991

Major improvements in rectal cancer treatment through strict quality control in a randomized trial

C.J.H. van de Velde. *Chairman of the Dutch Colorectal Cancer Group. On behalf of the participating groups*

In a prospective randomized trial in strictly defined rectal cancer patients between January 1996 and 2000 1861 patients were randomized between TME or preoperative radiotherapy followed by TME. Surgery and pathology was strictly supervised and a maximum effort was devoted to quality control.

In a former randomized trial curatively operated non-irradiated patients were compared with non-irradiated patients from the TME-study. Local recurrence rate decreased from 16.3% in the CRAB-trial to 8.6% in the TME-trial. Type of surgery showed to be an independent factor for local recurrence as well as overall survival. Quality control in TME-surgery let to a substantial lower local recurrence rate, where-as hospital volume and infrastructure did not have a significant influence and outcome. Pathologists were trained in order to standardize pathology and to evaluate the quality of surgery. Patients with an incomplete mesorectal had an increased risk for both local and distant recurrence. This study proved that patient's prognosis can be predicted by macroscopic analysis and pathologists have an important audit role in rectal cancer surgery. The overall results of the trial indicate the acceptability of the hypofrationated RT although significantly more blood loss and perineal complications in case of abdominal perineal resection were observed. Special attention was also devoted to nerve identification by the operating surgeons. Through workshops and videos and direct instruction of surgeons at the operating table in 75% of cases it was possible to identify and preserve to nerves, although morbidity was higher than esteemed by the surgeons. Preoperative radiation therapy in male increased impotence by 10% to 35%. Evaluation of quality of life as well as costs indicated that radiotherapy decreased short-term quality of life, but had a more favorable CE-ratio. Patients at interview preferred an additional treatment by radiation therapy in order to improve 3%. This goal was reached at a mean cost per patient of 39.400 Euro in RT-TME and 37.200 in TME-patients, which is quite acceptable. The nationwide study evaluating the role of radiotherapy in operable rectal cancer changed through its strict quality control, the structure of diagnosis and treatment of rectal cancer patients in the Netherlands with major benefits to all participants especially the patients. Future correlations will be made through the structure of a tumorbank in order to tailormade treatment further.

Plenary Lecture

992

Angiogenesis, progress and mechanisms of therapy

A.L. Harris. *Churchill Hospital, ICRF Oncology Unit, Oxford, United Kingdom*

Angiogenesis is essential for the growth and metastasis of cancer. Many studies have shown that assessment of the micro vessel density in cancers and leukaemias can be used to predict prognosis. The vessels are aberrant and recent studies of markers of vessel differentiation or measuring activation. pathways in the endothelium have helped refine the assessment of prognosis and mechanisms in human cancers SAGE RNA analysis has shown that there are specific profiles of genes upregulated in tumour endothelium compared to normal endothelium and that many of these are common to most cancers. They have provided direct targets for therapy. Other key pathways involved in tumour angiogenesis involve those regulated by hypoxia which occurs early in tumour growth and has been shown to be a major independent prognostic factor. Analysis of the pathways has shown that many angiogenic molecules are regulated, amongst which the most important is VEGF. However, other pathways are also activated involving invasion, metastases, cell adhesion and survival pathways. This provides the basis for specific inhibition of the hypoxia signalling pathway by gene therapy or small molecules. Clinical evidence shows that this pathway is activated in most tumours and associated with aggressive phenotype and radiation resistance.

A wide range of angiogenesis targets have been identified for drug development and for several angiogenic drugs responses have been reported, although at a much lower frequency than for cytotoxic chemotherapy. The methods for assessing anti-angiogenic agents are more difficult and complex and require further evaluation. A commonly used strategiy is to combine the anti-angiogenic agent with conventional treatments since pre clinical data shows synergy in many cases. Low dose chemotherapy is another way of selectively inhibiting tumour vessels with low normal tissue toxicity. Vascular targeting, oral VEGF kinase inhibitors and the drugs that block the aVb3 pathway, matrix metalloprotease inhibitors and discovery of natural anti angiogenic molecules such as endostatin and angiostatin has been a further major stimulus to drug development. Overall, therefore, there continue to emerge many new targets. It is likely that this mechanism of treating cancer will be important for both preventing early lesions progressing to invasion, in adjuvant therapy, management of curative and palliative chemotherapy.