Greater Manchester &
Cheshire Cancer Network

Network Guidelines for the Management of Oesophageal and Gastric Cancer

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CHEMOTHERAPY AND RADIOTHERAPY WITHIN MULTIMODALITY TREATMENT WITH CURATIVE INTENT

Gastric and oesophagogastric junction cancer

Perioperative chemotherapy

The MRC ST02 (MAGIC)[1] trial was a multi-centre, randomised controlled trial designed to assess the effect of peri-operative chemotherapy on patients with resectable adenocarcinoma of the stomach, oesophagogastric junction and lower oesophagus. 503 patients with stage II (through the submucosa) or higher disease, who were eligible for potentially curative resection, were randomised to receive either perioperative chemotherapy and surgery or surgery alone. In the chemotherapy arm, patients received 3 pre-operative and 3 postoperative cycles of epirubicin, cisplatin and infusional 5 fluorouracil (ECF) administered every 3 weeks. Postoperative complications rates were similar between the 2 groups, as were deaths within 30 days of surgery. Resection was considered curative in 79% of the perioperative chemotherapy patients compared with 70% of the patients who underwent surgery. At final analysis the survival rates were significantly different (a 5 year rate of 36% for the perioperative chemotherapy arm versus 23% in the surgery alone arm) with a hazard ratio (HR) of 0.75 (95% confidence interval (CI) = 0.60 to 0.93, p = 0.009). The progression-free survival was also significantly better in the chemotherapy arm (HR 0.66; 95% CI = 0.53 to 0.81, p=0.0001). Perioperative chemotherapy was subsequently accepted as a standard of care for these patients. Of note 74% of the patients in this trial had gastric cancer, 11.5% had oesophagogastric junction cancer and 14.5% had oesophageal

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cancer. The latter two tumour types were relatively under represented, but in subgroup analysis there were trends towards improved survival for patients in each of the three cancer subtypes receiving perioperative chemotherapy.

Since the inception of the MAGIC trial, capecitabine, an oral tumour-selective fluoropyrimidine has become available. Randomised evidence to justify the use of capecitabine instead of infused 5 fluorouracil (5FU) is accumulating, for example the REAL2 trial[2] was a multicentre randomised trial in advanced oesophagogastric tumours where the substitution of capecitabine for 5FU was shown to be non-inferior. Furthermore, in another study, the bioavailability of capecitabine has been shown not to be impaired in patients with upper gastrointestinal pathology and/or gastrectomy[3]. Therefore capecitabine is accepted as an alternative to infusional 5FU in perioperative chemotherapy.

Adjuvant chemotherapy

The usefulness of adjuvant chemotherapy for gastric cancer has long been debated. A number of meta-analyses of some of these trials have found that postoperative chemotherapy can lead to statistically significant reductions in mortality compared with surgery alone corresponding to an absolute risk reduction of around 4%[4-7]. However, randomized controlled clinical trials that have investigated different adjuvant regimens in gastric cancer have frequently yielded inconsistent results making definite conclusions about the benefits of adjuvant chemotherapy difficult[8-13]. A recently published Japanese trial has, however, reported promising results[12]. This trial explored the use of S-1, an oral fluoropyrimidine, as adjuvant chemotherapy in patients with stage II and III gastric cancer who had undergone curative gastrectomy and extended (D2) lymph node dissection. A total of 1059 patients were randomly assigned to treatment with S-1 or surgery alone. The 3-year survival was 80.1% in the S-1 group and 70.1% among those treated with surgery alone. The HR for death in the S-1 group compared with the surgery-only group was 0.68 (95% CI = 0.52 to 0.87, p = 0.003) However, it has long been proposed that there are differences in the natural history of gastric cancer in Western populations compared to that of the Japanese. In addition the routine practice of more extensive surgery (D2 resections) in Japan means that before adjuvant S-1 therapy can be accepted into routine clinical practice in the UK, further trials exploring its efficacy are required.

Adjuvant chemoradiotherapy

A large phase III trial of postoperative therapy has suggested a benefit from the combination of irradiation and chemotherapy after gastrectomy[14]. This trial, the Intergroup Study 0116 (INT 0116), enrolled more than 550 patients with R0 resection at gastrectomy who were then randomly assigned to either chemoradiation (5FU and leucovorin plus external-beam radiation delivered to the site of the gastric resection and the areas of draining lymph nodes), or no chemoradiation. These patients were at a clinically significant risk of relapse after gastric resection – 85% had lymph-node metastases and 65% had stage T3 or T4 tumours. Median survival in the surgery-only and chemoradiation groups was 27 and 36 months respectively (p=0.005); disease-free survival was 19 and 30 months respectively (p<0.001). However, more than 40% of patients in the chemoradiotherapy group had grade 3 or 4 toxic effects. In spite of this level of morbidity the demonstrated survival benefits have lead to the acceptance of postoperative chemoradiation as a standard of care among patients resected gastric adenocarcinoma. Of note, however is that over 50% of patients in the INT 0116 trial had a D0 resection (a resection in which not all of the N1 nodes were removed) and the trial is therefore criticised in that the benefits seen may have occurred in part due to chemoradiotherapy compensating for inadequate surgery. A joint phase I/II study between the Christie and NKI, Amsterdam was completed in patients with adenocarcinoma of the gastro-oesophageal junction or stomach in the post-op setting [15,16]. This trial showed that simplifying the chemotherapy from intravenous 5FU to oral capecitabine was possible and the treatment was also better tolerated compared to the toxicity shown in the MacDonald study.

Although most stomach cancer patients will receive peri-operative chemotherapy based on the above trial evidence, post-operative chemo-radiotherapy can be considered in selected patients who did not receive neoadjuvant chemotherapy with good performance status who have had a curative resection. Patients with microscopic positive margins can also be considered. Systemic chemotherapy rather than radiotherapy should be considered for patients with extensive nodal disease.

