ORIGINAL ARTICLE

Effect of stunning of diagnostic 131-iodine doses on ablative doses for differentiated thyroid cancer patient's outcome

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Received: September 22, 2013 **Accepted:** September 29, 2013 **Online Published:** October 18, 2013
DOI: 10.5430/jst.v3n6p11 **URL:** http://dx.doi.org/10.5430/jst.v3n6p11

Abstract

Background: Thyroid stunning was defined as transient reduction of thyroid tissue uptake 131I (RAI-131) ablative dose after a diagnostic 131I dose that decreases the final absorbed dose in ablative therapy.

Aim of the study: after following the proper precautions compare the response to the ablative dose given to patients with differentiated thyroid cancer with or without diagnostic radioactive iodine 131(RAI-131).

Patients and methods: One hundred patients with differentiated thyroid cancer were included and divided into two groups: Group I, ablative dose of RAI-131according to their risk stratification without diagnostic dose and Group II, patients performing diagnostic whole body scan [5mCi] followed by ablative dose.

Results: The current study have showed no significant associations between overall response in both groups and the different studied parameters except for the mean ablative dose of RAI-131 [r=0.9; P<0.001 and r=0.7, P<0.001 in group I and group II respectively]. Correlation matrix was used in all patients revealed that overall response was highly correlated with risk stratification; cervical nodal status and RAI-131 ablative dose [P values <0.01; <0.01 and <0.01 respectively], while regression proved that the only predictor for response is the mean RAI-131 ablative dose.

Conclusion: Following the proper precautions prevent stunning appearance after the diagnostic dose success rate to ablation will not be affected.

Key words

Differentiated thyroid carcinoma, Ablative dose, Thyroid stunning

1 Introduction

Differentiated thyroid carcinoma (DTC) represents 1% of all malignancies, with long-term survival (a 10-year survival of more than 90%) [1], following the available guidelines and experience of experts [2, 6].

Diagnostic RAI-131 scanning post thyroidectomy is mandatory to estimate the amount of residual tissue remaining, the tumor avidity of residual tissue, and the appropriate 131I dosimetry [7, 8]. In some patients, imaging of thyroid tissue residue using of RAI-131 diagnostic scan may induce within few hours up to days the so-called stunning phenomenon [8].

The latter is considered a radiobiological suppressive phenomenon defined as a temporary suppression of iodine trapping function of the thyrocytes and thyroid cancer cells as a result of the radiation given off by the scanning or first dose of RAI-131[5]. Concern for stunning has led some physicians to prescribe treatments of RAI-131 without prior diagnostic imaging in hopes of increasing the therapeutic effect [6, 7]. There was a marked difference in the ability to detect iodine-avid tissue when a post-therapy scan is read at 7-10 days, rather than at 2-3 days [8].

The current study aims to compare the response to the post operative ablation of patients with differentiated thyroid cancer using radioactive iodine 131(RAI-131) between two groups of patients: g*roup I* given ablative dose of RAI-131according to their risk stratification; and *Group II* performing diagnostic whole body scan (Dx-WBS) [5mCi] followed by ablative dose (following the required precautions to avoid stunning).

2 Patients and Methods

2.1 Patients

Inclusion criteria: The current study included 100 patients who had undergone surgery [near total thyroidectomy with cervical lymph nodes selective dissection) for well differentiated thyroid carcinoma and were referred to Nuclear Medicine unit Al-Hada Forced arm hospital, Taif Saudia Arabia for 131I ablation. None of them had received any prior radioiodine therapy.

Exclusion criteria: We excluded patients who had distant functioning organ metastases [as bone or lungs] on diagnostic or post therapy whole body scans.

The institutional review board approved our study and was made aware of the additional radiation dose. All patients consented to be subjected to the current study with full explanation of the protocol and they were informed of the radiation dose and its risks. They also consented to the use of their data for future retrospective research.

2.2 Methods

2.2.1 Clinical protocol

On presentation all patients were subjected to the following procedures: clinical history, serum thyroglobulin (Tg) and Neck ultrasonography (U.S.).

