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Editorial

Past, present and future perspectives of colorectal cancer—on the brink of a new era?

Colorectal cancer is a major cause of death in Western countries. Its incidence is increasing worldwide, rapidly in the East because of the adaptation of a Western lifestyle and slowly in the West due to aging. In general, 1 out of 20 people will be affected by this disease so that in the European Communitee alone some 200 000 cases per year are diagnosed. Nevertheless, our understanding of the development of this cancer and the genes involved has been increased. Furthermore, surgical treatments, in particular for rectal carcinoma, have also been improved, with a reduction in local recurrences now being observed. There are also several new therapies being tested. Therefore, it is timely that a Special Issue of the *European Journal of Cancer* is dedicated to this disease.

During the first Multidisciplinary Congress of Colorectal Cancer, scientists and clinicians gathered to discuss and communicate with one another about the many different aspects of cancer development, hereditary cancer, screening, different treatment types, etc. In this issue, several of the participants give an overview of the highlights and new developments in their discipline.

Jass and colleagues examine recently obtained data regarding the recognition of several different molecular pathways in colorectal cancer. This data not only allows the separation of hereditary from sporadic forms, but also the separation within these groups of several major subgroups. They propose the following groups:

1. Carcinomas in patients with familial adenomatous polyposis (FAP). In these patients the Adenomatous Polyposis Coli (*APC*) gene is mutated leading to chromosomal instability and the activation of mutated tumour suppressor genes (*DCC, TP53*) by allelic loss (loss of heterozygosity (LOH)). This exemplifies the paradigm of the adenoma–carcinoma sequence.
2. Sporadic microsatellite instability (MSI)-stable with acquired *APC*-mutation, LOH and tumour suppressor gene involvement.
3. Carcinomas in patients with hereditary nonpolyposis colorectal cancer (HNPCC). In these patients, a DNA mismatch repair gene is mutated in the germline, leading to high levels of MSI.
4. Sporadic MSI-high carcinomas, without a germline mutation of a DNA mismatch repair gene, no LOH, but with methylation of *hMLH1* and mutations in several genes.
5. Sporadic MSI-low carcinomas, with LOH, involvement of tumour suppressor genes and methylation of *MGMT,* but no widespread DNA methylation.

These types differ in clinical features, morphology and prognosis and therefore it may be relevant to recognise them when more specific treatment options are developed.

Fodde describes the role of the *APC* gene in colorectal cancer in more detail. Not only in FAP, but also in the majority of sporadic colorectal cancers, this gene plays a key role by the activation of the Wnt signal transduction pathway and also by causing chromosomal instability.

Liefers and Tollenaar discuss the enormous advances being made in the understanding of colorectal cancer genetics. The importance of molecular pathways in hereditary and sporadic carcinoma of the large intestine is already recognised, especially with regard to the Wnt-signalling pathways. Presently, this knowledge is being translated into clinically useful information: prognostic factors, detection of micrometastasis and recognition of the factors important for chemotherapy efficacy. They emphasise that the results are still preliminary and controversial. However, there are likely to be exciting developments resulting from the application of the newly developed micro-array technology and the authors illustrate the possibilities with a fictitious case from 2010.

The enormous developments in the field of imaging are described by Pijl and colleagues. The advances of magnetic resonance imaging, virtual colonoscopy and positron emission tomography are shown, but also the remaining place for barium enema studies is assessed. Developments are ongoing, including image-guided minimally invasive treatments and radio-frequency ablation therapy.

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Kapiteijn and van de Velde extensively overview the surgical techniques used for rectal cancer and provide data on recently performed trials for rectal cancer treatment including the Dutch Total Mesorectal Excision (TME) trial. They show that the different approaches that were developed during the last century sailed between the Scylla of a high recurrence rate and the Charibdes of high morbidity. The authors state that clear and reproducible definitions for rectal cancer, local recurrence and curative resection are very important in order to be able to compare the results of different trials. Moreover, the data from the literature suggest that there is high hospital- and surgeon-related variability of outcome, although volume and experience are certainly not the only factors contributing to this variability. Nevertheless, the surgeon and the technique chosen are crucial factors for patient outcome. These considerations led to the Dutch TME study in which surgery, pathology and radiotherapy were quality controlled. The conclusions from this study were that TME-type surgery is superior to other methods for the prevention of local recurrence, that preoperative radiotherapy further improves the results, and that this combination does not lead to unacceptable morbidity and mortality. Wiggers gives recommendations based on the Dutch TME study for all involved disciplines, the surgeon, the radiotherapist and the pathologist, which form the firm basis of future guidelines.

The different aspects of quality control that are necessary for a surgical oncology trial are described by Klein Kranenbarg and van de Velde, and exemplified by the Dutch TME trial. It is clear from the data that proper quality assessment is labour-intensive and expensive, but also crucial.

New developments in surgery are ongoing. Gerritsen van der Hoop describes the current views with regard to laparoscopic treatment of colon cancer: after initial enthusiasm for this technique, several problems were encountered. Predominant concerns were the violation of surgical oncological principles and a high rate of port-site metastasis. However, these problems have been largely overcome and may have been partly due to the learning curve that is associated with any new technique. The present data suggest that future trials can be implemented with cautious optimism. De Graaf and colleagues describe the elegant Transanal Endoscopic Microsurgery (TEM) technique, which has minimal morbidity. They explain that, with the proper training and equipment, good results are obtained in indicated cases.