Chemotherapy to downstage locally advanced disease for surgery

In a trial of ECF versus FAMTX, complete surgical resection was rendered possible in 10 of 43 patients with locally advanced disease treated with ECF; three had a pathological complete

response[17]. In a series of 30 patients with stage IIIA or IIIB or IV gastric cancer treated with neoadjuvant etoposide, doxorubicin, and cisplatin, multivariate analysis showed that complete clinical response to chemotherapy (n=8; p<0.01) and complete tumour resection (n=24; p<0,01) were the major independent predictors of long term survival[18]. The number of patients in this trial was small, but it may be appropriate to consider chemotherapy to downstage locally advanced disease prior to surgery for carefully selected patients.

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Oesophageal cancer

Adjuvant chemotherapy

The use of postoperative chemotherapy (in the absence of preoperative chemotherapy) is problematical given the recovery period that commonly follows oesophagectomy. This delay conflicts with the aims of adjuvant therapy. Evidence regarding postoperative therapy is limited. A randomised trial from the Japan Clinical Oncology Group (JCOG) of two cycles of postoperative cisplatin and vindesine versus surgery alone in 205 patients found no significant difference in survival[19]. In a subsequent study (JCOG 9204) using cisplatin and 5FU in 242 patients, there was an effect on disease free five year survival, but no overall five year survival benefit (surgery 51% vs surgery plus chemotherapy 61%; p=0.3)[20].

Preoperative chemotherapy

The MRC OEO2 trial involved 802 patients with resectable oesophageal cancer of any cell type who were randomised to surgery alone or surgery plus preoperative chemotherapy with 2 cycles of cisplatin (80 mg/m^2) plus 5FU (1g/m^2/day by infusion for four days) three weeks apart. About one third of patients had squamous cell histology and about two thirds had adenocarcinoma. Recently updated results have shown that the five-year overall survival rate was 23% in the group of patients who received preoperative chemotherapy compared with 17% in the group treated with surgery alone. At 5 years preoperative chemotherapy was associated with a significant 18% disease-free survival rate versus surgery alone. There was no evidence that the effect of chemotherapy varied by histology.

The JCOG followed on from the JCOG 9204 described above with a study designed to evaluate the optimal timing for giving chemotherapy around surgery, the JCOG 9907 study which has recently been presented. 330 patients with stage II or III oesophageal squamous cell carcinoma were randomised to receive two courses of cisplatin plus 5FU chemotherapy either before or after surgery. Results showed that preoperative chemotherapy was not statistically better in the primary endpoint of progression-free survival, but it was associated with a significant 36% improvement in overall survival compared with postoperative chemotherapy. Preoperative chemotherapy is therefore accepted as a standard of care for patients with oesophageal cancer.

Perioperative chemotherapy

The MRC ST02 (MAGIC) trial described in the gastric cancer section above included 73 patients with lower oesophageal adenocarcinoma[1]. Although subgroup analysis only showed a trend towards benefit for these patients, taken as a whole (ie lower oesophageal, oesophagogastric junction and gastric cancer) there was a significant improvement in progression-free and overall survival for patients randomized to perioperative chemotherapy.

Preoperative radiotherapy or chemoradiotherapy

A meta-analysis of five randomised trials comparing preoperative radiotherapy with surgery alone failed to detect a significant benefit of radiotherapy (HR 0.89; 95% CI = 0.78-1.01, p=0.062)[21] and therefore preoperative radiotherapy alone cannot be recommended in this setting.

Chemoradiotherapy followed by surgery (trimodality therapy) has been investigated for many years with the goal of improving survival by addressing issues of both local and distant control. This approach has been widely adopted in the USA where it is felt that the weight of evidence from multiple phase II trials, underpowered phase III trials and meta-analyses provide sufficient evidence for its acceptance as a standard of care[22,23]. Although an overall survival benefit from tri-modality therapy has been shown in some individual trials, and in a meta-analysis, concerns over the increased operative morbidity and mortality have proved off-putting in the UK. Until more persuasive evidence is available from well conducted phase III trials exploring the benefit of trimodality (chemoradiotherapy followed by surgery) over bimodality (definitive chemoradiotherapy or pre-operative chemotherapy followed by surgery) it is unlikely that trimodality will be widely adopted within the UK.

Definitive radiotherapy or chemoradiation

Definitive radiotherapy alone for management of oesophageal cancer has been reported to give 5 year survivals of less than 10% and median survivals ranging from 6 to 12 months[24-29]. The local failure rates are high – ranging from 68% to 84% and therefore this is rarely curative for this disease. There is, however, emerging evidence that combining chemotherapy with radiation as definitive therapy is superior to radiation alone[30].

The landmark RTOG 8501 trial[26,31] and an ECOG trial[32]established chemoradiotherapy without surgery as a curative option for patients whose disease is confined to the thorax. In RTOG 8501

patients were randomly assigned to the experimental treatment consisting of a total of four cycles (two during and two after radiation) of 5FU (1g/m^2/day by continuous infusion for 4 days) and cisplatin (75mg/m^2 day 1) plus 50 Gy of radiation therapy, or to the control arm of 64 Gy of radiation therapy alone. Both grade 3 (44% vs 25%) and 4 (20% vs 3%) acute toxicities were higher in the chemoradiotherapy arm[33], but survival was significantly better for patients treated with chemoradiotherapy, (30% at 3 years and 26% at 5 years) compared with the radiation-alone treatment group (0% at 3 years). At the 12 months follow-up point, however, the local failure rate of 46% in the chemoradiotherapy group was still felt to be unacceptably high. A number of successor trials have therefore attempted to escalate therapy including the INT 0122 and the RTOG 9405 (INT 0123) studies[34,35]. Results from these failed to demonstrate improvements in efficacy.

