



**PROPOSED REVIEW OF SIGN GUIDELINE
CONSULTATION SUMMARY**

Title of guideline	SIGN 87: Management of oesophageal and gastric cancer
Date of publication	June 2006
SIGN summary of the scoping search	<p>HTAs and systematic reviews:</p> <p>Bjelakovic et al. Antioxidant supplements for preventing gastrointestinal cancers. Cochrane Database of Systematic Reviews: 2008, Issue 3.</p> <p>Fuccio et al. Meta-analysis: can H.pylori eradication treatment reduce the risk for gastroc cancer. Ann Intl Med 2009; 96 (1) 26-33</p> <p>Rokkas et al. The long term impact of H.pylori eradication on gastric histology: a systematic review and meta-analysis. Helicobacter 2007 (12): 32-8</p> <p>Vakil N, Moayyedi P, Fennerty M B, Talley N J. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. <i>Gastroenterology</i>.2006;131(2):390-401.</p> <p>Li et al. A systematic review and meta-analysis of the treatment for barrett's esophagus. Digestive disease and sciences 2008; 53(11): 2837-46</p> <p>Chang et al. The effect of antireflux surgery on esophageal carcinogenesis in patients with Barrett esophagus: a systematic review. Annals of surgery 2007; 246(1):11-21</p> <p>Nurgalieva Z, Lowrey A, El-Serag H B. The use of cytokeratin stain to distinguish Barrett's esophagus from contiguous tissues: a systematic review. Digestive Diseases and Sciences 2007; 52(5): 1345-1354</p> <p>Scarpa et al. A systematic review on the clinical diagnosis of gastrointestinal stromal tumours. J of Surgical Oncology 2008; 98(5): 384-92</p> <p>Kwee et al. The accuracy of endoscopic ultrasonography in differentiating mucosal from deeper gastric cancer. American J of Gastroenterology. 2008; 103(7): 1801-9</p> <p>Puli et al. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. World j of gastroenterology 2008; 14(10):1479-90</p> <p>Dyer et al Systematic review of the impact of endoscopic ultrasound on the management of patients with esophageal cancer Int J Tech Asses in Health Care 2008: 24(1):25-35</p> <p>Van Vliet et al. Staging investigations for oesophageal cancer: a meta-analysis. British J or cancer 2008; 98(3): 547-57</p> <p>Parameswaran et al. The role of health-related quality of life outcomes in</p>

clinical decision making in surgery for esophageal cancer: a systematic review. *Annals of surgical oncology* 2008. 15(9):2372-9

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Yang S H, Zhang Y C, Yang K H, Li Y P, He X D, et al **An evidence-based medicine review of lymphadenectomy extent for gastric cancer.** *American Journal of Surgery*.2009;**197**(2):246-251.

Green et al **Surgery vs radical endotherapies for early cancer and high grade dysplasia in Barrett's oesophagus** *Cochrane Database of Systematic Reviews*: 2009, Issue 2.

Yang Z, Zheng Q, Wang Z. **Meta-analysis of the need for nasogastric or nasojejunal decompression after gastrectomy for gastric cancer.** *British Journal of Surgery*.2008;**95**(7):809-816.

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Main conclusions from new evidence

- Evidence that beta-carotene, vitamin A, vitamin C, and vitamin E or their combinations may prevent gastrointestinal cancers is not found. These antioxidant supplements even seem to increase mortality. Selenium alone may have preventive effects on gastrointestinal cancers. This finding is based on trials with flaws in their design and needs confirmation in properly conducted randomised controlled trials.
- H. pylori eradication treatment reduces gastric cancer risk.
- Alarm features have limited predictive value for an underlying malignancy.
- There have been only a limited number of RCTs that compare treatments for Barrett's oesophagus (BE). The pharmacological therapy, antireflux surgery, and endoscopic ablative techniques are promising in terms of treating BE, but the studies carried out to date have had no adequate power to assess the effect of treatment on reducing and preventing

progression to adenocarcinoma.

