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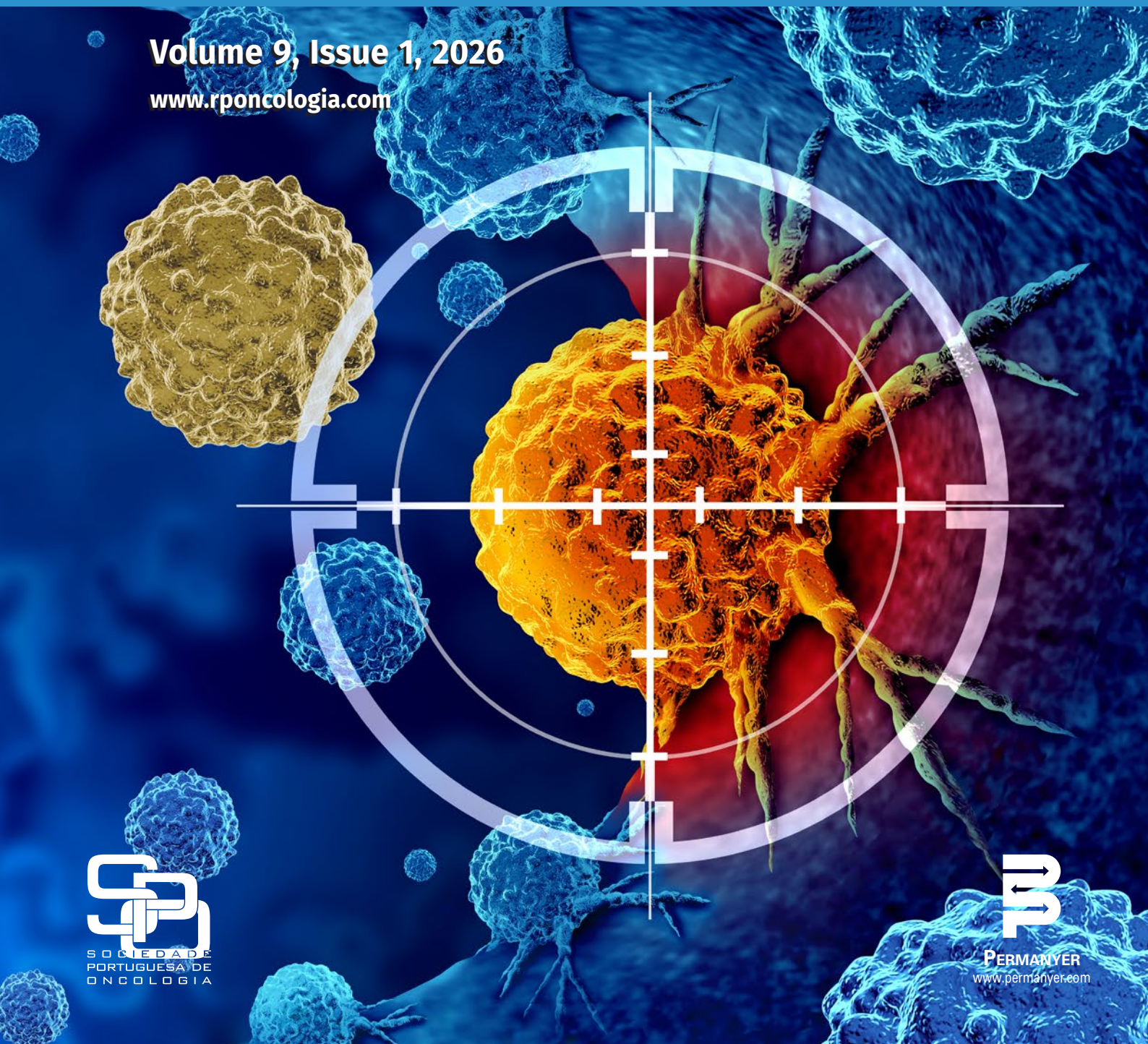
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ORIGINAL ARTICLE

Hyperbaric oxygen therapy for radiation-induced cystitis: a prospective study using the portuguese navy radiation-induced cystitis scale

Oxigenoterapia hiperbárica no tratamento da cistite induzida pela radiação: estudo prospetivo utilizando a escala da Marinha Portuguesa para a cistite induzida pela radiação

Diogo Alpuim-Costa[1,2,3,4,5,6], António Moreira-Monteiro[7], Virgínia Mareco[8], Nuno Guerra[9,10], Pedro Meneses[11], Carla Espiney-Amaro[12,13,14], and Tiago Ribeiro-de Oliveira[15]*

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Abstract

Background: Radiotherapy (RT) is a cornerstone of multidisciplinary cancer treatment and is administered to a substantial proportion of oncology patients worldwide. **Objectives:** The primary objective of this study was to validate the clinical applicability of the Portuguese Navy Radiation-induced Cystitis (PNRC) scale for grading the severity of radiation-induced cystitis (RC) and for monitoring response to hyperbaric oxygen therapy (HBOT). **Methods:** In this single-center cohort, the PNRC scale was prospectively applied over three years in patients with RC treated with HBOT, using retrospectively collected clinical data. Descriptive and inferential statistics were used to explore the association between changes in PNRC grade, macroscopic hematuria resolution, and selected clinical and treatment-related variables, with statistical significance set at $p < 0.05$. A multivariate logistic regression model was fitted to identify independent predictors of major response, defined as a reduction of at least three PNRC grades. **Results:** Ninety-four patients were included (mean age 71.7 years; 87.2% male; 85.1% prostate cancer). After a mean of 41.7 (10-120) HBOT sessions, the overall response and disease control rates were 84.1% and 98.9%, respectively, and macroscopic hematuria resolved in 83.7% of evaluable patients. More than half of the cohort improved by at least two PNRC grades, and 34.0% achieved a major response (≥ 3-grade reduction). In multivariate analysis, age ≥ 75 years showed the strongest association with major response (adjusted odds ratio 2.51, 95% CI 1.00-6.33; $p = 0.051$), whereas no other variable demonstrated an independent effect. HBOT was well tolerated, with complications in 17.0% of patients, predominantly middle-ear barotrauma (13.8%), and an RC recurrence rate of 8.5% over a median follow-up of 5 months. **Conclusion:** HBOT was effective and safe for the management of RC in this cohort, and the PNRC scale proved to be a practical tool for grading disease severity and capturing clinically meaningful changes in response to treatment. The scale may also help identify patients more likely to benefit from HBOT, supporting its broader integration into routine clinical practice.

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Keywords: *Radiation-induced cystitis. Hematuria. Hyperbaric oxygen therapy. Hyperbaric oxygen. Late radiation tissue injuries. Radiation injuries. Radiotherapy.*

Resumo

Introdução: A radioterapia (RT) é um pilar fundamental do tratamento multidisciplinar do câncer e é administrada a uma proporção substancial de pacientes oncológicos em todo o mundo. **Objetivos:** O principal objetivo deste estudo foi validar a aplicabilidade clínica da escala Portuguese Navy Radiation-induced Cystitis (PNRC) na avaliação da gravidade da cistite rádica (CR) e na monitorização da resposta à oxigenoterapia hiperbárica (OHB). **Métodos:** Num estudo unicêntrico, a escala PNRC foi aplicada prospetivamente, ao longo de três anos, em doentes com CR tratados com OHB, utilizando dados clínicos colhidos retrospetivamente. Foram realizados testes estatísticos descritivos e inferenciais para avaliar a associação entre a variação da pontuação PNRC, a resolução da hematúria macroscópica e variáveis clínicas e terapêuticas selecionadas, considerando significância estatística para $p < 0.05$. Foi ainda ajustado um modelo de regressão logística multivariável para identificar preditores independentes de resposta major, definida como uma redução de, pelo menos, três graus na escala PNRC. **Resultados:** Foram incluídos 94 doentes (idade média 71.7 anos; 87.2% homens; 85.1% com neoplasia da próstata). Após uma média de 41.7 (10-120) sessões de OHB, as taxas de resposta global e de controlo da doença foram de 84.1% e 98.9%, respetivamente, e a hematúria macroscópica resolveu em 83.7% dos doentes avaliáveis. Mais de metade da coorte apresentou uma melhoria de, pelo menos, dois graus na escala PNRC e 34.0% atingiram resposta major (redução ≥ 3 graus). Na análise multivariável, a idade ≥ 75 anos apresentou a associação mais forte com resposta major (OR ajustado 2.51; IC 95% 1.00-6.33; $p = 0.051$), não se verificando efeito independente das restantes variáveis. A OHB foi globalmente bem tolerada, com complicações em 17.0% dos doentes, predominantemente barotrauma do ouvido médio (13.8%), e uma taxa de recorrência de CR de 8.5% após um seguimento mediano de cinco meses. **Conclusões:** A OHB mostrou ser eficaz e segura no tratamento da CR nesta coorte, e a escala PNRC revelou-se uma ferramenta prática para graduar a gravidade da doença e captar alterações clinicamente relevantes na resposta ao tratamento. A escala poderá ainda contribuir para identificar doentes com maior probabilidade de beneficiarem de OHB, apoiando a sua integração mais alargada na prática clínica.

Palavras-chave: *Cistite induzida por radiação. Hematúria. Oxigenoterapia hiperbárica. Oxigénio hiperbárico. Lesões tecidulares tardias radioinduzidas. Lesões radioinduzidas. Radioterapia.*

Introduction

Radiotherapy (RT) is a cornerstone of multidisciplinary cancer treatment and is administered to a substantial proportion of oncology patients worldwide. Despite progressive refinements in RT planning and delivery, late radiation-induced tissue injuries (LRTIs) may still emerge after a symptom-free latency period ranging from a few months to several decades. The true incidence of LRTIs is difficult to ascertain, but it is estimated that approximately 5% of patients will develop clinically relevant late toxicity.[1]

The pathophysiology of LRTIs, including radiation-induced cystitis (RC), is intricate and involves a cascade of progressive microvascular and stromal alterations. Obliterative endarteritis, chronic hypoxia, and fibrosis are recognized as key mechanisms underlying their onset and progression towards chronic, often irreversible damage.[2-5] Importantly, most conventional treatments for LRTIs are essentially palliative, focusing on symptomatic relief without substantially modifying the natural history of the disease or addressing its underlying pathogenic mechanisms.[6-11]

A universally accepted therapeutic strategy for RC has not yet been established, and management is typically individualized according to symptom severity and the patient´s overall clinical status.[6-11] In this context, hyperbaric oxygen therapy (HBOT) is recommended by the European Committee for Hyperbaric Medicine[12] as a treatment option for RC (grade of recommendation 1/level of evidence B), as it increases tissue oxygenation, stimulates neoangiogenesis at the urothelial and detrusor levels, and favorably modulates the radiation-induced fibroatrophic process.

Multiple RC classification systems have been proposed, incorporating clinical, functional, laboratory, and endoscopic parameters, often linked to specific therapeutic strategies.[13-17] However, none of these classifications has been specifically validated for the prospective assessment of HBOT efficacy in chronic RC. The PNRC scale was recently developed as a comprehensive tool to grade RC severity.[18] The present study aims to validate the clinical usefulness of the PNRC scale for assessing and monitoring RC severity in response to HBOT.

Methods

Study objectives

Primary objective

- To evaluate RC control and overall response rates to HBOT based on changes in the PNRC scale.

Secondary objectives

- To determine the resolution rate of macroscopic hematuria after HBOT.
- To explore the association between PNRC scale variation and macroscopic hematuria resolution with selected categorical and continuous clinical variables.
- To estimate the recurrence rate of RC after HBOT, stratified by PNRC scale.
- To characterize the safety profile of HBOT in this population.

Study design

This was a single-center study with retrospective data collection and prospective application of an RC severity classification in a cohort of patients treated with HBOT between January 01, 2020, and December 31, 2022.

Study sample

Inclusion criteria were: age ≥ 18 years; prior RT treatment; RC symptoms persisting for at least 3 months after completion of RT; and completion of ≥ 10 HBOT sessions.

Exclusion criteria were: isolated microscopic hematuria without concomitant lower urinary tract symptoms (LUTS); coexisting medical conditions plausibly responsible for macroscopic hematuria; active, progressive malignancy; any contraindication to HBOT (such as uncontrolled epilepsy, pneumothorax, subpleural bullae, or recent barotrauma); and patient refusal or inability to provide written informed consent.

Protocol for assessing eligibility for treatment

Patients with RC were referred for hyperbaric treatment at the Centro de Medicina Subaquática e Hiperbárica (CMSH, Armed Forces Hospital, Lisbon Campus) by Urology Departments from multiple hospitals nationwide. On arrival, they underwent a comprehensive medical evaluation to confirm eligibility for HBOT and to exclude relevant contraindications.

This assessment systematically included a chest X-ray (to rule out subpleural bullae, pneumothorax, or other significant pulmonary disease), a 12-lead electrocardiogram (to exclude relevant cardiac pathology), and a tympanogram (to detect Eustachian tube dysfunction). Laboratory, imaging, and endoscopic studies previously performed to diagnose RC and to exclude alternative causes of LUTS were reviewed and used to complete the evaluation and to grade RC severity according to the PNRC scale. Patients then attended an initial nursing consultation focused on educational support, during which they received detailed instructions on measures to minimize complications before, during, and after HBOT.

All patients were treated in a multiplace, first-class hyperbaric chamber, breathing 100% oxygen at 2.5 ATA for 100-min sessions (Fig. 1). After an initial course of 20 sessions, clinical response was evaluated. Resolution of symptoms, particularly hematuria, was considered indicative of treatment completion, whereas persistent symptoms warranted extension of therapy with at least one additional cycle of 10 or 20 sessions.

Assessment of RC severity using the PNRC scale

The PNRC scale was created and validated by a multidisciplinary panel of national and international experts to capture all relevant disease domains comprehensively and to enable its systematic, standardized use in both clinical practice and research (Table 1).[18] It comprises five domains: hematuria, other LUTS, functional impairment, endoscopic findings, and therapeutic interventions, distributed across six severity levels.[1-6] For each patient, the overall RC grade is defined by the highest severity level observed in any of the assessed domains.

Data collection

All clinical records were reviewed on site at CMSH. The following data were collected: age, gender, date of cancer diagnosis, primary tumor type, oncological treatments received, RT technique, presence of LRTIs other than RC, interval from RT completion to onset of RC symptoms, interval from RC symptom onset to

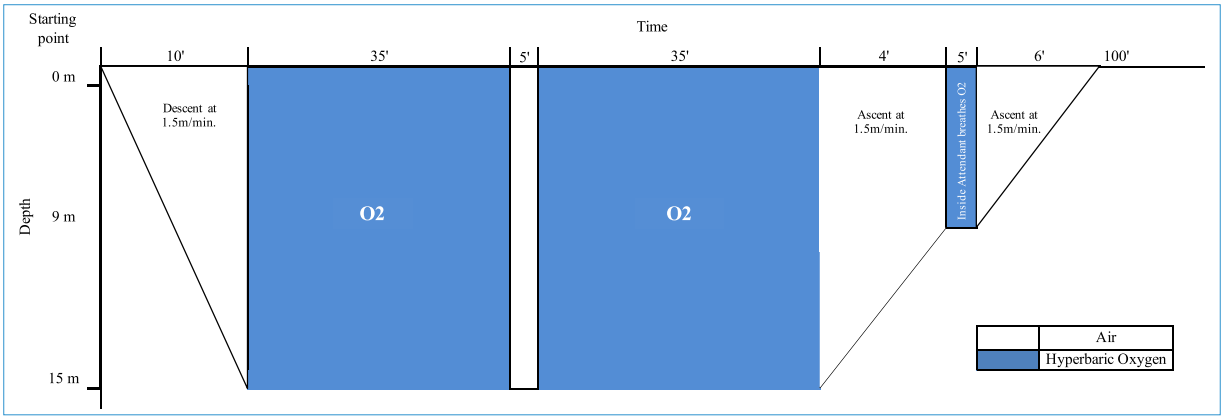


Figure 1. Hyperbaric oxygen therapy protocol for radiation-induced cystitis at Centro de Medicina Subaquática e Hiperbárica. In each treatment session, patients breathed 100% oxygen at 2.5 ATA for 70 min (total duration of 100 min, including descent, a 5-min break, and ascent) once daily, 5 times a week (*adapted from Moreira Monteiro et al.*[28] *with the author's permission*). 5'-AIRBK: 5-min air-break; ATA: atmospheres absolute.

Table 1. Portuguese navy radiation-induced cystitis scale

S. No.	Hematuria profile	Other lower urinary tract symptoms	Functional compromise	Endoscopic findings	Therapeutic interventions
1.	Microscopic hematuria	Asymptomatic	Without functional compromise or impairment of the ADLs	Epithelial atrophy	No need for therapeutic interventions
2.	Intermittent macroscopic hematuria	Mild increase of the urinary frequency, urgency, dysuria, or nocturia, or *de novo* incontinence	Functional compromise, but without impairment of the ADLs	Mild telangiectasias	Need for oral or intravesical treatment
3.	Persistent macroscopic hematuria	Moderate increase in urinary frequency, urgency, dysuria, nocturia, or incontinence	Functional compromise and mild impairment of the ADLs	Generalized telangiectasias	Need for bladder catheterization and rinsing
4.	Macroscopic hematuria requiring transfusions	Severe increase in urinary frequency or urgency, frequent urinary incontinence, decreased bladder capacity (< 150 mL)	Moderate impairment of the ADLs	Severe generalized telangiectasias (with petechiae)	Need for transfusion support, hospitalization, or elective invasive procedures
5.	Refractory macroscopic hematuria	Refractory urinary incontinence, severely decreased bladder capacity (< 100 mL)	Severe impairment of the ADLs	Any grade of mucosal necrosis	Need for urgent invasive procedures
6.	Death				

ADLs: activities of daily living; LUTS: lower urinary tract symptoms.

initiation of HBOT, RC grade according to the PNRC scale, baseline hematuria severity, total number of HBOT sessions, therapeutic response assessed as measured by change in PNRC grade and macroscopic hematuria status, occurrence of HBOT-related complications, RC symptom recurrence, and duration of follow-up.

Statistical analysis

The statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistics, version 23.0, and Microsoft Excel. Continuous variables are presented as mean and minimum–maximum range, and categorical variables as absolute and relative frequencies.

