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Network Guidelines for the Management of Oesophageal and Gastric Cancer - Chemotherapy and Radiotherapy

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WHAT CONSULTATION HAS TAKEN PLACE?	These are guidelines for the oncological management of patients with Oesophago-gastric cancer outlining treatment options available.
HAS AN EQUALITY IMPACT ASSESSMENT BEEN COMPLETED?	*N/A*
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1. CURATIVE INTENT - GASTRIC AND GASTRO-OESOPHAGEAL JUNCTION (GOJ) ADENOCARCINOMA

1.1 Gastric / GOJ Adenocarcinoma - Treatment Summary

According to Stage Surgical Candidates:

Stage	Treatment	Notes
T1N0M0	Surgical Resection	EMR may be considered for T1a Perioperative chemotherapy may be considered for T1b
T2N0 or above	Perioperative chemotherapy; Neoadjuvant FLOT x4 cycles + surgical resection + adjuvant FLOT x4 cycles Or Neoadjuvant ECX x3 cycles + resection + adjuvant ECX x 3	As per FLOT4-AIO1 or MAGIC 2 trials Surgery recommended within 4-6 weeks of completing neoadjuvant chemo Adjuvant chemo recommended within 12 weeks of surgery Chemo not recommended if presenting in gastric outlet obstruction or with uncontrolled bleeding
T2N0 or above and did not receive neoadjuvant chemo	Consider adjuvant chemotherapy with FLOT/ECX	R0 and R1 Resection R2 excluded Discussion and agreement of management plan via MDT is required prior to referral

Non-Surgical Candidates (may be due to disease (e.g. nodal disease sites) or patient factors):

Type I / II GOJ	Consider definitive chemoradiotherapy (dCRT) or high dose radiotherapy alone, if disease can be encompassed in radiotherapy field	Need <3cm of gastric extension PS 0-2
Gastric / Too extensive for dCRT / Poor PS	Consider palliative SACT if deemed fit	Please see section 3

1.2 T1 No Gastric carcinoma

Endoscopic resection is recommended for very early gastric cancers (T1a) if they are clearly (i) confined to the mucosa, (ii) well-differentiated G1-2, (iii) ≤2 cm and (iv) non-ulcerated 4.

T1 tumours which do not meet the criteria for endoscopic resection require surgery with or without perioperative chemotherapy, although less extensive surgery than other gastric cancers 4.

1.3 Perioperative chemotherapy

Recommendation:

Patients with adenocarcinoma of the stomach and gastro-oesophageal junction (GOJ) with stage T2N0M0 or above that are deemed amenable to surgical resection should be considered for perioperative chemotherapy based on evidence from the FLOT4-AIO1 and MRC ST02 (MAGIC) 2 trials.

The current recommended regimen is **FLOT (5-Flurouracil, Leucovorin, Oxaliplatin and Docetaxel)** administered as four 2-weekly cycles both pre- and post-operatively, provided the patient maintains adequate performance status following surgery.

The ECX (epirubicin, Cisplatin, and capecitabine) regimen may also be considered if patients are unsuitable for FLOT. The ECX regimen is a modification of the ECF (epirubicin, Cisplatin, and infusional 5-flurouracil) regimen used in the MAGIC trial based on data from the REAL2 trial which demonstrated at least equivalent efficacy for ECX as compared to ECF and greater convenience in the advanced disease setting.

The recommended time interval between completing neo-adjuvant (pre-operative) chemotherapy and undergoing surgery is 4-6 weeks, and adjuvant (post-operative) chemotherapy should be commenced within 12 weeks of surgery. Perioperative chemotherapy may also be considered for patients with clinical stage T1bN0M0 disease on a case-by-case basis at MDT discussion. Peri-operative chemotherapy is not recommended for patients who have clinical features which make chemotherapy unsuitable such as gastric outlet obstruction or uncontrolled tumour bleeding.

