Editorial

Medical oncology: challenges in 2022

The landscape of oncology drug development is currently experiencing fascinating revolutions. Noteworthy breakthroughs have occurred in the realms of screening, diagnosis and anti-cancer treatment, leading to a substantial improvement in the survival rates of cancer patients (1-4). Within cancer research, advanced technologies like DNA sequencing and genome-wide association studies provide us with the tools to identify and characterize the pivotal drivers in various forms of cancer (5). Numerous well-established alterations, both at the genetic and molecular levels, have become routine screening biomarkers and therapeutic targets for clinical interventions (6-9). An array of targeted agents and immunotherapeutic drugs are now playing an increasingly prominent role (10,11). These include tumor vaccines, cellular immunotherapeutic agents, immunomodulatory drugs targeting T cells, oncolytic virotherapy, and immune checkpoint inhibitors (ICI), all of which are gradually being applied to patients with stage I–IV tumors (12-14). Immunotherapy with ICI, notably the programmed cell death 1 (PD-1)/PD ligand 1 (PD-L1) inhibitors, has led to significant advancements in the treatment of various solid tumors. Additionally, ongoing research is actively exploring anti-tumor immunotherapies targeting multiple pathways and mechanisms (15). However, despite the successful utilization of various immunotherapeutic agents in a wide spectrum of human cancers, their effectiveness remains constrained and inconsistent. Only a limited number of advanced cancer patients have achieved enduring, life-altering survival benefits. This limitation underscores the intricate and tightly regulated nature of the immune system (16).

Oncologic emergencies are now more frequently encountered in emergency departments, both in community and academic healthcare settings. However, they may not always be prevalent in emergency departments that primarily cater to non-oncology patients. Additionally, some oncologic emergencies might manifest with subtle symptoms, potentially leading to oversight and, consequently, higher rates of morbidity and mortality.

Finally, over recent decades, the field of oncology has progressed in tandem with advancements in palliative care (PC). The multifaceted demands of cancer treatment, which encompass symptom management, psychosocial support, and related care aspects, place increasing demands on the time and expertise of oncologists. PC specialists aim to collaborate closely with oncologists to facilitate the comprehensive management of patients with advanced-stage cancer. Research consistently demonstrates the benefits of early integration of PC for patients diagnosed with advanced cancer, including improved quality of life through more effective symptom management and robust psychosocial support, increased survival rates, and reduced reliance on aggressive medical interventions during the end-of-life phase.

For a long time, urothelial carcinoma (UC) of the bladder has been recognized as responsive to the immune system. Intravesical administration of Bacillus Calmette-Guerin (BCG) has been known to stimulate the infiltration of cytotoxic T lymphocytes (CTLs) and promote cell-mediated cytotoxicity against bladder tumor cells in individuals with non-muscle invasive bladder cancer. Despite decades of research and clinical application, the mechanisms underlying BCG-induced immunotherapeutic effects remain incompletely understood due to the intricate nature of the various biological components involved, including the innate and adaptive immune systems. An effective anti-tumor immune response involves a sequence of events and namely the release of tumor antigens from damaged or dying cancer cells, the uptake and presentation of these antigens by dendritic cells and other antigen-presenting cells, the priming and activation of T cells, the migration, infiltration, and accumulation of T lymphocytes and natural killer (NK) cells and finally the recognition and elimination of cancer cells by CTLs and NK cells (17). This series of events provides a valuable framework for comprehending the mechanisms governing responses to immunotherapy and the development of resistance. As an example, therapeutic cancer vaccines and anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) antibodies function by initiating, activating, and amplifying T cells. In contrast, ICI like anti-PD-1/PD-L1 monoclonal antibodies work to restore T-cell function against cancer cells, mainly by blocking the interaction with PD-L1 on the tumor cell. This action inhibits immune evasion and tumor growth. In addition to breast, ovarian, and prostate cancer (PrCa), DNA damage response (DDR) alterations are also prevalent in UC and have been extensively examined as potential predictors of responsiveness to cisplatin. Furthermore, they are likely to influence the response to immunotherapeutic agents (18-20). Tumor mutational burden (TMB) has emerged as a recognized predictive biomarker for immune therapy response in various cancer types. UC demonstrates a notably elevated TMB when compared to the majority of other solid malignancies, suggesting a promising foundation for the development of immunotherapeutic