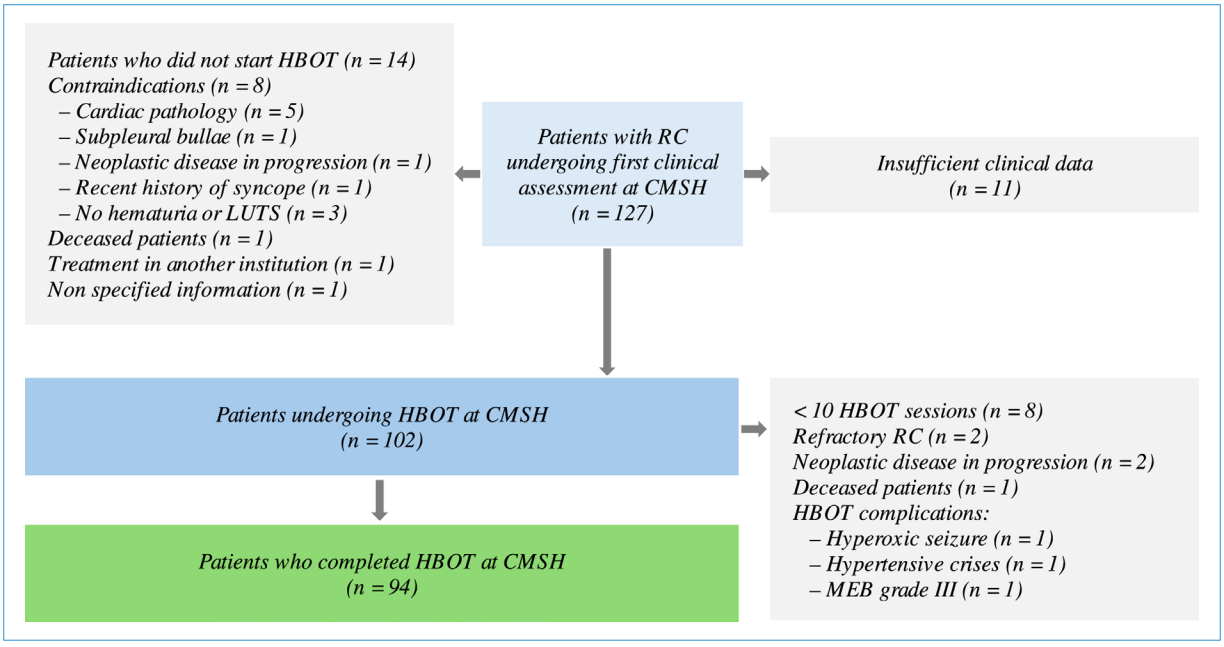


Figure 2. Flowchart showing patients with radiation-induced cystitis included in this study based on the specified criteria. CMSH: Centro de Medicina Subaquática e Hiperbárica; HBOT: hyperbaric oxygen therapy; LUTS: lower urinary tract symptoms; MEB: middle ear barotrauma; RC: radiation-induced cystitis.

The severity of RC was quantified using the PNRC scale, applied at baseline and after completion of HBOT. The PNRC variation was calculated as the difference between baseline and final scores, with a negative variation indicating clinical improvement. Based on this variation, two binary endpoints were defined: (i) "major response," corresponding to a negative variation of ≥ 3 grades in the PNRC scale (yes/no), and (ii) "macroscopic hematuria resolution," defined as the presence of macroscopic hematuria at baseline and its absence at reassessment (yes/no).

Initially, a univariate analysis was performed to explore the association between PNRC variation (including the "major response" and "macroscopic hematuria resolution" endpoints) and several clinical and treatment-related variables: age, sex, primary tumor location, presence of other LRTI, previous need for transfusion support, need for other therapies specifically targeting RC, time between RT and onset of cystitis symptoms, time between symptom onset and HBOT initiation, and total number of HBOT sessions. Depending on the expected frequencies, Pearson's Chi-square or Fisher's exact test was used, and $p < 0.05$ was considered statistically significant (Supplementary Material).

To identify independent predictors of "major response," a multivariate binary logistic regression model was fitted that include the following explanatory variables: age (≥ 75 vs. < 75 years), sex, prostate/endometrial cancer vs other primary tumors, presence of other LRTI, interval between RT and onset of cystitis symptoms (> 24 vs. ≤ 24 months), and interval between symptom onset and HBOT (≤ 3 vs. > 3 months). These variables were selected based on clinical relevance and/or a $p < 0.20$ in univariate analyses. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were estimated for each predictor (Supplementary Material).

For the "macroscopic hematuria resolution" endpoint, attempts were made to fit logistic regression models; however, the very high overall response rate and asymmetric event distribution led to (near) complete separation and non-convergence of the models, even after reducing the number of covariates, which precluded the estimation of a stable adjusted OR. Consequently, this endpoint was analyzed descriptively and by univariate methods only, without formal identification of independent predictors.

Results

Population characterization

Between January 01, 2020, and December 31, 2022, 127 patients with RC were referred for HBOT at CMSH. Of these, 33 were excluded from the final analysis for various reasons; thus, although 102 patients with RC initiated HBOT, only 94 met the inclusion criteria (Fig. 2).

Demographic and clinical data were evaluated to characterize the cohort (Table 2). The mean age was 71.7 years, most patients were male (87.23%), and prostate cancer was the predominant primary tumor (85.11%). The vast majority received multimodality treatment. In addition, 20.21% (n = 19) had at least one LRTI other than RC, most commonly radiation-induced proctitis (RP) (n = 13).

Table 2. Characterization of the study sample based on several variables: age, sex, localization, and timing of the primary neoplasm diagnosis, oncological treatments, and late radiation-induced tissue injuries other than radiation-induced cystitis

Variable	n (%)
Age (years) average (min-max)	71.7 (48-91)
Sex	
Female	12 (12.77)
Male	82 (87.23)
Localization of the primary neoplasm	
Bladder	1 (1.06)
Anal canal	1 (1.06)
Cervix uteri	8 (8.51)
Endometrial	3 (3.20)
Prostate	80 (85.11)
Rectum	1 (1.06)
Time of the diagnosis of the primary neoplasm	
1990-1999	4 (4.25)
2000-2009	25 (26.60)
2010-2019	59 (62.77)
2020-2022	5 (5.32)
Non-specified	1 (1.06)
Oncological treatments	
Brachytherapy	4 (4.25)
Surgery + Adjuvant CRT	2 (2.13)
Surgery + RT ± ADT	50 (53.20)
Surgery + RT + ADT + AA	1 (1.06)
Surgery + RT + ADT + AA + CT	1 (1.06)
RT + Brachytherapy ± Surgery	2 (2.13)
CRT ± Brachytherapy	7 (7.45)
RT ± ADT	26 (27.66)
CRT + Surgery + Adjuvant CT	1 (1.06)
Radiation-induced cystitis + Other LRTI	19 (20.21)
RC + RP	9 (9.57)
RC + RP + RU	3 (3.20)
RC + RP + Enterovesical fistulae	1 (1.06)
RC + RU	6 (6.38)

AA: abiraterone acetate; ADT: androgen deprivation therapy; CT: chemotherapy; CRT: chemoradiotherapy; LRTI: late radiation-induced tissue injury; RC: radiation-induced cystitis; RP: radiation-induced proctitis; RT: radiotherapy; RU: radiation-induced urethritis.

Clinical presentation

Table 3 summarizes the clinical characteristics of RC before HBOT initiation. Most patients initially presented with hematuria (91.49%, n = 86), with 33.72% (n = 29) classified as Grade 4 (macroscopic hematuria requiring transfusion) and 31.40% (n = 27) as Grade 3 (persistent macroscopic hematuria) on the PNRC scale. Over one-third of patients (37.2%, n = 32) required transfusional support. Although hematuria was the predominant manifestation, half of the cohort (50%, n = 47) reported other LUTS at presentation, with Grade 4 symptoms being the most frequent (44.69%, n = 42). Regarding functional status, almost 40% (n = 37) had severe impairment in activities of daily living (Grade 4 PNRC). Cystoscopy was performed in 51.06% of patients (n = 48), and generalized telangiectasias were observed in more than 70% of those examined.

The mean interval from RT to the onset of RC symptoms was 84 months (7 years). The average delay between RC diagnosis and initiation of HBOT was 23 months. Patients underwent a mean of approximately 42 (10-120) HBOT sessions (Table 4).

Clinical response and safety profile of HBOT

To assess the clinical response to HBOT, the rates of complete, partial, and stable responses, as well as the overall response rate (sum of complete and partial responses), were calculated (Table 5). A complete response was defined as the reduction of the initial severity grade(s) in the PNRC scale domain(s) to Grade 1 (the lowest score) at the final evaluation. A partial response was defined as an improvement of at least one grade in any affected domain compared with baseline. Stable disease was characterized by no change in the

Table 3. Characterization of the study sample regarding the clinical presentation of radiation-induced cystitis before the initiation of hyperbaric oxygen therapy

Variable	n (%)
PNRC scale for RC before HBOT (initial classification)	
Grade 1	0 (0)
Grade 2	19 (20.21)
Grade 3	27 (28.72)
Grade 4	42 (44.69)
Grade 5	6 (6.38)
Hematuria	
Yes	86 (91.49)
No	8 (8.51)
PNRC scale for hematuria before HBOT (initial classification) (n = 86)	
Grade 1	1 (1.16)
Grade 2	26 (30.23)
Grade 3	27 (31.40)
Grade 4	29 (33.72)
Grade 5	3 (3.49)
Need for transfusion support before HBOT (for a potential, n = 86)	
Yes	32 (37.20)
No	54 (62.80)
Other LUTS by PNRC scale	
Yes	47 (50)
No	47 (50)
Functional impairment by the PNRC scale	
Grade 1	13 (13.83)
Grade 2	21 (22.34)
Grade 3	20 (21.28)
Grade 4	37 (39.36)
Grade 5	3 (3.20)
Cystoscopy	
Yes	48 (51.06)
No	46 (48.94)
Endoscopic/histopathological findings by PNRC scale (n = 48)	
Grade 1	0 (0)
Grade 2	13 (27.08)
Grade 3	31 (64.58)
Grade 4	4 (8.34)
Grade 5	0 (0)

HBOT: hyperbaric oxygen therapy; LUTS: lower urinary tract symptoms; PNRC: Portuguese Navy Radiation-induced Cystitis; RC: radiation-induced cystitis.

severity grade(s), whereas disease progression was defined as an increase in grade(s) at the response assessment.

Table 4. Characterization of continuous variables associated with hyperbaric oxygen therapy

Variable	Average
Time between RT - RC symptomatology (months)	84 (3-260)
Time between RC symptomatology - HBOT initiation (months)	3 (0-382)
Time between RT - HBOT (years)	8.8 (0.4-31.9)
Number of HBOT sessions (average)	41.72 (10-120)

HBOT: hyperbaric oxygen therapy; RC: radiation-induced cystitis; RT: radiotherapy.

Following HBOT, most patients were classified as PNRC Grade 1 (69.16%, n = 65) or Grade 2 (15.96%, n = 15). More than half of the cohort achieved a robust response, with an improvement of at least two PNRC grades (negative variation) (Fig. 3). The overall response rate was 84.05%, and the disease control rate reached 98.94%. Macroscopic hematuria resolved in 83.72% of patients. Among those with non-hemorrhagic RC (n = 8), the overall response and disease control rates were 50% and 100%, respectively. Exploring the relationship between PNRC score variation and macroscopic hematuria resolution, alongside multiple categorical and continuous variables, identified potential predictors of a better response to HBOT (Supplementary Material).

Notably, no serious adverse events were recorded. Approximately 17% of patients experienced complications, most commonly middle ear barotrauma (MEB) (13.83%, n = 13). The recurrence rate of RC symptoms was 8% over a mean follow-up of 5 months.

Discussion

An ambispective study was conducted to evaluate the effectiveness of HBOT in patients with RC treated at the CMSH. Clinical and demographic data were retrospectively collected, while the PNRC Scale was prospectively applied within a predefined timeframe to assess and monitor treatment response. Before this implementation, this tool was validated by a multidisciplinary panel of national and international experts, ensuring scientific robustness and the reliability of its translation into clinical practice.[18]

After the initial application of the PNRC scale, most patients fulfilled criteria for moderate (Grade 3: 28.72%, n = 27), severe (Grade 4: 44.69%, n = 42), or refractory disease (Grade 5: 6.38%, n = 6). This severity distribution is consistent with the expected clinical profile of

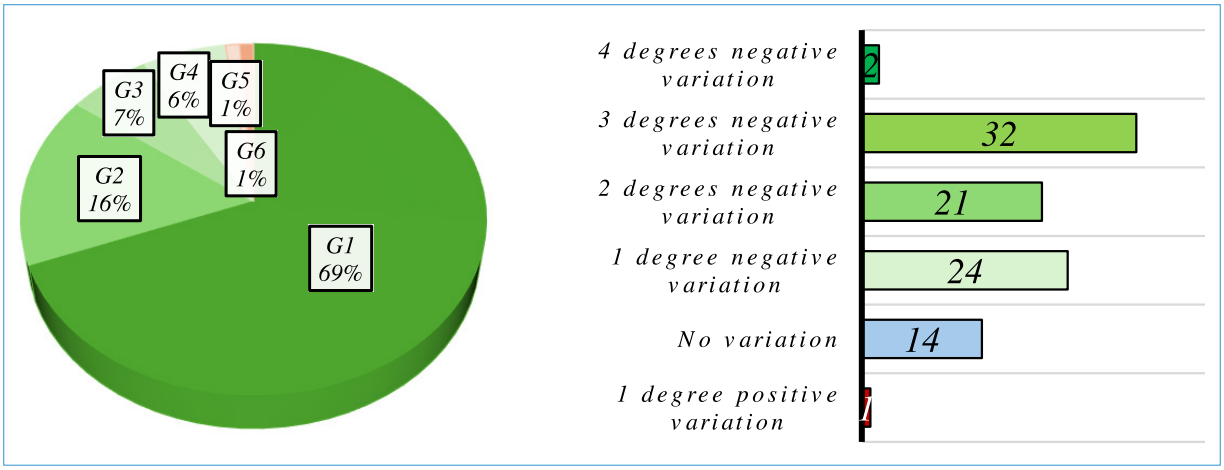


Figure 3. Final classification of radiation-induced cystitis using the Portuguese navy radiation-induced cystitis scale (on the left) and its variation with the initial assessment (on the right).

patients with CTCAE/RTOG-EORTC Grade 2-4 RC typically referred for HBOT.

The majority of the cohort presented with hemorrhagic RC (91.49%, n = 86), of whom over 60% were classified as PNRC grades 3 or 4. The PNRC scale allows a clearer distinction between severe and refractory disease, not only based on persistent macroscopic hematuria, but also by incorporating refractory urinary incontinence, markedly reduced bladder capacity (< 100 mL), bladder necrosis, major quality-of-life (QoL) impairment, and formal indications for urgent invasive intervention. It is also noteworthy that eight patients with non-hemorrhagic RC were included, a group usually underrepresented in interventional HBOT studies.

With regard to functional impact, almost 90% of patients demonstrated some grade of functional impairment. Although no validated Portuguese QoL instruments were used, clinicians relied on the PNRC scale and indirect markers such as transfusion requirement, which was observed in 37.2% of cases. In the series by Ferreira et al.,[19] involving 70 RC patients, 71.5% presented with persistent hematuria and clots, and 31.5% required multiple transfusions before HBOT, with subsequent improvement documented on the LENT-SOMA scale,[14,15] supporting the assumption of substantial baseline functional compromise in these patients.

In which concerns, prior management, it was not possible to accurately quantify the number of patients who received pharmacologic therapy, endoscopic fulguration, intravesical instillations, selective arterial embolization, or surgical interventions such as cystectomy. The subgroup of 38 patients for whom these data were available, therefore, likely underestimates the true frequency of previous treatments.

Comparison of initial and final PNRC scores showed an overall response rate to HBOT of 84.05% and a disease control rate of 98.94%. Although the sample size is modest, these results are encouraging for a condition that is often refractory to conventional therapies. These response and control rates, as captured by the multidimensional PNRC scale, are broadly in line with those reported in both retrospective and prospective studies, where overall response rates to HBOT for RC typically range from about 80% to over 90%. However, most published series define response almost exclusively by hematuria resolution, limiting the ability to capture the full clinical spectrum of RC beyond bleeding control.

In the first prospective study, Bevers et al.[20] targeted an overall response rate of 92.5% after 20 HBOT sessions. Hampson et al.[21] later reported an 89% overall response with a mean of 42 sessions, and Dellis et al.[22] documented a 100% overall response in a prospective cohort. Ferreira et al.[19] described long-term outcomes in 70 patients, with a median follow-up of 55.5 months and an overall response rate of 91.4%. Feldmeier and Hampson[1] systematic review of 17 studies (190 RC patients) found hematuria resolution in 76.3% of cases, while Cardinal et al.[10] reported hematuria resolution in 84% of 602 patients across 16 studies, closely matching our hematuria outcomes.

This real-world evidence study comprised a consecutive cohort of 94 patients treated with HBOT over a 3-year period. The majority were male (87.2%, n = 82), and older age was significantly associated with a favorable treatment outcome (p = 0.005), corresponding to an improvement of at least three grades on the PNRC scale, even among those aged ≥ 75 years

Table 5. Characterization of the study sample, including the final classification according to the Portuguese Navy Radiation-induced Cystitis scale (post-hyperbaric oxygen therapy) and its variation, clinical response to hyperbaric oxygen therapy, therapeutic side effects, recurrence rate, and follow-up

Variable	n (%)
PNRC scale for RC after HBOT (final classification)	
Grade 1	65 (69.16)
Grade 2	15 (15.96)
Grade 3	6 (6.38)
Grade 4	6 (6.38)
Grade 5	1 (1.06)
Grade 6	1 (1.06)
PNRC scale variation for RC	
1 Grade negative variation	24 (25.53)
2 Grades negative variation	21 (22.35)
3 Grades negative variation	32 (34.04)
4 Grades negative variation	2 (2.13)
No variation	14 (14.89)
1 Grade positive variation	1 (1.06)
Clinical response to HBOT based on PNRC scale final classification for RC	
Overall response rate (complete + partial responses)	79 (84.05)
Control rate (complete + partial + stable responses)	93 (98.94)
No response (progression of the disease)	1 (1.06)
Macroscopic hematuria resolution rate (for a potential n = 86)	
Yes	72 (83.72)
No	14 (16.28)
PNRC scale variation for non-hemorrhagic RC	
1. Grade negative variation	3 (37.5)
2. Grades negative variation	1 (12.5)
Maintenance of the severity grade	4 (50)
Clinical response to HBOT based on PNRC scale final classification for non-hemorrhagic RC	
Overall clinical response (complete + partial responses)	4 (50)
Control response (complete + partial + stable responses)	8 (100)
HBOT side effects	
Yes	16 (17.02)
No	78 (82.98)
Type of HBOT side effect (n = 16)	
Middle ear barotrauma	13 (13.83)
Nausea	2 (2.12)
Claustrophobia	1 (1.06)
RC symptoms relapse	8 (8.51)
PNRC scale for relapsed RC (n = 8)	
Grade 1	0 (0)
Grade 2	2 (25)
Grade 3	3 (37.5)
Grade 4	2 (25)
Grade 5	1 (12.5)
Follow-up (months)	5 (0-38)

A negative variation (a reduction of at least 1 grade in the PNRC scale) implies clinical improvement of RC; a positive variation implies the worsening of the severity grade(s), thus the progression of the disease; no variation means maintenance of the RC severity grade, hence no evolution.
HBOT: hyperbaric oxygen therapy; PNRC: Portuguese Navy Radiation-induced Cystitis; RC: radiation-induced cystitis.

(p = 0.016). The predominance of prostate cancer, which typically affects older men, may have contributed to these findings and may also explain the significant association between male gender and favorable treatment response (p = 0.021). These observations align with those reported by Chong and Rice et al.,[23] Degener et al.,[24] and Mougin et al.,[25] although those studies were retrospective and included smaller patient populations.

In the multivariate analysis, age ≥ 75 years emerged as the variable most strongly associated with a marked improvement in RC, defined as a ≥ 3-grade reduction on the PNRC Scale. Older patients showed approximately 2.5-fold higher odds of achieving this "major response" compared with younger individuals (adjusted OR 2.51; 95% CI 1.00-6.33; p = 0.051), suggesting a clinically meaningful effect, albeit at the threshold of statistical significance. These findings are consistent with the predominance of prostate cancer within the cohort and with the higher frequency of late-onset cystitis in elderly patients, whose more indolent fibroatrophic lesions may be particularly responsive to the neoangiogenic and tissue-oxygenating effects of HBOT. Exploratory analyses identified other subgroups with particularly favorable responses to HBOT, including those who had required transfusion support and individuals who had received additional therapies for RC beyond HBOT.

