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Gastric cancer: ESMO–ESSO–ESTRO clinical practice guidelines for diagnosis, treatment and follow-up☆,☆☆

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Incidence and epidemiology

In 2012, there were ~140 000 new cases of gastric cancer diagnosed across all European countries, making it the sixth commonest cancer diagnosis. Perhaps more importantly, it remains the fourth commonest cause of cancer-related death, being responsible for ~107 000 deaths annually.[1] Despite a gradual decline in the worldwide incidence of gastric cancers, there has been a relative increase in the incidence of tumours of the oesophago-gastric junction (OGJ) and gastric cardia. The peak incidence is in the 7th decade, and the disease is approximately twice as common in men as in women. There is marked geographic variation, with the highest rates in East Asia, South America and Eastern Europe and the lowest rates in the United States and Western Europe.[2]

The risk factors for gastric cancer include male gender, cigarette smoking, *Helicobacter pylori* infection, atrophic gastritis, partial gastrectomy, and Ménétrier's disease. A small number of patients may have a genetic predisposition syndrome including hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, hereditary diffuse gastric cancer and Peutz Jeghers syndrome. If this is suspected based upon family history then patients should be referred to a genetics specialist for assessment as per International Gastric Cancer Linkage Consortium guidelines[3] [V, B].

Diagnosis and pathology

Screening for gastric cancer is routine in Japan and Korea where the incidence is much higher than in Western countries. In symptomatic patients, the presenting features commonly include weight loss, dysphagia, dyspepsia, vomiting, early satiety, and/or iron-deficiency anaemia.

Diagnosis should be made from a gastroscopic or surgical biopsy reviewed by an experienced pathologist, and histology should be reported according to the World Health Organisation criteria [IV, C].

Ninety percent of gastric cancers are adenocarcinomas, and these are sub-divided according to histological appearances into diffuse (undifferentiated) and intestinal (well differentiated) types (Lauren classification). These Clinical Practice Guidelines do not apply to rarer gastric malignancies such as gastrointestinal stromal tumours (GIST), lymphomas and neuro-endocrine tumours.

Staging and risk assessment

Initial investigations include physical examination, blood count and differential, liver and renal function tests, endoscopy and contrast-enhanced computed tomography (CT) scan of the thorax, abdomen ± pelvis. Positron

☆ These guidelines do not refer to the separate entity of oesophago-gastric junction (OGJ) tumours.

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Table 1
Diagnostic and staging investigations in gastric cancer.

Procedure	Purpose
Routine blood tests	Check for evidence of iron-deficiency anaemia. Check hepatic and renal function to determine appropriate therapeutic options.
Endoscopy + biopsy	Obtain tissue for diagnosis, histological classification and molecular biomarkers e.g. HER-2 status
CT thorax + abdomen ± pelvis	Staging of tumour − particularly to detect local/distant lymphadenopathy and metastatic disease sites.
Endoscopic ultrasound (EUS)	Accurate assessment of T and N stage in potentially operable tumours. Determine proximal and distal extent of the tumour.
Laparoscopy + washings	To exclude occult metastatic disease involving the diaphragm/peritoneum.
Positron emission tomography (PET, if available)	May improve detection of occult metastatic disease in some cases.

emission tomography (PET) imaging, if available, may improve staging through increased detection of involved lymph nodes/metastatic disease. However, it may be uninformative in some patients, especially those with mucinous tumours [III, B] (Table 1).

Endoscopic ultrasound (EUS) is helpful in determining the proximal and distal extent of the tumour and provides further assessment of the T and N stages, although it is less useful in antral tumours [III, B]. Laparoscopy ± peritoneal washings for malignant cells is recommended in all stage IB-III stomach cancers considered to be potentially resectable to exclude occult metastatic disease[4,5] [III, B].

