Evidence-Based Series 2-14 Version 3 ARCHIVED 2018

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Neoadjuvant or Adjuvant Therapy for Resectable Gastric Cancer

Gastrointestinal Cancer Disease Site Group

Report Date: April 5, 2011

An assessment conducted in December 2018 ARCHIVED Evidence based Series (EBS) 2-14 Version 3. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 2-14 Version 3 is comprised of 3 sections. You can access the full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/351

Section 1: Updated Guideline Recommendations
Section 2A: Updated Evidentiary Base 2011
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Section 3: EBS Development Methods and External Review Process

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Earle CC, Maroun J, Zuraw L; Cancer Care Ontario Practice Guidelines Initiative Gastrointestinal Cancer

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Disease Site Group. Neoadjuvant or adjuvant therapy for resectable gastric cancer? A practice guideline. Can J Surg. 2002;45(6):438-46.

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Evidence-Based Series 2-14 Version 3.2011: Section 1

Neoadjuvant or Adjuvant Therapy for Resectable Gastric Cancer: Updated Guideline Recommendations

G. Knight, C.C. Earle, R. Cosby, N. Coburn, Y. Youssef, K. Spithoff, R. Malthaner, R.K.S. Wong, and the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: April 5, 2011

The guideline recommendations contained in Section 1 of this Evidence-based Series replace recommendations in previous versions of Guideline 2-14. These updated recommendations are based on a new systematic review of the relevant data from January 2002 to June 2010 (Section 2A) plus the original evidence up to January 2002 (Section 2B).

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QUESTION

Should patients with resectable gastric cancer (Stage 1B [invasion of the muscularis propria] and above) receive neoadjuvant or adjuvant therapy in addition to surgery? Outcomes of interest are overall survival (OS), disease-free survival (DFS), and adverse events.

TARGET POPULATION

These recommendations apply to adult patients with potentially curable, surgically resectable (Stage 1B [invasion of the muscularis propria] and above) gastric cancer.

INTENDED USERS

These guidelines are intended for use by clinicians and healthcare providers involved in the management and referral of patients with resectable gastric cancer.

RECOMMENDATIONS

- Postoperative 5-fluorouracil (5-FU)-based chemoradiotherapy (CRT) based on the Macdonald approach (1) (Section 2A, Appendix 6) or perioperative epirubicin/cisplatin/5-FU (ECF) chemotherapy based on the Cunningham/Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) approach (2) (Section 2A, Appendix 6) are both acceptable standards of care. Choice of treatment should be made on a case-by-case basis.

- Adjuvant chemotherapy is a reasonable option for those patients for whom the Macdonald (1) and MAGIC (2) protocols are contraindicated.

- Patients with resectable gastric cancer should undergo a pre-treatment multidisciplinary assessment to determine the best plan of care. In addition to surgery, all patients should be considered for neoadjuvant and/or adjuvant therapy.

KEY EVIDENCE

- Two secondary analyses of the Southwestern Oncology Group (SWOG)/Intergroup trial (1) were identified that reported updated survival data (3,4). These results are consistent with earlier data reported in Section 2B of this report. Updated results from Hundahl (3) indicated a median survival of 36 months for patients who received postoperative chemoradiotherapy (5-FU/Leucovorin) versus (vs.) 27 months for patients who underwent surgery alone (p=0.003). Relapse-free survival was 30 months vs. 19 months (p<0.001). A further update of this trial (4) demonstrates that the original SWOG/Intergroup trial results reported in 2001 are robust with almost identical results, even with more than 11 years of follow-up for both OS (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.63 to 0.92; p=0.005) and DFS (HR, 0.66; 95% CI, 0.55 to 0.80; p<0.001), favouring postoperative CRT over surgery alone.
- The MAGIC trial (2) is the largest trial incorporating preoperative therapy to date and the only randomized trial with a perioperative approach. A significant benefit for perioperative ECF was reported for overall survival (HR, 0.75; 95% CI, 0.60 to 0.93; p=0.009) and progression-free survival (PFS) (HR, 0.66; 95% CI, 0.53 to 0.81; p<0.001).
- A meta-analysis by Fiorica (5) of five trials that provided 3-year mortality data indicated a non-significant benefit for postoperative chemoradiotherapy over surgery (odds ratio [OR], 0.79; 95% CI, 0.59 to 1.05; p=0.10). However, the meta-analysis of three trials that provided 5-year mortality data indicated a significant benefit for postoperative CRT over surgery (OR, 0.45; 95% CI, 0.32 to 0.64; p<0.00001).
- An individual patient data meta-analysis by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group (6) found a modest advantage for postoperative chemotherapy for OS (HR, 0.82; 95% CI, 0.76 to 0.90; p<0.001) and for DFS (HR, 0.82; 95% CI, 0.75 to 0.90; p<0.001).

QUALIFYING STATEMENTS

- The Macdonald (1) and MAGIC (2) protocols have never been compared to each other in a single trial to determine if one is superior to the other.
- The mix of tumour sites in the Macdonald (1) and MAGIC (2) protocols were not the same. In the MAGIC trial (2), 74% of participants had a stomach tumour, 11.5% had a gastroesophageal junction (GEJ) tumour, and 14.5% had a lower esophageal tumour. In the Macdonald (1) trial, most participants had a tumour in the distal stomach. However, approximately 20% of participants had lesions present in the GEJ. There were no espophageal tumours.

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- The Boige et al. (7) study comparing preoperative 5-FU/cisplatin vs. surgery alone demonstrated a significant improvement in OS and DFS with preoperative chemotherapy. Since these data are currently only available in abstract form, the Gastrointestinal Disease Site Group (Gastrointestinal DSG) does not recommend this treatment at this time. However, should these stated benefits be maintained when published in full and there are no material differences in reported toxicities, the DSG would consider recommending the Boige protocol in patients with resectable gastric cancer.
- Technical considerations pertaining to the delivery of radiation therapy are provided in the Discussion in Section 2A of this report.

COMPARISON FROM PREVIOUS GUIDELINE RECOMMENDATIONS

- The Macdonald (1) approach of postoperative chemoradiation continues to be recommended.
- Perioperative ECF chemotherapy based on the MAGIC protocol is now currently recommended, whereas in the previous version (Version 2) there was insufficient evidence to recommend a particular regimen.
- Adjuvant chemotherapy continues to be an option for those for whom the main recommended treatments options (i.e., the Macdonald or MAGIC protocols) are contraindicated.

FUTURE RESEARCH

Future trials should examine new molecular targets in patients with gastric cancer to account for the genetic and molecular variation in this disease. In addition, given the results of S-1 trials in Asia as well as the improved safety profile of S-1 in the First-Line Advanced Gastric Cancer Study (FLAGS) trial in advanced gastric cancer (8), a trial of S-1 in the neoadjuvant and adjuvant setting in North America may be warranted. Finally, a trial of neoadjuvant chemoradiation would be helpful.

RELATED GUIDELINES

- PEBC Evidence-based Series #2-26: *Chemotherapy for Advanced Gastric Cancer* (available from: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=75973)

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REFERENCES

1. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725-30.
2. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.
3. Hundahl SA, Macdonald JS, Benedetti J, Fitzsimmons T, Southwest Oncology G, the Gastric Intergroup. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. Ann Surg Oncol. 2002;9(3):278-86.
4. Macdonald JS, Benedetti J, Smalley S, Haller D, Hundahl S, Jessup J, et al. Chemoradiation of resected gastric cancer: A 10-year follow-up of the phase III trial INT0116 (SWOG 9008). J Clin Oncol. 2009;27(15 Suppl):4515.
5. Fiorica F, Cartei F, Enea M, Licata A, Cabibbo G, Carau B, et al. The impact of radiotherapy on survival in resectable gastric carcinoma: a meta-analysis of literature data. Cancer Treat Rev. 2007;33(8):729-40.
6. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group. Benefit of adjuvant chemotherapy for resectable gastric cancer: A meta-analysis. J Am Med Assoc. 2010;303:1729-37.
7. Boige V, Pignon J, Saint-Aubert B, Lasser P, Conroy T, Bouche O, et al. Final results of a randomized trial comparing preoperative 5-flourouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703. J Clin Oncol. 2007;25(18 Suppl):4510.
8. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010;28(9):1547-53.

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Evidence-Based Series 2-14 Version 3.2011: Section 2A

Neoadjuvant or Adjuvant Therapy for Resectable Gastric Cancer: Updated Evidentiary Base 2011

G. Knight, C.C. Earle, R. Cosby, N. Coburn, Y. Youssef, K.Spithoff, R. Malthaner, R.K.S. Wong, and the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: April 5, 2011

Section 2A of this Evidence-based Series contains a systematic review of the relevant evidence from January 2002 to June 2010. A review of the original evidence up to January 2002 can be found in Section 2B

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QUESTION

Should patients with resectable gastric cancer (Stage 1B [invasion of the muscularis propria] and above) receive neoadjuvant or adjuvant therapy in addition to surgery? Outcomes of interest are overall survival (OS), disease-free survival (DFS), and adverse events.

INTRODUCTION

Although the incidence and mortality of gastric cancer has been steadily decreasing in Canadian men and women, this disease remains a global health problem, accounting for 10% of all new cancer cases and 12% of all cancer deaths worldwide (1). In Canada, the annual percent change in age-standardized incidence between 1996 and 2005 is -2.3% and -1.9% in males and females, respectively. The corresponding numbers for the change in age-standardized mortality between 1995 and 2004 is -3.6% and -3.1% for males and females, respectively (2). In Ontario in 2009, there will be an estimated 1090 new incident cases of stomach cancer (38% of new incident stomach cancer cases in Canada) and 670 deaths from stomach cancer (36% of stomach cancer deaths in Canada). The five-year relative survival ratio is 23% (95%CI: 21-24%) for males and females combined (2). However, the 5-year survival rate is much higher (about 75%) for patients with localized disease without regional lymph node involvement in whom the cancer is managed with surgery alone (3). Because the prognosis worsens with progressive lymph node involvement, there is interest in finding ways to improve the treatment results for this group of patients.

Although many clinical trials and meta-analyses have explored the value of neoadjuvant or adjuvant chemotherapy and radiation therapy in gastric cancer, these studies have produced conflicting results (4-6), making the role of neoadjuvant and adjuvant therapy controversial. Results of gastric cancer treatment have tended to be better for studies carried out in Asian countries, possibly because of etiologic or biologic differences in the disease or different practices such as screening for early stage cancer, the use of extended lymph node dissection, and the commencement of chemotherapy immediately after surgery.

This guideline is an update of Evidence-based Series (EBS) #2-14, which was originally developed in 2000 and then updated in 2003. The Gastrointestinal DSG believed that this further update was warranted, given the existence of new evidence published that could change the recommendations provided in the previous guideline.

METHODS

The EBS guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (7). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by one member of the PEBC Gastrointestinal DSG and a methodologist.

The systematic review is a convenient and up-to-date source of the best available evidence on neoadjuvant or adjuvant therapy for resectable gastric cancer. The body of evidence in this review is primarily comprised of mature randomized controlled trial (RCT) data and meta-analyses of RCTs. That evidence forms the basis of the recommendations developed by the Gastrointestinal DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

The MEDLINE (January 2002 to June week 3 2010), EMBASE (2002 to 2010 week 25), and Cochrane Library (February 2010), databases were systematically searched using revised literature search strategies (Appendix 1). In MEDLINE, the Medical Subject Heading (MeSH) "stomach neoplasms" and associated text words were combined with treatment-related terms, including the MeSH terms "chemotherapy, adjuvant," "radiotherapy, adjuvant," and "neoadjuvant therapy" and the text words "adjuvant," "neoadjuvant," "preoperative," and "postoperative." These terms were then combined with a search filter designed to identify randomized trials, systematic reviews, and meta-analyses adapted from a strategy developed by the Scottish Intercollegiate Guidelines Network (SIGN), available at www.sign.ac.uk. Modifications were made to the search terms, where appropriate, for use in EMBASE. The proceedings of the 2002 to 2010 American Society of Clinical Oncology (ASCO) and the 2002 to 2009 American Society for Therapeutic Radiology and Oncology (ASTRO) annual meetings were also searched for abstract reports of relevant studies. Reference lists of relevant reviews were searched for additional relevant reports.

Study Selection Criteria

The study inclusion and exclusion criteria used in the original systematic review (Section 2B) were modified for the updated review. Articles were selected for inclusion if they:

- were published abstracts or fully published reports of RCTs comparing preoperative or postoperative chemotherapy and/or radiotherapy versus potentially curative surgery

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alone or another preoperative or postoperative therapy approach. Syntheses of RCTs in the form of systematic reviews or meta-analyses were also included.
- were studies of adults with resectable gastric cancer. Trials of gastric cancer that also including patients with tumours of the gastroesophageal junction were included.
- included reports of OS data.

Articles were excluded if they:
- were studies of immunotherapy, immunochemotherapy, intraperitoneal chemotherapy, or intra-arterial chemotherapy.
- were published in a language other than English, due to unavailability of translation services.
- were abstract reports of preliminary or interim data only.
- were abstract reports of studies that were subsequently fully published.
- reported results of RCTs or meta-analyses in the form of a letter or editorial.
- included a majority of patients with esophageal tumours and did not report data separately for patients with gastric or GEJ tumours.

Study Quality Appraisal

The quality of the systematic reviews and meta-analyses was assessed using the AMSTAR tool (8). Randomized trials were assessed for key methodological characteristics, using information provided in the trial reports. The following elements were assessed: generation of allocation sequence, allocation concealment, blinding, intention-to-treat analysis, withdrawals, loss to follow-up, funding source, statistical power calculations, length of follow-up, differences in baseline patient characteristics, and early termination.

Synthesizing the Evidence

No data pooling was conducted in this review due to the availability of published meta-analyses comparing postoperative chemotherapy to surgery alone, postoperative CRT to either surgery alone or postoperative chemotherapy, and preoperative radiotherapy to surgery alone.

RESULTS

Literature Search Results

The updated search of MEDLINE and EMBASE yielded 1129 articles, of which 149 were retrieved for full-text review following title and abstract screening (Appendix 2). One hundred nineteen of the 149 articles were subsequently excluded because they were either duplicate citations or did not meet the inclusion criteria. One further meta-analysis conducted in Japan and that only included oral fluoropyrimidine trials was also excluded (9). Thirty-three abstracts from the ASCO annual meeting proceedings and six abstracts from the ASTRO proceedings were retrieved for review; 14 initially met the inclusion criteria. However, five of these 14 abstracts were reports of RCTs or meta-analyses that were subsequently fully published and are not discussed further. Two were meta-analyses conducted in Japan and that only included studies of oral fluoropyrimidines are not discussed further (10,11). No additional relevant studies were identified in a search of the Cochrane Library. Overall, 22 RCTs (12-33), 13 meta-analyses (34-46), and two secondary analyses that report survival data (47,48) are included in this systematic review. One article reported the results of two RCTs (17). Six systematic reviews without meta-analyses were identified, but none were included in this report as meta-analytic data was available. Table 1 provides a summary of the original evidence and new evidence used in this guidance document.

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Table 1. Summary of original (Section 2B) and new evidence (Section 2A).

	Original Evidence Section 2B (1966-January 2002)		New Evidence Section 2A (January 2002 – June 2010)		
	# of studies	Results	# of studies	Author & year (Ref)	Results
Randomized Controlled Trials					
Postoperative Chemotherapy vs. Surgery alone	30	*Table 3*	11	Bajetta 2002 (12) Nashimoto 2003 (JCOG 9206-1) (13) Chipponi 2004 (14) Popiela 2004 (15) Bouche 2005 (FFCD 8801) (16) Nitti 2006 (17) De Vita 2007 (GOIM 9602) (18) Nakajima 2007 (19) Sakuramoto 2007 (ACTS-GC) (20) Di Costanzo 2008 (21) Kung 2010 (22)	-
vs. Other postoperative Chemotherapy	-	-	5	Chang 2002 (23) Karacetin 2004 (24) Cascinu 2007 (25) Di Bartolomeo 2007 (26) Chang 2008 (AMC 0201) (27)	*Table 3*
Postoperative Radiation vs. Surgery alone	2	*Table 5*	0	-	-
Postoperative Chemoradiation vs. Surgery alone	3	*Table 2*	2	Hundahl 2002 (Intergroup 0116/SWOG 9008) (47)* Macdonald 2009 (Intergroup 0116/SWOG 9008) (48)*	-
vs. Postoperative Chemotherapy	-	-	1	Bamias 2010 (28)	-
Preoperative (or perioperative) Chemotherapy vs. Surgery alone	3	-	4	Hartgrink 2004 (29) Cunningham 2006 (MAGIC) (30) Boige 2007 (ACCORD07) (31) Schuhmacher 2009 (EORTC 40954) (32)	*Table 5*
Preoperative Radiation vs. Surgery alone	3	-	1	Skoropad 2002 (33)	-
Meta-analyses					
Postoperative Chemotherapy vs. Surgery alone	3	-	8	Hu 2002 (34) Janunger 2002 (35) Panzini 2002 (36) Hu 2007 (37) Zhao 2008 (38) Liu 2008 (39) Sun 2009 (40) GASTRIC 2010 (41)	-
Preoperative Chemotherapy vs. Surgery alone	3	-	2	Li 2010 (42) Ronellenfitsch 2010 (43)	-
Postoperative Chemoradiation vs. Surgery alone	1	-	1	Fiorica 2007 (44)	-
Preoperative Radiation vs. Surgery alone	-	-	3	Fiorica 2007 (44) Valentini 2009 (45) Lu 2009 (46)	-

*Secondary analyses

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Postoperative Chemotherapy

(a) Study/Trial Design and Quality

Five of the 17 RCTs identified were terminated early before reaching target accrual, four for poor accrual (16,17,19) (Nitti (17) reports on two trials) and one for early evidence of benefit after an unplanned interim analysis (26). An additional RCT was discontinued after evidence of benefit at a planned interim analysis, and the results were reported before the planned follow-up was completed (20). Target accrual was met for this trial. Randomization methods appeared adequate in most trials; however, some did not report allocation concealment. None of the trials reported that patients or healthcare providers were blinded to treatment allocation, although one trial reported blinded outcome adjudication (20) (Appendix 3).

The GASTRIC group (41) meta-analysis was an individual patient data (IPD) meta-analysis. Well-conducted IPD meta-analyses are superior to well-conducted published literature meta-analyses, and this meta-analysis scored well on the AMSTAR scale. It included most of the items deemed necessary for a well-conducted meta-analysis except a list of excluded studies, which few meta-analyses provide, and an assessment of the likelihood of publication bias (Appendix 4).

(b) Outcomes

Seven published literature meta-analyses were identified that compared postoperative chemotherapy versus surgery alone for patients with resected gastric cancer (34-40). Study inclusion criteria, literature search periods, and statistical methods differed between the seven meta-analyses although the basic research question was the same. There was considerable overlap in the studies included in each of these meta-analyses (Appendix 5). These seven meta-analyses will not be discussed further, owing to the availability of a recent IPD meta-analysis (41). These authors identified 31 eligible trials from 1970-2009 and were able to obtain IPD from 17 of them. An examination of the eligible studies does not indicate any bias with respect to studies for which the authors were and were not able to obtain the IPD. These authors used a fixed-effects model and determined that there is a modest advantage for postoperative chemotherapy for OS (HR, 0.82; 95% CI, 0.76 to 0.90; $p<0.001$) based on 17 trials and for DFS (HR, 0.82; 95% CI, 0.75 to 0.90; $p<0.001$) based on 14 trials. No heterogeneity was detected for either outcome measure. The GASTRIC group (41) subsequently conducted a sensitivity analysis for OS using IPD where available (17 trials) and published summary statistics for the other studies, where available (11 trials). The results of the sensitivity analysis were consistent with the main analysis for OS (HR, 0.82; 95% CI, 0.77 to 0.88; $p<0.001$).

