Chairman's introduction

Recent advances in the molecular pathology of human tumours, being particularly pronounced in colorectal cancer, have increased the possibilities to understand the causes of the diseases, reasons for progression and, above all, the behaviour of each tumour, spontaneously and after different therapeutic interventions. The presentation by Walker and Quirke provides an excellent and updated overview of the present knowledge in colorectal cancer. It describes the present unparalleled opportunities to understand this disease and also pinpoints the pitfalls prior to demonstration of clinical value. In spite of many claims of prognostic and clinical value of various markers, 20 to 30 years of extensive research on prognostic factors to help clinicians in the care of colorectal cancer patients has basically failed; the only clinically truly valid prognostic information is still provided by simple clinical parameters and anatomical extent of the disease.

The possibilities for greater success are presently, however, much more favourable, both with respect to the number of potentially valuable markers to explore and to the variety of treatments available. Prognostic and predictive studies can originate from basically two different standpoints, firstly to understand the potential clinical relevance of a new marker, alone and in relation to other markers, and, secondly, to guide the clinician in the selection of therapeutic and follow-up strategies through analyses of new and old markers. The quality requirements of the patient materials are much higher in the second situation, and basically requires large prospective studies. Several co-operative groups running randomised trials have also recognised this, and the studies we now see and likely will see within the next few years will hopefully provide conclusive and clinically relevant information.

It may be superfluous to state that surgery has been and still is the most important therapy for primary colorectal cancer. With the development of more effective systemic treatments the role of surgery will likely increase in relevance. This statement may possibly be unexpected to some. The increased use of surgery for liver metastases not optimally resectable in responding patients after modern combination chemotherapy is one example of this. The term 'not optimally resectable' liver metastases is likely more adequate in these patients than 'irresectable'. The definition of what constitutes resectable liver metastases is not always clear and changes with time. The type of surgery that will be performed when more efficient systemic treatments are available may well change, and be less extensive. Similarly, more conformed radiotherapy, or other loco-regional treatments, may be increasingly utilised. The surgeon will increasingly be an important contributor to the team caring for the colorectal cancer patient, as stressed in Hohenberger's review.

Recent experience has illustrated that therapeutic improvements are not restricted to medical oncology. The increasing awareness of the importance of the lateral margins during rectal cancer surgery and that this surgery is technically demanding requiring great skill and experience, has led to significant improvements for the patients. This progress has not been proven in randomised trials, but is now so evident from large, more or less population-based patient materials that this confirmation is no longer required. This fact is, however, not completely recognised by all, pointing to still unresolved details such as whether the excision should be total or not in all patients with a high rectal tumour. This improved surgery has not only reduced local failure rates from unacceptable to reasonable levels, but also improved survival. The 5-year survival for a rectal cancer is now more favourable than that for a colon cancer, as seen in recent cancer registry data. For decades, the opposite was the case. It would be a great success if the same surgical improvement could take place also for colon cancer. The challenges in rectal cancer surgery are still many, to convince those who do not yet believe in the total mesorectal excision (TME) concept, to assure that all who claim that they do TME actually do it in a proper way, and to maintain the skill at those centres where surgery today is optimised. The role of the pathologist in this quality assurance is fundamental. We have also recently learned, as reviewed in the chapter about radiotherapy, that preoperative radiotherapy has a role even in addition to optimal surgery. The relative efficacy of radiotherapy is actually higher in combination with optimised surgery than with regular surgery.

Radiotherapy has an established role in the primary management to lower local failure rates in

extirpable rectal cancers. Preoperative radiotherapy is more efficient and carries less toxicity than postoperative radiotherapy, although this knowledge is not always recognised. The relative efficacy of preoperative radiotherapy is likely as high in connection with a more adequate surgical procedure, like TME, as in less optimised procedures, although the absolute benefit will be smaller. Provided the dose and technique have been appropriate, preoperative radiotherapy has also slightly improved survival. Postoperatively, a combination of chemotherapy and radiotherapy appears to be more efficient in reducing local failure rates and improving survival than either modality alone, but the literature-based evidence is partly conflicting.

Radiotherapy has also an established role in primarily inextirpable rectal cancers to increase the chances to achieve locally radical surgery. It is possible that radiochemotherapy in this situation is more efficient than radiotherapy alone, but the scientific support for this notion is not particularly strong. Chemoradiation has also increasingly been used to facilitate a sphincter-preserving procedure in low-lying cancers. Again, the literature is inconclusive as to whether it is superior to radiotherapy alone, whether an optimal combination exists, or if it actually facilitates sphincter preservation at all. Long-term functional outcome is poorly known.

Knowledge about the value of chemotherapy in colorectal cancer has increased substantially during the past 10–12 years. About 10–12 years ago, we learned that chemotherapy could prevent recurrences and improve survival after surgery and that biochemically modulated 5-fluorouracil (FU) could relieve tumour-related symptoms, favourably influence the well-being of the patients with advanced disease, and prolong survival. From being a worthless therapy, clinically meaningful gains were seen. The best 5-FU-modulated regimen, considering activity, toxicity, convenience and costs was, however, not defined. During the last 2–3 years, new knowledge has emerged, revealing that further gains are seen in the palliative situation using a combination of leucovorin-modulated 5-FU with either of two new drugs, irinotecan or oxaliplatin. Irinotecan may, in spite of appreciable toxicity, also favourably influence well-being and prolong survival in the second-line situation. Trials have been completed that are expected to show even fewer recurrences after giving these combinations as adjuvant therapy. We have also learnt that oral 5-FU prodrugs may give the same antitumour activity as seen with intravenous (i.v.) bolus 5-FU regimens.

There is no doubt that the chemotherapy effects in colorectal cancer are well documented in the scientific literature. In the review by Philippe Rougier, the present knowledge is correctly described and the many meta-analyses of trial data performed in certain clinical situations are referred to. A systematic overview of all available evidence has recently been performed by The Swedish Council of Technology Assessment [1]. The gains seen are clinically meaningful, and appreciated both by patients and oncologists. The health care costs for the treatments are also reasonable and have a cost-effectiveness below what society generally accepts. The cost-effectiveness data are, however, not particularly well documented [2].

In spite of being clinically meaningful, the gains are not particularly large. In the adjuvant situation, few patients benefit and, apart from colon cancer stage III, the numbers are so few or the knowledge so uncertain, that therapy is not indicated outside clinical trials. In metastatic disease, tumour regression accompanied by symptom relief, or delay of symptom occurrence are frequently seen, but generally of short duration, and survival prolongation is still modest. Claims of substantial survival prolongation with median survival up to 18–20 months using several lines of therapy or sequential administration of different combinations, seen in some recent publications, are likely also to be a result of patient selection. Better diagnostic imaging and more intense follow-up programmes will detect metastasis at an earlier stage and thus apparently yield longer median survivals. A higher tumour cell-kill effect with more complete remissions and longer durations of a partial remission must be achieved. The presently available drugs can probably be used more efficiently, but newer drugs with different mechanisms of action must be developed. There is also a great need for clinically useful predictive assays, evaluated in prospective studies. If sequential administration of chemotherapy has a substantial influence on survival, early and accurate predictors of lack of response must be identified. The use of local tumour-destructive methods should also be properly evaluated as a means of consolidating the chemotherapy-induced remissions in selected patients.

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References

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