approaches in UC. High expression of PD-L1 protein in tumor cells and/or tumor-infiltrating cells has been linked to a more favorable response to ICI in various cancer types, including UC. PD-L1 is currently the primary biomarker widely adopted and validated in clinical practice to inform treatment decisions regarding the use of ICI in UC management. The significance of PD-L1 has been underscored by restricting the use of anti-PD-1/PD-L1 agents to first-line UC patients with a high level of PD-L1 expression. However, the predictive value of PD-L1 expression is somewhat limited, partly due to its dynamic expression and heterogeneity within the tumor microenvironment. For example, there appears to be substantial discordance in PD-L1 expression between primary and metastatic UC lesions. The accuracy of PD-L1 as a predictive factor for ICI response has been investigated in various cancer types, utilizing different PD-L1 diagnostic assays, antibodies, scoring methods, and cut-off values to measure PD-L1 expression in either tumor cells, immune cells, or both, resulting in some variability in results. Further research is necessary to establish a reliable predictive model incorporating PD-L1 expression and other biomarkers in UC. In addition to the improved efficacy outcomes delivered by ICI and other immunotherapy agents, the enhanced quality of life experienced by cancer patients undergoing immunotherapy is typically superior to those treated with conventional cytotoxic chemotherapy. This observation further strengthens the rationale for the clinical utilization of immunotherapeutic drugs in advanced UC.

In addition to assessing PD-L1 expression, there is an ongoing need to identify effective predictive factors that can optimize treatment selection. The immunomodulatory impact of the gut microbiome, for instance, is emerging as a crucial factor that could potentially address this unmet requirement. UC is undeniably sensitive to chemotherapy, and platinum-based regimens continue to play a significant role in the management of advanced or metastatic disease. However, the combination of ICI with enfortumab vedotin and/or fibroblast growth factor receptor (FGFR) inhibitors has the potential to reshape the current treatment landscape in the near future. Nonetheless, further research is essential to incorporate novel immunotherapy approaches into the therapeutic arsenal.

PrCa is currently the most prevalent solid tumor in developed countries and a significant cause of mortality. The incidence of both metastatic PrCa and localized PrCa has been on the rise, correlating with various genetic, hereditary, and environmental factors, such as advancing age, a family history of PrCa, and African ethnicity. It is now well-established that germline or somatic abnormalities in DDR genes are found in 19% of primary PrCa cases and roughly 23% of metastatic castration-resistant PrCa (21). The incidence of germline mutations in *BRCA* genes among newly diagnosed PrCa cases stands at 1.2–2%. Carriers of *BRCA1* and *BRCA2* genes face an approximately 4- and 8-fold increased risk of developing PrCa, respectively (22). The treatment landscape for PrCa has seen rapid transformation. Specifically, androgen receptor (AR) signaling inhibitors downregulate the expression of DDR genes and increase DNA damage, enhancing the responsiveness of PrCa to poly (ADP-ribose) polymerase (PARP) inhibitors. Androgen deprivation therapy (ADT) creates a state of 'BRCAness' when PARP and AR signaling pathways are simultaneously inhibited. Consequently, PARP inhibitors may prove effective even in PrCa cases without DDR mutations. Given that microvessel density is indicative of metastasis risk, ongoing research is focusing on targeting angiogenesis (23).