Patients in group I (50 patients) were given an ablative dose of RAI-131 directly followed by post therapy whole body scan using axis dual head Siemens gamma camera fitted with high-energy collimators for simultaneous anterior and posterior whole body images at speed 8 cm/sec. The energy window was set at 20% centered on 364 keV with a 256×1024 size matrix. Spot views of the head and neck using the same collimator and the same energy window as for the whole-body images were also obtained in a 128×128 matrix size with a total count of 300 K count and images were interpreted qualitatively by visual assessment of the size and tracer uptake intensity of the residual uptake.

Patients in group II (50 patients) were initially evaluated by the same manner as the group I but with initial diagnostic whole body scan (Dx-WBS), performed at variable periods after thyroidectomy, followed by the ablative dose. Diagnostic whole body scans were done after withdrawal of levothyroxine medication 3-4 weeks with TSH≥ 30 IU/mi before administration of 5 mCi of RAI-131. Seventy-two hours after oral intake of RAI-131, Dx-WBS was performed using dual-head Siemens gamma camera fitted with high energy collimators for simultaneous anterior and posterior whole-body images at speed 8 cm/sec. The energy window was set at 20% centered on 364 keV with a 256×1024 size matrix. Spot views of the head and neck using the same collimator and the same energy window were also obtained in a 128×128 matrix size with a 20% energy window for 15 min. The therapeutic dose was administered on the same day as or a few days after the scanning dose was read; the time elapsed between administration of the scanning dose and the therapeutic dose was

ISSN 1925-4067 E-ISSN 1925-4075

typically 2-5 days [8, 9]. Ablative doses given to patients ranged between 3700-7400 MBq (30-150mCi). All patients were instructed to follow a low iodine diet beginning 10-14 d before the initial scan, treatment, and follow-up scan.

All posttherapy scans were read at two intervals: 2 and 7-10 days after treatment. None of the patients treated had completely negative post-therapy scans. Images were interpreted by two observers blindly.

2.2.2 Follow up and evaluation of ablation efficacy

Follow up was done using neck ultrasound, serum TG level as well as Dx-WBS for all patients. Dx-WBS was done 6 months after initial therapy, all patients were prepared in the same way for the administration of radioiodine by withdrawal of levothyroxine medication 3- 4 weeks before administration of 3-5mCi of RAI-131.

Image interpretation was made qualitatively and our criteria for successful remnant ablation defined as: Absence of any significant RAI-131 uptake at the thyroid bed; Tg < 2 mg and negative neck sonography. Accordingly two categories were identified either complete or no response to ablation.

Risk of recurrence: Recurrence may be either local (in thyroid bed or cervical lymph node) or distant. Accordingly, risk stratification can be either low, intermediate or high risk according to the American Thyroid Association (ATA) as shown in table 1 [10, 11]. High risk patients were excluded from this study.

Table 1. Risk of recurrence stratification (low, intermediate or high risk) [10]

High-risk	**Intermediate-risk**	**Low-risk**
Any of the following is present	Any of the following is present	All the following are present
i. Macroscopic tumor invasion. i. Gross residual tumor (incomplete tumor resection). i. Distant metastases. v. Tg is out of proportion to what is seen on the post treatment scan.	i. Microscopic invasion into the peri-thyroidal soft tissues. i. Cervical LN metastases or 131I uptake outside the thyroid bed on the post-treatment scan done after thyroid remnant ablation. i. Tumor with aggressive histology or vascular invasion (e.g. tall cell, insular, columnar cell carcinoma, HCC, FTC).	i. No local or distant metastases. i. All macroscopic tumors have been resected. i. No invasion of loco-regional tissues. v. Tumor does not have aggressive histology (e.g. tall cell, insular, columnar cell carcinoma, HCC, FTC). v. No vascular invasion i. No 131I uptake outside the thyroid bed on the first post-treatment RAI WBS.

Note. High risk patients were excluded from this study.

2.3 Statistical method

Data were either parametric or non-parametric. Parametric data was statistically described in terms of mean +standard deviation (SD), and range. Non-parametric data was described as frequencies (number of cases) and percentages when appropriate. Comparison of parametric variables between the studied groups was done using unpaired Student t test. For nonparametric data, comparison was done using Chi square (χ^2) test. Multivariate analyses were done using two steps first correlation matrix followed by regression analysis. Test was considered significant when P values became less than 0.05.

All statistical calculations were done using computer programs SAS/STAT software (Statistical Analysis System, SAS Institute Inc.) Microsoft Windows.