In contrast to our findings, Chong et al.[26] suggested that younger age might predict better HBOT outcomes, whereas Ribeiro de Oliveira et al.[7] reported that prior

transfusion requirements were associated with lower response rates. These discrepancies, along with possible unmeasured confounders such as diabetes, atherosclerosis, peripheral arterial disease, and smoking,[27] indicate that inter-study comparisons must be interpreted with caution.

An interval > 4 years between completion of RT and onset of RC symptoms may reflect a more indolent disease course, with a prolonged latent phase before progression to chronic inflammatory injury, potentially rendering the bladder more amenable to HBOT's angiogenic and anti-fibrotic effects. In this regard, Moreira Monteiro et al.[28] found that a longer latency before the first manifestation of RP was associated with a more favorable prognosis, suggesting a similar mechanism may apply to RC.

In the present study, in line with the retrospective series by Ribeiro de Oliveira et al.,[7] the proportion of patients presenting with RC and at least one additional LRTI was approximately 20%. Similarly, in another retrospective cohort from CMSH, Moreira Monteiro et al.[28] reported that about one-third of patients with RP (38.6%, n = 34) had concomitant LRTIs and found that the presence of at least two LRTIs was significantly associated with complete responses to HBOT ($p = 0.029$); however, this association did not reach statistical significance in our study population ($p = 0.176$).

The reported incidence of MEB in HBOT studies varies widely, from 0.37% to 84% in non-ventilated patients. In our cohort, the MEB rate and overall complication profile were consistent with those described by Moreira Monteiro et al.[28] (20.5%, n = 18) and Bouaziz et al.[29] (14.2%, n = 19), reinforcing the conclusion that HBOT is a generally safe treatment with a low risk of serious adverse events.

This study has several limitations. First, the retrospective review of clinical records may have led to incomplete data on prior antineoplastic regimens and RC-directed interventions, thereby constraining the analysis of their potential impact on HBOT outcomes and PNRC validation. Second, data were more robust for hemorrhagic RC, and the small number of patients with non-hemorrhagic RC precludes extrapolation of results to this subgroup. Third, only about half of the cohort underwent cystoscopy, which may have introduced bias in both diagnosis and initial PNRC grading; the lack of systematic post-HBOT cystoscopy further limits assessment of endoscopic response. Finally, the referring physicians primarily conducted follow-up, and the relatively short follow-up duration limits the accuracy of recurrence rate estimates. Future studies with larger, prospectively followed cohorts and broader external application of the PNRC scale will be essential to confirm these findings and to support its integration into routine clinical practice.

Conclusion

This single-center cohort study provides additional clinical validation of the PNRC scale as a practical, multidimensional instrument for classifying and monitoring RC in patients treated with HBOT. The scale proved easy to apply in routine practice and captured changes in RC severity across multiple domains, enabling more precise baseline stratification and response assessment over time.

HBOT achieved high overall response and disease control rates, with macroscopic hematuria resolution in the majority of evaluable patients, reinforcing its effectiveness and favorable safety profile in this setting. More than half of the cohort improved by at least 2 PNRC grades, and one-third achieved a major response (reduction of ≥ 3 PNRC grades), supporting the scale's sensitivity to clinically meaningful change. Exploratory analyses suggested that older patients and those with previous transfusion requirements or a longer latency between RT and RC onset may be more likely to achieve a major response, although these findings require confirmation.

Taken together, these results support the PNRC scale as a useful tool not only for grading RC severity and monitoring HBOT outcomes, but also for identifying subgroups more likely to benefit from treatment. Larger, prospective, multicentre studies are warranted to consolidate these observations and to foster broader implementation of the PNRC scale in everyday clinical practice.

Ethical considerations

This study was conducted in accordance with the regulations established by the Ethics Committee of the Armed Forces Hospital (HFAR, Lisbon Campus) and with the principles of the Declaration of Helsinki of the World Medical Association. Formal review by the National Council of Ethics for the Life Sciences was waived, as this was not a clinical trial involving an investigational medicinal product and therefore did not alter the clinical management or therapeutic decisions regarding the patients included in this study.

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Authors' contributions

D. Alpuim-Costa: conception and design, acquisition, analysis and interpretation of data, writing, review and revision of the manuscript, manuscript supervision; A. Moreira-Monteiro: acquisition, analysis and interpretation of data, writing, review and revision of the manuscript; V. Mareco: acquisition, analysis and interpretation of data, writing, review and revision of the manuscript; N. Guerra: acquisition, analysis and interpretation of data, writing, review and revision of the manuscript; C. Espiney-Amaro: acquisition, analysis and interpretation of data, writing, review and revision of the manuscript, manuscript supervision; P. Meneses: writing, review and revision of the manuscript; T. Ribeiro-de-Oliveira: conception and design, writing, review and revision of the manuscript, manuscript supervision.

Data availability

Due to ethical or legal restrictions, the datasets generated and analyzed during the current study are not publicly available but can be obtained from the corresponding author upon reasonable request.

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None.

Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

Supplementary data

Supplementary data are available at 10.24875/RPO.25000017. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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REVIEW ARTICLE

Ovarian cancer in Portugal: a real-world evidence review

Cancro do ovário em Portugal: uma revisão da evidência do mundo real

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Abstract

The primary objective of this study was to address the gap in national data on the ovarian cancer (OC) patient pathway in Portugal. We aggregated and synthesized real-world evidence (RWE) studies conducted by AstraZeneca Portugal between 2016 and 2025 on OC, including fallopian tube and primary peritoneal carcinoma, to provide an overview of the patient journey. Moreover, we performed a literature search to include additional studies, using the keywords "ovarian cancer" AND "real world" OR "RWE" OR "real world evidence" AND "patient journey" AND "Portugal," but no relevant citations were identified in PubMed. This review includes five studies presented at various national and international meetings. The PADOC and the IPOP OC studies evaluated the prevalence of *BRCA* pathogenic variants in somatic and germline related to OC; the MAP-OCSur study focused on characterization of OC surgery in Portugal; the Portuguese subanalysis of the RESPONSE trial described the standard of care in patients with OC in Portugal; and the OLA effectiveness evaluated the use of olaparib in platinum-sensitive relapsed OC. The mentioned RWE studies play a crucial role in characterizing the OC patient pathway in Portugal, by enhancing the understanding of both the disease and patient profile, as well as identifying existing evidence gaps. This review illustrates the current state of OC care in Portugal, raising awareness of challenges and highlighting opportunities to improve access and patient outcomes.

Keywords: *Real-world evidence. Ovarian cancer. Fallopian tube carcinoma. Primary peritoneal carcinoma. Standard of care. Patient journey. Portugal.*

Resumo

O objetivo primário deste estudo foi adereçar a lacuna de dados nacionais sobre a jornada das doentes com cancro do ovário (CO) em Portugal. Agregámos e sintetizámos estudos de geração de evidência (RWE) conduzidos pela AstraZeneca Portugal entre 2016 e 2025 em CO, incluindo carcinoma das trompas de Falópio e carcinoma peritoneal primário, para fornecer uma visão global do percurso das doentes. Além disso, realizámos uma pesquisa bibliográfica para incluir estudos adicionais, utilizando as palavras-chave "ovarian cancer" E "real world" OU "RWE" OU "real world evidence" E "patient journey" E "Portugal", mas não foram identificadas citações relevantes no PubMed. Esta revisão inclui cinco estudos apresentados em vários encontros nacionais e internacionais. Os estudos PADOC e IPOP OC avaliaram a prevalência de variantes patogénicas *BRCA*, somáticas e germinativas, relacionadas com CO; o estudo MAP-OCSur centrou-se na caracterização da cirurgia em CO em Portugal; a subanálise portuguesa do ensaio RESPONSE descreveu o padrão de tratamento em

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doentes com CO em Portugal; e o estudo OLA effectiveness avaliou a utilização de olaparib no CO recorrente sensível à platina. Os estudos de RWE referidos desempenham um papel crucial na caracterização da jornada das doentes com CO em Portugal, ao aprofundar o conhecimento da doença e do perfil das doentes, bem como ao identificar lacunas de evidência existentes. Esta revisão ilustra o estado atual dos cuidados de saúde em CO em Portugal, sensibilizando para os desafios e destacando oportunidades para melhorar o acesso e os resultados em saúde das doentes.

Palavras-chave: *Evidência do mundo real. Cancro do ovário. Carcinoma das trompas de Falópio. Carcinoma peritoneal primário. Padrão de tratamento. Jornada do doente. Portugal.*

Key issues

- Real-world evidence (RWE) refers to the analysis and interpretation of data from real-world practice.
- RWE may help clinicians and health policymakers identify gaps in ovarian cancer (OC) patient pathways and define strategies to overcome the difficulties.
- RWE on *BRCA* mutations in Portuguese OC patients aligns with the published data.
- RWE on surgery in OC patients in Portugal shows a low number of complete and optimal cytoreduction, suggesting a need for improvement.
- Portuguese RWE on the use of olaparib in platinum-sensitive relapsed OC supports efficacy data of randomized clinical trials (RCTs) despite a higher-than-expected need for dose reductions, suggesting a need for clinician training in safety management of PARP inhibitors.

Introduction

The importance of an optimized patient journey

Ovarian cancer (OC) is the most lethal type of gynecologic cancer and one of the principal causes of death from cancer in women worldwide.[1] In 2022, almost 325,000 women were diagnosed with OC, and around 207,000 died.[2] Of those, 682 new cases were diagnosed in Portugal, with 472 deaths attributed to OC.[3]

Genetic predisposition is one of the main risk factors for developing OC cases, with around 10% of OC cases associated with germline mutations. The genes most commonly mutated are *BRCA1* and *BRCA2,* involved in the DNA repair pathway, which confer a 40% and 18% lifetime risk of OC, respectively. Mutations in other genes that also increase OC risk include *BRIP1*, *PALB2*, *ATM*, *RAD51C, RAD51D, CHEK2*, *MLH1*, *MSH2,* and *TP53.* The guidelines recommend genetic testing, since it can guide diagnosis and medical management of high-risk populations.[4-6]

The non-specific signs and symptoms of this malignancy and the absence of a validated screening method make early detection of OC difficult. Consequently, around 60% of OC is detected in an advanced stage (III or IV), when it has often already spread to other locations besides the ovary.[1,7] Radical surgery and chemotherapy are the mainstream treatments; however, around 70% of patients relapse within the first 3 years.[8] Despite the advances in treatments, the prognosis of OC remains poor, with a 5-year survival rate after diagnosis of 26% for stage III OC and 14% for stage IV disease.[9]

Portugal has one of the lowest incidence rates of OC among European countries, with 12 cases/100,000 inhabitants,[3] a statistic that may partially reflect underdiagnosis and could be potentially related to non-recognition of symptoms. According to one study, 84.2% of Portuguese women do not recognize the symptoms of OC, which could contribute to delayed diagnosis.[10] As a result, most OC cases are diagnosed in advanced stages, and 22% of patients proceed directly to best supportive care without receiving any therapeutic intervention.[10] This lack of awareness and absence of standardized emergency protocols prolongs the patient journey from symptom onset to referral. Identifying OC related symptoms remains an evidence gap, and ongoing research in Portugal is crucial to raise awareness among patients and healthcare professionals.

Understanding the trends in patient care and outcomes in real-world clinical practice has unquestionable value, allowing the identification of gaps that may be addressed,[11] but also the points of action that can contribute to improving patient and disease management.

The primary objective of this review was to assemble some real-world evidence (RWE) published on patients with OC in Portugal, including fallopian tube and primary peritoneal carcinoma, presented in various national and international meetings to evaluate the “state of the art” in OC in Portugal regarding testing of *BRCA*

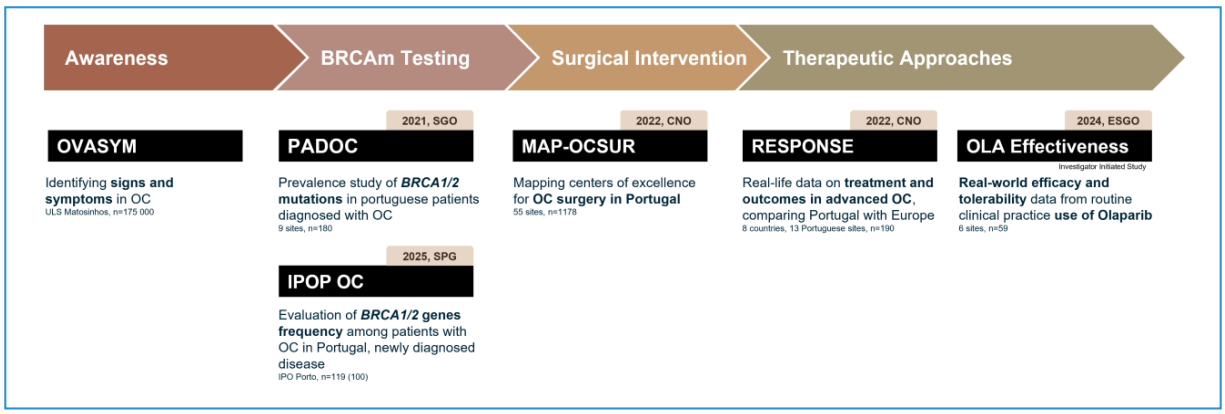


Figure 1. Real-world evidence regarding ovarian cancer in Portugal conducted by AstraZeneca Portugal between 2016 and 2025. CNO: National Congress of Oncology (Congresso Nacional de Oncologia); ESGO: European Society of Gynaecological Oncology; OC: ovarian cancer; SGO: Society of Gynecologic Oncology; SPG: Portuguese Society of Gynecology (Sociedade Portuguesa de Ginecologia), 2025.

mutations (*BRCAm*), surgery, and first and second line of therapy (Fig. 1).

BRCA1/2 mutation testing

Epithelial OC is associated with defective homologous recombination DNA repair in around half of the diagnosed cases, which include germline and/or somatic *BRCA1/2* mutations.[12] These mutations are associated with a family history of cancer and are a risk factor for developing OC.[12] In addition to *BRCA1/2*, other genes related to hereditary OC should also be considered in germline genetic testing, as they may provide valuable information for genetic counseling, even though targeted therapies are not currently available for all these gene mutations.[12] Maintenance therapy with a poly (adenosine diphosphate-ribose) polymerase inhibitor (PARPi) after platinum-based chemotherapy in patients with recurrent platinum-sensitive high-grade OC is a new standard of care option. The benefits of PARPi have been demonstrated in OC with homologous recombination deficiency (HRD), particularly in patients with a *BRCAm.*[12]

Considering the importance of *BRCA* status for genetic counseling and maintenance therapy with PARPi in advanced stages, all patients with high-grade OC should be tested for *BRCA1/2* mutations at diagnosis. Therefore, national and international guidelines recommend testing for both germline and somatic *BRCAm.*[12,13]

A significant percentage of patients are unaware of *BRCA*-related cancers in their family, and, before the PADOC and the IPOP OC studies, data on the prevalence of *BRCAm* in Portugal were scarce.[14] Given the value of *BRCAm* testing, these two studies were conducted in Portugal to determine the presence of *BRCAm* in patients with OC and further understand the prevalence of these mutations in the Portuguese OC population.

PADOC - Nationwide prevalence study of BRCA1/2 germline and somatic variants in patients diagnosed with non-mucinous OC in Portugal

The PADOC study[14] is an interventional, ambispective, multicenter study that included women aged 18 years or older diagnosed with non-mucinous epithelial OC, fallopian tube, or primary peritoneal carcinoma between January 01, 2014, and December 31, 2016. The study aimed to determine the prevalence of *BRCA1/2* variants (somatic and germline) in patients diagnosed with non-mucinous OC in several Portuguese hospitals nationwide to define the best strategy for screening germline/somatic variants in these genes in a routine diagnostic setting.

The study included 165 patients from 9 national reference centers for diagnosis and treatment of OC, with a median age at diagnosis of 58 years. Most patients (n = 124; 75.2%) were diagnosed with advanced disease, 93 had stage III (56.4%), and 31 had stage IV (18.8%). Formalin-fixed paraffin-embedded tumor tissue and a peripheral blood sample were available for 153; for the remaining 12 patients, only blood samples were available. Among the 153 tumors analyzed, 127 (83.0%) had pure serous histology, including 117 (76.5%) high-grade serous OC (HGSOC) and 9 (5.9%) low-grade serous OC. Non-serous histology was

observed in 26 tumors (17.0%), comprising 12 (7.8%) clear-cell carcinomas, 4 (2.6%) endometrioid carcinomas, and 10 (6.5%) other histologic subtypes.

Of the 153 samples screened for germline/somatic *BRCA1/2* variants, 32 (20.9%) patients harbored deleterious variants: 17 patients (54.5%) with a *BRCA*1 variant and 15 patients (45.5%) with a *BRCA2* variant. A total of 24 (15.7%) patients had germline variants (12 in the *BRCA1* gene and 12 in the *BRCA2* gene), and 8 (5.2%) presented mutations that were found to be somatic (5 in *BRCA1* and 3 in *BRCA2*). In addition, one *BRCA1* germline variant was detected in one of the 12 patients for whom only the blood sample was available. The most frequent germline deleterious variants were the *BRCA1* c.5266dup and the *BRCA2* c.3114dup, each representing 12% (3/25) of the germline pathogenic variants found in this series. The germline founder variant *BRCA2* c.156_157insAlu was only detected in one of the patients, representing 8.3% (1/12) of the *BRCA2* germline pathogenic variants found in this series. The two germline rearrangements, *BRCA2* c.156_157insAlu and *BRCA1* c. (80 + 1_81-1)_(134 + 1_135-1) del, identified in the respective blood samples, were not detected by the NGS tumor assay pipeline. Variants of unknown significance (VUS) were identified in seven (4.6%) of the 153 patients in which variant screening of the *BRCA1/2* genes was performed. Within this group, four (2.6%) patients had a germline VUS, and three (2%) patients had a somatic VUS.

A higher prevalence of pathogenic variants was observed among patients with HGSOC, namely 21 of 117 (17.9%) carried germline variants, and 29 of 117 (24.8%) carried either germline or somatic variants (16 in *BRCA1* and 13 in *BRCA2*). Among the 26 tumors with other histologies, three harbored a deleterious germline *BRCAm*: one occurred in a clear-cell carcinoma (1 of 12; 8.3%) and two in tumors classified as other histologies (2 of 10; 20%).

There was a statistically significant difference in age at diagnosis between the patients with somatic mutations (mean age of 68.1 years) and those with germline mutations (mean age of 54.6 years) ($p < 0.001$).

Regarding the family history of *BRCA*-related cancers for the total study population, 76.4% (n = 126) of the participants had no personal history of breast cancer. In the series of 153 patients, 32 reported having a family history of *BRCA*-related cancers, most of them in 1st relatives (n = 22; 68.8%). Within the germline and the somatic *BRCA1/2* mutated groups, 12 out of 24 (50%) and 2 out of 8 (25.0%) patients, respectively, reported having a family history of *BRCA*-related disease. However, the difference was not statistically significant.

