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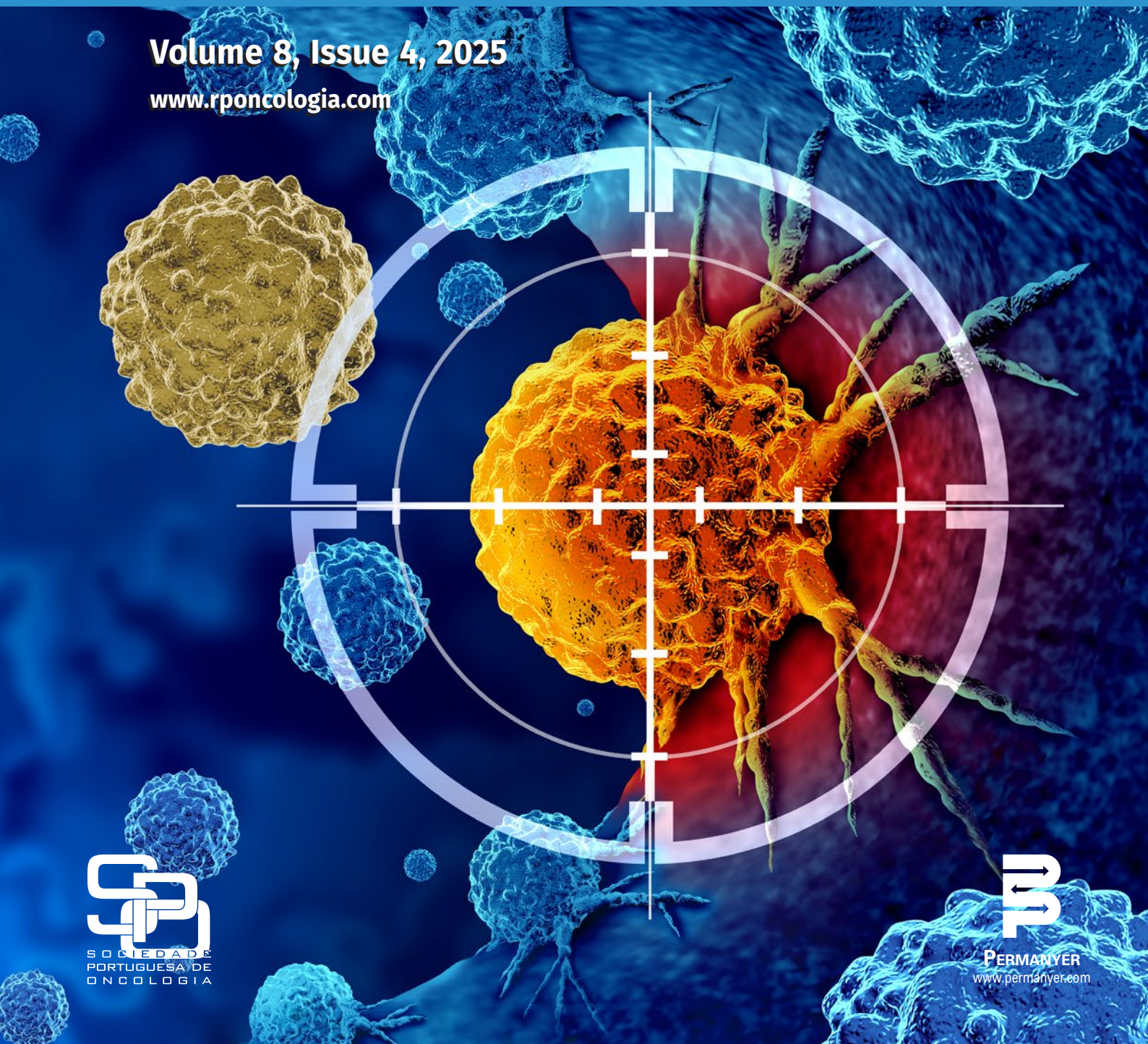

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Editorial for *Revista Portuguesa de Oncologia*, issue 4, 2025

Editorial para a *Revista Portuguesa de Oncologia*, edição 4, 2025

Cláudia Caeiro

Editor-in-Chief

As we bring to a close the fourth and final issue of the Revista Portuguesa de Oncologia (RPO) for this year, a brief reflection is warranted on the recent trajectory of this publication, which is increasingly and consistently affirming itself as an active and representative voice of the national oncology community.

The year 2025 witnessed a noteworthy rise in both the number of submissions and published articles – a clear testament to the scientific vitality that inspires professionals devoted to oncology in Portugal. The RPO has endeavored to mirror this vigor and, at the same time, serve as a platform for the dissemination and affirmation of national scientific output, along a path that aspires to ever-greater visibility and relevance within the international editorial landscape.

In this issue, we conclude our coverage of the Best of ASCO 2025 with articles dedicated to presentations concerning digestive and gynecological tumors – domains in constant evolution and of broad clinical impact. We further highlight the publication of an early-stage research project, with results yet to be determined, underscoring its value as an original article and a meaningful contribution to the journal's indexing process. In doing so, we are reminded that science is also built upon the sharing of foundational knowledge, and not solely on its final outcomes.

We extend our sincere gratitude to all authors, reviewers, and readers who, through their dedication and rigor, have contributed to the sustained growth of the RPO, which aspires to be an ever more prominent forum for the dissemination of oncological scientific research.

With best wishes for an excellent 2026,

The Editorial Board

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GYNECOLOGIC CANCER

Highlights from the 2025 ASCO annual meeting: gynecologic cancer

Ana J. Arede

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TRUST: Trial of Radical Upfront Surgical Therapy in Advanced Ovarian Cancer (ENGOT-ov33/AGO-OVAR OP7)

O TRUST foi um ensaio randomizado que comparou a melhor estratégia de tratamento cirúrgico em mulheres com carcinoma epitelial do ovário avançado (IIIB-IVB) recentemente diagnosticado, desde que a doença fosse considerada ressecável. Quase 800 mulheres elegíveis foram randomizadas numa proporção de 1:1 para cirurgia primária de citorredução (PCS) versus cirurgia de citorredução de intervalo (ICS), tendo cerca de 100 sido excluídas, a maioria por não ter sido confirmado histologicamente o carcinoma epitelial do ovário.

Este ensaio global e multicêntrico destacou-se pela qualidade das cirurgias realizadas, uma vez que apenas centros acreditados, com elevado volume de doentes e experiência, puderam participar nas intervenções. A qualidade da cirurgia foi uma das principais limitações apontadas em estudos prévios (evidenciada pela baixa percentagem de resseções completas), sendo este um dos fatores mais importantes para a interpretação dos resultados[1-4]. No TRUST, o esforço cirúrgico foi notável, tanto no tempo mediano de duração das cirurgias (aproximadamente 5 horas, menor para a cirurgia de intervalo), como nas elevadas taxas de resseções completas – cerca de 70% para a PCS e 85% para a ICS.

Relativamente ao endpoint primário do estudo, a sobrevivência global (OS), não se observaram diferenças estatisticamente significativas entre as duas abordagens cirúrgicas (54,3 vs 48,3 meses; HR = 0,89 [IC 95%, 0,74-1,08], p = 0,24). Já em relação à sobrevivência livre de progressão (PFS), verificou-se uma diferença estatisticamente significativa a favor da PCS (22,1 vs 19,7 meses; HR = 0,80 [IC 95%, 0,66-0,96]; p = 0,018).

Na análise exploratória dos dois maiores subgrupos (estádio III e doentes com resseção completa), observou-se, em ambos, um maior benefício a favor da cirurgia primária, tanto em termos de PFS como de OS, com uma diferença estimada na OS mediana de aproximadamente dez meses nos estádios III e de cerca de um ano nas doentes com resseção completa.

As taxas de morbilidade perioperatória foram superiores para a PCS, com mais complicações a curto prazo e maior número de doentes a necessitar de estoma (18,1% vs 11,9%), embora sem diferenças relevantes na qualidade de vida (QoL) a curto prazo ou na mortalidade perioperatória.

As principais conclusões a retirar desde ensaio são 1) a qualidade da cirurgia deve ser uma prioridade para a obtenção de melhores resultados; 2) na doença ressecável não existe benefício de sobrevida em realizar cirurgia primária, tendo sido este um endpoint bastante apropriado tendo em conta a maior morbilidade perioperatória verificada, como é o caso dos estomas; 3) apesar disso, e tendo em conta que a QoL parece não ser afetada, existem subgrupos que poderão continuar a beneficiar da cirurgia primária, como é o caso dos estádios III ou doença de baixo volume em que seja muito previsível a realização de resseção completa.

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O conhecimento dos dados de morbilidade e QoL a médio-longo prazo assim como a evolução de determinados subgrupos (como nas doentes mutadas ou com défice de proteínas de recombinação homóloga) poderão ajudar a solidificar as conclusões deste ensaio.

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FIRST/ENGOT-OV44: a phase 3 clinical trial of dostarlimab (dost) and niraparib (nira) in first-line (1L) advanced ovarian cancer (aOC).

O estudo FIRST foi desenhado com base em dados pré-clínicos que sugeriram uma maior eficácia dos inibidores de checkpoint imunitário quando combinados com quimioterapia (QT)[1], bevacizumab[2] ou inibidores de PARP (iPARP)[3-4].

Este ensaio randomizado de fase III, multicêntrico e duplamente cego, avaliou a eficácia da adição de um inibidor de PD-1 (dostarlimab) ao tratamento padrão com QT em primeira linha, seguido de manutenção com niraparib, com ou sem bevacizumab.

Os resultados obtidos com imunoterapia em primeira linha têm sido insatisfatórios ou inconclusivos, neste último caso devido ao facto de, no braço experimental, terem sido adicionados simultaneamente imunoterapia e iPARP (sem que este último fosse incluído no braço de controlo), tornando difícil interpretar os ganhos observados na PFS[5-7].

O estudo FIRST incluiu mulheres com carcinoma epitelial do ovário de alto grau, não mucinoso e de alto risco (estádio IV ou III com elevada carga tumoral). O desenho inicial do estudo incluía três braços; contudo, após a aprovação do niraparib em primeira linha, foi efetuada uma emenda ao protocolo, removendo-se o braço 1. As doentes passaram então a ser randomizadas na proporção 1:2 para tratamento padrão com placebo (braço 2) versus dostarlimab (braço 3), seguido de um período de manutenção até três anos com niraparib + placebo (braço 2) versus niraparib + dostarlimab (braço 3). Assim, o desenho do estudo assegurou um braço de controlo compatível com o tratamento padrão atual, ou seja, com adição de iPARP em manutenção.

O endpoint primário foi a PFS, avaliada pelo investigador (RECIST v1.1), com análise estatística definida de forma hierárquica.

Foram incluídas 1.162 doentes no estudo. Mais de um terço encontrava-se em estádio IV, cerca de dois terços tinham cirurgia de intervalo programada ou eram consideradas irressecáveis, e aproximadamente 70% das doentes submetidas a cirurgia primária apresentaram doença residual. Estas características foram equilibradas entre os dois braços, refletindo uma população representativa com doença de alto risco.

O endpoint primário do ensaio, a PFS, foi positivo; no entanto, a diferença na mediana foi inferior a um mês (19,19 versus 20,63 meses), traduzindo-se num benefício clinicamente muito modesto (HR = 0,85; IC 95%, 0,73-0,99; p = 0,0351).

A avaliação da OS (com 57% de maturidade à data do cut-off) revelou uma diferença não significativa (HR = 1,01; IC 95%, 0,86-1,19; p = 0,9060).

Na análise de subgrupos, não foi identificada nenhuma categoria em que o dostarlimab apresentasse maior benefício, incluindo na população PD-L1 positiva.

