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Australia and New Zealand Horizon Scanning Network

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AN INITIATIVE OF THE NATIONAL, STATE AND
TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

Perioperative epirubicin, cisplatin and 5- fluorouracil chemotherapy for resectable gastric cancer

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ASERNIP/S

**Australian
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Register
of New
Interventional
Procedures -
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PRIORITISING SUMMARY

REGISTER ID: S000044

NAME OF TECHNOLOGY: PERIOPERATIVE EPIRUBICIN, CISPLATIN AND 5-FLUOROURACIL CHEMOTHERAPY

PURPOSE AND TARGET GROUP: PATIENTS WITH RESECTABLE GASTRIC CANCER

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- | | |
|--|---|
| <input type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input checked="" type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- | | | |
|--|-------------|-----|
| <input type="checkbox"/> Yes | ARTG number | N/A |
| <input type="checkbox"/> No | | |
| <input checked="" type="checkbox"/> Not applicable | | |

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
Australia	✓		
Brazil	✓		
Germany	✓		
Netherlands	✓		
New Zealand	✓		
Singapore	✓		
United Kingdom	✓		

IMPACT SUMMARY:

Perioperative chemotherapeutic treatment in patients with operable, potentially curable gastric cancer using the ECF combination regimen is aimed at improving patient outcomes. This method of perioperative chemotherapeutic treatment is currently in the experimental stage in Australia.

BACKGROUND

Gastric cancer, or stomach cancer, is a serious condition in which patients diagnosed with the conditions often have a poor prognosis and low long term survival rates.

Early stage gastric cancer is often asymptomatic (Hassan 2006). As a result, patients are usually diagnosed once advanced¹ gastric cancer has developed (Hassan 2006). This constitutes approximately 84% of patients diagnosed with gastric cancer (Rivera et al. 2007). Patients diagnosed with advanced gastric cancer often experience epigastric pain, bloating, early satiety, nausea, vomiting, dysphagia, anorexia, weight loss and upper gastrointestinal bleeding (Hassan 2006).

Surgical treatment of gastric cancer is currently the only treatment method which offers curative potential to patients with locally (limited to mucosa and sub-mucosa) advanced gastric cancer (Findlay et al. 2007). Surgical treatment may involve total gastrectomy, oesophagogastrectomy (for tumours of the cardia and gastroesophageal junction), or a subtotal gastrectomy (for tumours of the distal stomach) (Mehta and Fisher 2004). Unfortunately in up to 60% of patients who undergo surgical resection of gastric cancer, relapse of the disease will occur (Rivera et al. 2007).

In addition to surgical treatment, radiotherapy and chemotherapy are also used in the treatment of gastric cancer. Radiotherapy has been used in combination with surgery and chemotherapy or in combination with chemotherapy for palliative purposes. Similarly, chemotherapy has been traditionally used for palliative purposes to reduce tumour size and improve survival times (Rivera et al. 2007).

There are currently many single agent and combination chemotherapy regimens available for the treatment of gastric cancer (Alberts et al. 2003). Of the many available agents, the drug 5-fluorouracil is one of the most widely used, and forms the basis of several combination chemotherapy regimens (Alberts et al. 2003). The combination regimen of epirubicin, cisplatin and 5-fluorouracil (ECF) has been documented as being superior to other combination regimens in terms of survival, quality of life and objective response rates for the treatment of gastric cancer (Rivera et al. 2007). As a result, the ECF regimen is currently considered by many European oncologists as standard chemotherapeutic treatment for gastric cancer (Rivera et al. 2007). In the United States however, due to epirubicin toxicity concerns, the cisplatin, 5-fluorouracil regimen is considered standard treatment (Rivera et al. 2007).

The method of administration of the ECF regimen may significantly impact patient outcomes. Pre-operative administration of ECF may provide the potential benefits of increased likelihood of curative resection by down-staging the tumour, eliminating micro-metastases and improving tumour-related symptoms (Cunningham et al 2006). Post-operative administration of the ECF regimen may destroy remaining cancerous cells following surgical resection (Cunningham et al. 2006).

