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TUMOUR REVIEW

The impact of radiotherapy on survival in resectable gastric carcinoma: A meta-analysis of literature data ☆

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KEYWORDS
Gastric carcinoma;
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Survival;
Meta-analysis.

Summary *Background:* The benefit of external radiotherapy for gastric carcinoma has been extensively studied, but data on survival are still equivocal.
Objective: To assess the effectiveness of surgery combined with preoperative radiotherapy or postoperative chemoradiotherapy in the reduction of all-cause mortality in patients with resectable gastric carcinoma.
Methods: Computerised bibliographic searches of MEDLINE and CANCERLIT (1970—2006) were supplemented with hand searches of reference lists.
Study selection: Studies were included if they were randomised controlled trials (RCTs) comparing mortality of surgery combined with preoperative radiotherapy or postoperative chemoradiotherapy to surgery alone, and if they included patients with histologically-proven gastric adenocarcinoma without metastases. Nine eligible RCTs, 4 of preoperative radiotherapy (832 patients) and 5 of postoperative chemoradiotherapy (869 patients), were identified and included in the meta-analysis.

Abbreviations: RT, radiotherapy; CRT, chemoradiotherapy; RCTs, randomised controlled trials; CI, confidence interval.

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Data extraction: Data on study populations, interventions, and outcomes were extracted from each RCT according to the intention to treat method by three independent observers and combined using the DerSimonian and Laird method.
Results: Surgery combined with preoperative radiotherapy compared to surgery alone significantly reduced the 3-year (OR 0.57; 95% CI 0.43—0.76: $p = 0.0001$) and 5-year (OR 0.62; 95% CI 0.46—0.84; $p = 0.002$) mortality rate. A significant reduction of the 5-year (OR 0.45; 95% CI 0.32—0.64; $p < 0.00001$) mortality rate was observed when surgery followed by chemoradiotherapy was compared to surgery alone.
Conclusions: In patients with resectable gastric carcinoma, adjuvant radiotherapy significantly reduces 3-year and 5-year all-cause mortality, but the magnitude of the benefit is relatively small. Available evidence is inadequate to determine whether postoperative chemoradiotherapy is superior to preoperative radiotherapy.

Introduction

Worldwide, gastric carcinoma still ranks high in mortality rate among tumor sites, despite a general decrease in its incidence.[1] The European weighted survival of gastric carcinoma, calculated from the pool of all carcinoma registries, was 40% at 1 year and 21% at 5 years.[2] The 5-year survival rate of patients with advanced loco-regional gastric carcinoma who have undergone curative resection remains low because of the high risk of local recurrence or distant metastases even when resection was considered curative.[3,4] Thus advanced gastric carcinoma is a treatable, but rarely curable, disease. The improvement in survival therefore remains a major issue in the long-term management of resectable gastric carcinoma.

Improved and standardised surgical techniques, as well as advances in supportive care, have contributed to an increase in the rate of curative resection. The current surgical issue concerns the extent of node resection in clinical practice (limited versus extended), though a Cochrane meta-analysis[5] failed to show a statistically significant benefit for extended node dissection, and indeed showed an increased postoperative mortality. Nevertheless, a plateau in the effectiveness of surgical resection may well have been reached, and further improvement in survival from a single modality approach seems unlikely.[6] Meta-analyses of adjuvant and neoadjuvant chemotherapy,[7—9] as well as randomised controlled trials (RCTs) of radiotherapy (RT) as a single adjuvant in the postsurgical setting[10—13] have shown conflicting results.

Since the first RCT of postoperative chemoradiotherapy (CRT) appeared in 1979,[14] several RCTs have been published.[15—19] The results of these trials are inconclusive or conflicting because of the relatively small samples. Additionally, it is difficult to draw general conclusions from them because of differences in patient characteristics and treatment regimens. A recently published large RCT, the Intergroup Study INT-0116,[19] concluded that postoperative CRT significantly improves survival compared to surgery alone.

More recently, the preoperative RT approach has become the focus of interest in an effort to prolong survival and reduce recurrence rates in patients with gastric carcinoma. However, the results of published RCTs[20—23] remain inconsistent, and the overall assessment of the treatment effect difficult to assess. The last published RCT, by Skoropad et al.,[23] failed to show a statistically significant benefit on survival. Therefore, the role of radiation therapy is far from definite. The aim of this systematic review and meta-analysis is to determine if there is a benefit of adjuvant radiotherapy, with or without chemotherapy, compared with surgery alone.

Methods

Selection of randomised trials

This meta-analysis was performed according to the QUOROM statement.[24] Retrieval of RCTs was based on the Cochrane Controlled Trials Register, The Cochrane Library, MEDLINE, CANCERLIT and ENBASE, limiting the search to randomised clinical trials and human studies and using the following medical subject headings: *gastric carcinoma*, *radiotherapy*, *chemotherapy*, *chemoradiotherapy*, *randomised or randomised trial*[25] *and clinical trial*. The search included literature published up to December 2006. The computer search was supplemented with manual searches of reference lists for all available review articles, primary studies, meetings abstracts and bibliographies of books, in order to identify other studies not found in the computer search. When the results of a single study were reported in more than one publication, only the most recent and complete data were included in the meta-analysis.

Studies were included in the meta-analysis if they were RCTs comparing preoperative RT plus surgery or CRT after surgery to surgery alone; if they included patients with resectable or resected histologically-proven gastric carcinoma without metastatic disease; and if all-cause mortality was assessed as an outcome measure of the effect of the treatment. Quasi-randomised trials and observational studies were excluded. Decisions on which RCTs to include were taken unblindly by two reviewers (F.F. and C.C.). Disagreements were resolved by discussion. Excluded RCTs were identified with the reason for exclusion.

Among the reviewed studies, 9 RCTs met the inclusion criteria.[14—16,18—23] Studies were excluded if they did not have surgery alone as a control group,[17] if they were non-randomised[10—12]; if they used only intraoperative radiation therapy (IORT)[26]; or if they were published as a preliminary report[27,28] and subsequently published as a final paper. As all the RCTs reported as abstracts were subsequently pub-