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Perspectives in adjuvant gastric cancer therapy

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It is well recognized that surgery is the basic treatment for gastric cancer, with an overall 5-year survival of approximately 30% for curatively resected cases. Resectable gastric cancer would represent the vast majority of stages IB and II and include some cases with stage III. The relapse rate rises sharply with more advanced stages and might be influenced by the extent of surgery.

Up to now postoperative adjuvant chemotherapy has failed to improve the survival in almost all Western series. Although a meta-analysis of adjuvant trials has provided some evidence of a small benefit of adjuvant therapy (1,2), the potential advantage has not been generally accepted and adjuvant treatment is not recommended outside of a clinical trial.

It should be realized, however, that in most adjuvant studies first-generation chemotherapy regimens were administered that are only marginally active in phase III trials in advanced disease. Furthermore in many of reported series surgery was not adequately defined and might have been insufficient.

Some Japanese series suggested benefit from systemic adjuvant therapy, but most of these data were not randomized. Factors, which might contribute to positive Japanese results, include more extensive surgery, resulting in less residual tumor cells.

Three European studies with second-generation regimens have more recently been reported. An EORTC postoperative adjuvant study with FAMTX (5-FU, methotrexate and adriamycin) versus control and another with FEMTX (5-FU, methotrexate and epirubicin) versus control conducted by the ICCG have included a total of 398 patients. A combined analysis has been carried out without disclosing a significant survival difference between surgery alone and combined treatment (3). A French trial with FOP (capsulation, 100 mg/sum plus 5 days infusional 5-FU, 1000 mg/sqm, q 4 weeks) included 278 patients with a similar outcome (4), while adjuvant chemotherapy with EAP (etoposide, adriamycin and cisplatin) and 5-FU/LV in 274 patients reported from Italy also yielded similar survival (5). A trial with PELF (cisplatin, epirubicin, 5-FU and leucovorin) has been completed in Italy and results are being awaited.

It is important to note that the five-year survival in the EORTC, the French and the Italian study was around 50% in the standard arm with surgery alone. In all these studies a D2 dissection was mandatory.

At ASCO 2000 the outcome of the Intergroup/SWOG study (INT 116) was reported (6). This study investigated radiotherapy plus 5-FU/leucovorin in resected gastric cancer. Although chemo + radiotherapy resulted in a significant survival benefit, 54% of the patients in this trial had resection < D1 and up to 90 % ≤ D1, leading to the criticism that the poor standard of surgery in this study contributed to the results obtained (7). Survival data with the combined modality were not superior to what has been achieved with more optimal surgery (≥ D1 resection) alone in recent European series (1-3). Similarly, the quality control of radiotherapy was poor because 32% of the patients required a change of radiation planning after central review. Had this not been performed, serious life threatening toxicity might have occurred in up to 10% of patients (8).

Different authors have commented on INT 116 more or less similarly (9-12). In Europe changes in clinical practice based on the strength of this study alone are unlikely.

Therefore it appears that there is a good rationale for performing a similar trial in Europe applying more optimal surgery (at least D1 resection) with more effective chemotherapy and carefully monitored radiotherapy. In fact a Pan-European Gastric Adjuvant Study with Uniform Surgery (PEGASUS) is now in discussion with several national groups. The hypothesis to be tested is the question whether there is equal benefit as reported from US when chemoradiotherapy is added to more optimal surgery. Increase in three-year survival of 10% from 60% to 70% would be considered as a relevant positive result, which would change clinical practice.

It is proposed to have a surgery alone control arm, because surgery alone is considered the standard of care by most European groups. A D1 resection would be the minimal requirement. The experimental arm will apply postoperative chemotherapy and chemoradiotherapy. The chemotherapy will consist of weekly or biweekly infusional 5-FU/LV plus CPT-11 or Taxotere. The choice will also depend on the outcome of two randomized phase III trials in advanced disease that will be reported at ASCO this year (13,14).

One full cycle of chemotherapy will be administered before and one after chemo-irradiation. Concomitantly with radiotherapy protracted daily infusional 5-FU will be applied. Several studies have shown that this combination can be safely applied.

Interest has also shifted to neoadjuvant chemotherapy. Some phase II trials have demonstrated the feasibility of this approach. In The Netherlands a randomized neoadjuvant study (POCOM trial) with 4 courses of FAMTX followed by surgery versus surgery alone was prematurely closed because of insufficient accrual and because an interim analysis with 56 patients did not show significant downstaging (15). With the small number of patients this study was clearly underpowered and imbalances in prognostic factors might well have occurred.

In the UK a similar trial with preoperative and postoperative ECF was launched in 1994 ("MAGIC" trial) and results will be presented at ASCO 2003 (16). Surgery in that study, however, was not well defined and will probably be considered as sub-optimal. In addition, it will remain difficult to make a strong argument for neoadjuvant chemotherapy only, because postoperative chemotherapy was also administered.

For the moment it appears therefore premature to include neoadjuvant chemotherapy in the PEGASUS proposal.

In conclusion, there is now a renewed interest in the adjuvant treatment of gastric cancer. CPT-11 and docetaxel are most probably active new drugs and their incorporation in a chemoradiotherapy regimen in conjunction with optimal surgery might move us ahead in the treatment of gastric cancer.

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