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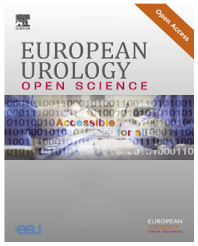

European Association of Urology

Pelvic Pain

Development of a Novel Clinical Classification for Radiation-induced Cystitis: The Portuguese Navy Radiation-induced Cystitis (PNRC) Scale

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Article info

Article history:
Accepted December 11, 2024

Associate Editor:
Roderick van den Bergh

Keywords:
Classification
Cystitis
Haematuria
Radiation injuries
Systematic review

Abstract

Background and objective: Radiation-induced cystitis (RIC) is an important consequence of pelvic radiotherapy that can cause high morbidity and, in extreme cases, mortality. The lack of a widely accepted classification system makes it difficult to compare treatment regimens. Our aim was to develop a new classification system covering the RIC spectrum to improve treatment comparisons and accurate incidence estimates for systematic use in clinical and research settings.
Methods: A three-phase project was planned. Phase 1 involved a literature review and development of the Portuguese Navy Radiation-induced Cystitis (PNRC) scale. In phase 2 the scale was applied to 20 clinical cases. Phase 3 involved assessment of the applicability, relevance, inter-rater reliability, and usability of the scale using numerical and graphical methods to achieve consensus among international experts.
Key findings and limitations: In phase 1, the panel analysed 13 existing classification systems and developed the PNRC scale, a comprehensive system encompassing five clinical domains: haematuria, other lower urinary tract symptoms, functional impairment, endoscopic findings, and therapeutic interventions. In phase 2, 114 experts from 30 countries completed the first validation round. Consensus was reached for 85% of cases. In phase 3, consensus was reached among 61 experts on the relevance and appropriateness of each domain, and on the exhaustiveness, hierarchy, clarity, mutual exclusivity, and clinical utility of the PNRC scale. Study limitations are the inclusion of only Medline-indexed manuscripts in the review and minor dispersion of responses, indicating subjectivity in the analysis of clinical case scenarios.

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https://doi.org/10.1016/j.euros.2024.12.006
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Conclusions and clinical implications: The PNRC scale showed reliability and face and construct validity in the stratification of RIC severity for clinical cases.
Patient summary: Radiation-induced cystitis is a debilitating complication of pelvic radiotherapy. A uniform classification system is needed to assess the incidence of this disease and to compare the results for different treatment options. We developed the Portuguese Navy Radiation-induced Cystitis (PNRC) scale, which was validated by an independent group of experts from 30 different countries.
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1. Introduction

Radiotherapy (RT) is frequently used to treat pelvic malignancies, either as a standalone technique or combined with other treatment options [1–4]. Although technological advances have increased the effectiveness of RT and reduced its toxicity, collateral soft-tissue injuries are still relatively frequent [5–7]. Owing to its considerable morbidity and a non-negligible mortality rate, radiation-induced cystitis (RIC) is one of the most important late adverse effects of pelvic RT [6,7]. Ionising radiation limits cellular growth and is associated with progressive obliterating endarteritis and hypocelullar, hypovascular, and hypoxic transformation of the vesical mucosa, with oedema, ulceration, a decrease in regeneration, and fibrosis, which are responsible for the symptoms that characterise RIC [6,8–10]. While RIC may develop in the acute setting, the onset of symptoms is usually several years after pelvic RT, and patients may present with symptoms as long as 14 yr after RT [10]. The development of RIC is highly dependent on the dose, modality, and template used for pelvic RT [10]. As many patients develop mild lower urinary tract symptoms such as dysuria and an increase in urinary frequency, RIC is often underdiagnosed [10]. The estimated global incidence of RIC varies greatly, from 3% to 80%; some 5–8% of patients present with severe disease, mainly involving severe and refractory haematuria, which may lead to urinary retention, anaemia requiring transfusions, and occasionally death [10].

Although conservative approaches are used as first-line treatment options for RIC, the low long-term effectiveness mean that many patients ultimately require more aggressive procedures to control their condition [10–12]. Although high-quality prospective randomised controlled trials are still lacking, several retrospective and some prospective studies have demonstrated the effectiveness of hyperbaric oxygen therapy for RIC treatment, making it one of the most important therapeutic options before the use of more invasive techniques [13–15].

