# NEW NEOADJUVANT TREATMENT STRATEGIES FOR GASTRIC AND GASTROESOPHAGEAL JUNCTION CANCERS

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## ABSTRACT

**Objective:** The feasibility of neoadjuvant chemotherapy for clinically unresectable gastric and gastroesophageal (GE) junction cancers.

**Methods:** Eleven patients with gastric and GE junction cancers underwent preoperative combined modality chemo and radiotherapy and a subsequent attempt for surgical resection.

**Results:** Combined modality periadjuvant therapies downsized 9 of 11 T3-4 gastric and gastroesophageal junction cancers and produced 4 pathologically proven complete remissions. Treatment appeared to convert lymph nodes to a cancer free status for 7 of 11 patients. After treatment, exploratory surgery found that 3 patients had only minute foci of occult metastatic disease. The quality of the responses was underestimated by both endoscopic ultrasound and CT scans. Responses were sometimes only achieved after 2-3 months of therapy.

**Conclusion:** Combined modality therapy demonstrates the feasibility of a flexible multistep approach to neoadjuvant therapy incorporating new drugs such as methotrexate and hydroxyurea in addition to fluorouracil and cisplatin. Long delays in surgery (gastrectomy) appear to be safe in the context of combined modality therapy. Median survival exceeds 2 years. The experience suggests new early end points for evaluation of neoadjuvant treatments: quality of life, quality of lymph node sterilization and extent of required gastrectomy in comparison to standard surgery.

**Key Words:** Neoadjuvant, Gastric cancer, Gastroesophageal cancer, Combined modality treatment

## INTRODUCTION

Advanced T 3-4 adenocarcinomas of the stomach and gastroesophageal junction present a difficult challenge and vast majority of patients fail conventional therapy. Forty five -66% of these patients have unresectable, locally advanced tumors (1). Patients with T4 tumors usually have (75-95%) disease in the lymph nodes and only a 15% or less chance of long disease free survival (2).

Phase II trials of preoperative treatment, when compared to historical surgical results, find a 10-20 % rate of pathologically proven complete response, improved rates of resectability approaching 60-80%, and 20-30 % improvement in disease free survival over 2-3 years (3-5). These recent trials describe median survivals of 9-18 months (3,5-8). Preoperative treatment while increasing in frequency of use, has not achieved the status of standard therapy.

Post operative adjuvant therapy remains controversial (1,9,10). Some trials combining 5Fluorouracil-Mitomycin C and immunotherapy appear to find modest benefit (9). A positive impact due to chemotherapy has only infrequently been described; it is usually found only for the subgroup of patients with a poor prognosis, due to their advanced invasive tumors (1,9). These are the same patients considered candidates for trials of preoperative treatment.

Relapse occurs with 90% frequency even when surgery is technically successful for patients with similar but less advanced tumors (2,3,5,6). T4 size, invasion of adjacent structures , proximal tumor location, poor grade and presence of symptoms due to the primary tumor all imply that the patient will have an extremely poor prognosis following conventional surgery alone (3). The recent availability of accurate preoperative staging with endoscopic sonography (11)

and improved (spiral) CT scans further strengthens these prognostic factors.

## METHODS

**Eligibility:** Patients were required to have T3-4, NX or 1 and M0 tumors clinically. They were also required to have biopsy proven adenocarcinoma of the stomach or GE junction crossing the Z line. The evaluation required evidence of invasive cancer on biopsy, without radiographic evidence of metastatic disease on CT scan. The tumors could not appear to be easily resectable or carry a greater than 25% surgical prognosis for long term ( 2-3 year) survival. All patients gave informed consent for preoperative treatment. Endoscopic sonography was used as needed to clarify the extent of the invasion, the size and the operability of the tumor. Patient characteristics are shown in Table IA.

**Radiation Methods:** Radiation was delivered by a linear accelerator, utilizing 6 or 15 mV photons.

**Table I A .** Patient Characteristics (n=11)

| | |
|---|---|
| Age(yr) | 64 (40-82) |
| Sex: Male/Female | 7/4 |
| Performance Status | |
| 1 | 3 |
| 2 | 6 |
| 3 | 2 |
| Location of Tumors: | |
| Gastro-Esophageal Junction | 2 |
| Proximal | 2 |
| Fundus | 3 |
| Corpus | 1 |
| Distal | 3 |
| Histologic Grade | |
| Well differentiated | - |
| Moderately differentiated | 5 |
| Poorly differentiated | 6 |
| Clinical Primary Stage | |
| T3 (penetrates the serosa) | 3 |
| T4 (invades adjacent structures) | 8 |
| No. underwent surgery | 11 |
| No. resected | 9 |

