urology 2021;153:270–6.

Conflicts of interest
Francesco Porpiglia has served as a consultant for Meditate.

Funding
This company sponsored trial was funded by Medi-Tate Ltd. (now acquired by Olympus Corporations). Medi-Tate Ltd. in its position as sponsor created the trial design/protocol with significant contribution of the lead author, led data management and funded the data analysis that was performed by an external statistician as directed by the lead author. The sponsor performed a technical review of the manuscript without any influence on the interpretation of the research data.

Authors' contributions
Daniele Amparore and Sabrina De Cillis contributed equally to first authorship. Daniele Amparore read and approved the final version of the manuscript; Sabrina De Cillis read and approved the final version of the manuscript; Claude Schulman read and approved the final version of the manuscript; Gragor Kadner read and approved the final version of the manuscript; Cristian Fiori read and approved the final version of the manuscript. Francesco Porpiglia read and approved the final version of the manuscript.

Congresses
This paper was presented at the AUA 2022 in New Orleans in the format of an oral presentation (abstract LBA01-06) on the 15th of May.

Acknowledgements
Investigators who enrolled study participants and participated in the acquisition of data: Prof. Nicolaas Luman (Belgium, Ghent University Hospital), Dr. Arya Manit (England, College of London Hospital), Dr. Neil Barber (England, Firmly Health Hospital), Dr. Valerio Massimo (Switzerland, Lausanne University Hospital (CHUV)), Dr. Brian Ho (Hong Kong, The university of Hong Kong) and Dr. Sergio Alonso (Spain, La Paz University Hospital); study coordinators for investigational center oversight: Anne Bouvier (Belgium, Edith Cavell Clinic) and Mike Ng (England, Firmly Health Hospital); data analysis: TechnoSTAT Clinical Services' statistical analysis work with Ms. Stav Edelstein as lead programmer.

History
Article first published online: June 23, 2023. - Manuscript accepted: June 12, 2023. - Manuscript revised: May 10, 2023. - Manuscript received: February 20, 2023.

This document is protected by international copyright laws. No additional reproduction is authorized. It is permitted for personal use to download and save only one file and print only one copy of this Article. It is not permitted to make additional copies (either sporadically or systematically, either printed or electronic) of the Article for any purpose. It is not permitted to distribute the electronic copy of the article through online internet and/or intranet file sharing systems, electronic mailing or any other means which may allow access to the Article. The use of all or any part of the Article for any Commercial Use is not permitted. The creation of derivative works from the Article is not permitted. The production of reprints for personal or commercial use is not permitted. It is not permitted to remove, cover, overlay, obscure, block, or change any copyright notices or terms of use which the Publisher may post on the Article. It is not permitted to frame or use framing techniques to enclose any trademark, logo, or other proprietary information of the Publisher.