There is currently no uniform classification or grading system for RIC that is widely used in the clinical setting. Given the wide array of clinical presentations of RIC, from mild functional symptoms to severe and life-threatening haematuria, the absence of a consensus classification makes it impossible to assess the correct incidence of this condition. Moreover, the absence of a validated grading system hampers adequate comparison of results for the different treatment options.

Our aim was to develop and validate a new RIC classification system that covers all domains of the disease and can be used in a systematic and standardised manner in both clinical and research settings.

2. Materials and methods

A three-phase project was planned: phase 1, to develop the new classification system; phase 2, to evaluate the reliability and construct validity; and phase 3, to evaluate face validity.

2.1. Phase 1: literature review and development of the new classification system

To identify RIC classification or grading systems, a member of the working group conducted a literature review by searching the PubMed database for the following keywords: radiation; cystitis; classification; score; scoring; scale; grading; categories. Additional records were identified using other sources. The main inclusion criterion was use of a specific classification or grading system to categorise the symptoms or consequences of RIC. Record evaluation and article selection were performed according to the Preferred Reporting Items for the Systematic Reviews and Meta-Analyses (PRISMA) statement. After elimination of duplicates, the remaining reports were analysed according to the inclusion criterion, and the relevant articles were selected for review (Fig. 1) [16–28].

The panel qualitatively analysed the 13 grading systems identified via the literature review in terms of their clinical applicability and their intrinsic limitations for clinical and research settings to identify the domains to include in the new grading system (Supplementary Table 1). The data collected were subsequently used by the panel in a multistage approach to develop a new and comprehensive grading system that covers all RIC domains and can be used in both clinical and research settings, called the Portuguese Navy Radiation-induced Cystitis (PNRC) scale.

2.2. Phases 2 and 3: validation process

Validation was performed by a group of international experts in two subsequent rounds. In phase 2, the PNRC scale was applied to a series of 20 representative clinical scenarios for patients with RIC to measure construct validity. The cases were pooled from a large database of patients with RIC previously treated at our reference centre to

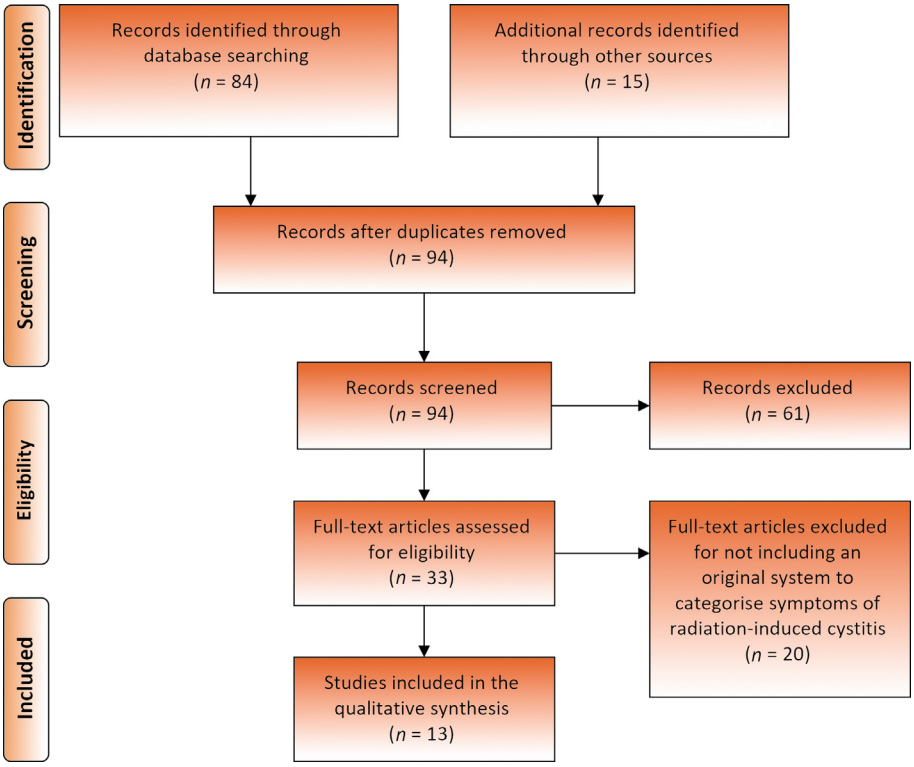

Fig. 1 – Flow diagram of evidence acquisition for the systematic review of classification and grading systems for radiation-induced cystitis.

ensure anonymisation (Supplementary Table 2), in accordance with the principles of the Declaration of Helsinki and with the approval of the institutional ethics committee. Consensus was defined as >70% agreement on the PNRC score for each scenario.

