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Sommario	Inflammation and cells of the innate immune system are known to contribute to tumour initiation and progression. Differently, the adaptive immune response controls growth and dissemination of established tumours . The double edge role of inflammatory and adaptive components of immune system in solid tumours are well represented in CRC. The progression and survival of patients with CRC is known to be modified by the interactions generated between the tumour and the host’s response in a milieu named tumour microenvironment, composed by local immune responses. The quantification of the density and the type of immune cells in the tumour microenvironment has been a challenge since the early 60’s of the last century. However their role and clinical significance in different human cancers has not been unequivocally addressed and still there is a strong interest in determining the dynamics of immunosurveillance and immunoevasion, and the role of immune cells infiltrating CRC. Recently, experimental support was provided that cancer infiltrating immune cells might be a crucial factor in chemotherapy mediated tumour cell death. Despite effort in this field there’s still no clinical evidence in CRC regarding any effect modification by tumour infiltrating cells in enhancing the benefit of chemotherapy treatment, or whether this parameter might help to identify patients who would benefit from adjuvant therapy. In this

	context, tumour associated macrophages (TAM) represent the prevailing population in different cancers and are thought to enhance tumour cells proliferation and survival. Tissue macrophages are players of the innate immune response capable of phagocytosis and antigen presentation, that play a key role in directing immune responses through secretion of a plethora of factors. In CRC data regarding TAM and tumour progression are controversial. Of interest, in an experimental model of cancer TAM “re-educated” by CD40 ligand treatment, were found to be necessary to mediate antitumour activity, whereas tumour infiltrating lymphocytes (TILs) were irrelevant, supporting the hypothesis that TAM might mediate anti-tumour activity in certain conditions. The aim of this thesis was to study the prognostic significance of different populations (CD3+ and FOXP3+ TILs and CD68+ TAMs) of immune cells in the tumour microenvironment, and their interactions with demographic and clinicopathological variables in a large dataset of stage II and III CRC patients. We first found that the cellular mediators of immunosurveillance seems to change along with the lymph-nodal involvement at diagnosis. Higher densities of TILs (both CD3+ and FOXP3+ cells) were associated with better prognosis among stage II CRC patients, but not in stage III. On the other hand, higher densities of TAM were associated with better prognosis only among stage III CRC patients, but not in stage II. This data suggest that TILs mediate immunosurveillance in early stages of disease, while when the tumour has the ability to invade and spread to metastatic lymphnodes the mediators of surveillance seem to be macrophages. In detailed analysis, higher densities of TAM in stage III CRC were found to interact only with the variable 5-Fluoro-uracyl (5-FU) adjuvant chemotherapy treatment in predicting patients prognosis. We found that in stage III CRC patients, higher densities of TAM were associated with better survival only among those who received 5-FU chemotherapy. Moreover, the predictive effect of TAM in determining the efficacy of 5-FU chemotherapy showed significance only in microsatellite Stable (MSS) CRC patients. This is in accordance with the fact that microsatellite instability in CRC is a well-known negative predictor of response to 5-FU chemotherapy. The positive predictive effect of TAM in stage III CRC prompted us to confirm our findings in the non-colonic metastatic site of those patients. The densities of TAM in metastatic lymphnodes retained a positive predictive effect in identifying patients obtaining a prognostic advantage with 5-FU chemotherapy treatment. Therefore, the antitumour effect of TAM in 5-FU treated patients is likely to be exerted mainly on tumour micrometastasis which spread from the primary site and may cause recurrence of CRC. Ultimately, our data are in accordance with clinical guidelines supporting the use of 5-FU as adjuvant treatment only in stage III CRC. This study shed basis for the future identification of the molecular basis and the functional role of TAM in mediating 5-FU tumour cell death in reliable experimental models of CRC.
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