¹ Advanced gastric cancer: refers to gastric cancer which is locally advanced, metastatic or relapsed. Advanced gastric cancer is considered to be in-operable.

Although the role of pre-operative and post-operative ECF administration in gastric patients has been previously reported, perioperative administration (pre- and post-operatively) of the ECF regimen is a relatively new administration method. The technique aims to improve outcomes in patients with operable gastric cancer. The technique also has the potential to convert previously inoperable gastric cancer into operable gastric cancer, thus offering the patient the possibility of improved survival.

CLINICAL NEED AND BURDEN OF DISEASE

Internationally, gastric cancer is the second most common type of cancer (Rivera et al. 2007). In Australia and New Zealand, the estimated five year survival rate for gastric cancer is 29% (Parkin et al. 1999).

In Australia, in 2001 there were 1902 new cases of stomach cancer reported (AIHW 2005). Additionally, in 2001, there were 1209 deaths (3.3% of all cancer deaths) in Australia attributed to gastric cancer (AIHW 2005).

DIFFUSION

Perioperative chemotherapeutic treatment with the ECF regimen is currently in the investigational stage in Australia and around the world.

COMPARATORS

At the time of writing no other chemotherapeutic perioperative treatment regimens currently used in the treatment of gastric cancer were identified.

SAFETY AND EFFECTIVENESS ISSUES

Cunningham et al. (2006) reported the results of a large multi-centre trial (MAGIC trial) in which perioperative ECF chemotherapy was compared to surgery alone. The study included 503 patients with locally advanced adenocarcinoma of the stomach or lower third of the oesophagus (with no evidence of distant metastases), or locally advanced inoperable disease and World Health Organisation performance status² of 0 or 1. Patients were randomised to perioperative chemotherapy and surgical resection (perioperative-chemotherapy group, n = 250) or surgical resection alone (surgery group, n = 253). The site of tumour location is shown in Table 1.

² WHO performance status: performance status of 0 indicates asymptomatic, performance status of 1 indicates symptomatic but fully ambulatory.

Table 1: Site of tumour

Site of tumour	Perioperative chemotherapy group, number (%)	Surgery only group, number (%)
Stomach	185 (74.0)	187 (73.9)
Lower oesophagus	37 (14.8)	36 (14.2)
Oesophagogastric junction	28 (11.2)	30 (11.9)

The chemotherapy regimen consisted of three pre- and three post-operative cycles. Each three week cycle consisted of epirubicin (50 mg/m²) by intravenous bolus on day 1, cisplatin (60 mg/m²) intravenously with hydration on day 1, and 5-fluorouracil (200 mg/m²) daily for 21 days by continuous intravenous infusion. Surgery was scheduled to take place within six weeks following randomisation of the surgery group and between three and six weeks following completion of the third cycle in the perioperative-chemotherapy group. Recommencement of post-operative chemotherapy was scheduled between six and 12 weeks after surgery.

Preoperative data was not available for four patients in the perioperative-chemotherapy group. Additionally, nine patients did not begin chemotherapy for a variety of reasons including patient request (n = 5), reassessment as inoperable (n = 1), patient deterioration (n = 1), need for immediate surgery (n = 1) and problems with the 5-fluorouracil catheter. Therefore, 237 patients in the perioperative-chemotherapy group began treatment. However, only 215 of these completed the three cycles. Reasons for not completing the cycles included toxic effects (n = 12), patient request (n = 3), problems with 5-fluorouracil catheter (n = 3), early cancer related death (n = 2) and other unspecified reasons (n = 2).

In total, 229 (91.6%) of the 250 patients originally randomised to the perioperative-chemotherapy group, including 208 patients who completed pre-operative chemotherapy (seven patients did not undergo surgery for un-stated reasons) and 21 patients who did not complete pre-operative chemotherapy, proceeded to surgery. This compared to 244 (96.4%) surgery group patients who underwent surgery. The reasons for the failure of nine surgery group patients to proceed to surgery were not stated. The type of surgery performed and the pathological tumour stage and nodal status are shown in Table 2.