The GASTRIC group report (41) does not include information about adverse events. However, searching through the individual studies demonstrates that the most common grade 3 and 4 hematologic toxicities are leucopenia, thrombocytopenia, and neutropenia, depending on the chemotherapy regimen. The most common grade 3 and 4 non-hematologic toxicities, other than alopecia, are nausea and/or vomiting, diarrhea, mucositis, and stomatitis, depending on the chemotherapy regimen. Not all of the studies reported toxicity or graded the toxicity if they did report it; this was especially apparent in the older trials.

The updated literature search identified 11 trial reports, representing 12 RCTs that compared postoperative chemotherapy with surgery alone (12-22). All of these studies, except one very recently published trial (22), were part of the meta-analyses described above and will not be discussed further. Kulig et al. (22) compared postoperative chemotherapy (etoposide, adriamycin, and cisplatin) to surgery alone. They report no survival advantage in the chemotherapy arm. Grade 3 or 4 toxicities were reported in 22% of patients, with leucopenia being the most common toxicity reported (6%).

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Five RCTs compared postoperative chemotherapy versus another postoperative chemotherapy regimen (23-27). Study characteristics and results are summarized in Tables 2 and 3 below. Three trials did not demonstrate a difference in OS, DFS, or local recurrence between treatment arms[1]: one compared FAM vs. FM vs. 5-FU (23); one compared PELF vs. 5-FU (25); and one compared MfP vs. Mf (27). A small trial comparing PELF vs. EtLF for completely resected advanced gastric cancer (clinical stage 3 or 4, M0) reported a significant benefit for PELF in OS and DFS (24). Another trial comparing FOLFIRI/docetaxel/cisplatin vs. MMC was stopped early for evidence of a DFS benefit favouring FOLFIRI/docetaxel/cisplatin at an unplanned interim analysis. Therefore, the results should be interpreted with caution (26). Other than alopecia, hematologic toxicities (leucopenia, thrombocytopenia, and neutropenia) and nausea and vomiting were the most often reported grade 3 and 4 toxicities, especially for regimens involving cisplatin, etoposide, or epirubicin.

Postoperative Radiotherapy

No meta-analyses or RCTs solely comparing postoperative radiotherapy vs. surgery alone for resectable gastric cancer were identified in the updated literature search.

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[1] 5-FU = 5-fluorouracil; EtLF = etoposide, leucovorin/folinic acid; FAM = fluorouracil, adriamycin, mitomycin; FM = fluorouracil, mitomycin; Mf =, mitomycin C, oral fluropyrimidine (doxifluridine); MfP = mitomycin C, oral fluropyrimidine (doxifluridine), cisplatin; MMC = mitomycin C; PELF = cisplatin, epirubicin, leucovorin/folinic acid.

Table 2. Characteristics of randomized controlled trials of postoperative chemotherapy vs. another postoperative chemotherapy published since 2002.

Author & year (ref)	Patient characteristics	Site of tumour (%)	Treatment	Number of patients randomized (evaluated)	Surgery	Median follow up (years)
Chang 2002 (23)	Gastric adenocarcinoma Stage IB, II, IIIA, or IIIB	NR	FAM FM F	138 (131) 139 (131) 139 (133)	Curative resection, macroscopically and microscopically free proximal and distal resection margins En bloc resection of greater and lesser omentum and adherent organs D2 extended lymphadenectomy	7.6
Karacetin 2004 (24)	Completely resected advanced gastric adenocarcinoma Clinical stage 3 or 4 (M0) Age 24-75 ECOG PS ≤2	Stomach[a] – 100 Locoregional Nodes[a] – 100 Visceral Peritoneum[a] – 58.9 Abdominal Wall[a] – 5.1 Other[a] – 7.6	PELF EtLF	(41) (37)	Complete macroscopic resection	NR
Cascinu 2007 (25)	Gastric or GEJ adenocarcinoma pT3 N0 and/or pT2 or pT3 N+ ECOG PS 0-1	Stomach Upper third – 32.5 Middle third – 41.8 Lower third – 25.4	PELF F	201 (201) 196 (196)	En-bloc resection and negative resection margins (R0) D1 or D2 lymphadenectomy (79%), D0 (21%) No quality control of surgery or pathology No more than 8 wks between surgery and treatment	4.5
Di Bartolomeo 2007 (26)	Gastric or GEJ adenocarcinoma At least one of: pT3, T4, or pN+ ECOG PS 0-2 (PS 0-1 in pts age >70) Age 18-75	Cardia/fundus[a] – 24.1/16.3 Antrus/pylorus[a] – 61.4/21.7 Corpus[b] – 48.2	ILF (FOFIRI) + DP M	(85) (81)	Radical resection, no microscopic residual tumour At least D1 lymphadenectomy (D2 recommended)	2.4
Chang 2008 (27) *abstract*	Gastric cancer Postoperative stage II-IV Age 18-70	NR	MfP Mf	436 (430) 435 (424)	Curative R0 resection D2 lymphadenectomy Randomization 3-6 wks after surgery	3.2

A=adriamycin; D=docetaxel; E=epirubicin; Et=etoposide; f=oral fluropyrimidine (doxifluridine); F= fluorouracil; GEJ=gastroesophageal junction; I=irinotecan; L=leucovorin/folinic acid; M=mitomycin C; NR=not reported; P=cisplatin; PS=performance status; ref=reference number; wks=weeks.

[a]Not mutually exclusive

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Table 3. Outcomes of randomized controlled trials of postoperative chemotherapy vs. other postoperative chemotherapy published since 2002.

Author & year (ref)	Treatment	N	Overall Survival			Disease Free Survival			Local recurrence (%)	Toxicity (Grade 3 or 4)			
			5-year (%)	Median (months)	HR (95% CI)	5-year (%)	Median (months)	HR (95% CI)					
Chang 2002 (23)	FAM FM F	131 131 133	66.7 67.0 67.2	NR	p=0.97	62.5 63.3 62.1	NR	p=0.83	12[a] 12[a] 14[a]		**FAM**	**FM**	**F**
										Leukopenia	2.3	0.0	1.5
										Thrombocytopenia	0.0	3.8	0.0
										Nausea/Vomiting	2.3	0.8	3.8
										Diarrhea	1.5	3.8	3.0
										Stomatitis	0.8	0.0	6.8
Karacetin 2004 (24)			2-yr								**PELF**	**EtLF**	
	PELF EtLF	41 37	24 8	17.2 12.3	p=0.01	NA	35 wks 17 wks	p=0.0004	NR	Nausea[b] Vomiting[b] Neutropenia[b] Anemia[b] Alopecia	10.9 19.1 13.6 13.6 26.8	14.9 17.9 11.9 20.8 24.3	
Cascinu 2007 (25)	PELF F	201 196	52 50	NA 60	0.95 (0.70-1.29)	41 40	42 42	0.98 (0.75-1.29)	7[c] 6[c]		**PELF**	**F**	
										Neutropenia	134.	8.7	
										Thrombocytopenia	4.0	<1	
										Anemia	6.5	<1	
										Diarrhea	2.5	7.7	
										Nausea/vomiting	5.0	4.6	
										Mucositis	0.0	8.2	
										Neurotoxicity	1.5	0.0	
										Alopecia	38.3	0.0	
Di Bartolomeo 2007 (26)			3-yr			3-yr					**ILF+DP**	**M**	
	ILF (FOLFIRI) + DP M	85 81	73.5 62.4	NR	0.70 p=0.1634	67.4 50.2	NR	0.65 p=0.0449	NR	Diarrhea Leukopenia Neutropenia Thrombocytopenia Mucositis Alopecia Nausea	11.8 15.2 35.2 NR 8.2 7.0 NR	2.5 6.2 14.8 17.3 NR NR 4.9	
Chang 2008 (27) *abstract*			3-yr			3-yr					**MfP**	**Mf**	
	MfP Mf	430 424	72.5 75.8	NR	1.100 (0.842-1.438) log-rank p=0.48	64.9 67.0	NR	1.067 (0.845-1.345) log-rank p=0.59	26.6[a] 19.4[a]	Neutropenia Thrombocytopenia	34.0 3.6	9.0 3.6	

A=adriamycin; CI=confidence interval; D=docetaxel; E=epirubicin; Et=etoposide; f=oral fluropyrimidine (doxifluridine); F= fluorouracil; HR=hazard ratio; I=irinotecan; L=leucovorin/folinic acid; M=mitomycin C; N=number of patients; NA=not applicable; NR=not reported; p=probability value; P=cisplatin; ref=reference number; wks=weeks.

[a] locoregional

[b] % of chemotherapy cycles (not patients)

[c] locoregional plus locoregional and systemic

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Postoperative Chemoradiotherapy

(a) Study/Trial Design and Quality

The one RCT found was terminated early for poor accrual, before reaching its target (28). These authors did conduct an ITT analysis and had less than 1% loss to follow-up (Appendix 3). One published literature meta-analysis was identified (44) that included most of the items deemed necessary by AMSTAR for a well-conducted meta-analysis except a list of excluded studies and an assessment of the quality of the included studies (Appendix 4).

(b) Outcomes

One Phase III RCT comparing postoperative CRT vs. postoperative chemotherapy was identified (28). Initially, the chemotherapy regimen consisted of docetaxel and cisplatin. However, the cisplatin was subsequently changed to carboplatin, owing to high rates of nausea and vomiting. The arms did not differ significantly with respect to median and 3-year OS or median and 3-year PFS. This was not surprising as the trial did not meet its accrual target and was, therefore, underpowered to detect a survival difference. The most common grade 3 and 4 toxicities reported, other than alopecia, were non-febrile neutropenia, febrile neutropenia, and diarrhea. However, the difference between the two arms was not statistically significant for any of these toxicities.

One meta-analysis of RCTs of postoperative CRT was identified (44). Five RCTs were included, three of which compared postoperative CRT vs. surgery alone, and two of which compared postoperative CRT vs. postoperative chemotherapy. Meta-analysis of the five trials indicated no significant benefit for postoperative chemoradiotherapy over control in 3-year mortality (OR, 0.79; 95% CI, 0.59 to 1.05; p=0.10); however, a meta-analysis of three trials that provided 5-year mortality data indicated a significant benefit for postoperative CRT over surgery (OR, 0.45; 95% CI, 0.32 to 0.64; p<.00001). No significant statistical heterogeneity between trials was reported. Fiorica et al. (44) report that 52% of patients did not complete the CRT protocol as planned. Grades 3 and 4 hematologic and gastrointestinal toxicities as well as mucositis were significantly greater in the CRT arms compared to controls in this meta-analysis.

Two secondary analyses of the SWOG/Intergroup trial (49) were identified that also reported updated survival data (47,48). The results from Hundahl (47) are consistent with earlier data reported in Section 2B of this report. Updated results indicated a median survival of 36 months for patients who received postoperative CRT (5-FU/leucovorin [LV]) vs. 27 months for patients who underwent surgery alone (p=0.003). Relapse-free survival was 30 vs. 19 months (p<0.001), respectively. Further updates of the SWOG/Intergroup trial were presented at ASCO in 2009 (48). The abstract based on 10 years of follow-up demonstrated continued benefit for the chemoradiotherapy group for both survival (HR, 0.76; p=0.004) and DFS (HR, 0.66; p<0.001). The presentation of this abstract was based on 11 years of follow-up and demonstrated similar results for both OS (HR, 0.76; 95% CI, 0.63 to 0.92; p=0.005) and DFS (HR, 0.66; 95% CI, 0.55 to 0.80; p<0.001). The original publication on the SWOG/Intergroup trial (49) reported that 33% and 54% of patients in the CRT arm had Grade 3 or higher hematologic and gastrointestinal toxicities, respectively.

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Preoperative or Perioperative Chemotherapy

(a) Study/Trial Quality and Design

Two of the four RCTs identified were terminated early for poor accrual before reaching target (29,32). Neither of these trials reported whether their analyses were intention-to-treat (ITT). Both the Cunningham (30) and Boige (31) trials achieved their accrual targets, and both conducted ITT analyses. Only Hartgrink (29) reported on the loss to follow-up, which was 0% (Appendix 3).

Two published literature meta-analyses were identified comparing preoperative chemotherapy to surgery alone. Neither of these meta-analyses scored well on the AMSTAR instrument, likely owing to the fact that they were only available in abstract form (Appendix 4).

(b) Outcomes

Two meta-analyses were identified that compared preoperative chemotherapy vs. surgery alone (42,43). Both of these meta-analyses were only available in abstract form, providing only a limited amount of methodological information, and for this reason will not be discussed further. No meta-analyses were identified that compared perioperative chemotherapy vs. surgery alone. Four RCT reports, comparing preoperative or perioperative chemotherapy vs. surgery alone, have been published since 2002 (29-32) (Table 4, Table 5). One of the reports (29) presents long-term results of the Dutch trial by Songun et al. (50) included in Section 2B of this report. This trial was stopped after accrual of 59 of a planned 450 patients, owing to the slow recruitment and poor interim results. No benefit for preoperative fluorouracil-doxorubicin-methotrexate (FAMTX) over surgery alone could be demonstrated. Another trial compared preoperative chemotherapy with folinic acid and cisplatin followed by surgery to surgery alone in patients with locally advanced adenocarcinoma of the stomach and cardia. This trial was stopped early owing to poor accrual. Only 144 of an expected 360 patients (40%) were accrued during more than four years of the study. No survival benefit for the addition of preoperative chemotherapy was demonstrated (32). The Fédération Nationale des Centres de Lutte Contre le Cancer (FNLCC) ACCORD07 (31) trial of 224 patients comparing preoperative 5-FU/cisplatin vs. surgery alone in resectable gastric and lower esophageal cancer is available only in abstract form. A significant improvement in OS and DFS with preoperative 5-FU/cisplatin was reported (Table 5).

The MAGIC trial reported by Cunningham et al. in 2006 (30) is the largest trial incorporating preoperative therapy to date and the only randomized trial with a perioperative approach. A total of 503 patients were randomized to preoperative and postoperative ECF or surgery alone. Patients with adenocarcinoma of the stomach or lower third of the esophagus who had stage II or higher (M0) disease or locally advanced inoperable disease were included. It should be noted that only 68% of patients underwent curative surgery, while the remaining patients had palliative surgery, no surgery, or surgery of unknown intent. Of the patients assigned to perioperative ECF, 41.6% completed all six cycles of chemotherapy, and 49.5% of patients who completed preoperative ECF also completed postoperative therapy. A significant benefit for perioperative ECF was reported for OS and PFS (Table 5). Although results for patients with gastric and GEJ tumours were not reported separately from results for tumours of the lower esophagus, no heterogeneity of treatment effect according to disease site was demonstrated (interaction p=0.25).

Overall, preoperative and perioperative chemotherapy approaches resulted in greater hematologic toxicities as well as nausea and vomiting compared to surgery alone (Table 5).

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Table 4. Characteristics of randomized controlled trials of preoperative or perioperative chemotherapy published since 2002.

Author & year (ref)	Patient characteristics	Site of tumour (%)	Treatment	Number of patients randomized (evaluated)	Surgery	Median follow-up (years)
	Preoperative or perioperative chemotherapy vs. surgery alone					
Hartgrink 2004[a] (29)	Gastric adenocarcinoma Resectable (no distant metastases, no T1, no cardia carcinoma) Age up to 75 PS 0-2	NR	FAMTX Surgery alone	29 (27) 30 (29)	Resection with limited (D1) lymphadenectomy 66.1% R0 resection, 12.5% incomplete resection (R1 or R2), 21.4% resection not possible	6.9
Cunningham 2006 (MAGIC Trial) (30)	Adenocarcinoma of stomach or lower third of esophagus Stage II or higher (M0), or locally advanced inoperable PS 0-1	Stomach – 74.0 Lower esophagus – 14.5 GEJ – 11.5	Perioperative ECF Surgery alone	250 253	Radical total gastrectomy or radical subtotal distal gastrectomy Surgeon decided the extent of lymph node dissection	ECF: 4.1 Surgery alone: 3.9
Boige 2007 (31) *abstract*	Adenocarcinoma of stomach, cardia, or lower esophagus Age ≤75 PS <2	Stomach – 25 Cardia – 64 Lower esophagus - 11	FC Surgery alone	113 111	R0 resection 84% in preoperative therapy arm and 73% in surgery alone arm	5.7
Schuhmacher 2009 (32) *abstract*	Adenocarcinoma of stomach or cardia cT3/4 NX M0 Age 18-70 PS 0-1	NR	FaC Surgery alone	72 72	Subtotal or total gastrectomy with extension depending on the localization of the primary tumour D1 or D2 lymphadenectomy	4.4

A=adriamycin; C=cisplatin; E=epirubicin; F=fluorouracil; Fa=folinic acid; GEJ=gastroesophageal junction; MTX=methotrexate; NR=not reported; PS=performance status; ref=reference number; RT=radiotherapy

[a] update of Songun 1999 included in Section 2B

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Table 5. Results of randomized controlled trials of preoperative or perioperative chemotherapy published since 2002.

Author & year (ref)	Treatment	N	Overall Survival			Disease Free Survival			Local recurrence (%)	Complete response (%)	Toxicity (Grade 3 or 4) in Experimental Arm (%)
			5-year (%)	Median (months)	HR (95% CI)	5-year (%)	Median (months)	HR (95% CI)			
Preoperative chemotherapy vs. surgery alone											
Hartgrink 2004[a] (29)	FAMTX Surgery alone	27 29	21 34	18.2 30.3	p=0.17	NR	NR	NR	NR	NR	NR
Cunningham 2006 (MAGIC Trial) (30)	Perioperative ECF Surgery alone	250 253	36.3 23.0	NR	0.75 (0.60-0.93), p=0.009	NR	NR	0.66 (0.53-0.81)[b], p<0.001	14.4 20.6	NR	Preoperative/Postoperative Granulocytopenia - 22.8/27.8 Lymphocytopenia - 19.9/16.9 Leukopenia - 11.5/11.1 Nausea - 6.4/12.3 Vomiting - 5.6/10.1
Boige 2007 (31) *abstract*	FC Surgery alone	113 111	38 24	NR	0.69 (0.50-0.95), p=0.02	34 21	NR	0.65 (0.48-0.89), p=0.003	NR	NR	Neutropenia - 20 Nausea & Vomiting - 9 Overall - 37
Schuhmacher 2009 (32) *abstract*	FaC Surgery alone	72 72	NR	NR	0.84 (0.52-1.35), p=0.466	NR	>36 >36	NR	NR	NR	Nausea & Vomiting - 4 patients

A=adriamycin; C=cisplatin; CI=confidence interval; E=epirubicin; F=fluorouracil; Fa=folinic acid; HR=hazard ratio; MTX=methotrexate; NR=not reported; p=probability value; ref=reference number; RT=radiotherapy

[a] update of Songun 1999 included in Section 2B

[b] progression-free survival

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Preoperative Radiotherapy

(a) Study/Trial Quality and Design

One RCT was identified (33), but it provided very little information with respect to methodological quality (Appendix 3). Three meta-analyses were identified (44-46). Fiorica et al. (44) scored well on the AMSTAR (Appendix 4 and Study Quality section of Postoperative Chemotherapy). The Valentini et al. (45) meta-analysis inappropriately combined many different types of comparisons, and the Lu et al. (46) study scored poorly as it was only available in abstract form (Appendix 4).