The TNM classification should be recorded and the corresponding stage determined according to the 7th edition of the Union for International Cancer Control (UICC)[6]/ American Joint Committee on Cancer (AJCC)[7] guidelines and staging manual (Tables 2 and 3). A careful tumour staging is fundamental to ensuring that patients are appropriately selected for treatment interventions.

Treatment planning

Multi-disciplinary treatment planning is mandatory. The core membership of the multi-disciplinary team should include surgeons, medical and radiation oncologists, gastroenterologists, radiologists, pathologists, dieticians and nurse specialists if available [IV, C].

Management of local/locoregional disease

Surgery

Surgical resection is the only treatment modality that is potentially curative, though the majority of patients still relapse following resection and therefore combined modality approaches are standard for ≥stage 1B disease. The extent of resection is determined by the pre-operative stage. Early gastric cancers (T1a) may be amenable to endoscopic resection if they are well-differentiated, ≤2 cm, confined to the mucosa and not ulcerated[8] [III, B]. The associated lymph node metastatic risk is virtually zero for this group. Guidelines from the National Cancer Centre in Tokyo have expanded these criteria in patients with intestinal-type histology and no evidence of lympho-vascular invasion to include: intra-mucosal cancers without ulceration regardless of tumour size; intra-mucosal cancers <3 cm with ulceration; or cancers with early invasion into the submucosa (sm1) measuring <3 cm. In this expanded group the risk of lymph node metastases also remains low, provided that an endoscopic submucosal *en bloc* resection is undertaken to permit precise histological assessment[9] [III, B].

T1 tumours which do not meet the criteria for endoscopic therapy will require surgery, though the extent is less than for other gastric cancers (see below). In particular, the lymph node dissection can be limited to perigastric nodes and include local N2 nodes, referred to as D1 alpha and D1 beta according to position of primary tumour. Sentinel node mapping may further modify these approaches.

Radical gastrectomy is indicated for resectable stage IB-III disease. Sub-total gastrectomy may be carried out if a macroscopic proximal margin of 5 cm can be achieved between the tumour and the OGJ. A margin of 8 cm has been advocated for diffuse type cancers. Otherwise a total gastrectomy is indicated [III, A]. Perioperative therapies should be considered in these patients (see below).

The extent of nodal dissection accompanying radical gastrectomy has been extensively debated (D1: removal of perigastric lymph nodes versus D2: removal of perigastric lymph nodes plus those along the left gastric, common hepatic and splenic arteries and coeliac axis). The current UICC/AJCC TNM classification recommendations (7th edition) include excision of a minimum of 15 lymph nodes to allow reliable staging.[6,7] Experience from both observational and randomised trials in Asian countries has demonstrated that D2 dissection leads to superior outcomes compared to D1 [II, B]. In the West, a Dutch[10] and a UK Medical Research Council (MRC) trial[11] failed to demonstrate any initial survival advantage with D2 resection. However the 15-year follow-up results from the Dutch trial[12] demonstrated fewer locoregional recurrences and gastric cancer-related deaths with D2 resection, though this was slightly offset by an increase in postoperative mortality and morbidity. A recent meta-analysis of 12 randomised, controlled trials (RCTs) confirmed no overall survival (OS) benefit for D2 lymphadenectomy, although a benefit was seen amongst patients who had

Table 2
TNM staging of gastric cancer (7th edition of AJCC/UICC guidelines).[6,7]

Primary tumour (T)		Regional lymph nodes (N)		Distant Metastasis (M)	
TX	Primary tumour cannot be assessed	NX	Regional lymph node(s) cannot be assessed	MX	Distant metastasis cannot be assessed
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	M0	No distant metastasis
Tis	Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria	N1	Metastasis in 1–2 regional lymph nodes	M1	Distant metastasis or positive peritoneal cytology
T1a	Tumour invades lamina propria or muscularis mucosae	N2	Metastasis in 3–6 regional lymph nodes		
T1b	Tumour invades submucosa	N3	Metastasis in 7 or more regional lymph nodes		
T2	Tumour invades muscularis propria				
T3	Tumour penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures[a]				
T4a	Tumour invades serosa (visceral peritoneum)				
T4b	Tumour invades adjacent structures[b]				

Edge SB, Byrd DR, Compton CC, editors. AJCC Cancer Staging Handbook, 7th ed. New York, NY: Springer; 2010. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Handbook, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

[a] T3 tumours also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures.