Evidence:

The **MAGIC trial** demonstrated that perioperative chemotherapy with **ECX** (epirubicin, cisplatin, and capecitabine) significantly improved survival compared to surgery alone in patients with adenocarcinomas of the stomach and gastroesophageal junction 2.
Subsequently, the **FLOT4 trial** showed that perioperative chemotherapy with **FLOT** (5-

fluorouracil, leucovorin, oxaliplatin, and docetaxel) offered superior survival outcomes compared to ECX/ECF, establishing it as the preferred regimen for these cancers 1.

1.4 Adjuvant Chemotherapy

A large individual patient-level meta-analysis by the GASTRIC group 5 has demonstrated a 6% absolute improvement in 5-year overall survival (OS) with 5-FU-based adjuvant chemotherapy compared to surgery alone (HR 0.82; 95% CI 0.76–0.90; P < 0.001), with consistent benefit across all subgroups, including Western patients.
Current recommendations support a 6-month regimen of doublet chemotherapy—typically a fluoropyrimidine combined with oxaliplatin or docetaxel. Adjuvant chemotherapy should be considered for patients with resected gastric or gastroesophageal junction (GOJ) adenocarcinomas staged T2N0M0 or higher who have not received neoadjuvant treatment.

1.6 Definitive chemoradiotherapy

For Sievert 1 or 2 adenocarcinoma of GOJ with <3cm of gastric extension, definitive chemoradiotherapy (CRT) may be considered for patients of good WHO PS (0-1) deemed unsuitable for surgical management. [See section 2.6]

In those for whom chemotherapy is contraindicated high dose radiotherapy alone can be considered.

2. CURATIVE INTENT – OESOPHAGEAL CARCINOMA

2.1 Resectable Summary:

Surgical candidate – patient fit and appropriate disease distribution

Treatment Summary According to Stage

2.1.1 Oesophageal Squamous Cell Carcinoma

Stage	Treatment	Notes
T1N0M0	Surgical Resection	EMR may be considered for T1a dCRT may be considered for T1b
T2N0/1 or T3/4a N0/1	Trimodality therapy with neoadjuvant chemoradiotherapy (CRT) as per CROSS 6 trial regimen If not a candidate for above, to consider definitive CRT (see section 2.6.1) If tumour factors make CRT for dCRT inappropriate, consider perioperative chemotherapy as per FLOT-AIO1/MAGIC 2 and surgery. Tumours in upper third may need extensive surgery (laryngectomy) and hence dCRT is preferred	For CRT: • Total disease length (including primary tumour and involved lymph nodes) ≤ 8 cm. • Need <3cm of gastric extension • PS 0-1 • Surgery recommended within 4-8 weeks of CRT and consideration of adjuvant Nivolumab in patients not achieving pCR[13] (See section 2.4)

2.1.2 Oesophageal Adenocarcinoma:

Stage	Treatment	Notes
T1N0M0	Surgical Resection	EMR may be considered for T1a Perioperative chemotherapy may be considered for T1b
T2N0 or above	Perioperative chemotherapy; neoadjuvant FLOT x4 cycles + surgical resection + adjuvant FLOT x4 cycles 1(or ECX x3 cycles neoadjuvant/adjuvant 2) ChemoRT followed by surgery and adjuvant Immunotherapy if indicated as above may be considered for certain patient (e.g. with DYPD deficiency precluding use of Fluoropyrimidine)6 If not a candidate for above, to consider definitive CRT (see section 2.6.1)	Surgery recommended within 4-6 weeks of completing neoadjuvant chemo Adjuvant chemo recommended within 12 weeks of surgery Chemo not recommended if presenting in gastric outlet obstruction or with uncontrolled bleeding

2.2 T1 No oesophageal carcinoma

- Offer endoscopic resection as first-line treatment to people with T1a oesophageal adenocarcinoma 7.
- Offer oesophagectomy to people with T1b oesophageal adenocarcinoma who are fit for surgery and at high risk of cancer progression. For example, where there is 7:
  1) incomplete endoscopic resection
  2) evidence of lymphovascular invasion or deep submucosal invasion (more than 500 micron) on histological examination of endoscopic resection specimens.