(b) Outcomes

Three published literature meta-analyses of trials comparing preoperative radiotherapy vs. surgery alone were identified in the updated literature search (44-46), as well as a full publication of a trial by Skoropad et al included in abstract form in the original systematic review (Section 2B) (33). The Skoropad trial (33) is included in the Fiorica et al. (44) meta-analysis and will not be discussed separately.

The meta-analysis by Fiorica et al. (44) included four RCTs of preoperative radiotherapy vs. surgery alone, one of which combined preoperative radiotherapy with local hyperthermia. Results indicated a significant survival benefit for preoperative radiotherapy at both three years (OR, 0.57; 95% CI, 0.43 to 0.76; p=0.0001) and five years (OR, 0.62; 95% CI, 0.46 to 0.84; p<0.00001), and no significant statistical heterogeneity between trials was demonstrated. All patients in the studies of this meta-analysis were able to complete the preoperative radiation without dose reductions.

The meta-analysis by Valentini et al. (45) included studies of preoperative, postoperative, and intraoperative radiation as well as radiation combined with chemotherapy all combined into one analysis. Because of this clinical heterogeneity, this meta-analysis will not be discussed further. The meta-analysis by Lu et al. (46) was only available in abstract form, and because only a limited amount of methodological information was provided, it will not be discussed further.

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Ongoing Trials

The NCI® database of ongoing clinical trials (http://www.cancer.gov/search/clinical_trials/) was searched on April 7, 2010. Twelve relevant phase III trials were identified and are described in Table 6.

Table 6. Ongoing randomized trials of chemotherapy for advanced gastric cancer.

Title	Phase III randomized trial of adjuvant capecitabine/cisplatin chemotherapy and chemoradiation therapy for gastric adenocarcinoma
Protocol ID	SMC IRB 2004-08-10 ; NCT00323830
Study start date	October 2004
Date last modified	May 8, 2006
Type of trial	Phase III RCT, open-label, active control, parallel assignment, efficacy study
Comparison	Xeloda/cisplatin vs. Xeloda/cisplatin + radiotherapy
Primary endpoint	Disease free survival; Secondary endpoint is overall survival
Accrual	Targeted enrolment = 490
Sponsorship	Samsung Medical Centre
Status	Recruiting
Title	Randomized multicenter controlled phase III study of postoperative adjuvant therapy for stage II/IIIA gastric cancer using TS-1 alone or TS-1+PSK combined therapy
Protocol ID	HKIT-GC ; NCT00216034
Study start date	March 2005
Date last modified	February 8, 2009
Type of trial	Phase III RCT, open-label, active control, parallel assignment, safety/efficacy study
Comparison	TS-1 vs. TS-1 + PSK
Primary endpoint	Overall survival and disease-free survival
Accrual	Targeted enrolment = 280
Sponsorship	Hokuriku-Kinki Immunochemotherapy Study Group
Status	Recruiting
Title	Randomized phase III trial of surgery plus neoadjuvant TS-1 and cisplatin compared with surgery alone for type 4 and large type 3 gastric cancer
Protocol ID	JCOG0501 ; C00000279 ; NCT00252161
Study start date	November 2005
Date last modified	August 2, 2009
Type of trial	Phase III RCT, open-label, active control, parallel assignment, efficacy study
Comparison	Surgery + neoadjuvant TS-1 and cisplatin vs. Surgery alone
Primary endpoint	Overall survival
Accrual	Target enrolment = 316
Sponsorship	Japan Clinical Oncology Group
Status	Recruiting
Title	A multicentre randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer (CRITICS)
Protocol ID	CRITICS ; NCT00407186
Study start date	December 2006
Date last modified	November 11, 2009
Type of trial	Phase III RCT, open-label, active control, parallel assignment, safety/efficacy
Comparison	Cisplatin/capecitabine + radiotherapy vs. Epirubicin/cisplatin/capecitabine
Primary endpoint	Overall survival
Accrual	Targeted enrolment = 788
Sponsorship	Dutch Colorectal Cancer Group
Status	Recruiting
Title	A randomized controlled Phase II/III trial of perioperative chemotherapy with or without bevacizumab in operable adenocarcinoma of the stomach and gastro oesophageal junction
Protocol ID	MRC-ST03; EU-20710; ISRCTN46020948; EUDRACT-2006-000811-12; CTA-00316/0221/001; NCT00450203
Study start date	October 2007
Date last modified	October 6, 2009
Type of trial	Phase II/III, RCT, open-label; active control
Comparison	Combination chemotherapy (epirubicin/cisplatin/capecitabine) vs. combination chemotherapy + bevacizumab
Primary endpoint	Safety; Efficacy; Overall survival
Accrual	Target enrolment = 1100
Sponsorship	MRC
Status	Recruiting
Title	Phase III randomized controlled study of postoperative adjuvant therapy using TS-1 or TS-1+PSK for stage II or III gastric cancer patients

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Protocol ID	TMOG-GC01' NCT00687843
Study start date	June 2008
Date last modified	July 16, 2008
Type of trial	Phase III, RCT, open-label, active control, parallel assignment, safety/efficacy
Comparison	TS-1 vs. TS-1+PSK
Primary endpoint	Relapse-free survival; Secondary endpoint is overall survival
Accrual	Target enrolment = 480
Sponsorship	Tokyo Metropolitan Oncology Group
Status	Recruiting
Title	A randomised, controlled trial of pre- and post-operative chemotherapy in patients with operable gastric cancer
Protocol ID	MRC-ST02; EU-94035; NCT00002615
Study start date	June 1994
Date last modified	February 6, 2009
Type of trial	Phase III RCT, active control
Comparison	Surgery + combination chemotherapy (cisplatin/epirubicin/fluorouracil) vs. Surgery alone
Primary endpoint	Survival; QOL
Accrual	Targeted enrolment = 500
Sponsorship	MRC
Status	Ongoing, but not recruiting
Title	Randomized phase III study of preoperative chemotherapy followed by surgery versus surgery alone in locally advanced gastric cancer (cT3 and cT4NxM0)
Protocol ID	EORTC-40954; NCT00004099
Study start date	July 1999
Date last modified	June 13, 2009
Type of trial	Phase III RCT, open-label, active control
Comparison	Chemotherapy (cisplatin/fluorouracil/leucovorin) + surgery vs. surgery alone
Primary endpoint	Overall survival
Accrual	Targeted enrolment = 360
Sponsorship	EORTC
Status	Ongoing, but not recruiting
Title	A phase III trial of preoperative vs. Postoperative chemotherapy with taxotere-cisplatin-5FU (TCF) in patients with locally advanced operative gastric carcinoma
Protocol ID	SWS-SAKK-43/99; EU-99042; NCT00005060
Study start date	November 1999
Date last modified	February 6, 2009
Type of trial	Phase III RCT, open-label, active control
Comparison	Preoperative TCF vs. Postoperative TCF
Primary endpoint	Event-free survival; Secondary endpoint is overall survival
Accrual	Targeted Enrolment = 240
Sponsorship	Swiss Group for Clinical Cancer Research
Status	Ongoing, but not recruiting
Title	Phase III Intergroup trial of adjuvant chemoradiation after resection of gastric or gastroesophageal adenocarcinoma
Protocol ID	CALGB-80101; NCCTG-CALGB-80101; ECOG-CALGB-80101; NCT00052910
Study start date	December 2002
Date last modified	June 2, 2009
Type of trial	Phase III RCT, active control
Comparison	5-FU/leucovorin + radiation therapy vs. cisplatin/epirubicin/5-FU + radiation therapy
Primary endpoint	Overall survival
Accrual	Target enrolment = 824
Sponsorship	Cancer and Leukemia Group B
Status	Ongoing, but not recruiting
Title	A phase III study comparing adjuvant chemotherapy consisting of capecitabine/oxaliplatin vs. surgery alone in patients with stage II (T1N2, T2N1, T3N0), IIIa (T2N2, T3N1, T4N0) and IIIb (T3N2) gastric adenocarcinoma
Protocol ID	L-9570; NCT00411229
Study start date	June 2006
Date last modified	September 14, 2009
Type of trial	Phase III RCT, open-label, active control, parallel assignment, safety/efficacy
Comparison	Surgery + capecitabine/oxaliplatin vs. surgery alone
Primary endpoint	Overall survival
Accrual	Targeted enrolment = 1024
Sponsorship	Sanofi-Aventis
Status	Ongoing, but not recruiting

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DISCUSSION

Many trials and meta-analyses of trials have investigated the value of neoadjuvant and adjuvant treatment in gastric cancer. These efforts have produced conflicting results. The Gastrointestinal DSG decided that an update of EBS #2-14, which was first developed in 2000 and updated in 2003, was justified, given the availability of new evidence that could change the recommendations made in the last version of this guidance document.

Postoperative Chemotherapy

The IPD meta-analysis by the GASTRIC group (41) demonstrated that there is a modest but significant survival advantage for postoperative chemotherapy, based on the 17 trials for which they could get IPD. This conclusion was maintained when a sensitivity analysis, which added in summary statistics for another 11 trials, was carried out.

Postoperative Radiation

No trials solely comparing postoperative radiation therapy to surgery alone were identified in the updated literature search.

Preoperative Radiation

A published literature meta-analysis by Fiorica et al. (44) included four RCTs of preoperative radiotherapy vs. surgery alone, one of which combined preoperative radiotherapy with local hyperthermia. Results indicated a significant survival benefit for preoperative radiotherapy at both three years (OR, 0.57; 95% CI, 0.43 to 0.76; p=0.0001) and five years (OR, 0.62; 95% CI, 0.46 to 0.84; p<0.00001), and no significant statistical heterogeneity between trials was demonstrated.

A preoperative radiotherapy approach seems to provide a superior outcome with respect to 3-year and 5-year OS. However, this treatment has not been taken up in the North American oncology community. There are four main reasons for this. First, the evidence for preoperative radiation originated predominantly from China and Russia. The generalizability of the results to Canadian/North America practice cannot be assumed. There was significant heterogeneity in the way the preoperative therapy was delivered. The radiotherapy used in three of the four studies used large dose per fraction (20 Gy in 5 fractions) (51,52) although one study did employ a standard 2 Gy dose per fraction (40 Gy in 20 fractions) (53). Similarly, the target volume included for radiotherapy varied across the studies. These differences create challenges toward understanding how to implement these findings into practice. The magnitude of benefit as demonstrated through meta-analysis (44) is potentially smaller compared with a postoperative CRT approach (Number Needed to Treat [NNT] for RT =10 and for CRT = 6) (44). Finally, the high probability of both local and distant recurrence in gastric cancer has led to a preference towards strategies that incorporated both radiotherapy and chemotherapy.

The preference towards incorporating chemotherapy into adjuvant or neoadjuvant approaches is reflected by the fact that none of the clinical trials currently ongoing evaluate the use of preoperative radiation therapy alone, although the evaluation of preoperative CRT, perioperative chemotherapy, and postoperative CRT approaches continue to be actively pursued.

Postoperative Chemoradiation

The meta-analysis by Fiorica et al. (44) of RCTs comparing postoperative chemoradiation to surgery alone did demonstrate a significant benefit with respect to 5-year mortality (OR, 0.45; 95% CI, 0.32 to 0.64; p<0.00001), although it is interesting to note that the results for 3-year mortality were not significant. This might be an indication that the 5-

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year results are spurious, though it is not possible to determine this. It should also be noted that one of the trials included in this meta-analysis is the Macdonald et al. (49) SWOG/Intergroup trial. Updated survival data from this specific trial was identified (47) and indicate superior median survival for patients receiving postoperative chemoradiation over surgery alone (36 vs. 27 months; p=0.003). Similarly, relapse-free survival was superior in the chemoradiation arm (30 vs. 19 months; p<0.001). A further update of SWOG/Intergroup trial demonstrates the robustness of these findings even after 11 years of follow-up for both OS (HR, 0.76; 95% CI, 0.63 to 0.92; p=0.005) and DFS (HR, 0.66; 95% CI, 0.55to 0.80; p<0.001) (48).

In the Macdonald et al. SWOG/Intergroup trial (49), the protocol recommended that a D2 (more extensive) lymph node dissection be performed, but as many of the referrals to the trial occurred postoperatively, this could not be mandated. Upon final analysis, only 10% of patients had a D2 lymph node dissection, 36% had a D1 lymph node dissection, and 54% had a D0 lymph node dissection (i.e., not all of the N1 nodes were removed). The lack of adequate lymph node dissection in over half of the SWOG/Intergroup patients has lead to criticism of the trial, with suggestions that the addition of adjuvant chemoradiation may be compensating for inadequate surgical resection (54,55). However, subsequent trials, in which a D2 lymph node dissection occurred in the majority of patients, have upheld a survival benefit for adjuvant chemoradiation in patients who underwent more aggressive surgery (56). Furthermore, the MAGIC (30) and the S-1 (20) trials had 68% and 100% of patients with a D2 resection, respectively, demonstrating a significant benefit to adjunct chemotherapy, even with cohorts of patients who have had a D2 lymph node dissection.

Preoperative or Perioperative Chemotherapy

The MAGIC trial (30) was a large trial of over 500 patients comparing perioperative chemotherapy (ECF) to surgery alone. This trial demonstrated significant improvement in 5-year OS (HR, 0.75; 95% CI, 0.60 to 0.93; p=0.009) and 5-year PFS (HR, 0.66; 95% CI, 0.53 to 0.81; p<0.001).

Considerations for Choice of Therapy

The Macdonald et al. (47-49) and the Cunningham et al./MAGIC (30) trials have provided strong support for either a postoperative chemotherapy/radiotherapy approach to treatment or a perioperative approach, respectively. Summaries of these protocols are provided in Appendix 6.

The decision to initiate a perioperative chemotherapy approach vs. the postoperative chemoradiation approach should be based on a number of patient and tumour-specific factors and ideally be made preoperatively.

Diagnostic laparoscopy is reasonable to consider prior to initiation of perioperative chemotherapy to determine if there is peritoneal spread of metastatic disease not detected on CT imaging, as this assessment may be less accurate following the administration of chemotherapy. While down-staging is not considered an indication for the MAGIC protocol, a perioperative approach does allow for assessment of biologic response to systemic chemotherapy, which may be important in clinical decision-making for patients with bulky tumours, or radiologically positive lymph nodes. Patients who are undergoing a total gastrectomy, as opposed to a sub-total gastrectomy, may have difficulty with nutrition postoperatively especially when additional therapy is introduced as described in the SWOG/Intergroup clinical trials (49). A feeding tube should be considered for patients undergoing a total gastrectomy with plans for post-operative therapies if there are doubts that the patient will be able to complete postoperative treatment because of poor caloric intake.

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Some factors can be associated with increased or escalated risk of radiotherapy toxicities specifically. The anastomosis is typically included in the radiotherapy portal. For patients where the esophagogastric anastomosis or planned location is above the carina, the inclusion of this region that is required would predict for excessive lung and cardiac radiotherapy toxicities. The nodal regions and the blind loop post resection are frequently immediately adjacent to the kidneys. For patients with borderline renal function, radiation is expected to be associated with an increased risk of chronic renal impairment. In these patients, consideration for the Cunningham approach (30) using chemotherapy alone should be considered.

Similarly, there are factors that need to be made for the use of perioperative chemotherapy. The presence of cardiac or renal dysfunction would contraindicate the use of epirubicin and cisplatin, respectively.

During the combined modality treatment of radiation and chemotherapy used during the Macdonald (49) protocol, some centres used a low-dose continuous 5-FU infusion or alternatively used oral capecitabine as a radiosensitizer. This would seem to be reasonable from a biologic perspective and is considered acceptable.

Clearly, all patients would benefit from a multidisciplinary care assessment prior to surgery in order to determine the best plan of care for each individual patient. Clinicians must tailor the decision to recommend postoperative CRT according to a patient's nutritional and performance status. Unless obviously contraindicated owing to poor performance status, all patients undergoing gastric surgery with curative intent should be considered for adjuncts to resection.

TECHNICAL CONSIDERATIONS FOR RADIATION THERAPY

Many technical issues for the provision of radiation therapy have been introduced to refine and enhance the quality of the radiotherapy plan. The target volume is in the upper abdomen targeting the tumour bed and regional nodes, 2 cm beyond the proximal and distal margin of resection.

The extent of regional node irradiation is further modified based on the location of the primary tumour: for example, for T3 lesions in the proximal stomach and the medial left hemidiaphragm was also included. The regional nodes were defined (based on the Japanese Research Society for Gastric Cancer) as perigastric, celiac, local para-aortic, splenic, hepatoduodenal or hepatic portal, and pancreaticodudenal. In addition, for GEJ tumours, the regional nodes included paracardial and para-esophageal lymph node beds but excluded the pancreatic duodenal and splenic nodal beds. The latter were also excluded in antral tumours. Guidelines for more specific tailoring of nodal regions based on tumour location as well as T and N stage are provided in Tepper and Gunderson (57) and a recent guideline for preoperative radiation treatments of the stomach published by the EORTC (58).

Strategies to incorporate internal organ motion into treatment planning allows for further individualization of treatment plans. Respiratory motion can be incorporated through the use of four-dimensional computerized tomography (4-D CT) (59), and gastric volume variation can be reduced through instructions for 'standardized meals' prior to treatment planning and each treatment (60). The use of renal perfusion scans allow for refinement of radiotherapy beam geometry based on risk and organ function.

The use of conformal radiotherapy has generally superseded the techniques described in the original MacDonald study. IMRT techniques may provide further incremental benefit with lower doses to normal structures being achieved, although the optimal way of adopting this continues to be investigated (61,62).

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Permissible radiation dose limits for organs at risk (OAR) may affect the expected and observed long-term risks. More conservative parameters than described in the original Macdonald (49) study have been recommended (58) and adopted into clinical practice.

CONCLUSIONS

OS in patients with resectable gastric cancer is significantly improved with the use of either postoperative chemoradiation implementing the Macdonald protocol (47-49) or perioperative ECF implementing the MAGIC protocol (30). The choice of which option to utilize should be based on individual patient factors affecting their ability to tolerate either the radiation used in the Macdonald protocol or the epirubicin/cisplatin used in the MAGIC protocol. If neither of these approaches is appropriate for a given patient, then postoperative chemotherapy is a reasonable alternative. All patients with resectable gastric cancer should undergo a multidisciplinary assessment to determine the best plan of care.

CONFLICT OF INTEREST

GI DSG members involved in the development of the systematic review and clinical practice guideline were polled for potential conflicts of interest. All authors declared no conflicts of interest.

