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Management of the malignant colorectal lesion, utlilizing monoclonal antibodies derived from tumor oncofetal proteins which result in improved survival via an effective ADCC response

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In general it is believed that colorectal carcinoma is induced via a field effect where a virus such as the polyoma, enters the normal appearing mucosal glands to initiate changes that indicate that genotypic changes have taken place while the phenotypic appearance appears normal. As one focus grows to a recognizable malignancy, the other foci are suppressed and lay dormant. Once genetic transformation has occurred at the site of primary transformation, the other sites will remain in a dormant state. When resecting the primary lesion it is essential that the dormant or premalignant foci be included. Failure to encompass these additional sites will result in anastomotic recurrence. While we have been led to believe that that major cause of bowel malignancies were due to the initiation of a polypoid growth that went through a process of changes from the adenomatous polyp to the adenocarcinoma, it is now recognized that this effect takes place in less than 5% of the clinical cases again, the majority of bowel malignancies are the result of a diffuse viral presence initiating the resulting field effect. The host immune system seems to tolerate the presence of the resulting malignant lesion as the latter continues to progress to that point that metastasis will eventually occur. Speculation as to mechanisms involved suggest that while foreign invaders such as bacteria and viruses express a threshold level of immunogen that can be identified by the host immune system, that the malignant growth, while containing immunogenic protein, express it at levels far below what is required for recognition by the hosts immunocytes. Thus progression of the malignant state continues. While polypoid lesions were considered as responsible for the initiation of the malignant transformation leading to bowel cancer, more recently it has been shown that *E. Coli* production of a mutation in cellulose structure results in the development of a sheath around clustered bowel cells representing the initiation of a polypoid growth. At this point the sheath begins to entrap carcinogenic bacteria that allow the gradual transformation of a the earliest polypoid growth to the malignant adenomatous polypoid which then progresses to the final invasive version. This is obviously a different mechanism from that resulting in a mutated field effect and the major cause of resulting bowel malignancies. Antigen preparation for use in clinical trials was started in the 1970's where with FDA supervision, pooled allogeneic tumor proteins were prepared. 20-30 operative specimens were used in preparing cell suspensions which were then sonicated to release surface membrane antigen. The suspension was passed over a Sephadex G-200 column to further separate those proteins in solution by MW. The cell suspension was then tested in patients by skin testing for DHR, three specific antigens were defined. mAbs were produced against them for purification and mass spec to develop a recombinant antigen. The antigens found for several GI malignancies examined were post-translational modifications of oncofetal proteins present, but in subtherapeutic levels of approximately 10-20ugms per entire lesion wherein semipurified form, 500ugms was needed to elicit a clinical response. In colon cancer, the 3 antigens that were defined were post-translational modifications of the oncofetal proteins A33, MUC5ac and CEAcam. The mechanisms of activity of these antigens after inducing an antibody response, occurred via ADCC (antibody dependent cell cytotoxicity) and not a cell mediated CD8 response. Enhanced survival was defined in patients (colon cancer, pancreas cancer) with recurrent metastatic lesions having failed all known therapeutic agents who were then given the therapeutic mAb. Marked improvement in survival was noted after patients having failed all therapeutic modalities received the therapeutic monoclonal.

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