[b] Adjacent structures include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine and retroperitoneum.

resection without splenectomy and/or pancreatectomy.[13] The current consensus view in the West is that, for patients deemed medically fit, D2 dissection should be the standard procedure carried out in specialised, high-volume centres with appropriate surgical expertise and postoperative care[14] [I, B].

Table 3
AJCC/UICC stage grouping (7th edition).[6,7]

Stage grouping	T-stage	N-stage	M-stage
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage IIA	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIB	T1	N3	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIIA	T2	N3	M0
	T3	N2	M0
	T4a	N1	M0
Stage IIIB	T3	N3	M0
	T4a	N2	M0
	T4b	N0-1	M1
Stage IIIC	T4a	N3	M0
	T4b	N2-3	M0
Stage IV	Any T	Any N	M1

Edge SB, Byrd DR, Compton CC, editors. AJCC Cancer Staging Handbook, 7th ed. New York, NY: Springer; 2010. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Handbook, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Laparoscopic surgery has been evaluated as an alternative to open surgery with the potential benefits of decreased operative morbidity and reduced recovery times. Meta-analyses confirm these benefits in distal gastrectomy, though some concerns remain regarding long-term outcomes and the possibility for reduced nodal harvest with a laparoscopic approach[15,16] [I, A]. In addition, operative morbidity is greater particularly in total gastrectomy and there remains a lack of consensus on the preferred approach to the technique of anastomosis following a laparoscopic total gastrectomy. Trials are currently ongoing in Japan (JCOG-0912), Korea (KLASS and KLASS-02) and China to compare open versus laparoscopic surgery in early gastric cancer, and these should provide further evidence regarding the role of laparoscopic surgery.

Perioperative chemotherapy

The UK MRC MAGIC trial was the first trial to evaluate the role of perioperative chemotherapy with six cycles of ECF [epirubicin 50 mg/m^2 D1, cisplatin 60 mg/m^2 D1 and 5-fluorouracil (5-FU) 200 mg/m^2/day D1-21 Q21] compared with surgery alone in patients with resectable stage II and III gastric cancers.[17] The results demonstrated that chemotherapy improved the 5-year survival rate from 23% to 36%, with manageable toxic effects. A subsequent FNCLCC (*Féderation Nationale des Centres de Lutte Contre le Cancer*) and FFCD (*Fédération Francophone de la Cancérologie Digestive*) trial has reported similar results with the use of a 28-day regimen of perioperative cisplatin (100 mg/m^2 D1) and 5-FU (800 mg/m^2/day D1-5).[18] Perioperative chemotherapy has therefore been widely adopted as the standard

of care throughout most of the UK and Europe [I, A]. Since capecitabine avoids the need for an indwelling central venous access device, and is non-inferior to 5-FU in the advanced disease setting,[19] many centres use ECX (epirubicin, cisplatin, capecitabine) peri-operatively in preference to ECF [IV, C]. Other platinum/fluoropyrimidine doublets may be considered in patients with specific drug contraindications.

Adjuvant chemoradiotherapy

For patients who undergo surgery for ≥stage IB oesophago-gastric cancer without administration of pre-operative chemotherapy, the treatment options include either chemoradiotherapy or chemotherapy delivered in the adjuvant setting (see below). Evidence is currently lacking to inform the choice between these two treatment modalities in the adjuvant setting. Further data on these options are awaited from the ongoing randomised, phase III CRITICS trial in which patients receive 3 cycles of pre-operative chemotherapy followed by surgery and are then randomised between adjuvant chemotherapy and chemoradiotherapy.

