TRANS-TASMAN RADIATION ONCOLOGY GROUP
INCORPORATED

A FEASIBILITY STUDY TO EVALUATE ADJUVANT CHEMORADIOTherAPy FOR
GASTRIC CANCER

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Foreword

This document is intended to describe a Trans-Tasman Radiation Oncology Group (TROG) study and to provide information about procedures for entering patients. It is not intended that the protocol be used as a guide for the treatment of other patients. TROG will not accept any data for analysis unless the local ethics committee has approved this study for patient entry.

Amendments to the document may be necessary; these will be circulated to known participants in the study, but centres entering patients for the first time are advised to contact the TROG Central Operations Office, Newcastle, to confirm the details of the protocol in their possession.
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Version dated 21/08/07
SCHEMA

A prospective, single-arm, non-randomized feasibility study to evaluate a new regimen of adjuvant chemoradiotherapy for gastric cancer.

Eligibility criteria:
- adenocarcinoma of the stomach or gastro-oesophageal junction
- completely resected with negative margins, and
- stage T3,4 and/or N1,2

Chemotherapy:

**ECF:**  Epirubicin 50 mg/m\(^2\) IV day 1, Cisplatin 60 mg/m\(^2\) IV day 1, 5-Fluorouracil 200 mg/m\(^2\)/d IV 21 day continuous infusion.

Cont. infusional 5-FU: 225 mg/m\(^2\)/day, 7 days per week, throughout the entire period of radiotherapy via CADD pump through a PICC line.

Radiotherapy: 45 Gy of radiation in 25 fractions, five days per week for five weeks.

The first cycle of postoperative ECF should preferably begin within 7 weeks of surgery and no later than 10 weeks after surgery.
1 INTRODUCTION AND BACKGROUND

Carcinoma of the stomach remains a major cause of cancer related death in most Western countries. Surgery is the only proven effective therapy, but overall 5-year survival rates remain low after resection. Patterns of failure data document that approximately 60% of those with positive lymph nodes or extension of the primary tumor through the serosa fail in the tumor bed, regional nodes, stump, or anastomosis (1, 2). Worldwide, large amounts of resources have been expended in the search for an effective adjuvant therapy to reduce the risk of postoperative relapse. Postoperative adjuvant chemotherapy for gastric cancer has been thoroughly explored over the past 10-15 years. Several recent meta-analyses have indicated that even with pooled data, postoperative adjuvant systemic therapy caused only a modest improvement in survival (3-5). Likewise, adjuvant radiotherapy alone has also failed to demonstrate any survival benefit (6). Recognition of the high loco-regional failure rates following surgery has resulted in four separate randomised trials evaluating the role of extended lymph node dissection (7-10). All four trials demonstrate substantial increase in morbidity and, in some series, operative mortality with extended lymph node dissection. None show improvement in overall survival.

The recently reported Gastric Surgical Adjuvant Trial (INT0116) has established combined chemoradiotherapy as an integral component of standard adjuvant therapy for high risk, completely resected adenocarcinoma of the stomach (11). There was a major survival advantage to the use of combined modality therapy postoperatively which was highly statistically significant. Following publication of INT0116, radiation oncologists are for the first time, being referred patients for treatment of gastric cancer. However, there remain several major concerns amongst oncologists regarding implementation of this treatment.

The first relates to the toxicity associated with the treatment. The combined modality regimen in this program was associated with considerable toxicity, with grade 3 and grade 4 toxicity occurring in 41% and 32% of cases, respectively.

The second area of concern relates to the optimal chemotherapy regimen. The Intergroup study employed bolus 5-FU and folinic acid delivered before, during and after radiation. This regimen was chosen because it had been through toxicity studies at the time the trial was developed in the 1980’s. However, some medical oncologists feel that this regimen is now outdated and that there are more active regimens available for gastric cancer. Failure pattern data from INT0116 suggests a minimal effect of 5-FU/folinic acid on regional and distant failure (11). The high recurrence rate, even in the superior chemoradiation arm, clearly indicates the need for improved systemic therapies.

The last area of concern relates to the radiotherapy planning and treatment technique. In the Intergroup study, radiotherapy fields were designed using conventional simulation only and there was no use of CT planning to define the clinical target volume (CTV) (12). All patients were treated with simple parallel-opposed anterior and posterior field arrangements. However, most radiation oncologists in this country are reluctant to treat such large abdominal volumes with anterior and posterior fields due to concerns with renal toxicity and irradiation of the spinal cord. Recent computer planning developments in radiotherapy techniques offer major advantages over the traditional opposed-field approaches devised in the 1960s. Confining the high radiation dose treatment region more precisely to the tumor has the potential to reduce toxicity and lead to more durable local disease control (13). Contemporary 3D CT planning further improves this targeting specificity and the employment of non-coplanar techniques is said to further reduce the dose to critical normal tissues such as the kidney and spinal cord (14).
Following the initial report of INT0116 at ASCO in May 2000, a pilot study was initiated at Peter MacCallum Cancer Institute (PMCI) to investigate combined chemoradiation for gastric cancer. The chemotherapy regimen consisted of continuous infusional 5-FU delivered concomitantly with radiation, and ECF (epirubicin, cisplatin, 5-FU) given before and after radiation. Continuous as opposed to bolus 5-FU during radiation is less toxic and better tolerated, and is proposed to maximize the opportunities for radiosensitization (15, 16). The ECF regimen has demonstrated response rates of up to 71% in patients with gastric cancer and is a commonly used regimen both in the neoadjuvant setting and in patients with advanced gastric cancer (17, 18). All patients in the pilot study were CT planned, and treated using a standardized 3D conformal technique that consisted of a “split-field”, mono-isocentric arrangement employing 6 radiation fields. Comparative dose volume histograms (DVH) comparing this technique with the INT0116 APPA technique demonstrate significant sparing of kidneys and spinal cord.

Between July 2000 and April 2002, twenty-six patients were accrued. Of the patients who commenced chemoradiation, 81% completed treatment as planned. All patients completed their radiotherapy and only one required a treatment break for nausea and vomiting. Four patients had their chemotherapy stopped early due to toxicity. In contrast, only 64% of INT0116 patients completed treatment as planned and 17% did not complete their RT because of toxic effects. Overall grade 3 toxicity occurred in 38% of patients and consisted mainly of nausea and leucopenia, while grade 4 toxicity occurred in only 15%. In INT0116, the rate of grade 3 toxicity was similar at 41%; however the rate of grade 4 toxicity was much higher at 32%. The rate of grade 3 GIT toxicity was 19%, compared to 33% in INT0116. The rate of haematologic grade 3/4 toxicity was 23%, compared to 54% in INT0116.

The rates of haematologic, GIT and overall grade 4 toxicity reported in this pilot study are lower than those reported in INT0116 and could be due to the use of continuous infusional rather than bolus 5-FU during RT, as well as the use of more conformal RT fields.

Because of the concerns relating to the Intergroup study and because gastric cancer represents a new area of activity for radiation oncologists, we need to devote significant efforts to the educational process needed to be able to correctly plan these patients and treat them safely. The complexity of this treatment was borne out in an evaluation of the radiotherapy treatment planning issues related to implementation of the adjuvant program in INT0116 (12). This evaluation demonstrated that 35% of the patients reviewed for initial compliance had major or minor deviations in protocol radiation therapy at the time of initial (pretreatment) review. Of these, 19% were known to have had major deviations at the end of treatment despite the requirement for preapproval of radiotherapy plans. These issues of quality control have arisen due to the fact that few radiation oncologists have been trained in how to treat gastric cancer and understand the patterns of spread. Until now there has been minimal use of radiation therapy for gastric cancer and this area of radiation oncology has not been systematically incorporated into our training programs.