- Consider radiotherapy (alone or in combination with chemotherapy) for people with T1b oesophageal adenocarcinoma at high risk of cancer progression (for example, incomplete endoscopic resection, or evidence of lymphovascular invasion or deep submucosal invasion (more than 500 micron) on histological examination of endoscopic resection specimens) and who are unfit for oesophagectomy

2.3 Pre-operative chemoradiotherapy (Tri-modality treatment):

The evidence base for neoadjuvant CRT is currently confined to improving outcomes in patients who are considered operable at time of initial staging. There is no current role in downstaging patients who are deemed inoperable. There is no role for radiotherapy alone in the pre-operative setting.

2.3.1 Squamous Cell Carcinoma

Recommendation:

Neoadjuvant CRT should be routinely considered for any operable patient deemed fit for trimodality treatment with WHO PS0-1 and the following disease criteria:

- T2 N0-1 or T3 –T4a N0-1
- Total disease length (including primary tumour and involved lymph nodes) ≤ 8 cm. where these parameters are exceeded, discussion with clinical oncologist should occur to judge if disease is encompassible within a tolerable radical radiation volume.

Mandatory staging required prior to neoadjuvant CRT;

1. PET CT with reference measurements of tumour relative to the top of aortic arch and carina. Reference measurements required for nodes felt to be malignant

2. Upper or middle third tumours: a bronchoscopy is required for all patients being considered for radiation therapy where the oesophageal tumours is encroaching, bulging and / or considered at risk of direct invasion into the airway on any imaging modality.

Prior physiological testing with echocardiogram, pulmonary function tests, NM medicine GFR and CPEX may be indicated, and there should be SMDT consensus that the patient has the required physiological fitness and limited co-morbidity. EUS may be needed with reference measurements of tumour ab oral relative to the top of aortic arch and carina. Reference measurements required for nodes felt to be malignant (Please see Manchester OG EUS Referral criteria https://gmcancer.org.uk/wp-content/uploads/2025/04/GM-OG-EUS-Referral-Criteria-FINAL.pdf)

In addition, careful attention to feeding is required with a feeding jejunostomy sited before referral for trimodality therapy for those with higher grade of dysphagia (modified O'Rourke score 3 or above) or where felt required by specialist dietician at surgical centre.

Any patient considered of insufficient fitness for trimodality treatment should be considered for definitive CRT.

Trimodality treatment CRT regimen for middle and lower third SCC:

• Radiotherapy: 41.4Gy in 23 fractions treating 5 days per week [CROSS] or 45 GY in 25
Fractions [Neo-Scope]

• Chemotherapy: Carboplatin AUC2 and Paclitaxel 50mg/m2 weekly days 2, 9, 16, 23
and 30.

Surgery should take place between 4-6 weeks of completion of CRT but no later than 10 weeks. Re-staging CT imaging should take place around 4 weeks after completion and should take place at surgical centre.

- For upper third oesophageal carcinoma, moderate dose escalation with intensity modulated radiotherapy (IMRT) can be considered, wherever possible within the context of a clinical trial (Grade C) 60–66 Gy in 30 fractions over 6 weeks
- For 30 fraction radiotherapy regime, induction cisplatin/ capecitabine chemotherapy is allowed followed by 3-weekly cisplatin 80-100mg/m2 for 2-3 cycles concurrently. Definitive chemoradiotherapy is recommended for tumours of the upper third oesophagus where extensive surgery would also involve a laryngectomy 9
- For tumours with <3cm of gastric extension, definitive chemoradiotherapy (CRT) may be considered for patients of good WHO PS (0-1) deemed unsuitable for surgical management [See section 2.6]

In those for whom chemotherapy is contraindicated high dose radiotherapy alone can be considered.

Evidence:

The landmark trial of neoadjuvant chemoradiotherapy is the Dutch CROSS trial. Radiotherapy with concomitant carboplatin and paclitaxel and 41.4 Gy in 23 fractions versus surgery alone demonstrated an increase in median survival from 24 to 49 months and no increase in perioperative mortality 6.