Patients underwent treatment planning CT scans and fields were tailored to the site and nodal group utilizing a 2, 3 or 4 field technique. Care was taken to limit dose to the spine, kidney and liver with cerrobend shaped fields in all cases. Except for 2 cases of bid radiation, daily doses of 180 cGy were given either continuously and simultaneously with chemotherapy or in a split course with simultaneous chemotherapy with 2 week rest periods between courses. The radiation was given with chemoterapy in a preoperative intent and total doses ranged from 3240 cGy to 4500 cGy. Total dose and number of courses was in part determined by safety and course assessment of the degree of down sizing of primary tumor.

**Staging:** Patients were staged initially, restaged after 2 and 3 cycles of therapy and again 3 weeks after the end of radiotherapy. Tests included CT or MRI scan, as well as endoscopy and endoscopic sonography as needed. Surgical and pathological evaluation followed completion of treatment.

**Treatment Selection:** Treatment was selected individually as follows: Initially chemotherapy alone for patients with the worst stage (T4), and the elderly (>75 years). Methotrexate, Calcium Leucovorin, Cisplatinum, 5- Fluorouracil (MLPF) for those with good performance status and tumors not in gastroesophageal junction or proximal stomach, Cisplatinum, Calcium Leucovorin, 5- Fluorouracil (PLF) for intermediate performance status and Methotrexate, Calcium Leucovorin, 5- Fluorouracil (MLF) for patients with numerous kinds of poor (chemotherapy) risk factors. Radiotherapy was added with additional chemotherapy if this failed to downstage tumors. Combined modality was attempted from the onset of therapy in patients with good performance status considered good risk for combined modality therapy, especially those with gastroesophageal junction or proximally located tumors. Distal tumors were initially treated with chemotherapy, radiation therapy was added, used simultaneously with chemotherapy as needed.

**Treatment Evaluation:** Pathological complete remission was defined as absence of carcinoma cells on microscopical examination of the surgically resected specimen. Clinical complete remission was defined as no evidence of disease on either radiological, endoscopic or serological assays prior to a surgical exploration. Minimal residual disease (m in table) defines surgical finding of lesions that are less than 0.5 cm in greatest diameter. Partial response was defined as a 50% or greater reduction in tumor volume (product) evident by radiographs, endoscopy, or computerized tomography. Minor response was defined as an objective but less than 50% regression

in product of tumor diameters. The purpose for defining minor clinical responses was the identification of patients who would receive further preoperative Combined Modality Therapy (CMT) and postoperative chemotherapy and ultimately to correlate these responses with outcome measures. Survival was measured from the date of registration to the date of death. Patients were assessed every 3 months for the first year following completion of all therapy. They were then examined every 6 months for 4 additional years.

**Statistical Methods:** Survival was examined in absolute terms. No actuarial projections were used, in order to avoid an unrealistic inflation of outcome analyses. This is an intent to treat analysis with no known exclusions. A prospective data base was available for identification of candidates.

**Toxicity:** Cancer and Leukemia Group B (CALGB) common toxicity criteria were used for assessment of toxicity. The Zubrod performance scale was used for evaluation of performance status.

## RESULTS

Table IB shows the characteristics of the 11 patients; their sites of residual disease and their degree of response. There were 4 pathological complete remissions. 3 patients had minute foci of occult metastatic disease. Nine of 11 patients were resectable, and in spite of an extensive search for lymph node metastasis only 1 patient had tumor in a lymph node. Five patients had residual resectable local disease. All patients with major responses had minimal residual disease in the stomach, the primary tumor site. Overall there were 36% pathological complete remission (pCR) of the primary tumor site. Absolute median survival is reached at 28.8 months, 81 % ( 9/11) survived beyond 18 months.

Table IC demonstrates that pCR have been achieved in all areas of the stomach. Distal stomach including fundus and corpus appears to be a more difficult challenge for this treatment. Radiation as salvage produced pCR in the tumor of fundus and distal stomach, its role is confirmed again as effective against tumors of the proximal stomach.