- Antireflux surgery is associated with regression of Barrett esophagus and/or dysplasia. However, evidence suggesting that surgery reduces the incidence of adenocarcinoma is largely driven by uncontrolled studies.
- Immunostaining for cytokeratin (CK) 7 or CK20 is reasonably accurate for differentiating Barrett's oesophagus (BE), especially LSBE, from antrum intestinal metaplasia (IM), fundus IM and noncardiac gastric IM. The accuracy of CK in distinguishing BE, especially SSBE, from gastric cardia IM is more conflicting.
- Four meta-analyses reported on endoscopic ultrasound (EUS) in gastric cancer. The first one concluded that endoscopy and mucosal biopsy should be reserved to patients with gastrointestinal bleeding. EUS-FNA provides direct visualisation of the neoplasm and adequate samples for molecular diagnosis. EUS, abdominal CT and MRI may be considered valid alternatives whenever EUS-FNA is unavailable or a cytological diagnosis is unnecessary. The second one concluded that it is unclear yet whether EUS can accurately differentiate between mucosal and deeper gastric cancer. The third found that EUS had excellent sensitivity and specificity in accurately diagnosing the TN stage of oesophageal cancer. It performed better in advanced (T4) than early (T1) disease. FNA improved accuracy of N stage assessment. The last study revealed a change in patient management following EUS for staging oesophageal cancer, a higher level of evidence for a clinical benefit than can be obtained from accuracy studies alone.
- Diagnostic performance of FDG-PET for distant metastases was significantly higher than that of CT, which was not significantly affected by study and patient characteristics. For the detection of regional lymph node metastases, EUS is most sensitive, whereas CT and FDG-PET are more specific tests. For the evaluation of distant metastases, FDG-PET has probably a higher sensitivity than CT. Its combined use could be of clinical value, with FDG-PET detecting possible metastases and CT confirming or excluding their presence and precisely determining the location(s).
- Health-related quality of life (HRQL) outcomes are relevant to surgical decision making. Methods to communicate HRQL outcomes to patients are required to inform consent and clinical practice.
- Laparoscopic assisted distal gastrectomy (LADG) was associated with a significantly reduced rate of intraoperative blood loss, at the expense of significantly longer operating time and significantly reduced lymph node retrieval compared to its open counterpart. Mortality and tumour recurrence were similar between the two groups. Time to commencement of oral intake, postprocedural discharge from hospital and perioperative complication rate, although not significantly different between the two groups, did suggest a positive trend toward LADG. It was not recommended on the routine use of LADG over ODG for the treatment of distal gastric cancer. However, significant limitations exist in the interpretation of this data due to the limited number of published RCTs, the small sample sizes to date, and the limited duration of follow up. Further large multicentre RCTs are required to delineate significantly quantifiable differences between the two groups. Another study also revealed that compared with CODG, LADG is associated with lower morbidity, less pain, faster bowel function recovery and a shorter hospital stay when used to treat early gastric cancer.
- D2 and D3 surgery may not offer specific advantages for gastric cancer and instead may lead to disadvantages for patient outcomes.