The demonstration that adjuvant chemoradiotherapy improves survival in gastric cancer will clearly change standards of care and provide new opportunities to develop improved treatment through multiinstitution collaborative studies. However, at present there is no common approach to the adjuvant treatment of gastric cancer in this country. This applies to both the chemotherapy regimen that is used, as well as radiotherapy planning procedures and treatment techniques that are employed. There is a need for an Australasian multicentre group to attempt to standardize radiation oncology techniques amongst centres that have different practices and equipment. It is imperative that radiation oncologists devote significant efforts to the educational process needed to be able to
implement this treatment safely and with acceptable toxicity. Only after a common base approach with acceptable toxicity has been established, can we initiate further developmental studies through multicentre collaborative groups within Australia and New Zealand.
2 HYPOTHESIS

The hypothesis to be tested is that the proposed adjuvant chemoradiation regimen for gastric cancer can be safely and reliably delivered using a standardized regimen of radiation and chemotherapy. The specific objectives are:

- To determine the feasibility of the proposed concurrent chemoradiation regimen.
- To determine the feasibility of a standardized technique for radiation treatment planning and delivery.
- To detail the acute toxicity associated with this treatment.
- To detail the late toxicity associated with this treatment.
- To determine the relapse-free survival and overall survival.

The aim of the study is to develop a common approach to the adjuvant treatment of gastric cancer, which is required before initiating further clinical trials in gastric cancer.
3 PATIENT ELIGIBILITY

3.1 Inclusion criteria

All of the following must apply:

1. Histologically proven adenocarcinoma of the stomach or gastro-oesophageal junction that is:
   a) completely resected with negative margins
   b) Stage T3,4 and/or N1,2
      Patients who have undergone a D2 nodal dissection can be entered on the study at the discretion of the treating clinician.
2. Age ≥ 18 years
3. ECOG performance status 0, 1, 2
4. Adequate organ function defined as follows:
   Bone marrow:
      Haemoglobin ≥ 90 g/L
      Neutrophil count ≥ 1.5 x 10⁹/L
      Platelet count ≥ 100 x 10⁹/L
   Hepatic:
      Serum bilirubin ≤ 1.5 x ULN
      AST and/or ALT ≤ 3.0 x ULN
   Renal:
      Se creatinine ≤ 0.150 mmol/L, and calculated creatinine clearance ≥ 50mL/min.
5. Adequate oral nutrition as assessed by a dietician prior to commencing treatment.
6. Disease which can be radically treated to 45 Gy with standard fractionation.
7. Patient able to be treated with infusional 5-FU and ECF chemotherapy.
8. Written informed consent

3.2 Exclusion criteria

None of the following must apply:

1. Evidence of metastatic disease.
2. Prior chemotherapy or radiotherapy
3. Patients with other significant underlying medical conditions that may be aggravated by the study treatment or are not controlled.
4. Pregnant or lactating females or female patients of childbearing potential who have not been surgically sterilized or are without adequate contraceptive measures.
5. Cardiac failure (relevant to the use of epirubicin)
   • Patients with myocardial infarction within the last 6 months
   • Patients with New York Heart Association class III/IV Congestive Heart failure
4 TREATMENT PLAN

4.1 Radiation Therapy

4.1.1 General irradiation information

The intent of treatment is to deliver 45 Gy in 25 fractions at 1.8 Gy/fraction, 5 days a week for 5 weeks, to the entire tumor bed, anastomoses and regional lymph nodes. The radiotherapy plus concurrent chemotherapy should begin 4 weeks after the start of the initial cycle of postoperative chemotherapy, and no later than 6 weeks. CT planning will be used. In the event of chemotherapy interruption and delay due to toxicity during concurrent chemoradiation, the radiotherapy should continue unless the radiation oncologist feels that this should also be delayed due to toxicity.

4.1.2 Treatment sites and definition of CTV

4.1.2.1 Introduction and general considerations

These guidelines have been produced with two aims: (1) to assist the radiation oncologist in delineating the clinical target volume (CTV) when planning adjuvant postoperative radiotherapy for gastric cancer; and (2) to assist the radiation therapist in the planning process when implementing conformal RT for gastric cancer. They have been produced following consultation with radiation oncologists, radiation therapists, gastric surgeons and diagnostic radiologists. In general they follow the recommendations outlined in INT0116 (11, 12), which are based on the patterns of relapse following surgery, as detailed in the University of Minnesota Reoperative Series (1). However, the INT0116 recommendations have usually resulted in very large RT volumes that have included most, if not all of the potential nodal groups. In an attempt to reduce RT volumes and toxicity we have recommended tailoring RT volumes according to tumor stage and location in the stomach (19). Although these guidelines may appear quite lengthy, the majority of this document comprises illustrative CT scans and diagrams which are designed to show practical examples of the planning process.

The first part of this document describes practically, the treatment sites that will need to be identified and incorporated in the CTV depending upon tumor stage and site. Detailed examples are provided, which illustrate the process of CTV marking for the two commonly encountered postoperative scenarios i.e. partial distal gastrectomy and total gastrectomy. The complete planning CT dataset with CTV marked on each CT slice is provided for each example. It should be noted that the CT scans used in these guidelines are of diagnostic quality, designed for illustrative purposes using oral and IV contrast for ease of identifying structures. In addition, we have included all of the potential nodal groups in the CTV for each example. Again this is for illustrative purposes only, and inclusion of particular nodal groups in the CTV should be individualized as discussed further on. The second part of the document details the planning/treatment process and our suggested RT technique. It has been produced to assist the planning radiation therapist who will be responsible for implementing this treatment. Radiation oncologists do not need to read this section in detail. A one page “Quick start checklist” is provided at the end of both sections for easy reference.

Prior to radiotherapy planning it is important to scrutinize the operative notes and pathology report, and even speak to the surgeon to identify the areas considered to be at highest risk for recurrence. The type of operation performed needs to be ascertained, e.g. partial distal gastrectomy or total gastrectomy, as this will dictate the nature and location of the anastomosis. Preoperative CT scans
should be reviewed to identify the location of the primary tumor and to aid in localization of important structures and nodal groups that need to be treated. It is strongly advised that diagnostic quality postoperative CT scans be performed in addition to RT planning CT scans. Planning CT scans are usually performed without oral and IV contrast making it difficult to identify organs such as duodenum and gastric remnant, and vascular structures such as portal vein and celiac artery. Prior to target volume marking we recommend reviewing the preoperative, postoperative and planning CT scans to identify the following structures and regions (see below for description and identification):

- oesophagus and gastric remnant (if applicable)
- anastomosis (eg. gastrojejunal, oesophagojejunal)
- duodenal stump and duodenum down to its third part
- hepatogastric ligament
- porta hepatis (extrahepatic portal vein)
- splenic hilum
- pancreas (head and body)
- celiac artery
- superior mesenteric artery

Initially this exercise will appear difficult and time consuming and we would advise that it be conducted in conjunction with a diagnostic radiologist. However, once familiar with the CT anatomy of the abdomen, this process becomes relatively straightforward and it will greatly facilitate target volume marking (i.e. once the important structures have been identified and marked, the CTV is delineated by simply “joining the dots”).