Quanto aos eventos adversos relacionados com o tratamento, as taxas foram semelhantes entre os dois braços, embora tenha sido observada uma percentagem ligeiramente superior de descontinuações terapêuticas no braço experimental, bem como, como esperado, maior incidência de eventos imunomediados. Apesar disso, não se registaram diferenças clinicamente relevantes nos PROs (Patient-Reported Outcomes), com preservação da QoL e da funcionalidade ao longo do tratamento.

Em suma, os resultados deste estudo reforçam a ausência de benefício em associar imunoterapia à primeira linha de tratamento do carcinoma epitelial do ovário, dado o ganho em PFS inferior a um mês, não justificando o aumento de toxicidades – sobretudo imunomediadas – nem o acréscimo de custos financeiros.

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ROSELLA: a phase 3 study of relacorilant in combination with nab-paclitaxel versus nab-paclitaxel monotherapy in patients with platinum-resistant ovarian cancer (GOG-3073, ENGOT-ov72)

O relacorilant, um fármaco oral com um mecanismo de ação único, é um inibidor seletivo do recetor de glicocorticoides, o qual se expressa frequentemente nos carcinomas do ovário e está envolvido em mecanismos de carcinogénese, associando-se a pior prognóstico[1-2]. Ao inibir este recetor, o relacorilant potencia os efeitos terapêuticos da quimioterapia[3].

O ROSELLA foi um ensaio aberto e randomizado que incluiu doentes com carcinoma epitelial do ovário previamente tratadas com 1 a 3 linhas de tratamento (incluindo bevacizumab) e com doença resistente à platina. Foram excluídas as doentes sem qualquer resposta prévia à platina ou com progressão em menos de 1 mês após o último tratamento.

O recrutamento decorreu num curto período de 15 meses, tendo sido randomizadas 381 doentes numa proporção de 1:1 para nab-paclitaxel isolado versus relacorilant + nab-paclitaxel. O relacorilant foi administrado na dose de 150 mg nos 3 dias peri-tratamento da infusão de nab-paclitaxel. O nab-paclitaxel foi administrado semanalmente durante 3 semanas em ciclos de 28 dias.

O estudo teve dois coendpoints primários: PFS avaliada por um comité independente de revisão central (BICR) e OS. A taxa de resposta objetiva (ORR) e a segurança foram avaliadas como endpoints secundários.

Num estudo com uma população de alto risco (> 80% das doentes tinham recebido pelo menos duas linhas de tratamento e > 60% tinham sido tratadas previamente com iPARP), observou-se um benefício estatisticamente significativo na PFS-BICR a favor da combinação experimental, com redução do risco de progressão em 30% (HR 0,70 [IC 95%, 0,54-0,91]; p = 0,0076). À data do cut-off, a OS (com 50% de maturidade) revelou uma diferença clinicamente relevante, com HR de 0,69 e uma diferença absoluta aos 6 meses de 11%.

Na análise de subgrupos, o benefício do relacorilant foi consistente em todas as categorias, com maior magnitude em alguns subgrupos de alto risco, como nas doentes previamente tratadas com iPARP, com resistência primária à platina e com doença de maior volume tumoral.

Em relação aos endpoints secundários, não se verificou diferença estatisticamente significativa na ORR (36,9% vs. 30,1%; p = 0,17). No entanto, observou-se uma menor percentagem de doentes a desenvolver ascite e a necessitar de paracentese no braço experimental. O relacorilant, ao aumentar o potencial da quimioterapia, também levou a um aumento dos seus principais eventos adversos, nomeadamente hematológicos e fadiga. Ainda assim, após ajuste para o tempo de exposição ao tratamento (30% superior no braço com relacorilant), a incidência de neutropenia e anemia foi praticamente comparável entre os dois braços.

Com base nos resultados deste ensaio, que ainda aguarda os dados finais de OS, surge a possibilidade de um novo standard of care na doença platino-resistente, que pode ser administrado independentemente da expressão de biomarcadores – ainda que esta combinação dependa da utilização de quimioterapia e das toxicidades associadas.

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KEYNOTE-A18 / ENGOT-cx11 / GOG-3047: pembrolizumab with chemoradiotherapy in patients with high-risk, locally advanced cervical cancer – final analysis of a phase 3 randomized, double-blind study

O tratamento standard do carcinoma do colo do útero localmente avançado tem sido, desde 1999, a quimiorradioterapia radical (QRT), seguida ou não de braquiterapia. Desde então, apenas a radioterapia (RT) sofreu alguma evolução, com a introdução de técnicas mais modernas (IMRT e VMAT), que reduziram substancialmente a toxicidade locorregional e melhoraram o controlo local da doença[1-3]. Mais recentemente, a quimioterapia (QT) de indução, seguida do tratamento standard, surgiu como uma nova possibilidade terapêutica por demonstrar um benefício na sobrevivência global (OS). No entanto, o ensaio INTERLACE foi alvo de algumas críticas, nomeadamente por utilizar predominantemente técnicas de RT convencionais (menos eficazes) e por apresentar um tempo de recrutamento muito prolongado[4].

O Keynote-A18 foi um ensaio randomizado e duplamente cego que incluiu 1060 doentes provenientes de 30 países, com carcinoma cervical de alto risco (estadio IB2-IIB com doença ganglionar, ou III-IVA independentemente do envolvimento ganglionar, segundo a versão de 2014 do sistema de estadiamento FIGO), naïve de tratamento e com doença mensurável. As doentes foram randomizadas na proporção 1:1 para tratamento standard versus tratamento standard + pembrolizumab (200 mg a cada 3 semanas, durante 5 ciclos), seguido de 15 ciclos de pembrolizumab de manutenção (400 mg a cada 6 semanas).

O ensaio teve dois endpoints primários, avaliados de forma hierárquica: a PFS (sobrevivência livre de progressão), avaliada pelo investigador ou por confirmação histológica, e a OS. Os endpoints secundários incluíram a taxa de resposta objetiva (ORR), a qualidade de vida (QoL) e a segurança.

O estudo previa duas análises interinas, pelo que os dados de PFS e OS já haviam sido apresentados em 2023 e 2024, respetivamente. Nesses momentos, a PFS mostrou-se estatisticamente significativa, com uma redução de 30% no risco de progressão (HR 0,70), assim como a OS, com uma redução de 33% no risco de mortalidade (HR 0,67).

A análise final, apresentada na ASCO 2025, confirmou os resultados preliminares, com uma diferença absoluta na PFS de quase 10% aos 3 anos (HR 0,72 [IC 95%, 0,59-0,87]) e na OS de aproximadamente 7% (HR 0,73 [IC 95%, 0,57-0,95]). A ligeira diferença observada na OS em relação à última análise interina foi justificada pelos autores pela elevada percentagem de doentes censuradas nesta fase e por uma maior proporção de doentes submetidas a imunoterapia subsequente no braço de controlo.

De acordo com os resultados prévios, o benefício foi consistente em todos os subgrupos, com a possível exceção das doentes com mais de 65 anos (devido ao baixo número de eventos observados).

O perfil de segurança da QRT combinada com pembrolizumab mostrou-se manejável e consistente com o esperado para cada terapêutica individualmente. A percentagem de eventos adversos de grau ≥ 3 e as

taxas de descontinuação foram muito semelhantes entre os dois grupos.

No Keynote-A18, quase 90% das doentes realizaram RT com as técnicas mais recentes, sendo de destacar a presença de doença ganglionar em aproximadamente 85% das participantes.

A qualidade metodológica deste ensaio foi amplamente reconhecida, uma vez que foi conduzido em plena pandemia, com a participação de múltiplos centros e países, mantendo o cumprimento rigoroso do calendário terapêutico definido no protocolo e um período de recrutamento de apenas dois anos.

Após mais 12 meses de follow-up, esta análise descritiva confirma, por fim, a melhoria clínica e estatisticamente significativa associada à adição do pembrolizumab em fases mais precoces da doença, quando considerada de alto risco. Tendo em conta o contexto atual das novas técnicas de RT, este regime terapêutico deverá provavelmente constituir o novo standard of care para doentes com carcinoma do colo do útero localmente avançado, de alto risco, que sejam candidatas a imunoterapia.

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DIGESTIVE ONCOLOGY

Evolving paradigms in digestive oncology: highlights and reflections from ASCO 2025

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Trastuzumab deruxtecan (T-DXd) versus ramucirumab (RAM) + paclitaxel (PTX) in second-line treatment of patients (pts) with human epidermal growth factor receptor 2-positive (HER2+) unresectable/metastatic gastric cancer (GC) or gastroesophageal junction adenocarcinoma (GEJA): primary analysis of the randomized, phase 3 DESTINY-Gastric04 (DG04) study

DG04, which evaluated T-DXd against the current standard of care combination of RAM and PTX in patients with unresectable or metastatic HER2+ gastric or gastroesophageal junction (GEJ) adenocarcinoma who had progressed on prior trastuzumab-based therapy. T-DXd demonstrated a statistically significant improvement in overall survival and met its primary endpoint, with a reduction of the risk of death of 30% (14.7 vs. 11.4 months; hazard ratio [HR] 0.70; p = 0.0044). This trial highlights the growing relevance of antibody-drug conjugates in gastrointestinal cancers. However, although most of the adverse events related to the treatment were manageable, the 13.9% incidence of interstitial lung disease warrants caution, underscoring the need for close monitoring and patient education. DG04 is a landmark study that will likely influence second-line treatment standards of HER2-positive gastric or GEJA.

Event-free survival (EFS) in MATTERHORN: a randomized, phase 3 study of durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel chemotherapy (FLOT) in resectable gastric/GEJ cancer (GC/GEJC)

In the early-stage setting, the MATTERHORN trial investigated the addition of durvalumab to the perioperative FLOT regimen in patients with resectable gastric or GEJ adenocarcinoma. Patients in the study arm received neoadjuvant durvalumab (2 cycles) plus FLOT, followed by adjuvant durvalumab (2 cycles) plus FLOT, and then durvalumab monotherapy (10 cycles). The primary endpoint was EFS. At 24 months, 67.4% of the participants in the durvalumab arm remained event-free, compared to 58.5% of the placebo group, with an HR of 0.71 (p < 0.001) and median EFS not yet reached (vs. 32.8 months for the placebo arm). The study suggests meaningful benefit from incorporating immunotherapy in curative-intent treatment. The safety profile of perioperative durvalumab in combination with FLOT was consistent with the known profiles of the individual agents, suggesting that the addition of durvalumab did not exacerbate treatment-related toxicity. As expected, given its mechanism of action, immune-mediated adverse events were more frequent in the durvalumab group than in the placebo group. Importantly, the combination did not impede patients' ability to undergo surgery or receive adjuvant

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therapy. While overall survival data are still maturing, this trial may pave the way for perioperative immunotherapy to become a standard approach. Nevertheless, the potential for overtreatment underscores the need for precise biomarker-based stratification, and further investigation is warranted to delineate the individual contributions of the neoadjuvant and adjuvant components.

Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) or NIVO monotherapy for microsatellite instability-high/deficient mismatch repair- (MSI-H/dMMR) metastatic colorectal cancer (mCRC): expanded analyses from CheckMate 8HW

The CheckMate 8HW trial was another landmark in the immunotherapy area, specifically for mCRC with dMMR or MSI-H). This study compared NIVO plus IPI to both NIVO monotherapy and chemotherapy in the first-line setting. With a median follow-up of 47 months, the dual checkpoint blockade demonstrated a 72% reduction in the risk of progression or death compared to chemotherapy and a 43% reduction versus monotherapy. In this year's update, an important exploratory endpoint was presented, the progression-free survival 2 (PFS2), defined as the time from randomization to disease progression following subsequent systemic therapy or death, providing a broader assessment of sustained therapeutic benefit beyond initial treatment. In treatment-naïve patients with centrally confirmed MSI-H/dMMR mCRC, the combination of NIVO and IPI led to a median PFS2 that was substantially prolonged with immunotherapy, remaining unreached versus 30.3 months with chemotherapy (HR 0.28). Another important finding was that only 16% of patients treated with first-line NIVO plus IPI required subsequent therapies, compared to 73% of those receiving chemotherapy, highlighting the superior efficacy of the immunotherapy combination in the frontline setting. These findings solidify dual immunotherapy as the preferred frontline strategy for this subgroup of patients.

Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III deficient DNA mismatch repair (dMMR) colon cancer (Alliance A021502; ATOMIC)

In the adjuvant setting, the ATOMIC trial examined the efficacy of adding atezolizumab to the standard mFOLFOX6 regimen in patients with stage III dMMR/MSI-H colon cancer. The trial reported a 3-year disease-free survival of 86.4% versus 76.6% (HR 0.50; $p < 0.0001$), representing a 50% reduction in the risk of death. The addition of atezolizumab offers substantial improvements in disease-free survival, representing a major advancement in adjuvant therapy for this subgroup of colon cancer patients. Yet, it remains to be seen whether chemotherapy is a necessary component or if immunotherapy alone could suffice in future protocols. In addition, the absence of mature overall survival data and detailed biomarker analyses, calls for cautious optimism.

First-line encorafenib + cetuximab + mFOLFOX6 in BRAF V600E-mutant mCRC (BREAKWATER): PFS and updated overall survival analyses

The BREAKWATER trial addressed a long-standing clinical challenge: treating BRAF V600E-mutated mCRC, a molecular subgroup historically associated with poor prognosis and limited therapeutic options. This study compared a triplet regimen – encorafenib, cetuximab, and chemotherapy – with the standard chemotherapy plus bevacizumab. The results were compelling, with a PFS of 12.8 months versus 7.1 months (HR 0.53) and an overall survival of 30.3 months versus 15.1 months (HR 0.49), with the triplet regimen resulting in a reduction of the risk of death by 51% compared to standard chemotherapy. The combination regimen had a manageable safety profile, consistent with what is known for each agent. These gains nearly doubled patient survival outcomes and positioned this triplet therapy as the new standard for this molecular subtype.

Conclusion

ASCO 2025 delivered transformative data in digestive oncology. These five trials underscore the promise of precision medicine and immunotherapy in improving patient outcomes across the disease spectrum. The shift toward biomarker-driven, individualized treatment approaches is not only promising but also essential for modern oncology practice. As further data emerge and these findings are integrated into clinical guidelines, multidisciplinary collaboration and real-world evidence will play a critical role in shaping the future of gastrointestinal cancer care.

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ORIGINAL ARTICLE

Personalised nutritional care in an integrated screening protocol: the green way of oncology nutrition in Portugal

Nutrição personalizada em protocolo de rastreio integrado: a via verde da nutrição oncológica em Portugal

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Abstract

Background: *Nutrition is critical in the management of cancer. Among patients with cancer, it is of utmost importance to identify clinical findings such as malnutrition, sarcopenia, impaired physical function, or cachexia, which may negatively impact treatment tolerance, quality of life, and survival. Experts agree on the importance of early identification of patients at risk of malnutrition or muscle loss, and recent international guidelines advocate for incorporating nutritional screening, assessment, treatment, and monitoring as integral components of cancer care.* **Objectives:** *With this article, we propose a standardized approach to nutritional diagnosis, referral for nutritional intervention, and monitoring, in a comprehensive manner adapted to various clinical scenarios.* **Methods:** *This approach should be multidisciplinary throughout the cancer patient's journey to ensure continuity of care and optimal outcomes.* **Results and Conclusion:** *It is recommended that physicians, nurses, pharmacists, dietitians/nutritionists, and other healthcare professionals working in oncology remain vigilant for signs and symptoms of nutritional impact.*

Keywords: *Malnutrition. Muscle depletion. Muscle function. Nutritional risk. Nutritional care process. Cancer. Oncology.*

Resumo

Introducão: *A nutrição é fundamental no tratamento do câncer. Entre os pacientes oncológicos, é de extrema importância identificar achados clínicos, como desnutrição, sarcopenia, redução da função física ou caquexia, que podem impactar negativamente a tolerância aos tratamentos, a qualidade de vida e a sobrevivência. Especialistas concordam quanto à importância da identificação precoce de pacientes em risco de desnutrição ou perda de massa muscular, e diretrizes internacionais recentes recomendam a incorporação do rastreamento, avaliação, tratamento e monitoramento nutricional como componentes integrais do cuidado oncológico.* **Objetivos:** *Com este artigo, propomos uma abordagem padronizada para o diagnóstico nutricional, encaminhamento para intervenção nutricional e monitoramento, de forma abrangente e adaptada a diversos cenários clínicos.* **Métodos:** *Essa abordagem deve ser multidisciplinar ao longo de toda a trajetória do paciente oncológico, a fim de garantir a continuidade do cuidado e os melhores resultados possíveis.* **Resultados e Conclusão:** *Recomenda-se que médicos, enfermeiros, farmacêuticos, nutricionistas e outros profissionais de saúde que atuam na área de oncologia mantenham-se atentos aos sinais e sintomas de impacto nutricional.*

Palavras-chave: *Malnutrição. Depleção muscular. Função muscular. Risco nutricional. Cuidados nutricionais. Cancro. Oncologia.*

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Introduction

Nutrition is critical to the management of cancer, and it is of utmost importance to identify clinical findings that may negatively impact tolerance to treatments, quality of life, and survival, e.g. malnutrition, sarcopenia (weight loss and depletion of muscle mass and function), physical function or cachexia (severe weight loss characterised by a persistent decline in skeletal muscle mass, with or without fat loss)[1-4].

Malnutrition affects between 30% and 80% of cancer patients, with the highest prevalence observed in pancreatic (60-80%), gastric (50-75%), oesophageal (60-70%), and head and neck cancers (50-70%), due to tumor location, systemic inflammation, and treatment side effects[5]. Furthermore, among cancer patients undergoing active treatment, the prevalence of malnutrition or nutritional risk ranges from 40% to 80%, regardless of cancer type, highlighting the need for routine nutritional screening and early intervention as soon as the patients start anti-cancer treatments[6].

Loss of muscle mass heightens the risk of dose-limiting toxicity, as depleted patients are less likely to benefit from anticancer treatments[7-16]. Muscle depletion can directly impair the treatment efficacy, making it essential to identify and assess nutritional risks in all cancer patients, regardless of disease stage[12,17,18].

Nutritional factors should be monitored continuously, before, during, and after treatments to enhance efficacy and minimize side effects. Early detection of nutritional impairment is crucial to ensure patients remain eligible for active treatment[19-21].

Apart from nutritional parameters, muscle function has emerged as a key marker of sarcopenia and, eventually, cachexia. In head and neck cancer, handgrip strength (HGS) measurement at diagnosis was adequate to discriminate patients with sarcopenia, shorter survival, and those at risk of relapse (Orell et al. 2025; data submitted)[22]. HGS is an indirect indicator of muscle mass and nutritional status, serving and stands as an important biomarker of health in this patient population. Its utility extends to identifying diverse health issues and its potential as a new vital sign throughout the disease trajectory[20,21].

A recent study involving patients with cancer at nutritional risk identified several malnutrition and muscle health parameters as independent prognostic indicators for mortality[23]. The modified Global Leadership Initiative on Malnutrition, (European Society for Clinical Nutrition and Metabolism [ESPEN]) criteria[24], low albumin concentration, reduced HGS, and decreased muscle radiodensity were reported to provide prognostic information regarding 180-day mortality. Again, several parameters reflecting malnutrition and muscle function emerged as independent prognostic indicators of mortality (Orell et al. 2025; data submitted)[22].

It is worth noting that nutrition is a fundamental human right that cannot be foreseen or overlooked[20]. Supporting early diagnosis of muscle loss ensures all patients receive the nutrition care essential for effective treatment. Engaged professionals and easy-to-apply protocols help ensure that all patients using healthcare services receive high-quality nutritional care. Human rights norms, ethical values, and principles can contribute to moving forward in promoting patient's access to appropriate nutritional care[20].

Based on this framework, maintaining an adequate nutritional status and body composition is linked to better tolerance of anticancer therapies, fewer post-surgical complications, and improved long-term outcomes, including survival[21,24-30].

Experts agree on the importance of early identification of patients at risk of malnutrition or muscle loss, and recent international guidelines advocate for incorporating nutritional screening, assessment, treatment, and monitoring as integral components of cancer care[31-34].

Therefore, a standardized approach to nutritional diagnosis, nutrition intervention, and monitoring is necessary.

Several tools/protocols exist for nutritional screening and stratification, but none integrates muscle function. A quick diagnosis integrating nutritional risk and muscle function seems the most useful and informative in the long term[30], and this is what we propose in the present article. It is mandatory to integrate this critical task into the whole process of the patient disease management, ensuring it is feasible and effective within a busy oncology practice[34].

Ideally, such a protocol can be integrated into a machine-learning model and swiftly transferred to any institution's patient management platform.

Objectives

Our main goal is to provide a practical protocol to identify the risk of malnutrition, of muscle mass depletion, and of muscle dysfunction in patients with cancer, which is key information for the treatment plan enabling timely evaluation and follow-up by a multidisciplinary team. Applicable at the start of any anti-cancer therapy, regardless of cancer type or stage, this protocol is

straightforward and efficient for regular monitoring and early detection of nutritional issues throughout treatment. With this article, we intend to empower clinicians to swiftly identify at-risk patients, facilitating prompt referral for comprehensive nutritional assessment by a clinical nutritionist. This protocol is not intended to replace existing guidelines or tools for nutritional evaluation but to ensure that patients needing such support are quickly identified and managed. As medicine evolves, we foresee that in a near future, this protocol could be integrated into patients' records using machine learning, allowing full integration of nutrition information in all medical decisions. It is noteworthy that universal nutritional care greatly benefits patients with cancer, and shared responsibility in identifying, referring to, and intervening nutritionally is the expected quality of all healthcare institutions.

Methods

A multidisciplinary group of national/international experts in oncology, with a specific focus on nutrition, and with medicine, oncology, nutrition, and nursing backgrounds was selected to integrate an expert panel, consisting of two physicians (one KOL in clinical nutrition, metabolism, and oncology), two clinical nutritionists, and an oncology nurse specialist. The panel met periodically to review existing literature, align objectives, and draft the protocol support text monthly. In these meetings consensus was reached through structured discussion, clarification of differing views, and formal agreement, supported by voting or rating methods. There was a final recap meeting in person, with additional discussions via email and Microsoft Teams® as necessary.

The plan was:

- The first meeting listed challenges and potential obstacles perceived by clinical teams regarding nutritional screening and assessment within the patient's journey.
- After carefully reviewing the literature, the second and third meetings identified key concepts that were used to build the protocol framework, for routine clinical use. Literature review was made by an integrative and narrative review, combining diverse types of evidence to provide context, background, and expert interpretation, to develop comprehensive clinical understanding useful for framing the clinical problem and justifying protocol need, to address complex, multidimensional aspects of care (e.g., nutrition care in cancer).
- Fourth and fifth meetings were used to gather and interpret the evidence generated by the review and consolidate practical recommendations.
- Subsequent meetings were used to discuss and align fundamental components and tools identified, to form the basis of the practical protocol to identify nutritional risk and muscle depletion in oncology and design a reproduceable format of the protocol.