The majority of PrCa cases are diagnosed and managed when the disease is localized. However, some patients present with metastatic PrCa, either initially or after having initially localized disease. From a treatment perspective, individuals with high-risk non-metastatic PrCa typically undergo ADT for three years, which may be complemented by radiotherapy. Recent reports have shown that combining abiraterone alone or with enzalutamide alongside ADT significantly improves metastasis-free survival compared to ADT alone (24,25). Biomarkers play a pivotal role in identifying patients who may benefit from specific treatment approaches. In this context, microRNAs (miRNAs), AR variants, markers related to bone metabolism, neuroendocrine factors, and metabolite indicators are emerging as promising candidates (26). This is especially significant in the era of precision medicine. In the case of oligometastatic PrCa (OMPC), a luteinizing hormone-releasing hormone (LHRH) antagonist can be considered for a six-month period following stereotactic ablative radiotherapy (SABR) (27). The rationale behind this strategy is to ensure precise localization of the treatment target for SABR planning and delivery while optimizing the response to radiotherapy (28).

Additional evidence is required to establish the significance of SABR in treating OMPC. This evidence is needed to confirm its clinical effectiveness and to assess its cost-effectiveness, particularly in light of the growing number of patients seeking this treatment. Current experiences suggest excellent local control and a delay in disease progression. Given that these are crucial surrogate markers for overall survival (OS), the prospect of achieving improved disease management and

better outcomes is indeed plausible.

The incidence of melanoma is steadily on the rise, as per GLOBOCAN estimates, with the global number of new cases reaching 324,635 in 2020 (29). In the same year, there were 1,092,818 individuals living with melanoma, and 57,043 melanoma-related deaths. Approximately 3% of melanomas present without an identifiable primary site, a condition referred to as melanoma of unknown primary (MUP) (30). This atypical subtype of melanoma remains biologically undefined compared to the classical melanoma of known primary (MKP). Recent research has indicated that patients with MUP may exhibit more favorable outcomes when compared to those with a stage-matched MKP site. This phenomenon is believed to be associated with a heightened immunogenicity, which is evident in the immunologically mediated regression of the primary site (31). The clinical presentation of melanoma exhibits variation, which can pose challenges for diagnosis. Screening techniques, including dermatoscopy, biopsies, and histopathological assessments, play a vital role in the early detection of melanoma. Prognostic and monitoring tools such as serum markers, lactate dehydrogenase (LDH), and S100 β protein are well-established. Additionally, DNA markers, such as BRAF and NRAS, are associated with patient selection and can predict how patients respond to targeted therapy (32). BRAF is a serine-threonine kinase within the RAS-RAF-MEK-ERK mitogen-activated protein kinase (MAPK) pathway. Mutations in BRAF lead to MAPK upregulation, triggering uncontrolled cell proliferation. The most prevalent mutation involves the substitution of valine with glutamic acid (BRAFV600E) at amino acid 600, found in up to 90% of BRAF-mutated tumors. The less common valine-to-lysine substitution (BRAFV600K) is present in up to 10% of BRAF-mutated tumors. These BRAF mutations occur more frequently in tumors of neural crest origin, accounting for 50–60% of cutaneous melanomas. Conversely, NRAS mutations are less common, occurring in up to 20% of cutaneous melanomas, as well as in 15% of acral lentiginous melanoma and sino-nasal mucosal melanomas. Active RAS proteins are in the GTP-bound state but become inactive after GTP hydrolysis to GDP. Active RAS proteins play a pivotal role in stimulating cellular proliferation, survival, differentiation, and apoptosis. Oncogenic missense mutations at codons 12, 13, or 61 result in RAS mutations. These mutations involve the substitution of glutamine with lysine, leucine, or arginine in the NRAS protein. Such mutations lead to conformational changes in the GTP-active state of Ras in 90% of cases or promote oncogenic alterations in the GTP hydrolysis mechanism. Consequently, the normal cell cycle becomes dysregulated, and T cell function is compromised. Biomarkers such as circulating tumor DNA (ctDNA), miRNAs, and long non-coding RNAs offer valuable insights into a tumor's genetic makeup. They enhance our understanding of the disease's pathophysiology and hold the significant advantage of enabling non-invasive, serial sampling for disease monitoring.