Table 2: Operations performed

Operation performed	Perioperative chemotherapy group, n (%)	Surgery group, n (%)
Esophagogastrectomy	58 (26.5%)	52 (21.8%)
D1 distal resection	19 (8.7%)	30 (12.6%)
D1 total resection	20 (9.1%)	20 (8.4%)
D2 distal resection	32 (14.6%)	24 (10.1%)
D2 total resection	61 (27.9%)	72 (30.3%)
Non resectional surgery	29 (13.2%)	40 (16.8%)
Unknown	10 (4.4%)	6 (2.5%)

Note: D1 indicates limited lymph node dissection, D2 indicates extended lymph node dissection

Of the 209 perioperative-chemotherapy group patients who completed pre-operative chemotherapy (including one patient who only received one pre-operative cycle), 137 (65.6%) subsequently recommenced post-operative chemotherapy and 104 completed the three scheduled post-operative cycles. Reasons for not recommencing postoperative chemotherapy after completion of first three cycles were disease progression or early death (n = 37), patient choice (n = 11), post-operative complications (n = 10), problems with the 5-fluorouracil catheter (n = 10), previous toxic effects (n = 3), lack of response to preoperative treatment (n = 2) and worsening of co-existing disease (n = 2). Therefore, 104 out of 250 patients (41.6%) randomised to the perioperative-chemotherapy group, completed post-operative chemotherapy and 103 out of 208 patients (49.5%) who completed preoperative chemotherapy and surgery also completed postoperative treatment.

Out of the 237 patients in the perioperative-chemotherapy group who began treatment, four died within 60 days after commencing treatment (two due to cancer, two due to cardiac problems).

Following surgery, no clinically significant increases in the incidence of grade three or grade four toxic effects associated with chemotherapy were reported.

The surgery outcomes for all randomised patients are reported in Table 3. Resection was considered curative by the operative surgeon in 69.3% of patients in the perioperative-chemotherapy group and in 66.4% of patients in the surgery group. When only patients who had undergone radical surgery were analysed, a higher proportion of resections were considered curative in the perioperative-chemotherapy group, 169/213 patients (79.3%) in the perioperative-chemotherapy group and 166/236 patients (70.3%) in the surgery group (p = 0.03).

Table 3: Surgery outcomes

Extent of resection	Perioperative chemotherapy group, n (%)	Surgery group, n (%)
Curative	169 (69.3%)	166 (66.4%)
Palliative	44 (18.0%)	70 (28.0%)
Opinion not specified	16 (6.6%)	8 (3.2%)
No surgery	15 (6.1%)	6 (2.4%)
Surgical status not known	6 (2.4%)	3 (1.2%)

The incidence of post-operative complications was similar in both groups (45.7% in perioperative-chemotherapy, 45.3% in surgery group), as were the number of deaths within 30 days (14 and 15, respectively) and median hospital stay (13 days in both groups).

At baseline, the median maximum tumour diameter was 5.0 cm in both groups. Following treatment, the median diameter of the resected tumour was significantly

smaller in the perioperative-chemotherapy group than in the surgery group (3 cm vs. 5 cm, $p < 0.001$).

Among patients undergoing resection, at operation, there was a significantly greater proportion of stage T1 and T2 tumours in the 172 perioperative-chemotherapy group patients in whom pathology reports were performed than in the 193 surgery group patients in whom pathology reports were performed (51.7% vs. 36.8%, $p = 0.002$) (Table 4). Nodal status was reported in 135 perioperative-chemotherapy group patients and 156 surgery group patients. A significantly less advanced nodal disease among patients with gastric cancer (i.e. N0 or N1) was observed in the perioperative-chemotherapy group (84.4% versus 70.5%, $p = 0.01$).