3 Results

The current study included 100 patients, 77 females (77%) and 23 males (23%) referred for 131I ablation post near total thyroidectomy. Their age ranged from 22-54 years; mean of 40.88±12.3. The commonest histopathology was papillary thyroid carcinoma, encountered in 73 patients (73%) while 27 patients (27%) have follicular thyroid carcinoma. Risk assessment of the patients showed 87 (87%) patients were intermediate risk and 13 patients (13%) with low risk. High risk patients were excluded from this study. The analysis of histopathological data showed presence of capsular invasion in 25 (25%) patients and vascular invasion in 8 (8%) patients. Metastatic lymph node involvement was found only in 13 patients (13%). There was no significant difference between the studied groups concerning the patient characteristics Table 2.

Table 2. Patient characteristics of the studied patients

	Group I [no. 50]	***P***	**Group II [no. 50]**	**Total**
Age				
< 45 years	35 [70%]	>0.05	30 [60%]	65 [65%]
≥ 45 years	15 [30%]	>0.05	20 [40%]	35 [35%]
Mean±SD [years] and Range	39.4±13.1 23-49	>0.05	43.8±11.3 22-54	40.88±12.3 22-54
Gender				
Males	15 [30%]	>0.05	8 [16%]	23 [23%]
Females	35 [70%]		42 [84%]	77 [77%]
Operation Type Near Total Thyroidectomy	50 [100%]	>0.05	50 [100%]	100 [100%]
Pathological Type				
Papillary	38 [75%]	>0.05	35 [70%]	73 [73%]
Follicular	12 [25%]		15 [30%]	27 [27%]
Histopathological				
Capsular Invasion	15 [30%]	>0.05	10 [20%]	25 [25%]
Vascular Invasion	3 [6%]	>0.05	5 [10%]	8 [8%]
Lymph node deposits	5 [10%]	>0.05	8 [16%]	13 [13%]
Maximum Tumor size				
< 1 cm	5 [10%]	>0.05	10 [20%]	15 [15%]
≥ 1 cm	45 [90%]	>0.05	40 [80%]	85 [85%]
Risk Stratification				
Low	5 [10%]	>0.05	8 [16%]	13 [13%]
Intermediate	45 [90%]	>0.05	42 [84%]	87 [87%]
Post-operative Radioactive I-131 Diagnostic Scan [3-5 mCi]	None	0.0001	All Cases 100%	50 [50%]
Ablative Dose [mCi]				
Mean±SD	107.25±27.4	>0.05	116.9±28.5	112.1±28
Range	30-150		30-150	30-150

 ISSN 1925-4067 E-ISSN 1925-4075

On follow up; there was no significant statistical difference between both groups concerning response. The study disclosed 38(76%) and 35 (70%) in group I and II respectively had negative results in the Dx WBS and neck sonography; Table 3. Comparison of response in both groups in relation to ablative dose revealed no significant statistical difference for each dose subgroup Figure 1.