Results and discussion

The nutritional care process, as a systematic approach that aims to provide the best nutritional care, is a process described in four stages: assessment, diagnosis, intervention, and monitoring/nutritional evolution[31]. This process is triggered by screening, and referral should be based on appropriate tools and methods, assuming a multidisciplinary involvement[35]. The multidisciplinary team is responsible for ensuring that the patient's nutritional needs are met and that the best care is provided during the disease journey[36]. This is aligned with Horizon 2030 strategy (Despacho nº 13227/2023)[37] that reinforced earlier legislation (Despacho nº 9984/2023)[38] to implement systematic nutritional risk screening (NRS) in cancer in the National Health Service (primary care, hospital, and palliative care).

For outpatients, in the National Plan for Oncological Diseases, screening is advised at each care stage or according to clinical indication. The suggestion is to assess, by 2030, nutritional risk in over 50% of patients within a month before their first consultation, and access to nutritional support by specialized professionals in more than 90% of patients at nutritional risk. Ideally, nutrition consultations for outpatients with cancer and at high risk of malnutrition should take place within 15 days after signaling access to nutritional support and nutritional therapy is now predicted in Portuguese legislation (*Portaria* nº 82/2025/1)[39].

Identification of patients with or at risk of malnutrition and/or muscle depletion

Protocol proposal

Among the validated tools for nutritional screening, for example, Malnutrition Universal Screening Tool, NRS, NutriScore and Mini Nutritional Assessment, the adequate one should be selected in each institution as the most valid and feasible (Supplementary data I-IV)[34-37,40,41]; Furthermore, a minimum set of informative questions was

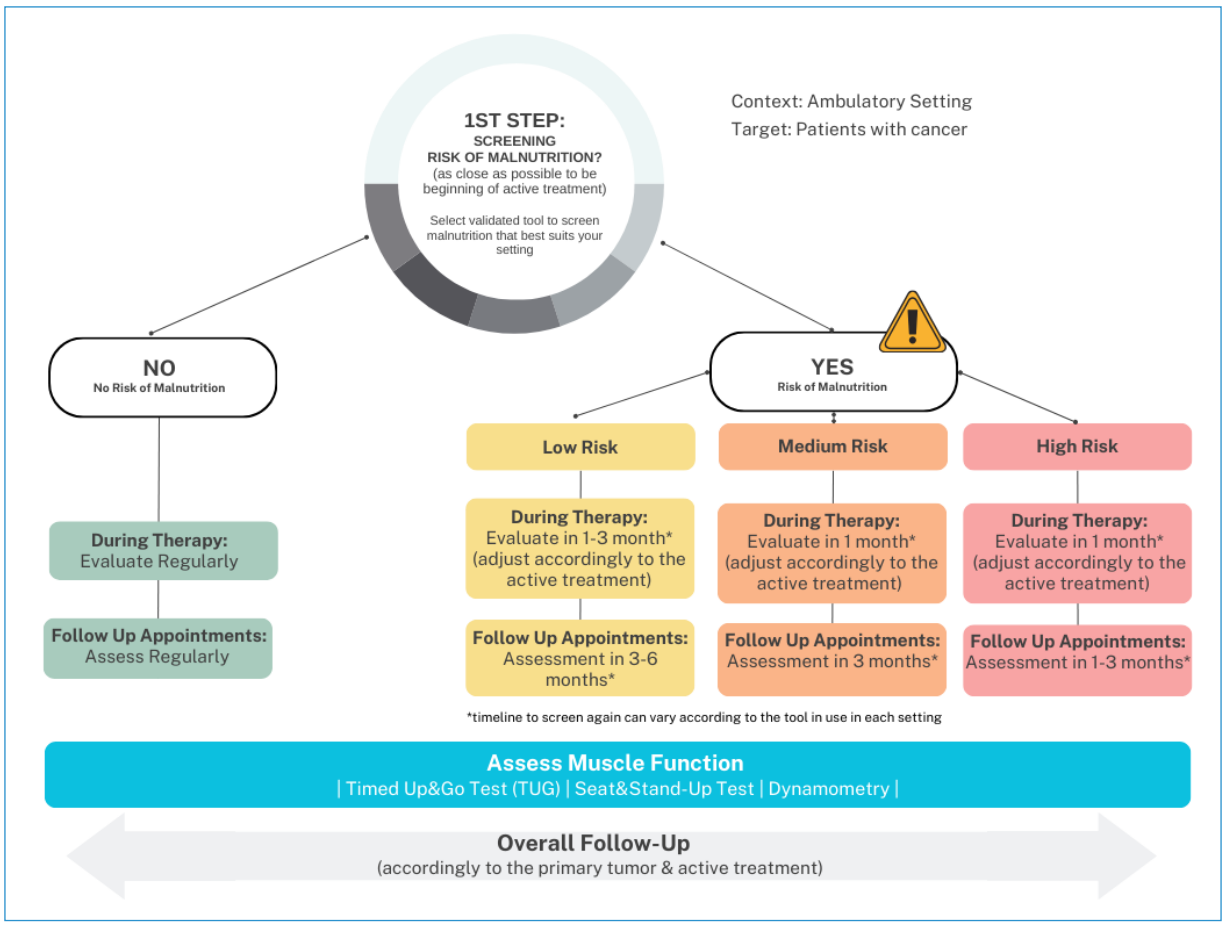

Figure 1. Flowchart for malnutrition and muscle depletion risk assessment.

identified to determine the risk of muscle depletion and muscle function in patients scheduled to begin antineoplastic therapy and to monitor any change in patients' nutritional status before and throughout treatments (Supplementary data IV). The expert panel identified factors as essential components to give a rapid understanding of patients' nutritional and physical status: (1) NRS by validated tool (Supplementary data II): weight history and nutritional intake, and (2) muscle function by dynamometry or test up and go or sit and stand-up test (Supplementary data). Nutritional monitoring and assessment of nutritional risk should be conducted at each treatment cycle, monthly, or as clinically indicated, to ensure timely identification and management of nutritional decline during cancer therapy.

Our proposal is that screening should be used to determine the risk of malnutrition and muscle mass depletion for systematic application[36,37]. The rapid identification of patients at-risk enables their prompt referral for additional assessment[24]. All patients with cancer referred for active treatment should be screened, regardless of their tumor type (Fig. 1).

Screening can be conducted by a nurse, physician, or clinical nutritionist using one of the tools indicated and validated for oncology patients (Supplementary data I-IV)[42-47].

Nutritional assessment should occur in patients identified at risk, using validated tools for oncology, ideally as close as possible to the timing of cancer diagnosis. This preliminary information allows for stratifying patients so that the nutritional care process is as efficient and appropriate as possible[36].

As muscle depletion is common in oncology patients, it is recommended that, in addition to nutritional screening, muscle mass screening be performed at the time of diagnosis (or as close as possible) and whenever there is a change in the patient's clinical situation[29,48-51].

If the expected survival is 3-6 months, the focus should be on identifying and managing symptoms that negatively interfere with eating and quality of life[29].

Reductions in patient-perceived strength and general mobility may be related to muscle depletion, such as their ability to carry out ordinary daily activities (i.e., open

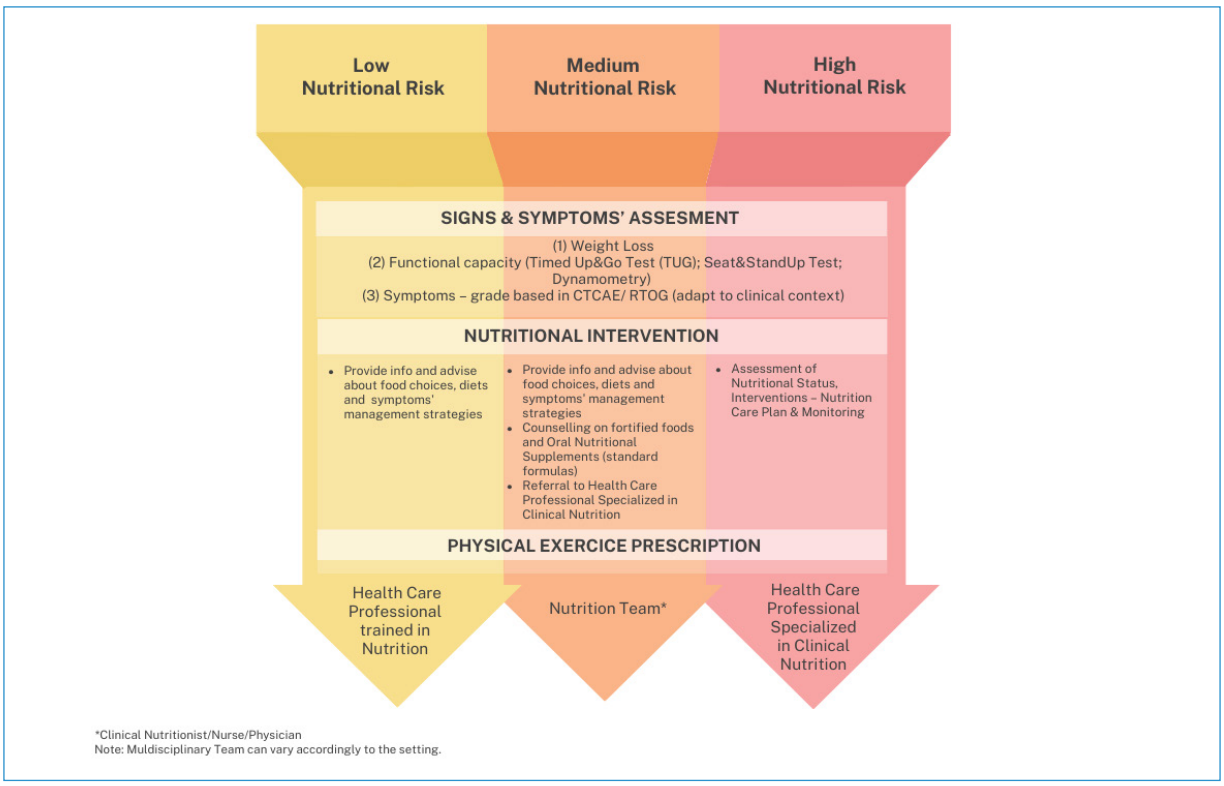

Figure 2. Flowchart of action for nutritional care provision following patient screening[43,52-54].

bottles, stand up from a chair, climb up the stairs, or lift heavy objects)[1-3,14,15,19]. Muscle loss is a common feature found in patients diagnosed with cancer, independent of the specific cancer type. Muscle depletion rates exceeding 50% have been observed in advanced cancer patients, especially those with pancreatic, lung, and gastrointestinal cancers, and are strongly associated with cancer cachexia. Importantly, muscle depletion may occur independently of body weight loss or a drop in body mass index. For this reason, changes in muscle mass should be identified in addition to changes in body weight[1-3,17], especially as muscle depletion can be hidden in patients with excess body weight (i.e., overweight or obese) at the time of diagnosis[12,13].

Although there is no specific instrument for Oncology, tools are validated for other contexts capable of assessing muscle function, such as the ones proposed in the present protocol (Supplementary data IV).

Managing the patient with or at risk of malnutrition and/or muscle depletion

After screening patients with the proposed protocol, the practical conduct of the clinician according to the level of risk encountered in the patient is presented in (Fig. 1). Fig. 2 represents the nutritional care process activated by the screening process (Supplementary data I for tools).

Identification of patients with or at risk of malnutrition and/or muscle depletion should ideally be followed by referral to appropriate multidisciplinary care team members for full nutrition and strength/mobility assessments to guide a tailored therapy intervention plan[27,28,55].

