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Has Progress Been Made in Gastrointestinal Cancer Treatment?

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This issue of *Acta Oncologica* includes the second article based on an *Acta Oncologica* lecture (1) presented at the annual meeting of the Finnish Society of Oncology in August 2001. The motif for the *Acta Oncologica* lectures was given in a previous editorial (2).

The survival prospects for many gastrointestinal tumour sites are poor and the population statistics in the past few decades do not indicate clear improvements (3–5). Many new treatments have been introduced in recent years, and there is hope that the treatments now being given will show up as improved results within a few years. In her article, Dr Maria Albertsson describes several attempts to improve outcome in oesophageal cancer and also the success seen in some trials (1). It is likely that further and more definite improvements will only be seen after multimodal therapy. The presently ongoing randomized Nordic trial, described in the article, offers hope for new knowledge of the potential of radiochemotherapy as opposed to surgery. The trial is a good example of what might be achieved if the different specialists at many hospitals could reach a consensus on important questions. In gastrointestinal oncology, besides rectal cancer, we have not previously seen many good examples of improvements in the Nordic countries.

Two large international cooperative trials on adjuvant therapy in other gastrointestinal cancers have been reported recently. The results of these trials must be discussed thoroughly, in the Nordic countries and world-wide, and the proper decisions about changes in routines or in the initiation of new trials must be made.

GASTRIC CANCER

In adenocarcinoma of the stomach or gastro-oesophageal junction, a US Intergroup Study recently reported improved survival after postoperative radiochemotherapy (6). In total, 556 patients with resected gastric cancer were randomly assigned to surgery alone or surgery plus postoperative radiochemotherapy. The adjuvant treatment consisted of one course of 5-fluorouracil (5-FU) plus leucovorin for 5 days (Mayo Clinic schedule) followed by 45 Gy radiation for 5 weeks with 5-FU and leucovorin followed by two more cycles of 5-FU/leucovorin. The trial included extensive quality assurance (QA) and quality control (QC) of the radiotherapy procedures. Forty-four percent of the patients had a D0 lymphadenectomy, i.e. a resection in which not all of the N1 nodes were removed, 36% had a D1 dissection and only 10% a D2 dissection. The median overall survival in the surgery-alone group was 27 months as compared with 36 months in the chemoradiotherapy group ($p = 0.005$). The 3-year survival rates were 41% and 50%, respectively. The survival curves indicate that the benefit is maintained beyond 5 years. Toxicity to treatment was predominantly haematologic and gastrointestinal and grade III or greater toxicity was seen in 41% of the patients.

PANCREATIC CANCER

The European Study Group for Pancreatic Cancer (ESPAC-1) assessed the role of postoperative chemoradiotherapy or chemotherapy in a randomized trial of 541 patients with ductal pancreatic adenocarcinoma (7). A two-by-two factorial design was used. After resection, patients were randomly assigned to adjuvant chemoradiotherapy using a 40 Gy split course with 5-FU, or chemotherapy with 5-FU/leucovorin for 6 months according to the Mayo schedule. Patients could be randomized to observation, chemoradiotherapy alone, chemotherapy alone or both. After a median follow-up of 10 months for surviving patients, the results did not show any benefit from adjuvant chemoradiotherapy (median survival about 16 months in both groups), whereas there was evidence of a survival benefit for adjuvant chemotherapy (median survival 20 months with chemotherapy vs. 14 months without, $p = 0.005$). Toxicity data were available only in a subset of patients, and 27% reported serious toxic effects, predominantly when chemotherapy was used alone. The follow-up is not long enough to assess whether the proportions of patients alive after 3 or 5 years is likely to differ.

WHY IS RADIOCHEMOTHERAPY EFFECTIVE IN GASTRIC CANCER BUT NOT IN PANCREATIC CANCER?

The two trials arrived at contrasting results concerning the influence of postoperative radiochemotherapy on survival. Most oncologists would immediately agree that the results could be anticipated in advance. First, gastric cancer

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shows higher sensitivity, at least in the short term, to both radiotherapy and chemotherapy than pancreatic cancer (8, 9). In pancreatic cancer a number of molecular changes occur, all suspected of conferring chemoradioresistance in other tumours (10–13), and distant metastases occur more frequently than in gastric cancer. The radiotherapy dose used in the pancreatic trial (40 Gy split dose) was lower than the dose in the gastric cancer trial (45 Gy). Finally, it could also be suspected that the cancer surgery was less optimal in the gastric cancer trial, although the quality of the surgery was not explicitly detailed in the pancreatic cancer trial. It is difficult to argue against these explanations of the contrasting results.

