



SEOM–GEMCAD–TTD clinical guideline for the diagnosis and treatment of esophageal cancer (update 2025)

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Abstract

Esophageal cancer represents an aggressive disease positioned as the seventh-leading cause of death from cancer. Esophageal cancer comprises two different diseases that should be distinguished by histology, i.e., squamous cell carcinoma and adenocarcinoma. The epidemiology and molecular differences between these two entities explain their different responsiveness to novel treatments which should be treated independently. The improvement in outcomes of patients with esophageal cancer are obtained when a multidisciplinary therapeutic strategy is utilized. The introduction of targeted therapies including immunotherapy has markedly improved patient outcomes. We present an updated version of the Spanish esophageal cancer guidelines, summarizing the current evidence and available therapies for the treatment of esophageal cancer.

Keywords Esophageal cancer · Squamous cell carcinoma · Adenocarcinoma · Diagnosis · Treatment

Introduction

Esophageal cancer is a major public health problem, being the eleventh most common cancer worldwide and the seventh leading cause of death from cancer, with a 5-year

survival rate of only 15–20% [1]. According to the report “Cancer figures in Spain 2025” published by SEOM, 1883 new cases of esophageal cancer are estimated for this year [2]. Of note, 70% of all cases of esophageal cancer occur in men [1]. The survival rate of esophageal cancer in Spain

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varies depending on gender, with survival rates for men increasing by 35% and in women decreasing by 9% from 2002–2007 to 2008–2013 [2].

There are two main histological types of esophageal cancer: squamous cell carcinoma (SCC), which makes up 85% of new cases globally and is located predominantly in the upper and mid-esophagus; and adenocarcinoma, which makes up the remaining 15% of new cases and occurs predominantly in the lower esophagus [3]. Although the SCC subtype of esophageal cancer is the most prevalent worldwide, especially in Asia and Eastern Africa, its incidence has decreased in recent decades [4]. The incidence of adenocarcinoma, however, has continued to rise sharply in developed countries, and now exceeds SCC rates in North America, Europe, and Australia [3]. These differences in incidence, trend, and geographic distribution reflect the particular etiology attributed to each type. More specifically, alcohol and tobacco use are predominantly associated with SCC, while gastro-esophageal reflux and central obesity are important risk factors for Barrett's esophagus (a precursor lesion) and adenocarcinoma [5].

Esophageal SCC (ESCC) has molecular features that are similar to those of SCC of the head and neck, while esophageal adenocarcinoma is more similar to gastric adenocarcinoma. In ESCC, alterations in cell cycle regulators with inactivation of cyclin-dependent kinase inhibitor 2A (CDKN2A) and amplification of *CCND1* are frequent [6]. Three molecular subtypes of ESCC have been described: ESCC1, with mutations of nuclear factor erythroid 2-related factor 2 (*NRF2*), is associated with a poor prognosis and resistance to chemo-radiotherapy; ESCC2, in which the neurogenic locus notch homolog protein 1 (*NOTCH1*) or zinc finger protein 750 (*ZNF750*) genes are frequently mutated; and ESCC3, which is characterized by alterations that activate the phosphatidylinositol 3-kinase (PI3K) pathway [6].

Expression of programmed death-ligand 1 (PD-L1) is higher in ESCC than in esophageal adenocarcinoma [7]. In contrast, E-cadherin expression and upregulation of adenosine diphosphate-ribosylation factor 6 (ARF6), Forkhead box protein A (FOX A), and the mitogen-activated protein kinase (MAPK) pathway are characteristic of adenocarcinoma, in which overexpression and amplification of Erb-B2 receptor tyrosine kinase 2 (ERBB2; also known as human epidermal growth factor receptor 2 [HER2]) are common features [6].

This article presents the 2025 update to the clinical practice guidelines for the management of esophageal cancer, developed jointly by the Spanish Society of Medical Oncology (SEOM), the Spanish Multidisciplinary Group for Digestive Cancer (GEMCAD), and the Digestive Tumor Treatment Group (TTD). The previous edition was published in 2022 [8]. The aim of the current update is to summarize current evidence and available therapies for the medical management of esophageal cancer and to provide evidence-based recommendations for clinical practice.