Although randomised trials have clearly demonstrated that chemoradiotherapy is a curative approach for squamous cell carcinoma, this is less well established for adenocarcinoma. Prospective trials, including RTOG 8501, have tended to include few, if any, patients with adenocarcinoma. Future trials are likely to stratify patients according to histology, but until the results of these are available the role of definitive chemoradiotherapy for adenocarcinoma must be interpreted with caution. Radical chemoradiotherapy should however still be considered in patients with adenocarcinoma in whom surgical excision with clear margins is unlikely to be achieved, and in patients unsuitable for surgery for co-morbid reasons.

Postoperative radiotherapy

Three trials exist from the 1980s and early 1990s which randomised patients between radiotherapy and no radiotherapy following oesophagectomy[36-38]. No survival benefit was seen, although one study showed a reduced local recurrence rate in patients with microscopic or macroscopic residual disease[36]. A further study showed a preferential reduction of local recurrence following radiotherapy for patients without lymph node involvement[37]. Again, most patients in these studies had squamous carcinoma, and some caution should be exercised in generalising the results to adenocarcinoma.

Postoperative radiotherapy is not routinely recommended due to a lack of evidence. In general, the volume at risk is so large that therapeutically useful doses cannot be given without significant morbidity. Furthermore, positive microscopic (R1) circumferential margins cannot reliably be

localised and will be in the vicinity of the gastric pull-up which tolerates RT poorly. However, in selected cases it may be used as a means of reducing local recurrence (but not influencing survival) if a definite site of gross residual disease can be identified (R2 resection) and encompassed in an appropriately small volume. Also, a positive microscopic proximal resection margin (R1) could be irradiated and is easier to localise. Ideally however, patients in whom clear resection margins are not likely to be achieved should be identified before surgery and alternative treatment options considered at that time. The usual dose is 50- 52.5Gy in 20 fractions.

PALLIATIVE CHEMOTHERAPY AND RADIOTHERAPY

The high proportion of patients presenting with advanced disease highlights the fundamental importance of palliative treatment in oesophageal and gastric cancer. Such a principal equally applies to patients with otherwise operable disease who are either unsuitable or unfit for radical intervention. These patients require as careful consideration by the specialist multidisciplinary team as those with potentially curable disease. Furthermore, close liaison between primary and secondary care is essential bearing in mind the short duration of life expectancy after diagnosis.

First line palliative chemotherapy

When considering palliative chemotherapy, careful patient selection is vital as those with good performance status and limited co-morbid disease are far more likely to benefit. Several randomised clinical studies of chemotherapy compared with best supportive care have shown a significant survival and quality of life benefit with chemotherapy[39-41]. This is supported by the 2010 Cochrane collaboration review of chemotherapy for advanced gastric cancer which also concluded that there is evidence for survival benefit in favour of combination chemotherapy over single agent chemotherapy (HR 0.82; 95% CI 0.74-0.90, 1914 participants)[42]. The price of this benefit is increased toxicity as a result of combination chemotherapy.

ECF is widely used in Europe, particularly in the UK. In a randomised comparison of ECF with FAMTX, ECF was shown to have superior response (45% vs 21%; p=0.0002), improved median survival (8.9 vs 5.7; p=0.0009) and greater 2 year survival (13.5% vs 5.4%; p=0.03)[39]. Substitution of epirubicin by mitomycin C has shown similar response rates and survival, although ECF appears to be preferable on quality of life measures[43]. Although the contribution of epirubicin to ECF has never been demonstrated in a phase III trial in gastric cancer, a recently

reported meta-analysis did indicate a 2-month improvement in median survival time for the addition of an anthracycline to CF compared with CF alone[44]. The Cochrane review also concluded that, when comparing 5FU/cisplatin contaning combination therapy regimens with versus without anthracyclines (HR 0.77; 95% CI 0.62 to 0.95, 501 participants) and 5FU/anthracycline-containing combinations with versus without cisplatin (HR 0.82; 95% CI 0.73 to 0.92, 1147 participants) there was a significant survival benefit for regimens including 5FU, anthracylines and cisplatin[42].

The REAL-2 trial evaluated oxaliplatin as an alternative to cisplatin and, as discussed in the section on treatment of early gastric cancer, capecitabine as an alternative to 5FU[2]. In a two-by-two design 1002 patients with previously untreated inoperable or metastatic cancer (any histological subtype) of the oesophagus, oesophagogastric junction or stomach, were randomised to receive triplet therapy with one of ECF, EOF, ECX or EOX. The primary endpoint, which was achieved, was noninferiority in overall survival for triplets containing cisplatin vs oxaliplatin and 5 florouracil vs capecitabine. In a secondary analysis, overall survival was longer with EOX compared to ECF (HR=0.80; 95% CI = 0.66 to 0.97). Oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, alopecia, renal toxicity and thromboembolism, but with slightly higher incidences of grated 3 or 4 diarrhoea compared to cisplatin. It was concluded that capecitabine and oxaliplatin are at least as effective as 5FU and cisplatin respectively in patients with previously untreated oesophagogastric cancer.

