Introduction

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Colorectal cancer, with over 1 million new cases every year, is the third most common cancer worldwide and in many countries in the western world is the first or the second cause of cancer death. More than one third of the colorectal cancers arise in the rectum, the fifteen most distal centimetres of the large bowel. Significant progress has been made in the understanding of the molecular mechanisms involved in colorectal cancer development and progression. In this respect, colorectal cancer is one of the most studied tumour types, and this knowledge has already had an impact on the diagnosis, staging, treatment and care of these patients. Many researchers have, during the past one or two decades, repeatedly stressed that this increased body of basic knowledge will very soon more or less revolutionize the care of patients. The clinical progress has, however, been much slower than expected, and the translation of the results from experimental systems to the human situation has been much more difficult than foreseen. The most recent clinical progress seen in the development of tests for screening and diagnostic purposes [1] and in the treatment using so called targeted drugs [2,3], all based upon the understanding of the molecular changes during colorectal carcinogenesis and progression, however, tell us that it is not unreasonable to be more optimistic now than in the past. Still, the vast majority of the knowledge behind our present routines for diagnosis, staging, treatment and follow-up of rectal cancer patients, as described here in five articles, are based upon knowledge achieved in successive clinical trials after clinical observations through many decades.

Multidisciplinary approach

The five different articles provide an update on clinically highly relevant issues in the care of patients with rectal cancer. The multidisciplinary approach to a patient with newly diagnosed rectal cancer is obvious, and the team discussions, prior to any therapeutic intervention, is a prerequisite for this. However, this is far from always the case. The purist can say that we do not have scientific evidence for sufficient patient gains from these team discussions, taking resources from other duties, but it is hard to understand how the quality of care otherwise could be improved for the patients seen by many different members in the teams. The team discussions should at the same time be both efficient so that all (difficult) cases are adequately presented and discussed and have an educational approach where also junior members understand the reasons for a particular decision.

Adequate staging

It has repeatedly been stressed during the past few years by many experts, and also in two of the articles, that adequate staging is a prerequisite for treatment decision and that the quality control by the pathologist of both staging and surgery is a must. Since preoperative additional radiotherapy is superior to postoperative radiotherapy, known since decades, and confirmed in systematic overviews/meta-analyses [4,5] and preoperative radiochemotherapy superior in terms of local control to postoperative radiochemotherapy [6], the preoperative staging must reach very high levels of standard. This is important both to find those who only need surgery, not to expose too many to the extra costs and risks of acute and late adverse effects from the radio(chemo)therapy, and to detect those who will have an unacceptably high risk of failing locally unless preoperative therapy is given. It is also necessary to know more about the very late consequences from all interventions, so that the balance between gains and risks can be adequately presented for the patients. So far, our knowledge about late toxicity is mainly derived from trials where 5×5 Gy has been given [7–10]. Since toxicity has been seen, it is easy to get the impression that 5×5 Gy is dangerous, alternatively more dangerous than other schedules. Since we have virtually no data from long-term follow-up after conventional radiotherapy, with or without chemotherapy it is actually not possible to draw any conclusions.

Balancing gains and risks

In the light of the risks so far seen with the 5 × 5 Gy schedule also after 10–15 years of follow-up [10] (Birgisson et al., pers. Commun.; Pollack et al., pers. Commun.) an absolute decrease in the number of local failures of about 5% (for example from 8% to 3%) may be worthwhile, although most patients (92–95%) are overtreated. Whether the same absolute gain is sufficient to recommend radiochemotherapy rather than radiotherapy is not known. The trials have shown that the acute toxicity is increased, although manageable [11,12]; however, we have no knowledge about the magnitudes of late effects. If radiochemotherapy is given to most patients, the German AIO study gave a clear answer, namely that preoperative is preferred to postoperative therapy [6]. On the other hand, our possibilities to evaluate the risks of local failure are better postoperatively, having the pathology report, than preoperatively, meaning that fewer patients will be irradiated, and thus at risk for late toxicity. A strategy of using postoperative radiochemotherapy for high-risk groups will thus likely continue to attract some clinicians.

Any survival gain from improving local control?

Much evidence indicates that the improved local control seen after better surgery also improves survival, as discussed in one of the articles, although this has not been confirmed in a randomised controlled trial. An overall survival gain was seen in one of the randomised trials using preoperative radiotherapy alone [13], was confirmed in a meta-analysis of all preoperative trials using a moderate radiation dose [4], but has not been seen in subsequent trials. The reason for this is likely rather easy to explain. In the Swedish rectal cancer trial, the absolute gain in local failures was about 17% (from 29% to 12%) [14]. This gain resulted in a survival gain of about 9% (from 30% to 39% at 13 years), that is about half of the decrease in local failure rates. In the subsequent trials, the incremental gain in local failures in the order of 5–8% (from 10–17% to 5–9%) [6,11,12,15,16] is so limited that any survival gain, if true (2–4%), cannot be detected in a trial unless many thousands of patients are included. Thus, the TME trial [15] was not powered sufficiently to exclude such a survival gain.

Improved sphincter preservation

The possibilities to increase sphincter preservation rates after preoperative therapy with a long interval between the radiation therapy and surgery, allowing downsizing is controversial, but attractive to many. This issue is particularly dealt with in one article, but discussed also in several of the others. Since differences in opinion exist, I believe it is appropriate to allow this overlap between articles. A better answer to the controversial question will not be available until we have complete prospectively collected data using validated instruments after long follow-up. Even then, differences in opinion may exist, since cultural differences appear substantial.

Looking at the future

The challenges in the treatment of primary rectal cancer are many. Several studies have reported promising short-term effects using combinations of chemotherapy with radiation therapy rather than single agent 5FU. It is a hope that randomised clinical trials can be initiated and completed, since the combinations are more toxic and carry a higher price. The use of targeted drugs, so successfully integrated in the treatment of metastatic colorectal cancer [2,17,18], with radiation also carries great promise. The likelihood that these drugs will be adequately tested in randomised trials is greater since the compounds need formal approval prior to their use and reimbursement. Let us hope that they can increase efficacy so that also the locally most advanced rectal cancers can be appropriately controlled without too much morbidity. Hopefully also, more widespread use of screening will decrease the appearance of these advanced cancers at presentation [19]. input ch81-r

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