Therapy of localized gastric cancer: preoperative and postoperative approaches

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Introduction

Although gastric cancer remains one of the most commonly diagnosed cancers worldwide, its incidence is declining in many countries. This decline is likely to be due partially to the increased use of refrigeration which has led to increased consumption of fresh foods, and decreased use of salt and pickling as methods of food preservation. The recent recognition of Helicobacter pylori as a cause of peptic ulcer disease and a co-carcinogen have led to treatments that may further decrease its incidence. In the USA, it is estimated that 21600 cases of gastric cancer will be diagnosed in 2002, and it will cause 12400 deaths [1].

Despite this overall decrease, proximal gastric and gastroesophageal junction cancer has been increasing in many countries [2–4]. Recent analyses of patients who sought treatment at M.D. Anderson Cancer Center between 1995 and 1998 showed that 41% of upper gastrointestinal carcinomas involve the esophagogastric junction. Obesity has been associated with proximal gastric cancer in several studies [2–4]. Tobacco use may also play a role. While gastroesophageal reflux disease and Barrett’s metaplasia are associated with esophageal adenocarcinoma, their association with gastric cancer is less clear.

Prognostic factors for patients who undergo resection include the type of resection (R), depth of invasion (T), the presence and the number of nodal metastases (N), and the ratio of involved and removed lymph nodes [5, 6]. Outside of Japan, where a screening program is active, gastric cancer is often diagnosed in advanced and unresectable stages. At the time of resection, 75–85% of gastric cancer patients are expected to have nodal involvement and are at high risk for postoperative relapse.

The location of cancer in the stomach also has important prognostic implications. The prognosis is worst for diffuse gastric involvement (linitis plastica). Several large studies have shown that proximal gastric cancer has a worse prognosis compared with mid or distal gastric cancer. Our own data show that the adverse effect of gastric cancer localization is limited in patients with local-regional disease [7].

In addition to these clinical pathological factors, molecular markers have also been found to be of prognostic value. Expression of PDGF-α, Her-2/neu, TGF-β and EGFR has been associated with inferior survival [8–12]. In addition, high TS and ERCC1 expression has been linked to poor prognosis among patients receiving fluoropyrimidine- and platinum-based chemotherapy [13–15].

Despite advances in cancer therapy, the survival duration of gastric cancer patients who have undergone surgical resection remains dismal in the West. In a recent report from the American College of Surgeons and the American Cancer Society, the 5-year survival rates for patients with resected stage II, IIIa, IIIb and IV gastric cancer were 34%, 20%, 8% and 7% [16]. To improve the outcome of these patients, numerous clinical trials of adjuvant chemotherapy have been carried out in the past decades. Recently, trials of newer approaches, such as combined modality chemoradiotherapy and preoperative therapy, have also been conducted. Here, we summarize key randomized adjuvant therapy for gastric carcinoma and review preoperative strategies.

Postoperative therapy

Adjuvant chemotherapy

Trials of postoperative adjuvant chemotherapy have been conducted by many researchers around the world using single agents, combined agents, agents given intraperitoneally and agents given with immunotherapy. Results have often been disappointing, and occasionally conflicting. Due to heterogeneity in the patient population, and the treatment strategies, meta-analyses are fraught with difficulties. Trials reporting no benefit are summarized in Table 1. Various trials that reported survival benefit are discussed in Table 2.

Currently, postoperative chemotherapy is not considered standard [17]. More active agents and newer treatment strategies are needed.

Adjuvant intraperitoneal therapy

A significant proportion of postoperative relapses occur in the peritoneal cavity. This has made intraperitoneal therapy an attractive avenue of investigation. A number of parameters, such as age, gender and histology, are known to affect the rate of peritoneal metastases. However, clinical trials have not
### Table 1. Adjuvant therapy trials in gastric cancer that report no survival benefits