Methodology

These guidelines have been developed based on the consensus of 10 medical oncologists specializing in esophageal cancer from the Spanish cooperative groups SEOM, GEMCAD, and TTD. The Infectious Diseases Society of America–US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines was used to assign the quality of evidence and the grade of recommendation to each of the consensus statements in this treatment guideline (Table 1) [9]. The recommendations in these guidelines were updated in 2025 to reflect the results of clinical trials released since the publication of the previous version of these guidelines in 2022 [8], along with some

Table 1 Levels of evidence and grades of recommendation [9]

<i>Levels of evidence</i>	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized 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, and experts' opinion
<i>Grades of recommendation</i>	
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 risk or disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally, not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

minor corrections to the wording of the original guidelines. These updated guidelines have been approved by all authors.

Diagnosis and staging

Confirmatory diagnosis of esophageal cancer relies on endoscopic biopsy. Multiple endoscopy biopsies should be taken to guarantee an adequate representation of the tumor and sufficient tissue for molecular analysis, with advice for obtaining 6 to 8 samples [IIIA]. Histology must be performed according to the WHO criteria [10] [IVA]. Once a pathologic diagnosis has been established, the clinical stage must be determined to estimate the prognosis and to define the therapeutic strategy. Patient performance status must be determined (i.e., by the Eastern Cooperative Oncology Group [ECOG] score), along with a complete physical examination, and geriatric (in case of elderly patients) and nutritional evaluation [VA]. Blood analysis (including a hemogram and renal/hepatic panel) and imaging tests (computed tomography [CT] scan of chest and abdomen) are also required [VA]. In patients who are candidates for surgery or radical treatment, consider expanding the investigations to include the following:

- Echoendoscopy [IIA] [11].
- Positron emission tomography (PET)-CT or contrast-enhanced CT [IIIA] [12].
- For distal esophageal adenocarcinomas cT3-4 or N+, an exploratory laparoscopy and peritoneal cytology is highly recommended [IVA] [13]; it should also be considered in cases with signet ring cell or diffuse-type histology [14].
- Bronchoscopy, highly recommended for those upper thoracic tumors [IIA].

The disease should be staged according to the 2017 UICC-AJCC classification (8th edition) [VB] (Table 2) and categorized according to histology [VA] (Table 3) [15]. The recommended molecular analyses for ESSC include the determination of the PD-L1 expression, reported as combined positive score (CPS), tumor proportion score (TPS), or tumor area positivity (TAP); being for esophageal adenocarcinoma the status of the mismatch repair (MMR) system/microsatellite instability (MSI), HER2 expression, and the PD-L1 expression (CPS and TAP scores) [IA]. For those tumors

Table 2 TNM staging for esophageal and gastroesophageal junction (GEJ) cancer [15]

<i>T—Primary tumor</i>	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ/high-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Tumor invades pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Tumor invades other adjacent structures such as aorta, vertebral body, or trachea
<i>N—Regional lymph nodes</i>	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 2 regional lymph nodes
N2	Metastasis in 3 to 6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
<i>M—Distant metastasis</i>	
M0	No distant metastasis
M1	Distant metastasis
<i>G—Histology grade</i>	
Gx	Unknown grade
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated or undifferentiated

Table 3 Stage grouping according to histology

SSC						Adenocarcinoma				
Group	T	N	M	Grade	Location	Group	T	N	M	Grade
0	Tis	N0	M0	N/A	Any	0	Tis	N0	M0	Any
IA	T1a	N0	M0	1,X	Any	IA	T1a	N0	M0	1, X
IB	T1a	N0	M0	2–3	Any	IB	T1a	N0	M0	2
	T1b	N0	M0	Any	Any		T1b	N0	M0	1, 2
	T2	N0	M0	1	Any					
IIA	T2	N0	M0	2,3,X	Any	IIA	T1a,b	N0	M0	3
	T3	N0	M0	Any	Lower		T2	N0	M0	1,2
	T3	N0	M0	1	Upper, middle		T2	N0	M0	3,X
IIB	T3	N0	M0	2,3	Upper, middle	IIB	T1	N1	M0	Any
	T3	N0	M0	Any	X		T3	N0	M0	Any
	T3	N0	M0	X	Any					
IIIA	T1	N1	M0	Any	Any	IIIA	T1	N2	M0	Any
	T2	N1	M0	Any	Any		T2	N1	M0	Any
IIIB	T2	N2	M0	Any	Any	IIIB	T2	N2	M0	Any
	T3 N1,2	M0 Any	Any				T3N1,2	M0	Any	
	T4a	N0	M0	Any	Any		T4a	N0	M0	Any
IVA	T4a	N2	M0	Any	Any	IVA	T4a	N2	M0	Any
	T4b	Any N M0	M0	Any	Any		T4b	Any N	M0	Any
IVB	Any T	Any N M1	M0	Any	Any	IVB	Any T	Any N	M1	Any

SCC squamous cell carcinoma

invading the gastroesophageal junction (GEJ), Claudin 18.2 (CLDN18.2) expression should be also determined [IA].