Approximately 70% of patients with cutaneous melanoma carry mutations in the MAPK pathway. Targeted therapies employ inhibitors to modulate these mutated proteins that are believed to manipulate signaling pathways, leading to uncontrolled cell proliferation. Selective BRAF-mutant inhibitors (BRAF-I) like vemurafenib, dabrafenib, and encorafenib have been approved as standalone agents for the treatment of BRAFV600E stage 3 unresectable or metastatic melanoma (33). Although these targeted therapies have demonstrated a significant objective response rate and positive progression-free survival (PFS) and OS outcomes, a portion of patients still develops resistance and experiences side effects, including the induction of keratoacanthoma. Paradoxical upregulation of the MAPK pathway due to unopposed activation of downstream effectors, such as MEK, has been identified as a major contributing factor. As a result, combining MEK inhibitors with BRAF-mutant inhibitors has proven highly effective in delaying the development of resistance, thereby reducing the side effects associated with BRAF-I.

Trametinib, cobimetinib, and binimetinib are all selective MEK inhibitors. The combined therapy of trametinib plus dabrafenib, as well as cobimetinib plus vemurafenib, has demonstrated long-lasting objective responses in advanced BRAF-mutant (BRAF-MT) melanoma, as evidenced in the COMBI and co-BRIM trials (34,35). Encorafenib and binimetinib have also gained approval for advanced BRAF-MT melanoma, based on the results from the COLOMBUS trial (36). These treatments all exhibit a comparable PFS rate within the range of 30–40%. In cases where combined therapy with BRAF-I and MEK-I is contraindicated, such as due to a poor performance status or the presence of comorbidities that may reduce tolerance to toxicity, BRAF-I monotherapy may be considered as a viable alternative.

BRAF non-V600E/K mutations are found in 3–14% of BRAF-mutated melanomas. In such cases, ICI remain the first-line treatment; however, they may not be suitable for certain patients. Retrospective and *in vitro/in vivo* analyses have revealed varying responses to BRAF-I/MEK-I combination therapy as well as BRAF-I and MEK-I monotherapy. Ongoing research is also exploring other potential targets, including pan-RAF inhibitors such as sorafenib, belvarafenib and naporafenib, as well

as BRAF dimer- and ERK inhibitors.

The neoadjuvant approach has transformed the management of cancers, leading to reduced morbidity, improved resectability through cytoreduction, organ preservation, and ultimately, enhanced rates of local recurrence and OS (37,38). In melanoma, promising findings from preclinical studies in mice comparing adjuvant and neoadjuvant strategies revealed that mice treated with the latter had higher levels of tumor-specific $CD8^+$ T cells, which were associated with improved OS. The most commonly employed and studied neoadjuvant regimens include nivolumab plus ipilimumab and pembrolizumab plus ipilimumab. These clinical observations have spurred the initiation of several phase-Ib and II studies assessing the current standard of care in the neoadjuvant setting.

The adoptive T-cell therapy strategy primarily employs tumor-infiltrating lymphocytes (TILs), engineered T-cell receptors (TCRs), and chimeric antigen receptor T-cells (CAR-T) to identify and target antigens on cancer cells. In clinical trials, this approach has demonstrated notable response rates, leading to long-lasting tumor regression in approximately 20–25% of melanoma patients.

Finally, intratumoral oncolytic therapies represent a newly emerging treatment option for melanoma. These intratumoral immunotherapies involve the injection of immunostimulatory agents that induce the lysis of tumor cells, thereby initiating both local and systemic immune responses. A wide range of intratumoral immunotherapies, including non-oncolytic viral treatments like PV-10 and toll-like receptor 9 agonists, as well as oncolytic viral treatments like CAVATAK, Pexa-Vec, and HF10, have been extensively studied and have demonstrated promising antitumor activity with manageable levels of toxicity in melanoma and other solid tumor types.