Recent trials have explored the use of taxanes as active agents in advanced gastric cancer. For example, a phase II trial of 119 patients with advanced gastric cancer explored the following combinations: docetaxel plus 5FU (DF), docetaxel plus cisplatin plus 5FU (DCF) and ECF[45]. Although the phase II design limits direct comparisons of the treatment arms, the three treatments had comparable response rates (18% to 37%) and median survival (8.3 to 11 months). Of note however, DCF was associated with a high incidence of ferile neturopenia (41% compared to 18% for ECF) and detrimental quality of life effects of weight loss and decline in role functioning. The authors concluded that DCF should be taken forward in preference to DC for comparison to ECF in a randomised phase III study and this would seem to be appropriate prior acceptance of the use of DCF in standard clinical practice. The V325 phase III trial of DCF vs CF showed a significant response rate advantage for DCF compared to CF (37% vs 25%) although there was only a

modest 0.6 month improvement in median survival for DCF and the gains were at the cost of substantial toxicity, for example grade 3 and 4 stomatitis up to 27%[46,47]. There was a 50% discontinuation rate for DCF for either adverse events or patient refusal. In addition the patients in this trial had a Karnofsky Performance (KP) score (99% had KP of 80-100%) and young age (median age 55 years) that fails to reflect the norm in routine clinical practice.

The recent ToGA trial[48] screened approximately 3,800 gastric cancer patients from 24 countries and noted that HER2 expression was detectable in 22% of patients. There was a specific pattern of disease which correlated with HER2 expression with higher rates occurring in intestinal and proximal or gastroesophageal junction cancers than with diffuse or distal gastric cancers. Patients tested positive for HER2 expression were enrolled into a large phase III trial comparing combination of 5-FU or capecitabine and cisplatin chemotherapy with or without trastuzumab. In the final analysis, median overall survival improved from 11 months with chemotherapy alone, to 13.5 months with the addition of trastuzumab ($p = 0.0048$). Response rate was 47% in the study arm vs. 34% in the control arm. There were no differences in the rates of congestive heart failure between the two groups although there was a higher rate of asymptomatic decrease in cardiac function in the trastuzumab group. This study demonstrated that HER2 targeted therapy will be beneficial for 20-25% of gastric cancer cases, and it is awaiting approval by NICE. The role of trastuzumab as a single agent or as a part of perioperative therapy is being investigated further.

Promising results are beginning to emerge from a number of phase II trials particularly those combining the use of cetuximab or bevacizumab with chemotherapy. These early phase trials have lead to the establishment of several ongoing phase III trials, the results of which are eagerly anticipated.

Second line palliative chemotherapy

A number of phase I and II studies have demonstrated responses to new combinations following failure of first line chemotherapy[48,49]. For example a phase II trial involving 38 patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma explored the use of irinotecan plus infusional 5FU (given as modified deGramont regimen) There was a response rate of 29% and improvement in tumour-related symptoms in over half of patients and the authors concluded that this regimen was a valuable regimen for second line treatment in these patients.

Importantly the patients were carefully selected with good performance status (PS 0-2) and life expectancy >3 months[49].

Radiotherapy in the palliative setting

Dysphagia is the predominant symptom in advanced oesophageal carcinoma, and the principal goal of palliation is restoration of swallowing. Such a benefit has been shown to correlate strongly with quality of life[50]. A variety of means may be employed to achieve this goal and the choice of treatment should be tailored to the individual, and will depend on the site, length, and appearance of the tumour, as well as the physical condition of the patient. Palliative radiotherapy improves dysphagia in 50-85% of patients and pain is also significantly lessened[51,52]. The time to onset of improvement however is relatively slow and improvement is more likely in patients with milder dysphagia. In a retrospective analysis of 140 patients who received radiotherapy, chemotherapy or a stent, median time to improvement in symptoms was two months after radiotherapy, variable, but prolonged after chemotherapy and immediate after stent insertion[53]. One randomised study comparing endoluminal brachytherapy to stenting as palliation also showed more rapid relief of dysphagia with stenting, but more durable symptom control with brachytherapy[54]. Thus stents are the palliative treatment of choice for dysphagia rather than radiotherapy, but radiotherapy can be considered if there is tumour bleeding, overgrowth of tumour over a stent which cannot be easily re-stented, or if there is tumour pain. At present there is not enough evidence to support the routine use of radiotherapy following the insertion of a stent.

Radiotherapy can play a role in palliation of distant metastatic disease in oesophagogastric cancer, for example to skin, bone or brain metastases. In gastric cancer local palliative radiotherapy can be considered for persistent low level tumour bleeding or tumour pain.

Other circumstances

Elderly patients tend to be under-represented in clinical trials and as a result there has been uncertainty as to the role of palliative chemotherapy for those over the age of 70 years. In a retrospective analysis using original data from 3 large multi-centre randomised trials Trumper *et al.* examined the benefit of systemic chemotherapy in elderly (≥ 70 years) patients with locally

advanced or metastatic oesophagogastric cancer[55]. Of the 1080 patients randomised, 257 were aged ≥ 70 years. Their analysis showed that compared to younger patients, older patients achieved similar benefits from palliative chemotherapy with respect to symptomatic response, tumour regression and survival, without increased toxicities. In a multivariate analysis, independent prognostic factors for survival were performance status and locally advanced disease, not age.

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CRITERIA FOR RADICAL (CHEMO-) RADIOTHERAPY TREATMENT

- Adequate WHO performance score (PS) 0 or 1 for chemo-RT or 0, 1 or 2 for radical RT alone.

- A histological diagnosis of malignancy is mandatory if chemo-RT is being considered and highly desired if RT alone is being contemplated, although it is realised that occasionally it is impractical to get a positive biopsy from tumours in the cervical or upper thoracic oesophagus without running an unacceptable risk of oesophageal perforation.

- Full staging work-up to include OGD with report stating start position of tumour relative to incisors and tumour length if able to pass scope, CT scan thorax/ abdomen with contrast and PET CT scan is mandatory to exclude distant metastatic disease. EUS is highly recommended and preferred before referral for radical non-surgical treatment, and reference measurements of tumour *ab oral* relative to the cross of aorta and carina are recommended.

