

Optimizing the timing of surgery after neoadjuvant radiotherapy for decreasing tumor metastasis.

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Neoadjuvant radiotherapy (RT) is considered as a key actor in many treatments and aims at improving tumor local control and patient overall survival. In many cases the RT schedule and the timing of surgery are mostly empirical based on clinical experiences. Here, we propose to bring some scientific rationale for determining the best association between the radiotherapy schedule and the timing of surgery. We develop a pre-clinical model that mimics neoadjuvant RT. With this model we study the impact of different neoadjuvant RT schedules and timing of surgery on tumor microenvironment and tumor dissemination.

We inject, subcutaneously, human tumor cells into the flank of SCID mice. The tumors arising at the injection site are treated with “neoadjuvant RT” at a total dose and dose per fraction of 10Gy/2Gy and 10Gy/5Gy. We surgically remove carefully tumors at different time points after the end of RT. After surgery, we let the mice alive during 5 weeks for metastatic growth. At sacrifice, organs are collected to count metastatic islets highlighted by human Ki-67 immunolabeling. RT is known to influence several pathways involved in tumor survival and dissemination. Therefore, based on tumor extract, we study the HIF-1 survival and MMP’s pathways.

We first demonstrate the feasibility of the model with less than 10% mortality. With this model we observe that lung metastases occurrence is linked to both the RT schedule and the timing of surgery. When surgery is performed 11 days after RT and we compare the two radiotherapy schedules together, lung metastases are less important in size and less frequent in the hypofractionated RT schedule (10Gy/5Gy) as compared to the conventional one (10Gy/2Gy). This phenotype is completely abolished when surgery is performed earlier at 4 days after RT. Moreover, the timing of surgery is important in a same RT schedule. Indeed, with 10Gy/5Gy, when surgery is performed at 11 days after the end of RT, the size and the number of lung metastases are smaller compared to 4 days. Inversely, in the 10Gy/2Gy schedule, applying surgery at 4 days protects the mice against lung metastases compared to surgery at 11 days. Tumor volume, tumor necrosis or hypoxia are similar in all groups. Neither MMP’s, nor HIF-1 expression change significantly between groups and cannot be correlated to the number of lung metastases.

We have established a very powerful pre-clinical model enabling us to study the impact of neoadjuvant RT schedules and the timing of surgery on tumor dissemination. We report here that both dose per fraction and timing of the surgery influence the occurrence of lung metastases. These results are in view with a clinical trial in the locally advanced rectal cancer that demonstrates the importance of the timing of surgery on tumor dissemination. Such a pre-clinical model offers new opportunities for developing new therapeutic strategies.

- 1 Coucke PA, Notter M, Matter M, et al. – Effect of timing of surgery on survival after preoperative hyperfractionated accelerated radiotherapy (HART) for locally advanced rectal cancer (LARC): is it a matter of days? *Acta Oncol*, 2006, **45**, 1086-1093