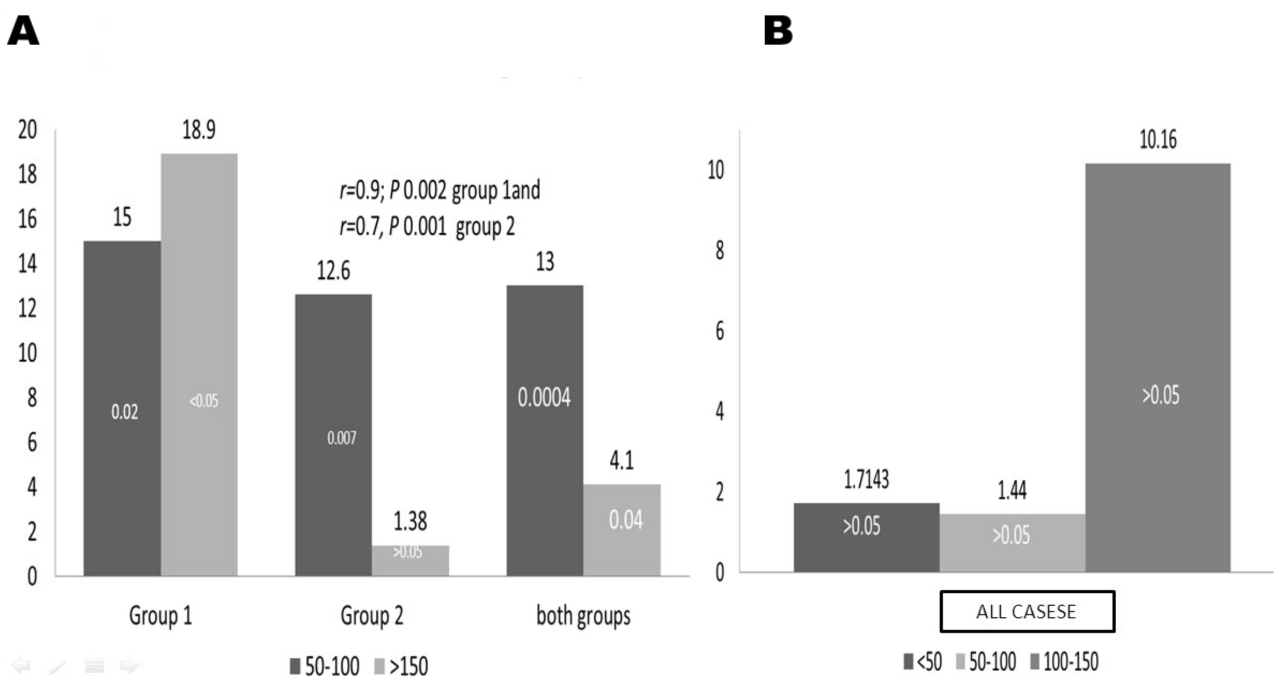

Figure 1. Impact of ablative dose rate on the response of thyroid cancer remnant in both groups

A. Logistic regression using odd ratio of ablation doses in both groups. B. Odd Ratio of Ablation doses each in both groups.