In conclusion, the PADOC study showed a prevalence of 20.9% of *BRCA1/2* mutations in patients with OC in Portugal, with germline mutations accounting for 15.7% and somatic mutations for 5.2%. These results are consistent with the literature prevalence of *BRCAm* and highlight the importance of performing broad genetic testing, even without a family history of *BRCA*-related cancers, leading to the identification of more patients with a higher likelihood of benefiting from PARPi targeted therapy.[15]

IPOP OC - Evaluation of BRCA1/2 gene frequency among newly diagnosed patients with OC in Portugal: a single-center, retrospective cohort, database real-world study

A retrospective cohort, observational study was conducted on new patients diagnosed with non-mucinous epithelial OC, including carcinosarcomas, at a single comprehensive cancer center (IPO-Porto, Portugal), where *BRCA1/2* testing at diagnosis began to be implemented in clinical practice in 2017.[16]

This study included female patients aged 18 years or more with confirmed newly diagnosed non-mucinous epithelial OC who underwent surgery or biopsy at IPO-Porto between January 01, 2017, and December 31, 2019. Patients were required to have up to 5 years of data available until December 2022. This project aimed to evaluate the frequency of *BRCA1/2* mutations, either somatic or germline, in patients newly diagnosed with non-mucinous epithelial OC at a single comprehensive cancer center.

After a database search, 228 patients were identified, of which 119 were included in the study. The other 109 patients were excluded due to oncology disease-specific treatments before admission or outside IPO-Porto (n = 37), no medical appointments at IPO-Porto (n = 64), enrolled in a clinical trial (n = 2), and lost to follow-up (n = 6).

Genetic testing was performed in 100 patients, with 19 patients excluded, mainly due to a lack of conditions for systemic treatment (n = 7) and overall survival (OS) < 3 months (n = 9). *BRCA1/2* mutations were identified in 15 patients (15.0%), characterized as germline *BRCA1* (n = 4), somatic *BRCA1* (n = 5), germline *BRCA2* (n = 3), and somatic *BRCA2* (n = 3). Table 1 summarizes the patients' demographic and clinical characteristics overall and in *BRCA*-mutated patients.

There were no differences in the frequency of *BRCA1/2* mutations considering primary debulking

Table 1. Baseline demographic and clinical characteristics of the IPOP OC study population

Characteristics	*BRCAm*		Overall
	Negative	Positive	
	(n = 85)	(n = 15)	(n = 100)
Age at diagnosis			
Mean (SD)	62.0 (11.4)	59.2 (8.12)	61.6 (11.0)
Median (min, max)	63.0 (32.0, 81.0)	59.0 (46.0, 72.0)	62.0 (32.0, 81.0)
BMI at diagnosis			
Mean (SD)	26.7 (5.07)	27.6 (6.39)	26.8 (5.27)
Median (min, max)	26.3 (16.8, 40.1)	27.6 (18.3, 43.9)	26.3 (16.8, 43.9)
Missing	1 (1.2)	-	1 (1.0)
ECOG at diagnosis (%)			
0	46 (54.1)	9 (60.0)	55 (55.0)
1	22 (25.9)	4 (26.7)	26 (26.0)
2	14 (16.5)	1 (6.7)	15 (15.0)
3	3 (3.5)	1 (6.7)	4 (4.0)
Family history (breast or ovary/uterus) (%)			
No	53 (62.4)	9 (60.0)	62 (62.0)
Yes	27 (31.8)	6 (40.0)	33 (33.0)
Missing	5 (5.9)	-	5 (5.0)
Patient history (other cancer diseases) (%)			
No	72 (84.7)	12 (80.0)	84 (84.0)
Yes	13 (15.3)	3 (20.0)	16 (16.0)
Histology (%)			
Endometrioid	14 (16.5)	-	14 (14.0)
Other	14 (16.5)	1 (6.7)	15 (15.0)
Serous	57 (67.1)	14 (93.3)	71 (71.0)
Grade (%)			
Well-differentiated	11 (12.9)	-	11 (11.0)
Moderately differentiated	2 (2.4)	-	2 (2.0)
Poorly differentiated	58 (68.2)	12 (80.0)	70 (70.0)
Grade cannot be assessed	14 (16.5)	3 (20.0)	17 (17.0)
Tumor location (%)			
Ovary	61 (71.8)	8 (53.3)	69 (69.0)
Fallopian tube	23 (27.1)	7 (46.7)	30 (30.0)
Fallopian tube/ ovary/peritoneum	1 (1.2)	-	1 (1.0)
FIGO staging (%)			
I-II	24 (28.2)	3 (20.0)	27 (27.0)
III	41 (48.2)	6 (40.0)	47 (47.0)
IV	20 (23.5)	6 (40.0)	26 (26.0)

SD: standard deviation; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics.

surgery (PDS) (n = 6) or interval debulking surgery (IDS) (n = 6), and 20.0% of patients with *BRCA1/2* mutations were treated only with palliative chemotherapy.

The results of this study indicate a 15.0% prevalence of *BRCA1/2* mutations in patients with OC, with germline mutations accounting for 7.0% and somatic mutations for 8.0%. This prevalence is lower than reported in previous publications, such as the PADOC study.

Given that this is a single cancer-center study, and some patients were excluded because they received treatment prior to admission or outside IPO-Porto, there could be some bias in the patient selection that would justify the different prevalence of *BRCAm*. The lower prevalence of germline mutations observed in this study, compared to other publications, may be attributed to the close monitoring of familial risk and implemented genetic counseling appointments at IPO Porto, which facilitate prophylactic surgeries and monitor *BRCAm* carriers. Overall, this finding highlights the relevance of prevention strategies for OC.[17,18]

Surgical intervention

Despite the advances in treatments, OC still has a poor prognosis. Multiple studies have shown that optimal primary cytoreduction surgery (without residual disease) improves patient survival.[19-21] Surgery reduces tumor burden but also allows for the pathological diagnosis of the OC subtype and the establishment of appropriate systemic treatment based on tumor and patient characteristics.[22]

The surgical management of advanced OC is complex and is a major component of the multidisciplinary management of the disease. Assuring the quality of the surgery has a high impact on the survival of patients with advanced OC.

The European Society of Gynaecologic Oncology (ESGO) developed a list of quality indicators for advanced OC surgery to audit and improve clinical practice, including, among other criteria, a benchmark of at least 24 cytoreductive surgeries per center per year as a quality indicator.[23,24] Portugal is one of the few European countries without ESGO-certified centers, which may indicate a higher number of suboptimal surgeries performed. The need to evaluate the status of OC surgery in Portuguese centers led to the MAP-OCSur study, designed to map national surgery centers and characterize surgical quality and patient outcomes.[25]

MAP-OCSur – MAPping OC Surgery centers in Portugal

MAP-OCSur[25] is a retrospective study based on hospital records from the Unified Health System (SUS, *Sistema Único de Saúde*). Registries of hospital production from 55 hospitals were included according to the following criteria: International Classification of Diseases, Tenth Revision (ICD-10) OC diagnosis code in 2017 or 2018; OC surgical procedure in 2018; or surgical ICD-10 codes (excisions and resections of ovaries, uterus, fallopian tubes, and lymph nodes or excisions of the peritoneum). Additional surgical procedures were analyzed to characterize the surgeries (omentum, colon, small intestine, peritoneum, and other intra-abdominal organs). Hospitals were classified into six categories: oncological Centers, University Hospitals, regional Hospitals, medium Hospitals, small Hospitals, and very small Hospitals.

There were 1778 patients identified with an ICD-10 code of OC, fallopian tube, or peritoneum cancer diagnosis. Of these, 57% (n = 672) were 70 years or older at diagnosis. In 2018, 514 patients underwent surgical/biopsy procedures (70 biopsy only; 448 surgery and biopsy), and 59% (n = 303) of them underwent additional surgery procedures: 42% (n = 215) omentum, 25% (n = 128) colorectum, 24% (n = 121) peritoneum, 6% (n = 30) small intestine, and 6% (n = 33) other organs.

Around 50% of the patients had surgical treatment at Oncological Centers or University Hospitals. On average, Oncological Centers performed 37 surgical procedures, University Hospitals carried out 20 surgeries, and the other hospital categories performed 20 surgical procedures (Table 2).

Although ICD-10 is complex and missing data may introduce bias, this study represents the first attempt to map OC surgery in Portugal.

OC is an uncommon tumor usually diagnosed in the advanced stage. Surgical treatment is complex, time-consuming, and potentially associated with a high rate of complications; therefore, patients must be referred to specially dedicated hospitals. This study revealed that only the Oncological Centers performed more than 24 surgical procedures, one of the criteria of the ESGO certification. A national study must be carried out to define the number of centers needed for the surgical treatment of patients with advanced OC in Portugal.

Therapeutic approaches

The standard of care for OC consists of PDS followed by carboplatin plus paclitaxel, or neoadjuvant chemotherapy followed by IDS or palliative treatment when extensive surgery or complete tumor resection is not feasible. The maintenance therapies available for platinum-sensitive OC include bevacizumab and PARPi, such as niraparib, rucaparib, and olaparib.[26] These targeted therapies have become essential in OC treatment, demonstrating a significant improvement in patients' outcomes.[26]

Based on the phase III SOLO-2 trial[27] results, olaparib, a PARPi, was initially approved as maintenance therapy for platinum-sensitive relapsed OC in patients with BRCAm. Later, the substantial impact of olaparib on survival outcomes observed in the phase III SOLO-1 trial[13] led to extending the approval to frontline maintenance in *BRCAm* patients. Olaparib received European Medicines Agency (EMA) approval in December 2014. In Portugal, reimbursement began in September 2019 for platinum-sensitive relapsed OC maintenance in *BRCAm* patients and in January 2022 for first-line treatment in *BRCAm* patients. This delay impacted national implementation and contributed to an initial learning curve in managing treatment-related toxicities. The phase III PAOLA-1 trial led to the EMA approval of olaparib combined with bevacizumab as first-line maintenance for HRD-positive advanced OC in November 2020. However, this combination is not currently available for clinical use in Portugal, limiting patient access to this therapeutic option.

Two real-world studies were conducted in Portugal to characterize the treatment of advanced OC. One evaluated the standard of care and identified patients eligible for PARPi, whereas the other assessed the effectiveness and tolerability of olaparib in platinum-sensitive relapsed OC. The findings from these studies may help identify opportunities to improve clinical practice and optimize access to targeted therapies.

RESPONSE – Real-life data on treatment and outcomes in advanced OC: an observational, multinational cohort study

The main purpose of RESPONSE[28] was to describe the standard of care of patients with newly diagnosed advanced (stage III or IV) high-grade serous or endometrioid OC in eight countries (Austria, Belgium, Denmark, Finland, the Netherlands, Norway, Portugal, and Israel). Other objectives included determining the percentage of patients undergoing PDS with complete or optimal resection, characterizing the effects of *BRCA* status, estimating how many patients would be candidates for first-line PARPi maintenance treatment, and

Table 2. Number of ovarian cancer patients and surgical procedures in the different hospitals included in MAP-OCSur study

Hospital category	n hospitals	n hospitals with surgical procedures	n total surgeries	n procedures/hospital
IPO – oncology hospital	3	3	111	37
Central university hospitals	6	6	119	20
Regional hospitals	10	10	114	11
Medium hospitals	17	14	84	6
Small hospitals	12	8	20	3
Very small hospitals	5	0	0	0

evaluating the use of bevacizumab on patients' outcomes.

Each country retrospectively identified patients until a target of 120 was reached, with all patients followed for at least 20 months. 1119 women with high-grade serous or endometrioid OC between 2002 and 2018 were included. Most of the patients (97.5%) had high-grade serous carcinoma, and 66.9% of all patients had stage III disease. *BRCA* testing was available in 66% of the patients (739 of 1119), showing that 11.7% had a germline *BRCAm*, and 5.8% had a somatic *BRCAm*. Around a fourth of patients (26.6%) received bevacizumab simultaneously with first-line chemotherapy and as maintenance.

Regarding surgery, 41% of the patients underwent PDS, and 39.3% had IDS. Of those who had PDS, 55.5% had complete resection (no visual residual disease > 1 cm after surgery), and 15.1% had optimal resection (residual disease of ≤ 1 cm). Of the patients who underwent IDS, 63.9% had complete resection, and 20.9% had optimal resection.

The response to treatment, defined as the proportion of patients with a normal CA-125 level or > 90% decrease from the baseline CA-125 level, was achieved by 66.2% of patients, while, according to physician assessment, 78.9% had a response to treatment (53.2% had a complete response [CR] and 25.7% had a partial response [PR]). These results suggest that 78.9% of the patients would have been eligible for PARPi maintenance.

The disease status of the patients was followed up for at least 20 months. Six months after the completion of chemotherapy, 71.9% of the patients were disease-free, 26.2% had progressive disease, and 1.9% had died. After at least 20 months of follow-up, 32.9%, 46.4%, and 20.9% were disease-free, had progressive disease, or had died, respectively.

Bevacizumab significantly improved the OS of patients (hazard ratio [HR] 0.62; 95% confidence interval [CI] 0.42-0.91; p = 0.01), but not the progression-free survival (PFS). The presence of a *BRCAm* had a significant positive effect on PFS (HR 0.60; 95% CI 0.41-0.84; p < 0.01), whereas the effect on OS was uncertain.

Even though the results may not apply to other regions, this study offers valuable insight into the treatment landscape of OC in Europe.

RESPONSE – Portuguese cohort

In November 2022, a poster summarizing the Portuguese results compared to the global RESPONSE results was presented at the 19th *Congresso Nacional de Oncologia.*[10] Portugal included patients from 13 centers in Portugal, exceeding the target of 120 patients with a total of 190 participants. The majority of these patients were diagnosed between 2015 and 2018 (n = 140).

Similar to the overall RESPONSE population, approximately 68% of the Portuguese patients had stage III disease. The proportion of patients with a germline *BRCAm* was higher in Portugal than in the global cohort (20.0% vs. 11.7%) and exceeded rates reported in the PADOC and IPOP OC studies.

The median time from diagnosis to surgery was higher in the Portuguese population, with 2.5 months from diagnosis to PDS and 5 months from diagnosis to IDS, compared to 0.5 months and 3.5 months in the overall RESPONSE population, respectively.

In Portugal, 26% of patients had no surgery, 50% underwent PDS, and 22% received palliative chemotherapy (vs. 19%, 41%, and 10% globally). A complete

Table 3. Comparing clinical data from the global RESPONSE study versus data from the Portuguese cohort

Parameter	RESPONSE (n = 1119) (%)	Portugal (n = 190) (%)
High-grade serous tumor	97.5	96.8
Stage III	66.9	68.4
ECOG 0-1	69.6	72.6
Family history of ovarian/breast cancer	~5%/~22	~5%/~22
*gBRCA*1/2m	11.7	20
Surgery	80.1% (surgery); 19.9% (no surgery)	73.7 (surgery); 26.3 (no surgery)
PDS and IDS	40.8 (PDS); 39.3 (IDS)	50.7 (PDS); 49.3 (IDS)
Use of chemotherapy in 1st line	1L: ~38; Neo: ~50; palliative: ~10	1L: ~30; Neo: ~48; palliative: ~22
CA-125	60.60	~60

1L: first line; ECOG: Eastern Cooperative Oncology Group; gBRCA1/2m: BRCA1/2 germline mutation; IDS: interval debulking surgery; Neo: neoadjuvant; PDS: primary debulking surgery.

cytoreduction was achieved in 37% of patients who had PDS (vs. 55% globally), and 59% of the patients who underwent IDS (vs. 64%), whereas 11% of PDS (vs. 15%) and 14% of the IDS (vs. 21%) had residual disease of ≤ 1 cm. Table 3 identifies the clinical data from the Portuguese cohort versus the global study.

The histology, percentage of stage III disease, PDS, and CA-125 expression were comparable between the Portuguese patients and the overall RESPONSE population. However, the median time from diagnosis to surgery was longer in Portugal compared with the global cohort, both PDS and IDS. Furthermore, complete and optimal cytoreduction rates were lower in Portugal than in RESPONSE.

These findings indicate opportunities to reduce time to surgery and improve surgical outcomes in Portugal.

OLA effectiveness beyond trials: olaparib's real-world data in platinum-sensitive relapsed OC – a multicenter experience from Portugal

The study OLA effectiveness aimed to assess the effectiveness and tolerability of olaparib in real-world settings across multiple centers in Portugal, exploring the extent to which phase III trial outcomes are replicated in clinical practice.[29] The effectiveness and tolerability of olaparib were evaluated regardless of *BRCA* status, adding valuable RWE for local authorities and potentially informing future treatment guidelines.

This retrospective study included patients with platinum-sensitive relapsed OC, fallopian tube cancer, or primary peritoneal cancer who were treated with olaparib as maintenance therapy, irrespective of *BRCAm* status. Clinical data were collected at diagnosis and recurrence, before and after initiating olaparib treatment. The primary objectives were to evaluate olaparib's effectiveness by calculating median PFS and OS from the start of olaparib treatment to radiologically confirmed disease progression and death/last contact, respectively, and to evaluate tolerability (CTCAE v5.0).[30] Secondary objectives included assessing olaparib effectiveness according to *BRCAm* status and patient response to subsequent lines of chemotherapy after olaparib treatment. Patients were recruited from six Portuguese hospitals, with 59 patients meeting the inclusion criteria.

Table 4 shows the baseline characteristics and prior treatment patterns of patients included in the OLA effectiveness study. Of the 59 patients, 17 (29%) were aged ≥ 65 years, 33 (56%) had an Eastern Cooperative Oncology Group (ECOG) 0, and 24 (41%) had an ECOG 1. In total, 45 patients (76%) had *BRCAm*, subdivided as follows: 24 patients with *BRCA1*, 19 with *BRCA2*, and 2 with mutations in both *BRCA1* and *BRCA2*. Among those with *BRCAm*, 31 were germline, whereas 14 were somatic. The remaining 14 patients (24%) were *BRCA* wild-type (*BRCAwt*). At the time of diagnosis, 97% had HGSOC, predominantly with stage III (70%) and stage IV (22%).

Regarding prior treatments, 54% of patients received two prior lines of platinum-based chemotherapy, whereas 46% received more than two. The response to the most recent line of platinum chemotherapy included 21 patients (36%) achieving a CR and 38 patients (64%)

Table 4. Patient characteristics and prior therapies (n = 59) in the OLA effectiveness study

Patient characteristics	n (%)
Age	
< 65 years	42 (71)
≥ 65 years	17 (29)
ECOG at baseline	
0	33 (56)
1	24 (41)
2	2 (3)
Surgery in first line treatment	
Surgery performed - yes	56 (95)
Upfront surgery	32 (54)
Interval surgery	24 (41)
R0	34 (61)
High-grade serous ovarian cancer	
Yes	57 (97)
No	2 (3)
FIGO stage at diagnosis	
I	2 (3)
II	3 (5)
III	41 (70)
IV	13 (22)
Time to recurrence after penultimate platinum-based regimen (platinum sensitivity)	
6-12 months	22 (37)
> 12 months	37 (63)
Surgery for the current relapse	
Yes	15 (25)
No	44 (75)
Number of prior platinum-based therapies	
2	32 (54)
> 2	27 (46)
Response to the most recent platinum-based therapy	
CR	21 (36)
PR	38 (64)
Prior bevacizumab	
Yes	20 (34)
No	39 (66)
BRCA mutation status	
BRCAm	45 (76)
BRCA1/BRCA2/BRCA1+2	24/19/2
Germline/Somatic	31/14
BRCAwt	14 (24)

ECOG: Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; PR: partial response; CR: complete response; *BRCAwt:* BRCA wild-type; *BRCAm: BRCA* mutated.

achieving a PR. Concerning platinum sensitivity, 63% of patients had a platinum-free interval of more than 12 months, whereas 37% had a platinum-free interval of 6-12 months. Surgery was performed in 95% of patients during their first-line treatment, with upfront surgery conducted in 54% of the patients and interval surgery in 41%, achieving R0 resection in 61% of the cases.