The design of the radiation treatment volume will require some individualisation, and is based on documented patterns of loco-regional failure following complete resection of gastric cancer, and on the type of surgery that has been performed. For distal tumors, a partial distal gastrectomy (Billroth II or Polya gastrectomy) is usually performed with closure of the duodenal stump and lesser curvature of the stomach and reconstruction with a gastrojejunal anastomosis (Fig 1.d). For proximal tumors, a total gastrectomy is usually performed with closure of the duodenal stump and reconstruction with Roux-en-Y oesophagojejunal anastomosis (Fig 1.a). Occasionally a partial proximal gastrectomy will be performed for patients with proximal tumors (Fig 1.b). Patients with gastro-oesophageal junction (GE) tumors will occasionally be referred following a radical oesophagogastrectomy (Ivor-Lewis procedure) in which most of the oesophagus and a cuff of stomach are removed (on the assumption that it is an oesophageal tumor). The reconstruction involves a gastric pull-up with the anastomosis placed very high up in the chest. In this situation it is very difficult, and sometimes impossible to deliver RT safely, if the anastomosis and gastric remnant are to be covered, without exceeding tolerance doses for lung and heart. For these patients the decision as to whether or not to treat will depend on an evaluation of the likely risk of recurrence versus the risk of acute and late morbidity. Patients undergoing this type of surgery represent only a small minority and will not be included in these guidelines.

The areas of loco-regional relapse include the anastomosis and stumps, gastric remnant, tumor bed, and regional lymphatics. The following notes and figures describe how to identify these structures and regions on planning CT scans. Included is a set of preoperative CT scans (corresponding to the partial distal gastrectomy patient) to illustrate normal anatomy (Fig 2).
4.1.2.2 Anastomoses

For patients who have undergone a partial distal gastrectomy for tumors of the antrum/distal stomach, the gastrojejunal anastomosis and distal deafferented duodenal stump should be treated. The anastomosis is readily identified on CT by following the gastric remnant caudally until the staple line becomes visible (Fig 3.k). A margin of 1cm of jejunum (for CTV) beyond the staple line should be given (Fig 3.l). The duodenal stump and duodenum can sometimes be difficult to identify on CT if no oral contrast has been given. Diagnostic quality postoperative CT scans can be very helpful in this situation. Another useful hint is to first identify the third part of the duodenum as it crosses the aorta (usually readily visible) (Fig 3.o) and then to follow the duodenum cranially through the second part until the stump can be visualized (identified by staple line) (Fig 3.i).

For patients who have undergone a total gastrectomy for tumors of the proximal stomach or GE junction, the oesophagojejunal anastomosis needs to be treated. It is important to note that patients with such tumors may have anastomoses that extend considerably above the left hemidiaphragm. The anastomosis is readily identified on CT by following the oesophagus caudally until the staple line becomes visible (Fig 4.c and Fig 4.d). A margin of 1cm of proximal oesophagus (for CTV) beyond the staple line should be given for tumors of the proximal stomach. However, for tumors of the GE junction, a 4cm margin of oesophagus (for CTV) should be treated to encompass the paraoesophageal nodes that are at risk. As these patients with proximal tumors have undergone a total gastrectomy, the likelihood of recurrence at the distal resection margin (duodenal stump) is small, and therefore it is not necessary to treat the duodenal stump.

4.1.2.3 Gastric remnant

The gastric remnant (which includes perigastric nodes) should be treated in all cases. Not applicable following total gastrectomy. (Note: in the example shown in Figure 3, the gastric remnant appears unusually large because the CT scans have been performed using diagnostic CT protocols which involve administration of Buscopan to relax the stomach.)

4.1.2.4 Tumor bed

The tumor bed does not need to be treated for T1 and T2 tumors (no invasion through the serosa) but does need to be treated for all T3 and T4 tumors, including any sites of adherence for T4 tumors. The organs and structures that constitute the tumor bed (where the tumor was originally located) will vary depending on the location of the primary tumor within the stomach (Table 1). Pre- and postoperative diagnostic imaging studies, clip placement and operative findings should be used to identify the tumor bed.

It is not necessary to cover the entire preoperative gastric silhouette as recommended in INT0116. Following gastrectomy, much of the preoperative gastric volume will be filled by bowel and liver, and treating this volume will only add to toxicity.

The hepatogastric ligament should be treated in all cases as it is at high risk of recurrence. It represents that part of the lesser omentum that runs between the lesser curvature of the stomach and the liver, and contains the left and right gastric nodes (perigastric nodes) that are not always completely removed at surgery. The hepatogastric ligament appears as a thin film at surgery and is not visible on CT. However, its location can be easily delineated on CT (particularly preop. CT) as the region lying between the liver and the lesser curvature of the stomach (Figs 2.b, 3.e, 4.h, 4.i).
Preoperative CT scans will demonstrate that the body of the stomach is related to the liver and hepatogastric ligament on its right side, and to the abdominal wall anteriorly (Fig 2.b). Following gastrectomy, the gastric remnant usually falls away from the anterior abdominal wall. We recommend inclusion of the anterior abdominal wall in the CTV for this part of the volume that previously contained the body of the stomach (not required for tumors confined to the GE junction where it is only necessary to cover the hepatogastric ligament). Preoperative CT will be helpful in defining the appropriate levels, which are usually above the level of the splenic hilum (Fig 2.b). When marking the CTV at these levels, the contour should follow the medial edge of the liver from the right paraaortic region, anteriorly to the anterior abdominal wall (to incorporate the hepatogastric ligament, inferior surface of the liver and anterior abdominal wall) (Figs 3.d, 3.e, 4.i, 4.j). It should then loop posteriorly and to the left and continue along the left side of the gastric remnant. The CTV is completed by contouring around the left paraaortic nodes (plus splenic hilum if appropriate level). The need to include the anterior abdominal wall in all cases may be questioned, as it adds to the treatment volume, and potentially toxicity. However, INT0116 guidelines stress that the anterior abdominal wall should always be covered in the CTV. With the use of more conformal RT techniques, there is a potential risk of marginal misses because oblique or noncoplanar beams could exclude target volumes that would be included in APPA techniques (as used in INT0116). It should be noted that the anterior abdominal wall was treated in all patients in the PMCI pilot study. If radiation oncologists feel strongly on this issue, then some individualization of treatment may be possible. For example, it is probably not necessary to cover the anterior abdominal wall for T1 or T2 lesions involving the proximal stomach.

4.1.2.5 Regional lymphatics

Japanese data demonstrate that the relative risk of nodal metastases at a specific nodal location is dependent on the site of origin of the primary tumor. Although many different classifications exist, it is reasonable to divide them in the manner proposed by the Japanese Research Society for Gastric Cancer (JRSGC) (20, 21) (Fig 5). Indeed, the nodal regions to be treated when considering adjuvant postoperative radiation for gastric cancer are based on the Japanese surgical data (12).

(a) Description and coverage of nodal groups

Although initial drainage is usually to perigastric lymph nodes along the lesser and greater curvatures that are removed (not always completely) with most types of gastrectomy (lymph node stations 1, 2, 3, 4, 5 and 7 in the JRSGC), primary node drainage includes nodes along all three branches of the celiac axis (common hepatic, splenic, left gastric) and the celiac itself (Japanese lymph node stations 7, 8, 9, 11). The CTV should therefore include the gastric remnant and the hepatogastric ligament to cover the perigastric nodes in all cases (Fig 3.e and Fig 4.i). The CTV also needs to include the celiac axis, which can be identified as the first branch arising from the front of the abdominal aorta, usually at the level of T12 (Figs 2.d, 3.j, 4.i). It can be confused with the superior mesenteric artery (SMA), which arises from the aorta approximately 1cm below the celiac artery. However, the SMA can be readily identified by the left renal vein which crosses horizontally from left to right between the SMA and the aorta (Figs 2.f, 3.k, 4.n).