The North American Intergroup-0116 trial demonstrated that adjuvant therapy with five cycles of 5-FU/leucovorin (Q28) plus concomitant radiotherapy (45 Gy in 25 fractions over 5 weeks) during cycles 2 and 3 resulted in improved OS at 5 years compared with surgery alone. After 10 years of follow-up, this result remains significant with a hazard ratio for OS of 1.32 in favour of adjuvant chemoradiotherapy[20] [I, A]. This treatment approach is considered standard therapy in the United States, though it has not gained wide acceptance in Europe due to concerns about potential late toxic effects and the quality of surgery within the trial. Fifty-four percent of patients underwent less than a D1 lymphadenectomy, suggesting that postoperative chemoradiation may be compensating for sub-optimal surgery [II, B]. This is supported by retrospective data from the Dutch D1D2 trial, demonstrating that chemoradiotherapy reduces local recurrence rates following D1 resection, but provides no benefit in patients who have undergone D2 resection[21] [IV, B]. However, other randomised and non-randomised data suggest potential benefits from postoperative chemoradiation even after optimal D2 dissection[22–24] [I, B] and this is the subject of ongoing randomised trials. A retrospective comparison of the Dutch D1D2 trial has also confirmed significant improvements in OS and local recurrence rates with use of chemoradiotherapy after a microscopically incomplete (R1) resection[21] [IV, B].

In current postoperative chemoradiation regimens, radiotherapy may be given to a total dose of 45 Gy in 25 fractions of 1.8 Gy, 5 fractions/week by 3D-conformal or intensity-modulated radiation therapy techniques. The clinical target volume encompasses the gastric bed (with stomach remnant when present), anastomoses and draining regional lymph nodes (for delineation manual: www.critics.nl).

Adjuvant chemotherapy

A large, individual patient-level meta-analysis of adjuvant chemotherapy in gastric cancer has confirmed a 6% absolute benefit for 5-FU-based chemotherapy compared with surgery alone (HR 0.82, 95% CI 0.76–0.90; $p < 0.001$) in all subgroups tested[25] [I, A]. However, historically a greater benefit has been noted with this approach in Asian studies compared with those in Western populations and uptake of this approach in Europe remains limited due to a perceived lack of benefit and routine use of perioperative chemotherapy. In Asian populations, an OS benefit following adjuvant chemotherapy was confirmed following D2 resection in the ACTS-GC trial evaluating adjuvant S-1[26] [I, A]. The CLASSIC trial evaluated an adjuvant capecitabine-oxaliplatin doublet and has reported significantly improved overall and disease-free survival[27] See Fig. 1.

Management of advanced/metastatic disease

Palliative chemotherapy and radiotherapy

Patients with stage IV disease should be considered for palliative chemotherapy, which improves survival compared with best supportive care alone[28] [I, A]. However, co-morbidities, organ function and performance status must always be taken into consideration [II, B]. Although resection of the primary tumour is not generally recommended in the palliative setting, a small number of advanced disease patients may be deemed to be operable following a good response to systemic therapy. Response to systemic treatments should normally be assessed with interval CT imaging of chest, abdomen and pelvis. Alternative imaging techniques may be used if required to monitor known sites of disease (e.g. magnetic resonance imaging for bone lesions).

Combination regimens based upon a platinum/fluoropyrimidine doublet are generally used, and there remains controversy regarding the need for triplet regimens. However, a meta-analysis has demonstrated significant benefit from adding an anthracycline to a platinum and fluoropyrimidine doublet[28] [I, A]. The UK REAL-2 trial demonstrated non-inferiority between ECF, ECX, EOF (epirubicin, oxaliplatin, 5-FU) and EOX (epirubicin, oxaliplatin, capecitabine).[19] The EOX regimen was associated with numerically longer median OS (11.2 versus 9.9 months, HR 0.80, 95% CI, 0.66–0.97; $p = 0.02$) than ECF without the need for an indwelling catheter and with reduced rates of thrombo-embolism.[29] Additionally, a meta-analysis has demonstrated that capecitabine is associated with improved OS compared to infused 5-FU within doublet and triplet regimes[30] [I, A].