- For upper or middle third tumours, bronchoscopy is indicated for T3 or T4 tumours to exclude a tracheo-oesophageal fistula or direct invasion of the tracheal mucosa. Distortion or compression of the trachea with normal mucosa is not considered a contraindication to radiotherapy in the majority of cases.

- Cranio-caudal length of primary tumour plus involved lymph nodes should not be longer than 10 cm on combined information from PET CT scan and EUS (endoscopic ultrasound). However, the volume of disease safely encompassible in a radical radiation field will still depend on technical factors at the time of RT planning and cannot be reliably predicted before then.

- To be eligible for concurrent chemo-RT patients must have no prior history of troublesome angina, ischemic heart disease, cerebrovascular or peripheral vascular disease. Adequate renal function with estimated creatinine clearance > 60 ml/min and hepatic function are required.

TREATMENT REGIMES

Radical Chemo-RT:

In patients who decline surgery or who are medically unfit for surgery, but may be suitable for chemoradiation the following regime may be used:

RT: **50Gy/ 25#/ 5wks**

Chemo: **iv CISPLATIN 75 mg/m2 (day 1 and day 29)**
oral CAPECITABINE 625mg/m2 (days 1-35)

with a further 2 cycles of chemotherapy starting weeks 8 and 11.

Radical RT alone:

Patients who are not suitable for chemoradiotherapy may be suitable for radical radiotherapy alone. The radiotherapy dose in this situation is 55Gy in 20 fractions over 4 weeks.

Preoperative Chemo-RT:

This is highly controversial and should not be offered outside the context of a well-conducted clinical trial.

SPECIAL SITUATIONS

1. **Carcinomas of the upper thoracic and cervical oesophagus.**
   Some of these tumours are managed by the head and neck team. They can be managed as described, but occasionally it is necessary to use a 5-point thermoplastic fixation shell to immobilise the patient with their arms by their side and with their neck hyper-extended to allow access of the radiation beams. A different chemo-RT schedule may be offered combining 55Gy in 20 fractions and cisplatin 80mg/m2 weeks 1 & 4. There has been no

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randomised comparison of the 2 treatment regimes for upper third tumours and the anatomical overlap allows application of either regime.

2. Gastrostomy tubes

Patients with ≥ 10% weight loss or dysphagia for solids require prior placement of a gastrostomy feeding tube for either immediate use or as a prophylactic measure. Involvement of specialist dieticians, upper GI cancer nurses are crucial in holistic care for such patients before, during and after RT. Metal stents should be avoided as they cause artefact on RT planning scans, attenuate the radiation beams and affect radiation dosimetry around the tumour.

Appendix A

Radiotherapy details:

- *All the patients are CT planned. Before CT planning, to ensure adequate coverage of the PTV (roughly 3 cm above and below tumour) by the RTP scan all patients are simulated in the same position as treatment i.e. supine with arms abducted comfortably above the head on an immobilization (or lung) board. They have a barium / gastrograffin swallow (about 20 – 30 mls) during simulation. Fluoroscopy done at this time will give an idea about the range of movement associated with respiration. This information, along with all the diagnostic / planning CT data, endoscopic findings (and endoscopic ultrasound findings if any) should be taken into consideration for planning.*
- *The planning scan is done with the patient supine on an immobilization board with arms placed in abduction comfortably above the head. The scan should include the entire thorax and the upper abdomen to adequately cover the PTV region. IV contrast can be given and is particularly useful if there are involved lymph nodes; oral contrast is avoided and the planning scan cannot be done on same day as simulation if barium/ gastrograffin has been administered.*

1. Oesophagus cancer (definitive RT)

<u>Definitions of Volumes</u>

1. GTV (Gross Tumour Volume)
    - Contoured on mediastinal windows, this is the gross palpable or visible/ demonstrable extent and location of the malignant growth (ICRU 50 definition)
    - Lymph nodes are considered significant if avid on staging PET and/ or are suspicious on endoscopic ultrasound (EUS). Traditional radiological size criteria are not strictly adhered to (short axis >10mm, 12mm for subcarinal)

    Clusters of small contiguous nodes can, in some situations, be considered as significant and contoured accordingly.

2. CTV (Clinical Target Volume)

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This is a tissue volume that contains a GTV and/or subclinical microscopic malignant disease, which has to be eliminated (ICRU 50 definition).

a. The expansion from GTV to CTV can be
Uniform: expansion for microscopic adjacent spread
Non-uniform: expansion to follow a route of spread in a particular direction deemed risky; for oesophageal cancer there is special attention given for superior-inferior (S-I) longitudinal spread in the submucosal space.

c. Note:

- Margins from GTV to CTV can be edited manually
    - if it is felt that there is a low risk of involvement of the adjacent tissue eg- bone, vascular adventita, lung. Note the oesophagus has no serosal layer and careful attention is required to note adjacent organ invasion.
    - Around a lymph node as the risk of microscopic spread beyond it is probably low

3. PTV (Planning Target Volume)

- A geometrical concept defined to select appropriate beam sizes and beam arrangements, taking into the consideration the net effect of all the possible geometrical variations and inaccuracies in order to ensure that the prescribed dose is actually absorbed in the CTV. 2 components:

- Internal Margin (IM):
A margin that must be added to the CTV to compensate for expected physiological movements and the variations in size, shape and position of the CTV during therapy in relation to the Internal Reference Point and its corresponding Co-ordinate system.

Day-to-day organ motion resulting from part of/ adjacency to digestive or respiratory system.
Also affected by patient weight gain or loss.
CTV + IM comprises the Internal Target Volume (ITV)

- Set-up Margin (SM):
Margin to account specifically for uncertainties (inaccuracies and lack of reproducibility) in patient positioning and alignment of the therapeutic beams during treatment planning and through all treatment sessions. Includes variation in patient

positioning, mechanical uncertainties of the equipment, dosimetric uncertainties, transfer set-up errors and human-related uncertainties.