<table>
<thead>
<tr>
<th>Treatment arms</th>
<th>Reference</th>
<th>Treatment arms</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td>5FU plus mitomycin → UFT versus surgery alone</td>
<td>[40]</td>
</tr>
<tr>
<td>Thiotepa versus surgery alone</td>
<td>[37, 39]</td>
<td>Intraperitoneal therapy</td>
<td></td>
</tr>
<tr>
<td>Mitomycin versus surgery alone</td>
<td>[41]</td>
<td>Cisplatin versus surgery alone</td>
<td>[18, 19]</td>
</tr>
<tr>
<td>Mitomycin (IA, IP) plus cyclophosphamide versus mitomycin (IA + IP) versus surgery alone</td>
<td>[41]</td>
<td>Carbon-adsorbed mitomycin versus surgery alone</td>
<td>[20, 21]</td>
</tr>
<tr>
<td>Mitomycin versus mitomycin plus 5-FU plus cytarabine versus surgery alone</td>
<td>[41]</td>
<td>Mitomycin C plus 5-FU versus surgery alone</td>
<td>[22, 44]</td>
</tr>
<tr>
<td>MeCCNU plus 5-FU versus surgery alone</td>
<td>[42, 43]</td>
<td>Immunochemistry</td>
<td></td>
</tr>
<tr>
<td>FAM versus surgery alone</td>
<td>[45, 46, 47]</td>
<td>5-FU plus MeCCNU versus 5-FU plus MeCCNU plus levamisole versus surgery alone</td>
<td>[23]</td>
</tr>
<tr>
<td>5-FU plus doxorubicin versus surgery alone</td>
<td>[49]</td>
<td>Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>5-FU plus mitomycin versus 5-FU plus mitomycin plus CMFV course 1 versus surgery alone</td>
<td>[50]</td>
<td>5-FU plus 20 Gy versus surgery alone</td>
<td>[26]</td>
</tr>
<tr>
<td>UFT plus mitomycin versus surgery alone</td>
<td>[38]</td>
<td></td>
<td></td>
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</tbody>
</table>

CMFV, cyclophosphamide, methotrexate, 5-fluorouracil and vincristine; FAM, 5-fluorouracil, doxorubicin and mitomycin C; 5-FU, 5-fluorouracil; IA, intraarterial; IP, intraperitoneal; MeCCNU, methyl-CCNU; MMC, mitomycin C; UFT, uracil plus tegafur.

### Table 2. Adjuvant chemotherapy trials that report survival benefits

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Survival (%)</th>
<th>P value</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitomycin versus surgery alone</td>
<td>68 at 5 years</td>
<td>0.05</td>
<td>Results not duplicated in a trial reported by the same group [41]</td>
<td>[41]</td>
</tr>
<tr>
<td></td>
<td>53 at 5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitomycin versus surgery alone</td>
<td>41 at 5 years</td>
<td>&lt;0.025</td>
<td>Small number of patients. Numerous other mitomycin-based chemotherapy trials are negative</td>
<td>[51]</td>
</tr>
<tr>
<td></td>
<td>26 at 5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeCCNU plus 5-FU versus surgery alone</td>
<td>NS</td>
<td>&lt;0.03</td>
<td>Small number of patients. Results not duplicated in trials conducted by VASOG [42] and ECOG [43].</td>
<td>[52]</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epirubicin plus 5-FU plus folinic acid versus surgery alone</td>
<td>25 at 3 years</td>
<td>&lt;0.01</td>
<td>Small number patients. Need confirmation.</td>
<td>[53]</td>
</tr>
<tr>
<td></td>
<td>13 at 3 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitomycin alone versus</td>
<td>44 at 5 years</td>
<td>0.04</td>
<td>Small number patients; 11-year accrual; improper control group. Two trials using uracil plus tegafur and mitomycin trials are negative [38, 40].</td>
<td>[54]</td>
</tr>
<tr>
<td>Mitomycin plus tegafur</td>
<td>67 at 5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitomycin plus tegafur versus surgery alone</td>
<td>56 at 5 years</td>
<td>0.04</td>
<td>More node positive patients in control group. Needs confirmation.</td>
<td>[55]</td>
</tr>
<tr>
<td></td>
<td>36 at 5 years</td>
<td></td>
<td></td>
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</table>

Log-rank testing revealed $P = 0.06$; covariate analysis showed $P < 0.03$.
ECOG, Eastern Cooperative Oncology Group; 5-FU, 5-fluorouracil; MeCCNU, methyl-CCNU; NS, not stated; VASOG, Veterans Administration Surgical Oncology Study Group.
stratified patients by these parameters. Further, many trials using this approach were underpowered.

Initial trials using cisplatin did not show survival benefits [18, 19]. Intraoperative intraperitoneal treatment with carbogen-adsorbed mitomycin was found to be promising by Japanese investigators [20]. However, a confirmatory trial done outside of Japan showed no survival benefit and increased postoperative morbidity and mortality in the treated group [21].

Finally, Korean investigators randomly assigned 248 patients to receive surgery alone or surgery and intraperitoneal mitomycin and 5-fluorouracil (5-FU) [22]. No significant difference in overall survival between the two groups was observed. Larger trials, newer agents and better stratification for risk of peritoneal relapse are needed to evaluate the role of this approach in gastric cancer.