Alternative first-line chemotherapy options include taxane-based regimens or irinotecan plus 5-FU.[31] The addition of 3-weekly docetaxel to 5-FU/cisplatin (DCF) is

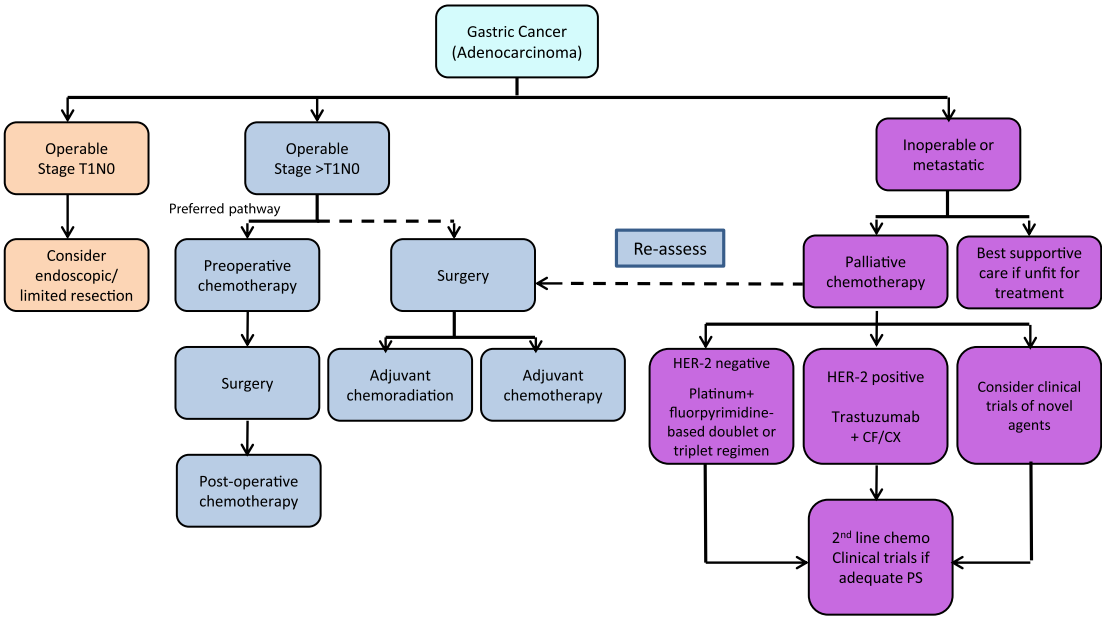

Figure 1. Algorithm for the management of gastric cancer. See attached ppt file.

associated with increased activity, but also adds toxic effects including increased rates of febrile neutropaenia[32] [I, C]. Modified DCF regimens therefore continue to be explored in an attempt to maintain activity whilst mitigating against excessive toxic effects.

In patients of adequate performance status, second-line chemotherapy is associated with proven improvements in OS and quality of life compared with best supportive care, with treatment options including irinotecan, docetaxel or paclitaxel[33–37] [I, A]. A randomised phase III trial directly comparing weekly paclitaxel with irinotecan has demonstrated similar efficacy for both the regimens, with the median OS of 8–9 months in a Japanese population[37] [I, A]. Additionally, consideration should always be given to inclusion in any appropriate clinical trials [V, B]. Alternatively, in patients with disease progression >3 months following first-line chemotherapy, it may be appropriate to consider a re-challenge with the same drug combination [IV, C].

In patients with symptomatic locally advanced or recurrent disease, hypo-fractionated radiotherapy is an effective and well-tolerated treatment modality which may palliate bleeding, obstructive symptoms or pain[38] [III, B]. See Fig. 1.