Treatment

Initial treatment approaches for patients with esophageal cancers mainly depend on tumor histology and staging (Table 4 and Figs. 1, 2, 3, 4, 5, 6), and each case should be individualized within a multidisciplinary team.

Early disease (cT1 N0M0)

Depending on their depth of infiltration, mucosal carcinomas (T1a) are divided into m1, m2, and m3, while submucosal carcinomas (T1b) are classified as sm1, sm2, and sm3. While lymph node metastases are very rare in mucosal carcinomas, in submucosal cancers their incidence increases as infiltration reaches deeper layers [16].

Endoscopic submucosal dissection [IIIA] or surgery [IVB] may be performed in early (cT1 N0M0) adenocarcinoma that is cT1a–cT1b sm1 or SCC that is cT1a, as long as high-risk factors are not present (e.g., vascular invasion, ulceration, grade 3, size > 2 cm, positive margin). In

adenocarcinoma T1b sm2–sm3 or T1 with high-risk factors or SCC that is T1b or T1 associated with high-risk factors, surgery is the standard approach [IA]. After curative endoscopic dissection, the surrounding Barrett's mucosa should be ablated to prevent metachronous lesions [IIIA]. Although no randomized controlled trials have compared endoscopic resection with surgery in early disease, retrospective series showed that endoscopic procedures were an alternative associated with shorter hospital stays, fewer readmissions, and lower 90-day mortality rates, but survival data in these studies were inconsistent [17], and it requires specialized expertise.

Surgery remains the gold standard for T1b–T2 tumors and mucosal carcinomas associated with high-risk factors after endoscopic resection (extensive carcinoma in situ, high-grade, lymphovascular invasion, or positive deep margins). Subtotal transthoracic esophagectomy (Ivor Lewis esophagectomy) with two-field lymphadenectomy is the procedure of choice [IA]. If the carcinoma is located in the upper thorax, total esophagectomy with cervical anastomosis (McKeown esophagectomy) may be needed [18]. Minimally invasive procedures are becoming more widespread in clinical practice and are expected to reduce postoperative morbidity [19].

Table 4 Summary of recommendations on diagnosis and treatment

General	Recommendation grade ^a
Diagnosis and staging	
Confirmatory diagnosis relies on multiple (6–8) endoscopic biopsies to guarantee an adequate representation of the tumor and sufficient tissue for molecular analysis	IIIA
Histology reports should follow the WHO criteria	IVA
ECOG status, complete physical examination, geriatric and nutritional evaluation should be assessed	VA
Blood analysis, including hemogram and renal panel, and imaging tests (computed tomography scan of chest and abdomen) are required	VA
For patients candidate for surgery or radical treatment, also consider:	
- Echoendoscopy	IIA
- PET-CT or contrast-enhanced CT	IIIA
- Exploratory laparoscopy and peritoneal cytology in distal esophageal adenocarcinoma cT3-4 or N+	IVA
- Bronchoscopy (upper thoracic tumors)	IIA
Stage the disease according to the 2017 UICC-AJCC classification (8 th edition)	VB
Recommended molecular testing: PD-L1 (TPS/CPS/TAP), dMMR/MSI, HER2, and CLDN 18.2	IA
Treatment	
<i>Early stage (cT1 N0M0)</i>	
Adenocarcinoma cT1a–cT1b sm1 or SCC cT1a, without high-risk factors (e.g., vascular invasion, ulceration, grade 3, size ≤ 2 cm, positive margin)	
Endoscopic resection	IIIA
Surgery	IVB
Adenocarcinoma T1b sm2-sm3 or T1 with high-risk factors or SCC T1b or T1 with high-risk factors	
Surgery	IA
After curative endoscopic resection, the surrounding Barret's mucosa should be ablated to prevent metachronous lesions	IIIA
Subtotal transthoracic esophagectomy with two-field lymphadenectomy is the procedure of choice for T1b–T2 tumors	IA
<i>Locally advanced disease (cT2-4 or N1-3 M0)</i>	
Cervical spine tumors	
Cisplatin-5-FU + RDT	IIA
T1–2 N+	
Adenocarcinoma	
Perioperative 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) and surgery	IA
Preop paclitaxel-carbo + RDT and surgery	IC
Squamous cell carcinoma	
Preop paclitaxel-carbo + RDT and surgery	IA
T2–4 N0–2	
Adenocarcinoma	
Perioperative 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) + surgery	IA
Preop (paclitaxel-carbo or cisplatin-FU) + RDT and surgery	IC
Neoadjuvant CT and surgery (distal tumors)	IIB
**For ADC surpassing the GEJ: perioperative FLOT + durvalumab	IA
Squamous cell carcinoma	
Preop (paclitaxel-carbo or cisplatin-FU) + RDT and surgery	IA
Definitive CT (platinum doublets) + RDT $\pm$ salvage surgery	IIB
Neoadjuvant CT (platinum doublets) and surgery	IIB
Adjuvant treatment if no pCR	
Nivolumab	IA
Chemotherapy backbone for combination with RDT	
Fit patients	
Definitive cisplatin-5-FU + RDT	IIB