JOURNAL REFERENCE

The following systematic review and practice guideline have been published in Gastric Cancer (© The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2012; http://www.springerlink.com/content/1436-3291/):

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For a complete list of the Gastrointestinal DSG members, please visit the CCO website at http://www.cancercare.on.ca/

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REFERENCES

1. Parkin DM, Pisani P, Ferlay J. Global Cancer Statistics. Ca A Cancer J Clin. 1999;49(1):33-64.
2. Canadian Cancer Society's Steering Committee. Canadian Cancer Statistics 2009. Toronto: Canadian Cancer Society; 2009.
3. Middleton G, Cunningham D. Current options in the management of gastrointestinal cancer. Ann Oncol. 1995;6(Suppl 1):S17-S26.
4. Hermans J, Bonenkamp JJ, Boon MC, Bunt AMG, Ohyama S, Sasako M, et al. Adjuvant therapy after curative resection for gastric cancer: Meta-analysis of randomized trials. J Clin Oncol. 1993;11(8):1441-7.
5. Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-asian patients: Revisiting a meta-analysis of randomised trials. Eur J Cancer. 1999;35(7):1059-64.
6. Mari E, Floriani I, Tinazzi A, Buda A, Belfiglio M, Valentini M, et al. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente). Ann Oncol. 2000;11(7):837-43.
7. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: A conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13(2):502-12.
8. Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS ONE. 2007 [cited YEAR Mon Day];2(12):e1350. Available from: http://www.plosone.org/article/info:doi/10.1371/journal.pone.0001350.
9. Oba K, Morita S, Tsuburaya A, Kodera Y, Kobayashi M, Sakamoto J. Efficacy of adjuvant chemotherapy using oral fluorinated pyrimidines for curatively resected gastric cancer: a meta-analysis of centrally randomized controlled clinical trials in Japan. J Chemother. 2006;18(3):311-7.
10. Sakamoto J, Morita S, Tsuburaya A, Kodera Y, Matsui T, Kobayashi O, et al. Efficacy of adjuvant chemotherapy with oral fluorinated pyrimidines for patients with curatively resected gastric cancer. A meta-analysis of centrally randomized clinical trials. J Clin Oncol. 2005;23(16 Suppl):4022.
11. Sakamoto J, Tsuburaya A, Morita S, Matsui T, Oba K, Kodera Y, et al. Adjuvant chemotherapy with tegafur/uracil (UFT) for gastric cancer. A meta-analysis of centrally randomized clinical trials. J Clin Oncol. 2006;24(18 Suppl):4033.
12. Bajetta E, Buzzoni R, Mariani L, Beretta E, Bozzetti F, Bordogna G, et al. Adjuvant chemotherapy in gastric cancer: 5-year results of a randomised study by the Italian Trials in Medical Oncology (ITMO) Group. Ann Oncol. 2002;13(2):299-307.
13. Nashimoto A, Nakajima T, Furukawa H, Kitamura M, Kinoshita T, Yamamura Y, et al. Randomized trial of adjuvant chemotherapy with mitomycin, Fluorouracil, and Cytosine arabinoside followed by oral Fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology Group 9206-1. J Clin Oncol. 2003;21(12):2282-7.
14. Chipponi J, Huguier M, Pezet D, Basso N, Hay J-M, Quandalle P, et al. Randomized trial of adjuvant chemotherapy after curative resection for gastric cancer. Am J Surg. 2004;187(3):440-5.
15. Popiela T, Kulig J, Czupryna A, Szczepanik AM, Zembala M. Efficiency of adjuvant immunochemotherapy following curative resection in patients with locally advanced gastric cancer. Gastric Cancer. 2004;7(4):240-5.

ARCHIVED

16. Bouche O, Ychou M, Burtin P, Bedenne L, Ducreux M, Lebreton G, et al. Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801). Ann Oncol. 2005;16(9):1488-97.
17. Nitti D, Wils J, Dos Santos JG, Fountzilas G, Conte PF, Sava C, et al. Randomized phase III trials of adjuvant FAMTX or FEMTX compared with surgery alone in resected gastric cancer. A combined analysis of the EORTC GI Group and the ICCG. Ann Oncol. 2006;17(2):262-9.
18. De Vita F, Giuliani F, Orditura M, Maiello E, Galizia G, Di Martino N, et al. Adjuvant chemotherapy with epirubicin, leucovorin, 5-fluorouracil and etoposide regimen in resected gastric cancer patients: a randomized phase III trial by the Gruppo Oncologico Italia Meridionale (GOIM 9602 Study). Ann Oncol. 2007;18(8):1354-8.
19. Nakajima T, Kinoshita T, Nashimoto A, Sairenji M, Yamaguchi T, Sakamoto J, et al. Randomized controlled trial of adjuvant uracil-tegafur versus surgery alone for serosa-negative, locally advanced gastric cancer. Br J Surg. 2007;94(12):1468-76.
20. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med. 2007;357(18):1810-20. Erratum published in N Engl J Med. 2008 May 1;358(18):1977.
21. Di Costanzo F, Gasperoni S, Manzione L, Bisagni G, Labianca R, Bravi S, et al. Adjuvant chemotherapy in completely resected gastric cancer: a randomized phase III trial conducted by GOIRC. J Natl Cancer Inst. 2008;100(6):388-98.
22. Kulig J, Kolodziejczyk P, Sierzega M, Bobrzynski L, Jedys J, Popiela T, et al. Adjuvant chemotherapy with etoposide, adriamycin and cisplatin compared with surgery alone in the treatment of gastric cancer: A phase III randomized, multicenter, clinical trial. Oncology. 2010;78:54-61.
23. Chang HM, Jung KH, Kim TY, Kim WS, Yang HK, Lee KU, et al. A phase III randomized trial of 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil and mitomycin C versus 5-fluorouracil alone in curatively resected gastric cancer. Ann Oncol. 2002;13(11):1779-85.
24. Karacetin D, Incekara O. A randomized trial of 5-fluorouracil, leucovorin, cisplatin and epirubicin (PELF) versus 5-fluorouracil, leucovorin and etoposide (ELF) given as adjuvant chemotherapy to patients with resected advanced gastric adenocarcinomas. Journal BUON. 2004;9(3):263-7.
25. Cascinu S, Labianca R, Barone C, Santoro A, Carnaghi C, Cassano A, et al. Adjuvant treatment of high-risk, radically resected gastric cancer patients with 5-fluorouracil, leucovorin, cisplatin, and epidoxorubicin in a randomized controlled trial. J Natl Cancer Inst. 2007;99(8):601-7.
26. Di Bartolomeo M, Buzzoni R, Mariani L, Ferrario E, Katia D, Gevorgyan A, et al. Feasibility of sequential therapy with FOLFIRI followed by docetaxel/cisplatin in patients with radically resected gastric adenocarcinoma: A randomized phase III trial. Oncology. 2007;71(5-6):341-6.
27. Chang H, Kang Y, Min Y, Zang D, Kim G, Yang D, et al. A randomized phase III trial comparing mitomycin-C plus short-term doxifluridine (Mf) versus mitomycin-C plus long-term doxifluridine plus cisplatin (MFP) after curative resection of advanced gastric cancer (AMC 0201) (NCT00296335). J Clin Oncol. 2008;26(15 Suppl):4531.
28. Bamias A, Karina M, Papkostas P, Kostopoulos I, Bobos M, Vourli G, et al. A randomized phase III study of adjuvant platinum/docetaxel chemotherapy with or without radiation therapy in patients with gastric cancer. Cancer Chemother Pharmacol. 2010;65:1009-21.

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29. Hartgrink HH, van de Velde CJH, Putter H, Songun I, Tesselaar MET, Kranenbarg EK, et al. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. Eur J Surg Oncol. 2004;30(6):643-9.
30. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.
31. Boige V, Pignon J, Saint-Aubert B, Lasser P, Conroy T, Bouche O, et al. Final results of a randomized trial comparing preoperative 5-flourouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703. J Clin Oncol. 2007;25(18 Suppl):4510.
32. Schuhmacher C, Schlag P, Lordick F, Hohenberger W, Heise J, Haag C, et al. Neoadjuvant chemotherapy versus surgery alone for locally advanced adenocarcinoma of the stomach and cardia: Randomized EORTC phase III trial #40954. J Clin Oncol. 2009;25(15 Suppl):4510.
33. Skoropad V, Berdov B, Zagrebin V. Concentrated preoperative radiotherapy for resectable gastric cancer: 20-years follow-up of a randomized trial. J Surg Oncol. 2002;80(2):72-8.
34. Hu J-K, Chen Z-X, Zhou Z-G, Zhang B, Tian J, Chen J-P, et al. Intravenous chemotherapy for resected gastric cancer: meta-analysis of randomized controlled trials. World J Gastroenterol. 2002;8(6):1023-8.
35. Janunger K-G, Hafstrom L, Glimelius B. Chemotherapy in gastric cancer: a review and updated meta-analysis. Eur J Surg. 2002;168(11):597-608.
36. Panzini I, Gianni L, Fattori PP, Tassinari D, Imola M, Fabbri P, et al. Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses. Tumori. 2002;88(1):21-7.
37. Hu J-K, Li C-M, Chen X-Z, Chen Z-X, Zhou Z-G, Zhang B, et al. The effectiveness of intravenous 5-fluorouracil-containing chemotherapy after curative resection for gastric carcinoma: A systematic review of published randomized controlled trials. J Chemother. 2007;19(4):359-75.
38. Zhao S-L, Fang J-Y. The role of postoperative adjuvant chemotherapy following curative resection for gastric cancer: a meta-analysis. Cancer Invest. 2008;26(3):317-25.
39. Liu TS, Wang Y, Chen SY, Sun YH. An updated meta-analysis of adjuvant chemotherapy after curative resection for gastric cancer. Eur J Surg Oncol. 2008;34(11):1208-16.
40. Sun P, Xiang JB, Chen ZY. Meta-analysis of adjuvant chemotherapy after radical surgery for advanced gastric cancer. Br J Surg. 2009;96(1):26-33.
41. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group. Benefit of adjuvant chemotherapy for resectable gastric cancer: A meta-analysis. J Am Med Assoc. 2010;303:1729-37.
42. Li H, Zhu F, Cao Y, Zhai L, Lin T. Meta-analyses of randomized trials assessing the effect of neoadjuvant chemotherapy in locally advanced gastric cancer. American Society of Clinical Oncology Annual Meeting: J Clin Oncol. 2010;28(Abstract) 4042.
43. Ronellenfitsch U, Schwarzbach M, Hofheinz R, Kienle P, Hohenberger P, Jensen K, et al. Meta-analysis of preoperative chemotherapy (CTX) versus primary surgery for locoregionally advanced adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus (GE adenocarcinoma). J Clin Oncol. 2010;28(15 Suppl):4022.
44. Fiorica F, Cartei F, Enea M, Licata A, Cabibbo G, Carau B, et al. The impact of radiotherapy on survival in resectable gastric carcinoma: a meta-analysis of literature data. Cancer Treat Rev. 2007;33(8):729-40.

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45. Valentini V, Cellini F, Minsky BD, Mattiucci GC, Balducci M, D'Agostino G, et al. Survival after radiotherapy in gastric cancer: systematic review and meta-analysis. Radiother Oncol. 2009;92(2):176-83.
46. Lu JJ, Liu T, Leong C, Tey J, Zhang Z. Survival benefits from preoperative radiation therapy in gastric carcinoma: a meta-analysis. Int J Radiat Oncol Biol Physics. 2009;75 Suppl 1:2172;S258.
47. Hundahl SA, Macdonald JS, Benedetti J, Fitzsimmons T; Southwest Oncology Group, Gastric Intergoup. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. Ann Surg Oncol. 2002;9(3):278-86.
48. Macdonald JS, Benedetti J, Smalley S, Haller D, Hundahl S, Jessup J, et al. Chemoradiation of resected gastric cancer: a 10-year follow-up of the phase III trial INT0116 (SWOG 9008). J Clin Oncol. 2009;27(15 Suppl):4515.
49. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725-30.
50. Songun I, Keizer HJ, Hermans J, Klementschitsch P, de Vries JE, Wils JA, et al. Chemotherapy for operable gastric cancer: results of the Dutch randomised FAMTX trial. The Dutch Gastric Cancer Group (DGCG). Eur J Cancer. 1999;35(4):558-62.
51. Skoropad VY, Berdov BA, Mardynski YS, et al. A prospective, randomized trial of pre-operative and intraoperative radiotherapy versus surgery alone in resectable gastric carcinoma. Eur J Surg Oncol. 2000;26:773-9.
52. Shchepotin IB, Evan SRT, Chorny V, et al. Intensive preoperative radiotherapy with local hypoterhmia for the treatment of gastric carcinoma. Surg Oncol. 1994;3:37-44.
53. Zhang ZX, Gu XZ, Yin WB, et al. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC) – report on 370 patient. Int J Radiat Oncol Biol Phys. 1998;42:929-34.
54. Lordick F, Siewert JR. Recent advances in multimodal treatment for gastric cancer: a review. Gastric Cancer. 2005;8(2):78-85.
55. Dikken JL, Jansen EPM, Cats A, Bakker B, Hartgrink HH, Meershoek-Klein Kranenbarg E, et al. Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. J Clin Oncol. 2010:26(15 Suppl):9654.
56. Kim S, Lim DH, Lee J, Kang WK, MacDonald JS, Park CH, et al. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys. 2005;63(5):1279-85.
57. Tepper JE, Gunderson LL. Radiation treatment parameters in the adjuvant postoperative therapy of gastric cancer. Semin Radiat Oncol. 2002;12(2):187-95.
58. Matzinger O, Gerber E, Bernstein Z, Maingon P, Haustermans K, Bosset JF, et al. EORTC-ROG expert opinion: radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach. Radiother Oncol. 2009;92(2):164-75.
59. Zhao K-l, Liao Z, Bucci MK, Komaki R, Cox JD, Yu ZH, et al. Evaluation of respiratory-induced target motion for esophageal tumors at the gastroesophageal junction. Radiother Oncol. 2007;84(3):283-9.
60. Watanabe M, Isobe K, Takisima H, Uno T, Ueno N, Kawakami H, et al. Intrafractional gastric motion and interfractional stomach deformity during radiation therapy. Radiother Oncol. 2008;87(3):425-31.

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61. Alani S, Soyfer V, Strauss N, Schifter D, Corn BW. Limited advantages of intensity-modulated radiotherapy over 3D conformal radiation therapy in the adjuvant management of gastric cancer. Int J Radiat Oncol Biol Phys. 2009;74(2):562-6.
62. van der Geld YG, Senan S, van Sornsen de Koste JR, Verbakel WFAR, Slotman BJ, Lagerwaard FJ. A four-dimensional CT-based evaluation of techniques for gastric irradiation. Int J Radiat Oncol Biol Phys. 2007;69(3):903-9.

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Appendix 1. Literature search strategies.

MEDLINE

1 stomach neoplasms/
2 ((gastric or stomach) adj3 (tumour: or tumor: or neoplasm: or cancer:)).tw.
3 1 or 2
4 chemotherapy, adjuvant/
5 radiotherapy, adjuvant/
6 (postoperative or adjuvant).tw.
7 (preoperative or neoadjuvant).tw.
8 neoadjuvant therapy/
9 or/4-8
10 3 and 9
11 Meta-Analysis as topic/
12 meta analy$.tw.
13 metaanaly$.tw.
14 meta analysis.pt.
15 (systematic adj (review$1 or overview$1)).tw.
16 exp Review Literature as topic/
17 or/11-16
18 cochrane.ab.
19 embase.ab.
20 (psychlit or psyclit).ab.
21 (psychinfo or psycinfo).ab.
22 (cinahl or cinhal).ab.
23 science citation index.ab.
24 bids.ab.
25 cancerlit.ab.
26 or/18-25
27 reference list$.ab.
28 bibliograph$.ab.
29 hand-search$.ab.
30 relevant journals.ab.
31 manual search$.ab.
32 or/27-31
33 selection criteria.ab.
34 data extraction.ab.
35 33 or 34
36 review.pt.
37 35 and 36
38 comment.pt.
39 letter.pt.
40 editorial.pt.
41 animal/
42 human/
43 41 not (41 and 42)
44 or/38-40,43
45 17 or 26 or 32 or 37
46 45 not 44

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47 Randomized controlled trials as topic/
48 randomized controlled trial.pt.
49 random allocation/
50 Double blind method/
51 Single blind method/
52 clinical trial.pt.
53 exp clinical trials as topic/
54 or/47-53
55 (clinic$ adj trial$1).tw.
56 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
57 Placebos/
58 Placebo$.tw.
59 Randomly allocated.tw.
60 (allocated adj2 random).tw.
61 or/55-60
62 54 or 61
63 Case report.tw.
64 Letter.pt.
65 Historical article.pt.
66 or/63-65
67 62 not 66
68 67 or 46
69 10 and 68
70 (2002: or 2003: or 2004: or 2005: or 2006: or 2007: or 2008: or 2009:).ed.
71 69 and 70

EMBASE

1 exp *stomach cancer/
2 exp adjuvant therapy/
3 (preoperative or neoadjuvant).tw.
4 (postoperative or adjuvant).tw.
5 or/2-4
6 1 and 5
7 exp Meta Analysis/
8 ((meta adj analy$) or metaanalys$).tw.
9 (systematic adj (review$1 or overview$1)).tw.
10 or/7-9
11 cancerlit.ab.
12 cochrane.ab.
13 embase.ab.
14 (psychlit or psyclit).ab.
15 (psychinfo or psycinfo).ab.
16 (cinahl or cinhal).ab.
17 science citation index.ab.
18 bids.ab.
19 or/11-18
20 reference lists.ab.
21 bibliograph$.ab.
22 hand-search$.ab.
23 manual search$.ab.

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24 relevant journals.ab.
25 or/20-24
26 data extraction.ab.
27 selection criteria.ab.
28 26 or 27
29 review.pt.
30 28 and 29
31 letter.pt.
32 editorial.pt.
33 animal/
34 human/
35 33 not (33 and 34)
36 or/31-32,35
37 10 or 19 or 25 or 30
38 37 not 36
39 clinical trial/
40 randomized controlled trial/
41 randomization/
42 single blind procedure/
43 double blind procedure/
44 crossover procedure/
45 placebo/
46 randomi?ed controlled trial$.tw.
47 rct.tw.
48 random allocation.tw.
49 randomly allocated.tw.
50 allocated randomly.tw.
51 (allocated adj2 random).tw.
52 single blind$.tw.
53 double blind$.tw.
54 ((treble or triple) adj blind$).tw.
55 placebo$.tw.
56 Prospective study/
57 or/39-56
58 Case study/
59 case report.tw.
60 abstract report/ or letter/
61 or/58-60
62 57 not 61
63 6 and (38 or 62)
64 63 and (2002: or 2003: or 2004: or 2005: or 2006: or 2007: or 2008: or 2009:).ew.

