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Inclusive oncological trials and targeted treatments cannot ignore sex and gender

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Sex-sensitive and gender-sensitive medicine is a novel field that explores the impact of sex and gender on health and disease. Sex is defined by biological features such as genetic, hormonal, anatomical and physiological characteristics.[1] Gender is a multidimensional attribute enacted in human social interaction and operationalised as gender identity, roles, norms and behaviours among others.[1 2] Biological differences between male and female patients have implications for the prevention, screening, diagnosis and treatment of various diseases,[3] and gender impacts access to care and quality of life.[4] For example, clinically relevant sex-specific differences in the presentation of disease[5] or efficacy of drugs[6] have been described in the field of cardiology. Pharmacological response and drug safety potentially differ in relation to sex[7] and gender appears to impact the quality of life of patients with neurological diseases.[8] Given this knowledge from other clinical fields, the need for greater consideration of sex and gender issues in oncology clinical trials is evident and should become a major focus in future research and publishing practice.

Biological differences between male and female patients and the impact of gender on trajectories of care and patient-reported outcome measures (PROMs) are gaining growing attention. Biological sex influences the epidemiology of non-sex-dependent cancers, tumour biology, the metabolism of anticancer drugs and immune system activity.[9 10] Several retrospective analyses suggest relevant differences in toxicity and, potentially, efficacy of anticancer drugs between male and female patients.[11–13] Specifically, a retrospective analysis of over 20 000 patients (37.9% female and 62.1% male) from 202 oncological trials demonstrated an increased risk of severe symptomatic adverse events in female patients across different treatments such as chemotherapy, immunotherapy and targeted treatments.[14] These differences could be explained by many factors, one of them being the widespread practice of dosing of anticancer drugs according to body weight or body surface area (BSA).[15] Fat-free body mass would be a far better estimate of the metabolically active body mass[16] and, contrary to BSA, its calculation would take potential sex differences in body composition into account.

Although recruitment practices for clinical studies are becoming more inclusive, significant underreporting of sex-specific differences in efficacy and tolerability against female participants persists. Currently, female patients appear adequately represented in oncological trials,[17] but discrepancies are still evident for certain highly prevalent cancer types[18] and for solid tumours in general.[19] For example, although colorectal cancer occurs with almost equal frequency in male (55%) and female (45%) patients in Western societies,[20 21] female patients only account for 30%–40% of trial participants in clinical trials investigating metastatic colorectal cancer.[22–26] The reasons for these discrepancies are not clear and need to be further investigated.[27] These clinically relevant inequalities prompted the European Society of Medical Oncology to publish a consensus paper addressing the need of implementing sex and gender in oncological research and practice in 2019[10] stating that 'clinical trials of all phases need to ensure that the number of men and women enrolled is proportionate to the incidence of the cancer type. Sex should become a standard stratification factor in phase III studies'.[10]

In addition to sex, gender is a still poorly investigated aspect in clinical care that could significantly impact the role and social function of patients with cancer.[28] Although the investigation of gender is complicated by its multidimensional nature,[29] variation over time and difference in salience for individual patients,[30] researchers should not refrain from investigating its impact on PROMs and

access to treatment. As the availability of methodological tools to investigate gender in the context of biomedicine increases,[31] a systematic incorporation of this variable into oncological research is warranted to improve access and PROMs.

In the era of precision oncology and individualised treatment, where clinical trials investigate small subgroups to maximise treatment efficacy while limiting toxicity, it appears paradoxical that sex and gender are not systematically taken into account. The currently available information about sex differences in oncology is mostly based on retrospective analyses, but as we move towards prospective studies some easily actionable steps could substantially improve the data quality and clinical value of the output. Trials should offer unequivocal definitions of the variables measured and the operationalisation of sex and gender.[32 33] Trial recruitment should be designed to allow for appropriate sex-disaggregated analysis, which should be systematically reported, as requested by a growing number of scientific journals.[34–36] This includes rigorous sex-sensitive trial design and transparent reporting of analytical approaches and their limitations,[37] for example, in the case of limited sample sizes due to rare tumours. Sex-specific complementary subgroup analyses, or tests of interaction, should be carefully planned and registered before execution of the trial.[38] Information about potential sex-dependent differences in efficacy and incidence of side effects should be made easily available.[10] Gender should be considered in trial access, recruitment and in the long-term care of cancer survivors. Only the systematic consideration of sex and gender at all levels, from the molecular to the clinical and societal, will allow a truly comprehensive evidence-based precision oncology approach in the future.[39]

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