Metastatic spinal cord compression (MSCC) is a debilitating and potentially irreversible complication of cancer, first described by Spiller in 1925 as a cause of progressive paraplegia in cancer patients. While the exact incidence of MSCC remains uncertain, it is estimated to affect approximately 5–10% of patients with malignancies (39). MSCC can be attributed to various solid tumors, but it is more frequently encountered in cancers with a propensity to metastasize to the spine, including breast, prostate, and lung cancers (40). It results from metastatic spread to the spine, either by causing the collapse or compression of the vertebral body or by direct tumor extension into the vertebral canal. Magnetic resonance imaging (MRI) is the gold standard for investigating MSCC, and it should ideally be conducted within 24 hours of presentation.

Various prognostic factors and risk factors for spinal stability have been proposed to guide patient selection for surgery and treatment planning. The Spinal Instability Neoplastic Score (SINS) (41) is employed to identify and evaluate patients for potential surgical intervention. Other scoring systems, such as the Tokuhashi score, can help predict prognosis following MSCC (42). The objectives of treating MSCC are multifaceted, encompassing pain relief, management of spinal stability, tumor eradication, reduction of mid- to long-term neurological deficits, preservation of function, and the potential for survival benefit.

The standard treatment options for MSCC typically involve either radiotherapy or surgery, often followed by radiotherapy (41). Surgery is typically the preferred choice for patients with an unstable spine, single-level involvement, or oligometastatic disease, who exhibit a good performance status, and when tissue sampling is needed for disease characterization. On the other hand, radiotherapy is favored for patients with comorbidities, widespread disease, and a limited prognosis due to the extent of their disease burden. A recently emerging and effective treatment option is radiosurgery. Radiosurgery, guided by imaging, can deliver a highly precise and concentrated dose of radiotherapy to a very small target area. However, there is limited evidence to establish the superiority of stereotactic radiosurgery over conventional fractionated radiation or decompressive surgery in patients with MSCC.

One of the factors that significantly influences the outcome in MSCC is the presence or absence of neurological symptoms before treatment (43). Delay in treatment can result in irreversible neurological damage, leading to a subsequent reduction in the quality of life and an increased burden on healthcare resources. Patients who have experienced a loss of neurological function for more than 24 hours are unlikely to show improvement and are typically not considered for surgery unless spinal stabilization is necessary for pain relief. Various studies, informed by patient experiences, have underscored the significance of effective communication among healthcare teams as a primary factor contributing to delays in effective management (44).

In a pilot study conducted by Hakim *et al.*, a comparison was made between the time from the confirmation of MSCC on imaging to the initiation of radiotherapy treatment before and after the introduction of the MSCC coordinator role in 2020 and 2021, respectively (45). The analysis revealed a median time of 1 day between imaging and radiotherapy in 2021

(mean 2.8 days, range, 0–10 days), as opposed to a median time of 2 days in 2020 (mean 4.1 days, range, 0–22 days), with a significant difference (P=0.04). Hakim *et al.*'s study represented the first prospective data, albeit a pilot study, illustrating the impact of the coordinator on the MSCC pathway within a regional cancer network in the United Kingdom. The introduction of this service led to improved radiotherapy treatment times and enhanced engagement with critical medical support services, ultimately enhancing patient care and recovery. The longest time to treatment was significantly reduced from 23 to 11 days following the introduction of the new role. Additionally, the percentage of patients treated within 24 hours increased significantly, with a rate of 37% compared to 65% (P=0.044) after the introduction of this role. This is of critical importance in achieving the best possible neurological and functional outcomes for patients.

Oncology and PC have traditionally maintained a close relationship. However, over the last decade, paradigm-shifting multiple randomized control trials have emphasized the significance of early integration of PC and oncology in enhancing patient outcomes (46). In the past, PC was often associated with end-of-life (EoL) care for oncology patients, but it has now evolved to be provided in the early stages of the disease trajectory, regardless of prognosis. Importantly, this includes the delivery of PC for patients undergoing anticancer treatment, regardless of whether the treatment's intent is curative, aimed at symptom relief, or focused on prolonging survival.

