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Commentary

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Are Current Cancer Treatments on Target for Our Ageing Cancer Population?

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Abstract: Worldwide the cancer population is ageing – within a decade almost two-thirds of newly diagnosed patients will be aged 65 years and older. Despite this, the majority of oncology clinical trials continue to recruit patients who are younger and fitter than those typically encountered in clinical practice. As such, there is a lack of clinical data to guide management, particularly in those patients living with frailty and/or comorbidity. Importantly, the lack of older adults in trials also means that the subsequent translational work that underpins biomarker and therapeutic discovery may not be relevant to those we see in clinic. In this commentary, we discuss this challenge and the ways we as an Oncology community can look to address this pressing issue.
Keywords: Geriatric Oncology; Personalised medicine; Translational research

We are facing a pandemic of population ageing and growth, which is accompanied by a rising tide of cancer cases in older adults. By 2035, 60% of cancer diagnoses worldwide will be in patients aged older than 65[1]. Increasing age is associated with poorer cancer outcomes including survival and treatment tolerance[2]. Despite this, few oncology clinical trials specifically recruit older adults or have meaningful endpoints for an older population such as maintenance of independence or impacts on functional status and quality of life[3, 4]. Those older adults recruited to clinical trials are often not representative and typically fitter compared with real-world populations[5].

Consequently, many treatment strategies have only been demonstrated to be beneficial in the younger, fitter populations traditionally recruited to clinical trials. Inappropriate use of or selection for treatments could

cause greater harm than benefit, therefore decisions relating to systemic therapy, surgery or radiation must be made based on an assessment of both tumour biology and of the individual capacities of the older adult.

The lack of data relating to an older cancer population is a challenge to real-world clinical practice for several reasons. Firstly, it is difficult to accurately predict the impact of age on treatment tolerance for an individual patient, particularly in the context of the increasing use of complex multimodal and multiagent approaches. Age is associated with comorbidity and frailty[6], both of which are risk factors for poorer treatment tolerance[7].

To help clinicians, chemotherapy toxicity prediction tools are available and feasible for use in busy clinics[8, 9], however they have limitations; they have only been validated for cytotoxics, they were developed in US-based populations only and individual patients' toxicity risk may reflect multiple additional factors they do not capture. In addition, while these predictive tools used development populations which were balanced across older age groups, sex and comorbidity, they were primarily caucasian and of at least high school education. This may further limit their applicability to a wider population base.

Similar tools exist relating to complication risk from surgery in older adults (e.g. Vulnerable Elders Surgical Pathways and outcomes Assessment (VESPA)[10]) but no tool exists to predict either toxicity from radiotherapy alone or in combination with chemotherapy.

Secondly, there is an increasing appreciation that treatment efficacy may differ with age. For example, older adults appear to derive greater benefits from immune checkpoint inhibitors (ICI)[11]. These differences could be due to both age-related patient factors (e.g. drug pharmacokinetics and pharmacodynamics, reduced organ function and reserve, co-existing comorbidity or the impact of polypharmacy) or age-related differences in tumour biology and immunology. Recent studies have shown that older hosts (human and mice) have a more favourable tumour microenvironment for ICI response[12, 13]. Benefits of treatment must always be balanced against the predicted life expectancy of an individual patient to help frame cancer treatment decisions.

While there have been several large studies in older adults investigating tools using patient factors to predict treatment toxicity and tolerance[9, 14], as well as studies investigating the role of frailty screening and subsequent intervention on cancer outcomes [15-17], there has been little focus to date on the impact of age on tumour biology.

This is important as translational work derived from traditional clinical trials may not be representative of our real-world patients. As such, the current treatments we are using and identified potential biomarkers of outcome may not be personalised to our older real-world population. For instance, in older adults with hormone receptor-positive early breast cancer, the benefits of chemotherapy are not clear[18, 19].

A growing body of evidence in the literature has demonstrated the differing biomarker profiles across a range of tumour groups[2]. These differences are not only observed using immunohistochemistry but also extend to differences at the genomic and transcriptomic level (**Figure 1**). However, data relating to these age-related differences is not available for all tumour sites, the number of patients included in studies is often small and response/survival data is often not available or powered to draw firm conclusions.