In addition, the following nodal groups may also need to be treated depending upon risk (see Table 1). The lymph nodes of the splenic hilum (JRSGC station 10) and the nodes of the superior retropancreatic chain (which lie on the posterior margin of the superior portion of the pancreas) are at risk. The splenic hilum is easily identified on planning CT (Fig 3.h and Fig 4.m). A CTV that covers the splenic hilum will usually dictate the left lateral extent and, often, the most posterior
extent of the volume (Fig 4.m). Although the body of the pancreas may sometimes be difficult to
define on planning CT, volumes that cover the splenic hilum, gastric remnant and paraaortic nodes
will usually encompass the pancreas (Fig 3.h).

The lymph nodes of the hepatoduodenal ligament (JRSGC station 12) are also at risk and are
treated by fields corresponding to the porta hepatitis. The location of the porta hepatitis on CT is
variably interpreted by radiologists. Because the hepatoduodenal ligament nodes that need to be
covered in the CTV surround the extrahepatic portal vein, common bile duct and hepatic artery, we
define the right lateral extent of the porta hepatitis as being the right margin of the extrahepatic
portal vein just before it enters the liver, and not where the portal vein divides (which is usually
further to the right) (Figs 2.d, 3.i, 4.m). Although this distinction may seem trivial, it does impact
upon the amount of liver that is included in the CTV. When planning CT scans are performed
without IV contrast, it can be difficult at times to identify the extrahepatic portion of the portal vein
(although the hepatic portion can usually be identified). In this situation, the right margin of the
portal vein can be inferred from the right margin of the inferior vena cava (IVC), which sits just
posterior to the portal vein. The IVC is visible even without contrast and its right margin runs
approximately in line with that of the portal vein (Fig 4.m).

Lymph nodes in the infrapyloric area (JRSGC station 6) and pancreaticoduodenal nodes (which lie
between the medial portion of the duodenal C loop and the head of the pancreas) are also at risk, as
are lymph nodes posterior to the pancreatic head and superior portion of the pancreas (JRSGC
station 13). The second part of the duodenum can be identified as described above. The head of the
pancreas sits directly adjacent to the duodenum on its left side. In covering the pancreaticoduodenal
nodes, the CTV need only include the medial half of the duodenal circumference rather than the
entire circumference of the duodenum (Fig 3.i and Fig 4.o). Again this distinction may seem trivial,
but as the duodenum often sits directly in front of the right kidney, it does impact upon the amount
of right kidney that will be included in RT fields. Needless to say, if there has been direct invasion
of the duodenum, then the entire duodenal circumference needs to be treated. A CTV that covers
the pancreaticoduodenal nodes will often dictate the right lateral extent of the volume (Fig 3.i).

Node groups that are more distal include nodes at the root of the mesentery (superior mesenteric
artery) and paraaortic nodes. The paraaortic nodes include the aortocaval nodes between the IVC
and the aorta, and nodes anterior to and along the left side of the aorta. The CTV should extend
beyond the circumference of the aorta for 1cm in all radial directions, except posteriorly where it
should extend only to the anterior vertebral body (Fig 3.n and Fig 4.p). In practice however, we
usually place the posterior margin of the CTV midway through the aorta in an attempt to reduce
spinal cord dose (shown by dotted line). The planning target volume (PTV) that is generated by
adding a margin to the CTV will then usually cover the entire aorta. The paraaortic nodes should be
included for the entire length of the CTV, from its inferior extent cranially to the aortal hiatus. For
proximal lesions involving the GE junction, the paraoesophageal nodes are also at risk. A 4cm
margin of the oesophagus (CTV) should be included superiorly.

(b)  Guidelines for inclusion of nodal groups in CTV

Based upon documented patterns of nodal spread from surgical and pathologic series, it is possible
to individualize RT volumes depending upon the site of the primary tumor in the stomach. Tumors
arising from the proximal stomach and GE junction have a higher propensity to spread to
pericardial and paraoesophageal nodes but a lower propensity to spread to pancreaticoduodenal
nodes and nodes in the region of the pyloris and porta hepatitis (~10%). Tumors arising from the
body of the stomach can spread to all nodal sites but have the highest likelihood of spreading to
nodes along the greater and lesser curvature near the location of the primary tumor. Tumors arising from the distal stomach have a higher propensity to spread to pancreaticoduodenal and porta hepatis nodes but a lower propensity to spread to paraoesophageal, pericardial and splenic hilar nodes.

Table 1 outlines the nodal groups that need to be treated depending upon the site of the primary tumor in the stomach. If the tumor is found to be N0 following adequate surgical node dissection (preferably D2 dissection with at least 10-15 nodes examined), then it is optional whether or not to treat the nodal stations. In our experience, most patients will only have undergone a limited nodal dissection (D1 or less) and will therefore require treatment of nodal stations.
TROG 03.02  A feasibility study to evaluate adjuvant chemoradiotherapy for gastric cancer

Please refer to document titled: Protocol Pages 16 – 17 160103
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TROG 03.02  A feasibility study to evaluate adjuvant chemoradiotherapy for gastric cancer

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Please refer to document titled: Protocol Pages 25 – 29 160103
Please refer to document titled: Protocol Pages 25 – 29 160103
TROG 03.02   A feasibility study to evaluate adjuvant chemoradiotherapy for gastric cancer

Please refer to document titled: Protocol Pages 25 – 29 160103
Please refer to document titled: Protocol Page 30 160103
**Table 1**

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>Tumor bed</th>
<th>Nodes treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE junction</td>
<td>Medial left hemidiaphragm and adjacent body pancreas (plus any sites of adherence for T4 lesions)</td>
<td>Paraoesophageal, proximal perigastric (hepatogastric ligament), celiac</td>
</tr>
<tr>
<td>Cardia/Proximal 1/3</td>
<td>Medial left hemidiaphragm and adjacent body pancreas (plus any sites of adherence for T4 lesions)</td>
<td>Perigastric, celiac, splenic hilar, suprapancreatic.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If extensive nodal involvement (≥ 3 nodes positive), consider treating porta hepatis and pancreaticoduodenal nodes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If oesophageal involvement, treat paraoesophageal nodes.</td>
</tr>
<tr>
<td>Body/Middle 1/3</td>
<td>Body pancreas (plus any sites of adherence for T4 lesions)</td>
<td>Perigastric, celiac, splenic hilar, suprapancreatic, porta hepatis, pancreaticoduodenal, ie. all nodal groups</td>
</tr>
<tr>
<td>or multiple gastric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sites.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antrum/Distal 1/3</td>
<td>Head pancreas, 1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt; parts of duodenum (plus any sites of adherence for T4 lesions)</td>
<td>Perigastric, pancreaticoduodenal, porta hepatis, celiac, suprapancreatic.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If extensive nodal involvement, consider treating splenic hilar nodes.</td>
</tr>
</tbody>
</table>

Note: The paraaortic nodes should be included for the entire length of the CTV, from its inferior extent cranially to the aortal hiatus.