- The expansion from CTV to PTV **should not** be edited manually as the expansion from CTV to PTV takes into account set up errors and breathing motion.
- Systematic errors (treatment preparation errors) should be identified from random errors by performing on-line treatment verification using either XVI or EPI according to departmental protocols. The usual setup error tolerance is 5 mm and if necessary corrections can be implemented to reduce systematic errors. In particular cases e.g. a tumour close to the spinal cord where the PTV or coverage has had to be compromised, consider requesting XVI imaging and/or a tighter tolerance for setup errors.

4. Organs at risk (OAR)

- Lungs, Spinal cord are to be contoured routinely. Heart should be contoured for upper & middle third tumours, whereas liver should be contoured for lower third tumours.
- Heart- should be outlined along with the pericardial sac.
  The pericardial sac surrounds the heart and extends superiorly to encompass the main pulmonary artery, the ascending aorta and the superior vena cava. Outlining should extend superiorly to the inferior limit of the aortic arch (the aortopulmonary window) and the superior limit of the trunk of the pulmonary artery if it can be identified on the RT planning CT scan.
- Spinal canal- The spinal cord should be contoured based on the bony limits of the spinal canal i.e. the spinal canal is outlined and not the spinal cord itself. The spinal cord should be contoured starting at least 5cm above the superior extent of the PTV, continuing on every CT slice to at least 5cm below the inferior extent of the PTV.

<u>Contouring Method</u>

GTV

- Collate information from CT, PET-CT, endoscopy and EUS (if available) including all gross visible disease. PET-CT scans may be fused to planning RTP scan as an aid.
- Non- FDG avid areas of the primary may be included if there is suspicion of involvement based on CT, endoscopy or EUS. Clinical judgement will be required. Contour the entire outer muscular wall (up

to adventita) of oesophagus on all slices in which there is deemed gross tumour.

- The sensitivity of PET for detecting small involved nodes is poor, whereas EUS has a higher sensitivity (provided the nodes are within reach of the endoscope). Therefore nodes which appear involved on either PET or EUS should be included. Clinical judgement will be required for nodes or groups of small nodes which appear suspicious on CT only, especially where it has not been possible to assess the node(s) at EUS.

CTV

- Create an additional ROI (region of interest) labelled GTVsup and GTVinf by contouring the oesophagus longitudinally on extra slices both superior and inferior to GTV for 2 or (if tumour length allows) 3cm. This is to account for longitudinal submucosal spread of disease.
- Expand* by 5mm laterally and A-P but not S-I.
- Switch off or delete the extra S-I oesophageal slices
- Adjust by trimming off areas unlikely to be involved (eg CTV overlapping with bone, blood vessel and lung parenchyma). This may be done either by manually trimming the volume or, at the expansion step above (*) by growing the extended GTV and specifying avoidance structures e.g. lungs in Pinnacle.

PTV

Expand CTV by 10 mm uniformly including S-I.

OAR

Contour spinal canal, heart as required (contour pericardium), liver or kidney as required.

- lung V20<30% (preferably), 35% (maximum). Collect data on lung V5 for inverse-plan IMRT method.
- spinal cord
  - (SC+0.5) max limit 40Gy for 4-weeks treatment
  - (SC+0.5) max limit 44Gy for 5-weeks treatment
- Heart V40<30%
- Liver V30<60%
- Kidney V20<25%.

Beam Arrangement

Typically 3 or 4 beams.
95% of PTV to be covered by 95%-107% prescribed dose to isocentre.
If PTV coverage poor or V20 too high, an inverse IMRT plan solution can be sought

RT dose

Radical RT alone:	55Gy in 20# treating once daily
Concurrent chemo-RT:	50Gy in 25# treating once daily

(mandatory to start concurrent patients on Monday. Tuesday only acceptable if bank holiday)
Category 1 treatment (no interruptions)
Verification films taken on treatment to check set-up.

2. Gastric cancer (post-operative)

Target volume defined in terms of field borders.
Maximum field size 20x20 cm or the equivalent.
CT based planning

Target Volume

- The tumour-nodal fields should include the tumor bed and major draining nodal chains.
    - The tumour bed includes the entire pre-operative location of the stomach (in all patients) plus the perigastric local tumour extension in T3 and T4 primary tumors.
    - The nodal areas at risk include the gastric and gastroepiploic (usually resected with primary); celiac nodes, porta hepatis, subpyloric, gastroduodenal, splenic-suprapancreatic and retropanceatico-duodenal nodes.
- The following situations require special consideration:
    - the original tumour bed including the anastomosis and distal deafferented duodenum limb will be treated in all cases. If the specimen has less than a 2 cm tumor free resection margin, a 5 cm margin should be taken.
    - Extension through gastric wall: for proximal T3 and T4 lesions the medial 2/3-3/4 of the left hemidiaphragm should be included as target volume with 1.5 cm margins. If the lesion is confined to the gastric wall or is distal, left hemidiaphragm treatment is not necessary.
    - Proximal lesions involving the gastric cardia or gastro-oesophageal junction: the para-oesophageal nodes are at risk and, if other nodes in the operative specimen are tumour positive, should be included in the target volume. A 5 cm margin of oesophagus should be included in the cranial field margin.

Beam Arrangement

- 2 beams parallel opposed ant-post fields, sparing as much bone marrow, small bowel, liver and kidney as possible.
- If the target volume is sufficiently located anterior on preoperative CT scan or barium swallow, treatment via laterals (with or without ant-post fields) sparing the spinal cord, is allowed
- 95% of PTV to be covered by 95%-107% prescribed dose to isocentre.