There is, however, an alternative explanation. In the gastric cancer trial, the clinical target volume was clearly defined and included the tumour bed, the regional lymph nodes and a margin beyond the resection margins. Extensive QA and QC procedures of the radiotherapy plans were made both before and after the treatment. In the pragmatic pancreatic cancer trial, details of the radiotherapy were not given in the publication and only local QA procedures were available. It is possible that many patients only had radiotherapy to the tumour bed, with margins. Admittedly, it is easy to blame failures on improper 'whatever you can think of'excuses, and radiation oncologists may in this respect be no exception (some would actually argue that they (we) are the worst offenders). I would argue that adequate coverage not only of the resection bed but of *all* regional lymph nodes is essential for an effect of radiotherapy, whether given pre- or postoperatively, and that this is more important than the radiotherapy dose. It is known that the dose-response relationship to radiotherapy for subclinical disease is linear and therefore some effects could be seen also when using rather low doses (14, 15). Regional node involvement is common in pancreatic cancer. Using sensitive markers (immunohistochemistry, PCR-based techniques), tumour cells can be found in 100% of the cases also in nodes removed only during an extended lymph node dissection (16). If lymph node metastases are seen, distant metastases are extremely common, albeit not present in 100% of the cases. Thus, there may be an opportunity for effective use of a regional therapy such as radiotherapy. Regional therapy, whether extended surgery or radiotherapy, must then cover *all* regional nodes at risk of containing tumour cells and not just those that are easily removed/irradiated.

COMPENSATION FOR POOR SURGERY?

It has been argued that the effect of radiochemotherapy in gastric cancer merely compensates for poor surgery. These arguments have repeatedly been raised in rectal cancer radiotherapy also. The recently reported TME trial, where surgery was of a higher quality than that in all previous rectal cancer radiotherapy trials (17), clearly showed a beneficial effect of radiotherapy also in combination with optimal surgery (18). In fact, the relative efficacy of radiotherapy was higher with good surgery than with 'standard' surgery, as might be anticipated (19, 20). The hypothesis could then be raised that the positive radiochemotherapy effects, seen in gastric cancer in the US trial (6), would have been even greater if the patients had had adequate surgery (all had at least a D1 resection). The radiotherapy coverage of the regional nodes could then be more complete than is the case if surgery removes only the bulk of the tumour cells in order to lower the risk of failure. The success story in rectal cancer may be a result of the large clinical target volumes that include not only the nodes close to the bowel but also all lateral nodes (19).

NEED FOR FURTHER TRIALS

The extrapolations of trial data, including the comparisons made between different gastrointestinal tumour sites described above, are all speculative, and speculations can never form the basis for treatment recommendations. Adjuvant therapy is thus not yet routine therapy in either gastric or pancreatic cancer. If based upon sound clinical and tumour biological knowledge, speculations can, however, form the basis for hypotheses to be tested in appropriate trials. Thus a Nordic, or a European, initiative on a large gastric cancer trial with good QA of all relevant aspects (staging, surgery, additional therapy and pathology) is urgently needed. In the US, a decision has already been made that postoperative radiochemotherapy is standard therapy (21). In the consensus report, detailed descriptions of the radiotherapy portals are given for various localizations of the primary tumour in the stomach.

In pancreatic cancer, the positive and statistically significant trend in improved survival seen with chemotherapy should be confirmed. The results are supported by a few previous trials, although the results then were inconclusive (9). Participation in the subsequent ESPAC-3 trial is thus strongly recommended. In the trial, patients are randomized between surgery alone, surgery with postoperative 5-FU/leucovorin or surgery plus gemcitabine. Meanwhile, better knowledge of the most adequate target volume in pancreatic cancer must be defined in a cooperation between surgeons, radiation oncologists and pathologists, and the tolerability of these treatments, whether given before or after the surgery, must be investigated. Only then can we gain substantial knowledge that is of benefit for the patients.

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