### 4.1.2.6 Generation of planning target volume (PTV)

Planning target volume is equal to the CTV and an appropriate margin for organ and setup variation as per the discretion of the clinician. We recommend a margin of 1 cm.

ie. PTV = CTV + 1 cm

In some cases, the margin may have to be greater, such as when respiratory variation causes significant superior-inferior movement of the gastric remnant.
4.1.2.7 Definition of CTV – Quick start checklist

- Determine the T-stage and nodal status of the tumor.
- Determine the location of the primary tumor in the stomach and the type of operation that has been performed ie. partial distal gastrectomy or total gastrectomy.
- Using the above information, determine from table 1 which nodal groups need to be included in the CTV.
- Determine the type and location of the anastomosis:
  - partial distal gastrectomy→gastrojejunal anastomosis in abdomen
  - total gastrectomy→oesophagojejunal anastomosis in chest
- With the help of a diagnostic radiologist, use the preoperative and diagnostic postoperative CT scans to identify the following structures and regions on the planning CT scans:
  - oesophagus and gastric remnant (if applicable)
  - anastomosis (eg. gastrojejunal, oesophagojejunal)
  - duodenal stump and duodenum down to its third part
  - hepatogastric ligament
  - porta hepatis (extrahepatic portal vein)
  - splenic hilum
  - pancreas (head and body)
  - celiac artery
  - superior mesenteric artery

  Note: not all of the above will be relevant in all cases.

- Once the appropriate structures have been identified and marked, contour the CTV by simply “joining the dots”.
- Generate the PTV by adding a margin of 1 cm in all dimensions.
4.1.3 Treatment planning and delivery (Radiation Therapist Section)

For this section: Please refer to document titled: Protocol pages 33 – 45 160103
TROG 03.02 A feasibility study to evaluate adjuvant chemoradiotherapy for gastric cancer
TROG 03.02  A feasibility study to evaluate adjuvant chemoradiotherapy for gastric cancer
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4.1.4 Radiation oncology quality control review procedure

Patients will undergo CT planning shortly after registration to the study (before or during their first cycle of induction chemotherapy).

All radiotherapy treatment plans will be sent to the Trial centre for review by a subgroup of radiation oncologists to be designated by the Trial Chairperson. For each participating centre, the first 3 treatment plans will be reviewed in “real time” (preferably 3-4 weeks before radiotherapy is to begin, to allow any adjustments to be made). Approval of the first 3 plans must be obtained prior to the patient starting radiotherapy. After the first 3 treatment plans have been reviewed, subsequent plans will not need to be reviewed in “real time”, unless there have been major protocol violations detected. If major protocol violations have been detected, the subgroup will continue to review all plans in “real time”, until a total of 3 treatment plans have been assessed which show no major deviations.

The following are required for the RT review process:

1) Axial CT images as listed below that show both anatomy with CTV, as well as dosimetry (ie. isodoses and CTV overlaid on CT slices) (see diagram below). At least one slice MUST include the measurement scale for the CT images.
   - Effective Central Axis of Upper Section plan (ECAUS), in percentage, or Gy.
   - 1/2 way between ECAUS and junction in percentage, or Gy.
   - 1/2 way between ECAUS and upper level of field in percentage, or Gy.
   - Effective Central Axis of Lower Section plan (ECALS), in percentage, or Gy.
   - 1/2 way between ECALS and junction in percentage, or Gy.
   - 1/2 way between ECALS and lower level of field in percentage, or Gy.
   - Junction level, with both upper and lower plans summed, displayed in Gy.

2) A reconstructed sagittal image at approximately midline showing PTV and dosimetry (with both upper and lower plans summed, displayed in Gy).
3) A reconstructed coronal image at the isocenter, showing PTV and dosimetry (with both upper and lower plans summed, displayed in Gy).
4) An AP digitally reconstructed radiograph (DRR) (used to assess overall shape of the entire PTV).
5) DVH for CTV, PTV, liver, right kidney, left kidney and spinal cord.
The submitted RT plans will be evaluated regarding initial compliance, and type/site of any protocol violations. The parameters that will be evaluated are: 1) coverage of the CTV (both adequacy of coverage as well as excessive coverage), and 2) dose to critical normal tissues. Submitted CT images will be reviewed to determine how closely the CTV conforms to the “ideal CTV” as detailed in the RT guidelines (ie. to confirm that the target and only the target is covered). CTV coverage of the following key anatomical structures will be assessed to score major and minor RT protocol violations:

- oesophagus and gastric remnant (if applicable)
- anastomosis (eg. gastrojejunal, oesophagojejunal)
- duodenal stump and duodenum
- hepatogastric ligament (right hepatic border)
- porta hepatis (extrahepatic portal vein)
- splenic hilum
- pancreas (head and body)
- celiac artery
- superior mesenteric artery
- aorta

CTV contouring of these key anatomical structures is described in detail in the RT guidelines (not all structures will need to be covered in all cases). We will not assess those sections of the CTV contour that are generated by “joining the dots” after contouring the above key structures, as they do not necessarily relate to any anatomical structures and will be subject to some variation. Protocol violations will be scored as follows:

- If the CTV is within 10 mm of the “ideal CTV” as described in the guidelines with regard to all of the key anatomical structures listed above (either inside or outside the “ideal CTV”), then the plan will be deemed acceptable.
- If the CTV is within 11-15mm of the “ideal CTV” with regard to any one of the key anatomical structures, then it will be scored as a minor protocol violation.
- If the CTV is more than 15mm inside or outside the “ideal CTV” with regard to any one of the key anatomical structures, then it will be scored as a major protocol violation. This category will of course include those cases that partially or totally exclude regions that should be covered in the CTV (eg. porta hepatis nodes).

The criteria for protocol violations have been arbitrarily designed so that we can record and assess QA procedures in a uniform and systematic fashion. The presence of a protocol violation does not necessarily imply that the plan is incorrect or unacceptable. We realize that some structures can be difficult to visualize on planning CT scans (eg. porta hepatis, pancreas), and this will be taken into account when assessing plans. Some plans may have more than one planning error.

Dose to critical normal tissues will be assessed by DVH analysis. If the doses exceed the recommended tolerance doses specified in the RT guidelines, this will constitute a major protocol violation.

Enquiries regarding materials to be sent for RT QA should be directed to Mr David Willis (radiation therapist PMCI). Phone: (03)96561111, E-mail: David.Willis@petermac.org.
4.2 Chemotherapy

4.2.1 Drug description, packaging and storage.

1. Cisplatin
   
   **Mechanism of action:** formation of DNA interstrand and intrastrand DNA adducts.
   
   **Chemical name:** Cis-diamminedichloroplatinum II
   
   **Composition:** Cisplatin. Mannitol BP 1 mg/mL, Sodium Chloride BP 9 mg/mL, Water for Injections BP; preservative free.
   
   **Packaging**
   
   - 10 mg /10 mL
   - 50 mg /50 mL [1]
   - 100 mg /100 mL [1]

2. Epirubicin
   
   **Mechanism of action:** Antitumor antibiotic acts by DNA intercalation.
   
   **Preparation:** Epirubicin (4'epi-doxorubicin) HCl; lactose, methyl hydroxybenzoate;
   
   **Packaging**
   
   - 2 mg /1 mL 5 mL [4]
   - 2 mg /1 mL 10 mL [4]
   - 2 mg /1 mL 25 mL [3]
   - 2 mg /1 mL 100 mL [1]

3. 5FU
   
   **Mechanism of action:** Antimetabolite, inhibits thymidylate synthase and RNA function.
   
   **Preparation:** Fluorouracil BP. Sodium Hydroxide BP (for pH adjustment), Water for Injections BP.
   
   **Packaging**
   
   - 25 mg /1 mL 10 mL [5]
   - 25 mg /1 mL 20 mL [5]
   - 25 mg /1 mL 100 mL [1]
Storage of chemotherapy agents:

<table>
<thead>
<tr>
<th>Presentation from manufacturer</th>
<th>Storage of original vial</th>
<th>Reconstitution solution</th>
<th>Storage of reconstituted product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Do NOT refrigerate</td>
<td>N/S 500ml &lt;500mcg/ml</td>
<td>Refrigerate Protect from light</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;500mcg/ml and &lt;1mg/1ml</td>
<td>Do NOT refrigerate, Protect from light</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Refrigerate</td>
<td>&lt;90mg/m² N/S 100ml;</td>
<td>Refrigerate Protect from light</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;90mg/m² N/S 250ml;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;120mg/m² N/S 500ml.</td>
<td></td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Do NOT refrigerate</td>
<td>N/S 100ml</td>
<td>Refrigerate Protect from light</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N/S 1000ml Infusion</td>
<td>Refrigerate Protect from light</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D5W 100ml</td>
<td>Refrigerate Protect from light</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50mg/ml CADD</td>
<td>Do NOT refrigerate, Protect from light</td>
</tr>
</tbody>
</table>

4.2.2 Dose definition and number of cycles (including the use of actual or ideal weight in the calculation of BSA).

1. Dose definition and number of cycles:
   ECF:
   - Epirubicin 50 mg/m² IV day 1
   - Cisplatin 60 mg/m² IV day 1
   - 5-Fluorouracil 200-mg/m²/d IV 21 day continuous infusion via a CADD through a central venous access device, i.e. PICC line.
   - 1 cycle prior to combined chemoradiotherapy (week 1), and 2 cycles post. (weeks 14 and 17).
   - The first cycle of postoperative ECF should preferably begin within 7 weeks of surgery and no later than 10 weeks after surgery.

   Infusional 5FU 225mg/m²/day throughout the entire duration of the radiotherapy via a CADD pump through a central venous access device, i.e. PICC line.

2. Dose calculation
   The body surface area will be calculated by using the actual body weight. Patients with a BSA in excess of 2.2 m² who are obese i.e. body mass index in excess of 30kg/m² will have BSA rounded off at 2.2m².
There will be no intrapatient dose escalation.

4.2.3 Technique of drug administration including premedication:

Epirubicin in 100ml sodium chloride 0.9%.
Cisplatin in 500ml sodium chloride 0.9%.
5-fluorouracil 25mg/1ml undiluted via CADD pump.

Below will serve as a guide, or otherwise local institutional protocols are to be followed.

(1) 1000ml sodium chloride 0.9% with 5ml MgSO4 49.3% (10mmol) over 2 hours.
(2) Premeds
(3) Epirubicin in 100ml sodium chloride 0.9% over 15 min.
(4) 400ml mannitol 10% over 30 minutes. If urine output >400ml give cisplatin over 1 hour, if not give:
   1000ml sodium chloride 0.9% over 2 hours + frusemide 20mg IV
(5) Cisplatin over 1 hour.
(6) 1000ml sodium chloride 0.9% with 5ml MgSO4 49.3% (10mmol) over 2 hours.
(7) 5-fluorouracil undiluted via CADD pump as continuous infusion.

Premedication:
Directly before the administration of the Epirubicin, in the sequence above, IV Dolansetron (Anzemet) (or other equivalent 5HT3 antagonist) 100mg plus Dexamethasone 16mg IV and Metaclopramide 10mg IV.

On discharge, Metaclopramide 10 mg, p.o. q6-8 hourly prn, Dolansetron 200mg. p.o. daily for 3 days and Dexamethasone 4mg p.o. daily for 3 days.

Anticoagulation:
All patients are recommended to be prescribed Warfarin 1mg p.o. daily as a prophylactic measure to maintain the patency of the central venous access device. The INR must be checked on a weekly basis and be maintained at a level of < 1.4.

4.2.4 Toxicity and grading criteria, expected effects and approximate times that these effects will be seen.

(1) Toxicity and grading criteria:
The National Cancer Institute- Common Toxicity Criteria, Version 2 will be used.

(2) Expected effects:
Cisplatin:
(a) Emesis: Acute within 24 hours and delayed within 72 hours
(b) Nephrotoxicity and magnesium wasting
(c) Neurotoxicity
(d) Ototoxicity
(e) Myleosuppression: within 10 days

Epirubicin:
(a) Emesis: within 12 hours
(b) Mucositis: within 7-10 days
(c) Alopecia: commencing from 4 weeks
(d) Myelosuppression: Within 7-10 days  
(e) Cardiomyopathy: Increased risk at a cumulative dose in excess of 900mg/m2.  
(f) Radiation recall.

Infusional 5FU:

(a) Emesis: throughout exposure  
(b) Mucositis: from 7-10 days  
(c) Diarrhea: from 7-210 days  
(d) Myelosuppression: Within 7-10 days  
(e) Hand-foot syndrome: Cumulative from 4-8 weeks.

### 4.2.5 Dose modification:

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>Dose adjustments on day of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epirubicin, Cisplatin and</strong></td>
<td>Continuous Infusion 5FU Day 8, 15</td>
</tr>
<tr>
<td><strong>Continuous Infusion 5FU</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Haematological toxicities</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>Defer 1 week until ≥ 1.5x10^9/L and reduce dose by 25%</td>
</tr>
<tr>
<td>Or</td>
<td>Defer 1 week until ≥ 1.5x10^9/L</td>
</tr>
<tr>
<td>ANC &lt;0.5x10^9/L</td>
<td>Defer 1 week until ≥ 1.5x10^9/L and reduce dose by 25%</td>
</tr>
<tr>
<td>ANC 0.5-1.0x10^9/L</td>
<td>Defer 1 week until ≥ 1.5x10^9/L</td>
</tr>
<tr>
<td>1.0x10^9/L &lt; ANC ≤ 1.5x10^9/L</td>
<td>Defer 1 week until ≥ 1.5x10^9/L and reduce dose by 25%</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td></td>
</tr>
<tr>
<td>Plt &lt; 100x10^9/L</td>
<td>Defer 1 week until ≥ 100x10^9/L and reduce dose by 25%</td>
</tr>
<tr>
<td><strong>Specific non-hematological toxicities</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Renal toxicity (cisplatin only)</strong></td>
<td>Defer treatment by 1 week, and reduce dose by 25% if recovers to ≥ 50 ml/min</td>
</tr>
<tr>
<td>On treatment day Creat clear &lt; 50 ml/min</td>
<td></td>
</tr>
<tr>
<td><strong>Other non-haematological toxicities outside the radiation field (except alopecia, or inadequately treated nausea)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Worst grade</strong></td>
<td>Cease chemotherapy</td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>Defer 1 week and reduce subsequent dose of the responsible agent by 25% if recovers to grade 1</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Defer 1 week, commence at same dose if recovers to grade 1</td>
</tr>
</tbody>
</table>
4.2.6 Procedures for monitoring patient compliance:

Patients will be reviewed on a weekly basis for chemotherapy administration and assessment of toxicities as specified by the Patient Assessment section.

4.2.7 Medical oncology quality control review procedure:

For each patient, copies of department records (ie. treatment charts/’flowsheets’) which clearly demonstrate the prescription and administration of chemotherapy drugs should be attached to the chemotherapy CRF and returned to the Coordinating Trial Centre.

