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ACTIVATION OF PROTO-ONCOGENES IN HUMAN CANCER: MOLECULAR ANALYSIS OF THYROID TUMORS

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In recent years, molecular biology, molecular genetic and cytogenetic and biochemistry have made it possible to disclose the origin of cancer by identifying a number of genes and proteins involved in the transformation of a normal cells in a malignant one. Two classes of tumor-associated genes have been characterized: the oncogenes derived from the activation of proto-oncogenes involved in positive control of normal cell growth and the tumor-suppressor genes normally devoted to a down-regulation of growth and inactivated or altered in tumor cells. The analysis of the alterations of these genes has allowed to propose models of human tumorigenesis such as those related to colon cancer or thyroid tumors. The latter is a particularly interesting model since comprises a spectrum of benign and malignant tumors that, in spite of their common histogenic origin, display different biological and clinical features. Therefore, it represents a model of human tumorigenesis where to explore the possibility that the pathogenesis and the progression of the various histological types associate with the occurrence of different genetic events involving both oncogenes and tumor-suppressor genes. The work of our laboratory has contributed to determine that, among differentiated carcinomas of the thyroid gland, a frequent activation of ras oncogenes is present in all the stages of progression from follicular adenoma to follicular and undifferentiated carcinomas whereas in papillary carcinomas the two genes ret and proto-trk, whose products display all the features of a receptor tyrosine kinase, are activated in about 50% of the analyzed cases. Specific chromosome aberrations have been related to the activation of different oncogenes derived by ret gene rearrangements. Moreover, our results suggest that mutations of the tumor suppressor gene p53 are restricted to the more aggressive histological types of thyroid carcinomas and are associated with both dedifferentiation and progression.

Key words: Thyroid tumors, oncogenes, tumor suppressor genes.

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LONG TERM MORBIDITY AND MORTALITY AFTER ADJUVANT CHEMOTHERAPY AND/OR RADIOTHERAPY

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MULTIMODALITY TREATMENT FOR SOFT TISSUE SARCOMAS.

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Surgery of primary soft tissue sarcoma is frequently vanished by local recurrence (20-30% of non amputative operations) and pulmonary metastases (40-50%). In the past decade the combination with other therapeutic procedures, mainly radio and/or chemotherapy was expected to improve results. The timing and techniques of multimodal strategies make the number of combinations almost endless, customized by institutions thus intriguing comparison.

Radiotherapy (RT) is devoted to improve local control after marginal surgery; the postoperative external beam administration of 60-65 Gy is the typical indication. There are experiences with preoperative RT, frequently completed postoperatively up to adequate total dose. A sophisticated postop procedure, brachytherapy, employes iridium isotope seeds (Ir 192) inserted through probes positioned during the operation, The overall validity of RT is almost axiomatic and is rarely matter of randomized study, nevertheless its real role is difficult to be assessed for the different criteria in selecting cases and evaluating results. Our conclusive points are that RT is effective if surgery is classified at least as marginal in a small area; it is not a remedy for unproper margins leading to only a delay of the recurrence onset. The indication to preop RT depends on the institutional experience and therapeutic program: there is evidence that large liposarcoma can be easier operated after induction RT. Brachytherapy is only possible where there are experience and facilities.

The main purpose of adjuvant postop. **chemotherapy** (CT) is to improve survival by reducing the occurrence of metastases, and to provide contemporarely a better local control. Randomized studies are many but results still controversial, and basically discouraging the expectancies on a dramatic improvement in survival. Other experiences scheduled CT preoperatively and documented the possibility to obtain a shrinkage of the primary lesion with better surgical margins, and to provide an in vivo evaluation of chemosensitivity, but the impact on final outcome in terms of survival and local recurrence is not verified. A controlled study is ongoing under the EORTC soft tissue sarcoma group. The intra-arterial access for CT was explored in order to improve the effect on the primary lesion. Results of several non randomized studies are descriptive and confirmed the possibility to obtain a local response in 30 to 40% of cases thus improving the quality of surgical margins sometimes resulting in limb salvage procedure, but the final impact of this response and the real necessity of intrarterial delivery is not yet clear. Preoperative CT is however suggested where an amputation could be avoided, provided that a tumor shrinkage is obtained.

Other strategies. Hyperthermic perfusion of drugs in extracorporeal circulation (ECC) has been sporadically employed for sarcomas. A possible response rate in 30% of cases was documented, not enough to overlook the complexity of methodology. More recently this procedure utilized the tumor necrosis factor (TNF) with similar results as adriamycin but increased toxicity: pilot experiences are in progress. The drug delivery by ECC do not have any expected effect on systemic disease and their indication is for limb salvage only.

Arguments. The final survival of STS did not improve by means of multimodal strategies, they refined only local control, a sure success which is shared with technical and cultural improvement of surgery.