NEOSCOPE 8, a multicentre study of preoperative chemoradiotherapy, showed that neoadjuvant carboplatin and paclitaxel with radiotherapy to a dose of 45 Gy could be safely delivered to patients with locally advanced resectable oesophageal adenocarcinoma with acceptable toxicity and low incidence of postoperative mortality.

Patients with squamous cell carcinomas (SCC) of the oesophagus stage T2N0M0 deemed amenable to surgical resection may also be considered for neo-adjuvant chemotherapy triplet taxane based SACT based on the NEXT trial[27]

2.3.2

Adenocarcinoma

Recommendation:

Perioperative chemotherapy with FLOT as gastric adenocarcinomas is the preferred regimen for patients able to tolerate the treatment compared to trimodality treatment.

Evidence:

Multiple large prospective randomised controlled trials (RCTs) have established preoperative and perioperative chemotherapy as standards of care for locally advanced oesophageal and gastro-oesophageal junction (GOJ) adenocarcinomas. The phase III MAGIC 2 trial first demonstrated the benefit of perioperative chemotherapy using three cycles of epirubicin, cisplatin, and 5-FU (ECF) before and after surgery. This regimen was associated with improved tumour downstaging, higher R0 resection rates, and improved overall survival compared to surgery alone.

Subsequently, the phase II/III FLOT4-AIO 1 trial compared perioperative ECF with four preoperative and four postoperative cycles of 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT). The FLOT regimen showed superior overall survival and has since become the preferred perioperative regimen in patients with resectable oesophageal or GOJ adenocarcinoma who are fit to tolerate intensive treatment.

Several trials have attempted to directly compare perioperative chemotherapy with neoadjuvant chemoradiotherapy. The Neo-AEGIS trial 11, while underpowered and incomplete, found no significant difference in outcomes between trimodality

therapy (CROSS regimen: carboplatin, paclitaxel, and concurrent radiotherapy) and

perioperative chemotherapy, including both a modified MAGIC regimen and later the FLOT regimen. More recently, the ESOPEC trial 12 provided stronger evidence in this setting. It demonstrated that perioperative chemotherapy with FLOT was superior to the CROSS regimen in patients with resectable oesophageal adenocarcinoma, showing a significant survival advantage. Hence is the new standard of care.

2.4 Adjuvant Nivolumab

- Following the results of the Checkmate 577 trial 13, adjuvant nivolumab for 12 months is recommended for patients with completely resected but residual pathologic disease (ypT1 and/or ypN1) after previous neoadjuvant chemoradiotherapy (trimodality treatment) for oesophageal squamous cell cancers.

2.5 Adjuvant Chemo-Radiotherapy

Consider in patients who have positive margins and prognosis estimated to be mainly influenced by local relapse 9. Do not offer it to cases with high nodal burden and lympho-vascular invasion. If radiotherapy is given, concomitant chemotherapy is preferred to radiotherapy alone with conventionally fractionated doses of 40–50 Gy.

2.6. Not surgical candidate

may be due to disease (e.g. nodal disease sites) or patient factors. This applies to both SCC and Adenocarcinoma of oesophagus.

Stage	Treatment	Notes
T1N0 or above	Consider definitive chemoradiotherapy (dCRT) if disease can be encompassed in radiotherapy field	Need <3cm of gastric extension GFR >40ml/min
Not fit for dCRT	Consider high dose palliative radiotherapy if disease can be encompassed in radiotherapy field	
Too extensive for RT	Consider palliative SACT if deemed fit. These cases may still be suitable for palliative radiotherapy for symptoms eg bleeding, or to maintain dysphagia-free interval and this should be considered prior to commencement of SACT.	