- Two reviews mentioned lack of RCTs in which endoscopic mucosal resection (EMR) is compared with surgery for early stomach cancer. There is a need for well-designed RCTs to determine the effects of EMR compared to gastrectomy. Current use of endotherapies in the care of patients with early cancer or high grade dysplasia or Barrett's oesophagus should be at the recommendation of the multi-disciplinary team involved in individual care.
- Routine nasogastric or nasojejunal decompression is unnecessary after gastrectomy for gastric cancer.
- A combination of chemotherapy and radiotherapy is more effective than radiotherapy alone for localised cancer of the oesophagus.
- Three studies addressed neoadjuvant therapies on oesophageal carcinoma. The first one showed that postoperative adjuvant chemotherapy can improve the 3-year survival rate of the patients with oesophageal carcinoma. The second one found that there was a significant survival benefit with neoadjuvant chemoradiotherapy and, to a lesser extent, with neoadjuvant chemotherapy in patients with adenocarcinoma of the oesophagus. The third revealed that there was evidence of a dose-response relationship between increasing protocol prescribed radiotherapy, 5FU and cisplatin dose and pCR.
- In patients with resectable gastric carcinoma, adjuvant radiotherapy significantly reduces 3-year and 5-year all cause mortality, but the magnitude of the benefit is relatively small. Available evidence is inadequate to determine whether postoperative chemotherapy is superior to preoperative radiotherapy.
- Postoperative adjuvant chemotherapy for gastric cancer confers slightly significant benefits compared to the surgery alone. In another study, intravenous 5-FU containing chemotherapy could improve survival after curative gastrectomy, but the methodological limitations of the studies mean that further research is required to confirm these results. In another study conducted in Japan for gastric cancer patients following curative resection, adjuvant chemotherapy using o-FP for long-term maintenance therapy appears to be effective compared to surgery alone.
- Statistically, adjuvant chemotherapy could improve the survival rate and disease-free survival rate in gastric cancer after curative resection and reduce the relapse rate.
- Adjuvant immunochemotherapy with PSK improves the survival of patients after curative gastric cancer resection.
- Hyperthermic intraoperative intraperitoneal chemotherapy with or without early postoperative intraperitoneal chemotherapy after resection of advanced primary gastric cancer is associated with improved overall survival. However, there is increased risk of intra-abdominal abscess and neutropenia.
- Chemoradiotherapy followed by surgery is effective in increasing QALYs in patients with locally invasive oesophageal cancer, but patients potentially at risk from multimodal treatments may benefit from surgery alone.
- A small review concluded that it has not yet been proven that chemotherapy prolongs survival and/or improves quality of life of patients with metastatic esophageal cancer.
- Postoperative chemotherapy can improve overall survival after radical