Nagtegaal and van Krieken outline several different aspects of the pathology of rectal cancer and focus on the role of the pathologist as a quality controller. A large amount of their data was derived from the TME study, in which a standardised pathology approach was mandatory. The trial included a pathology coordinator and also a pathology review was installed. The importance of having primary pathology data and quality control is clearly shown. By using the Quirke method for dissection of the specimens, it was possible to show the importance of circumferential involvement. In addition, the possibility that pathological examination of the resected specimen can be used for surgical quality control is documented.

Another important aspect of the pathology is staging, especially the determination of the N-stage. The paper of Steup and colleagues gives a detailed analysis of the pattern of lymph node metastasis related to tumour characteristics. The results give a model by which the likelihood of metastasis can be predicted preoperatively. Nevertheless, approximately one-third of node-negative patients have recurrent disease. Bilchik and colleagues developed a sensitive technique to detect early lymph node involvement and used their method on sentinel nodes. In the majority of patients, the sentinel node procedure was successful and almost a one-quarter of the node-negative patients had submicroscopic disease, which might have profound clinical implications.

Staging is still the most important factor for prognosis. Walker and Quirke discuss other parameters that affect prognosis and guidelines for accurate staging, after therapy as well. More difficult is the prediction of response to therapy, but several approaches that are being followed might give answers in the near future.

Marijnen and Glimelius discuss the role of radiotherapy in rectal cancer. The results of the Dutch TME study are extensively described, showing that short-term radiotherapy does result in lower numbers of local recurrences, even in patients with wide margins. In patients with extensive tumours, long-term radiotherapy can be successful and lead to radical surgery and more sphincter-saving procedures. The differences between short- and long-term radiotherapy have a theoretical biological basis: short-term therapy may affect small groups of tumour cells by preventing repopulation, whereas long-term radiotherapy affects larger masses because higher doses in fractions can be given.

Presently, it is unknown whether postoperative radiotherapy is as effective as preoperative therapy. Side-effects of radiotherapy are limited and acceptable, as was the experience in the TME study. Chemoradiotherapy has led to improved survival rates, but the same results can be achieved with short-term preoperative radiotherapy, improved surgery with less morbidity.

Even though the local results of surgery are now very good, distant metastasis will still occur in approximately half the patients. Therefore, the treatment of liver metastasis, as well as systemic treatments, is very relevant. Several new developments are discussed. Ruers and Bleichrodt give an overview on the surgical treatment of liver metastasis. The importance of proper patient selection is stressed, which includes high quality

imaging. Although surgical resection remains the main treatment, adjuvant modalities have their place in selected patients: cryotherapy, radiofrequency therapy, adjuvant chemotherapy portal vein embolisation or isolated liver perfusion. Tebutt and colleagues describe the effects of chemotherapy in metastatic colorectal cancer, as well as in the adjuvant setting. At present 5-fluorouracil (5-FU) is the most important drug, best used in a protracted intravenous (i.v.) regimen. Oral doses are much more convenient, but have a variable bioavailability. This problem is circumvented by using 5-FU prodrugs like capecitabine or UFT, which have both been shown to be effective. Further progress is expected from combination regimes including either mitomycin-C or irinotecan. Another effective drug is oxaliplatin. Several trials are being performed to study the optimal combination of drugs, but the results are pending. In these trials molecular markers are also being studied that may help to predict the response to therapy. However, the results are not yet reliable enough to enable their routine use to be advocated. Adjuvant treatment aims to eliminate the relatively low tumour load after surgical treatment. In more advanced stages, 5-FU/folinic acid is accepted as the standard care. Studies on the value of such treatment in intermediate stage disease are being performed. Future developments are expected from gaining a better insight into the molecular biology of colorectal cancer. Preliminary data from antisense therapy for APC, farnesyl transferase inhibitors, monoclonal antibodies against the epidermal growth factor (EGF)-receptor and vascular endothelial growth factor (VEGF), as well as cyclo-oxygenase (COX)-2 inhibition is described.

De Kleijn and Punt give a review on the immunogenity of colorectal cancer and also the mechanisms by which tumour cells escape from the immune response. They show that the mechanisms act on several levels including human leucocyte antigen (HLA) down-regulation and FasL overexpression. Several different approaches have been developed to circumvent the insufficiency of the immune response. Non-specific immune therapy, i.e. Bacillus Calmette Guerin (BCG), has only a marginal effect, and the most newly tested methods are based on several elements of the specific immune response. There is fairly substantial experience available for therapies using an antibody against EpCam, an adhesion molecule expressed on colorectal cancer but also on normal epithelial cells. After initial promising reports, prospective trials gave disappointing results. In addition, antibodies against carcinoembryonic antigen (CEA), a glycosylated molecule that is often overexpressed on colorectal cancer cells, but is also expressed on normal epithelial cells, have been used. Presently, only limited data are available using radiolabelled antibodies. Active specific immunotherapy is more promising. Vaccination with irradiated tumour cells or specific peptides has been developed. Several different studies are in progress where preliminary data are promising.

After successful treatment, the issue of follow-up becomes important. Kievit discusses the goals and results. He shows that follow-up is relevant for quality assessment and patient support, but that there is no proof that it leads to improved survival. He therefore suggests that the follow-up of successfully treated colorectal cancer patients can be done very well by general practitioners or specialised nursing personnel.

Costs of treatment are increasingly influencing decision-making. Van den Hout and colleagues describe the methodology of cost-effectiveness analyses, and cost studies for colorectal cancer treatments are reviewed.

The human genome project has led to the availability of more information on the genes involved in cancer. Future expression profiling studies will give vast amounts of information on specific aspects of individual cases and should lead to tailored therapies or prevention programmes. These developments will have far-reaching public health consequences. We hope that this issue will provide the reader with 'state-of-the-art' knowledge at the brink of this fascinating era.

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