Personalised medicine

As in other solid organ tumours, the biological abnormalities underpinning the development and progression of gastric cancer are being increasingly elucidated through ongoing international research. These tumours are now known to be highly molecularly diverse and may be driven by a number of different genetic and epigenetic abnormalities. Perhaps most notably, gastric cancers are frequently found to harbour copy number alterations in key oncogenes and tumour suppressor genes.[39] These findings have potentially important therapeutic implications as oncologists attempt to target the key pathways driving the tumour in each individual patient.

In HER-2 positive gastric cancer (10–15% of cases), the phase III ToGA trial demonstrated clinically and statistically significant improvements in response rate, progression-free survival (PFS) and OS with the addition of trastuzumab to a cisplatin–fluoropyrimidine doublet (median OS 13.8 versus 11.1 months, HR 0.74, 95% CI, 0.60–0.91; $p = 0.0048$).[40] The benefits of trastuzumab were even more marked in the traditionally defined HER-2 positive subgroup with IHC 2+/FISH-positive tumours, or IHC 3 + tumours. In these patients the median OS was improved from 11.8 months to 16.0 months (HR 0.65). Following the ToGA trial results, trastuzumab was licenced in Europe for use in HER-2 positive disease (IHC3+ or 2+/FISH-positive) in combination with capecitabine or 5-fluorouracil and cisplatin. This regimen now represents the standard of care for these patients [I, A].

The AVAGAST trial evaluating bevacizumab in combination with first-line chemotherapy failed to demonstrate any improvement in OS, though both PFS and response rate were significantly improved[41] [I, C]. A second anti-angiogenic agent, ramucirumab, has recently been confirmed to have single-agent activity in the second-line setting with a modest 1.4 month improvement in OS compared to best supportive care[42] [I, B]. Neither agent is currently in routine clinical use.

Anti-EGFR therapies have failed to improve outcomes with recently reported negative phase III results when cetuximab[43] or panitumumab[44] was added to first-line

Table 4
Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a]).

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs,...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a] Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among haematopoietic stem cell transplant recipients. *Clin Infect Dis* 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

chemotherapy, and a negative phase III trial of single-agent gefitinib compared to best supportive care in the second-line[45] [I, D].

Other molecular targets which are currently showing promise in the advanced disease setting include:

- Overexpression or amplification of the MET receptor – MET targeted therapies are currently entering phase III trials in this population.
- Amplification of FGFR – anti-FGFR therapy is currently undergoing evaluation.

Follow-up and long-term implications

In the setting of operable gastric cancer, the complexity of treatment frequently induces symptoms which adversely affect health-related quality of life. A regular follow-up may allow investigation and treatment of symptoms, psychological support and early detection of recurrence, though there is no evidence that it improves survival outcomes[46–48] [III, B].

New strategies for patient follow-up are currently undergoing evaluation, including patient-led self-referral and services led by clinical nurse specialists.

In the advanced disease setting, identification of patients for second-line chemotherapy and clinical trials requires regular follow-up to detect symptoms of disease progression prior to significant clinical deterioration [IV, B].

If relapse/disease progression is suspected then a clinical history, physical examination and directed blood tests should be carried out. Radiological investigations should be carried out in patients who are candidates for further chemo- or radiotherapy [IV, B].

The aggressive nature of gastric cancer, and historically poor outcomes even in the setting of operable disease, mean that the concept of survivorship is only now beginning to evolve. Long-term implications, late effects of therapy, and psychosocial implications of treatment are poorly studied to date.

Note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 4. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

Conflict of interest

Dr Allum has received speaker's honoraria for conferences and workshops from Lilly, Nestle and Astellas Oncology. Prof. Cunningham has reported advisory board of Amgen and Roche Pharmaceuticals; research funding from Amgen, Celgene, Novartis, Roche and Sanofi. Prof. Arnold has reported research grants from Roche and Sanofi. The other authors have reported no potential conflicts of interest.

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