	<p>surgery for advanced gastric cancer; there is no standardised chemotherapy regimen. Japanese-style D2 radical surgery plus oral 5-fluorouracil appears to be an effective treatment.</p> <ul style="list-style-type: none"> ▪ Comparing the efficacy of chemotherapy and support treatment in patients with advanced non-resectable gastric cancer, chemotherapy was found to increase the 1-year survival rate of the patients and provided a longer symptom-free period of 6 months and an improvement in quality of life. ▪ Best survival results on chemotherapy in patients with advanced gastric cancer were achieved with a three-drug regimen of chemotherapy, containing fluorouracil, an anthracycline and cisplatin. ▪ Response to treatment was related to time to progression and overall survival time. The potential role of objective response as a surrogate in chemotherapy trials of advanced gastric cancer warrants further investigation, especially with regard to treatment with new drugs. 		
New areas that could be added to the guideline	<ul style="list-style-type: none"> ▪ The use of antioxidant supplements in the prevention of gastrointestinal cancer. ▪ Benefits and harms of Helicobacter pylori eradication. ▪ Combination of chemotherapy and radiotherapy for treatment of patients with localised cancer of the oesophagus 		
Summary of the recommendations that could be updated	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%; vertical-align: top;"> <ul style="list-style-type: none"> ▪ Patients presenting with any alarm symptom should be referred for early endoscopy (B) ▪ Routine use of chromoendoscopy during upper GI endoscopy is not recommended, but may be of value in selecting patients at high risk of oesophageal or gastric malignancy (D) ▪ Patients with oesophageal or oesophagogastric junction cancers who are candidates for any curative therapy should have their tumours staged with endoscopic ultrasound +/- fine needle aspiration (B) ▪ PET is not routinely indicated in the staging of oesophageal or gastric cancers (C) ▪ Laparoscopic and thoracoscopic techniques should only be carried out by experienced surgeons within specialise units as part of a controlled prospective study with full informed consent and local clinical governance committee support (GPP) ▪ D2 lymphadectomy, with minimum of 25 lymph nodes removed, should be considered for patients undergoing gastrectomy. (B) ▪ Superficial oesophageal cancer limited to the mucosa and early gastric cancer limited to the superficial submucosa should be treated by EMR (B) ▪ Various recommendations on neoadjuvant and adjuvant therapies (ranging from Grade A to good practice points) </td> <td style="width: 30%; vertical-align: top; text-align: center;"> Section: 3.3 4.2.1 5.1.2 5.1.7 7.3.2 7.5.2 7.8.2 8 </td> </tr> </table>	<ul style="list-style-type: none"> ▪ Patients presenting with any alarm symptom should be referred for early endoscopy (B) ▪ Routine use of chromoendoscopy during upper GI endoscopy is not recommended, but may be of value in selecting patients at high risk of oesophageal or gastric malignancy (D) ▪ Patients with oesophageal or oesophagogastric junction cancers who are candidates for any curative therapy should have their tumours staged with endoscopic ultrasound +/- fine needle aspiration (B) ▪ PET is not routinely indicated in the staging of oesophageal or gastric cancers (C) ▪ Laparoscopic and thoracoscopic techniques should only be carried out by experienced surgeons within specialise units as part of a controlled prospective study with full informed consent and local clinical governance committee support (GPP) ▪ D2 lymphadectomy, with minimum of 25 lymph nodes removed, should be considered for patients undergoing gastrectomy. (B) ▪ Superficial oesophageal cancer limited to the mucosa and early gastric cancer limited to the superficial submucosa should be treated by EMR (B) ▪ Various recommendations on neoadjuvant and adjuvant therapies (ranging from Grade A to good practice points) 	Section: 3.3 4.2.1 5.1.2 5.1.7 7.3.2 7.5.2 7.8.2 8
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	<ul style="list-style-type: none"> In patients with locally advanced or metastatic cancer of the oesophagus and stomach with good performance status, combination chemotherapy including cisplatin and infusional 5-FU should be considered (B). <p>Patients should be made aware of the modest survival benefit and potential symptomatic improvement, but potential toxicities. (GPP)</p>	10.9.1
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Please answer the following questions as fully as possible:

Specialties:	Surgery (3), Gastroenterology (2), Oncology (2). Palliative Medicine (1), Radiology (1)	
1(a) Is there still a requirement for an evidence-based guideline on this topic?	Yes	
1(b) If no, should the guideline be withdrawn?		
2(a) Based on the information given above, and your own clinical judgement, does the guideline require revision in the light of new evidence? <i>Please give details.</i>	<p>Section 2.2: Revise where there is evidence of carcinogenic compounds and medications or previous surgery.</p> <p>Section 3: Revise in the light of advances in endoscopic imaging techniques with narrow band, autofluorescence and zoom techniques which improve diagnostic yield.</p> <p>Section 3.3: Revise to stress the importance of early diagnosis of oesophageal pre and early malignancy.</p> <p>Sections 4.3.2 and 4.5.1: Revise to include additional immunohistochemistry where helpful</p> <p>Section 5: Update CT-PET along with the other staging.</p> <p>Section 5.1: Needs updated to include TNM 7 classification.</p> <p>Section 5.1.2: Add EUS</p> <p>Section 5.1.7: the role of PET CT in identifying distant metastases in patients considered suitable for curative surgery should be revised.</p> <p>Section 5.2.1: Update to include new staging radiological criteria for oesophago-gastric cancer.</p> <p>Section 7: New evidence on minimally invasive surgery should be incorporated into this section.</p> <p>Section 8: Update neoadjuvant and adjuvant therapies and include managing Barrett's HGD/Mucosal cancer with EMR/mucosal ablation with RFA.</p> <p>Section 8.2: Updated to cover pre-operative chemotherapy in operable gastric cancer.</p> <p>Section 10: Revise recommendations for the referral for palliative care assessment of most, if not all, patients with very advanced disease.</p>	
2(b) If no, is there a need to scope for new evidence on a yearly basis?	Yes	
2(c) Do you agree with the assessment of the impact of the new evidence and its likely effect on recommendations?	<p>Yes</p> <p>The summary of the impact and changes potentially to recommendations is valid based on studies identified, but there are some caveats in that data from patients in the Far East must be interpreted with caution when applied to a western population due to:</p> <ul style="list-style-type: none"> Demographic differences in the patient populations with oesophagogastric cancer in the west and east as reflected for example in differential co-morbidity in general for eastern and western patients and different epidemiological patterns for the disease which is particularly relevant with regard to data on surgical practice and adjuvant and neoadjuvant treatment and less so for advanced disease Differences in surgical practice in the east and the west again relevant for the interpretation of data on surgical practice and especially data adjuvant and neoadjuvant treatment Different biology of the disease in the east and the west, as indicated by studies reporting different molecular features in eastern and western populations which have relevance for therapy <p>In addition there are some clinically significant omissions in terms of the evidence identified and assessed. In</p>	