Table 4: Tumour stage and nodal disease outcomes

Pathology reports	Perioperative chemotherapy group, n (%)	Surgery group, n (%)
Tumour stage		
T1	27 (15.7%)	16 (8.3%)
T2	62 (36%)	55 (28.5%)
T3	75 (43.6%)	106 (54.9%)
T4	8 (4.7%)	16 (8.3%)
Nodal status		
N0	42 (31.1%)	42 (26.9%)
N1 (<7 nodes involved)	72 (53.3%)	68 (43.6%)
N2 (7–14 nodes involved)	19 (14.1%)	34 (21.8%)
N3 (>14 nodes involved)	2 (1.5%)	12 (7.7%)

At the time of analysis, the median follow-up in the patients randomised to the perioperative-chemotherapy group was 49 months and 47 months in the patients randomised to the surgery group. By this time 90% of patients had died or were followed up for more than two years. There were 17 perioperative-chemotherapy patients and 35 surgery group patients who were alive with less than two years follow-up. Local recurrence was confirmed in 36 out of 250 patients (14.4%) randomised to the perioperative-chemotherapy group and 52 patients (20.6%) in the surgery group, with distant metastases in 61 patients (24.4%) and 93 patients (36.8%) respectively.

Overall, 319 patients died (149 in the perioperative-chemotherapy group and 170 in the surgery group) and 353 patients had disease progression or died (163, and 190 respectively). Compared with the surgery group, patients randomised to the perioperative-chemotherapy group had a significantly higher likelihood of progression free survival (hazard ratio for progression, 0.66; 95% CI, 0.53 to 0.81; $p = 0.001$) and of overall survival (hazard ratio for death, 0.75; 95% CI, 0.60 to 0.93; $p = 0.009$). There was no indication of heterogeneity of treatment effect according to the site of primary tumour, age group, sex or WHO performance status.

Findlay and colleagues reported the results of an Australasian feasibility study based on the MAGIC trial (Findlay et al. 2007). The study included 59 patients with locally advanced, operable gastric or cardioesophageal adenocarcinoma, in generally good condition (WHO patient performance status 0-1). The site of tumours is presented in Table 5.

Table 5: Site of tumour

Site of tumour	Number of patients (%)
Oesophagogastric junction	17 (30)
Upper third	9 (16)
Middle third	9 (16)
Antrum	16 (28)
Pylorus	6 (10)

Patients received a pre-operative ECF regimen of daily 5-fluorouracil (200 mg/m²) by continuous infusion for nine weeks, epirubicin (50 mg/mg²) intravenous bolus on day one every three weeks for three cycles and cisplatin (60 mg/m²) on day one every three weeks with hydration for three cycles. The scheduled post-operative ECF regimen was identical to the pre-operative regimen.

Patients were scheduled to undergo surgery between four and 12 weeks from the end of the third cycle of chemotherapy, with post-operative commencing between four and 12 weeks after surgery.

Grade three or four chemotherapy toxicities were evaluated both for their effect on participants and their effect on surgical complications. Pre- and post-operative chemotherapy related toxicities are presented in Table 6. During pre-operative treatment the most common grade three or four toxicities reported were neutropenia, lymphocytopenia, anaemia and, nausea and vomiting. In those patients recommencing chemotherapy, the incidence of grade three or four toxicity was similar to that for the preoperative phase.

Table 6: Pre- and post-operative grade 3 and 4 toxicities

Type of toxicity	Pre-operative (n=57), n (%)	Post-operative (n=28), n (%)
Neutropenia	12 (21)	5 (18)
Lymphocytopenia	15 (26)	4 (14)
Anaemia	10 (18)	0 (0)
Nausea and vomiting	7 (12)	4 (14)
Infection	4 (7)	0 (0)
Diarrhoea	2 (4)	1 (4)
Alopecia	3 (5)	1 (4)
Other toxicity	0	1 (4)

One death was reported in the pre-operative period. The death was attributed to a cardiac cause (possibly chemotherapy related). Myocardial infarction during the third cycle was reported in another patient while liver metastases were detected in another patient following completion of pre-operative ECF. Surgery was cancelled in this patient.