However, as the availability of professionals and time limitations might hinder such actions, our protocol also guides managing and monitoring patients during treatment (Fig. 2). The ESPEN recommendations for actions also link to further evidence-based nutrition resources for healthcare professionals and patients[56].

Patients with no nutritional risk should be recommended to monitor their weight. In addition, these patients should receive basic dietary counseling to maintain or improve their nutrient intake during treatment. Physical activity should be encouraged. It has many benefits, including improved muscle strength, reduced fatigue and anxiety, and improved quality of life[56] (Fig. 2). Patients reporting no change in strength or mobility should be advised to monitor their activity levels and engage in regular physical activity to reduce the risk of atrophy.

Early nutritional support for patients identified with moderate or high risk of malnutrition or muscle depletion can reduce the possibility of therapy-threatening adverse events and optimize the likelihood of treatment success and long-term survival. Early nutritional intervention may be associated with improved outcomes and a better quality of life, including emotional and psychological status. Additional studies highlight the benefits of early and prospective nutritional management during systemic antineoplastic therapy. Specifically, studies have shown the benefits of oral nutritional supplements (ONS) and enteral nutrition for patients undergoing antineoplastic treatment[57-60].

When a clinical nutritionist is part of a multidisciplinary oncology team, best practice involves the immediate and direct referral of patients who are malnourished or at risk of malnutrition, or who have low strength or mobility, for further assessment. However, the expert panel recognized that referral for a clinical nutritionist is not always available, and the treating oncologist may be required to advise and ensure that patients have access to nutritional supplementation, as required[61]. Globally, in most developed countries, nutrition products are reimbursed by the state for patients. In Portugal, this became a partial reality in 2025. The *Portaria* No. 82/2025/1[39], of March 4, establishes the exceptional reimbursement scheme for health technologies related to enteral nutrition, covering enteral formulations, modular formulations, and ONS, which will take effect from August 1, 2025."

The ESPEN and the European Society for Medical Oncology provide detailed guidance on nutritional support and intervention for patients diagnosed with cancer and undergoing antineoplastic treatment[31,56].

These guidelines provide recommendations for total daily energy that should meet the standard daily energy expenditure of healthy adults of between 25 and 30 kcal/kg/day, protein intake of > 1.2 g/kg/day, and, if possible, up to 1.5 g/kg/day, and vitamin and mineral supplementation equal to the recommended daily amounts for healthy individuals or to correct any diagnosed deficit. The source of protein is a relevant factor for muscle anabolism. The source of protein should also be considered for optimal muscle anabolism[4,21,62].

Energy requirements might be achieved with the usual recommendations of "little and often" and "fortified foods" or with ONS, which can also improve protein and micronutrient intake. Furthermore, enteral nutrition must be considered if oral intake remains inadequate to meet requirements despite added ONS. Guidelines also recommend maintenance or an increased level of physical activity in patients with cancer to support muscle mass, strength/mobility, and metabolic pattern (ESPEN)[56,61,63].

Physical activity and individualized resistance exercise can support health-related quality of life and self-esteem, as well as a reduction in fatigue and anxiety for patients with cancer, and should be encouraged to reduce risks of atrophy due to inactivity (ESPEN)[56].

When should nutritional checks be undertaken in patient consultations, and by whom?

The expert panel suggests that early identification of nutritional risk should be undertaken at diagnosis, regardless of age, disease stage, or cancer type (Fig. 1). As such, checkpoints for identification of nutritional risk should be undertaken at any scheduled or unscheduled medical oncology/radiation oncology visit. Nutritional monitoring and assessment of nutritional risk should be conducted at each treatment cycle, monthly, or as clinically indicated, to ensure timely identification and management of nutritional decline during cancer therapy. The panel recommended that checkpoints for the identification of nutritional risk should be performed at the time of disease recurrence and whenever a treatment change is considered before and after surgery[2,4,64,65].

The expert panel endorses that the initial identification of nutritional risk should be undertaken by the medical or radiation oncologist and/or the oncology nurse, clinical nutritionist (when available), or other attending healthcare professional leading patient care. Some specialist centers may have a Nutrition Service to which patients are automatically referred for nutritional evaluation and support at diagnosis. However, for most patients, their primary interaction will be with their treating physician, which is the reason for the recommendation. Ideally, patients identified at regular checkpoints and *via* monitoring of nutritional status during antineoplastic treatment can then be referred for a detailed nutritional assessment by nutrition experts. There was consensus that it is not expected that medical oncology specialists undertake complete nutritional assessments, unless if fully trained and scientifically differentiated in clinical nutrition, according to the recently created competence in Clinical Nutrition of the National Board of Physicians (*Ordem dos Médicos*), with already more than 50 physicians experts in clinical nutrition. Thus, given the national reality, if a referral is

not possible, early identification of malnutrition and muscle depletion should be a key point for management by members of the multidisciplinary team[31,32,56].

Conclusion

Malnutrition and/or muscle depletion significantly impact cancer patients and, consequently, their prognosis. State-of-the-art cancer care involves a multidisciplinary and multimodal intervention supported by the best evidence and clinical practice recommendations. Timely and systematic screening for malnutrition and muscle depletion, using validated tools, allows the identification and stratification of nutritional risk and, consequently, structuring the most appropriate needs and interventions.

The proposed protocol aims to streamline the integration of key issues for nutritional management and treatment of cancer patients in a comprehensive and adapted manner to various clinical scenarios. To achieve this, we propose identifying and stratifying nutritional risk and muscle depletion in oncology for a prompt approach and intervention by healthcare professionals. This approach should be multidisciplinary throughout the patient's journey to ensure continuity of care and the best outcomes. Therefore, it is recommended that physicians, nurses, pharmacists, nutritionists, and other healthcare professionals working in the field of oncology be vigilant for signs and symptoms with nutritional impact.

For most patients, the focus should be identifying those at increased risk of malnutrition and/or muscle depletion at the time of diagnosis and monitoring for any change in status throughout treatment. Nutritional support should be valued as an essential component of the management of all patients with cancer undergoing antineoplastic therapy. In the same way, oncologists routinely evaluate a range of factors, including standard considerations such as blood counts and organ function, to determine whether a patient can commence antineoplastic treatment.

Where possible, delays in initiating antineoplastic therapy due to poor nutritional status should be avoided via the early identification of nutritional status and patient risk. However, the need to initiate immediate antineoplastic therapy must be considered alongside the risk of treatment-related toxicities and early treatment discontinuation in those whose nutritional status is poor. To prevent this nutritional decline, a standardized approach to identify and monitor the nutritional risk of patients commencing and undergoing antineoplastic therapy is proposed with the present protocol, which is feasible within the context of a demanding oncology practice.

Nutritional care has to be aligned with nutritional screening, both integrated with the oncological diagnosis and the initiation of medical therapy. Based on the most recent evidence, early identification of patients at risk or already malnourished during antineoplastic therapy is crucial to optimize treatment success. However, the need does not deflate on malnutrition screening; hence, frailty, muscle mass depletion, and muscle function are markers of early nutritional and clinical impairment that should be priority parameters for clinical assessment of all patients. Depletion of these variables predicts that the patient may not tolerate the recommended treatment intensity and duration, potentially impacting its effectiveness and short- and long-term outcomes.

Looking ahead in the field of medicine and nutrition, the proposed protocol offers more than just clinical guidance; it lays the groundwork for innovation through data integration. Designed to be simple, efficient, and applicable at the start of any anticancer therapy regardless of type or stage, the protocol enables continuous monitoring and early detection of nutritional issues. Building on this vision, the Centre for Interdisciplinary Research in Health and Católica Medical School are already developing a machine learning model that incorporates the full spectrum of patient data. This model aims to enhance diagnostic accuracy and personalize nutrition care across healthcare institutions, making proactive, data-driven interventions a reality in oncology.

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Supplementary data

Supplementary data are available at DOI: 10.24875/RPO.25000015. 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.

Author contributions

All authors contributed to the conception, design, writing, and approval of the protocol presented in the

manuscript. The opinions and recommendations presented here are those of the authors only.

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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 study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

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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PROTOCOLS

Definition of therapeutic limits and do-not-resuscitate decision in Oncology: the perception of different healthcare professionals in a portuguese hospital

Definição de limites terapêuticos e decisão de não reanimação em Oncologia: a perceção de diferentes profissionais de saúde de um hospital português

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Abstract

Introduction: *The definition of therapeutic limits and the establishment of do-not-resuscitate decisions are complex decisions that involve multidimensional assessments and the consideration of individual, prognostic, and ethical factors. In cancer patients, this is often necessary in advanced stages of the disease, in the absence of therapeutic options, and with a prognosis of short-term irreversibility.* **Analysis and Methods:** *The terminology used and the clarity of the information are essential in the management of cancer patients by multidisciplinary teams, with different healthcare professionals from various fields. This project aims to assess the perception of different healthcare professionals regarding the definition of therapeutic limits and do-not-resuscitate decisions in cancer patients, through the application of an anonymous questionnaire with responses based on a Likert scale and one open-ended question.* **Discussion:** *These data will be analyzed with the goal of developing more robust future tools for therapeutic decision-making. It is expected that this could positively contribute to the prevention of dysthanasia and the minimization of suffering for patients and their families.*

Keywords: *Therapeutic limits. Do-not-resuscitate decision. Terminology. Healthcare professionals. Oncology.*

Resumo

Introdução: A definição de limites terapêuticos e o estabelecimento de decisões de não reanimação são processos complexos que envolvem avaliações multidimensionais e a consideração de fatores individuais, prognósticos e éticos. Em pacientes oncológicos, essas decisões tornam-se frequentemente necessárias em estágios avançados da doença, na ausência de opções terapêuticas e diante de um prognóstico de irreversibilidade a curto prazo. **Métodos e Análise:** A terminologia utilizada e a clareza das informações são essenciais na gestão dos pacientes com câncer por equipes multidisciplinares, compostas por diferentes profissionais de saúde de diversas áreas. Este projeto tem como objetivo avaliar a percepção de diferentes profissionais de saúde em relação à definição de limites terapêuticos e às decisões de não reanimação em pacientes oncológicos, por meio da aplicação de um questionário anônimo com respostas baseadas em escala

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Likert e uma questão aberta. **Discussão:** Esses dados serão analisados com o intuito de desenvolver ferramentas futuras mais robustas para a tomada de decisões terapêuticas. Espera-se que isso possa contribuir positivamente para a prevenção da distanásia e a minimização do sofrimento dos pacientes e de suas famílias.

Palavras-chave: *Limites terapêuticos. Decisão de não reanimação. Terminologia. Profissionais de saúde. Oncologia.*

Introduction

The definition of therapeutic limits and the establishment of do-not-resuscitate decisions are complex decisions that involve multidimensional assessments and the consideration of individual, prognostic, and ethical factors[1,2]. In cancer patients, they are often necessary in advanced stages of the disease, in the absence of therapeutic options, and in situations with a prognosis of short-term irreversibility[3]. This type of decision is frequently made by the attending medical team, rather than by an individual decision-maker. Empiricism and prior experiences should not be exclusive factors in the decision-making process; instead, decisions should be clearly and comprehensibly documented in the clinical record[3,4]. Effective communication is key, and the terminology used, as well as the clarity of the information, are essential in the management of cancer patients by multidisciplinary teams, with different healthcare professionals from various fields. The perception of the communicated information quality should be assessed, to ensure the provision of optimal healthcare[5]. Despite the available literature about the definition of therapeutic limits and do-not-resuscitate decisions in the general population of patients[6-8], for the cancer patient was not possible to find information regarding previously established studies or instruments aimed at standardizing terminology when defining therapeutic limits in this setting.