The median duration of olaparib treatment was 8 months (range, 2-65). Treatment was discontinued in 45 patients (75%), mainly due to disease progression (42 patients), whereas 14 patients (24%) remained on the therapy at study end. Notably, 4 patients (7%) received olaparib for 5 years or longer. Median PFS was 12 months (95% CI 8.4-15.6), with better outcomes in patients with *BRCAm* than in those with *BRCAwt* (13 vs. 4 months; log-rank p = 0.007). Median OS was 28 months (95% CI, 21.2-34.7), longer in *BRCAm* than *BRCAwt* patients (30 vs. 22 months), though the difference was not statistically significant (log-rank p = 0.266).

Upon disease progression, 39 of the 42 patients who experienced progression received a subsequent line of chemotherapy, with a median of 2 lines per patient (range, 1-4 lines). Of these, 62% received platinum-based chemotherapy, and 15% also received bevacizumab. The median PFS of subsequent chemotherapy was 5 months (95% CI 3.8-6.2), with similar values regardless of whether patients received platinum-based or non-platinum-based regimens (5 vs. 4 months, respectively; log-rank p = 0.426).

Treatment-related toxicities of any grade occurred in 41 patients (69%), leading to dose reductions in 27 patients (46%) and permanent treatment discontinuation in 3 patients (5%) due to severe adverse events, including anemia, acute myeloid leukemia, and acute renal failure. Grade ≥ 3 toxicities were reported in 13 patients (22%). Adverse events included anemia in 42% of patients (grade ≥ 3 anemia in 12%), nausea in 19%, asthenia in 12% (with 2% grade ≥ 3), thrombocytopenia in 3% (all grade ≥ 3), and neutropenia in 3% (all grade ≥ 3). Additional adverse events were vomiting in 5%, leucopenia in 2%, lymphopenia in 2% (grade 3), rash in 2%, and single cases of acute renal failure and acute myeloid leukemia.

This is the first multicenter study in Portugal to demonstrate the effectiveness and safety of olaparib in a real-world platinum-sensitive relapsed OC population. The findings indicate that olaparib is effective as a maintenance therapy in *BRCAm* platinum-sensitive relapsed OC patients and can also benefit selected

BRCAwt patients. Despite a higher-than-expected rate of dose reductions (46%), the low rate of permanent discontinuations reflects a manageable safety profile with appropriate monitoring, supporting olaparib's feasibility in clinical practice. The significant benefits observed in *BRCA*m patients align with phase III trial data, although it highlights challenges in toxicity management in real-world settings.

These results emphasize the need for continued research, clinician training in toxicity management, and faster and more comprehensive access to innovative therapies. This study provides valuable RWE by documenting treatment patterns, clinical responses, and associated challenges that can inform local treatment guidelines and healthcare policy. Olaparib's RWE reaffirms its role as an effective maintenance therapy option in platinum-sensitive relapsed OC patients.

Conclusion

RWE studies offer vital insights into healthcare by providing comprehensive data on patients and disease characterization, and helping healthcare professionals to understand the journey from diagnosis to treatment. Furthermore, assessing diagnosis methods and treatment effectiveness in real-world settings could offer practical outcomes that complement clinical trial data. Overall, RWE studies play a crucial role in enhancing personalized patient care, optimizing treatment strategies, improving healthcare systems, and can contribute to health policy changes.

The RWE gathered and presented in this manuscript emphasizes several insights and gaps from the Portuguese OC patient journey that need to be addressed. One important finding is that the prevalence of *BRCA* pathogenic variants in OC in Portugal aligns with what is described in the literature; however, there appears to be a disparity in germline mutations, highlighting the need for genetic testing in all patients. The MAP-OCSur study revealed that in Portugal, only the Oncological Centers meet one of the quality indicators of the ESGO certification. Furthermore, the RESPONSE trial results point out the importance of shortening the time from diagnosis to surgery and improving OC surgery outcomes in Portugal, given its great importance in the prognosis of the disease. These key highlights may trigger a broader discussion on the establishment of specialized reference centers for OC surgery in Portugal, which is crucial for enhancing surgical care and patient outcomes. Regarding targeted therapies, which can improve long-term disease control, the OLA effectiveness study shows olaparib's similar clinical results, but higher dose-reduction rates than reported in clinical trials, suggesting a need for better management of the PARPi toxicity that enables clinical benefit without compromising the quality of life.

Although these results do not represent all the Portuguese OC patients, nor all the hospitals that treat OC, the studies presented in this review offer a comprehensive evaluation of the disease in Portugal. Additional studies could be implemented to improve knowledge that encompasses all the pathways of OC patients, including disease symptoms, time to diagnosis and treatment, and palliative care characterization. When interpreting these results, the retrospective design of the studies should be considered, which can be associated with certain biases, such as patient identification issues and missing data.

Nevertheless, RWE represents an important tool in the generation of evidence, allowing for a comprehensive assessment of therapeutic effectiveness in real-world clinical practice and characterizing the patient journey and clinical outcomes. This review summarizes five studies that characterize the standard of care for OC on diagnosis and treatment, identify gaps and unmet needs, and, ideally, provide valuable insights into patient pathways, with the aim of improving care and prognosis for this disease in Portugal.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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PERSPECTIVES

Current perspectives on endometrial cancer in Portugal: prevention, diagnosis, clinical management, challenges and opportunities

Perspetivas atuais sobre o cancro do endométrio em Portugal: prevenção, diagnóstico, gestão clínica, desafios e oportunidades

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Abstract

Endometrial cancer (EC) is one of the most common gynecological malignancies, with a rising global incidence driven by increasing obesity rates and aging populations. This growing burden highlights the need for enhanced prevention strategies, early detection, and equitable access to innovative treatments. This paper presents an expert-driven perspective on the current state of EC care in Portugal, addressing epidemiology, risk factors, diagnostic pathways, therapeutic innovations, and health policy challenges. Based on expert panel discussions and a structured questionnaire, key barriers were identified, including diagnostic delays, limited integration of molecular profiling, and unequal access to emerging therapies such as immunotherapy. Despite high adherence to National and European clinical guidelines, disparities in treatment access persist due to regulatory and financial constraints. Public health strategies targeting risk reduction, timely and enhanced diagnostic pathways, and expansion of treatment availability are needed. Experts emphasized the critical need for hospitals to adopt molecular classification, given its key role in guiding decisions on adjuvant treatment. In addition, the limited availability of certain emerging tests was noted as a challenge to the broader adoption of precision oncology. By bridging gaps in prevention, diagnosis, and treatment, this paper aims to support healthcare professionals, researchers, and policymakers in optimizing EC care and improving patient outcomes in Portugal.

Keywords: *Endometrial cancer. Diagnosis. Treatment. Immunotherapy. Molecular profiling. Portugal. Public health. Personalized medicine.*

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Introduction

Endometrial cancer (EC) was the second most common gynecological cancer in Portugal, with an age-standardized incidence of 8.9/100.000 and a mortality of 3 deaths/100.000 in 2022.[1,2] The global increase in EC of over 130% in three decades is mirrored at the national level and is primarily driven by aging, obesity, and metabolic disorders.[3-6]

EC typically affects postmenopausal women, with peak incidence occurring between the ages of 65 and 75. It is often diagnosed at an early stage, leading to a favorable prognosis, with a 5-year survival rate exceeding 95%. However, up to 20% of endometrioid and 50% of non-endometrioid carcinomas ultimately experience recurrence.[7] High-grade and serous subtypes are associated with a poorer prognosis, often presenting with aggressive behavior and a higher risk of recurrence.[8-11]

Surgery remains the first-line treatment for early-stage EC. For advanced or recurrent cases, systemic chemotherapy, usually involving carboplatin and a taxane, has traditionally been the standard of care.[12] Management of advanced and recurrent EC is still a challenge, and several questions remain unanswered.[7]

In recent years, significant advances have been made in the diagnostic and therapeutic armamentarium for EC,[7] including immunotherapy and targeted treatments guided by molecular profiling, which are increasingly integrated into clinical practice. In particular, the incorporation of molecular markers such as microsatellite instability (MSI), mismatch repair deficiency (dMMR), POLE mutations, and p53 expression into risk stratification has enabled more personalized treatment decisions, improving the precision of therapeutic approaches. Molecular profiling also plays a key role in guiding adjuvant treatment decisions, with significant implications for both survival outcomes and treatment-related toxicity.

Several guidelines for the management of EC, including the European Society of Gynaecological Oncology (ESGO)/European Society for Radiotherapy and Oncology (ESTRO)/European Society of Pathology/(ESP), the European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN), have been developed and are constantly updated.[8,10,13] In Portugal, the Portuguese Society of Gynecology has a national consensus for the clinical approach to gynecological cancers,[14] Despite this, full adherence to recommendations is not always feasible across different resource settings and geographies, resulting in variability in clinical practice and care delivery.[11,15-17]

Portugal has kept pace with international advances in the treatment of EC, providing patients with access to new therapies and surgical techniques.[18] The most recent Portuguese Gynecologic Oncology Consensus, which includes recommendations for EC, was published in 2020 by experts from national medical societies. An update is anticipated following the publication of the latest 2025 ESGO/ESTRO/ESP guidelines. However, despite these advances, there is still a lack of information on the current state of EC treatment in Portugal, particularly regarding access to innovative therapies, success rates, and the implementation of international guidelines. This makes it difficult to accurately assess the country's progress compared to other healthcare systems.

Through an expert panel, we aimed to provide a comprehensive overview of the current EC landscape in Portugal, focusing on prevention, diagnosis, clinical management, and access to innovative therapies within the healthcare system. This collaborative effort also aimed to emphasize key challenges and opportunities for healthcare professionals, researchers, and policymakers to implement effective strategies and improve patient outcomes.

Methodology

Expert panel

To gain in-depth insights into the EC landscape in Portugal, a panel of medical experts was organized by the Institute for Evidence-Based Health. This panel comprised six esteemed specialists in medical oncology selected by their extensive clinical and research experience in the management of EC, from Portuguese reference centers located in Lisbon, Coimbra, and Porto.

A first online expert meeting was held in September 2024 to gather expert opinions on the most relevant topics related to EC, including epidemiology trends, risk factors, prevention, screening, diagnosis, patient management, treatment, innovation, access, health policies, and myths. Following this, each expert independently and anonymously completed an electronic survey with 80 questions covering these topics during November 2024. The responses were analyzed and summarized. A second meeting was held in December 2024 to present the main results obtained from the survey and

obtain further information, promoting discussions between experts on less consensual topics.

Ethical considerations

Before the expert panel, all participants were informed of its nature and purpose. Ethical considerations were upheld throughout the entire process, ensuring that participants' contributions were voluntary.

Results

Epidemiology

The expert panel reached a consensus that EC incidence is rising in Portugal, primarily due to increasingly unhealthy lifestyles, including sedentary behavior and poor dietary habits, which contribute to obesity. An aging population was also identified as a driver, as EC primarily affects postmenopausal women. Although mortality is also perceived to be increasing, this trend is largely explained by the increasing number of diagnoses, which results in a greater absolute number of deaths. Despite this, survival rates have improved due to advancements in treatment, allowing a greater proportion of patients to live longer.

Risk factors

Regarding EC risk factors, specialists consistently identified metabolic factors, particularly obesity, as paramount. Excess adipose tissue elevates estrogen levels unopposed by progesterone, stimulating endometrial proliferation and increasing malignancy risk. They also noted that lower educational attainment and income levels are linked to a higher risk of obesity, further exacerbating this risk. Other risk factors include hormonal and reproductive factors such as early menarche, late menopause, nulliparity, delayed childbirth, and hormone replacement therapy with unopposed estrogen, as well as genetic predispositions, including Lynch syndrome, Cowden syndrome, and mutations in PTEN and p53.

Some experts noted that EC is increasingly being diagnosed in younger women, in line with global trends, likely reflecting earlier onset of obesity and metabolic syndrome, as well as changes in reproductive patterns. This trend raises concerns, as younger cases may be more likely to involve aggressive histological subtypes, such as serous and clear cell carcinomas, which are associated with poorer prognoses. In addition, concerns were raised regarding the potential role of endocrine-disrupting chemicals, including bisphenol A, phthalates, and pesticides, which may mimic estrogenic activity. However, experts expressed differing views on the strength of the current evidence, emphasizing the need for further research in this area.

Other ongoing shifts in patient profile include increasing multimorbidity, a growing number of cases with prior breast cancer (often with tamoxifen exposure), and a higher number of patients presenting with advanced disease.

Looking ahead, specialists anticipate that EC incidence will keep rising, mainly due to obesity and population aging. Some expect an increase in early-stage diagnoses due to improved awareness and timelier diagnostic pathways.

Prevention

Overall, the panel observed that Portugal lacks public health campaigns specifically targeting EC risk factors, despite existing initiatives for other cancers and cardiovascular diseases that address some shared risks. In addition, there is uncertainty regarding their effectiveness, as these campaigns are often not sufficiently engaging, and their impact remains largely unmeasured. In their opinion, effective campaigns need to be transversal across all social media platforms, appealing, well-structured, and interactive, with support from associations of patients, healthcare professionals, health institutions, and medical influencers. Furthermore, campaigns should be implemented at schools and should be continuous over time rather than sporadic.

Screening

There was a consensus that routine screening for EC is not recommended for the general population, reflecting the absence of a cost-effective test for asymptomatic women.[8,13,19] Screening should be targeted at high-risk individuals, particularly those with a family history of Lynch syndrome (the highest-risk group) or a previous diagnosis of Lynch-associated colorectal cancer. In hereditary syndromes, prophylactic surgery may be recommended to significantly lower the risk of developing EC. Nevertheless, some experts identify a gap in the systematic referral of these patients to genetic counseling. Addressing this gap could enhance early detection and prevention strategies for these high-risk populations.

Experts stressed the importance of vigilant assessment of postmenopausal bleeding, as it is a common early symptom of EC. Public awareness campaigns have been shown to enhance knowledge of symptoms and risk factors, leading to increased medical consultations and potentially earlier diagnoses. For optimal impact, these campaigns should be meticulously designed and culturally tailored, forming a multifaceted strategy that includes public education, guaranteed access to healthcare services (including imaging and biopsy when indicated), evidence-based screening, and active engagement of healthcare providers.[20-22]

Diagnosis

Limited awareness of postmenopausal bleeding as a warning sign and unequal access to healthcare, particularly in certain regions, were highlighted as barriers to early diagnosis. Several experts stressed that lower socioeconomic status increases the risk of late-stage diagnosis due to lower health literacy and reduced healthcare access.

According to experts, the Portuguese National Gynecology Cancer Consensus, along with ESGO, ESMO, and NCCN guidelines, are followed in the diagnosis of more than 90% of the cases.

Although gynecology is typically the first specialty to diagnose EC, patients' pathway often begins in the emergency room due to abnormal uterine bleeding, rather than through primary care. Time from the onset of initial symptoms to EC diagnosis may range between 1 and 4 months.

In advanced disease, experts point out that computed tomography or positron emission tomography scans are used to evaluate potential metastases. However, delays in scheduling imaging and receiving pathology results are frequently cited as bottlenecks in the diagnosis. These waiting periods, combined with the limited capacity of some primary care settings, contribute to the overall time gap between first suspicion and EC diagnosis.

Experts expressed being satisfied with the diagnostic quality, but highlighted the need for more timely access to diagnostic exams. A key suggestion is to develop "fast-track pathways" with enforced maximum waiting times and to centralize care in reference centers. Experts also underscore the uneven distribution of diagnostic tools between urban and rural areas, noting resource constraints that can delay hysteroscopic biopsy and imaging.

To improve outcomes, they stressed that raising public health literacy and encouraging earlier evaluation of postmenopausal bleeding are essential measures. Although transvaginal ultrasound, hysteroscopy, and endometrial biopsy remain standard, additional molecular profiling is a point of debate. Some clinicians support universal testing to guide personalized therapy, while others question its immediate benefits and feasibility.

Current treatment and access to medication

Clinical practice in Portugal closely follows national and European recommendations and also integrates the American NCCN guidelines. At the time of the panel, some experts noted that current protocols fall short in certain scenarios, specifically (a) when standard therapies have been exhausted or (b) in the management of advanced disease, including decisions around neoadjuvant systemic therapy, the integration of immunotherapy, and the use of locoregional treatments based on individual response.

In Portugal, the interval from diagnosis to treatment may span between 1 and 4 months, influenced by molecular testing, histopathology, accurate imaging staging, and operating room availability. Experts mentioned that 80-90% of cases undergo proper surgical staging and all are managed by multidisciplinary teams. The panel agreed that surgery is the first-line treatment for early-stage EC, with minimally invasive techniques such as laparoscopy, use of sentinel lymph node staging, or robotic surgery becoming more prevalent. Experts noted some variability in treatment approaches for advanced or recurrent EC. All practitioners adhere to consensus guidelines for chemotherapy and/or radiotherapy, and advocate for a broader therapeutic approach in selected cases, including the use of chemo-immunotherapy or target therapies.

Advanced or metastatic disease typically involves two or three therapy lines, with several experts observing increases in palliative hormonal therapy, chemo-immunotherapy combinations, or targeted agents such as anti-human epidermal growth factor receptor 2 (HER2). According to expert opinion, around 90% of patients with locally advanced disease and 10% with metastatic disease undergo locoregional therapy with curative intent. Approximately 20-30% of patients with advanced disease are eligible for targeted therapies upon confirmation of molecular alterations. However, many may remain untreated due to barriers such as reimbursement challenges, logistical constraints, and

socioeconomic factors. Financial and administrative hurdles hindered access to novel treatments, with some experts noting that Hospital Pharmacy and Therapeutics Committees could be overly restrictive, demanding that patients match trial inclusion criteria exactly to access new therapies.

Some experts highlighted that distributing clinical trials more evenly across Portugal would reduce geographic disparities and speed patient enrolment in novel therapeutic options. The German model was referred to, where European Medicines Agency (EMA)-approved drugs were used. At the same time, reimbursement was finalized, while several underscored the uneven distribution of clinical research across the country. Despite the limited use of targeted therapies, significant benefits have been observed in terms of quality of life and overall survival. This gap between scientific evidence and access in real-life underscores the need for policy-level interventions to make these life-prolonging treatments more widely available.

The management of recurrent disease poses additional challenges, including the need to rely solely on chemotherapy in patients with microsatellite instability-high (MSI-H)/dMMR disease, despite strong evidence that this subgroup derives greater benefit from immunotherapy; limited access to clinical trials; and insufficient scientific evidence to guide treatment decisions after exhaustion of standard therapeutic options. Additional challenges include low health literacy regarding palliative care, difficulties in care coordination, and barriers to the early integration of palliative care following recurrence diagnosis. Experts also noted structural constraints, particularly limited consultation time, which hampers adequate support for patients and their caregivers.

From their experience, there is a growing trend in patients using complementary or alternative therapies.

Most experts confirmed some disparities in drug access across Portuguese centers, particularly for immunotherapy, due to heterogeneity in the treatment eligibility decisions by Ethics Committees or Hospital Pharmacy and Therapeutics Committees, prolonged national approval procedures, and fragmentation within the healthcare system, leading to inconsistent care pathways. Experts recommended centralized decision committees or expedited approval pathways to align with EMA decisions and broaden patient access more equitably.