Field Borders

- Ant-post field borders
    - superior: T8/9 or T9/10 interspace (covering celiac axis, gastro-oesophageal junction, gastric fundus and dome of diaphragm)
    - inferior: L3/4 interspace (covering gastroduodenal nodes and gastric antrum)
    - right margin: 3-4 cm lateral to the vertebral body (covering porta hepatis, gastric antrum, deafferented duodenal limb and gastroduodenal nodes)
    - left margin: lateral to include 2/3 - 3/4 of the left hemidiaphragm (covering gastric fundus, splenic and suprapancreatic nodes, and left hemidiaphragm in proximal T3, T4 lesions)

- Lateral field borders:
    - superior and inferior: identical to ant-post field
    - posterior: 1/2 - 2/3 of the vertebral bodies along the entire field length
    - anterior: anterior abdominal wall

OAR tolerances

- kidneys: shield at least 2/3 of one kidney. For proximal gastric lesions at least 1/2 of the left kidney is within the radiation portal; in these cases the right kidney must be appropriately spared
- heart: no more than 30% of the cardiac silhouette should receive 40 Gy or more (V40<30%). Lateral fields can be very useful to decrease cardiac volume
- liver must not have greater than 60% of its volume exposed to more than 30 Gy (V30<60%)

RT dose

Adjuvant chemo-RT 45Gy in 25# treating once daily in 5 weeks

(mandatory to start concurrent patients on Monday. Tuesday only acceptable if bank holiday)
Category 2 treatment
Verification films taken on treatment to check set-up.

Capecitabine will be given at day 1-14 followed by a weeks break prior to commencement of radiotherapy at a dose of 1000 mg/m2 orally bd. During concurrent radiotherapy capecitabine will resume at the same dose of 1000 mg/m2 orally bd for 5 days per week for 5 weeks.

Appendix B
Chemotherapy details (oesophageal cancer)

Concurrent treatment	*Adjuvant treatment*
i. Cisplatin 75mg / m^2 day 1(week 1) and day 29 (week 5) *ii. Capecitabine 625 mg/m^2 B.D. from days 1-35.*	*i. Cisplatin 75mg / m^2 day 1 and day 29* *ii. Capecitabine 625mg/m^2 B.D. from days 1-21.* *If performance status or renal function is not adequate then chemotherapy can be either dose reduced or omitted.*

Chemotherapy schedule and hydration:

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Regimen	**Cisplatin and Capecitabine concurrent with radiotherapy for Oesophageal Cancer (OUTPATIENT TREATMENT)**	Concurrent cycle 1	Hospital No: Fill in or affix label Surname: First Name: Sex D.O.B.
Dosage/m^2	Cisplatin 75 mg/m^2 IV on the first day of weeks 1 and 5 of radiotherapy (50 Gy in 25 fractions). Capecitabine 625 mg/m^2 po bd days 1-35. (This may be followed by 2 cycles of adjuvant chemotherapy on the first day of weeks 8 and 11 as per separate chart).		**Calculated creatinine clearance or EDTA GFR and FBC, U&E, LFT required before each dose of cisplatin.**

Disease Group	GI		**Ward**		**Height**	cm
Stage	Locally advanced/ Localised (medically inoperable or declines surgery)		**Consultant**		**Weight**	kg
			NHS / PP (circle one)		**BSA**	m^2
					EDTA GFR (ml/min)	
Date ordered			**Print name** **Pager no.** **Ext no.**		**Serum creatinine (umol/L) and date**	
Ordered by (signed)					**Calculated creatinine clearance (ml/min)**	
					Confirmed by (pharmacist)	

Order given	**Date required**	**Drugs**	**Dose**	**Volume (ml)**	**Route & duration**	**Time given (signed)**	**Batch No.**
1		Ondansetron	8 mg		IV bolus		
2		Dexamethasone	8 mg		IV bolus		
3		0.9% Sodium chloride Potassium chloride Magnesium sulphate	 20 mmol 10 mmol	1000 ml	IVI over 90 minutes		
4		0.9% Sodium chloride Cisplatin	 …….mg	1000 mls	IVI over 2 hours		
5		0.9% Sodium chloride Potassium chloride Magnesium sulphate	 20 mmol 10 mmol	1000 mls	IVI over 2 hours		
6		0.9% Sodium chloride Magnesium sulphate	 10 mmol	500 mls	IVI over 1 hour		

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Notes:
1) Capecitabine from supply of "Medication to take home" to start day 1 of radiotherapy (if possible give first dose by 11 am when attends for IV chemotherapy; otherwise start in the evening).
2) The patient should at least have completed cisplatin and preferably 1-2 hours of post-hydration when going for radiotherapy.

Regimen	**Cisplatin and Capecitabine concurrent with radiotherapy for Oesophageal Cancer (OUTPATIENT TREATMENT)**	Concurrent cycle 1	Hospital No: Fill in or affix label Surname: First Name: Sex D.O.B.
Dosage/m^2	Cisplatin 75 mg/m^2 IV on the first day of weeks 1 and 5 of radiotherapy (50 Gy in 25 fractions). Capecitabine 625 mg/m^2 po bd days 1-35. (This may be followed by 2 cycles of adjuvant chemotherapy on the first day of weeks 8 and 11 as per separate chart).		**Calculated creatinine clearance or EDTA GFR and FBC, U&E, LFT required before each dose of cisplatin.**

Disease Group	GI		**Ward**		**Height**	cm
Stage	Locally advanced/ Localised (medically inoperable or declines surgery)		**Consultant**		**Weight**	kg
			NHS / PP (circle one)		**BSA**	m^2
					EDTA GFR (ml/min)	
Date ordered			**Print name**		**Serum creatinine (umol/L) and date**	
Ordered by (signed)			**Pager no.** **Ext no.**		**Calculated creatinine clearance (ml/min)**	
					Confirmed by (pharmacist)	