In phase 3, experts evaluated the global applicability of the PNRC scale in terms of its exhaustiveness, hierarchy, clarity, mutual exclusivity, clinical utility, and quality assessment, as well as each individual domain for relevance and appropriateness, using a 5-point Likert scale ranging from 1 (low) to 5 (high). Consensus was defined as >70% agreement on the sum for scores 4 and 5 on the 5-point Likert score.

2.3. Statistical analysis

In the validation stage, the inter-rater reliability (IRR) and ease of use of the PNRC scale were assessed using graphical (Cleveland dot plots) and numerical (Fleiss κ) statistical methods [29]. The distribution of responses for the applicability, relevance, and appropriateness of the PNRC scale was analysed using simple descriptive statistics and graphical methods.

3. Results

3.1. Phase 1: development of the PNRC scale

The PNRC scale encompassing five clinical domains (haematuria, other lower urinary tract symptoms, functional impairment, endoscopic findings, and therapeutic interventions) was developed by the panel. Each domain was divided into six progressive levels of severity (1 = least severe, 6 = most severe). The highest degree of severity for any of the five domains corresponds to the patient's PNRC score. The PNRC scale was analysed by an independent group of experts who assessed the relevance and clarity in a modified Delphi consensus process, with consensus defined as >70% agreement. After incorporation of suggestions, the final version of the PNRC scale was established (Table 1).

3.2. Characteristics of the respondents

A total of 114 experts from 30 different countries on five continents completed the first validation round in an independent and anonymous manner (Supplementary Table 3). Of these, 49.1% worked in an academic/university hospital, 35.1% in a nonacademic major urban public hospital, 5.3% in a nonacademic rural public hospital, and 10.5% in a private hospital. Most respondents were urologists (86.9%), while 4.4% were gynaecologists, 5.3% were radiation oncologists, and 3.5% were medical oncologists. In terms of age, 46.5% were <40 yr, 48.2% were 40–69 yr, and 5.2% were >70 yr of age.

The majority of the respondents had frequent contact with patients with RIC in either an outpatient clinic (58.7% at least every month), infirmary (51.7% at least every month) or emergency department (50% at least every month). Some 86% of the respondents considered RIC to be a relevant or extremely relevant clinical problem. Moreover, 65.8% estimated that RIC occurs in more than 10% of patients undergoing pelvic RT (Supplementary Table 3).

Table 1 – Portuguese Navy Radiation-induced Cystitis scale

Grade	Domains				
	Haematuria	Other lower urinary tract symptoms	Functional compromise	Endoscopic findings	Therapeutic interventions
1	Microscopic haematuria	Asymptomatic	Without functional compromise or impairment of daily activities	Epithelial atrophy	No need for therapeutic interventions
2	Intermittent macroscopic haematuria	Mild increase in urinary frequency, urgency, dysuria, or nocturia, or de novo incontinence	Functional compromise but without impairment of daily activities	Mild telangiectasias	Need for oral or intravesical treatment
3	Persistent macroscopic haematuria	Moderate increase in urinary frequency, urgency, dysuria, nocturia, or incontinence	Functional compromise and mild impairment of daily activities	Generalised telangiectasias	Need for bladder catheterisation and rinsing
4	Macroscopic haematuria requiring transfusions	Severe increase in urinary frequency or urgency, frequent incontinence, decreased bladder capacity (<150 ml)	Moderate impairment of daily activities	Severe generalised telangiectasias (with petechiae)	Need for transfusions, hospitalisation, or elective invasive procedures
5	Refractory macroscopic haematuria	Refractory incontinence, severely decreased bladder capacity (<100 ml)	Severe impairment of daily activities	Any degree of mucosal necrosis	Need for urgent invasive procedures
6	Death				

3.3. *Phase 2: assessment of reliability and construct validity*

In the first round of validation, which was completed by 114 respondents, >70% consensus was reached for 85% (17/20) of the clinical scenarios considered (construct validity). For the remaining three clinical scenarios, >62% agreement was observed. The Cleveland dot plot in Fig. 2 shows the degree of clustering of the classifications for each of the 20 scenarios. The IRR measure was $\kappa = 0.6$, indicating moderate to substantial agreement among respondents, which is consistent with the relative uniformity of the responses in the Cleveland dot plot. The mode frequency ranged between 62.3% and 98.2%, indicating a high agreement rate (Supplementary Table 4).