Experts identified a lack of sharing best practices among healthcare centers treating EC patients.

Development and innovation

Regarding biomarkers, experts identified the most promising advances in the EC as the integration of molecular classification into clinical practice, including the assessment of POLE mutations, p53 status, and MMR/MSI deficiency in guiding adjuvant treatment decisions, allowing treatment de-intensification in patients with POLE-mutated tumors, which are associated with an excellent prognosis, while guiding more aggressive strategies in p53-aberrant tumors linked to poorer outcomes. The identification of dMMR/MSI-H also has significant predictive value, enabling the selection of patients most likely to benefit from immunotherapy. Additional biomarkers, such as HER2 overexpression in serous or high-grade carcinomas, alterations in the PI3K/AKT/mTOR pathway (e.g., PTEN and PIK3CA), and hormone receptor expression, further support a more targeted approach, particularly in advanced or recurrent disease. In parallel, the development of integrated genomic and molecular profiles has refined risk assessment, helping to avoid overtreatment in patients with favorable prognostic features while supporting closer surveillance and more intensive treatment in higher-risk subgroups. Finally, experts mentioned that minimally invasive biomarkers, including circulating microRNAs (blood), circulating tumor DNA, and biomarkers in urine samples, represent significant emerging tools, although they remain largely under investigation.

Another potential advancement in biomarker research is the ongoing investigation into homologous recombination deficiency (HRD) in EC, which aims to determine its prevalence, predictive value, and utility as a biomarker to guide treatment strategies.

Regarding advances in personalized medicine, experts mentioned (a) immunotherapy as a major step forward for advanced, metastatic, or recurrent disease, as it has shown significant improvements in progression-free survival, (b) the use of next-generation sequencing test, for heavily pretreated patients with no remaining therapeutic options, to identify genomic alterations predictive of treatment response (it is important to ensure access through referral to clinical trials or off-label treatment administration), (c) the use of clinical data combined with genomic data to predict treatment responses and patient outcomes, (d) the use of drugs targeting specific molecular pathways, such as PI3K inhibitors for treating specific subtypes of EC, (e) the use of immunotherapy with chemotherapy, and (f) the

identification of patients with HRD and HER2 in therapeutic decisions.

Notably, only one of the six represented centers is currently participating in clinical trials related to gynecological cancers. However, experts agreed that broader enrollment would be key to driving further innovation.

Health policies and health literacy

There was a consensus that significant policy reforms are essential to enhance prevention, early detection, treatment, and outcomes in Portugal. Experts believe that public health campaigns addressing both EC and its risk factors, such as obesity, are vital. They also emphasized the importance of supporting expert groups to develop and issue recommendations. Earlier access to innovative treatments and a strengthened network of centers for diagnosis and care should also be prioritized. Some experts emphasized that complex or high-risk cases should be managed in specialized centers by gynecologic oncology teams, citing evidence that high-volume centers achieved better outcomes. However, others argued that with proper training and networking, regional hospitals could provide adequate care without overburdening tertiary centers. In their opinion, treatment decisions should be made by multidisciplinary teams at highly experienced centers.

They also recognized the need to balance the cost-benefit of innovative treatments and genetic testing in a context of limited resources, and they stated that prevention should remain a priority to reduce the number of patients requiring advanced therapies. They discussed the value of evaluating the entire patient journey, including the avoidance of unnecessary adjuvant therapies, and the potential long-term savings from referring families for genetic consultation when syndromes such as Lynch were identified. They added that any new approach for cost-effectiveness should include evidence-based prioritization, price negotiation, continuous monitoring of treatments, and equitable access without discrimination between public institutions.

Experts emphasized the crucial need to enhance awareness and health literacy about this disease, as misconceptions persist, particularly regarding postmenopausal bleeding, which is often mistakenly dismissed as benign. This unawareness and the mistaken belief that EC only affects women after menopause delay diagnosis and compromise clinical outcomes.

They also acknowledged other myths, such as the assumption that removing the uterus would eliminate the need for further treatment or that endometriosis automatically constituted a direct risk factor for EC, and reiterated that these misunderstandings underscored the ongoing need for education, prevention, and research to support both patients and healthcare professionals alike.

Discussion

According to the Global Cancer Observatory, Portugal registered around 1400 new EC cases and 440 related deaths in 2022. Recent data confirmed the consistent rise in EC incidence worldwide, and Portugal is expected to follow this global trend. An aging population and escalating obesity rate appear to be drivers. Despite relatively high early-stage survival rates, advanced or recurrent cases still pose therapeutic challenges, especially given limited access to novel therapies.

By collecting the feedback and clinical experience of experts in EC, this panel allowed for a better understanding of the current EC landscape, challenges, and opportunities in Portugal. This panel is representative of the main centers treating EC in Portugal, acknowledging that while most cases are managed in these centers, peripheral units also provide treatment, albeit at lower volumes. It is foreseen that centers here represented treat at least 50% of the patients with EC in more advanced stages, which are treated by specialists in Portugal.

The Portuguese context reveals persistent challenges in early diagnosis, optimal disease management, and access to innovative treatments.

One of the key challenges is delayed diagnosis, with a typical interval of 1-4 months between symptom onset and histological confirmation. This gap is consistent with findings from other European countries contributing to poorer prognosis. Experiences from other countries show that public awareness campaigns and fast-track referral pathways can reduce the diagnostic interval.[22] National strategies, including dedicated patient education and referral guidelines, could reduce the rate of late-stage disease and mortality. Furthermore, liquid biopsies may represent a promising minimally invasive tool for earlier detection in the future.

Public health interventions targeting obesity and sedentary lifestyles could have a major impact on primary prevention, given that an estimated 60% of EC cases in Europe are linked to overweight and obesity.[5] Evidence suggests that weight loss interventions and hormonal contraceptives can significantly reduce EC risk.[23,24] As with other gynecological cancers, an

effective approach should integrate education, widespread lifestyle modification programs, accessible screening for high-risk groups, and structured referral protocols. Currently, there is no comprehensive national strategy for EC in Portugal, unlike those in place for breast or cervical cancers, underscoring the urgent need for a dedicated plan to strengthen prevention, early detection, and equitable access to treatments.

According to the panel, approximately 80-90% of EC cases undergo appropriate surgical staging, and all EC patients are managed within multidisciplinary teams. While this reflects good adherence to recommended standards of care, ensuring consistent and comprehensive staging remains essential given its prognostic and therapeutic implications. Treatment pathways in Portugal largely follow European and national guidelines, complemented by the NCCN recommendations. Nevertheless, challenges arise in the management of advanced-stage disease and molecular subtypes with limited targeted therapies. In locally advanced disease, the high reliance on locoregional therapies, with curative intent in around 90% of patients, contrasts with the limited use of targeted therapies in metastatic settings. Research indicates that biomarkers such as POLE, MSI, and MMR status can refine prognosis and guide adjuvant therapy decisions,[8,10] suggesting that biomarker-driven treatment strategies should be fully integrated into routine clinical practice.

The introduction of immunotherapy has shown significant efficacy in clinical trials and is becoming the standard of care. In Portugal, immunotherapy is currently used; however, its access remains a challenge. In October 2024, the Portuguese National Authority of Medicines and Health Products authorized the use of dostarlimab in the treatment of patients with recurrent or advanced EC exhibiting dMMR, who have progressed following prior platinum-containing chemotherapy. There are currently three early access programs ongoing in Portugal for advanced or recurrent EC, including dostarlimab, pembrolizumab, and durvalumab. However, access to innovation in Portugal often lags due to slower drug approval processes and potential funding constraints, which delay timely patient access to these therapies.

Overall, while Portugal adheres to evidence-based practices in EC management, there remains a pressing need to reduce diagnostic delays, expand access to innovative treatments, and raise public awareness of EC risk factors. Integrating molecular profiling into standard care and ensuring equitable access to novel therapies should be prioritized to optimize patients' outcomes.

Table 1 summarizes the strengths of EC healthcare in Portugal, and table 2 describes challenges and opportunities in this area.

Implementing effective measures fast will help Portugal stay aligned with evolving international standards and more effectively address the needs of patients with EC.

Therefore, several recommendations can significantly reduce the future EC burden, including:

- Early detection and diagnosis
  - Implement targeted screening strategies for high-risk individuals, particularly those with Lynch syndrome
  - Analyze molecular profiles to identify genetic predispositions to hereditary syndromes, thereby enabling the detection of at-risk family members and guiding the implementation of prophylactic surgeries to reduce the risk of EC development
  - Reduce diagnostic delays by streamlining referral pathways from primary to specialized care.
- Treatment and therapeutic innovation
  - Increase access to molecular profiling to support personalized treatment decisions
  - Expand the availability of immunotherapy and targeted treatments through centralized drug approval pathways
  - Enhance multidisciplinary collaboration to standardize treatment across healthcare centers.
- Public health interventions
  - Develop and implement national awareness campaigns on EC risk factors and early symptoms
  - Promote lifestyle interventions aimed at obesity reduction and metabolic health improvement
  - Encourage gynecological health literacy to improve early medical consultations for abnormal uterine bleeding.
- Healthcare policy and system improvements
  - Establish reference centers for EC treatment to ensure standardized, high-quality care
  - Advocate for fast-track approval processes for innovative treatments
  - Strengthen research investment in EC to improve evidence-based guidelines implementation and optimal treatment.

Table 1. Strengths of EC healthcare in Portugal

Area	Strengths
Diagnosis and disease management	High adherence to national and European guidelines: implementation in 90-100% of patients.
	Use of imaging for staging: CT or PET scans are used to evaluate potential metastases in advanced disease.
	Effective multidisciplinary approach: 80-90% undergo proper surgical staging, and 100% are managed by multidisciplinary teams.
Treatment	Advanced surgical techniques: minimally invasive techniques such as laparoscopy surgery are widely used.
	Consensus guidelines are widely followed.
	High curative intent for locally advanced disease: 90% of patients with locally advanced disease receive locoregional therapy with curative intent.
Technological strengths	Integration of molecular profiling: molecular classification (POLE, p53, MMR) in guiding personalized therapy.
	Immunotherapy as a major advancement: immunotherapy has significantly improved progression-free survival in advanced cases.

MMR: mismatch repair, CT: computed tomography; PET: positron emission tomography; EC: endometrial cancer.

Table 2. Challenges and opportunities for EC healthcare in Portugal

Area	Challenges
Epidemiology and preventions	Rising EC incidence due to lifestyle and aging: incidence of EC is increasing in Portugal due to widespread obesity, metabolic syndrome, and changes in reproductive patterns. In addition, an aging population contributes to a higher burden of disease.
	Increasing mortality due to late-stage diagnosis: late-stage diagnosis remains a major issue, driven by a lack of awareness regarding early symptoms, particularly postmenopausal bleeding, and unequal access to healthcare. Socioeconomic disparities further exacerbate this problem.
	Increasing incidence in younger women: there is a growing trend of EC diagnoses in younger women, which is likely linked to the earlier onset of obesity and metabolic syndrome. This shift is concerning because younger patients often present with more aggressive disease subtypes.
	Endocrine-disrupting chemicals EDCs as a potential risk factor: the potential role of EDCs (such as BPA and phthalates) in increasing EC risk remains uncertain, highlighting the need for further research to understand their impact.
	Socioeconomic disparities in EC prevention: lower education and income levels reduce access to preventive care and early diagnosis, increasing the likelihood of late-stage presentation and poorer outcomes.
	Lack of public health campaigns: few public health initiatives specifically target EC risk factors, resulting in a missed opportunity to raise awareness and encourage preventive behaviors.
	Lack of systematic referral for genetic counseling: there is an absence of systematic referrals for genetic counseling, particularly for hereditary cancer syndromes such as Lynch syndrome, which could improve prophylactic and preventive care.
Diagnosis	Diagnostic delays: long waiting times for imaging and pathology results cause significant delays in EC diagnosis, prolonging the time from first suspicion to histological confirmation.
	Uneven access to diagnostic tools. Healthcare resource disparities between urban and rural areas result in unequal access to essential diagnostic procedures, causing delays in biopsy and imaging.
	Limited capacity in primary care settings: The shortage of resources in primary care settings leads to longer diagnostic intervals, affecting early detection and timely treatment.
Treatment	Limited access to innovative therapies: financial and administrative barriers currently prevent many patients from accessing EMA-approved novel treatments, restricting treatment options.
	Delays from diagnosis to treatment: the time from diagnosis to treatment initiation is prolonged due to delays in molecular testing, imaging, and surgical scheduling.

(*Continues*)

Table 2. Challenges and opportunities for EC healthcare in Portugal (*continued*)

	Unequal access to palliative care: there are significant gaps in palliative care services, including inadequate inpatient and outpatient capacity, which affects the management of advanced disease.
Innovation	Lack of routine biomarker testing, which may limit the ability to tailor treatments based on genetic profiles.
Health policy	Regional disparities in healthcare resources: differences in healthcare infrastructure result in uneven access to diagnostic and treatment services, particularly between urban and rural areas.
	Need for stronger networks of diagnosis and treatment centers: high-risk cases would benefit from specialized centers, but current networks remain inadequate to ensure optimal care.
Prevention	Improved awareness and literacy: public awareness campaigns should be implemented to educate the population about risk factors, early symptoms, and the importance of timely medical evaluation, particularly for high-risk groups.
Screening	High-risk group screening potential: targeted screening strategies for high-risk groups, such as Lynch syndrome carriers, to improve early detection and reduce mortality rates.
Diagnosis	Fast-track pathways: implementing fast-track pathways with enforced waiting time limits could reduce diagnostic delays and improve patient outcomes.
Treatment	Expansion of clinical trial participation: increasing participation in clinical trials across Portugal could provide more patients with access to cutting-edge therapies and reduce regional disparities.
Innovation	Molecular profiling and genomics: advances in molecular profiling and genomic medicine offer opportunities for personalized treatments that improve patient outcomes.
Health policy	Centralized approval pathways for new treatments: streamlining approval processes and aligning with EMA recommendations could facilitate broader and faster access to new treatments.
Health literacy	Education campaigns to enhance awareness: well-designed public awareness campaigns could encourage early medical consultations and improve EC outcomes.

EC: endometrial cancer; EMA: European medicines agency; BPA: bisphenol A; EDC: endocrine-disrupting chemicals.

Conclusion

The incidence and mortality of EC are increasing in Portugal, in line with global trends. Although national and European guidelines are in place, significant challenges remain, particularly in early diagnosis, equitable access to treatment, and public awareness. There is an urgent need for robust public health initiatives, streamlined diagnostic pathways, increased participation in clinical trials, and expanded access to innovative therapies. Addressing these gaps through well-structured policies and reforms in clinical practice is essential to improving patient outcomes and reducing the overall burden of the disease in Portugal.

Authors' contributions

All authors provided substantial contributions to the conceptualization, design, and methodology of the study. J. Pedro-Aguiar and Catarina Pestana-Silva were involved in collecting and analyzing information from questionnaires. All authors substantially contributed to critically reviewing the manuscript for important intellectual content. All authors read and approved the final version of the manuscript. All authors agreed to be accountable for the work in ensuring that questions related to the integrity of any part of the work are appropriately investigated and resolved.

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J. Rodrigues has participated in advisory boards or acted as a consultant for GSK. A.R. Lopes, D. Pessoa, M. Magalhães, and R. Texeira de Sousa established a financial contract with GlaxoSmithKline Portugal to participate in the project. J.P. Aguiar, C. Pestana-Silva, and A. Vaz-Carneiro are employees of ISBE, which established a financial contract with GlaxoSmithKline Portugal

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Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

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Data availability

Data are not publicly available due to the confidentiality agreement with experts.

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CASE REPORT

Olaparib desensitization using the non-crushable tablet formulation

Dessensibilização ao olaparib utilizando a formulação em comprimido não triturável

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Abstract

Previously reported desensitization protocols for olaparib relied on capsule or tablet suspensions that allowed very low starting doses, which are no longer commercially available in Europe. We describe a 40-year-old female with a pathogenic germline BRCA2 mutation, with triple-negative breast cancer with residual disease after neoadjuvant chemotherapy, who developed immediate cutaneous hypersensitivity after the first dose of adjuvant olaparib. A 2-day, hospital-based desensitization protocol was performed using the currently available non-crushable tablet formulation. A 2-day hospital build-up was performed, achieving a total dose of 400 mg, followed by a single-day build-up 7 days later to a cumulative dose of 600 mg, established as the maintenance regimen. This case supports the feasibility of olaparib desensitization using current tablet formulations and highlights the role of allergy-guided strategies in maintaining access to anticancer guided therapies.

Keywords: *Olaparib. Drug desensitization. Drug allergy. Oncoallergology.*

Resumo

Os protocolos de dessensibilização a olaparib previamente publicados utilizaram suspensões a partir de cápsulas ou comprimidos, permitindo doses muito baixas, atualmente não comercializadas na Europa. Os autores relatam o caso de uma doente do sexo feminino de 40 anos com mutação germinativa BRCA2 patogénica com o diagnóstico de cancro da mama triplo negativo, com doença residual após quimioterapia neoadjuvante, com reação de hipersensibilidade imediata após a primeira dose de olaparib. Foi realizado protocolo de dessensibilização em meio hospitalar, com comprimidos não-trituráveis compreendendo uma fase de indução de dois dias com atingimento de uma dose de 400mg, seguido de um dia de indução, 7 dias depois, com incremento da dose para 600mg, estabelecido como regime de manutenção diária. Este caso apoia a viabilidade da dessensibilização a olaparib utilizando as formulações atuais e sublinha o papel das estratégias guiadas pela Imunoalergologia, para garantir que os doentes mantenham em curso tratamento antineoplásico recomendado.

Palavras-chave: *Olaparib. Dessensibilização a fármacos. Alergia a fármacos. Oncoalergologia.*

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Introduction

Drug allergy accounts for 10-15% of adverse drug reactions.[1] Type I, immunoglobulin E (IgE)-mediated reactions occur within minutes to hours after exposure.[1] Adverse drug reactions are reported in approximately 5% of oncology treatments.[2] Based on presentation, severity, and mediators released, these reactions can be classified according to phenotype and endotype, reflecting the underlying immune pathways (infusion reactions, IgE/non-IgE type I reactions, mixed reactions, cytokine-release syndromes, and types II-IV hypersensitivity reactions).[3,4]

Case report

We report the case of a 40-year-old premenopausal female with a known history of Gilbert syndrome and a recent diagnosis of triple-negative metaplastic breast cancer (cT1cN0M0) with a pathogenic germline BRCA2 mutation. She underwent neoadjuvant chemotherapy (carboplatin, paclitaxel, followed by dose-dense doxorrubicin/cyclophosphamide) and then mastectomy with sentinel lymph node biopsy. The breast specimen revealed residual cancer disease, ypT1aN0, and became eligible for adjuvant olaparib 300 mg bid for 1 year, according to the Olympia trial, which demonstrated significant improvement in overall survival in this setting.[5,6] Two hours after the initial 300 mg oral dose, she developed ocular itching, facial flushing, and a generalized pruritic macular exanthema. Tryptase and interleukin-6 were not measured at the time. Given the pharmacological characteristics of the drug, no skin or *in vitro* tests were feasible, leaving the mechanism of sensitization undetermined. Since adjuvant olaparib prolongs overall survival in this context, drug desensitization was attempted.