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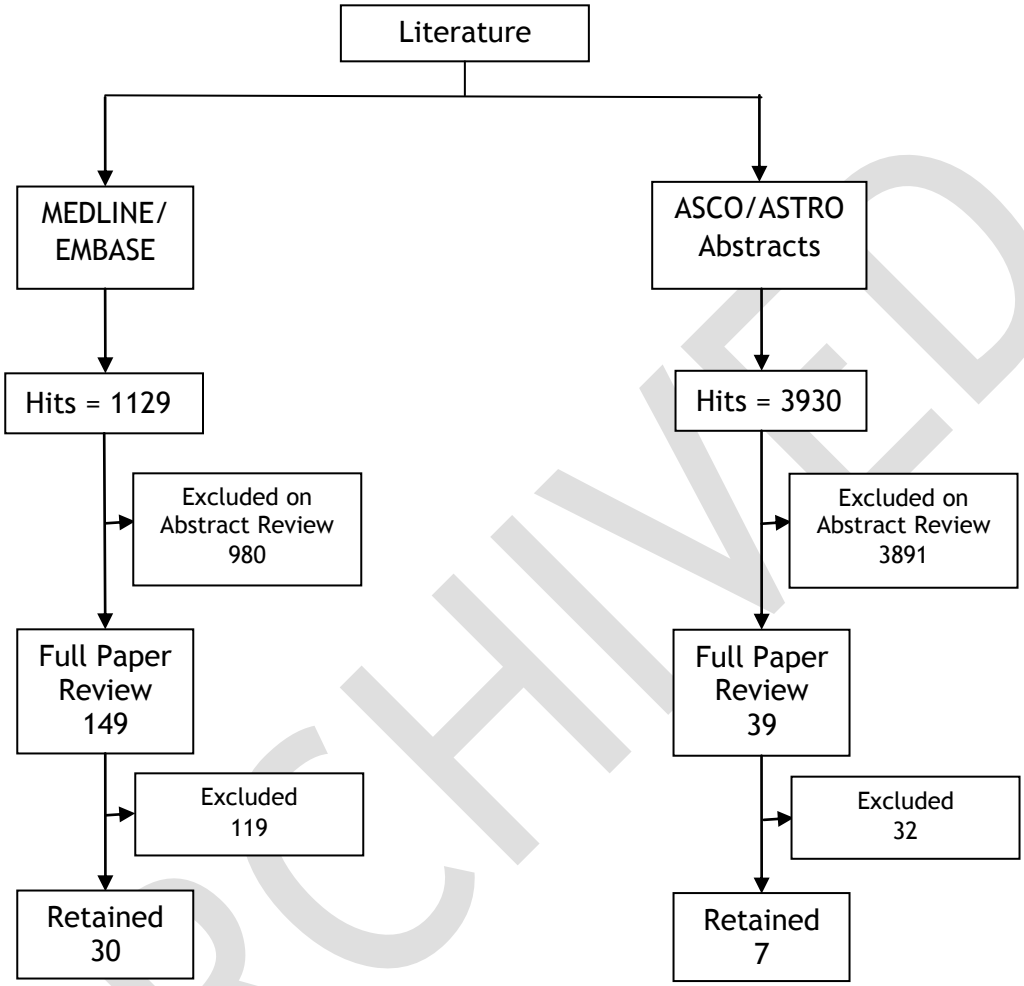
Appendix 2. Flow diagram of literature search results.



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Appendix 3. Methodological quality characteristics of identified randomized controlled trials published since 2002.

Trial	Generation of allocation sequence reported	Allocation concealment	Blinding	ITT	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
Postoperative chemotherapy										
Bajetta 2002 (12)	Yes	Yes	No	Yes	Yes	No	80% power to detect 15% difference in 5-yr OS with 250 pts	3.3%	Yes	No
Nashimoto 2003 (13)	Yes	Yes	NR	Yes	Yes	No	80% power to detect 15% difference in 5-yr OS with 220 pts	NR	Yes	No
Chipponi 2004 (14)	Yes	NR	NR	Yes	Yes	NR	90% power to detect 15% difference in 5-yr OS with 200 pts	1.5%	Lower mean age in chemo arm	No
Popiela 2004 (15)	No	NR	NR	NR	Yes	No	80% power to detect 25% difference in OS with 50 pts per arm	NR	More men and less intestinal type tumours in FAM arm	No
Bouche 2005 (16)	No	NR	NR	Yes	Yes	No	80% power to detect 15% difference in 5-yr OS with 400 pts. Actual accrual 278 pts (47% power).	2.2%	More advanced tumours in chemo arm	Stopped for poor accrual
Nitti 2006 (EORTC) (17)	Yes	NR	NR	Yes	Yes	No	80% power to detect 10% difference in 3-yr OS with 760 pts. Actual accrual 206 pts.	NR	Yes	Stopped for poor accrual
Nitti 2006 (ICCG) (17)	Yes	NR	NR	Yes	Yes	Yes	90% power to detect 15% difference in 5-yr OS with 480 pts. Actual accrual 191 pts.	NR	Yes	Stopped for poor accrual
De Vita 2007 (18)	No	NR	NR	Yes	Yes	NR	80% power to detect 15% difference in 5-yr OS with 226 pts	NR	Yes	No
Nakajima 2007 (19)	Yes	Yes	NR	Yes	Yes	Yes	80% power to detect 33% reduction in HR with 244 pts. Actual accrual 190 pts.	NR	Yes	Stopped for poor accrual
Sakuramoto 2007 (20)	Yes	Yes	Blinded event adjudication	NR	Yes	Yes	80% power to detect HR for death of 0.70 with 1000 pts. Actual accrual 1059 pts.	NR	Yes	Stopped for benefit
Di Costanzo 2008 (21)	Yes	Yes	No	Yes	Yes	No	90% power to detect 20% difference in 5-yr OS with 250 pts	NR	Yes	No
Kulig 2010 (22)	Yes	NR	NR	Yes	Yes	No	80% power to detect 15% increase in 5-year survival with 272 pts. Actual accrual 309 pts.	0.0%	Yes	No
Chang 2002 (23)	Yes	?	NR	NR	Yes	No	90% power to detect 20% difference in 5-yr OS with 256 pts	5.0%	Yes	No
Karacetin 2004 (24)	No	NR	NR	NR	Yes	NR	NR	2.6%	NR	No
Cascinu 2007(25)	Yes	?	NR	Yes	Yes	NR	90% power to detect 15% difference in 5-yr OS with 400 pts	NR	Yes	No
Di Bartolomeo 2007 (26)	Yes	NR	NR	NR	Yes	No	80% power to detect 10% difference in 5-yr DFS with 403 tumour relapses. Actual accrual 169 pts.	NR	More pN2-pN3 cases in polychemotherapy arm	Stopped for benefit at unplanned interim analysis

Trial	Generation of allocation sequence reported	Allocation concealment	Blinding	ITT	Withdrawals described	Industry funding	Statistical power and target sample size	Loss to follow-up	Baseline characteristics balanced	Terminated early
Chang 2008 (27)(abstract)	NR	NR	NR	NR	No	NR	90% power to detect 10% difference in 3-yr RFS with 881 pts and 207 events. Actual accrual 871 and 284 events.	NR	Yes	No
Postoperative Chemoradiation										
Bamias 2010 (28)	Yes	NR	NR	Yes	Yes	NR	80% power to detect 20% increase in survival rate in RT arm with 206 pts. Actual accrual 147.	<1%	Histological subtype significantly different in the two arms	Stopped for poor accrual
Preoperative or Perioperative Chemotherapy										
Hartgrink 2004 (29)	Yes	Yes	NR	NR	Yes	No	90% power to detect 15% difference in curative resectability with 450 pts. Actual accrual 59 pts.	0%	NR	Stopped for poor accrual and poor results
Cunningham 2006 (30)	Yes	Yes	NR	Yes	Yes	Yes	90% power to detect 15% difference in 5-yr OS with 500 pts	NR	Yes	No
Boige 2007 (31) (abstract)	No	Yes	NR	Yes	No	NR	80% power to detect 15% difference in 5-yr OS with 250 pts	NR	Yes	No
Schuhmacher 2009 (32) (abstract)	No	NR	NR	NR	No	No	80% power to detect improvement in median survival from 17 to 24 months with 360 pts. Actual accrual 144 pts.	NR	Yes	Stopped for poor accrual
Preoperative Radiation										
Skoropad 2002 (33)	No	No. Sealed envelopes	NR	NR	NR	NR	NR	NR	More proximal tumours in experimental arm	No

EORTC=European Organization for Research and Treatment of Cancer; HR=hazard ratio; ICCG=International Collaborative Cancer Group; ITT=intent-to-treat analysis; No.=number; NR=not reported; OS=overall survival; pts=patients.

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Appendix 4. Methodological evaluation of included meta-analyses using AMSTAR.

ITEM	POSTOPERATIVE CHEMOTHERAPY vs SURGERY ALONE								PREOPERATIVE CHEMOTHERAPY vs SURGERY ALONE		PREOPERATIVE RADIATION vs SURGERY ALONE		
	Hu, 2002 (34)	Janunger, 2002 (35)	Panzini, 2002 (36)	Hu, 2007 (37)	Zhao, 2008(38)	Liu, 2008 (39)	Sun, 2009(40)	GASTRIC, (2010) (41)	Li, 2010 (42)	Ronellenfitsch, 2010 (43)	Fiorica, 2007 (44)[a]	Valentini, 2009 (45)	Lu, 2009 (46)
1. Was an '*a priori*' design provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was there duplicate study selection and data extraction?	Y	CA	Y	Y	Y	Y	Y	NA*	CA	Y	Y	Y	CA
3. Was a comprehensive literature search performed?	Y	CA	Y	Y	Y	Y	Y	Y	CA	N	Y	Y	Y
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Was a list of studies (included and excluded) provided?	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N
6. Were the characteristics of the included studies provided?	N	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N
7. Was the scientific quality of the included studies assessed and documented?	Y	N	N	Y	Y	Y	Y	Y	N	CA	N	Y	N
8. Was the scientific quality of the included studies used appropriately in formulating	Y	Y	Y	Y	Y	Y	Y	Y	CA	CA	Y	N	CA
9. Were the methods used to combine the findings of the studies appropriate?	Y	CA	Y	Y	Y	Y	Y	Y	CA	CA	Y	N	CA
10. Was the likelihood of publication bias assessed?	N	N	N	N	Y	Y	Y	N	CA	CA	Y	Y	CA
11. Was the conflict of interest stated?	N	N	N	N	N	Y	Y	Y	Y	Y	Y	N	Y
TOTAL AMSTAR POINTS	7	3	8	9	10	11	10	8*	3	4	9	7	4

[a] also includes meta-analysis of Postoperative Chemoradiation vs. Surgery alone; CA=cannot answer; N=no; NA=not applicable; Y=yes; *plus one NA

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Appendix 5. Individual studies used in each of the postoperative chemotherapy meta-analyses.

STUDY	Hu 2001 (34)	Janunger 2002 (35)	Panzini 2002 (36)	Hu 2007 (37)	Zhao 2008 (38)	Liu 2008 (39)	Sun 2009 (40)	GASTRIC 2010 (41)
Serlin 1969		•						
Nakajima 1978		•				•		
Huguier 1980		•	•	•		•		†
Nakajima 1980		•						
Lawton 1981	•							
GITSG 1982		•						
Schlag 1982		•	•			•		†
Douglass 1982			•	•	•	•		#
VASOG 1983		•						
Higgins 1983			•	•				
Nakajima 1984		•	•	•		•		#
Engstrom 1985		•	•	•	•	•		#
Schlag 1987	•			•				
IGTSG (Bonfanti) 1988		•	•	•	•	•		†
Jakesz 1988		•						†
Allum 1989		•						†
Coombes 1990		•	•	•	•	•		#
Estape 1991	•							
Krook 1991		•	•	•	•	•		#
Kim 1992	•			•				
Hermans 1993	•							
Grau 1993		•	•			•		#
Hallissey 1994	•	•						†
Li LJ 1994	•			•				
Wang BD 1994	•			•				
Li HX 1994	•							
Chou 1994		•	•			•		†
Chen 1994				•				
Fujii 1994								†
Lise 1995	•	•	•		•	•		#
Macdonald 1995		•	•		•	•		#
Carrato 1995								†
Neri 1996	•	•	•					†
Tsavaris 1996		•	•	•	•	•		#
Coombes 1998	•							
Zhou GX 1998	•							
Cirera 1990	•		•		•	•	•	†
Nakajima 1999			•	•	•	•	•	#
Neri 2001				•	•	•	•	
Bresciani 2001						•		
Bajetta 2002				•	•	•	•	#
Nashimoto 2003				•	•	•	•	#
Chipponi 2004				•	•	•	•	†
Popiela 2004				•			•	#
Uslu 2004						•		
Bouché 2005				•	•		•	#
Nitti 2006				•			•	#
Sakuramoto 2007						•	•	
De Vita 2007							•	†
Nakajima 2007							•	#
Di Costanzo 2008								†

• study included; # individual patient data obtained; † individual patient data could not be obtained

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Appendix 6. Macdonald (49) and MAGIC (30) protocols.

PROTOCOL DETAILS	
Macdonald, 2001 (49) Surgery + Postoperative Chemoradiation	**MAGIC, 2006 (30)** Perioperative Chemotherapy + Surgery
Chemotherapy: Fluorouracil: 425 mg/m^2, d1-5 Leucovorin: 20 mg/m^2, d1-5 Chemoradiation: Radiation: 180cGy/day, 25 fractions over 5 weeks beginning 28 days after Day 1 of chemotherapy, Total of 4500 cGy Fluorouracil: 400 mg/m^2, first 4 and last 3 days of radiation therapy Leucovorin: 20 mg/m^2, first 4 and last 3 days of radiation therapy Chemotherapy: 2 cycles one month apart beginning one month after completion of radiation Fluorouracil: 425 mg/m^2, d1-5 Leucovorin: 20 mg/m^2, d1-5	Chemotherapy: 3 preoperative and 3 postoperative cycles are given Epirubicin: 50 mg/m^2, bolus, d1, q3w Cisplatin: 60 mg/m^2, IV with hydration, d1, q3w Fluorouracil: 200 mg/m^2, CIV, d1-21, q3w

d=day; q3w=every 3 weeks

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Evidence-Based Series 2-14 Version 3.2010: Section 2B

Neoadjuvant or Adjuvant Therapy for Resectable Gastric Cancer: Original Evidentiary Base 2002

C.C. Earle, J. Maroun, L. Zuraw,
and the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The systematic review that makes up Section 2B of this Evidence-based Series was originally completed in 2002 and contains the relevant data on adjuvant and neoadjuvant therapy for resectable gastric cancer as of that time. Section 2A of this Evidence-based Series is a systematic review of the relevant data from January 2002 to June 2010, as well as a complete discussion and interpretation of all the relevant data, including the data found here in Section 2B.

Report Date: May 21, 2003

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QUESTION

Should patients with resectable gastric cancer (T1-4,N0-2,M0) receive neoadjuvant or adjuvant therapy in addition to surgery?

CHOICE OF TOPIC AND RATIONALE

The incidence of gastric cancer has been decreasing steadily since the 1930s (1). Despite this, it is the eighth leading cause of cancer death because the majority of patients present with advanced disease (2). The survival rate is about 75% at five years for patients with localized disease without regional lymph node involvement in whom the cancer is managed with surgery alone (3). However, the prognosis worsens with progressive lymph node involvement, which predicts an increase in the probability of local and distant recurrences. As a result, there is great interest in finding ways to improve the treatment results for this group of patients.

Adjuvant treatments following surgery have been shown to improve survival in several other cancers with similar patterns of relapse. Although many clinical trials have explored the value of neoadjuvant or adjuvant chemotherapy, radiotherapy, and immunotherapy in gastric cancer, these trials have produced conflicting results, making the role of neoadjuvant and adjuvant therapy controversial. Results of gastric cancer treatment have tended to be better

for studies carried out in Asian countries, possibly related to etiologic or biologic differences in the disease or different practices such as screening for early stage cancer, the use of extended lymph node dissection, and the commencement of chemotherapy immediately after surgery. Attempts to replicate these interventions outside the Asian setting have not been successful (4), raising questions as to whether these trials should be compared to studies conducted in Western countries. A systematic review and practice guideline is therefore warranted.

METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using methods of the Practice Guidelines Development Cycle (5). Evidence was selected and reviewed by one member of the PGI Gastrointestinal Cancer Disease Site Group (DSG) and methodologists. Members of the Gastrointestinal Cancer DSG disclosed potential conflict of interest information. External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

Literature Search Strategy

MEDLINE (1966 through January 2002), CANCERLIT (1983 through October 2001), and the Cochrane Library (Issue 1, 2002) databases were searched with no language restrictions. "Stomach neoplasms" (Medical subject heading [MeSH]) and the text word "gastric cancer" were combined with "chemotherapy, adjuvant" (MeSH), "radiotherapy, adjuvant" (MeSH), "immunotherapy" (MeSH), and the following phrases used as text words: "preoperative or neoadjuvant", "chemotherapy", "radiotherapy", "radiation therapy", "irradiation", "immunotherapy", "chemoimmunotherapy", "immunochemotherapy", "immunoradiotherapy", and "radioimmunotherapy". These terms were then combined with the search terms for the following study designs and publication types: practice guidelines, meta-analyses, and randomized controlled trials. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://cancer.gov/search/clinical_trials/), and the proceedings of the 1996 to 2001 annual meetings of the American Society of Clinical Oncology (ASCO) and the 1999 to 2001 annual meetings of the American Society for Therapeutic Radiology and Oncology (ASTRO) were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by one reviewer and the reference lists from these sources were searched for additional trials.

Study Selection Criteria

Articles were selected for inclusion in this overview of the evidence if they were fully published reports or published abstracts of randomized trials or systematic overviews of randomized trials of adjuvant or neoadjuvant treatments compared with "curative" surgery alone in patients with resectable gastric cancer. Data on overall survival had to be reported. Other outcomes of interest were disease-free survival and adverse effects.

Synthesizing the Evidence

It was decided not to pool the results of trials of adjuvant chemotherapy for gastric cancer because of the availability of up-to-date, published meta-analyses that included the most recent randomized trials of adjuvant chemotherapy compared with surgery alone. The

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trials of other neoadjuvant and adjuvant therapies not included in these literature-based meta-analyses were felt to be too clinically heterogeneous to pool.

RESULTS

Literature Search Results

A classification of the nature of the published evidence is shown in Table 1. The literature search identified 47 randomized trials of adjuvant therapy, including combined chemoradiotherapy, systemic and intraperitoneal chemotherapy, radiotherapy, and chemoimmunotherapy, as well as three literature-based meta-analyses of adjuvant chemotherapy compared with surgery alone. Nine randomized trials of surgery alone compared with neoadjuvant chemotherapy, radiotherapy, or immunotherapy were also found. Where results have been reported or updated in more than one publication, only the most recent publication is listed. Patients with very early stage tumours were excluded from many studies or were not reported separately.

Table 1. Randomized trials and meta-analyses of neoadjuvant or adjuvant therapy with surgery versus surgery alone in resectable gastric cancer.