3.4. *Phase 3: assessment of relevance, appropriateness, and applicability*

A total of 61 experts (53.5%) completed the second round of validation. The low response rate for the second round might be attributable to the large number of clinical scenarios in the first round, resulting in response fatigue.

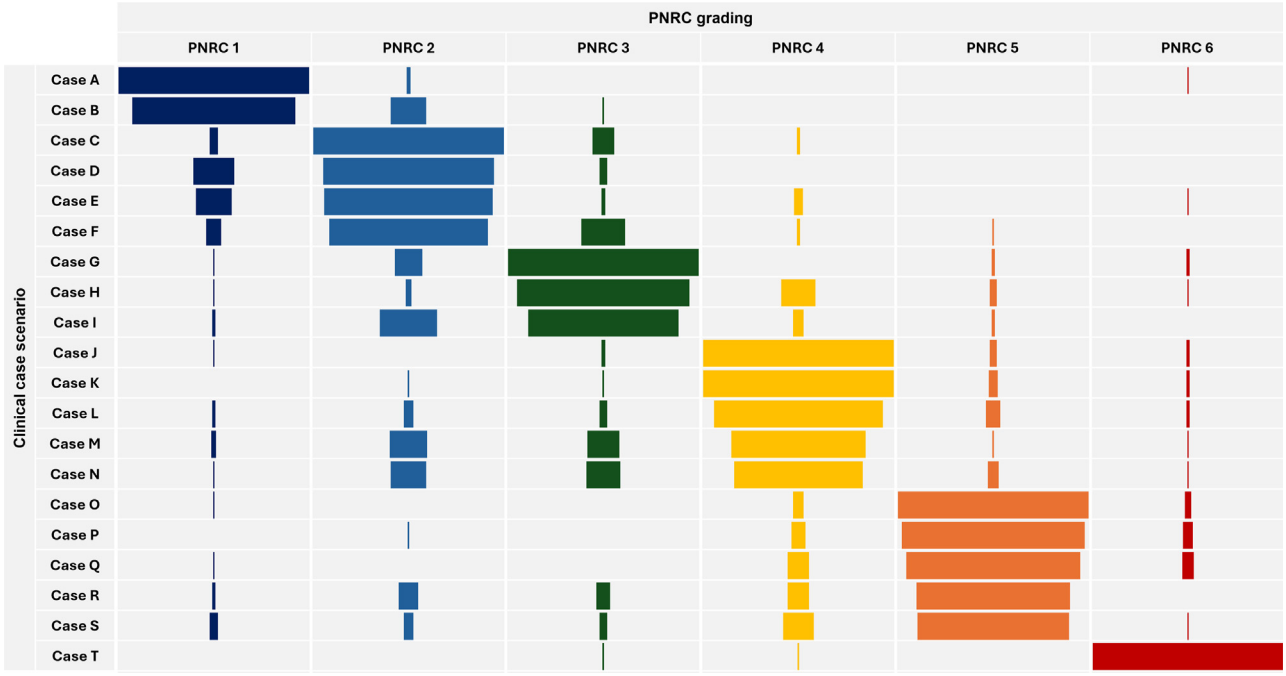

Fig. 2 – Cleveland dot plot of the first validation round on use of the Portuguese Navy Radiation-induced Cystitis (PNRC) scale for classification of 20 representative clinical scenarios for patients with radiation-induced cystitis.

Consensus of >70% was reached for the relevance (either extremely relevant or relevant) and appropriateness (either very appropriate or appropriate) of each of the individual five domains (Tables 2 and 3).

Moreover, consensus of >70% was reached for the global applicability of the PNRC scale, with hierarchy, quality assessment and improvement, clarity, exhaustiveness, clinical utility, and mutual exclusivity ranked in decreasing order of consensus achieved (Table 4).