A desensitization protocol has previously been reported for this drug; however, it involved olaparib in capsule or tablet suspension form, which enabled lower starting doses.[7-9] As these formulations are no longer commercially available in Europe and olaparib is currently marketed exclusively as 100 mg and 150 mg tablets that cannot be crushed, dissolved, or divided according to the product's regulatory information, this posed a practical challenge requiring protocol adaptation.[2] Pre-medication was tailored to the initial clinical reaction; anti-H1 and anti-H2 antihistamines were used, and acetylsalicylic acid (ASA) was given, the symptoms of flushing and maculopapular rash.[2,4,10]

Desensitization was performed in the hospital setting under continuous monitoring, with 30-min intervals between doses. A 2-day, hospital-based desensitization protocol was performed using the currently available non-crushable tablet formulation. A 2-day hospital build-up was performed, achieving a total dose of 400 mg, followed by a single-day build-up 7 days later to a cumulative dose of 600 mg, established as the maintenance regimen (Table 1).

On day 1, the patient received sequential doses of 100 mg, 100 mg, 100 mg, and 150 mg of olaparib (cumulative dose 450 mg). Twenty-five minutes after the final dose, she developed a pruritic macular exanthema and flushing that resolved with antihistamine treatment. On day 2, olaparib was re-administered at 200 mg twice daily (400 mg cumulative) under premedication (bilastine, famotidine, and ASA) with good tolerance. Seven days later, the dose was escalated to 300 mg twice daily (600 mg/day), which has since been maintained for 16 weeks without breakthrough reactions or hypersensitivity signs (Table 1).

Discussion

Olaparib is a potent poly(ADP-ribose) polymerase (PARP) inhibitor targeting PARP1 and PARP2 that suppresses the growth of selected tumor cell lines and is currently approved for the treatment of patients with breast, ovarian, endometrial, and prostate cancers, usually in the setting of pathogenic BRCA 1/2 mutations.

Desensitization allows patients who experience type I, cytokine-release type, mixed type, or type IV hypersensitivity reactions (except for severe cutaneous adverse reactions) to continue receiving the offending drug when no therapeutically equivalent alternatives exist.[10] It induces a temporary state of tolerance through the gradual administration of subthreshold doses (typically 1/1000-1/100 of the target dose) at fixed intervals, thereby blocking mast cell signaling and mediator release.[2,4]

This adapted protocol enabled the continuation of adjuvant olaparib, despite the initial hypersensitivity reaction. To our knowledge, this is the first successful desensitization using the currently available non-crushable tablet formulation. Our case highlights the feasibility of tailoring desensitization strategies when conventional formulations are unavailable, thereby expanding treatment options for patients requiring uninterrupted therapy.[1,10]

The main limitation of this report is the absence of confirmatory tests (tryptase, basophil activation, or skin testing), which preclude definitive mechanistic

Table 1. Olaparib desensitization protocol using the non-crushable tablet formulation

Day	Step	Time (h:min)	Olaparib tablet dose (mg)	Cumulative daily dose (mg)
1	1	00:00	100	100
	2	00:30	100	200
	3	01:00	150	350
2-6*	1	00:00	200	200
	2*	12:00	200	400
7	1	00:00	300	300
	2*	12:00	300	600

*Outpatient administration.

classification. Nevertheless, the clear temporal relationship, reproducibility of symptoms, and success of desensitization support the diagnosis of a hypersensitivity reaction.

We emphasize the importance of a multidisciplinary team, including allergists, oncologists, nurses, and pharmacists, in the identification and management of potentially severe hypersensitivity reactions that would otherwise limit therapeutic options.

Authors' contributions

L.P. Viegas: conceptualization, study design, protocol development, desensitization procedure, writing – original draft; J. Godinho: patient provision, data analysis, writing – review and editing; M.N. Rosado: pharmacological support, writing – review; L.P. Coelho: writing – review; L.M. Borrego: conceptualization, writing – review and editing.

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Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

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CASE REPORT

Breast carcinoma with neuroendocrine differentiation: a personalized therapeutic approach using somatostatin analogs

Carcinoma da mama com diferenciação neuroendócrina: uma abordagem terapêutica personalizada utilizando análogos da somatostatina

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Abstract

Breast carcinomas with neuroendocrine differentiation represent a rare and heterogeneous entity, associated with diagnostic and therapeutic challenges, particularly in the metastatic setting. We report the case of a 70-year-old woman with metastatic breast carcinoma, hormone receptor-positive and human epidermal growth factor receptor-2-negative, with histologically confirmed neuroendocrine differentiation and somatostatin receptor expression documented by 68Ga-DOTANOC positron emission tomography (PET-DOTANOC) positron emission tomography. The patient initiated treatment with letrozole and palbociclib, followed by the addition of octreotide, achieving a complete clinical and radiological response that was maintained throughout follow-up. This case highlights the importance of comprehensive histological, molecular, and functional characterization, enabling a personalized therapeutic approach. The combination of somatostatin analogs with endocrine therapy and cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors may represent an effective strategy in selected patients with breast carcinoma with neuroendocrine differentiation.

Keywords: *Breast cancer. Neuroendocrine differentiation. Somatostatin analogs. Personalized therapy.*

Resumo

Os carcinomas da mama com diferenciação neuroendócrina constituem uma entidade rara e heterogénea, associada a desafios diagnósticos e terapêuticos, particularmente em contexto metastático. Apresenta-se o caso de uma mulher de 70 anos com carcinoma da mama metastático, recetores hormonais positivos, HER2 negativo, com diferenciação neuroendócrina confirmada histologicamente e expressão de recetores de somatostatina documentada por PET-DOTANOC. A doente iniciou tratamento com Letrozol e Palbociclib, com posterior associação de Octreótido, obtendo resposta clínica e imagiológica completa, e mantida ao longo do seguimento em consulta. Este caso demonstra a importância da caracterização histológica, molecular e funcional aprofundada, permitindo uma abordagem terapêutica personalizada. A associação de análogos da somatostatina à terapêutica endócrina e aos inibidores de CDK4/6 pode representar uma estratégia eficaz em doentes selecionados com carcinoma da mama com diferenciação neuroendócrina.

Palavras-chave: *Cancro da mama. Diferenciação neuroendócrina. Análogos da somatostatina. Terapia personalizada.*

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Introduction

Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer-related mortality among women worldwide.[1] Breast carcinomas with neuroendocrine differentiation represent a rare entity, accounting for < 1% of all breast neoplasms.[2,3] According to the most recent World Health Organization (WHO) classification, these neoplasms are currently included within the group of neuroendocrine neoplasms of the breast and are subdivided into well-differentiated neuroendocrine tumors, poorly differentiated neuroendocrine carcinomas, and invasive breast carcinomas of no special type with neuroendocrine differentiation.[2-4]

The diagnosis requires the presence of suggestive morphology in association with immunohistochemical expression of neuroendocrine markers, such as chromogranin A and synaptophysin. Exclusion of metastatic involvement of the breast from an extramammary neuroendocrine neoplasm is essential, given its distinct prognostic and therapeutic implications.[4,5]

Prognosis is variable and depends on the degree of differentiation, stage at diagnosis, and molecular characteristics, generally being less favorable in poorly differentiated and metastatic forms.[6-9] Owing to their rarity (< 1% of breast cancers), the available literature is limited, and despite ongoing advances in research, particularly in molecular biology, specific treatment guidelines are still lacking.[3] Therefore, in the absence of dedicated recommendations, therapeutic strategies are usually extrapolated from treatment algorithms for conventional invasive breast carcinoma.[5,8]

Case report

A 70-year-old woman with an Eastern Cooperative Oncology Group performance status of 1 was evaluated in May 2021 for a verrucous lesion located in the right inframammary fold (Fig. 1), associated with a progressively enlarging indurated nodule. The patient did not present with symptoms suggestive of carcinoid syndrome. Other than the inframammary lesion, she remained clinically asymptomatic. Breast ultrasonography performed in August 2021 revealed a mass in the lower inner quadrant of the right breast, associated with suspicious ipsilateral axillary lymphadenopathy.

Biopsy of the cutaneous lesion demonstrated dermal infiltration by invasive breast carcinoma of no special type, with strong expression of estrogen and progesterone receptors (> 95%) and absence of human epidermal growth factor receptor-2 (HER2) expression (0). Staging computed tomography revealed bilateral pulmonary metastases and osseous involvement; these findings were confirmed by positron emission tomography (PET), which demonstrated locally advanced disease with nodal and pulmonary metastases. A lung biopsy was performed and confirmed pulmonary metastasis of carcinoma, consistent with a breast primary showing features of neuroendocrine differentiation. Immunohistochemical analysis showed diffuse positivity of the neoplastic cell population for GATA3, estrogen receptors, progesterone receptors, and synaptophysin, with absence of staining for thyroid transcription factor 1. DOTANOC PET demonstrated expression of somatostatin receptors in right axillary lymph node metastases.

In January 2022, palliative systemic treatment was initiated with letrozole 2.5 mg once daily in combination with palbociclib 125 mg once daily administered on days 1-21 of a 28-day cycle. In February 2022, long-acting release octreotide 30 mg intramuscularly every 28 days was added to the treatment regimen.

In March 2023, 13 months after treatment initiation, the patient achieved a complete clinical and radiological response, with resolution of the cutaneous lesion (Fig. 2) and no evidence of active disease on subsequent imaging. After 40 treatment cycles, she continues to tolerate therapy well, with no significant toxicities and preservation of her general condition.

Discussion

Breast carcinomas with neuroendocrine differentiation represent a rare entity, accounting for < 1% of breast neoplasms, and are characterized by pronounced clinical, morphological, and biological heterogeneity.[2,3] The recent WHO classification update has reinforced this heterogeneity by including these neoplasms within the spectrum of neuroendocrine breast neoplasms, distinguishing well-differentiated neuroendocrine tumors, poorly differentiated neuroendocrine carcinomas, and invasive breast carcinomas of no special type with neuroendocrine differentiation.[2,4] Diagnosis relies on the identification of suggestive morphology in combination with immunohistochemical expression of neuroendocrine markers, such as chromogranin A and synaptophysin, typically associated with a luminal profile, including hormone receptor (HR) expression, absence of HER2 expression, and low Ki-67 index, although other molecular subtypes have been described.[4-6] The lack of uniform diagnostic criteria and morphological overlap with



Figure 1. Verrucous lesion located in the right inframammary fold at initial presentation.

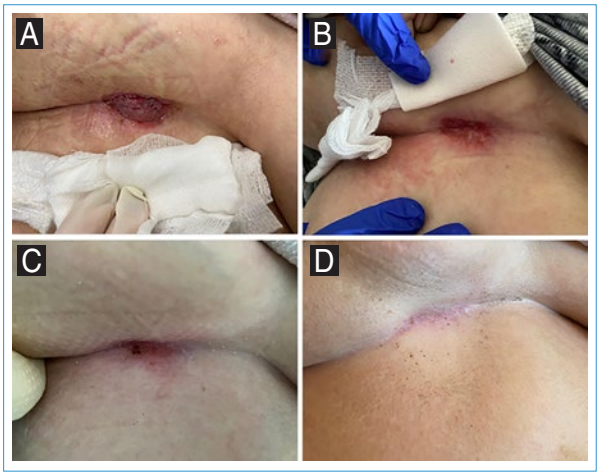


Figure 2. Evolution of the verrucous lesion during treatment. **A:** February 2022; **B:** May 2022; **C:** September 2022; **D:** March 2023.

invasive breast carcinoma of no special type contribute to underdiagnosis and to the limited robustness of available data in the literature.[4,5]

From a biological standpoint, most breast carcinomas with neuroendocrine differentiation exhibit a luminal profile, with HR expression and absence of HER2 expression (HR+/HER2–), resembling classical invasive breast carcinoma.[6] However, clinical and molecular studies demonstrate that this entity is not biologically homogeneous, with the degree of differentiation, proliferative index, and genetic alterations being key determinants of clinical behavior.[7,9] Poorly differentiated neuroendocrine carcinomas, for instance, are characterized by frequent TP53 and RB1 alterations, higher genomic instability, and aggressive clinical behavior, and are associated with an increased risk of early metastasis and significantly poorer overall prognosis.[9-11]

In the absence of specific therapeutic guidelines, the management of breast carcinomas with neuroendocrine differentiation has generally been extrapolated from HR+/HER2– breast cancer treatment algorithms, particularly in the metastatic setting.[8] The combination of endocrine therapy with CDK4/6 inhibitors has demonstrated consistent benefits in terms of response rate, progression-free survival, and quality of life, and currently represents the gold standard treatment for this patient subgroup.[12] This approach appears particularly suitable for tumors with a luminal profile and less aggressive biological behavior, such as well-differentiated neuroendocrine tumors and invasive carcinomas with neuroendocrine differentiation.

A distinctive and clinically relevant feature of these tumors is the expression of somatostatin receptors, reported in approximately 50-70% of cases.[5,13] Functional identification of these receptors through molecular imaging techniques, such as DOTANOC PET, not only allows for improved disease characterization but also enables consideration of additional targeted therapeutic strategies. Somatostatin analogs, namely octreotide and lanreotide, have demonstrated antiproliferative, antisecretory, and disease-stabilizing effects in well-differentiated neuroendocrine neoplasms, and are associated with prolonged disease control and good treatment tolerability.[13,14] Although evidence in breast carcinoma with neuroendocrine differentiation is limited and primarily based on small case series and reports, the physiological rationale for their use appears sound.[13]

In the present case, histological confirmation of neuroendocrine differentiation, combined with functional demonstration of somatostatin receptor expression, enabled a truly personalized therapeutic approach. The combination of palbociclib and letrozole, in line with recommendations for metastatic HR+/HER2– breast carcinoma, together with octreotide therapy, resulted in a complete and sustained clinical and radiological response over 40 treatment cycles, with excellent tolerability and preservation of the patient's functional status. This outcome suggests a potential synergistic effect between endocrine therapy, cell cycle inhibition, and modulation of neuroendocrine signaling, translating into prolonged metabolic and tumor control.

Notably, in this patient, neuroendocrine differentiation was identified on histological evaluation of a metastatic lesion, underscoring the importance of comprehensive pathological reassessment not only of the primary breast tumor but also of metastatic sites whenever

feasible. This finding highlights the potential biological heterogeneity between primary and metastatic disease and emphasizes that biopsy of metastatic lesions may provide additional diagnostic and predictive information with direct implications for therapeutic decision-making and treatment personalization.

Overall, this case underscores the importance of comprehensive histological, molecular, and functional characterization in breast carcinoma with neuroendocrine differentiation, enabling the identification of patient subgroups that may benefit from integrated and targeted therapeutic strategies. Despite the inherent limitations of a single case report, the sustained response observed supports the need for prospective studies and multicenter registries to clarify the role of somatostatin analogs in this context and to define more specific therapeutic approaches for this rare entity.

Conclusion

Breast carcinoma with neuroendocrine differentiation is rare and exhibits a variable prognosis. Histological and functional characterization using DOTANOC PET can identify important therapeutic targets. The combination of somatostatin analogs with endocrine therapy and CDK4/6 inhibitors demonstrated a prolonged and clinically meaningful response, illustrating the potential of integrated, targeted, and personalized approaches in breast cancer.

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Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

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CASE REPORT

Case report: fallopian tube metastasis to the breast

Relato de caso: metástase da trompa de Falópio para a mama

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Abstract

Breast metastasis from carcinoma of the ovary, fallopian tube, and peritoneum (OTP) is rare, occurring in advanced stages of the disease, with chemoresistance and a poor prognosis. Its approach, due to the scarcity of described cases, remains undefined. We present the case of a 70-year-old female with high-grade serous carcinoma of the fallopian tubes, with progressive disease, despite multidrug chemotherapy. Three and a half years after the initial diagnosis, a breast metastasis was diagnosed. The diagnosis was made in the context of hospitalization due to intestinal occlusion, secondary to progression of the disease, and there was a progressive worsening of the patient's clinical condition. This case describes the unusual occurrence of breast metastasis of OTP carcinoma. Currently, no standardized treatment protocol exists for this condition. Several therapeutic modalities are described to improve quality of life and local control of metastatic lesions; however, they are associated with a limited response.

Keywords: *Fallopian tube cancer. Non-mammary breast metastasis. Gynecologic cancer.*

Resumo

A metastização mamária do carcinoma do ovário, trompa e peritoneu (OTP) é invulgar, verificando-se em estadios avançados da doença, com quimiorresistência e mau prognóstico. A sua abordagem, pela escassez de casos descritos, permanece por definir. Descreve-se o caso de uma mulher, 70 anos, com carcinoma seroso de alto grau da trompa, estadio IA. Realizou cirurgia de citorredução primária, seguida de quimioterapia, apresentando recidiva ganglionar abdominal aos 7 meses e posteriormente cervical, apesar de retratamento com platino. Três anos e meio após o diagnóstico, documentou-se metastização mamária, em contexto de internamento por oclusão intestinal, secundária à progressão local da doença, com agravamento clínico progressivo e óbito. Este caso descreve a rara ocorrência de metástases mamárias de carcinoma do OTP, não tendo sido possível tratamento dirigido à doença mamária. Na literatura são descritas várias abordagens para controlo das lesões metastáticas e melhoria da qualidade de vida, com limitada duração da resposta.

Palavras-chave: *Cancro da trompa de Falópio. Metástase mamária não primária. Cancro ginecológico.*

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Introduction

Ovarian, fallopian tube, and peritoneal (OTP) cancer is the second most common gynecological malignancy in developed countries, with an estimated prevalence in Portugal in 2020 of 9.5/100,000 women.[1] Despite its relatively low incidence, OTP carcinoma is among the most lethal cancers in women, exhibiting high mortality rates.[2]

The most frequent histological subtype is high-grade serous carcinoma (HGSC), with approximately 75% of patients being diagnosed at advanced stages.[2] Among these, 85% present with metastases confined to the peritoneal cavity.[3] Breast metastases in this context are rare, estimated at 0.07%,[4] and the literature addressing this clinical scenario remains limited. The main diagnostic challenge in such cases lies in distinguishing between a primary breast neoplasm and metastatic disease, to avoid unnecessary surgical intervention and to tailor treatment appropriately to the primary tumor.

There is no established standard approach for these cases. The only therapeutic option with a curative intent currently available is chemotherapy, although palliative strategies, such as radiotherapy or breast surgery, may be considered for symptomatic control. The most frequently reported approach in the literature is the combination of chemotherapy followed by local irradiation.[2,3]

Given the rarity and complexity of this presentation, the authors deem it relevant to report the present clinical case, despite its unfavorable outcome.

Case report

A 70-year-old caucasian female (G2P2) with a medical history of glaucoma, hypertension and depression, and no relevant family or surgical history, was referred to Gynecology for evaluation of an adnexal mass. This mass, localized in the right ovary, was heterogeneous, with 39 × 43 mm, multilocular, and had increased vascularization. Thoraco-abdominopelvic computed tomography (CT) showed no evidence of other lesions, and CA125 was 222 U/mL.

An exploratory laparotomy was performed, and intraoperative frozen section suggested HGSC of the fallopian tube. Complete surgical staging followed, including total hysterectomy, contralateral adnexectomy, infracolic omentectomy, pelvic and para-aortic lymphadenectomy, and multiple peritoneal biopsies. No macroscopic residual disease was identified. The final diagnosis was International Federation of Gynecology and Obstetrics (FIGO) stage IA HGSC of the fallopian tube. Immunohistochemistry (Fig. 1) showed positivity for paired box gene 8 (PAX 8), wingless-related integration site 1 (WT1), p16, and p53 (null-type), estrogen receptors (50-75%), and high Ki-67 (> 70%). breast cancer gene (BRCA) 1/2 testing was negative.

