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CLINICAL RELEVANCE OF LOCAL CONTROL - M. TUBIANA

The local control of a tumor has two main benefits : firstly, it avoids the death of the patient caused by local infiltration into the surrounding tissues. Secondly, it avoids distant metastatic dissemination. Indeed within each group of cancers there is a clear correlation between the probabilities of local recurrence and of distant spread. For example in carcinomas of breast, prostate, head and neck, uterine cervix, etc.. the incidence of relapses due to metastases is much higher in patients who have experienced a local recurrence.

It has been claimed by some authors, such as B. Fisher, that a local recurrence is not the nidus for a metastatic dissemination but only an index of the aggressiveness of the tumor, therefore, these authors claim that local control should not significantly reduce the incidence of distant metastases.

It is true that tumors with a high degree of malignancy (for example grade 3 breast cancers) have a higher propensity to both invade surrounding tissues and distant spread ; however, there is some evidence against this reasoning :

1. In most controlled clinical trials comparing two treatment regimens for the local control of the tumor, the number of patients with distant metastases is higher in the arm in which the number of local recurrences is the highest. The only possible explanation is that the residual tumor is the source of distant spread.

2. In several studies the mean time interval between initial treatment and clinical emergence of distant metastases is longer in patients with local recurrence than in patients without local recurrence. This points out that distant on average spread occurred later in patients with local recurrence and therefore that some of them originated from the residual tissues.

3. The analysis of the natural history of human cancers does not substantiate the concept that there are two types of cancers: the most malignant ones with very early distant dissemination and the less malignant ones with very late dissemination. Rather they show a unimodal distribution of the tumor size at dissemination from the most malignant tumor to the less malignant ones.

It can be concluded that whereas local control cannot avoid the dissemination which has already occurred, it can avoid further dissemination and thereby markedly increase long term survival.

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LOCATION CONTROL OF THE PRIMARY TUMOR AND PATIENT SURVIVAL

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Cure of the cancer patient requires that all cells of the primary tumor and, if present, of distant foci of disease be inactivated. Local regrowth of tumor *always* leads to patient death unless a salvage therapy is effective, available *and* applied. Further, if the primary neoplasm has the capability to establish distant metastasis then the regrowth would also have had capacity. The concept that improvements in efficacy of radiation treatment would result in no gains in disease free survival because the new local controls would fail due to distant metastasis requires : tumors which fail locally are intrinsically different from those treated successfully, *viz*, they are exceptionally efficient in establishing metastasis. Further, as they have failed locally, they would also be expected to be more radiation resistant.

Abundant evidence from clinical and laboratory animal studies demonstrates that subjects with recurrent tumor experience higher rates of distant metastasis than those with locally controlled tumors. To what extent are these metastases secondary from the recurrent lesion as distinct from an intrinsically exceptionally aggressive primary tumor ? Experimental data will be presented in an examination of the question : are the probabilities of local failure and of distant metastasis independent ? These will include data from clinical radiation therapy and from experiments on isografts of murine tumors and on xenografts of human glioblastoma multiform and squamous cell carcinoma.

Pertinent to this presentation, data from 6 centres on SF_2 of human and murine tumor cells and TCD_{50} values of isografts do not indicate a correlation between cellular radiation sensitivity and metastatic activity.

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LOCAL CONTROL IN CANCER TREATMENT Holmberg L. Dept of Surgery, Cancer Epidemiology Unit, University Hospital, 751 85 Uppsala, Sweden.

In deciding the amount of local control appropriate for an individual patient, three categories of cancer patients should be considered: 1. Patients with very limited disease where local control in the majority of patients will be the curative therapy. 2. An intermediate group with a more advanced local disease, sometimes combined with limited regional lymphatic spread. 3. A third group with locally advanced disease who are almost certain to have established distant micrometastases or the group of patients with locally limited disease but where extensive regional or distant spread is evident already from the outset. In the group with limited disease, the local therapy must be meticulous enough the prevent remnants of the primary tumour to give rise to secondary distant metastases. In the patient group with advanced disease, systemic therapy is the overriding priority and local control is only to be viewed as a palliative therapy without chance to prolong life. The largest clinical challenge is to determine the appropriate amount of local control needed in the intermediate group. In this group, a large proportion of patients will have established distant micrometastases which will ultimately determine the prognosis, but a subset of patients might still have a disease with very limited metastatic capacity. Regrettably, for most cancers we have no tools to separate the prognostic subsets at time of diagnosis. Thus local control in this intermediate group will seem to have three aims that should be considered simultaneously: It should be extensive enough to help prolong life in those patients with a disease with low malignant potential. In patients with micrometastases, morbidity of a local recurrence should be prevented to a fair cost in terms of side effects. The local control must be compatible with adjuvant systemic therapy.

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WILL AN ENHANCED LOCAL CONTROL WITH CONFORMAL RADIATION THERAPY LEAD TO IMPROVED TREATMENT OUTCOME ?

Z. Fuks