Treatment Approach	Number	Reference(s)	Summary of Results
Adjuvant			
Chemoradiotherapy	3	7-9	Table 2
Systemic Chemotherapy	30	10-39	Table 3
Literature-based meta-analyses	3	43,46,47	-
Intraperitoneal Chemotherapy	7	40,49,50-54	Table 4
Radiotherapy	2	28,55	Table 5
Chemoimmunotherapy	9	19,23,24,41,42,56-59	Table 6
Neoadjuvant			
Chemotherapy	3	65-67	-
Radiotherapy	3	68-70	-
Immunotherapy	3	71-73	-

Outcomes

Combined Chemoradiotherapy versus Surgery

Interest in adjuvant radiation as a treatment is based on the observation that over 80% of patients who die from gastric cancer experience a local recurrence some time in their illness (6). However, as described below, adjuvant radiotherapy alone has been disappointing. To improve the efficacy of radiation, 5-fluorouracil (5-FU) has been used as a radiosensitizer in three randomized trials (7-9) (Table 2). A study by Dent et al (7) detected only a non-significant trend towards improved survival in patients randomized to adjuvant chemoradiotherapy. Conversely, a study by Moertel et al (8) detected improved survival in treated patients, but this study has been criticized because randomization took place before consent, and 25% of patients refused treatment. The patients who refused treatment actually had the best survival of all groups (five-year survival rate was 30%). Furthermore, there was a high rate of treatment discontinuation in both studies (7,8) due to local side effects from radiotherapy.

Recently, an intergroup trial led by the Southwest Oncology Group (SWOG) randomized 556 patients following potentially curative resection of gastric cancer to either observation alone (n=275) or adjuvant combined chemoradiotherapy (n=281) (SWOG-9008) (9). Eligibility criteria for this study included histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction followed by complete resection of the neoplasm (stage IB through IVM0 according to American Joint Commission on Cancer's staging criteria (1988)), a SWOG performance status of 2 or lower, and adequate function of major organs. The treatment

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consisted of one cycle of 5-FU (425 mg/m2/day) and leucovorin (20 mg/m2/day) in a daily regimen for five days, followed one month later by 4,500 cGy (180 cGy/day) of radiation given with 5-FU (400 mg/m2/day) and leucovorin (20 mg/m2/day) on days 1 through 4 and the last three days of radiation. One month after completion of radiation, two cycles of 5-FU (425 mg/m2/day) and leucovorin (20 mg/m2/day) in a daily regimen for five days were given at monthly intervals. Median follow-up was five years. Compared to surgery alone, overall survival at three years was improved by 9% (50% versus 41%, p=0.005), and relapse-free survival was increased from 31% to 48%, p=0.001 [two-sided log-rank test] in the chemo-radiotherapy group. At five years, adjuvant chemo-radiotherapy increased overall survival by 11.6% (40% versus 28.4%), and improved relapse-free survival from 25% to 38%, p<0.001 [two-sided log-rank test] compared to surgery alone. The treatment was described as tolerable, although there were three (1%) toxic deaths, 41% grade 3 toxicity, and 32% grade 4 toxicity. The most frequent adverse effects (> grade 3) were hematologic (54%), gastrointestinal (33%), influenza-like (9%), infectious (6%), and neurologic (4%). Furthermore, it is now suspected that the radiation fields used are known to possibly damage the left kidney, resulting in hypertension and other renal problems. Also, there has been some suggestion that the surgery performed in this trial was often not up to the desired standards. For example, extensive (D2) lymph-node dissection was recommended for all patients, but only 10% actually received this treatment. For this reason, radiotherapy may have been making up for incomplete surgery. Initial patient compliance with radiotherapy treatment was reported in abstract form, and 35% had major or minor protocol deviations, but final quality analysis reviews of radiotherapy compliance showed major protocol deviations in only 6.5% of all treatment plans.

Table 2. Adjuvant combined chemoradiotherapy versus surgery alone.

Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
Dent, 1979 (7)	NR	Obs 5-FU + RT	17 18	NR		NS (estimated survival rate at 140 weeks was 40% versus 32%)
Moertel, 1984 (8)	NR	Obs 5-FU + RT	23 39	7* 35*	4* 20*	p=0.024
Macdonald, 2001 (9)	60	Obs 5-FU/LV + RT	275 281	41 50	28 40	p=0.005 [two—sided log-rank test]

Note: 5-FU/LV, 5-fluorouracil and leucovorin; NR, not reported; NS, not significant; Obs, observation; RT, radiotherapy.
* Estimated from survival curve.

Adjuvant Systemic Chemotherapy

Table 3 presents 30 randomized trials of postoperative adjuvant systemic chemotherapy versus surgery alone in resectable gastric cancer. A literature-based meta-analysis of 11 randomized trials (17,18,22,24-26,28,29,40,41,42) by Hermans et al (43) initially detected only a non-significant trend towards improved survival for adjuvant chemotherapy. Hermans et al (43) tested for statistical heterogeneity, and they attributed the significant heterogeneity to one particular trial. An early report (44) of the trial by Grau (29) detected a strong positive effect with mitomycin C, and the upper limit of the confidence interval (CI) around the odds ratio for this trial was far below the lower limit of the confidence interval around the pooled odds ratio for the other trials. The interventions were also varied as trials of intraperitoneal chemotherapy and immunochemotherapy were included in this meta-analysis of published reports. The authors wrote an addendum in 1994 (45) in which they recalculated the odds ratio (OR). This addendum included two trials

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missing from the original meta-analysis (16,21). The mortality OR was 0.82 (95% CI, 0.68 to 0.98) in favour of adjuvant chemotherapy. Testing for heterogeneity was not reported.

Several subsequently reported trials detected at least trends towards benefit with adjuvant chemotherapy. A second literature-based meta-analysis (46) of 13 Western randomized trials of adjuvant systemic chemotherapy versus surgery alone (15-18,22,24,26,27,29,30,32,34,35) detected a statistically significant survival benefit favouring adjuvant treatment (OR, 0.80; 95% CI, 0.66 to 0.97). There was no significant heterogeneity in the results across trials. Subgroup analyses showed a trend towards a larger magnitude of the effect for trials in which at least two thirds of the patients had node-positive disease (OR, 0.74; 95% CI, 0.59 to 0.95).

A third literature-based meta-analysis of 20 trials (21 comparisons) reached similar conclusions; pooling detected a relative 18% reduction in the risk of death with adjuvant chemotherapy compared with surgery alone (hazard ratio, 0.82; 95% CI, 0.75 to 0.89; $p<0.001$) (47). The test for heterogeneity was statistically significant, and Mari et al (47) conducted separate pooled analyses for the subgroup of mono-chemotherapy trials, poly-chemotherapy trials with anthracycline, and poly-chemotherapy trials without anthracycline. The results indicated a larger magnitude of effect with mono-chemotherapy (mitomycin C) compared with poly-chemotherapy. The upper limit of the confidence interval around the hazards ratio for the mono-chemotherapy subgroup did not overlap with the lower limit of the confidence interval around the hazards ratio for either of the poly-chemotherapy subgroups. Mari et al (47) examined possible explanations including a dose-response relationship and study quality, but they noted that the pooled results of the trials of poly-chemotherapy would be more reliable because 17 trials involved poly-chemotherapy compared with only three mono-chemotherapy trials. Of note, Mari et al (47) included in the mono-chemotherapy subgroup both the trial by Grau (29) and an earlier report of the same trial (44). It is likely that this error contributed to the significant heterogeneity since the positive results of this trial were counted twice in the literature-based meta-analysis.

Adverse effects, such as hematologic toxicity, infection, nausea and vomiting, stomatitis, and alopecia, can be significant with adjuvant chemotherapy, although often balanced by symptomatic improvement (48). However, toxicity has resulted in less than 80% of planned doses being administered in many trials (15,16,18,26,30).

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Table 3. Randomized trials of adjuvant systemic chemotherapy compared with surgery alone in resected gastric cancer.

Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
Longmuire/VASOG, * 1968 (10)	NR	Obs	272	26	19	NS (survival analysis excluded 30-day deaths)
		Thiotepa	259	31	21	
Serlin,* 1969 (11)	NR	Obs	212	34	NR	NS (survival analysis excluded 30-day deaths)
		FUDR	185	32	NR	
Imanaga, 1977 (12)						
Study 1	NR	Obs	283	60†	54	p< 0.05 for study 1 (MMC twice weekly x 5 weeks) (survival analysis excluded 30-day deaths)
		MMC	242	72†	68	
Study 2	NR	Obs	265	64†	60	
		MMC	255	72†	60	
Study 3	NR	Obs	152			
		MMC	135	NR		
		MMC+cyclo	146			
Study 4	NR	Obs	217	68	NR	
		MMC	197	74	NR	
		MMC+5-FU+Ara-C	208	69	NR	
Nakajima,1978 (13)	NR	Obs	223	NR	44	NS, best results in high risk patients
		MMC	207	NR	52	
Nakajima, 1980 (14)	NR	Obs	38	55†	50	p<0.05 for MMC+Ara-C+ 5-FU versus observation
		MMC	42	67†	64	
		MMC+Ara-C+5-FU	40	77†	67	
Huguier, 1980 (15)	NR	Obs	26	30	18	NS
		5-FU+VLB+cyclo	27	38	16	
Schlag, 1982 (16)	NR	Obs	54	52	NR	NS
		5-FU+BCNU	49	52	NR	
Douglass/GTSG, 1982 (17)	NR	Obs	71	47†	33†	NS (p=0.06), after adjusting for covariates p=0.03
		5-FU+mCCNU	71	62†	46†	
Higgins/VASOG, 1983 (18)	NR	Obs	68	42†	NR	NS (p=0.88)
		5-FU+mCCNU	66	45†	NR	
Ochiai,* 1983 (19)	NR	Obs	40	32†	32†	NS for chemotherapy alone versus observation
		MMC+5-FU+Ara-C	49	36†	18†	
		MMC+5-FU+Ara-C +BCG	49	52†	35†	
Matsubara, 1984 (20)	NR	Obs	152			NS
		Cyclo, short-term	158	NR		
		Cyclo, long-term	151			
Nakajima, 1984 (21)	NR	Obs	74	73†	51	NS (p=0.09)
		MMC+5-FU+Ara-C	73	73†	68	
		MMC+ftorafur+Ara-C	76	73†	62	
Engstrom, 1985 (22)	64	Obs	89	50†	36†	NS (p=0.73)
		5-FU+mCCNU	91	52†	27†	
Yamamura, 1986 (23)	NR	Obs	34			NS
		MMC+5-FU	32	NR		
		MMC+5-FU+OK-432	33			
Bonfanti/GTSG, 1988 (24)	81	Obs	69	66†	50	NS
		MCCNU+5-FU	75	65†	50	
		MCCNU+5-FU+levamisole	69	55†	50	

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Table 3. continued.

Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
Allum, 1989 (25)	100	Obs 5-FU + MMC 5-FU + MMC+induction (FU, VCR, cyclo, MTX)	130 141 140	25† 27† 25†	18† 12† 18†	NS
Coombes/ICCG, 1990 (26)	68	Obs FAM	148 133	52 55	35 46	NS (p=0.21), high-risk subgroup reached significance
Krook, 1991 (27)	84	Obs 5-FU+ doxorubicin	64 61	38† 50†	33 32	NS
Hallissey, 1994 (28)	NR	Obs 5-FU+doxorubicin+MMC Radiotherapy	145 138 153	27† 25† 23†	20 19 12	NS (p=0.14)
Grau, 1993 (29)	105	Obs MMC	66 68	36† 50†	26 41	p<0.025
Lise/EORTC, 1995 (30)	78	Obs FAM	159 155	52† 50†	44† 41†	NS (p=0.295)
Chou, 1994 (31)	NR	Obs Ftorafur	56 59	Stage II 31 69 Stage III 22 41	 31 34 11 29	p<0.05 for stage III subgroup
Macdonald/SWOG, 1995 (32)	114	Obs FAM	100 93	43† 48†	32 37	NS (p=0.57)
Carrato, 1995 (33)	37	Obs MMC+tegafur	75 69	NR		NS
Neri, 1996 (34)	NR	Obs Epirubicin+levamisole+5-FU	55 48	15† 26†	NR NR	p<0.05
Tsavaris, 1996 (35)	60	Obs 5-FU+epirubicin+MMC	42 42	28† 40†	15† 21†	NS (p=0.248)
Nakajima, 1999 (36)	72	Obs MMC+5FU	291 288	85† 90†	82.9 85.8	NS (p=0.17)
Cirera, 1999 (37)	37	Obs MMC+tegafur	72 76	46† 58†	36 56	p=0.04
Ducreux, 2000 (38)	NR	Obs 5-FU+cisplatin	133 127	54.5 55.6	NR NR	NS
Di Bartolomeo, 2000 (39)	66	Obs EAP + 5FU+leucovorin	137 137	NR NR	48 52	NR

Note: 5-FU, 5-fluorouracil; Ara-C, cytarabine; BCG, bacillus Calmlette-Guerin; BCNU, carmustine; cyclo, cyclophosphamide; EAP, etoposide, doxorubicin, cisplatin; FAM, fluorouracil, adriamycin, mitomycin; FUDR, fluorodeoxyuridine; mCCNU, methyl lomustine; MMC, mitomycin C; MTX, methotrexate; NR, not reported; NS, not significant; Obs, observation; OK-432, picibanil; VCR, vincristine; VLB, vinblastine.

* Includes some patients resected for palliation.

† Estimated from survival curve.

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Adjuvant Intraperitoneal Chemotherapy

Intraperitoneal (i.p.) chemotherapy has been studied in several randomized trials because of the observation that resected gastric cancer tends to recur in the peritoneum or liver (40,49-54). Survival results have been conflicting, however, and have even indicated harm from i.p. therapy (Table 4). For example, a trial by the Austrian Working Group for Surgical Oncology was terminated early because the intervention group had higher rates of postoperative complications (35% versus 16% in the control group, p<0.02) and postoperative deaths (11% versus 2%), without any benefit in overall or recurrence-free survival (52).

Table 4. Randomized trials of adjuvant intraperitoneal chemotherapy compared with surgery alone in resected gastric cancer.

Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
Schiessel, 1989 (40)	NR	Obs i.p. cisplatin	33 31	NR		NS (estimated 2-year survival was 35% versus 37%)
Hagiwara, 1992 (49)	NR	Obs i.p. MMC	25 25	27 69	NR NR	P<0.01
Sautner,* 1994 (50)	72	Obs i.p. cisplatin	34 33	30 33	24 21	NS (p=0.6)
Hamazoe, 1994 (51)	NR	Obs i.p. MMC	40 42	56† 67†	52.5 64.2	NS (p=0.24)
Rosen, 1998 (52)	20	Obs i.p. MMC	45 46	NR		NS (median survival 739 days versus 515 days, p=0.44)
Yu, 1998 (53)	~26 (mean)	Obs i.p. MMC+5-FU	92 92	NR NR	41 56	NS (p=0.194)
Lygidakis, 1999 (54)	~26 (mean)	Obs neoadjuvant + adjuvant i.p. MMC+5-FU+LV+ farmorubicin neoadjuvant + adjuvant i.p. MMC+5-FU+LV+ farmorubicin + systemic CT using the same drugs	19 19 20	29.8 37.2 48.6 (4-year survival)		NR

Note: 5-FU, 5-fluorouracil; CT, chemotherapy; i.p., intraperitoneal; LV, leucovorin; MMC, mitomycin C; NR, not reported; NS, not significant; and Obs, observation.
* Includes some patients resected for palliation.
† Estimated from survival curve.

Adjuvant Radiotherapy

Two randomized trials (28,55) of adjuvant radiotherapy versus surgery alone are presented in Table 5. Radiotherapy alone as adjuvant treatment was investigated as one arm in a randomized trial conducted by the British Stomach Cancer Group (28). They reported that radiotherapy had no effect on local recurrence or survival. Similarly, a German study detected no benefit for intra-operative radiotherapy (49).

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Table 5. Randomized trials of adjuvant radiotherapy compared with surgery alone in resected gastric cancer.

Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
Hallissey, 1994 (28)	NR	Obs RT	145 153	27* 23*	20 12	NS (p=0.14)
Kramling, 1996 (55)	29.2 (mean)	Obs Intra-op RT	64 51	NR		NS (mean survival 26.9 months for RT versus 30.8 months for Obs)

Note: NR, not reported; NS, not significant; Obs, observation; and RT, radiotherapy.
* Estimated from survival curve.

Adjuvant Chemoimmunotherapy

Randomized studies comparing adjuvant chemoimmunotherapy with a surgery-alone control group have had mixed results (Table 6). Two Korean studies, a Japanese study, and a Polish study detected significant survival benefits favouring adjuvant chemoimmunotherapy (19,42,56,58), whereas several European and other Japanese studies found no significant difference in survival for adjuvant chemoimmunotherapy compared with surgery alone (23,24,41,57). No obvious pattern or type of immunotherapy tested, trial size, or study quality explains these mixed results. Immunotherapeutic compounds studied included levamisole (24), BCG (19) and OK-432 (picibanil) (23). Based on the ability of H2 antagonists to block T-suppresser cells, Langman et al (59) randomly assigned 442 patients with stage I-IV gastric cancer to placebo or cimetidine in doses of 400 mg or 800 mg. In the subgroup of 226 patients who underwent surgery with curative intent (stage I-III), there was no significant difference in survival between the cimetidine and placebo groups (median survival, 26 versus 20 months; five-year survival rate, 34% versus 30%; p=0.44). Several other Asian studies have compared adjuvant chemoimmunotherapy with adjuvant chemotherapy but without a surgery-alone control group (60-64). These results have also been inconsistent.

Table 6. Randomized trials of adjuvant chemoimmunotherapy compared with surgery alone in resected gastric cancer.

Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
Ochiai,* 1983 (19)	NR	Obs MMC+5-FU+Ara-C MMC+5-FU+Ara-C+BCG	40 49 49	32† 36† 52†	32† 18† 35†	p<0.01 for immunotherapy versus control, p<0.05 for immunotherapy versus CT)
Yamamura, 1986 (23)	NR	Obs MMC+5-FU MMC+5-FU+OK-432	34 32 33	NR		NS, trend in favour of treatment
Bonfanti/GTSG, 1988 (24)	81	Obs mCCNU+5-FU mCCNU+5-FU+levamisole	69 75 69	66† 65† 55†	50 50 50	NS
Jakesz, 1988 (41)	60	Obs MMC+5-FU+Ara-C±OK-432	34 53	37† 55†	29 45	NS
Kim, 1992 (42)	NR	Obs OK-432+ MMC+ 5-FU+Ara-C	64 74	44† 54†	23 45	p<0.05
Popeila, 1982 (56)	NR	Obs 5-FU 5-FU+BCG	44 16 39	NR		p<0.005 at 2 years for immunotherapy versus control (estimated 2-year survival rates, 71% versus

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Author, Year (Reference)	Median Follow-up, Months	Treatment Groups	Number of Patients	% Survival 3yr	% Survival 5yr	p-value
						45%)
Imaizumi, 1990 (57)	NR	Obs MMC+5-FU MMC+5-FU+PSK or OK-432	284 253 282	 NR	73 76 74	NS
Kim, 1997 (58)	NR	Obs 5-FU+MMC OK-432+5-FU+MMC	100 100 170	35† 50† 61†	24 30 45	p<0.05 for chemo-immunotherapy versus Obs and chemo-immunotherapy versus CT
Langman, 1999 (59)	NR	Obs cimetidine	220 215	25† 28†	18 21	NS

Note: 5-FU, 5-fluorouracil; Ara-C, cytarabine; BCG, bacillus Calmlette-Guerin; CT, chemotherapy; MMC, mitomycin C; mCCNU, methyl lomustine; NR, not reported; NS, not significant; Obs, observation; OK-432, picibanil; PSK, polysaccharide K.
* Includes some resected patients for palliation.
† Estimated from survival curve.

