Novel Therapeutics in Lung Cancer

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Opinion

In contrast to the widely held belief that a higher BMI reduces the survival and/or incidence of many malignant tumours (such as colonic, pancreatic, and postmenopausal breast cancers), obesity (defined as BMI>30 kg/m2)

would be protective for the survival and/or occurrence of a few malignancies, including large B-cell lymphomas, renal, and Non-Small Cell Lung Cancer (NSCLC). This "obesity paradox" has been proposed by epidemiological studies and a recent meta-analysis focusing on NSCLC.

However, these studies were unable to determine whether these differences in survival were truly due to BMI or to potentially relate confounding factors, such as disease extent, which was frequently not recorded. However, nutritional status as measured by plasmatic markers has recently been recognised as an important determinant of survival in operated NSCLC. Furthermore, sarcopenia and low BMI have been linked to an increase in post-operative morbidity and/or mortality. A recent study by our group found that a pre-surgery BMI of more than 25 kg/m2 improves long-term survival in patients who had undergone pneumonectomy for NSCLC, regardless of stage. This beneficial effect of a higher BMI has been confirmed in obese cancer patients who underwent lobectomy. Given that Weight Loss (WL) significantly reduces survival in advanced NSCLC, the negative prognostic impact of lower BMI may simply be a result of WL. Thus, in order to better understand the impact of BMI on outcome, it should be useful to study pre-disease BMI alongside pre-surgery BMI, with the idea that baseline reserves may impact survival on their own. Indeed, BMI and sarcopenia can be used to predict fat storage and muscular loss, respectively. Sarcopenia is linked to fatigue, frailty, ageing, and a variety of chronic diseases such as Chronic Obstructive Pulmonary Disease (COPD) and advanced cancers. It is also associated with a poor long-term outcome following pneumonectomy. Sarcopenia is now defined as a muscle disease that can be confirmed through quantification of muscle mass and whose severity correlates with loss of strength, according to an updated definition; low muscle mass has also been proposed as part of the definition of malnutrition. However, sarcopenia is debatable in terms of definition, calculation, and cut-off points, as well as measurement methods. However, as recently reviewed, existing imaging technologies (CT scan and magnetic resonance imaging, MRI) have been verified by a few studies establishing a link between cross-regional muscle mass measurement and whole-body muscle mass calculation. As a result, some authors have emphasised the need of comparing imaging approaches with the traditional clinical assessment of sarcopenia obtained from Heymsfield's formulas for calculating height indexed Total Muscular Mass (iTMM).

This anthropometric approach has long been regarded as reliable, as evidenced by cadaver studies or Bioelectrical Impedance Analysis (BIA), Dual-Energy X-Ray Absorptiometry (DEXA), CT, and MRI assessments. Also discussed were the vast heterogeneity and small sample sizes of available imaging studies on sarcopenia, the absence of effective confounder control, and the lack of references to WL, stage of disease, and medication.

Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 27% of all cancer-related fatalities worldwide, making it a major public health issue. In theory, as with all malignancies, healing requires complete, long-term tumour elimination (usually by surgery or radiation), although considerable shrinking (typically by systemic treatments) could result in long-term disease control. More realistically, host-tumour interactions, which are major determinants in the natural history of diseases in the absence of treatments, will have a significant impact on disease progression, with treatments primarily aimed at inducing the balance host-tumour to tip toward improvement or, if possible, healing. As a result, when possible, complete tumoral resection of the primary tumour (and, if possible, of oligometastatic disease) is still considered the best treatment, with the hope that the host-immune response will be in charge of destroying microscopic residual disease, possibly with the help of systemic adjuvant treatments. However, the vast majority of patients are ineligible for surgery and have been treated for decades with standard chemotherapy (cisplatin-based regimens) and/or radiotherapy. Targeted therapy (mostly Tyrosine Kinase Inhibitors, TKIs) and immunotherapies may produce outstanding results in select subgroups. The benefit of targeting immune cells (that is, restoring their physiologic function that has been altered by the presence of tumour) has changed the therapeutic paradigm, which now aims to target, alongside cancer cells, the interface host-tumour, i.e., the Tumour Micro Environment (TME), as well as host-related factors, the latter two having a strong impact on tumour development and response to therapies.

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