Numerous organizations emphasize the significance of early PC integration in the management of oncological diseases. These organizations include the World Health Organization (WHO), the National Comprehensive Cancer Network (NCCN), and the American Society of Clinical Oncology (ASCO). In particular, ASCO recommends that the interdisciplinary PC team ideally becomes involved within 8 weeks of an advanced cancer diagnosis (47). It is crucial to underline that the concurrent management of oncology and early PC is recommended as the standard of care for patients who are actively receiving treatment for their cancer. The NCCN highlights that PC can commence at the time of diagnosis and be delivered alongside life-prolonging and disease-directed therapies (48).

Early integration of PC into oncology can also have a positive impact on the satisfaction of the patient's family and caregivers. This may involve providing social support, emotional care, and resources to assist with the overall care of the patient. A comprehensive PC assessment should include the involvement of the patient's family members, contributing to an individually tailored PC management plan. Furthermore, patient- and family-centered care promotes active collaboration and encourages shared decision-making. Introducing the PC team early in the patient's cancer journey can foster improved rapport between the PC team, the patient, and their family members. Becoming familiar with available services and enhancing continuity of care can be achieved through the early integration of palliative and oncology care. The collaboration between these specialties further optimizes the delivery of coherent and consistent care. Patients diagnosed with advanced cancer face several barriers to receiving early PC and integrating it with concurrent oncology practices.

From a PC perspective, the growing need for services and the necessity for earlier involvement in the cancer patients' disease trajectory pose a risk of overburdening an already highly sought-after and under-resourced workforce. It has long been acknowledged that there is a shortage of hospice and PC physicians. Current training capacity is also insufficient to meet the future needs of a growing population and an increased demand for services. This emphasizes the importance of oncologists adopting exemplary primary PC practices and adapting to the methodologies used by PC teams. Equally, from a systems perspective, having a robust PC delivery infrastructure will be crucial to meet the rising demand for services. The ambulatory nature of oncology means that patients are frequently seen in specialized outpatient clinics, while PC clinics and providers may be located elsewhere, possibly even in different institutions.

Sustainable outpatient clinic structures play a vital role in facilitating the integration of oncology and PC services. They offer patients early access to specialized PC services within the context of the ambulatory care setting, allowing for the accommodation of a significant number of patients. The Center to Advance PC has identified three innovative models for outpatient PC delivery and namely stand-alone, co-located, and fully embedded clinics. Stand-alone PC clinics operate independently of other specialty clinics, while co-located clinics may share workspace, financial resources, or clinical staffing with the oncology team. Fully embedded or integrated PC clinics are co-located with the oncology team, enabling the coordination of treatment protocols, the implementation of common clinical pathways, and the enhancement of communication between multidisciplinary teams. These models assist the specialized multidisciplinary PC team in assessing the physical, psychological, and spiritual needs of oncology patients, facilitating the delivery of comprehensive holistic care.

In this special series, we have endeavored to examine the challenges within specific domains of medical oncology in 2022.

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References

1. Choi S, Ismail A, Pappas-Gogos G, et al. HPV and Cervical Cancer: A Review of Epidemiology and Screening Uptake in the UK. Pathogens 2023;12:298.
2. Ghose A, Gullapalli SVN, Chohan N, et al. Applications of Proteomics in Ovarian Cancer: Dawn of a New Era. Proteomes 2022;10:16.
3. Moran S, Martinez-Cardús A, Boussios S, et al. Precision medicine based on epigenomics: the paradigm of carcinoma of unknown primary. Nat Rev Clin Oncol 2017;14:682-94.
4. Rassy E, Parent P, Lefort F, et al. New rising entities in cancer of unknown primary: Is there a real therapeutic benefit? Crit Rev Oncol Hematol 2020;147:102882.
5. Chebly A, Yammine T, Boussios S, et al. Chromosomal instability in cancers of unknown primary. Eur J Cancer 2022;172:323-5.
6. Adeleke S, Haslam A, Choy A, et al. Microsatellite instability testing in colorectal patients with Lynch syndrome: lessons learned from a case report and how to avoid such pitfalls. Per Med 2022;19:277-86.
7. Rassy E, Boussios S, Pavlidis N. Genomic correlates of response and resistance to immune checkpoint inhibitors in carcinomas of unknown primary. Eur J Clin Invest 2021;51:e13583.
8. Aliyuda F, Moschetta M, Ghose A, et al. Advances in Ovarian Cancer Treatment Beyond PARP Inhibitors. Curr Cancer Drug Targets 2023;23:433-46.
9. Boussios S, Ozturk MA, Moschetta M, et al. The Developing Story of Predictive Biomarkers in Colorectal Cancer. J Pers Med 2019;9:12.
10. Brown JE, Royle KL, Gregory W, et al. Temporary treatment cessation versus continuation of first-line tyrosine kinase inhibitor in patients with advanced clear cell renal cell carcinoma (STAR): an open-label, non-inferiority, randomised, controlled, phase 2/3 trial. Lancet Oncol 2023;24:213-27.