Neoadjuvant Chemotherapy

Three randomized trials have compared neoadjuvant chemotherapy prior to surgery versus surgery alone. Only one of these has been fully published, and it detected no significant improvement in either the rate of "curative" resection or downstaging in 59 patients with operable gastric cancer (65). The other two studies, one from Japan (66) and the other from Korea (67), have been published only as abstracts. However, neither was able to demonstrate a survival benefit from neoadjuvant treatment.

Neoadjuvant Radiotherapy

A Chinese study of 370 patients indicated a significant survival benefit favouring neoadjuvant radiation compared with surgery alone (five-year survival rates, 30.1% versus 19.8%, p=0.0094) (68). More recently, two Russian studies published in abstract form suggest improved survival with preoperative radiation compared with surgery alone, especially in the subgroup of patients with lymph node metastases (69,70). Neoadjuvant radiotherapy was described as well tolerated. Consequently, it is being considered an important area of research for future refinement of adjuvant treatment in North American settings.

Neoadjuvant Immunotherapy

There have been three randomized trials of neoadjuvant immunotherapy versus surgery alone. These trials demonstrated no significant survival advantage for neoadjuvant intratumoural injection of OK-432 (71), infusional propionibacterium avidum KP-40 (72), and PSK (73).

Adverse Effects

Many of the adjuvant regimens reported in the literature have caused significant treatment-related morbidity and even death. Chemotherapy in particular can cause hematological toxicity, infections, and gastrointestinal side effects, as described above with combined chemoradiotherapy.

JOURNAL REFERENCE

Earle CC, Maroun J, Zuraw L; Cancer Care Ontario Guidelines Initiative Gastrointestinal Cancer Disease Site Group. Neoadjuvant or adjuvant therapy for resectable gastric cancer? A practice guideline. Can J Surg 2002;45(6):438-46.

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REFERENCES

1. Physician Data Query. Gastric Cancer. CancerNet. Available at: www.cancer.gov/cancer_information/cancer_type/stomach (accessed April 1996).
2. Agboola O. Adjuvant treatment in gastric cancer. Cancer Treat Rev 1994;20:217-40.
3. Middleton G, Cunningham D. Current options in the management of gastrointestinal cancer. Ann Oncol 1995; 6 Suppl 1:S17-S26.
4. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. Lancet 1996;347:995-9.
5. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13:502-12.
6. Gunderson LL, Sosin H. Adenocarcinoma of the stomach: areas of failure in re-operation series (second or symptomatic look) clinicopathologic correlation and implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 1981;8:1-11.
7. Dent DM, Werner ID, Novis B, Cheverton P, Brice P. Prospective randomized trial of combined oncological therapy for gastric carcinoma. Cancer 1979;44:385-91.
8. Moertel CG, Childs DS, O'Fallon JR, Holbrook MA, Schutt AJ, Reitemeier RJ. Combined 5-fluorouracil and radiation therapy as a surgical adjuvant for poor prognosis gastric carcinoma. J Clin Oncol 1984;2:1249-54.
9. Smalley S, Benedetti J, Gunderson L, Martenson J, Tepper J, Kiel K, et al. Intergroup 0116 (SWOG 9008) phase III trial of postoperative adjuvant radiochemotherapy for high risk gastric and gastroesophageal junction adenocarcinoma: evaluation of efficacy and radiotherapy treatment planning [abstract]. Int J Radiat Oncol Biol Phys 2000;3:111-2. Abstract 3. UPDATED BY: Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes, NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. New Engl J Med 2001;345(10):725-30.
10. Longmire WP, Kuzma JW, Dixon WJ. The use of triethylenethiophosphoramide as an adjuvant to the surgical treatment of gastric carcinoma. Ann Surg 1968;167:293-312.
11. Serlin O, Wolkoff HS, Amadeo HM, Keehn RJ. Use of 5-fluorodeoxuridine (FUDR) as an adjuvant to the surgical management of carcinoma of the stomach. Cancer 1969;24:223-8.
12. Imanaga H, Nakazato H. Results of surgery for gastric cancer and effect of adjuvant mitomycin C on cancer recurrence. World J Surg 1977;2:213-21.
13. Nakajima T, Fukami A, Ohashi I, Kajitani T. Long-term follow-up study of gastric cancer patients treated with surgery and adjuvant chemotherapy with mitomycin C. Int J Clin Pharmacol Biopharm 1978;16:209-16.
14. Nakajima T, Fukami A, Ohashi I, Kajitani T. Adjuvant chemotherapy with mitomycin C, and with a multi-drug combination of mitomycin C, 5 fluorouracil and cytosine arabinoside after curative resection of gastric cancer. Jpn J Clin Oncol 1980;10:187-94.
15. Huguier M, Destroyes H, Baschet C, Le Henand F, Bernard PF. Gastric carcinoma treated by chemotherapy after resection: a controlled study. Am J Surg 1980;139:197-9.
16. Schlag P, Schreml W, Gaus W, Herfarth C, Linder MM, Queisser W, et al. Adjuvant 5 fluorouracil and BCNU chemotherapy in gastric cancer: 3 year results. Recent Results Cancer Res 1982;80:277-83.

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17. The Gastrointestinal Tumor Study Group. Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. Cancer 1982;49:1116-22.
18. Higgins GA, Amadeo JH, Smith DE, Humphrey EW, Keehn RJ. Efficacy of prolonged intermittent therapy with combined 5FU and methyl CCNU following resection for gastric carcinoma. A Veterans Administration Surgical Oncology Group Report. Cancer 1983;52:1105-12.
19. Ochiai T, Sato H, Hayashi R, Asano T, Sato H, Yamamura Y. Postoperative adjuvant immunotherapy of gastric cancer with BCG-cell wall skeleton. 3- to 6-year follow up of a randomized clinical trial. Cancer Immunol Immunother 1983;14:167-71.
20. Matsubara Y, Uragari Y, Yamamoto M, Goto M, Nakazato H, Imanaga H. A randomized clinical trial of adjuvant chemotherapy after resection in patients with stomach cancer. Clin Ther 1984;6:689-92.
21. Nakajima T, Takahashi T, Takagi K. Comparison of 5-fluorouracil with ftorafur in adjuvant chemotherapies with combined inductive and maintenance therapies for gastric cancer. J Clin Oncol 1984;2:1366-71.
22. Engstrom PF, Lavin PT, Douglas HO, Brunner KW. Postoperative adjuvant 5 fluorouracil plus methyl CCNU therapy for gastric cancer patients. Eastern Cooperative Oncology Group Study (EST 3275). Cancer 1985;55:1868-73.
23. Yamamura Y, Nishimura M, Sakamoto J, Yasui K, Morimoto T, Kato T, et al. A randomized controlled trial of surgical adjuvant therapy with mitomycin C, 5-fluorouracil and OK-432 in patients with gastric cancer. Gan to Kagaku Ryoho 1986;13:2134-40.
24. The Italian Gastrointestinal Tumor Study Group. Adjuvant treatments following curative resection for gastric cancer. Br J Surg 1988;75:1100-4.
25. Allum WH, Hallissey MT, Kelly KA. Adjuvant chemotherapy in operable gastric cancer. 5 year follow-up of first British Stomach Cancer Group trial. Lancet 1989;1:571-4.
26. Coombes RC, Schein PS, Chilvers CED, Wils G, Beretta JM, Bliss A, et al. A randomized trial comparing adjuvant fluorouracil, doxorubicin and mitomycin with no treatment in operable gastric cancer. J Clin Oncol 1990;8:1362-9.
27. Krook JE, O'Connell MJ, Wieand HS, Beart RW, Leigh JE, Kugler JW, et al. A prospective, randomised evaluation of intensive course 5-fluorouracil plus doxorubicin as surgical adjuvant chemotherapy for resected gastric cancer. Cancer 1991;67:2454-8.
28. Hallissey MT, Dunn HA, Ward LC, Allum WH. The second British Stomach Cancer Group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow-up. Lancet 1994;343:1309-12.
29. Grau JJ, Estape J, Alcobendas F. Positive results of adjuvant mitomycin C in resected gastric cancer: a randomized trial on 134 patients. Eur J Cancer 1993;29A:340-2.
30. Lise M, Nitti D, Marchet A, Sahmoud T, Buyse M, Duez N, et al. Final results of a phase III clinical trial of adjuvant chemotherapy with the modified fluorouracil, doxorubicin, and mitomycin regiment in resectable gastric cancer. J Clin Oncol 1995;13:2757-63.
31. Chou FF, Sheen-Chen SM, Liu PP, Chen FC. Adjuvant chemotherapy for resectable gastric cancer: a preliminary report. J Surg Oncol 1994;57:239-42.
32. MacDonald JS, Fleming TR, Peterson RF, Berenberg JL, McClure S, Chapman RA, et al. Adjuvant chemotherapy with 5-FU, adriamycin, and mitomycin-C (FAM) versus surgery alone for patients with locally advanced gastric adenocarcinoma: A Southwest Oncology Group study. Ann Surg Oncol 1995;2:488-94.
33. Carrato A, Diaz-Rubio E, Medrano J, Calpena R, Marcuello E, Sanz J, et al. Phase III trial of surgery versus adjuvant chemotherapy with mitomycin and tegafur plus uracil

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(UFT), starting within the first week after surgery, for gastric adenocarcinoma [abstract]. Proc Annu Meet Am Soc Clin Oncol 1995;14:198. Abstract 468.
34. Neri B, de Leonardis B, Romano S, Andreoli F, Pernice LM, Bruno L, et al. Adjuvant chemotherapy after gastric resection in node-positive cancer patients: a multicentre randomised study. Br J Cancer 1996;73:549-52.
35. Tsavaris N, Tentas K, Kosmidis P, Mylonakis N, Sakelaropoulos N, Kosmas CH, et al. A randomized trial comparing adjuvant fluorouracil, epirubicin, and mitomycin with no treatment in operable gastric cancer. Chemotherapy 1996;42:220-6.
36. Nakajima T, Nashimoto A, Kitamura M, Kito Y, Iwanaga T, Okabayashi K, et al for the Gastric Cancer Surgical Study Group. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. Lancet 1999;354:273-7.
37. Cirera L, Balil A, Batiste-Alentorn E, Tusquets I, Cardona T, Arcusa A, et al. Randomized clinical trial of adjuvant mitomycin plus tegafur in patients with resected stage III gastric cancer. J Clin Oncol 1999;17:3810-5.
38. Ducreux M, Nordlinger B, Ychou M, Milan C, Bouche O, Ducerf C, et al. Resected gastric adenocarcinoma: randomized trial of adjuvant chemotherapy with 5 FU-cisplatin (FUP). Final results of the FFCD 8801 trial [abstract]. Proc Annu Meet Am Soc Clin Oncol 2000;19:241a. Abstract 932.
39. Di Bartolomeo M, Bajetta E, Bordogna G, Aitini E, Fava S, Schieppati G, et al. Improved adjuvant therapy outcome in resected gastric cancer patients according to node involvement. 5-year results of a randomized study by the Italian Trials in Medical Oncology (ITMO) group [abstract]. Proc Annu Meet Am Soc Clin Oncol 2000;19:241a. Abstract 934.
40. Schiessel R, Funovics J, Schick B, Bohmig HJ, Depisch D, Hofbauer F, et al. Adjuvant intraperitoneal cisplatin therapy in patients with operated gastric carcinoma. Results of a randomized trial. Acta Med Austriaca 1989;16:68-9.
41. Jakesz R, Dittrich C, Funovics J, Hofbauer F, Rainer H, Reiner G, et al. The effect of adjuvant chemotherapy in gastric carcinoma is dependent on tumor histology: 5-year results of a prospective randomized trial. Recent Results Cancer Res 1988;110:44-51.
42. Kim J-P. Results of surgery on 6589 gastric cancer patients and immunochemosurgery as the best treatment of advanced gastric cancer. Ann Surg 1992;216:269-78.
43. Hermans J, Bonenkamp JJ, Boon MC, Bunt AMG, Ohyama S, Sasako M, et al. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. J Clin Oncol 1993;11:1441-7.
44. Alcobendas F, Mula A, Estape J, Curto J, Pera C. Mitomycin-C as an adjuvant in resected gastric cancer. Ann Surg 1983;198:13-7.
45. Hermans J, Bonenkamp H. In reply [letter]. J Clin Oncol 1994;12:879-80.
46. Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. Eur J Cancer 1999;35:1059-64.
47. Mari E, Floriani I, Tinazzi A, Buda A, Belfiglio M, Valentini M, Cascinu S, et al. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of the GISCAD. Ann Oncol 2000;11:837-43.
48. Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjoden PO, Haglund U, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 1997;8:163-8.
49. Hagiwara A, Takahashi T, Kojima O, Sawai K, Yamaguichi T, Yamane T, et al. Prophylaxis with carbon absorbed mitomycin against peritoneal recurrence of gastric cancer. Lancet 1992;339:629-31.

ARCHIVED

50. Sautner T, Hofbauer F, Depisch D, Schiessel R, Jakesz R. Adjuvant intraperitoneal cisplatin chemotherapy does not improve long-term survival after surgery for advanced gastric cancer. J Clin Oncol 1994;12:970-4.
51. Hamazoe R, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Final results of a randomized controlled study. Cancer 1994;73:2048-52.
52. Rosen HR, Jatzko G, Repse S, Potrc S, Neudorfer H, Sandbichler P, et al. Adjuvant intraperitoneal chemotherapy with carbon-adsorbed mitomycin in patients with gastric cancer: results of a randomized multicenter trial of the Austrian Working Group for Surgical Oncology. J Clin Oncol 1998;16:2733-8.
53. Yu W, Whang I, Suh, Averbach A, Chang D, Sugerbaker PH. Prospective randomized trial of early postoperative intraperitoneal chemotherapy as an adjuvant to resectable gastric cancer. Ann Surg 1998;228:347-54.
54. Lygidakis NJ, Sgourakis G, Aphinives P. Upper abdominal stop-flow perfusion as a neo and adjuvant hypoxic regional chemotherapy for resectable gastric carcinoma. A prospective randomized clinical trial. Hepatogastroenterology 1999;46:2035-8.
55. Kramling HJ, Wilkowski R, Duhmke E, Cramer C, Willich N, Schildberg RW. Adjuvant intraoperative radiotherapy of stomach carcinoma. Langenbecks Archiv fur Chirurgie - Supplement - Kongressband 1996;113:211-3.
56. Popiela T, Zembala M, Oszacki J, Jedrychowski W. A follow-up study on chemoimmunotherapy (5-fluorouracil and BCG) in advanced gastric cancer. Cancer Immunol Immunother 1982;13:182-4.
57. Imaizumi M, Kondo T, Kamei H, Ichihashi H. Cooperative studies on surgical adjuvant immunochemotherapy for prevention of postoperative recurrence of gastric cancer (II). Gan to Kagaku Ryoho 1990;17:2397-403.
58. Kim J-P. Recent advances in gastric cancer therapy with immunochemosurgery. Asian J Surg 1997;20:115-8.
59. Langman MJ, Dunn JA, Witing JL, Burton A, Hallissey MT, Fielding JW, et al. prospective, double-blind, placebo-controlled randomized trial of cimetidine in gastric cancer. Br J Cancer 1999;81:1356-62.
60. Sakamoto J, Nakazato H. Evaluation of adjuvant immunochemotherapy in advanced gastric cancer. Gan to Kagaku Ryoho 1993;20:2525-30.
61. Niimoto M, Hattori T, Ito I, Tamada R, Inokuchi K, Orita K, et al. Levamisole in postoperative adjuvant immunochemotherapy for gastric cancer. A randomized controlled study of the MMC + Tegafur regimen with or without levamisole. Report I. Cancer Immunol Immunother 1984;18:13-8.
62. Ochiai T, Sato H. Evaluation of postoperative immunotherapy of gastric cancer. Gan to Kagaku Ryoho 1983;10:373-9.
63. Ochiai T, Sato H, Sato H, Hayashi R, Asano T, Isono K, et al. Randomly controlled study of chemotherapy versus chemoimmunotherapy in postoperative gastric cancer patients. Cancer Research 1983;43:3001-7.
64. Fujimoto S, Furue H, Kimura T, Kondo T, Orita K, Taguchi T, et al. Clinical evaluation of schizophyllan adjuvant immunochemotherapy for patients with resectable gastric cancer – a randomized controlled trial. Jpn J Surg 1984;14:286-92.
65. Songun I, Keizer HJ, Hermans J, Klementschitsch P, De Vries JE, Wils JA, Et Al For The Dutch Gastric Cancer Group (DGCG). Chemotherapy for operable gastric cancer: results of the Dutch randomised FAMTX trial. Eur J Cancer 1999;35:558-62.
66. Fujii M, Kosaki G, Tsuchiya S, Kimura K, Suzuki H, Nakajima T, et al for the Gastric Cancer Chemotherapy Group of Japan. Randomized trial of preoperative adjuvant

ARCHIVED

chemotherapy using oral 5-FU in operable gastric cancer [abstract]. Proc Annu Meet Am Soc Clin Oncol 1999;18:272a. Abstract 1045.
67. Kang YK, Choi DW, Im YH, Kim CM, Lee JI, Moon NM, et al. A phase III randomized comparison of neoadjuvant chemotherapy followed by surgery versus surgery for locally advanced stomach cancer [abstract]. Proc Annu Meet Am Soc Clin Oncol 1996;15:215. Abstract 503.
68. Zhang ZX, Gu XZ, Yin WB, Huang GJ, Zhang DW, Zhang RG. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC) – report on 370 patients. Int J Radiat Oncol Biol Phys 1998;42:929-34.
69. Skoropad V, Berdov B. Preoperative short-term radiotherapy of resectable gastric cancer: complete 20-years follow up of a randomized trial [abstract]. Eur J Cancer 1999;35 Suppl 4:S147. Abstract 542.
70. Skoropad V, Berdov B. Randomized trial of preoperative and intraoperative radiotherapy versus surgery alone in resectable gastric cancer [abstract]. Eur J Cancer 1999;35 Suppl 4:S139. Abstract 508.
71. Gouchi A, Orita K, Fuchimoto S, Konaga E, Satoh K, Mannami T, et al. Randomized control study of preoperative intratumoral injection of OK-432 in gastric cancer patient. Ten years survival [abstract]. Proc Annu Meet Am Soc Clin Oncol 1997;263a. Abstract 931.
72. Peters KM, Beuth J, Ko HL, Pulverer G, Kluger J, Grundmann R. Preoperative immunostimulation with propionibacterium avidum KP-40 in patients with gastric carcinoma: a prospective randomized study. Onkologie 1990;13:124-7.
73. Terashima M, Takagane A, Sasaki T, Kusaka S, Kanno Y, Yashima T, et al. A prospective randomized trial of preoperative immunotherapy using PSK for the treatment of gastric cancer [abstract]. Proc Annu Meet Am Soc Clin Oncol 1998;17:304a. Abstract 1170.

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Evidence-Based Series 2-14 Version 3.2011: Section 3

Neoadjuvant or Adjuvant Therapy for Resectable Gastric Cancer: EBS Development Methods and External Review Process

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A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: April 5, 2011

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THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Gastrointestinal DSG of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on adjuvant or neoadjuvant therapy for resectable gastric cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

This guideline is an update of EBS #2-14, which was originally developed in 2000 and then updated in 2003. The Gastrointestinal DSG believed that this further update was warranted, given the existence of new evidence published that could change the recommendations provided in the previous guideline.