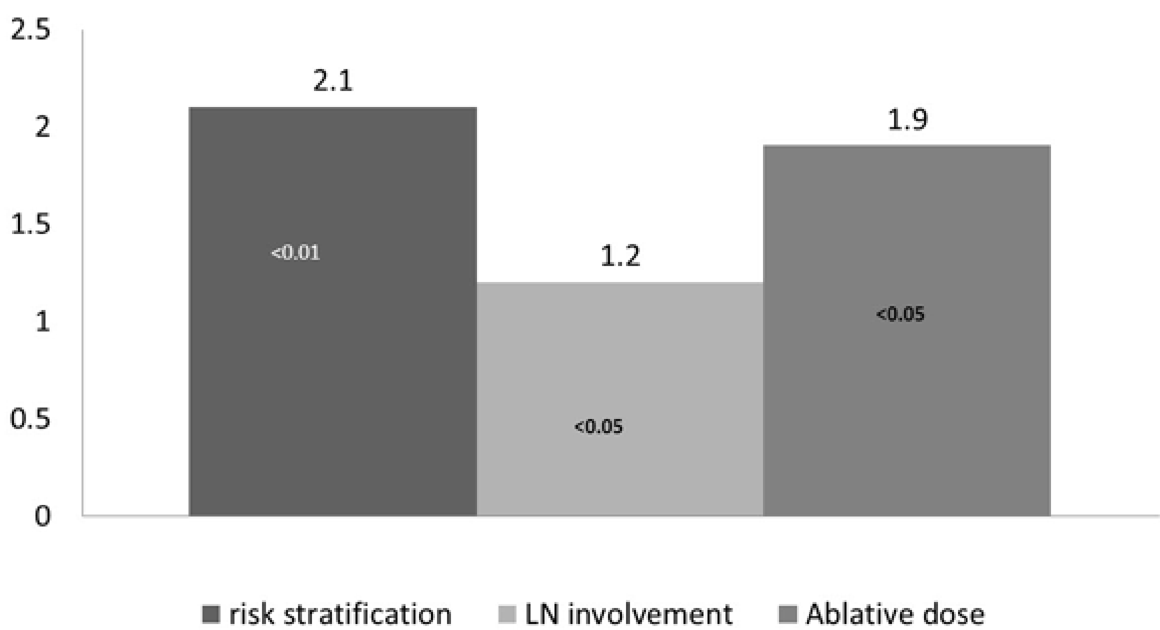

Figure 2. Factors affecting response to radioiodine131 in Cancer thyroid

Table 3. Response assessment in the studied groups

Follow-up Tool	Group I [no. 50]	P	Group II [no. 50]	Total
Radioactive I-131 Diagnostic Scan [3-5 mCi]				
Negative	45 [90%]	>0.05	42 [84%]	>0.05
Positive for residue or metastasis	5 [10%]	>0.05	8 [16%]	>0.05
Neck Sonography				
Negative	38 [76%]	>0.05	35 [70%]	>0.05
Positive for residue or cervical lymph nodes	12 [24%]	>0.05	15 [30%]	>0.05
Thyroglobulin				
Negative < 2	40 [80%]	>0.05	40 [80%]	>0.05
Positive ≥ 2	10 [20%]	>0.05	10 [20%]	>0.05

No significant associations were elicited between overall response in both groups and the different studied parameters except for the mean dose of radioactive 131I [*r*=0.9; *P* <0.001 and *r*=0.7, *P* < 0.001 in group I and group II respectively and table 4]. Table 4 revealed the highly significant dependence of response on the dose in each group separate where doses below 50mCi showed statistically the lowest response. Fig.1a but no difference in the same dose subgroup Fig1b, where odd ratio was found insignificant in the three subgroups, <50, 50-100 and >100-150 between group I and II.

Table 4. Impact of dose of ablation and presence or absence of diagnostic dose on the response

	Group I				Group II				Both groups				Total	
	Responders		Non-responders		Responders		Non-responders		Responders		Non-responders			
Ablation dose	No.	% of total	No.	% of total	No.	% of total	No.	%of total	No.	%of total	No.	%of total	No.	%of total
≤50	1	2	6	12	2	4	7	14	3	2	13	12	14	14
≥50-100	15	30	6	12	18	36	5	10	33	49	11	10	59	59
≥100-150	22	44	0	0	15	30	3	6	37	32	3	6	37	37
total	38	76	12	24	35	70	15	30	73	73	27	27	100	100
	χ^2=18.1, *P* <0.0001				χ^2=12.1, *P* <0.001				χ^2=62.8, *P* <0.0001					

Correlation showed: r=0.9; *P* <0.001 and *r*=0.7, *P* <0.001 in Group I and Group II respectively

Accordingly, correlation matrix analysis was used in all patients to find that the significant predictor for overall response were risk stratification; cervical nodal status and the mean ablative dose (Figure 2). However, multiple regression analysis revealed that the only predictor for response was the mean ablative dose.

4 Discussion

The current study revealed no significant associations between overall response in both groups and the different studied parameters except for the mean dose of RAI-131 [*r*=0.9; *P* <0.001 and *r*=0.7, *P* <0.001 in group I and II respectively]. It has been found that ablation depends on risk stratification; cervical nodal status and the mean RAI-131 ablative dose, while regression proved that the only predictor for response is the mean RAI-131 ablative dose.

Rawson et al in 1951 [12], were the first to describe thyroid stunning as a temporal reduction in the cell's ability to concentrate iodine after exposure to relatively low radioactive iodine-131 for diagnostic images (2-10mCi), but did not kill the cell. Its significance was attributed to suppression the efficacy of radioactive 131I ablative dose [13].

It had been reported that administration of 2-5mCi of diagnostic radioactive iodine 131 (RI131) deliver absorbed doses of 4-38 and 10-58Gy to thyroid remnants [14, 15]. Medvedec 200516 added that absorbed doses >4Gy might result in thyroid stunning. However, Lundh et al [17, 18] showed that absorbed doses of >0.15Gy produced a statistically significant reduction (20%) in iodide transport 3 days after the end of irradiation. They added that 131I irradiation likely inhibited iodide transport independently of its action on cell cycle control mechanisms. This notion is further emphasized by the fact that thyroid stunning can readily be induced by 131I in growth-arrested G0 cells [17, 18].

In addition to the above, previous studies revealed an early increase in iodide transport/uptake after irradiation [19, 20]. Meller et al. reported increased iodide uptake in 2 thyroid cell lines at various stages of differentiation up to 72 h after external irradiation [19]. Similarly Postgard et al [20]; reported an increase in iodide transport at times of less than 48 h after 131I irradiation of primary cultured pig thyrocytes, and if they were delayed in iodine administration, stunning was observed. These findings indicate that the time elapsed between diagnostic administration and therapeutic administration of 131I is crucial when the stunning phenomenon is being studied.