11. Revythis A, Limbu A, Mikropoulos C, et al. Recent Insights into PARP and Immuno-Checkpoint Inhibitors in Epithelial Ovarian Cancer. Int J Environ Res Public Health 2022;19:8577.
12. Boussios S, Devo P, Goodall ICA, et al. Exosomes in the Diagnosis and Treatment of Renal Cell Cancer. Int J Mol Sci 2023;24:14356.
13. Linares CA, Varghese A, Ghose A, et al. Hallmarks of the Tumour Microenvironment of Gliomas and Its Interaction with Emerging Immunotherapy Modalities. Int J Mol Sci 2023;24:13215.
14. Das A, Ghose A, Naicker K, et al. Advances in adoptive T-cell therapy for metastatic melanoma. Curr Res Transl Med 2023;71:103404.
15. Parent P, Marcq G, Adeleke S, et al. Predictive biomarkers for immune checkpoint inhibitor response in urothelial cancer. Ther Adv Med Oncol 2023;15:17588359231192402.
16. Mathew BG, Aliyuda F, Taiwo D, et al. From Biology to Diagnosis and Treatment: The Ariadne's Thread in Cancer of Unknown Primary. Int J Mol Sci 2023;24:5588.
17. Uccello M, Adeleke S, Moschetta M, et al. Immunotherapy for advanced urothelial carcinoma (UC): rational and current evidence. Ann Palliat Med 2023;12:1345-54.
18. Shah S, Cheung A, Kutka M, et al. Epithelial Ovarian Cancer: Providing Evidence of Predisposition Genes. Int J Environ Res Public Health 2022;19:8113.
19. Shah S, Rachmat R, Enyioma S, et al. BRCA Mutations in Prostate Cancer: Assessment, Implications and Treatment Considerations. Int J Mol Sci 2021;22:12628.
20. Boussios S, Rassy E, Moschetta M, et al. BRCA Mutations in Ovarian and Prostate Cancer: Bench to Bedside. Cancers (Basel) 2022;14:3888.
21. Ghose A, Moschetta M, Pappas-Gogos G, et al. Genetic Aberrations of DNA Repair Pathways in Prostate Cancer: Translation to the Clinic. Int J Mol Sci 2021;22:9783.
22. Boussios S, Rassy E, Shah S, et al. Aberrations of DNA repair pathways in prostate cancer: a cornerstone of precision oncology. Expert Opin Ther Targets 2021;25:329-33.
23. Ioannidou E, Moschetta M, Shah S, et al. Angiogenesis and Anti-Angiogenic Treatment in Prostate Cancer: Mechanisms of Action and Molecular Targets. Int J Mol Sci 2021;22:9926.
24. Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet 2022;399:447-60.
25. Attard G, Murphy L, Clarke NW, et al. Abiraterone acetate plus prednisolone with or without enzalutamide for patients with metastatic prostate cancer starting androgen deprivation therapy: final results from two randomised phase 3 trials of the STAMPEDE platform protocol. Lancet Oncol 2023;24:443-56.
26. Saxby H, Mikropoulos C, Boussios S. An Update on the Prognostic and Predictive Serum Biomarkers in Metastatic Prostate Cancer. Diagnostics (Basel) 2020;10:549.
27. Saxby H, Boussios S, Mikropoulos C. Androgen Receptor Gene Pathway Upregulation and Radiation Resistance in Oligometastatic Prostate Cancer. Int J Mol Sci 2022;23:4786.
28. Mikropoulos C, Saxby H, Boussios S. Prostate cancer-what about oligometastatic disease and stereotactic ablative radiotherapy?-a narrative review. Ann Palliat Med 2023;12:646-52.
29. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
30. Boussios S, Rassy E, Samartzis E, et al. Melanoma of unknown primary: New perspectives for an old story. Crit Rev Oncol Hematol 2021;158:103208.
31. Rassy E, Boussios S, Chebly A, et al. Comparative genomic characterization of melanoma of known and unknown primary. Clin Transl Oncol 2021;23:2302-8.
32. Revythis A, Shah S, Kutka M, et al. Unraveling the Wide Spectrum of Melanoma Biomarkers. Diagnostics (Basel) 2021;11:1341.
33. Adeleke S, Okoli S, Augustine A, et al. Melanoma-the therapeutic considerations in the clinical practice. Ann Palliat Med 2023;12:1355-72.
34. Dummer R, Long GV, Robert C, et al. Randomized Phase III Trial Evaluating Spartalizumab Plus Dabrafenib and Trametinib