Chemoimmunotherapy

The incorporation of immunotherapy in the postoperative setting has also been explored. Both levamisole and OK-432 (Picibanil) have been studied postoperatively.

While postoperative chemotherapy with or without levamisole did not result in survival benefits [23], results with OK-432 were more mixed. Kim et al. [24] reported the results of two random assignment trials using different chemotherapy regimens with this non-specific immune stimulant. Superior 5-year survival rates were reported in treated groups. Only one of the trials compared chemotherapy to chemotherapy plus OK-432 and surgery alone. However, a similar trial reported by Jakesz et al. [25] did not observe any benefit in overall survival. A larger trial is needed to define the contribution OK-432 can make in the postoperative setting.

Chemoradiotherapy

On the basis of the activity of chemoradiotherapy in patients with unresectable or residual local disease, investigators have studied postoperative adjuvant chemoradiotherapy. Both single-arm and randomized studies have been conducted, and results have shown that concurrent chemotherapy and irradiation is feasible [26–33]. However, early chemoradiotherapy trials suffered from inadequate numbers of patients, heterogeneous treatment groups, poor randomization schemes, high dropout rates and lack of proper control groups.

The Gastrointestinal Cancer Intergroup 0116 trial randomly assigned 603 patients with stage Ib–IV (M0) gastric cancer who had undergone curative resection to surgery alone or surgery followed by 5-FU, folinic acid and external-beam irradiation (Figure 1) [34]. With a median follow-up of 5-years, 3-year overall survival rate (50% versus 41%; \( P = 0.005 \)) and the 3-year disease-free survival rate (48% versus 31%; \( P = 0.001 \)) were both better in the treated group. This trial also shows that extensive lymphadenectomy is not commonly performed in the USA. Only 10% of patients entering the trial had D2 dissection; 36% had D1 dissection. Most patients (54%) had less than a D1 dissection. Given the large number of patients and the inclusion of a surgery alone control group, postoperative chemotherapy plus chemoradiotherapy should now be considered the standard of care for patients who have undergone curative resection.

Preoperative therapy

Preoperative chemotherapy

Potential advantages of preoperative therapy include improved tolerance, early initiation of systemic therapy and downstaging of the primary tumor that may improve resectability. Pathological evaluation of response to therapy also adds prognostic information [35]. The evaluation of this promising approach in clinical trials requires accurate pretreatment staging. Endoscopic sonography and laparoscopy of all enrolled patients will allow for a more uniform comparison.

Results of preoperative chemotherapy are summarized in Table 3. These trials indicate that preoperative chemotherapy is feasible and that delayed definitive local therapy (surgical resection) can be carried out without adverse impact on rate of R0 resections. Indeed, these trials show objective tumor-downstaging occurs with this treatment strategy. Patient selection and treatment plans are heterogeneous in these trials making their results difficult to compare. Larger randomized trials with prospectively defined endpoints will be needed.
Preoperative chemoradiotherapy

The strategy of preoperative chemoradiotherapy is also under investigation. In a pilot study, 24 patients were treated with 45 Gy of external beam radiation at 1.8 Gy per day 5 days per week concurrent with continuous infusion 5-FU 300 mg/m²/day on days of radiation [36]. Surgery was carried out 4–6 weeks after completion of chemoradiotherapy in 19 (83%) patients. Intraoperative radiotherapy (10 Gy) was given at resection. Complete pathological response was observed in two (11%) patients and a major treatment effect was observed in 63 patients. At the M.D. Anderson Cancer Center, the approach of induction chemotherapy incorporating newer agents followed by 5-FU-based chemoradiotherapy is under investigation in the preoperative setting.

Conclusions

Although numerous adjuvant therapy trials in gastric cancer have been conducted, inadequate numbers of patients and improper control groups have made much of the data inconclusive. Recent results from the Gastrointestinal Cancer Intergroup 0116 trial have established postoperative chemoradiotherapy as the standard for gastric cancer patients who have undergone gastric resection. Preoperative strategies have been shown to be feasible and result in a high rate of curative resections. Randomized trials are needed to assess the survival benefits.

Recent advances in molecular biology have introduced new tools for the understanding of gastric cancer. Efforts at correlating molecular profile and clinical behavior are ongoing. Studies of genes involved in drug resistance may allow better drug selection in the future. New drugs targeting growth factors, angiogenesis and apoptosis may allow less toxic therapy to be given postoperatively.

References


40. Nakajima T, Nashimoto A, Kitamura M et al. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-