However, in 1994, Park [5] and his associates showed that amounts of 131I larger than 2mCi have a sufficiently harmful effect on thyroid tissues to interfere with subsequent uptake of therapeutic amounts of 131I on the post ablation whole body scan for detection of any thyroid remnants or tumor foci. This had been noted at 3mCi dose, and becoming progressively greater with larger doses. This was attributed by shorter interval between administration of the ablation dose and postablation scanning, which leads to higher soft-tissue background, as a 24-48 hour interval between ablation administration and postablation scanning. That is why it had been recommended to make the interval between the administration of the ablative dose and time of post ablative scanning 72 hours as in Cholewinski et al [21] study.

Meanwhile; some authors argued that diagnostic scanning does not compromise I-131 therapy because the decreased uptake that has been attributed to temporary stunning is actually due to radiation damage that will ultimately result in cell death. If this "kill rather than stun" theory is true then thyroid stunning is likely to enhance I-131 cancer therapy because a Dx-WBS study would in fact be the first step in ablating cells that concentrate RAI-131 [13].

Since the current study shortened the time elapsed between the diagnostic and therapeutic doses as much as possible, no statistical difference between both groups was noted in response. The overall response was almost identical [76% vs.70%; $P > 0.05$] indicating the possibility of avoiding stunning. Similar findings had been reported by Morris et al, 2011 and 2003 [8, 9].

Fatourechi et al [22], compared diagnostic 1-3mCi (37-111MBq) of RAI 131 and post-therapy scans in a study designed to assess stunning. The authors did not specify when therapy was administered, but post-treatment scans were obtained after 3-5 days. They found reduced uptake in only 4% (5 of 117) of post- treatment scans to be hardly attributed to a stunning effect.

On the contrary, Bajen et al [23] actually showed higher ablation success rates (61.6% *vs.* 36.9%) in patients with stunning than in patients with no stunning. Therefore, the authors concluded that a therapeutic effect, rather than stunning, occurred with a diagnostic dose of 185MBq (5mCi) i. e. adjuvant therapy. However, the time from diagnostic scanning to ablation was long in that study, namely an average of 7.9 weeks (range, 1-16 weeks), which raises the question as to whether stunning actually occurred or was there simply a decrease in tissue remnant. This was supported by Dam et al [24] divided, in a retrospective study, their patients into no stunning and stunning groups and they found insignificant higher ablation success rates in stunning group. However, they concluded that stunning does not affect patient outcome.

Karam et al retrospectively reported that success of RAI-131 ablation in 389 patients was mainly due to the size of the therapeutic dose [25]. Zaman et al [26] confirmed that a single administration of about 30mCi failed to fully ablate the remnant (46%) compared to 77-100mCi (27%, P<0.001) 26 which is very similar to the current study. The current study in spite of being prospective still used ablative doses <50mCi (in some patients) depending on those studies reporting complete ablation in thyroid bed in 80% of patients treated with 30-50mCi of 131I, providing the surgeon had left small remnant of functioning tissue seen on a diagnostic WBIS using 2-3mCi 131I [27, 28].

Accordingly the current study agrees with the above findings regarding that the most influential and predicting factor in the final outcome [Response] is Radioactive Iodine-131 Ablative Dose. However, the current study showed in group II insignificant difference between odd ratio of patients treated with ablative dose between >50-100 and those treated above >100-150mCi, which could be explained by the fact that the amounts of 131I that deliver more than 300Gy do not result in a higher ablation rate. Lower success rates were found when large pretreatment scanning doses were used, regardless of the therapeutic dose of 131I and are attributed to thyroid stunning [26 , 29].

In the current study, the ablative dose masked the impact of all other factors such as risk stratification and presence of cervical lymph nodes and even the histopathology that had been commented upon by Zaman et al [26]. This could be attributed by the fact that in our institute, the ablative dose was determined according to the other factors.

5 Conclusion

Thyroid stunning post-diagnostic iodine-131 dose could be avoided by taking the essential precautions when administering the ablative dose by giving it as soon as possible after reading the diagnostic image, and prolonging the interval between the ablative dose administration and time of imaging post therapy. If present, stunning will not affect the success of ablation dose. The most deterministic predictor for higher success ablation was the ablation dose.

Declaration of interest

The authors declare that they have no competing interest.

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