This project aims to assess the perception of different healthcare professionals regarding the definition of therapeutic limits and do-not-resuscitate decisions in cancer patients, as well as the quality of communicated information. We hope this work will help in the development of robust future tools for therapeutic decision-making. It is expected that these tools could positively contribute to the prevention of dysthanasia and the minimization of suffering for patients and their families.

Materials and methods

Study design

This was longitudinal, prospective, and single-center study.

Study timeline

The study schedule is planned to take place between January 2024 and January 2026.

Participant identification, inclusion and exclusion criteria

The study's first target is the identification of healthcare professionals with potential direct contact with cancer patients, among different departments of *Hospital de Braga*, *ULS de Braga*.

The inclusion criteria are:

- 18 years of age or older
- Hospital de Braga healthcare professionals, among the following groups:
  - Medical Oncology Doctor (the one who provides care to the cancer patient in the context of urgent consultation in the oncology day care unit and/or the medical oncology ward, including residents and specialists)
  - Internal Medicine Doctor (the one who provides care to the cancer patient in the context of the emergency department and/or the internal urgency service and/or the internal medicine ward, including residents and specialists)
  - Emergency Department Doctor (the one who provides care to the cancer patient in the context of the emergency department (medical and/or surgical areas), including residents and specialists from different fields/medical specialties, as well as doctors with no differentiation/medical specialty)
  - Intensive Care Medicine Doctor (the one who provides care to the cancer patient in the context of the intensive care medicine department (level 2 and 3 of care), including residents and specialists)
  - Oncology Day Care Unit Nurse
  - Ward Nurse (oncology and/or internal medicine ward).
- Contact with cancer patients (defined as a contact that occurs at least once a month).

The exclusion criteria are:
- Healthcare professionals having contact with cancer patients less than once a month
- Healthcare professionals of pediatric cancer patients.

Data collection

Data collection will be performed through the application of an anonymous questionnaire to assess the perceptions of healthcare professionals regarding the definition of therapeutic limits and the establishment of do-not-resuscitate decisions. The definition of the terms "therapeutic limits" and "do-not-resuscitate decisions" was established based on previous internal institutional consensus[6]. The questionnaire was developed after extensive bibliographic research, based on previous studies that included both cancer and non-cancer patients. It comprises the following domains: (1) sociodemographic characteristics; (2) professional category (physician/nurse) and respective specialty; (3) nature and frequency of contact with cancer patients; (4) perceptions regarding the terminology and communication practices used by healthcare professionals when defining therapeutic limits and do-not-resuscitate decisions; (5) perceptions regarding the quality of communicated information towards other healthcare professionals, the patient and the family; and (6) perceived adequacy of diagnostic, treatment, and follow-up plans in light of those decisions. Majority of the questions require an answer based on a Likert scale. The last question is an open-ended question and demands the enumeration of variables that the respondents consider most relevant for the definition of therapeutic limits in cancer patients.

The questionnaire will be developed and distributed through digital form, through the *Microsoft Forms* online tool, available on the institutional *Office 365* (service provided by the Portuguese regulator, *Serviços Partilhados do Ministério da Saúde*).

The initial approach, contact, and recruitment of potential participants will be made after previous contact with the different team leaders (for doctors, the department director, and for nurses, the nurse manager). Through the mailing list of the department, which encompasses each healthcare professional's institutional email address, team leaders will divulge the study, as well as the access link to the questionnaire.

The questionnaire will demand a completely anonymous answer. No information that would allow a subsequent identification of the respondent will be collected. No further information about the participant will be collected other than the answers obtained through the questionnaire. A random numerical code will be assigned to each questionnaire, and the analyzed data will be protected to minimize the possibility of the identification of an individual. The approach to potential participants (through the divulgation of the study by team leaders) is another measure to minimize the personal data processing, aiming for quasi-anonymization.

Data analysis

The data will be collected by the investigation team and compiled in a *Microsoft Excel* file (directly exported from *Microsoft Forms*). This file will be protected by a robust password (according to *ULS de Braga* policies and internal procedures). The collected data will be analyzed using the software *IBM Statistical Package for the Social Sciences Statistics* version 29. A descriptive analysis will be performed for each question on the questionnaire. Inferential analysis will be conducted in an exploratory manner, focusing on the most relevant sociodemographic and clinical variables in accordance with the objectives of the study. The selection of an appropriate statistical model will be guided by the nature and distribution of the collected data. All subsequent inferential analyses will consider a p-value inferior to 0.05 as statistically significant.

Ethical considerations

The application of the questionnaire will begin following formal approval by the Institutional Data Protection Officer and Ethics Committee. Data collection will be carried out exclusively by the investigators through a secure electronic platform. No additional data will be collected beyond the responses to the questionnaire, and no information enabling direct identification of participants will be gathered. Data will be stored securely within Microsoft Office 365 cloud environments contracted by the institution, with access restricted to the investigators' team. All files will be password-protected and anonymized, in accordance with institutional data protection policies.

Team leaders will be contacted in advance to support and share the access link to the electronic questionnaire among their teams. This step serves as an additional measure to minimize the handling of personal data and promote quasi-anonymization.

The prospective application of a questionnaire demands the previous signature of informed consent.

Participants will provide digitally documented informed consent through *Microsoft Forms*, accessible exclusively through authenticated institutional login credentials, with a time-stamp record. Given that the questionnaire will be answered through *Forms*, the first page of the questionnaire will have the digital informed consent. Access to the questionnaire will be conditioned by the acceptance of the informed consent on the first page. The participant will not have access to the study questions until this step is fulfilled. This procedure ensures authentication and confidentiality while ensuring the reliability of the participant's signature of informed consent in accordance with ethical standards and data protection regulations.

Throughout the study, ethical conduct and good clinical practices will be upheld to ensure compliance with the principles outlined at the Declaration of Helsinki (including the amendments of Tokyo 1975, Venice 1983, Hong Kong 1989, Oviedo 1997, Washington 2002, Tokyo 2004, Seoul 2008); the EMEA Guidelines on Good Clinical Practice (London 2000); the World Health Organization International Ethical Guidelines for Health-Related Research Involving Humans (Geneva 2002); the International Ethical Guidelines for Epidemiological Studies of the Council for International Organizations of Medical Sciences (Geneva 2009); and Resolution No. 1/2001 of the Portuguese Assembly of the Republic.

This study will respect the current legal provisions relating to clinical research (Law No. 21/2014, 73/2015 and 49/2018; Directive of the European Parliament 2001/20/CE), as well as the rules of Ethical Conduct and Good Practice, to fulfill the precepts of the Declaration of Helsinki, the Good Clinical Practice of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use 2021 and the "*Parecer sobre Bioética e Saúde Mental*," of the *Conselho Nacional de Ética para as Ciências da Vida* (CNEV, National Council of Ethics in Life Sciences). The study will also respect the data protection legislation (Law No. 58/2019 and European Union Regulation (EU) 2016/679).

This investigation study was approved by *Comissão de Ética para a Saúde* (Health Ethics Committee) of *Hospital de Braga*, *ULS de Braga*, approval reference No. 222_2024, on 27/November/2024.

Funding

None.

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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CASE REPORT

Pneumocystis jirovecii *pneumonia during adjuvant chemotherapy of breast cancer: a hidden complication of the prophylactic corticosteroids?*

Pneumonia por *Pneumocystis jirovecii* durante a quimioterapia adjuvante do cancro da mama: o papel oculto dos corticosteróides antieméticos

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Abstract

We report three cases of Pneumocystis jirovecii *pneumonia (PJP) in patients with early-stage breast cancer undergoing (neo) adjuvant chemotherapy. All cases were associated with cumulative prophylactic corticosteroid exposure exceeding thresholds for PJP prevention thresholds accompanied by significant lymphocytopenia. Disease severity varied, with one patient requiring invasive mechanical ventilation. Despite this, all cases achieved favorable clinical and oncological outcomes. These cases underscore the importance of increased vigilance, optimization of corticosteroid dosing, and the implementation of prophylactic measures to reduce infection risk. In response, our institutional protocols were updated to lower corticosteroid prophylactic doses in the chemotherapy regimens.*

Keywords: *Breast cancer.* Pneumocystis jirovecii *pneumonia. Adjuvant chemotherapy. Corticosteroids.*

Resumo

Relatamos três casos de pneumonia por Pneumocystis jirovecii *(PJP) em pacientes com câncer de mama em estágio inicial submetidas à quimioterapia (neo)adjuvante. Todos os casos estavam associados à exposição cumulativa a corticosteroides profiláticos acima dos limites recomendados para a prevenção de PJP, acompanhada de linfocitopenia significativa. A gravidade da doença variou, com uma paciente necessitando de ventilação mecânica invasiva. Apesar disso, todos os casos apresentaram desfechos clínicos e oncológicos favoráveis. Esses casos ressaltam a importância de uma vigilância aumentada, da otimização da dosagem de corticosteroides e da implementação de medidas profiláticas para reduzir o risco de infecção. Em resposta, nossos protocolos institucionais foram atualizados para reduzir as doses profiláticas de corticosteroides nos regimes de quimioterapia.*

Palavras-chave: *Câncer de mama. Pneumonia por* Pneumocystis jirovecii*. Quimioterapia adjuvante. Corticosteroides.*

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Introduction

Breast cancer remains the leading cause of cancer-related death among women in Europe[1], despite recent declines in mortality rates. Over the last 5 years, most European countries have reported significant reductions in breast cancer mortality[2], mainly attributed to advances in systemic treatment and, to a lesser extent, improvement in screening and diagnostic methods.

Neoadjuvant chemotherapy has emerged as a key component of breast cancer treatment. Among neoadjuvant strategies, dose-dense chemotherapy regimens, such as those combining doxorubicin and cyclophosphamide (ddAC), have demonstrated superior disease-free and overall survival compared to conventional schedules[3]. These regimens are administered every 2 weeks with growth factor support and routinely include corticosteroids for antiemetic prophylaxis. Similarly, taxane-based regimens, such as paclitaxel or docetaxel, require corticosteroids in the pre-medication. However, corticosteroid use, particularly at high cumulative doses, has raised concerns regarding immunosuppression and infection risks.

Pneumocystis jirovecii pneumonia (PJP) is a life-threatening opportunistic infection typically affecting immunocompromised individuals. Historically, PJP was commonly associated with HIV infection and hematological malignancies, but its incidence in non-HIV populations, including patients with solid tumors, is increasing due to the growing use of immunosuppressive therapies and corticosteroids[4-6]. Several reports have described PJP cases in breast cancer patients receiving dose-dense chemotherapy, often occurring between the third and fourth cycles[8-11]. Waks et al. reported a 0.6% incidence of PJP in patients undergoing ddAC, emphasizing the potential role of corticosteroid exposure and lymphopenia in disease pathogenesis[11].

Here, we present three cases of PJP in patients with early-stage breast cancer treated with ddAC followed by paclitaxel chemotherapy at our institution. We aim to heighten awareness of this infectious complication among breast cancer patients and highlight the role of cumulative dosage of prophylactic corticosteroids as a potential risk factor in this clinical setting.

Patient #1

A 46-year-old premenopausal female with no significant past medical history was diagnosed with invasive lobular carcinoma of the right breast (pT2mN1(sn)M0, Luminal B-like subtype). After lumpectomy and sentinel lymph node dissection, she received adjuvant chemotherapy with ddAC every 2 weeks, with pegfilgrastim support, followed by weekly paclitaxel. Antiemetic prophylaxis included dexamethasone 12 mg on day 1, followed by 4 mg twice daily for the subsequent 3 days during ddAC cycles and dexamethasone 20 mg before each weekly paclitaxel infusion.