Development of Version 1

Disease Site Group Consensus

The Gastrointestinal DSG readily agreed upon and approved the contents of this guideline. The group added a general statement at the beginning of the recommendation that surgical resection alone is the standard treatment. There was also agreement that patients should be encouraged to participate in clinical trials, and this recommendation was added before the practice guideline was submitted to the Practice Guidelines Coordinating Committee for final approval.

Draft Recommendation

This recommendation applies to patients with potentially curable gastric cancer.

- Surgical resection alone is the standard treatment.
- There is insufficient evidence from randomized trials to recommend neoadjuvant or adjuvant chemotherapy, radiation therapy or immunotherapy, either alone or in combination, outside of a clinical trial.

Practitioner Feedback

Methods

Practitioner feedback was obtained through a mailed survey consisting of nine questions asking for ratings on the quality of the practice-guideline-in-progress report and whether the draft recommendation should serve as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (postcard) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Gastrointestinal DSG.

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Results

Number surveyed: 125 practitioners in Ontario
Return rate: 72%
Respondents providing written comments: 32%
Quality of data synthesis: 97% agreed or strongly agreed that the summary of the evidence was acceptable
Agreement with the draft recommendation: 99%
Approval of the draft recommendation as a guideline: 89%

Main Points Made as Comments

Most practitioners agreed with the draft recommendation and indicated that it reflected their own practice and that of their colleagues. A few respondents pointed out that some patients, especially young patients with aggressive tumours, may desire adjuvant treatment, and that it should not be considered inappropriate to treat such patients.

Modifications/Actions

The Gastrointestinal DSG reviewed the practitioner feedback, but no modifications to the draft recommendation were necessary as a result of feedback from practitioners. The Gastrointestinal DSG approved the draft recommendation as a practice guideline.

Feedback from the Coordinating Committee

One member of the Cancer Care Ontario Practice Guidelines Coordinating Committee (CCO PGCC) suggested that patients not participating in clinical trials should be informed that there may be a small survival benefit with adjuvant chemotherapy, particularly among patients with node-positive gastric cancer, but that there is also the potential for significant adverse effects. A fourth bullet was added to the recommendations to address this issue.

Practice Guideline (Version 1)

This practice guideline applies to patients with potentially curable gastric cancer.

- Surgical resection alone is the standard treatment.
- There is insufficient evidence from randomized trials to recommend neoadjuvant or adjuvant chemotherapy, radiation therapy or immunotherapy, either alone or in combination, outside of a clinical trial.
- Patients should be encouraged to participate in randomized controlled trials of adjuvant and neoadjuvant treatments.
- The option of adjuvant chemotherapy should be discussed with patients not participating in clinical trials. Issues to take into consideration include the balance between adverse effects and the small survival benefit for adjuvant chemotherapy that has been observed in pooled clinical trials, particularly in patients with node-positive disease.

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Development of Version 2

Draft Recommendations

Based on the evidence from Section 2B above, the Gastrointestinal DSG drafted the following recommendations:

Target Population

These recommendations apply to adult patients with potentially curable gastric cancer.

Recommendations

- Following surgical resection, patients should be considered for adjuvant combined chemoradiotherapy. The current standard protocol consists of one cycle of 5-FU (425 mg/m^2/day) and leucovorin (20 mg/m^2/day) in a daily regimen for five days, followed one month later by 4500 cGy (180 cGy/day) of radiation given with 5-FU (400 mg/m^2/day) and leucovorin (20 mg/m^2/day) on days 1 through 4 and the last three days of radiation. One month after completion of radiation, two cycles of daily x five 5-FU (425 mg/m^2/day) and leucovorin (20 mg/m^2/day) are given at monthly intervals.

- For patients unable to undergo radiation, adjuvant chemotherapy alone may be of benefit, particularly for patients with lymph node metastases. The optimal regimen remains to be defined.

- Patients should understand the tradeoffs between survival benefit and toxicity before making treatment decisions.

- There is insufficient evidence from randomized trials to recommend neoadjuvant chemotherapy, or neoadjuvant or adjuvant radiation therapy or immunotherapy, either alone or in combination, outside of a clinical trial.

Practitioner Feedback

Methods

Practitioner feedback was obtained through a mailed survey of 166 practitioners in Ontario (27 medical oncologists, 21 radiation oncologists, 155 surgeons, and three gastroenterologists). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Gastrointestinal DSG.

Results

Key results of the practitioner feedback survey are summarized in Table 1. Ninety-nine (63%) surveys were returned. Seventy-four (75%) respondents (13 medical oncologists, 10 radiation oncologists, 50 surgeons, and one gastroenterologist) indicated that the practice-guideline-in-progress report was relevant to their clinical practice and completed the survey. Of the 74 clinicians who completed the survey, 70% agreed that the document should be approved as a practice guideline, and 88% agreed that they would use it in their own clinical practice. The approval rate of 70% was felt to be borderline but acceptable, and mostly due to concerns about the toxicity of adjuvant treatment in this population.

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Table 1. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)*		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	74 (100%)	0	0
There is a need for a clinical practice guideline on this topic.	70 (95%)	4 (5%)	0
The literature search is relevant and complete.	57 (77%)	12 (16%)	1 (1%)
The results of the trials described in the report are interpreted according to my understanding of the data.	68 (92%)	5 (7%)	0
The draft recommendations in this report are clear.	69 (93%)	1 (1%)	4 (5%)
I agree with the draft recommendations as stated.	67 (91%)	3 (4%)	4 (5%)
This report should be approved as a practice guideline.	52 (70%)	13 (18%)	6 (8%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	65 (88%)	6 (8%)	3 (4%)

* Percentages may not total 100% due to missing data.

Summary of Written Comments

Thirty (40%) respondents provided written comments. Most practitioners agreed with the recommendations, although several expressed reservations about the toxicity of chemoradiotherapy, its impact on radiation resources, and the risk/benefit trade-off for very early stage patients with a relatively good prognosis. There was interest in seeing the final complete publication of the SWOG-9008 trial results, as well as in seeing confirmatory randomized trials. Some practitioners commented that they are already using more modern chemotherapy regimens such as ECF combination therapy.

Modifications/Actions

Minor changes were made to the text of the document but not to the final recommendation. A statement about the possibility of radiation damage to surrounding organs, such as the kidney, was added to the abstract and full report. The Gastrointestinal DSG members noted that the SWOG-9008 trial detected a clear benefit for chemoradiotherapy. Interim results for this trial had been presented at both the 2000 annual meetings of ASCO and the ASTRO. Also, as an intergroup trial, there has been the added benefit of peer review from a large group of investigators. In the period of time since approval of this practice guideline by the Practice Guideline Initiative (PGI), the five-year results of the SWOG-9008 trial have been published in full (9).

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Practice Guideline (Version 2)

This practice guideline (Version 2) reflects the integration of the draft recommendations with feedback obtained from the external review process. It was approved by the Gastrointestinal DSG and the PGCC.

Target Population

These recommendations apply to adult patients with potentially curable surgically resected (T1-4,N0-2,M0) gastric cancer.

Recommendations

- Following surgical resection, patients whose tumours penetrated the muscularis propria or involved regional lymph nodes should be considered for adjuvant combined chemoradiotherapy. The current standard protocol consists of one cycle of 5-FU (425 mg/m2/day) and leucovorin (20 mg/m2/day) in a daily regimen for five days, followed one month later by 4,500 cGy (180 cGy/day) of radiation given with 5-FU (400 mg/m2/day) and leucovorin (20 mg/m2/day) on days 1 through 4 and the last three days of radiation. One month after completion of radiation, two cycles of 5-FU (425 mg/m2/day) and leucovorin (20 mg/m2/day) in a daily regimen for five days are given at monthly intervals.
- There is no evidence on which to make a recommendation for patients with node-negative tumours that have not penetrated the muscularis propria.
- For patients unable to undergo radiation, adjuvant chemotherapy alone may be of benefit, particularly for patients with lymph node metastases. The optimal regimen remains to be defined.
- There is insufficient evidence from randomized trials to recommend neoadjuvant chemotherapy, or neoadjuvant or adjuvant radiation therapy or immunotherapy, either alone or in combination, outside of a clinical trial.

Qualifying Statements

- Patients should understand the tradeoffs between survival benefit and toxicity before making treatment decisions.

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Development of Version 3

Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel (RAP), which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the RAP included:

- a concern about the absence of adverse events as an outcome of interest. *Adverse event data were extracted and included in the report.*
- a query about whether the meta-analyses included were published literature, or individual patient data meta-analyses. *This was clarified in the document.*
- a query about why all meta-analyses about postoperative chemotherapy were discussed even though there was likely overlap between them and a further query about whether any of the new RCTs identified in this section were included in the meta-analyses. *The meta-analyses were checked, and as there was considerable overlap in the studies included, they did not all need to be discussed. Most of the individual RCTs identified were included in one or more of the meta-analyses and, therefore, did not need to be discussed individually. Furthermore, at the same time this report was sent to RAP, a new IPD meta-analysis was published. It was decided that this meta-analysis superseded all the other the meta-analyses on postoperative chemotherapy as they were all published literature meta-analyses. The identification of this recent IPD meta-analysis necessitated the systematic update of the entire literature search.*
- a query concerning the lack of a recommendation for postoperative chemotherapy. *Given the identification of the IPD meta-analysis on postoperative chemotherapy, the recommendations were revised.*
- a query about the meaning of the qualifying statement, in Section 1, describing the differences in the study populations included in the Macdonald and Cunningham trials. *This statement was meant to give guidance as to which population had evidence for a particular approach. This was clarified in the document.*
- a concern that the significant 5-year mortality data in the Fiorica et al. meta-analysis might be spurious given that the 3-year data was not significant. *The 3-year data was added to the Key Evidence in Section 1, and this issue is now considered in the Discussion in Section 2.*
- a query about how the Boige et al. data might fit into the recommendations about preoperative/perioperative chemotherapy. *Currently, the Boige et al. data are only available in abstract form, and it is unknown when they will be published in full. A qualifying statement was added to Section 1 outlining that, if these data are confirmed in a full publication with no material differences in the reported toxicities, the DSG would consider recommending the protocol used in the Boige study.*
- a suggestion that the results be reorganized so that the quality of the evidence and the outcomes for each type of treatment be grouped together so that it would be easier to evaluate each type of treatment. *This change was made.*
- some small editorial changes. *These changes were made.*

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External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC Report Approval Panel, the Gastrointestinal (GI) DSG circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the GI DSG.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review October 20, 2010

QUESTION

Should patients with resectable gastric cancer (Stage 1B and above) receive neoadjuvant or adjuvant therapy in addition to surgery? Outcomes of interest are overall survival (OS), disease-free survival (DFS) if available, and adverse events.

TARGET POPULATION

These recommendations apply to adult patients with potentially curable, surgically resectable (Stage 1B and above) gastric cancer.

INTENDED USERS

These guidelines are intended for use by clinicians and healthcare providers involved in the management and referral of patients with resectable gastric cancer.

RECOMMENDATIONS

- Postoperative 5-fluorouracil (5-FU)-based chemoradiotherapy (CRT) based on the Macdonald approach (1) (Section 2A, Appendix 6) or perioperative epirubicin/cisplatin/5-FU (ECF) chemotherapy based on the Cunningham/Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) approach (2) (Section 2A, Appendix 6) are both acceptable standards of care. Choice of treatment should be made on a case-by-case basis.

- Adjuvant chemotherapy is a reasonable option for those patients for whom the Macdonald (1) and MAGIC (2) protocols are contraindicated.

- Patients with resectable gastric cancer should undergo a pre-treatment multidisciplinary assessment to determine the best plan of care. In addition to surgery, all patients should be considered for neoadjuvant and/or adjuvant therapy.

KEY EVIDENCE

- Two secondary analyses of the Southwestern Oncology Group (SWOG)/Intergroup trial (1) were identified that reported updated survival data (3,4). These results are consistent with earlier data reported in Section 2B of this report. Updated results from Hundahl (3) indicated a median survival of 36 months for patients who received postoperative chemoradiotherapy (5FU/Leucovorin) versus (vs.) 27

months for patients who underwent surgery alone (p=0.003). Relapse-free survival was 30 months vs. 19 months (p<0.001). A further update of this trial (4) demonstrates that the original SWOG/Intergroup trial results reported in 2001 are robust with almost identical results, even with more than 11 years of follow up for both OS (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.63 to 0.92; p=0.005) and DFS (HR, 0.66; 95% CI, 0.55 to 0.80; p<0.001), favouring postoperative CRT over surgery alone.

- The MAGIC trial (2) is the largest trial incorporating preoperative therapy to date and the only randomized trial with a perioperative approach. A significant benefit for perioperative ECF was reported for overall survival (HR, 0.75; 95% CI, 0.60 to 0.93; p=0.009) and progression-free survival (PFS) (HR, 0.66; 95% CI, 0.53 to 0.81; p<0.001).
- A meta-analysis by Fiorica (5) of five trials that provided 3-year mortality data indicated a non-significant benefit for postoperative chemoradiotherapy over surgery (odds ratio [OR], 0.79; 95% CI, 0.59 to 1.05; p=0.10). However, the meta-analysis of three trials that provided 5-year mortality data indicated a significant benefit for postoperative CRT over surgery (OR, 0.45; 95% CI, 0.32 to 0.64; p<0.00001).
- An individual patient data meta-analysis by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group (6) found a modest advantage for postoperative chemotherapy for OS (HR, 0.82; 95% CI, 0.76 to 0.90; p,0.001) and for DFS (HR, 0.82; 95% CI, 0.75 to 0.90; p<0.001).

QUALIFYING STATEMENTS

- The Macdonald (1) and MAGIC (2) protocols have never been compared to each other in a single trial to determine if one is superior to the other.
- The mix of tumour sites in the Macdonald (1) and MAGIC (2) protocols were not the same. In the MAGIC trial (2), 74% of participants had a stomach tumour, 11.5% had a gastroesophageal junction (GEJ) tumour, and 14.5% had a lower esophageal tumour. In the Macdonald (1) trial, most participants had a tumour in the distal stomach. However, approximately 20% of participants had lesions present in the GEJ. There were no espophageal tumours.
- The Boige et al. (7) study comparing preoperative 5FU/cisplatin vs. surgery alone demonstrated a significant improvement in OS and DFS with preoperative chemotherapy. Since this data is currently only available in abstract form, the Gastrointestinal Disease Site Group (Gastrointestinal DSG) does not recommend this treatment at this time. However, should these stated benefits be maintained when published in full and there are no material differences in reported toxicities, the DSG would consider recommending the Boige protocol in patients with advanced gastric cancer.
- Technical considerations pertaining to the delivery of radiation therapy are provided in the Discussion in Section 2A of this report.

Methods

Targeted Peer Review: During the guideline development process, three targeted peer reviewers from Ontario and the United States considered to be clinical and/or methodological experts on the topic were identified by the working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. The three reviewers agreed, and the draft report and a questionnaire were sent via email for

their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on October 20, 2010. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The GI DSG reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All medical oncologists, radiation oncologists and surgical oncologists from Ontario in the PEBC database were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on October 26, 2010. The consultation period ended on December 14, 2010. The GI DSG reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received from three reviewers. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	**Lowest Quality (1)**	**(2)**	**(3)**	**(4)**	**Highest Quality (5)**
1. Rate the guideline development methods.					3
2. Rate the guideline presentation.					3
3. Rate the guideline recommendations.			1	1	1
4. Rate the completeness of reporting.					3
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1		2
6. Rate the overall quality of the guideline report.					3
	Strongly Disagree (1)	**(2)**	**Neutral (3)**	**(4)**	**Strongly Agree (5)**
7. I would make use of this guideline in my professional decisions.		1		1	1
8. I would recommend this guideline for use in practice.		1		1	1

9. What are the barriers or enablers to the implementation of this guideline report?
There were no consistent barriers or enablers identified by the reviewers. One reviewer did identify the perceived urgency of the situation, by patients and their families, on not wanting to wait to see multidisciplinary team members.

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Summary of Written Comments

The main points contained in the written comments were:

i. A concern that these guidelines will equate GE junction cancer and gastric cancer.
ii. A request for more discussion of surgical considerations with respect to downsizing.
iii. A request for discussion of the challenges of postoperative radiotherapy in elderly or infirm patients.
iv. A request that the target population be better clarified beyond just 'Stage 1B and above' to include criteria related to invasion of the muscularis propria.
v. A suggestion to include the POET study.
vi. A suggestion to add neoadjuvant chemoradiation as a potential topic for future research.
vii. A concern that in the 'Considerations for Choice of Therapy Section,' basing a decision of treatment choice on whether or not a tumour is 'large' is a vague descriptor.
viii. A few small editorial changes.

Professional Consultation: Twenty-eight responses were received. Key results of the feedback survey are summarized in Table 3.

Table 3. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	**Lowest Quality (1)**	**(2)**	**(3)**	**(4)**	**Highest Quality (5)**
1. Rate the overall quality of the guideline report.			2 (7)	18 (64)	8 (29)
	Strongly Disagree (1)	**(2)**	**(3)**	**(4)**	**Strongly Agree (5)**
2. I would make use of this guideline in my professional decisions.			1 (4)	15 (54)	12 (43)
3. I would recommend this guideline for use in practice.			2 (7)	12 (43)	14 (50)

4. What are the barriers or enablers to the implementation of this guideline report?

Many reviewers identified timely access to a multidisciplinary team as a potential barrier to implementation of the guideline especially preoperative access to a medical oncologist.

Summary of Written Comments

The main points contained in the written comments were:

ix. A request that an educational component possibly including case-based teachings be provided along with the guideline.
x. A request that all oncologists, and especially community-based surgeons, be made aware of the guideline.
xi. A request to include median survival improvements from the MAGIC trial rather than just the hazard ratio.
xii. A query as to why there was no discussion regarding substituting capecitabine for 5-FU in the ECF regimen.

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Modifications/Actions

i. It was decided that it acceptable to apply the recommendations to GEJ tumours, because such tumours were included in both the Macdonald (3) and Cunningham (4) studies, albeit in smaller proportions than those with gastric tumours.
ii. Some discussion on down-staging was added to the section "Considerations for Choice of Therapy" in the Discussion.
iii. There are no data to support how elderly or infirm patients should be treated.
iv. The target population was clarified with respect to invasion of the muscularis propria.
v. The POET study was determined not to meet the inclusion criteria for this guideline.
vi. Neoadjuvant chemoradiation was added as a potential topic in the Future Research section of the guideline.
vii. The term 'large' was changed to 'bulky.' There are no standardized size criteria that define a large/bulky tumour.
viii. Several small editorial changes were made.
ix. The DSG agrees that an educational component to accompany the guideline would be useful. However, this falls under the domain of dissemination, which is under the mandate of Cancer Care Ontario.
x. The DSG agrees that this guideline should be widely disseminated. Again, dissemination is the purview of Cancer Care Ontario and not the PEBC.
xi. Median survival was not reported in the MAGIC trial. This is noted in Table 5 of Section 2A.
xii. Currently, there are no data to support the substitution of capecitabine for 5-FU in the adjuvant setting. Therefore, it is not discussed.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the GI DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.
3. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725-30.
4. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20.

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