4. Discussion

RT has become one of the most important options for treating pelvic malignancies [1–4]. Despite several technological advances, collateral soft-tissue lesions are still relatively frequent, and RIC is an important sequela because of considerable morbidity and mortality rates and the modest effectiveness of most of the less invasive treatment options [10–12].

Because of the absence of a consensus classification system widely used in clinical practice, and the wide array of possible symptoms that differ in their severity and consequences, RIC is often underdiagnosed, with an estimated global incidence varying from 3% to 80% [10]. Among our group of 114 experts, which included urologists, gynaecologists, radiation oncologists, and medical oncologists working in all hospital settings in 30 countries on five continents, 86% considered RIC to be a relevant or extremely relevant clinical problem. Moreover, 65.8% of respondents estimated that RIC occurs in more than 10% of patients undergoing pelvic RT, and 35.2% estimated that it occurs in more than 20% of patients (Supplementary Table 3). Although this might be attributable to selection bias related to exposure of the experts to patients with RIC, these results suggest that the burden of RIC is greater than previously considered.

Furthermore, the absence of a consensus classification system for both clinical and research settings means that it has been very difficult to undertake an adequate comparison of treatment options for patients with RIC [10–15]. Our systematic review of the literature identified 13 different systems used to classify patients with RIC [16–28]. Although some systems have a multidimensional approach, most focus on a specific RIC domain, which compromises their ability to accurately categorise a condition with such wide symptom and severity ranges. Nevertheless, analysis of these 13 systems supported our panel in the development of a comprehensive grading system that encompasses the full RIC spectrum, including haematuria, other lower urinary tract symptoms, functional compromise, endoscopic findings, and therapeutic interventions (Table 1). We believe that the PNRC scale can be easily used to both categorise RIC severity in patients and accurately evaluate treatment success for individual patients in both clinical and research settings. We also believe that the PNRC scale can have an important role in comparing the effectiveness of different treatment options available for RIC to facilitate the development of a comprehensive treatment algorithm for this condition.

Among the group of 114 international experts who analysed the 20 representative RIC clinical scenarios, the mode frequency for the agreement rate ranged between 62.3% and 98.2%, with >70% consensus for 85% of the clinical scenarios, and >62% agreement for the remaining cases (Supplementary Table 4). The agreement rate is supported qualitatively by the high degree of clustering on a Cleveland dot plot (Fig. 2) and quantitatively by the IRR measure of $\kappa = 0.6$, which indicates moderate to substantial agreement among respondents, demonstrating the reliability of the PNRC scale [30].

The majority of respondents in phase 3 of our validation consistently rated the PNRC scale favourably (4 or 5 on a 5-point Likert scale) in terms of its hierarchy, quality assessment and improvement, clarity, exhaustiveness, clinical utility, and mutual exclusivity (Table 4), which demonstrates the applicability of the scale and supports its face validity [30].

Moreover, respondents in phase 3 reached >70% consensus for both the relevance (either extremely relevant or relevant) and the appropriateness (either very appropriate or appropriate) of each of the individual five domains (Tables 2 and 3), supporting the construct validity of the PNRC scale as a tool for accurate categorisation of patients with RIC [30].

Our study has some limitations that need to be considered. First, only Medline-indexed manuscripts were included in the review, which may constitute an important selection bias, as other classification or grading systems may only be published in national journals that are not indexed in Medline. Second, phase 3 of the validation process was only completed by 53.5% of the experts. Although response fatigue due to the large number of clinical case scenarios in phase 2 and the exhaustiveness of the assessment performed in phase 3 are clearly the major contribu-

Table 2 – Assessment of the relevance of the Portuguese Navy Radiation-induced Cystitis (PNRC) scale

Domain	Relevance, % (*n*)					Total	Median
	Not relevant	Slightly relevant	Moderately relevant	Relevant	Extremely relevant	responses	score
Haematuria	0 (0)	0 (0)	0 (0)	14.8 (9)	85.2 (52)	61	5
Other lower urinary tract symptoms	0 (0)	0 (0)	13.1 (8)	23 (14)	63.9 (39)	61	5
Functional compromise	0 (0)	0 (0)	6.6 (4)	26.2 (16)	67.2 (41)	61	5
Endoscopic findings	0 (0)	6.6 (4)	11.5 (7)	14.8 (9)	67.2 (41)	61	5
Therapeutic interventions	0 (0)	0 (0)	3.3 (2)	24.6 (15)	72.1 (44)	61	5