Fifty-five patients proceeded to surgery, of which 40 (73%) had what appeared to be curative resection. Four patients (7%) did not undergo resection, one (2%) was not evaluable and 10 (18%) underwent resection with gross residual disease (palliative surgery). The operation performed was determined by the site of the tumour and included 27 D2 (extended lymph node dissection), 13 D1 (limited lymph node dissection) and two D0 (no systemic lymph node dissection) operations.

Following surgery, complete response (disappearance of disease) was reported in two patients (4%). The tumour stage of the remaining patients after surgery was as follows: eight patients T1 (15%), 19 patients T2 (35%), 20 patients T3 (37%) and five patients T4 (9%).

Regional lymph node analysis following surgery was as follows: 22 patients N0 (42%), 22 patients N1 (42%), six patients N2 (12%) and two patients N3 (4%).

Surgery safety was evaluated by the rate of complications. Of the 40 patients with apparent curative resections, 16 (40%) experienced complications. This included two deaths (due to anastomotic leak and sepsis). Ten of these patients experienced one complication only (including wound, anastomotic leak, pneumothorax, significant persistent fatigue, subphrenic abscess, chest infection, abdominal fistula and confusion/delirium). Four patients experienced two complications (including anaemia/emphysema, wound infection/abdominal pain, wound infection/wound dehiscence, and respiratory failure/chest infection). One patient experienced three complications (chest infection, wound infection and residual motor neuron muscular blockade). One patient had eight complications (haemorrhage, chest infection, wound infection, epileptic fits, anorexia, nausea, vomiting and confusion).

Only 27 patients recommenced post-operative chemotherapy. Reasons for not recommending included death (n = 2), lack of efficacy (n = 11), unacceptable toxicity (n = 4), patient request (n = 3), postoperative complications (n = 3), motor vehicle accident (n = 1), colon cancer diagnosis (n = 1) and unknown (n = 3). Twenty-one of the 27 patients recommencing chemotherapy (78%) completed the full course. This translated to 21/57 (37%) of the original patients completing the full six cycles of chemotherapy.

At the last analysis, 33 patients (58%) had died (29 from tumour, three from other causes and one from unknown causes), two patients (3%) were alive with disease and 22 (39%) were alive without disease. Three patients died without relapse and 14 (25%) had persistent disease, all of whom subsequently died.

The median follow-up was 46 months (range: 1 to 73 months). The median survival was 22 months, and the median progression free survival (time from registration to first evidence of disease progression or death) was 19.6 months.

According to the authors of this study, perioperative ECF chemotherapy did not increase the surgical morbidity or mortality of patients over accepted rates found in the literature.

COST IMPACT

Perioperative ECF chemotherapy is currently under investigation. The literature search conducted did not reveal the cost of the treatment.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

No issues were identified from the retrieved material.

OTHER ISSUES No issues were identified from the retrieved material.

SUMMARY OF FINDINGS The available evidence on perioperative ECF chemotherapy for resectable cancer demonstrates that while the most patients who receive perioperative chemotherapy are able to complete the pre-operative schedule (86% in Cunningham et al. 2006, 93.2% in Findlay et al. 2007), a much smaller portion of patients are able to recommence post-operative chemotherapy (54.8% in Cunningham et al. 2006, 45.8% in Findlay et al. 2007). Even fewer patients are able to complete the post-operative chemotherapy (41.6% in Cunningham et al. 2006, 35.6% in Findlay et al. 2007). Therefore it appears that only a small proportion of patients who receive perioperative ECF chemotherapy and surgery may actually survive the complete chemotherapy regimen. In terms of effectiveness, further randomised controlled studies are required to determine the true effectiveness of perioperative ECF chemotherapy relative to conventional post-operative chemotherapy.

HEALTHPACT ACTION:

Perioperative ECF chemotherapy will be archived considering the lack of evidence currently available.

NUMBER OF STUDIES INCLUDED

Total number of studies	2
Level II evidence	1
Level IV evidence	1

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SEARCH CRITERIA TO BE USED:

Gastric cancer
Stomach cancer
ECF
Chemotherapy
Perioperative
Epirubicin
Cisplatin
5-fluorouracil