2.6.1 Definitive chemoradiotherapy

Definitive CRT (dCRT) can be considered for any oesophageal cancer, T1N0M0 or above, that can be encompassed within a radical radiotherapy field. For oesophageal squamous cell carcinoma, where trimodality therapy is not recommended due to tumour factors (e.g. sites of nodal disease) or patient related factors, dCRT is the recommended standard of care. For early-stage squamous cancers (T1-T2N0) surgery alone (T1N0) or neoadjuvant chemotherapy/ surgery (T2N0) is an alternative option for patients deemed fit.

Patients who may have underlying Respiratory and / or cardiac co morbidities or overlaps with previous radiotherapy fields which may benefit from Proton Beam Therapy may be referred for consideration via the NHS proton beam referral portal. Patients will only receive PBT if approved via the NHS following the application through the portal.

The required mandatory staging investigations are as for neo-adjuvant CRT (see above). Patients should have WHO PS 0-1, and a glomerular filtration rate (GFR) > 60ml/min is required for cisplatin based chemotherapy but carboplatin and paclitaxel may allow dCRT in patients with GFR 40-60ml/min. Placement of a percutaneous gastrostomy

tube (RIG), is recommended for patients with high grades of dysphagia or where felt necessary by specialist dietician.

Radiotherapy regimens for dCRT:

- 50Gy in 25 fractions treating 5 days per week
- 45-50.4Gy in 1.8Gy per fraction can be considered if gastric/small bowel tolerance is of concern and / or clinically indicated.

Chemotherapy regimens for dCRT

- Two cycles of cisplatin (60 mg/m2) /capecitabine (625 mg/m2 BD) induction followed by radiotherapy and cisplatin/capecitabine week 1 and week 5.
- Weekly carboplatin/paclitaxel as per pre-operative regimen can be considered in patients where cisplatin/capecitabine is contraindicated e.g. history of ischaemic heart disease or suboptimal renal function (GFR 40-60ml/min).

2.6.2 High dose palliative radiotherapy Recommendation:

For patients who have localised disease encompassible within a radical radiotherapy volume, but who are deemed unsuitable for dCRT treatment, high dose radiotherapy to the local disease may be considered. The suitability for dCRT or radiotherapy alone can only be decided after review by a clinical oncologist. A discussion should be conducted by a clinical oncologist in relation to the rationale for selection, risks and benefits with the patient. Patients should be WHO PS 0-2, and placement of a percutaneous gastrostomy tube (RIG), is recommended for patients with high grades of dysphagia or where felt necessary by specialist dietician.

Mandatory staging required prior to definitive radiotherapy;

- PET CT with reference measurements of tumour relative to the top of aortic arch and carina. Reference measurements required for nodes felt to be malignant
- Where EUS has been used, the superior and inferior extent of the tumour with reference measurements of tumour ab oral relative to the top of aortic arch and carina. Reference measurements required for nodes felt to be malignant. Please see Manchester EUS referral criteria https://gmcancer.org.uk/wp-content/uploads/2025/04/GM-OG-EUS-Referral-Criteria-FINAL.pdf

- A bronchoscopy is required for all patients being considered for radiation therapy for oesophageal tumours encroaching, bulging and / or considered at risk of direct invasion into the airway on any imaging modality

Radiotherapy regimens:

- 55Gy in 20 fractions treating 5 days per week
- 50Gy in 16 fractions treating 5 days per week can be considered as shorter course for tumour length < 5cms.
- A lower dose of RT (45Gy) may be considered if gastric/small bowel tolerance is of concern.

Evidence:

More recently a retrospective UK single-centre analysis of 61 consecutive patients managed with hypofractionated radiotherapy with radical intent (50 Gy in 16 fractions or 50–52.5 Gy in 20 fractions) revealed 3-year survival of 56.9% and median overall survival of 29 months 9.

3. Palliative Patients:

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. When considering palliative chemotherapy, careful patient selection is vital as those with good performance status (PS) and limited co-morbid disease are far more likely to benefit.
Patients should be offered enrolment into a clinical trial whenever possible.

