Lung oligometastatic disease

Impact paragraph

Cancer is the second cause of death worldwide and its incidence is age-related, with a higher frequency in subjects older than 60 years[1]. Parallelly, mainly in western countries, life expectancy is constantly increasing, and incidence of communicable diseases is declining, making cancer one of the most common lethal conditions diagnosed every year[1]. Development of distant metastases is the cause of death in almost 90% of cancer patients[2]. This phenomenon determines the necessity of long-term expensive treatments, which account for an expected increase of average costs for cancer care[3]. Furthermore, the presence of a neoplastic conditions often determines the need for prolonged assistance of the affected individuals, with consequent relevant costs at both the family and community level. In addition, coping with a cancer diagnosis almost invariably causes a significant perturbation of the psychological sphere of patients: several meta-analyses and large multicentre studies have shown that, during the time of cancer diagnosis, about 30% of the patients suffer from a mental health condition[4] and the rate of suicide is twice as high as that of the general population[5].

Standard treatment for cancer metastases has always typically been systemic chemotherapy, with usually only limited benefits on survival. In recent years new highly effective systemic treatments have been introduced for patients with a metastatic condition, but the indication for such treatments is usually determined by the expression of specific molecules on the neoplastic cells, which act as drivers of therapeutic response. Lung is one of the preferred sites of metastases and when cancer recur with an oligometastatic pattern, pulmonary metastasectomy may be performed with a curative intent. Apart for its potential therapeutic role, metastasectomy offers the advantage of providing tissue for thorough molecular studies and identification of potential targets of treatment which, in the era of targeted therapies, represents a point of paramount importance.

However, since metastases recur in more than half of the operated patients and are eventually responsible for an unfavorable outcome, surgery, even when performed with a radical intent, should not be merely seen as a definitive treatment, but rather as a step of a multidisciplinary approach to metastatic disease. Nonetheless, development of recurrence after a potentially radical intervention insinuates a weak

comprehension of the biological bases of cancer, a scarce reliability of current radiological investigations in detecting all tumor foci or an inadequate application of perioperative schemes of pharmacological treatments for controlling further development of metastases.

At the same time, the prognosis of patients with overt metastatic states is almost invariably poor, suggesting a low appropriateness and specificity of the currently employed systemic treatments.

Therefore, major efforts should be made to better understand the pathogenetic basis of cancer metastases and identify more reliable target of treatment. Indeed, the typical slow-evolving behavior of oligometastatic tumors offers the opportunity for a deeper comprehension of the metastases' formation process and of the pathogenetic aspects of the tumor/host balance.

Target group

The present thesis aims to investigate on several aspects of cancer metastases, from the role of the currently available treatments modalities to the effects of the interaction between cancer cells and the immune system on the whole body. Our research focuses on the peculiar subgroup of patients with lung oligometastases, who represent a unique source of information on cancer behavior *in vivo*. Nevertheless, our research should represent a starting point for future investigation which aim to elucidate the effects of cancer on the body homeostasis and identify possible, still undiscovered targets of treatment. This might ultimately translate into a survival advantage even for patients with a more extensive metastatic pattern.

Output

Hitherto, the treatment of patients with a metastatic cancer has been systemic chemotherapy, while surgical resection is currently reserved for patients with a low burden of disease and the potential of having their cancer foci radically resected, albeit the effectiveness of this practice is based upon a low level of evidence. These treatments are usually performed as the most effective current treatments, without considering the complexity of the tumor/host balance and the humoral and cellular drivers of cancer behavior. Unsurprisingly, the results in terms of cure are quite frustrating. This thesis presents the results of a series of investigations on the biological behavior of cancer metastases and their interaction with the normal body homeostasis. The included arguments should promote a debate between surgeons, medical

and radiation oncologists and promote further research on these still not fully elucidated aspects of cancer pathogenesis. A deeper comprehension of these aspects might lead to identify the most appropriate surgical techniques and implement the current protocols of treatment with specific dietary regimens and molecules that enhance cancer immune surveillance and reduce tumor-associated inflammation and its detrimental effect on cancer progression. The employment of such still unexplored adjuvant treatments might not only consolidate the role of surgery in the setting of oligometastatic disease, but also extend its application in patients with more widespread patterns of disease. Ultimately, this might translate into an increased chance of cure for patients with cancer metastases.

References

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