After multidisciplinary evaluation, the patient received six cycles of adjuvant carboplatin-paclitaxel chemotherapy (QT), achieving a partial response (CA125 45 U/mL; negative CT). It was decided to maintain surveillance.

Seven months later, recurrence was diagnosed: abdominal and pelvic lymphadenopathies were identified in CT (adenopathies superior to the celiac trunk and adjacent to the right iliac vessels) and raised CA125 (maximum value of 282 U/mL). The patient was asymptomatic. A biopsy confirmed inguinal metastasis. Six additional cycles of carboplatin-paclitaxel achieved partial radiological response (reduction of the volume of the adenopathies), and CA125 declined to 61.9 U/mL.

Two months later, the disease progressed (abdominopelvic lymph node regrowth). Second-line treatment was offered, which the patient refused.

Clinical surveillance was maintained and, 15 months later, bilateral cervical lymphadenopathy (in the jugulocarotid and accessory spinal chains) and CA125 elevation (332 U/mL) were observed. Cervical biopsy confirmed metastatic HGSC. Monotherapy with pegylated liposomal doxorubicin was initiated and subsequently discontinued after five cycles due to treatment-related toxicity (worsening of cardiac function), which led to clinical deterioration.

There was a subsequent elevation in CA125, and the patient reported cervical pain. An increase in the number and size of cervical lymphadenopathies was observed, with the largest nodes located on the left side, measuring up to 2 cm in maximum diameter. The case was discussed, in a multidisciplinary context, with the radiooncology team of the tertiary reference hospital: to achieve local control of the disease and symptomatic relief, it was decided to perform cervical radiotherapy (total dose of 30 Gy, in 10 fractions).

Three weeks post-radiotherapy, the patient presented at the emergency service with bowel obstruction. Clinical examination revealed, besides the cervical enlarged lymph nodes, a new breast lesion, with 4.5 cm, in the inner quadrants of the left breast, associated with skin retraction and erythema (Fig. 2). Imaging (CT) showed a suspicious retroareolar lesion (Fig. 3). Both breast and axillary biopsies confirmed metastatic HGSC, with the same immunohistochemical profile of the primary lesion, GATA3 negative, with marked lymphovascular invasion (Fig. 4).

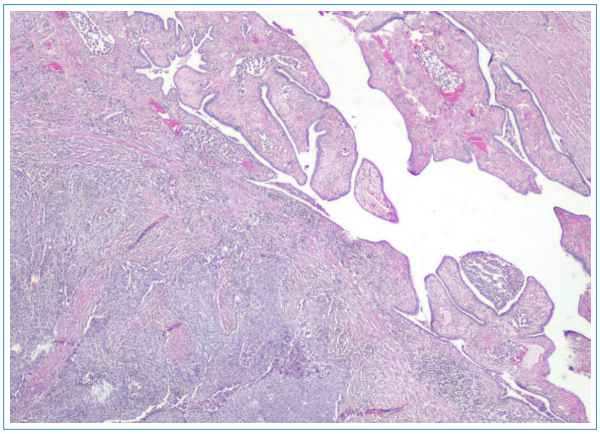


Figure 1. H&E stain (amplified ×20) section showing high-grade serous carcinoma involving the fallopian tube. Lymphovascular permeation is identifiable.



Figure 3. Thoracic computed tomography showing, on the left breast, an irregular and hyperdense retroareolar lesion, measuring approximately 6 cm, with associated skin thickening.



Figure 2. Left breast, portraying skin retraction and erythema, mostly on the inner quadrants; left side of the neck, showing enlarged and erythematous lymph nodes.

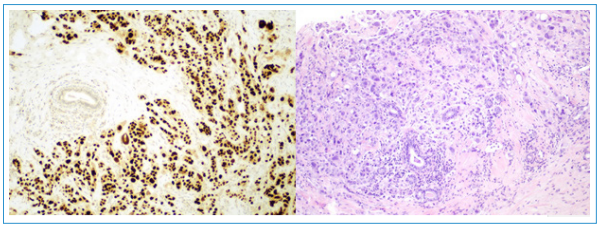


Figure 4. H&E (amplified ×100) breast lesion biopsy illustrating the high-grade serous carcinoma, with intense and diffuse expression of PAX8.

Despite supportive measures, the patient died on day 23 of hospitalization, 3½ years after initial diagnosis.

Discussion

The management of this case followed both national and international guidelines for the treatment of tubo-ovarian and peritoneal carcinoma (OTP).[2,5] All decisions regarding patient monitoring and care were made within a multidisciplinary team, involving gynecology and obstetrics, medical oncology, pathology, and radiology, in collaboration with the referral radio-oncology department, ensuring appropriate surveillance.

HGSC is characterized by widespread chromosomal copy number alterations, contributing to its notable genomic instability,[6] rapid proliferation, and dissemination.

Currently, no established screening strategy exists for ovarian carcinoma. In this case, diagnosis followed incidental ultrasound detection of an asymptomatic adnexal lesion. Despite early-stage disease at diagnosis and appropriate initial treatment, comprising R0 surgical resection and adjuvant chemotherapy, the patient's disease progressed. Although post-operative CT imaging showed no evidence of residual disease, the CA125 level remained above normal (a known adverse prognostic factor). Early recurrence (within 7-8 months of chemotherapy) indicated aggressive and chemoresistant tumor behavior consistent with the literature on HGSC prognosis.

OTP carcinoma usually metastasizes through peritoneal dissemination, resulting in widespread abdominopelvic involvement. In rare cases, distant metastases may occur hematogenously or through the lymphatic system, most commonly involving the pleura, liver, lungs, and lymph nodes, particularly pelvic and para-aortic.[7]

Mammary involvement is extremely rare and is associated with advanced-stage disease and poor prognosis. When it occurs, HGSC is the most frequent histologic subtype implicated.[7] It usually presents as a solitary mass, only 4% of cases demonstrate diffuse mammary involvement.[8] This type of metastasis poses a diagnostic challenge due to its capacity to mimic a primary breast carcinoma, with non-specific or even

misleading imaging findings. In our case, the lesion mimicked inflammatory breast cancer, with a rapid growth, and was identified during hospitalization for complications related to disease progression. Given the clinical context, metastatic disease was suspected, albeit rare. The role of the pathologist was critical in this scenario: immunohistochemical profiling allowed differentiation between primary breast carcinoma and metastatic OTP, revealing features consistent with the original adnexal tumor.

Progesterone and estrogen receptor expression can be present in both ovarian and breast carcinomas. However, immunohistochemical markers such as WT1, PAX8, and GATA3 allow distinguishing between primary and metastatic breast tumors: PAX8 and WT1 are expressed in approximately 88% and 72% of primary OTP carcinomas, respectively.[9] In this case, the metastatic breast lesion showed positivity for WT1 and PAX8, consistent with literature findings. Conversely, GATA3, typically expressed in primary breast tumors, was negative, supporting the diagnosis of metastasis from OTP.[9]

Accurate lesion characterization is essential, as treatment, prognosis, and follow-up strategies differ significantly between primary breast carcinoma and metastatic OTP.

Given the patient's extensive disease burden and deteriorating performance status, further systemic or localized breast-directed therapies were deemed inappropriate, and palliative care was prioritized.

Given its rareness, there is no standardized approach for managing breast metastases from OTP carcinoma. Fewer than 100 cases have been reported to date.[3] Therapeutic strategies described include systemic chemotherapy, currently the only curative-intent option, alongside palliative modalities such as local radiotherapy, mastectomy, or lumpectomy. Surgery is typically reserved for patient's refractory to chemotherapy, primarily for symptom relief.[3] The most reported approach is the combination of chemotherapy followed by local irradiation.

Cases reported in the literature describe advanced, treatment-resistant disease, often with recurrent breast involvement after multiple chemotherapy regimens. Prognosis remains poor: reported overall survival ranges from 13 days to 3.5 years, with a 1-year survival rate of approximately 40%.[10] Our patient's survival fell within the median reported range. Contributing factors likely included advanced age,[11] tumor biology, rapid progression, and poor performance status that precluded further systemic treatment.

Despite the unfavorable outcome, we present this case hoping to contribute to improving management and outcomes for similar patients. It adds to the scarce literature on breast metastasis as a late manifestation of OTP carcinoma, highlighting its diagnostic and therapeutic challenges. Further studies are needed to establish standardized diagnostic and therapeutic protocols, with effective systemic strategies, ideally based on histological and molecular profiling, to guide a multimodal treatment approach in such rare cases.

Authors' contributions

S. Forjaz: conceptualization, writing – original draft, review and editing; L. Cunha-Silva: conceptualization, writing – original draft, review and editing; R. Coutada: clinical contribution, review; A. M. Simas: clinical contribution, review; S. Carvalho: clinical contribution, review.

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Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

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IMAGES IN ONCOLOGY

Hepatic adrenal rest tumor: a pitfall in liver lesions

Tumor de resto adrenal hepático: uma armadilha nas lesões hepáticas

Miriam Marques, Marta Manso, Catarina Costa, and Rita Cruz*

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A 71-year-old male was referred to our hospital for hepatology assessment due to suspected chronic liver disease. His past medical history was unremarkable, except for moderate chronic alcohol consumption. Physical examination and vital signs were within normal limits. Laboratory evaluation revealed normal alpha-fetoprotein levels, normal liver function tests, and normal prothrombin time.

Considering the patient's medical history and the unfavorable body habitus for abdominal ultrasound evaluation, contrast-enhanced computed tomography (CECT) of the abdomen was performed. A lesion was identified in segment VII of the liver, demonstrating arterial phase enhancement (Fig. 1), with washout in the portal venous phase (Fig. 2). The right adrenal gland was not clearly visualized (Fig. 2). No intralesional macroscopic fat or imaging signs of chronic liver disease were detected on CECT. To better characterize the hepatic lesion, magnetic resonance imaging (MRI) with extracellular gadolinium-based contrast was requested, showing signal intensity loss on in-phase and out-of-phase T1-weighted sequences (Figs. 3 and 4), consistent with the presence of intralesional microscopic fat.

Hepatocellular carcinoma (HCC) was initially suspected; however, after multidisciplinary discussion, follow-up imaging at 3 months was recommended. This decision was based on the unclear visualization of the right adrenal gland, raising the possibility of a hepatic adrenal rest tumor (HART). Subsequent imaging demonstrated lesion stability, supporting the diagnosis of HART.

Adrenal rest tumors are defined as collections of aberrant adrenocortical tissue located outside the adrenal gland.[1,2] They are rare entities, most commonly found in the abdomen or pelvis, with the kidneys being the most frequent location. HARTs are extremely rare.[1,2]

Some lesions may be hormonally active and present with endocrine syndromes,[1] and immunohistochemical studies can confirm steroidogenic capability.[1] Malignant transformation is exceedingly rare.[2]

On imaging, HARTs usually appear as well-defined, round subcapsular masses in the posterior right lobe of the liver.[3] They typically present as hypervascular, fat-containing lesions.[3] Intralesional fat may be detected on CECT or ultrasound, but it is more accurately characterized by MRI.[3] The differential diagnosis includes fat-containing HCC, focal nodular hyperplasia, hepatic adenoma, hepatic angiomyolipoma, hepatic lipoma, and primary hepatic or metastatic liposarcoma.[3] Another important imaging feature is hypervascularity with early arterial enhancement and washout, which makes differentiation from HCC particularly challenging, especially in cirrhotic patients.[2,4]

Histologically, HARTs resemble adrenal cortical tumors and are composed of low columnar or cuboidal

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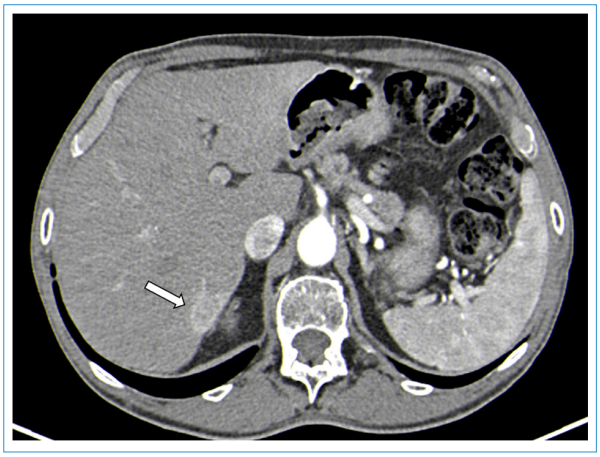


Figure 1. Computed tomography scan, axial arterial phase. The white arrow shows a hypervascular nodule in the VII segment measuring 19 mm.

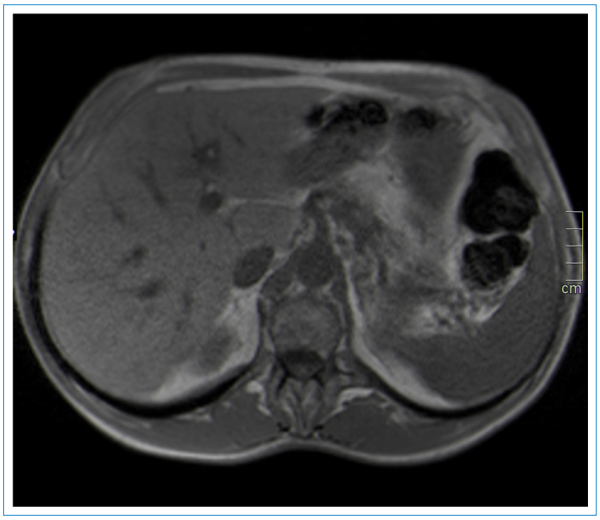


Figure 3. Magnetic resonance T1 in-phase sequence axial.

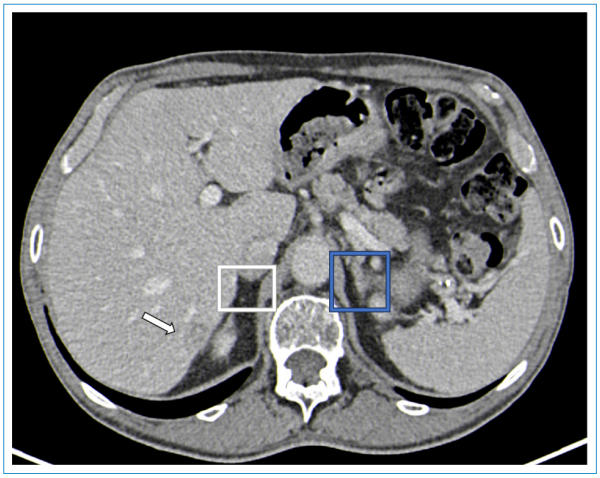


Figure 2. Computed tomography scan, axial portal phase. The white arrow shows washout; white square shows where the right adrenal gland was supposed to be observed; the blue square shows the left adrenal gland.

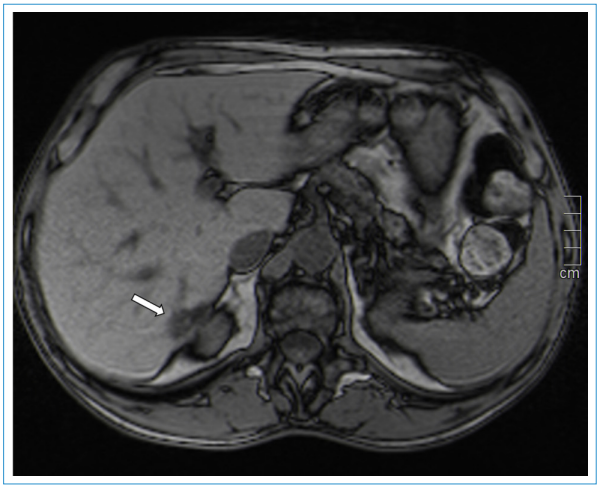


Figure 4. Magnetic resonance T1 out-of-phase sequence axial. The white arrow shows signal drop of the subcapsular lesion in segment VII.

clear cells, typically rich in lipid content and arranged in cord-like patterns separated by thin fibrous septa.[1] Immunohistochemistry usually demonstrates positivity for Melan-A, confirming adrenal origin, and negativity for HepPar-1 and PAX8, excluding hepatocellular and renal origin, respectively.[5]

Although no pathognomonic imaging findings exist, HART should be considered in the differential diagnosis of hypervascular, fat-containing hepatic lesions located in segment VII, particularly in patients with normal alpha-fetoprotein levels and an unidentifiable right adrenal gland. Recognizing this entity is essential to avoid unnecessary hepatectomy or liver transplantation without curative intent, given the benign nature of HART.

Authors' contributions

All the authors mentioned above contributed to the preparation of this article, namely in the case follow-up, image collection, literature review, and manuscript writing.

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Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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Right paratracheal pseudotumor: an interesting radiological appearance

Pseudotumor paratraqueal direito: um achado radiológico interessante

Cristiana Honrado-Martins[1] and Guilherme Castro-Gomes[2]*

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Pulmonary pseudotumors are relatively common radiologic findings. Most frequently caused by a loculated pleural effusion confined to the pleural fissures, other etiologies have been described, such as inflammation, atelectasis, fat, mucoid, or calcifying impaction, among others.[1]

We report the case of a 62-year-old man, previously a house-constructor, current smoker (45 pack-years), with a known history of hypertension and alcohol-related liver cirrhosis. He was referred to our department with a diagnosis of bilateral pneumonia with no signs of heart failure or ascites.

Chest X-ray (Fig. 1) showed a suspicious right paratracheal fusiform opacity and features suggestive of pulmonary congestion. Computed tomography of the chest (Fig. 2) revealed the presence of an accessory azygos lobe (a rare anatomical variation) with a loculated pleural effusion in the respective fissure (forming an "hourglass" shape).

The image had significant variation after diuretic treatment, and a completed resolution was registered. This case aligns with the classic concept of "pulmonary pseudotumor", sometimes also described as "phantom tumor".[1]

These types of images are relatively common in the pulmonary major fissures,[2-5] and they may raise diagnostic difficulties, particularly among less trained clinicians.[1,5] In our bibliographic research, we could not find

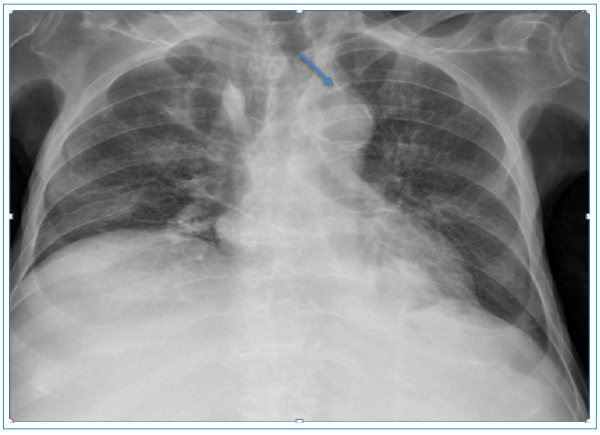


Figure 1. Chest X-ray demonstrating a suspicious right paratracheal fusiform opacity (arrow).



Figure 2. Computed tomography of the chest showing an accessory lobe of the azygos vein (anatomical variation) with a loculated pleural effusion within the azygos fissure (arrow).

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previous case-reports of azygos fissure pseudotumor, hence the relevance of the image reported above.

Authors' contributions

C. Honrado-Martins: conception, drafting, and critical review; G. Castro-Gomes: critical review and approval of the final version.

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