particular, several studies recently reported that are clinically significant but not included in meta-analyses and some systematic reviews and a few Meta-analyses not included.

2(d) If yes, please suggest clinical questions that could be addressed in the revision?

- Which patients should undergo PET CT?
- Role of staging modalities / suggested staging algorithm
- Staging : role of various tests including PET and EUS
- The role of analgesia post-operatively and whether epidural or para-spinal analgesia
- Value of alarm symptoms in predicting those who need urgent referral
- Role of HP eradication therapy in preventing gastric cancer
- Accuracy of staging investigations – CT, PET, EUS
- Role of neoadjuvant chemotherapy in oc
- Role of perioperative chemotherapy in gastric cancer
- Role of minimally invasive surgical techniques on oc and gc surgery.
- Role of endoscopic mucosal resection for early cancers of oesophagus or stomach
- Role of endoscopic radiofrequency ablation in early Barrett’s neoplasia.
- How to increase diagnosis of Barrett’s oesophagus and early neoplasia
- Revisiting the role of adjuvant, neoadjuvant, perioperative therapies for both oes and gastric; revisiting role of palliative therapies including chemo and radiotherapy.
- Role of endotherapies for early lesions would be appropriate
- What are the indications for laparoscopic gastrectomy and minimally invasive oesophagectomy and which procedure is best.
- Which is the best open operation for gastric cancer/lymphadenectomy
- What is the role of FDG PET in staging and also prediction of response to systemic therapy?
- What is the value of addition of Trastuzumab to chemotherapy in advanced gastroesophageal cancer?
- Can oxaliplatin and capecitabine replace cisplatin and 5FU in chemotherapy treatment of advanced disease?
- Is Concurrent chemoradiotherapy an alternative to surgery in Squamous cell carcinoma of the oesophagus?
- How effective is concurrent chemoradiotherapy in the management of localised and locally advanced oesophageal and gastroesophageal junctional adenocarcinoma?
- What is the value of second line chemotherapy in advanced gastroesophageal cancer?

3(a) Please list any additions to the remit of the guideline that you think would be beneficial

- Further data on volume outcome suggesting size of population/unit which should be performing OG cancer surgery.
- The role of post-operative nutrition
- The role of stereotactic radiotherapy and brachytherapy

3(b) Please list any sections of the guideline that are no longer required

Sections 4.1, 10.7, 10.8.2

4 Please tick your preferred option for reviewing this guideline

- | | |
|---|---|
| a. there is no new evidence that will affect existing recommendations and the guideline should not be reviewed at this time | |
| b. some recommendations will change in the light of the new evidence and elements of the guideline should be reviewed | ✓ |

5 SIGN COUNCIL			Date: 11/11/2011
Revalidate	Refresh	Revise	Remove
		✓	