Table 3 – Assessment of the appropriateness of the Portuguese Navy Radiation-induced Cystitis (PNRC) scale

Domain	Appropriateness, % (*n*)					Total responses	Median score
	Very inappropriate	Inappropriate	Neutral	Appropriate	Very appropriate		
Haematuria	0 (0)	0 (0)	0 (0)	14.8 (9)	85.2 (52)	61	5
Other lower urinary tract symptoms	0 (0)	0 (0)	4.9 (3)	24.6 (15)	70.5 (43)	61	5
Functional compromise	0 (0)	0 (0)	1.6 (1)	27.9 (17)	70.5 (43)	61	5
Endoscopic findings	0 (0)	1.6 (1)	8.2 (5)	18 (11)	72.1 (44)	61	5
Therapeutic interventions	0 (0)	1.6 (1)	1.6 (1)	23 (14)	73.8 (45)	61	5

Table 4 – Assessment of the global applicability of the Portuguese Navy Radiation-induced Cystitis (PNRC) scale

Grade	Likert score, % (*n*)					Total responses	Median score
	1 (low)	2	3	4	5 (high)		
Hierarchy: in terms of order of severity, how well organised is this classification of radiation-induced cystitis?	0 (0)	0 (0)	1.6 (1)	14.8 (9)	83.6 (51)	61	5
Exhaustiveness: how well does this classification cover the entire range of radiation-induced cystitis?	0 (0)	0 (0)	6.6 (4)	14.8 (9)	78.7 (48)	61	5
Clarity: how clearly defined are the different levels of the classification of radiation-induced cystitis?	0 (0)	1.6 (1)	3.3 (2)	11.5 (7)	83.6 (51)	61	5
Mutual exclusivity: how mutually exclusive are adjacent levels of the classification of radiation-induced cystitis?	0 (0)	1.6 (1)	8.2 (5)	26.2 (16)	63.9 (39)	61	5
Clinical utility: how clinically useful is this classification of radiation-induced cystitis?	0 (0)	0 (0)	8.2 (5)	18 (11)	73.8 (45)	61	5
Quality assessment and improvement: how useful do you think such a classification of radiation-induced cystitis is from a quality assessment and improvement perspective?	0 (0)	0 (0)	3.3 (2)	18 (11)	78.7 (48)	61	5

tors to the dropout rate, this poses an important constraint on the results obtained. Finally, although the IRR and the mode frequency data are quite favourable, there is still minor dispersion of responses; this indicates a certain degree of subjectivity in the evaluation of the clinical scenarios by the respondents, which is typical in the development and validation of every grading system evaluated.

Another prospective study is under way to assess the clinical utility of the PNRC scale for patients with RIC treated with hyperbaric oxygen.

5. Conclusions

The PNRC scale showed reliability and face and construct validity in the stratification of RIC severity for clinical cases. Our results support use of the PNRC scale as the main tool for categorising patients with RIC in both clinical and research settings.

***Author contributions*:** Tiago Ribeiro de Oliveira had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ribeiro de Oliveira, Biyani, D'Espiney Amaro, Palma dos Reis.
Acquisition of data: Ribeiro de Oliveira.
Analysis and interpretation of data: Ribeiro de Oliveira, Henriques Pereira, Sousa Castro.
Drafting of the manuscript: Ribeiro de Oliveira, Biyani, Henriques Pereira, Sousa Castro.
Critical revision of the manuscript for important intellectual content: D'Espiney Amaro, Henriques Pereira, Sousa Castro, Gomes Monteiro, Cardoso Felício, Bernardo, Chambino, Palma dos Reis.
Statistical analysis: Ribeiro de Oliveira.
Obtaining funding: None.
Supervision: Biyani.
Administrative, technical, or material support: None.
Other: None.

Financial disclosures: Tiago Ribeiro de Oliveira certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** None.

***Acknowledgments*:** An abstract of this work was presented at the 2024 European Association of Urology congress. We would like to thank the 114 international experts who collaborated in the study, without whom nothing would have been possible. We would like to acknowledge the excellent work of all the personnel of the Portuguese Armed Forces Undersea and Hyperbaric Medicine Centre, who are available 24/7 to treat both military and civilian patients from all around the country.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2024.12.006.

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