3.1 Palliative SACT for oesophageal, GOJ, and gastric cancers

3.1.1 Adenocarcinoma

All patients with gastric or GOJ adenocarcinomas should have human epidermal receptor 2 (HER2) status, Mismatch repair (MMR), PD-L1 combined positive score (CPS) status of their cancer.

Summary:

Oesophageal Adenocarcinoma	Gastric / GOJ Adenocarcinoma
-	Her 2 positives: cisplatin, capecitabine, and trastuzumab
PDL1CPS > 10* - Pembrolizumab + Chemo 3 weekly - Nivolumab + Chemo 3 weekly	PDL1 > 1 or CPS > 1 - Pembrolizumab + Chemo 3 weekly
PDL1 CPS > 5 - Nivolumab + Chemo 3 weekly	PDL1 CPS > 5 - Nivolumab + Chemo 3 weekly

- *Cases need to be discussed in MDT to conclude that this is purely oesophageal adenocarcinoma and not Siewert 1 GOJ Adenocarcinoma.

3.1.1 First Line

HER2-positive cancers:

Recommendation:
Patients with gastric or GOJ adenocarcinomas who have HER2-positive tumours (3+ on immunohistochemistry (IHC), or 2+ on IHC and fluorescence in-situ hybridisation (FISH) amplified) are recommended to receive chemotherapy with CX-H regimen

(cisplatin, capecitabine, and trastuzumab) which provides a survival advantage when compared to chemotherapy without herceptin15. Alternatives are Trastuzumab and Carbo-X or Trastuzumab and OX 14.

Evidence:
Trastuzumab in combination with chemotherapy can be considered as a new standard option for patients with HER2-positive advanced gastric or gastro-oesophageal junction cancer as improved median overall survival of 13·8 months (95% CI 12–16) in those assigned to trastuzumab plus chemotherapy compared with 11·1 months (10–13) in those assigned to chemotherapy alone (hazard ratio 0·74; 95% CI 0·60–0·91; p=0·0046) 14

HER2-negative cancers:

Recommendation:

The recommended first-line chemotherapy regimen for PS 0-2 patients with advanced oesophageal SCC, oesophageal adenocarcinoma, or HER2-negative adenocarcinomas of the GOJ and stomach is dependent on PD- L1 combined positive score (CPS) status. Immunotherapy is given for a maximum of two years.

- Patients with PD-L1 CPS > 10 are recommended to have Pembrolizumab, Platinum and Fluoropyrimidine (for oesophageal adenocarcinomas) 15.
- Patients with PD-L1 CPS > 1 are recommended to have Pembrolizumab, Platinum and Fluoropyrimidine (for gastric and GE junction adenocarcinomas) 16.
- Patients with PD-L1 CPS > 5 are recommended Nivolumab, Platinum and Fluoropyrimidine (for All cancer sites) 17.
- Patients with PD-L1 CPS<1 are recommended to receive Cisplatin and Capecitabine or Oxaliplatin and Capecitabine or Carbo-X or Paclitaxel and Carboplatin (in those who have a contraindication to fluoropyrimidines).

Evidence:
Keynote 590 15 compared with placebo plus chemotherapy, pembrolizumab plus chemotherapy improved overall survival in patients with previously untreated, advanced oesophageal squamous cell carcinoma and PD-L1 CPS of 10 or more, and overall survival and progression-free survival in patients with oesophageal squamous cell carcinoma.

Keynote 859 16 compared with placebo plus chemotherapy, pembrolizumab plus chemotherapy improved overall survival in patients with previously untreated, advanced gastric or GE junction adenocarcinomas and PD-L1 CPS of 1.

Checkmate 649 17 trial shows overall survival benefit patients with PDL1 CPS ≥5 with Nivolumab plus chemo versus chemo alone for oesophageal, gastric and gastro-oesophageal junction adenocarcinomas.