She completed four cycles of ddAC with good tolerance. Two weeks after completing the last ddAC cycle, before initiating paclitaxel, the patient developed fever (38°C) without focal signs of infection and with a neutrophil count of 4.450/µL and a lymphocyte count of 270/µL. Empiric treatment with amoxicillin/clavulanic acid was initiated for a suspected urinary tract infection (UTI) and proceeded with the first cycle of paclitaxel 24 h later. After being afebrile for 72 h, the fever and generalized malaise recurred, leading to escalation of antibiotic therapy to ciprofloxacin, after a urine culture identified *Escherichia coli* resistant to amoxicillin.

The patient maintained daily febrile episodes in the following 7 days. Laboratory findings documented no neutropenia (3.360 neutrophils/uL), lymphopenia (380 lymphocytes/µL), and elevated inflammatory markers (C-reactive protein [CRP] 21 mg/dL). Her condition worsened over the subsequent 48 h with progressive dry cough, asthenia, and fatigue. Physical examination revealed tachypnea, decreased bibasilar lung sounds, and severe hypoxemia (partial pressure of oxygen 40 mmHg). Empiric treatment with piperacillin-tazobactam was initiated, and the patient was admitted to the intensive care unit (ICU).

A contrast-enhanced thoracic computed tomography (CT) scan revealed diffuse ground-glass opacities, predominantly in the middle and lower lung lobes and, in a perihilar distribution, multiple areas of established consolidation (Fig. 1). Testing for respiratory viruses such as SARS-CoV-2, Influenza A/B, and respiratory syncytial virus was negative. A flexible bronchoscopy was performed, and *P. jirovecii* was isolated in the bronchoalveolar lavage fluid (BAL). She was started on trimethoprim-sulfamethoxazole (TMP-SMZ) and methylprednisolone, with progressive clinical, laboratory, and radiological improvement.

Upon recovery, the patient resumed adjuvant paclitaxel without further complications, completing paclitaxel adjuvant treatment successfully. Radiotherapy was subsequently administered, and she has been on hormonal therapy for 18 months without recurrence or further complications.

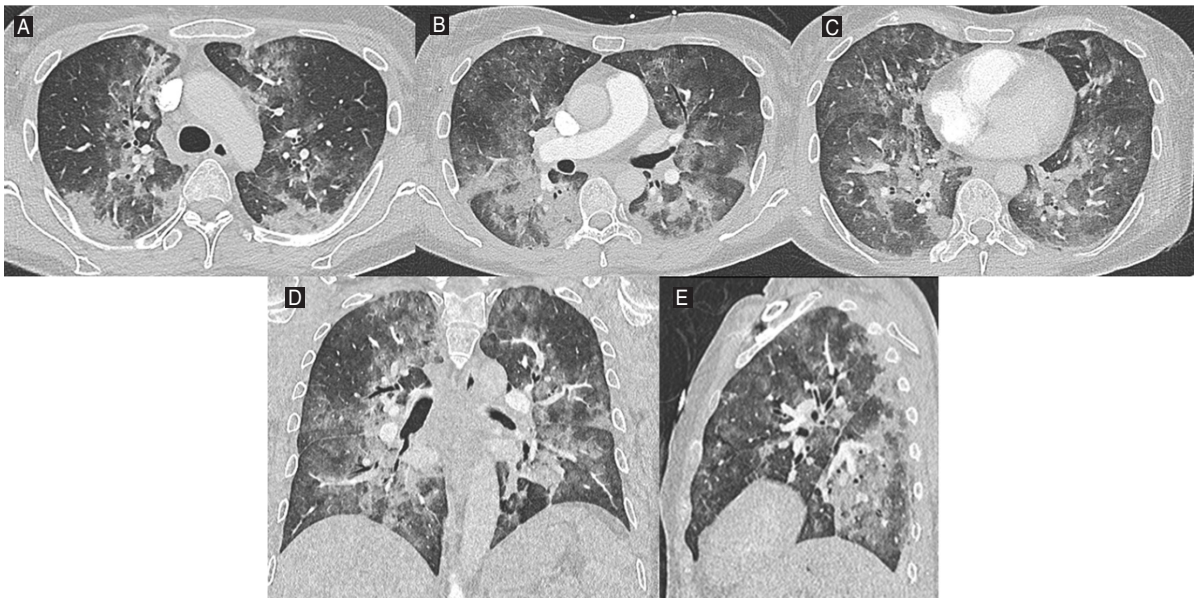

Figure 1. Axial lung window images of the **A:** upper, **B:** middle, and **C:** lower levels, along with **D:** coronal and **E:** sagittal reconstructions from thoracic computed tomography angiography of Patient #1. Diffuse ground-glass opacities are observed, predominantly in the middle and lower lung zones and in a perihilar distribution, with multiple areas of consolidation.

Patient #2

A 47-year-old female with a past medical history of migraine was diagnosed with left-sided invasive breast carcinoma (cT2N0M0, estrogen receptor and progesterone receptor negative, human epidermal growth factor receptor 2 [HER2] immunohistochemistry [IHC] 3+). She received neoadjuvant chemotherapy with ddAC, followed by paclitaxel, trastuzumab, and pertuzumab. The anti-emesis prophylaxis regimen was identical to Patient #1.

Four cycles of ddAC were administered without toxicity. One week after the first cycle of paclitaxel, she presented with fever and myalgia, prompting a visit to the emergency department. Laboratory tests revealed a neutrophil count of 4000/µL, lymphopenia of 480 lymphocytes/µL, an elevated CRP level (7 mg/dL), and urinalysis with leukocyturia. An UTI was suspected, and she was discharged on cefuroxime. Subsequent urine culture, however, yielded negative results.

One week later, the patient continued with a fever and developed a dry cough and dyspnea. Laboratory tests documented lymphopenia (730 lymphocytes/µL) and an increase in CRP to 27 mg/dL. Chest X-ray documented bilateral basal consolidation. She was admitted to the hospital and started on piperacillin-tazobactam.

During hospital stay, there was worsening hypoxemia with increasing oxygen support and admission to the ICU. Thoracic CT angiography excluded pulmonary embolism and documented extensive pulmonary parenchymal involvement with ground-glass opacities and consolidations, sparing only a few areas in the upper lung lobes (Fig. 2). Tests for respiratory viruses (such as SARS-CoV-2, influenza A/B, and respiratory syncytial virus) and *Legionella pneumophila* and *Streptococcus pneumoniae* antigens were negative.

There was worsening respiratory status, with acute respiratory distress syndrome (ARDS), requiring invasive mechanical ventilation. A bronchoscopy with BAL was performed, and empirical treatment with azithromycin, high-dose TMP-SMZ, and prednisolone (40 mg twice daily) was initiated. *P. jirovecii* was identified in BAL, establishing the diagnosis of PJP, leading to discontinuation of azithromycin and piperacillin-tazobactam.

There was steady clinical improvement, which enabled ventilatory weaning and successful extubation. Following extubation, oxygen therapy was gradually reduced, and she was discharged in stable condition without the need for supplemental oxygen.

Upon recovery, the patient resumed neoadjuvant therapy without further complications, successfully completing the chemotherapy regimen with a pathologic complete response at surgery. She subsequently underwent radiotherapy and has since been on trastuzumab to complete 1 year of treatment along with

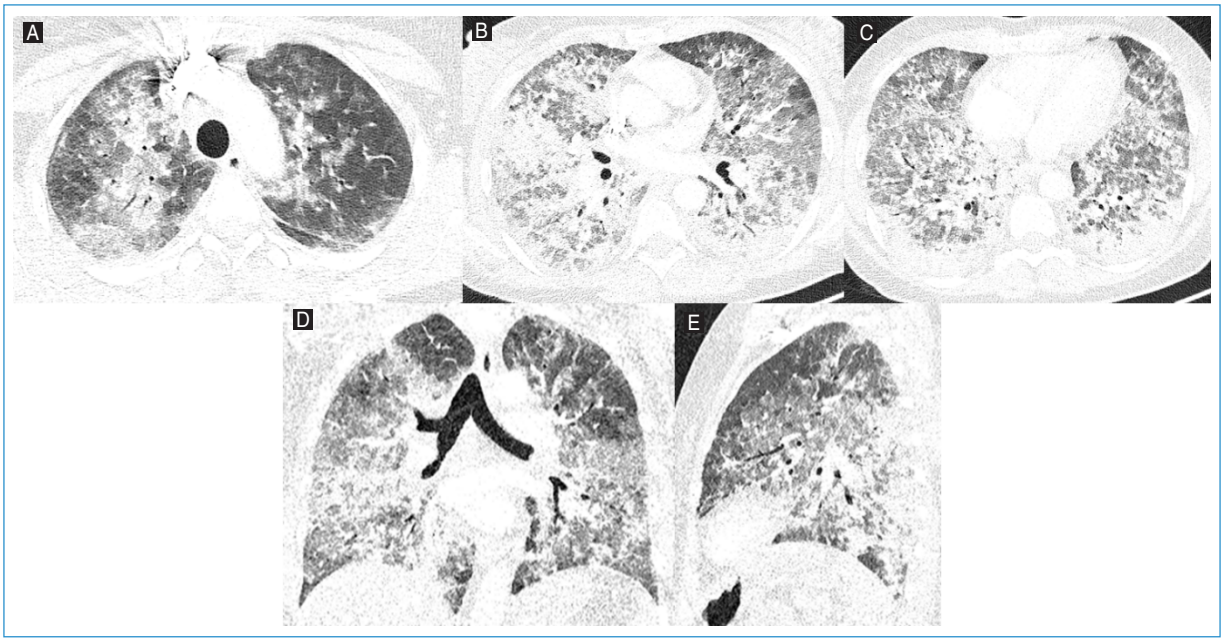

Figure 2. Axial lung window images of the **A:** upper, **B:** middle, and **C:** lower lobes, along with **D:** coronal and **E:** sagittal reconstructions from thoracic computed tomography angiography of Patient #2. Extensive pulmonary parenchymal involvement with ground-glass opacities and consolidations, sparing only a few areas in the upper lung lobes.

hormonal therapy, both well well-tolerated without unexpected toxicity.

Patient #3

A 63-year-old female with multiple comorbidities, including peripheral arterial disease (with stent placement 5 years before), hypertension, dyslipidemia, and a heavy smoking history of 66 pack-years, was diagnosed with invasive carcinoma of the left breast. She underwent lumpectomy and axillary lymph node dissection, with a pathological stage pT2N1aM0, Luminal A-like subtype, HER2-low (IHC 2+ *in situ* hybridization negative) cancer. Adjuvant chemotherapy was recommended - four cycles of ddAC, followed by 12 weeks of paclitaxel. The anti-emesis regimen for the ddAC protocol was the same for Patients #1 and #2, but the dexamethasone dose for paclitaxel pre-medication was reduced to 8 mg in response to knowledge of the previously reported cases.

The patient presented to the emergency department 6 days after her second paclitaxel treatment with a 4-day history of productive cough with white sputum, dyspnea on minimal exertion, fatigue, and fever (38.5°C). Physical examination documented low peripheral blood saturation (SpO_2 93%), tachypnea, and bilateral basal crackles. Arterial blood gas analysis confirmed hypoxemia (pO_2 41 mmHg). Laboratory investigations demonstrated lymphopenia (470 lymphocytes/μL) and elevated CPR (15 mg/dL) without neutropenia (7360 neutrophils/uL).