The trial centre will review Case Record Forms (CRF) and the copies of chemotherapy records (‘source data’) for each patient to assess and verify compliance with the protocol. Audits will focus on delivered dose, method of administration, treatment timing and dose modifications. Any chemotherapy treatment violations will be categorised according to TROG policy (Quality Assurance Statement of Minimum Requirements for Clinical Trials). The results of audits will be reported to the TMC at least 6 monthly, and to the TROG Scientific Committee meetings biannually.
5  PATIENT ASSESSMENTS

5.1  Pretreatment evaluation

- History and examination
- Blood for FBE, urea and electrolytes, liver function tests, clotting profile
- Creatinine clearance (not required if performing GFR)
- CT scan chest, abdomen and pelvis (preoperative and postoperative)
- Renal (DMSA) scan to measure differential renal function and GFR. (This will allow assessment of baseline renal function, as part of one or both kidneys may be in the radiation fields. If abnormal function is detected eg. reduced function in one kidney, then radiation fields may need to be modified to spare more of one or both kidneys from the radiation fields)
- Dietary assessment
- Body weight

5.2  Evaluation during treatment (weekly)

- Physical examination
- Performance status assessment
- Toxicity assessment
- FBE and biochemistry
- Dietary assessment
- Body weight

5.3  Post-treatment evaluation

- Two weekly clinical review for six weeks post-treatment, including:
  - FBE and biochemistry
  - Performance status assessment
  - Toxicity assessment

5.4  Toxicity assessment

- Performance status will be assessed using ECOG criteria.
- Acute toxicities will be graded using the NCI Common Toxicity Criteria, Version 2.0. Toxicity will be scored on the basis of the worst grade experienced in the previous three days.
- Late effects occur more than three months after treatment and should be graded according to RTOG/EORTC late effects criteria.
### Table summarizing patient assessments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-treatment</th>
<th>Weekly during treatment</th>
<th>Two weekly post-treatment for 6 weeks</th>
<th>Three monthly post-treatment for 2 years</th>
<th>Six monthly post-treatment years 3 to 5&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Full blood examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Urea and electrolytes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Liver function tests</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Clotting profile</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance (not required if performing GFR)</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CT chest, abdomen, pelvis</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Renal scan (DMSA) plus GFR</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Performance status assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Dietary assessment</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Toxicity assessment</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>a</sup> Preferably both pre- and post-operative diagnostic CT scans.

<sup>b</sup> Patients will be followed for late toxicity & survival endpoints to the study close-out date.
6 SERIOUS ADVERSE EVENTS

Serious adverse events (SAE) must be reported to the Trial Centre and to the TROG Operations Office by the investigator within 24 hours of the occurrence of the event.

A serious adverse event is any event which occurs during or within 30 days of completing all protocol treatment and which:

- results in death
- is life threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- development of a new cancer
- is an overdose of radiation or study drug.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above.

For all serious adverse events, the following must be assessed and recorded on the SAE form:

- intensity/severity
- relationship to chemotherapy, radiotherapy or surgery
- action taken
- outcome to date

Please fax completed SAE form to:

Trial Centre  
Peter MacCallum Cancer Centre  
+61 (0)3 9656 1420

The Institutional Ethics Committee should also be notified of Serious Adverse Events.

On notification of a Serious Adverse Event, the Trial Centre data manager will inform the Study Chairperson and forward a copy of the SAE form to the TROG Central Operations Office.
7 ENDPOINTS

Endpoints for the acute toxicity and feasibility objectives are:

- The percentage of patients who complete the planned chemoradiation protocol.
- The percentage of major RT protocol violations, as determined by review of the pre-treatment RT plan.
- The percentage of patients who develop grade 3 or grade 4 haematological and GIT acute toxicity.

There will be monitoring of the rates of acute G3/4 haematological and GI toxicity throughout the accrual period and the trial will be stopped if these exceed specified limits.

Additional endpoints are:

- The percentage of patients who develop grade 3 or grade 4 late radiation toxicity.
- Relapse-free survival, defined as the time from the start of study treatment to the date of first evidence of relapsed disease at any site or death from any cause.
- Overall survival, defined as the time from the start of study treatment to the date of death from any cause.
8 STATISTICAL CONSIDERATIONS

8.1 Sample size determination

The target sample size will be 52 patients.

Rates of grade 3/4 haematological toxicity above 40% are unacceptable. If the true rate is 20% (the rate observed in the pilot study), with 52 patients in the study, a 95% confidence interval (CI) would lie completely below 40% with 95% probability.

Similarly, rates of grade 3 GIT toxicity above 50% are unacceptable. If the true rate is 30% (the rate observed in the pilot study), with 52 patients in the trial, a 95% CI would lie completely below 50% with 88% probability.

With 52 patients the above endpoints could be estimated with standard errors of at most 6.9%. If, for example, 13 of 52 patients (25%) develop grade 3/4 haematological toxicity, the 95% CI for the rate of grade 3/4 toxicity would be 15% – 38%.

8.2 Accrual and expected duration

The accrual rate at PMCI in the pilot study has been 40 patients in 24 months. It is feasible to open this trial to accrual for 2 years during which time it is be reasonable to expect that approximately 50 patients will be accrued.

8.3 Statistical Methods

The feasibility rate for the combined chemoradiation treatment will be estimated as a simple fraction of the number of patients completing the planned chemoradiation treatment divided by the number of patients commencing protocol treatment. A 95% two-sided confidence interval for the true rate will be calculated, estimated using the Blyth-Still-Casella method.

The rate of major RT protocol violations will be estimated by the proportion of patients having a major RT protocol violation after review of the pre-treatment plan. A 95% two-sided confidence interval for the true rate will be calculated, estimated using the Blyth-Still-Casella method.

Frequencies and percentages by grade of toxicities will be calculated for each type of acute toxicity. The percentage of patients who develop a grade 3 or 4 haematological or GIT acute toxicity will be computed together with the 95% confidence interval. Kaplan-Meier estimates of late RT toxicity rates will be calculated if feasible.

A study close-out date will be determined for the time to event analyses in order to prevent bias in the reporting of results. This will generally be taken to be the earliest of the dates of last contact for patients still alive and not lost to follow-up. The event times of patients not lost to follow-up will be censored at the close-out date if the event has not previously occurred. The Kaplan-Meier product limit method will be used to estimate relapse-free survival and overall survival. Ninety-five percent confidence intervals will be estimated for median event times using the Brookmeyer-Crowley method, and for rates using the logit transformation.
9 EARLY CLOSURE CRITERIA

Consideration will be given to stopping the trial early if:

1) The number of patients accrued within two years of activation of the trial is less than 50 patients, or

2) There is unacceptable acute toxicity:
   - grade 3/4 haematological toxicity >40%, or
   - grade 3 GIT toxicity >50%.
REFERENCES


Appendix 1 – Sample Patient Information Sheet / Consent Form

Dated: 16 January 2003

Information Sheet

A Feasibility Study to Evaluate Adjuvant Chemoradiotherapy for Gastric Cancer

Research study:

The following document may help you to understand the information already discussed by your doctor regarding your participation in a clinical research study. It may give you the opportunity to decide whether or not to participate – after knowing the possible risks and benefits of such a study. The information obtained from this study may possibly be helpful to others.

Purpose of the study:

Your doctor has explained to you that, although your stomach cancer has been surgically removed, there is still a risk that it may come back if no further treatment is given. It has been shown recently in a study conducted in the USA that giving radiotherapy and chemotherapy after surgery may improve the chances of curing your cancer. This treatment is relatively new and we are still investigating the optimal chemotherapy drugs to use and the best way to deliver the radiotherapy safely. You are invited to take part in a clinical research study to find out what effects (good and bad) chemotherapy alone followed by chemotherapy given with radiation together and then followed by more chemotherapy alone have on you and your cancer. The type of chemotherapy that is used, and the way in which the radiotherapy is delivered differs to that described in the abovementioned US study, and we believe that it is a better treatment package. The main purpose of this study is to test the safety and effectiveness of this new treatment regimen. We want to see how many patients can tolerate this treatment without severe side effects. We also want to standardize the radiotherapy for this type of cancer in Australia and New Zealand because it is a technically very difficult area to treat with radiation. This should improve the standard of care for patients receiving this treatment. We anticipate that about 50 patients will take part in this study over the next 2 years.