for BRAF V600-Mutant Unresectable or Metastatic Melanoma. J Clin Oncol 2022;40:1428-38.
35. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016;17:1248-60.
36. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2018;19:603-15.
37. Moschetta M, Boussios S, Rassy E, et al. Neoadjuvant treatment for newly diagnosed advanced ovarian cancer: where do we stand and where are we going? Ann Transl Med 2020;8:1710.
38. Osseis M, Nehmeh WA, Rassy N, et al. Surgery for T4 Colorectal Cancer in Older Patients: Determinants of Outcomes. J Pers Med 2022;12:1534.
39. Boussios S, Cooke D, Hayward C, et al. Metastatic Spinal Cord Compression: Unraveling the Diagnostic and Therapeutic Challenges. Anticancer Res 2018;38:4987-97.
40. Vassiliou A, Osunronbi T, Enyioma S, et al. Prognostic Factors in Patients with Metastatic Spinal Cord Compression Secondary to Lung Cancer-A Retrospective UK Single-Centre Study. Cancers (Basel) 2023;15:4432.
41. Fisher CG, DiPaola CP, Ryken TC, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine (Phila Pa 1976) 2010;35:E1221-9.
42. Tokuhashi Y, Uei H, Oshima M, et al. Scoring system for prediction of metastatic spine tumor prognosis. World J Orthop 2014;5:262-71.
43. Boussios S, Hayward C, Cooke D, et al. Spinal Ewing Sarcoma Debuting with Cord Compression: Have We Discovered the Thread of Ariadne? Anticancer Res 2018;38:5589-97.
44. Shah S, Kutka M, Lees K, et al. Management of Metastatic Spinal Cord Compression in Secondary Care: A Practice Reflection from Medway Maritime Hospital, Kent, UK. J Pers Med 2021;11:110.
45. Hakim RA, Galante JR, Zahid H, et al. Evaluating the impact of the metastatic spinal cord compression coordinator in a regional cancer network: a prospective, non-randomized pilot study. Ann Palliat Med 2023;12:846-54.
46. Caglayan A, Redmond S, Rai S, et al. The integration of palliative care with oncology: the path ahead. Ann Palliat Med 2023;12:1373-81.
47. Ferrell BR, Temel JS, Temin S, et al. Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017;35:96-112.
48. Dans M, Kutner JS, Agarwal R, et al. NCCN Guidelines® Insights: Palliative Care, Version 2.2021. J Natl Compr Canc Netw 2021;19:780-8.

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