The lack of data in older adults has been recognised by the American Society of Clinical Oncology (ASCO) and the International Society of Geriatric Oncology (SIOG) as a major challenge to cancer research and suggestions have been made regarding changes at every level of trial design[20, 21].

To specifically address the gap in translational knowledge, we need to increase the number of prospective oncology trials designed for and collecting samples (both tissue and serum) in older adults. Exemplar's of such an approach include the GO2 trial in advanced gastroesophageal cancer[22] and the currently recruiting FOXTROT2 study in early-stage colorectal cancer[23]. The translational work that emerges from these studies will provide vital insight into the potential differing tumour characteristics and biology that occurs in an older population. This will also provide an opportunity to identify novel biological targets as well as the ability to explore the overlap between tumour biology and patient biomarkers such as geriatric assessment and biomarkers of ageing.

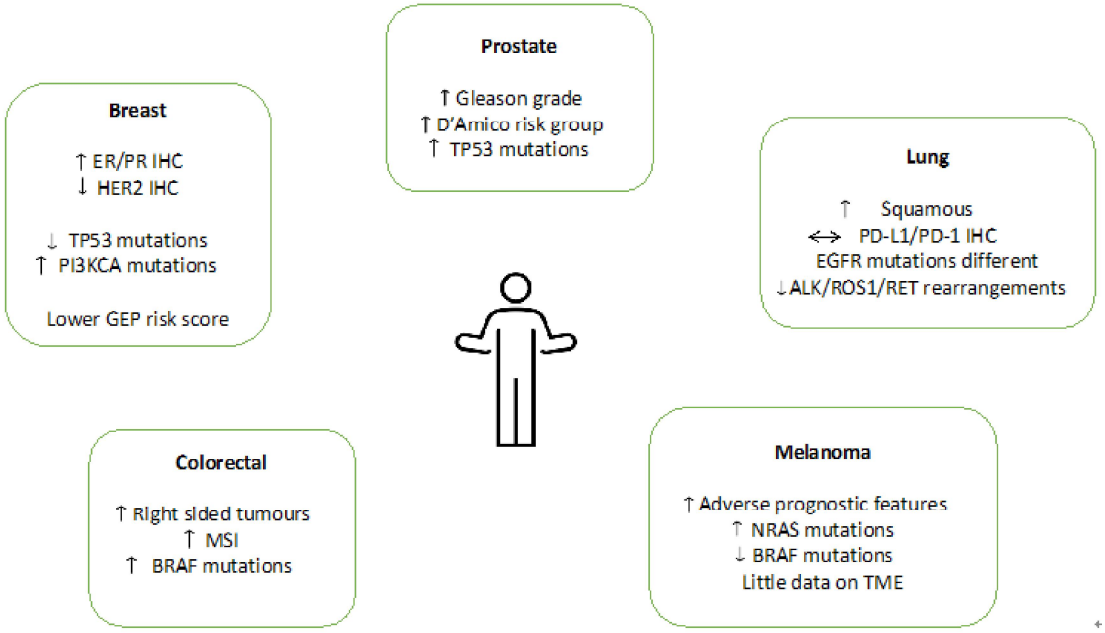

Figure 1. Differences in tumour biology and immunology with age in prostate, breast, colorectal, lung and melanoma. EGFR – epidermal growth factor receptor, ER – oestrogen receptor, GEP – gene expression profile, MSI – microsatellite instability, PD-L1 – programmed death ligand-1, PR – progesterone receptor, TME – tumour microenvironment. Adapted from van Herck *et al.* [2]

While we wait, there is an opportunity for researchers to make use of stored tumour tissue from completed clinical trials, existing biorepositories of samples from real-world patients and registry databases to explore age-related differences both in tumours as well as treatment response and survival. Examples in breast cancer are the translational work by the Nottingham Breast Cancer Group[24-26] and population linkage studies in Belgium[27]. By doing this, we will be able to generate research questions to help guide future studies. This will require funding and a collaborative approach, which has led to the formation of the SIOG Translational Group.

These steps are essential as we strive for a precision cancer medicine approach for our older adults – choosing the correct treatment for the correct patient at the correct time. Only by this approach, can we ensure our current and future treatments for our older adults with cancer are on target.

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