Study design:

If you take part in this study you will receive one cycle of chemotherapy called epirubicin, cisplatin, and 5-FU (ECF). On the first day of this treatment, you will receive epirubicin through a tube into your vein (intravenously) over approximately 1 hour. After this, you will then receive cisplatin intravenously over approximately 1 hour. Once the cisplatin has been given you will then receive intravenous 5-FU continuously for the next 21 days. Because you need to be well hydrated before receiving the cisplatin, you may need to be admitted to hospital overnight for intravenous fluids. Apart from this possible one night admission to hospital, the remainder of your chemotherapy and radiotherapy treatment is usually given as an outpatient. After this 21 day cycle of chemotherapy you will then have one week without any treatment. Following this, you will begin radiotherapy (week 5) once a day, five days a week, Monday through Friday, for 5 weeks. During your radiation, you will receive 5-FU continuously through a tube in your vein. The 5-FU will be given continuously, 7 days a week, for the full 5 weeks of radiation. Four weeks after
completing the radiotherapy you will then receive 2 further cycles of ECF chemotherapy which are exactly the same as the first cycle. The entire treatment package will take 20 weeks or approximately 5 months to deliver. If you take part in this study, you will have the following tests and procedures:

**Prior to start of treatment:**
- History and physical examination
- Blood tests for blood counts, liver and kidney function
- CT scan chest, abdomen and pelvis
- A kidney scan called a “renal scan” to look at the function of both kidneys
- Assessment of nutritional status
- Body weight

**During treatment (weekly):**
- Physical examination
- Blood tests for blood counts, liver and kidney function
- Dietary assessment
- Body weight

**At completion of treatment:**
Every 2 weeks for the first 6 weeks after treatment:
- Physical examination
- Blood tests for blood counts, liver and kidney function

Then every 3 months:
- Physical examination
- Additional blood tests and “X-rays” may be done if indicated by your doctor

**Possible Risks and Benefits:**

- Treatments (drugs, therapies) for a number of illnesses often carry side effects. Side effects can be both short term and long term.

**Side effects associated with radiation therapy to the stomach**
Radiotherapy may cause reddening or tanning of the skin, hair loss in the treatment area, nausea, vomiting, loss of appetite, weight loss, and weakness. Kidney damage or liver damage may occur if the kidney or liver is in the same field of radiation.

**Very likely:**
- Nausea and/or vomiting
- Weakness and fatigue
- Loss of appetite
- Weight loss
- Reddening or tanning of the skin
- Hair loss in the treatment area

**Less likely, but serious:**
- Kidney damage - decreasing the kidneys’ ability to handle the body’s waste which may be permanent;
- Liver damage - decreasing the liver’s ability to handle the body’s waste which may be permanent;
Damage to the small bowel eg causing bowel obstruction.

**Side effects associated with epirubicin**

*Very likely:*
- Nausea and/or vomiting
- Mouth sores
- Hair loss which is temporary
- Decrease in blood counts which can lead to a risk of infection and bleeding

*Less likely, but serious:*
- Damage to the muscles of the heart

**Side effects associated with cisplatin**

*Very likely:*
- Decrease in blood counts which can lead to a risk of infection and bleeding
- Loss of appetite and/or taste; metallic taste in your mouth
- Nausea and/or vomiting
- Fatigue
- Hearing loss or ringing in the ears
- Numbness or tingling in the hands or feet

*Less likely:*
- Muscle cramps or spasm
- Loss of coordination
- Involuntary movements or shaking

*Less likely, but serious:*
- Loss of muscle or nerve function which may cause weakness or numbness in your hands and feet
- Facial swelling
- Decreasing ability of the kidneys to handle the body’s waste which may be permanent
- Allergic reactions which can cause difficulty in breathing, fast heartbeat, and sweating
- Decrease in liver function
- Other cancer called acute leukemia

**Side effects associated with 5-FU**

*Very likely:*
- Decrease in blood counts which can lead to a risk of infection and bleeding
- Loss of appetite
- Nausea and/or vomiting
- Diarrhea with cramping or bleeding
- Skin rash
- Fatigue
- Headaches
- Hair loss which is temporary
- Mouth sores
- Sore throat
Less likely:
- Confusion
- Inflammation of the fingers and toes
- Increased sensitivity to sunlight
- Darkening of the skin, nails, or veins
- Loss of coordination or balance
- Inflammation of the veins
- Loss of coordination

Less likely, but serious:
- Chest pain that may be associated with damage to the heart

Reproductive risks
Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.

While receiving treatment you will be reviewed regularly by your doctor. During chemotherapy you will be seen each week by the medical oncologist to assess any side effects of treatment and to monitor your nutritional status and weight. You will also have weekly blood tests to monitor your blood counts, as well as kidney and liver function. While you are receiving radiotherapy, you will also be seen weekly by the radiation oncologist to assess any side effects of treatment. Your doctor may prescribe medication to keep these side effects under control. Most of the side effects from chemotherapy and radiotherapy should subside 3 to 4 weeks after completing treatment. However, symptoms of tiredness and fatigue may persist for several months and your weight may take several months to return to normal.

It is not possible to predict if any personal benefit will result from this treatment. The possible benefit of this treatment is to reduce the chances of your cancer coming back, and therefore improving the likelihood of curing your cancer, though there is no guarantee of this. We hope the information learned from this study will benefit other patients with stomach cancer in the future.

Do you need to take part?:

You do not need to take part in this study unless you want to. If you agree to enter this study you will be asked to sign a consent form. You may however withdraw your consent at any time without giving a reason. Your decision will in no way affect the quality of the treatment you will receive. Your doctor may decide you should stop if the treatment is causing intolerable side effects, for example, severe nausea and vomiting which does not respond to medication.

Your doctor will discuss other treatments that may be available if you do not wish to take part in the study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; or (3) no treatment except medications to make you feel better. With the latter choice, your tumor may continue to grow. These treatments could be given either alone or in combination with each other. If any new information becomes available during the study that is relevant to your treatment you will be informed.

Confidentiality:
The information to be collected in this study will be kept for at least 15 years in the Department of Radiation Oncology at .......... Hospital under lock and key and computer password protection. It may be released in confidence to investigators from other participating centres, with the understanding that this information will be used only in connection with carrying out our obligations relating to this trial. Access will be by permission of the trial management committee only. The results of the study may be published in the medical literature, however your identity will not be revealed.

Contact Persons:

If at any time, you have questions about the study, please feel free to contact:

Dr ........................... (tel:....................) Radiation Oncologist

..............................(tel:....................).Data Manager
I agree to participate in the above named clinical research study and give my consent freely. I understand that the study will be carried out as described in the information statement, a copy of which I have retained. I realise that whether or not I decide to participate, my decision will not affect my further medical treatment. I also realise that I may withdraw from the study at any time and do not have to give any reasons for doing so. I have had all my questions answered to my satisfaction. I agree to the publishing of the results of the study provided my identity is not revealed. I consent to the access of my medical records by authorised persons for the purpose of verification of clinical trial procedures and data.

Name of Patient ________________________________________________

Signature of Patient ________________________________ Date: _________

I, (investigator’s name)______________________________ have explained the

nature and purpose of the study to the patient

Signature of Investigator______________________________ Date: _________