3.1.2 Second line palliative

Recommendation:
If progression following first line treatment for HER2 positive and negative adenocarcinomas a platinum (if tolerated well as 1st Line) and fluoropyrimidine can be rechallenged if there has been a progression free interval >4 months. Alternatives treatments are Docetaxel, Paclitaxel weekly or Irinotecan monotherapy. Taxanes, as 3-weekly docetaxel or weekly paclitaxel, or irinotecan can be considered having demonstrated improved survival and quality of life compared with best supportive care16-19.
Note: A caveat to this is patients that are HER2 negative and PD-L1 CPS<1 plus MMR deficient/MSI-H gastric carcinoma a single agent Pembrolizumab can be used. If further progression second line treatment above can be used 18.

Evidence:
Keynote 181 18 Pembrolizumab prolonged OS versus chemotherapy as second-line therapy for advanced oesophageal adenocarcinomas ad squamous cell cancer in patients with PD-L1 CPS ≥ 10, with fewer treatment-related adverse events.

Third line palliative chemotherapy
If further progression on or after treatment following at least 2 lines for Adenocarcinoma irrespective of HER2 status. The 3rd line is Trifluridine and Tipiracil for Stomach and GOJ cancers 19.

3.1.2 Squamous cell carcinoma

Patients with oesophageal or GOJ (Siewert 1) squamous cell carcinomas treatment is dependent on their PD-L1 combined positive score (CPS) and tumour proportion score (TPS).

First line:

Oesophageal Squamous cell cancer
PDL1 CPS > 10 - Pembro + Chemo 3 weekly
CPS < 10 and TPS > 1 - Nivolumab + Chemo 3 weekly

Recommendations:

- The recommended first-line chemotherapy regime for PD-L1 CPS <10 and TPS <1% is Cisplatin +Capecitabine.
- The recommended first-line chemotherapy regime for PD-L1 CPS <10 and TPS > 1% is Nivolumab in combination with Platinum. If Oesophageal cancer Fluoropyrimidine should be added 20.
- The recommended first-line chemotherapy regime for PD-L1 CPS 10 is Pembrolizumab in combination with Platinum. If Oesophageal cancer Fluoropyrimidine should be added 15.

Evidence:

Keynote 590 Summary: The greatest OS gain was observed in patients with SCC and elevated PD-L1 expression (CPS >10; HR 0.57, 95% CI 0.43- 0.75; P < 0.0001), but modest improvements were also demonstrated in (i) all patients with a CPS 10 (HR 0.62, 95% CI 0.49-0.78; P < 0.0001); (ii) all patients with SCC (HR 0.72, 95% CI 0.60-
0.88; P ¼ 0.0006) and (iii) all randomised patients (HR 0.73, 95% CI 0.62-0.86; P < 0.0001). A post hoc analysis suggested no benefit in patients with a PD-L1 CPS <10. Checkmate 648 summary: Patients treated with nivolumab, and chemotherapy had improved OS compared with patients treated with chemotherapy alone; this benefit was most pronounced in patients with tumour cells expressing PD-L1 > 1% using TPS (HR 0.54, 99.5% CI 0.37-0.80; P < 0.001)

Second line:

If progression on or after treatment irrespective of CPS and TPS score, a Platinum and Capecitabine rechallenge can be used (if there has been a progression free interval > 4 months and first line platinum was tolerated). Alternatives are Docetaxel or Paclitaxel weekly.

Note: A caveat to this is in patients with PD-L1 CPS <10 and TPS <1% and Oesophageal cancer Nivolumab monotherapy until progression can be used. If further progression second line treatment above can be used 21.

Evidence:

second-line nivolumab monotherapy is an option based on the results of the phase III ATTRACTION-3 trial. nivolumab was associated with improved OS compared with ChT (HR 0.77, 95% CI 0.62- 0.96; P ¼ 0.019). Treatment outcomes were not affected by PD-L1 expression assessed on tumour cells 21.

Third Line:

As Adenocarcinomas

Platinum-combination re-challenge

Re-challenge with first line platinum-based chemotherapy may be considered in patients who have progressed >6 months post completion of treatment and derived initial clinical benefit 22.