MEDICATION TO TAKE HOME (capecitabine from this supply to be started on day 1 of radiotherapy)

	Date required	**Drugs**	**Dose, route and duration**	**For pharmacy use No. of tablets supplied**
1		Capecitabine	……. mg BD orally for 35 days (to start day 1 of radiotherapy while in hospital)	
2		Ondansetron	8 mg po bd for 3 days	Supply 6 tablets
3		Dexamethasone	8 mg po bd for 3 days	Supply 24 x 2 mg tablets
4		Metoclopramide	10 – 20 mg max qds if needed for nausea	Supply 56 tablets
5		Loperamide	4 mg po initially then 2 mg after each loose stool if required, maximum 8 tablets daily	Supply 20 tablets

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N.b. Prescriber to consider alternatives for patients with swallowing difficulty or RIG tube: ondansetron is available as syrup or Zofran Melt, dexamethasone as oral solution, metoclopramide as oral solution, loperamide as syrup.				

Available capecitabine tablets: 500 and 150 mg – round dose to nearest whole tablet.

IV chemotherapy pre-order and prescription form Outpatient Adjuvant Cisplatin & Capecitabine after chemoradiotherapy

 for Oesophageal Cancer

Regimen	**Adjuvant Cisplatin and Capecitabine after chemoradiotherapy for Oesophageal Cancer (OUTPATIENT TREATMENT)**	Adjuvant cycle ……. of 2	Hospital No: Fill in or affix label Surname: First Name: Sex D.O.B.
Dosage/m^2	Cisplatin 75 mg/m^2 IV day 1, Capecitabine 625 mg/m^2 po bd for 21 days, 21 day cycle. Two adjuvant cycles commencing weeks 8 and 11 (weeks 1 to 5 are the chemoradiotherapy weeks).		**Calculated creatinine clearance <u>or</u> EDTA GFR and FBC, U&E, LFT required before each dose of cisplatin.**

Disease Group	GI		**Ward**		**Height**	cm
Stage	Locally advanced/ Localised (medically inoperable or declines surgery)		**Consultant**		**Weight**	kg
			NHS / PP (circle one)		**BSA**	m^2
					EDTA GFR (ml/min)	
Date ordered			**Print name**		**Serum creatinine (umol/L) and date**	
Ordered by (signed)			**Pager no.** **Ext no.**		**Calculated creatinine clearance (ml/min)**	
					Confirmed by (pharmacist)	

Order given	**Date required**	**Drugs**	**Dose**	**Volume (ml)**	**Route & duration**	**Time given (signed)**	**Batch No.**
1		Ondansetron	8 mg		IV bolus		
2		Dexamethasone	8 mg		IV bolus		
3		0.9% Sodium chloride Potassium chloride Magnesium sulphate	 20 mmol 10 mmol	1000 ml	IVI over 90 minutes		
4		0.9% Sodium chloride Cisplatin	 …….mg	1000 mls	IVI over 2 hours		
5		0.9% Sodium chloride Potassium chloride	 20 mmol	1000 mls	IVI over 2 hours		

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		Magnesium sulphate	10 mmol				
6		0.9% Sodium chloride Magnesium sulphate	10 mmol	500 mls	IVI over 1 hour		
N.b. Capecitabine from supply of "Medication to take home" to start day 1 of cycle (if possible give first dose by 11 am; otherwise start in the evening).							

Sign appropriate box on day of treatment

IV chemotherapy pre-order and prescription form chemoradiotherapy
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Outpatient Adjuvant Cisplatin & Capecitabine after for Oesophageal Cancer

Regimen	**Adjuvant Cisplatin and Capecitabine after chemoradiotherapy for Oesophageal Cancer (OUTPATIENT TREATMENT)**	Adjuvant cycle ……. of 2	Hospital No: Fill in or affix label Surname: First Name: Sex D.O.B.
Dosage/m^2	Cisplatin 75 mg/m^2 IV day 1, Capecitabine 625 mg/m^2 po bd for 21 days, 21 day cycle. Two adjuvant cycles commencing weeks 8 and 11 (weeks 1 to 5 are the chemoradiotherapy weeks).		**Calculated creatinine clearance <u>or</u> EDTA GFR and FBC, U&E, LFT required before each dose of cisplatin.**

Disease Group	GI		**Ward**		**Height**	cm
Stage	Locally advanced/ Localised (medically inoperable or declines surgery)		**Consultant**		**Weight**	kg
			NHS / PP (circle one)		**BSA**	m^2
					EDTA GFR (ml/min)	
Date ordered			**Print name**		**Serum creatinine (umol/L) and date**	
Ordered by (signed)			**Pager no.** **Ext no.**		**Calculated creatinine clearance (ml/min)**	
					Confirmed by (pharmacist)	

MEDICATION TO TAKE HOME (capecitabine from this supply to be started when attending for outpatient IV chemotherapy)

	Date required	**Drugs**	**Dose, route and duration**	**For pharmacy use No. of tablets supplied**
1		Capecitabine	…… mg BD orally for 21 days (to start day 1 of cycle when attending for outpatient IV chemotherapy)	

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2		Ondansetron	8 mg po bd for 3 days, starting on evening of chemotherapy	Supply 6 tablets
3		Dexamethasone	8 mg po bd for 3 days, starting on evening of chemotherapy	Supply 24 x 2 mg tablets
4		Metoclopramide	10 – 20 mg max qds if needed for nausea	Supply …. tablets
5		Loperamide	4 mg po initially then 2 mg after each loose stool if required, maximum 8 tablets daily	Supply …. tablets
N.b. Prescriber to consider alternatives for patients with swallowing difficulty or RIG tube: ondansetron is available as syrup or Zofran Melt, dexamethasone as oral solution, metoclopramide as oral solution, loperamide as syrup.				