Thoracic CT angiography ruled out pulmonary embolism and showed diffuse ground-glass opacities, predominantly in the upper and middle lung lobes, plus reticular opacities and septal thickening, suggestive of an inflammatory/infectious process (Fig. 3). The patient was admitted for further investigation and management. Initial treatment consisted of amoxicillin-clavulanate, azithromycin, and corticosteroids. However, due to rapid respiratory deterioration, the antibiotic regimen was changed to piperacillin-tazobactam within 48 h. Bronchoscopy revealed thick mucus secretions bilaterally, and BAL diagnosed PJP. Empirical antibiotics were de-escalated, and targeted treatment with high-dose TMP-SMZ and corticosteroids was initiated. Additional diagnostic tests, including bacterial cultures, respiratory viral panels, and galactomannan antigen, were negative. Cytological analysis of BAL showed no malignant cells.

The patient improved and was gradually weaned off supplemental oxygen and discharged home in stable condition without the need for further oxygen support. Following recovery, the patient completed adjuvant paclitaxel followed by radiotherapy and has since been on hormonal therapy for 9 months without further toxicities.

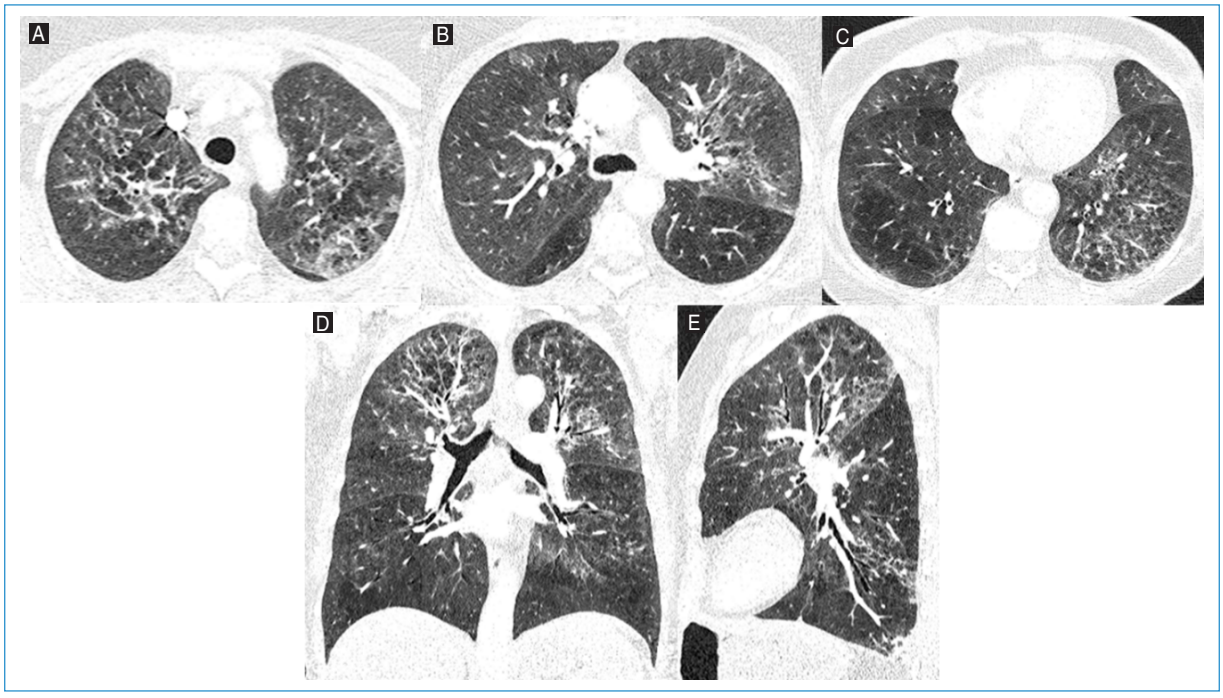

Figure 3. Axial lung window images of the **A:** upper, **B:** middle, and **C:** lower lobes, along with **D:** coronal and **E:** sagittal reconstructions from thoracic computed tomography angiography of Patient #3. Diffuse ground-glass opacities, predominantly in the upper and middle lung lobes, are present, accompanied by reticular opacities and septal thickening, suggestive of an inflammatory/infectious process.

Discussion

The three reported cases are consistent with previously reported PJP in patients undergoing dose-dense chemotherapy for breast cancer[7,9,12,13]. Ours is the second series reported from Portugal[8] in this context, stressing the clinical relevance of this treatment complication. Larger population-based studies are essential to accurately assess the incidence and risk factors associated with PJP in this context.

Dose-dense ddAC improves disease-free and overall survival in patients with breast cancer[14]. Although hematopoietic growth factors, such as pegfilgrastim, promote neutrophil recovery and lower the likelihood of febrile neutropenia, other factors may increase the risk of immunosuppression from intensified chemotherapy.

Lymphocytopenia is a significant contributing factor to the risk of infection with *P. jirovecii*. Cellular immunity, particularly CD4 lymphocytes, is essential to prevent PJP. Published data indicate that nearly 90% of individuals diagnosed with PJP had lymphocyte counts below 1000 cells/mm[3,15]. All of our patients exhibited lymphocytopenia below the threshold[3].

Another key factor contributing to immunosuppression and PJP is corticosteroid treatment. Patients with breast cancer treated with sequential ddAC and paclitaxel receive corticosteroids over 20 weeks as antiemetics and for paclitaxel hypersensitivity prophylaxis. Corticosteroids are a cornerstone in the prevention and management of chemotherapy-induced nausea and vomiting, offering significant benefits in controlling both acute and delayed symptoms, and are also required for the prevention of infusion and hypersensitivity reactions (HSR) to paclitaxel. However, their immunosuppressive effects warrant consideration, particularly in high cumulative doses.

Intermittent courses of corticosteroids have been previously identified as a significant risk factor for PJP[16]. In the cases now reported, patients received a total of 144 mg of dexamethasone over four cycles of ddAC administered over 56 days (8 weeks). This translates to an average daily dose of 2.57 mg of dexamethasone, equivalent to 17.1 mg of prednisolone per day based on the dexamethasone-to-prednisolone conversion ratio of 1:6.67, as established in pharmacokinetic studies[17]. In addition, the first and second cases reported received 20 mg of dexamethasone before each paclitaxel administration, accumulating to a total of 240 mg over 12 weeks. This increased the overall corticosteroid exposure over 20 weeks to a daily equivalent of 18.3 mg of prednisolone. Such exposure exceeds the established threshold for PJP prophylaxis (equivalent of 16-25

mg/day of prednisolone for 4 or more weeks[18]). The third case received a lower dexamethasone dose (8 mg) as paclitaxel pre-medication. This dosing alteration was made after the evaluation of the first two unexpected cases of PJP and after reviewing with the pharmacy the labeling recommendations of the paclitaxel provider. Although the dexamethasone dose was reduced, the third patient still developed PJP, underscoring the need for caution when using corticosteroids in this setting.

Current guidelines from ASCO[19], NCCN, and MASCC/ESMO recommend multimodal antiemetic regimens, incorporating agents with complementary mechanisms of action. Despite overlapping recommendations, slight variations exist between these guidelines[17,18]. The core recommendations include a 5HT3 receptor antagonist, an NK1 receptor antagonist, dexamethasone, and olanzapine. ASCO and NCCN recommend a three-drug combination of an NK1 receptor antagonist, a 5-hydroxytryptamine type 3 receptor antagonist (5-HT3) receptor antagonist, and dexamethasone for highly emetogenic chemotherapy regimens. MASCC/ESMO advocates for a four-drug regimen incorporating the above three agents plus olanzapine. Regarding dexamethasone pre-medication in breast cancer AC regimens, ASCO and MASCC/ESMO no longer recommend dexamethasone administration on days 2-4 after AC (while NCCN suggests it may be considered), due to limited data supporting dexamethasone use beyond day 1 when an NK1 receptor antagonist is included[21,22]. These differences highlight the need for a patient-centered approach, where individual risk factors and clinical scenarios guide the choice of antiemetic strategies. By understanding and aligning these recommendations with patient-specific needs, clinicians can optimize antiemetic outcomes while minimizing unnecessary corticosteroid exposure.

Current guidelines emphasize the role of corticosteroids in paclitaxel pre-medication primarily for HSR prevention, rather than for antiemetic purposes. Regulatory-approved prescribing information (RCM)[23] recommends dexamethasone doses ranging from 8 to 20 mg before paclitaxel infusion, yet national guidelines and institutional protocols vary in their dosing and duration recommendations. The NHS Northern Cancer Alliance protocol[24] recommends 8 mg IV dexamethasone 30-60 min before weekly infusion, aligning with a standardized approach to minimize corticosteroid-related toxicities. Similarly, Clinical Care Ontario[25] suggests 10 mg IV dexamethasone before weekly paclitaxel to ensure adequate HSR prophylaxis.

Notably, growing evidence supports reducing or omitting corticosteroid pre-medication in later cycles. A prospective study by Barroso-Sousa et al.[26] evaluating a corticosteroid-sparing regimen for dose-dense paclitaxel (biweekly) demonstrated that dexamethasone can be safely omitted in cycles 3 and 4 if no HSRs occur in the first two cycles. This strategy reduced dexamethasone use by 92.8%, with a low overall HSR incidence (4.5%) and < 1% for grade 3/4 reactions in later cycles, supporting the feasibility of a simplified pre-medication approach. These variations highlight a shifting paradigm in corticosteroid pre-medication, moving toward individualized risk stratification rather than routine administration.

The severity of the PJP clinical course varied among the three cases. Patient number 1 required ICU admission for respiratory support, but without the need for invasive ventilation. In contrast, patient number 2 developed ARDS, necessitating invasive mechanical ventilation despite rapid recovery. Patient number 3, despite significant respiratory deterioration, did not progress to ARDS or require intubation. All three patients were able to resume cancer treatment after rapid recovery from PJP.

Our findings, as other published case series[7-10,12,13], emphasize the need for heightened awareness of PJP risk in this population. They suggest that corticosteroid exposure in combination with chemotherapy-induced lymphopenia and the underlying malignancy significantly increases susceptibility to opportunistic infections. Consideration should be given to TMP-SMX prophylaxis in patients undergoing dose-dense regimens with high cumulative corticosteroid exposure and lymphocytopenia, as well as evaluating the potential for reducing corticosteroid dosages in chemotherapy protocols to mitigate infection risks.

Our experience with these three PJP cases prompted a revision of our chemotherapy ddAC/paclitaxel protocol, with the reduction of the antiemetic dexamethasone dose currently under review and an adjustment of paclitaxel pre-medication to 8 mg before the first four cycles, followed by a decrease to 4 mg after week 4 if well tolerated.

We acknowledge that this case series is limited by its small sample size but is consistent with published literature. We hope to increase awareness of PJP, an opportunistic infection not usually considered in the setting of (early) breast cancer treatment. Attempts to reduce corticosteroid dosage or consideration of TMP-SMX prophylaxis should be considered when prescribing ddAC paclitaxel chemotherapy.

Conclusion

PJP is a rare but critical infectious complication from chemotherapy treatment of early breast cancer. The combined effect of chemotherapy-induced lymphopenia and corticosteroids for antiemetic prophylaxis and paclitaxel administration requires vigilant monitoring and prompt management. Minimization of preventive steroid dosage or temporary PJP antimicrobial prophylaxis should be considered.

In response to these three PJP cases, adjustments were implemented in our institutional ddAC/paclitaxel chemotherapy protocol. Specifically, dexamethasone pre-medication for paclitaxel was revised to 8 mg during the first four cycles, followed by a reduction to 4 mg from week 5 onward in patients with good tolerance. These adjustments may help guide future clinical practice in balancing effective supportive care with infection risk mitigation. However, further large-scale, population-based studies are essential to better define its true incidence and to identify patients at the highest risk.

Funding

None.

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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