3.4 Palliative radiotherapy

Gastric cancer

Radiotherapy can be used for management of bleeding. It is recommended that patients with heavy or acute upper GI bleeding should be considered for gastric artery embolization by interventional radiology or for palliative surgery. Patients need to have an attempt at bleeding control with OGD.

Radiotherapy regimen:

- 30Gy in 10 fraction/20Gy in 5 fractions
- Single 8-10 Gy for bleeding control

Oesophageal cancer

Brachytherapy:

Brachytherapy is a form of radiotherapy where a radioactive source or sources are placed close to or within the tumour. This results in the treatment area receiving a high dose of radiation whilst the dose to surrounding tissue is lower. It is not currently offered in Greater Manchester so suitable patients should be referred to a unit with appropriate expertise.
The main indication for brachytherapy is evidence local recurrence (>6 months) after external beam radiation which is not amenable to salvage surgery as evidence suggests advantage in QOL and intervention- free survival 23.
This option will require a referral to a specialist unit with expertise in Intra Luminal Brachytherapy for oesophageal cancer (e.g. Leeds Cancer Centre).

Palliative EBRT:
Palliative external beam may also be considered for symptom control e.g. dysphagia/bleeding and as consolidation therapy following response to systemic chemotherapy. The UK ROCS study 24 has shown that palliative radiotherapy in addition to oesophageal stenting does not improve outcomes over stent insertion alone and should not be routinely offered.

Radiotherapy regimens:
30Gy in 10 fraction/20Gy in 5 fractions (this regimen may also be used for Type I/II GOJ adenocarcinomas)

4. SMALL CELL CARCINOMA OESOPHAGUS

Small cell carcinoma of the oesophagus is a rare but well recognised histological subtype. Diagnosis requires specialist upper GI pathologist review with neuro-endocrine immuno-histochemistry and Ki67 or MIB-1 proliferative index score. Staging should be the same as for other histological subtypes. For patients with ‘limited stage’ disease, defined as being encompassible in a tolerable thoracic radiation volume, the recommended treatment is concurrent or sequential CRT as described below 25-27. Patients who do not meet these criteria are defined as ‘extensive stage’ and should be referred for palliative platinum/etoposide-based chemotherapy under the care of the Neuroendocrine Team at the Christie.

4.1 Concurrent

CRT Eligibility:

- Age ≤ 75 years
- WHO PS 0-1
- No co-morbidity contra-indicating use of cisplatin
- glomerular filtration rate (GFR) >

60ml/min Recommended Regimen:

- Cycle 1; induction cisplatin/etoposide chemotherapy
- Cycle 2; cisplatin/etoposide chemotherapy with radiotherapy.
- 45Gy in 30 fractions twice-daily (3 weeks overall treatment time), with minimum 6-hour inter-fraction interval. RT planning scan will be done after cycle 1 has been delivered.

Alternate Regimen:

- Cycles 1 & 2; induction cisplatin/ etoposide chemotherapy
- Cycles 3 & 4; cisplatin/ etoposide chemotherapy with radiotherapy.
- 50Gy in 25 fractions once daily (5 weeks overall treatment time). RT planning scan done after first cycle of chemotherapy delivered

4.2 Sequential

CRT Eligibility:

- patients who do not fit concurrent criteria but are deemed fit enough for chemotherapy
- glomerular filtration rate (GFR) > 40ml/min
- Regimen: Carboplatin-based chemotherapy, 4 cycles (or more if well tolerated) with an interim restaging CT scan Radiotherapy; 50-55Gy in 20 daily fractions once daily (4 weeks overall treatment time)

4.3 Prophylactic cranial irradiation (PCI):

The evidence for a benefit for PCI in small cell cancer of oesophagus is limited and based mainly on data from small cell lung cancer. This can be discussed on a case-by-case basis in patients age ≤ 75 years, PS 0-2, with no prior intra-cranial pathology, and who have achieved a good response seen to chemotherapy. PCI cannot be given concurrently with chemotherapy, and the minimum time period between chemotherapy and commencing PCI should be 2 week.

References:

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