**Table I B.** Disease characteristics of patients.

| Case | Age | Size | Location | Hist. Grade | Treatment | Survival (months) | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | 40 | T3 | GE Junction | Moderate | MLPF! PFVelbane/42Gy | 11 | M |
| 2 | 48 | T4 | Proximal | Moderate | MLPF/MLF! PFVelbane/45Gy | 20 | pCR |
| 3 | 82 | T4 | Fundus | Poor | PLF/41Gy | 18 | pCR |
| 4 | 74 | T4 | Fundus | Poor | MLF | 50 | m |
| 5 | 69 | T4 | Proximal | Moderate | MLPF!PLF 40Gy | 44+ | m,0/8 LN |
| 6 | 73 | T4 | Corpus | Moderate | PLF | 42+ | m,0/35 LN |
| 7 | 73 | T4 | Fundus | Poor | MLPF | 29 | m,0/5 LN |
| 8 | 66 | T4 | Distal | Moderate | PLF/32Gy | 26+ | m,1/23 LN |
| 9 | 69 | T4 | Distal | Poor | PLF/45Gy | 27+ | pCR |
| 10 | 53 | T3 | GE Junction | Poor | PLF/45Gy | 25+ | pCR |
| 11 | 60 | T3 | Distal | Poor | MLPF!PLF/36Gy | 25+ | M |

m:local disease, M:metastatic disease, pCR: pathological complete remission, LN: lymph node, m: minimal residual disease.

**Table I C.** Response characteristics at each location

| Location | # | Tumor Status (Local) | Metastasized Lymph Nodes | Distant Metastasis | pCRs in Radiation Tx |
|---|---|---|---|---|---|
| Gastro-Esophageal Junction | 2 | 1 pCR | n/a | 1M | 1pCR/2 |
| Proximal | 2 | 1m, 1pCR | 0/8 | - | 1pCR/2 |
| Fundus | 3 | 2m, 1pCR | 0/5 | - | 1pCR/1 |
| Corpus | 1 | 1m | 0/35 | - | - |
| Distal | 3 | 1m, 1pCR | 1/23 | 1M | 1pCR/3 |

m: local disease; M: metastatic disease pCR: pathological complete remission, m: minimal residual disease, n/a: not available

## DISCUSSION

Prior neoadjuvant efforts for patients with tumors of the true stomach (not gastroesophageal junction) rarely yielded pCR (3,5-8). Our experience suggests individualized and sequential especially CMT efforts warrant testing and development because they appear to improve the rates of resectability and pCR. It is apparently possible to achieve pCR even after initial neoadjuvant attempts failed. This and our experience with pancreatic cancers suggest further emphasis on examination of novel forms of sequential therapy and in particular multidrug chemotherapy used simultaneously with split course radiation treatment (9,12-14). These novel chemotherapy regimens have proven components and promising results against metastatic disease, especially intraperitoneal disease (15). There is a case for testing new forms of chemotherapy especially methotrexate's direct activity and its ability to produce biochemical modulation. Cisplatin probably potentiates both methotrexate and fluorouracil with leucovorin in combination (15).

Conventional surgical methods normally find many involved lymph nodes in patients with T4 tumors, especially in the patients with poorly differentiated or obstructing lesions (2,3,9,10). The rarity of lymph node involvement (one involved node found in the entire series) suggests that neoadjuvant treatment often sterilizes lymph nodes. The observation suggests a role for further efforts to improve the evaluation of apparently cancer free nodes by use of more sensitive methods i.e. fluorescent in situ hybridization (FISH) for evaluating the presence of tumor. None of these patients relapsed locally except the two which were not resected at surgery. This points to the continued importance of surgery as a therapeutic measure where cure is the goal. Ability to perform less extensive resection may be a quality of life and cost effective goal and another measure to be considered in comparing neoadjuvant therapies to standard primary surgery.

This experience confirmed that endoscopy is not entirely reliable following preoperative therapy (11). Radiologic and endoscopic ultrasound grossly underestimated the quality of the remissions. These tumors regress slowly and an inflammatory mass remains for months. The implication of these limitations - slow response and pseudo tumors- for design of treatment and for selecting the time of surgery clearly needs further consideration.

The peritoneum is widely viewed as the major site of failure when local control has been successful (2,10). This was true in the current series as well. Future efforts may integrate preoperative treatment measures which produce good local control with intraperitoneal therapy. The successful response to second attempts at therapy represents an important new observation as may the degree of success in the use of radiation for some distal tumors (12-14). In theory the use of novel chemotherapy either before or concurrently with radiotherapy may improve the utility of radiotherapy. Prognostic evaluation may soon be improved by objective tests, specifically measurement of EGF (16) and abdominal fluid cytology (2). Also measurements of thymidilate synthase and other in vitro tests of tumor sensitivity may identify those tumors likely to benefit from adjuvant therapy (17,18).

It may be possible to improve quality of life and short term survival with neoadjuvant treatment: Quality of life, extent of surgery and sterilization of lymph nodes deserves evaluation as possible early indicators of benefit in new analyses of preoperative therapy.

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