Table 4 (continued)

General	Recom-mendation grade ^a
Unfit patients	
Oxaliplatin-5-FU ± RDT	VB
Paclitaxel-carboplatin ± RDT	VB
Unresectable T4b tumors	
CT ± anti-PD-1	VB
<i>Metastatic disease</i>	
1st-line therapy for SCC	
Platinum-Fluoropyrimidine if PD-L1 negative/low	IIA
CT-pembrolizumab if CPS ≥ 10	IA
CT-nivolumab or nivolumab + ipilimumab ^b if TPS ≥ 1%	IA
CT-tislelizumab if TAP ≥ 5%	IA
CT-toripalimab ^c regardless of PD-L1 expression	IB
1st-line therapy for adenocarcinoma	
Platinum-fluoropyrimidine	IA
CT-nivolumab if PD-L1 CPS ≥ 5	IA
CT-pembrolizumab if PD-L1 CPS ≥ 10	IA
CT-tislelizumab if PD-L1 TAP ≥ 5%	IA
**HER2-positive: CT + trastuzumab	VA
**dMMR/MSI-H tumors: CT + anti-PD1 therapy	IIA
**For ADC (claudine 18.2-positive) surpassing the GEJ: CT + zolbetuximab	IA
2nd line and beyond	
Monotherapy (irinotecan or taxane) (ADC)	IIB
**dMMR/MSI-H tumors, if no previous immunotherapy: pembrolizumab (ADC)	IIA
Previous IT, irinotecan or taxane monotherapy (SCC)	IIB
Tislelizumab after failure of platinum-based CT regardless of PD-L1 status, or nivolumab ^b (only SCC)	IA
Follow-up	
After complete response to definitive cisplatin-5-FU + RDT without surgery, perform endoscopy, biopsies, and PET-CT at 3-monthly interval	IVB
Focus on symptoms, nutrition, and psychosocial support	VA

CPS combined positive score, *CT* chemotherapy, *ECOG*: *dMMR* deficient DNA mismatch repair, *5-FU* 5-fluorouracil, *GEJ* gastroesophageal junction, *HER2* human epidermal growth factor receptor 2, *MSI-h* microsatellite instability high, *PD-L1* programmed death-ligand 1, *PET-CT* positron emission tomography-computed tomography, *pCR* pathologic complete response, *RDT* radiotherapy, *SCC* squamous cell carcinoma, *TAP* tumor area positivity, *TPS* tumor proportion score

^aQuality of evidence and strength of recommendations [9]

^bNot reimbursed in Spain

^cPending reimbursement in Spain. **Special situations

Locally advanced disease (cT2–T4 or N1–3 M0)

Surgery Surgery remains the cornerstone of curative treatment for resectable oesophageal cancer. Esophagectomy should be performed in experienced, high-volume centers and within a multidisciplinary framework. The type of surgery depends on tumor location: Ivor Lewis esophagectomy (transthoracic, with two-field lymphadenectomy) is preferred for middle and distal lesions, while McKeown esophagectomy (with cervical anastomosis) is indicated for upper thoracic tumors [18]. Minimally invasive and hybrid

approaches are increasingly adopted, with evidence of reduced postoperative morbidity and comparable oncologic outcomes morbidity [19].

In cervical esophageal cancer, surgery is generally not feasible due to the morbidity of mutilating resections like pharyngo-laryngo-esophagectomy; thus, definitive chemoradiotherapy (CRT) with platinum/5-fluorouracil (5-FU) doublets remains the standard approach [IIA] [20, 21].

Evidence-based studies enhance the necessity for comprehensive and multidisciplinary prehabilitation frameworks that should be implemented to optimize the patient's

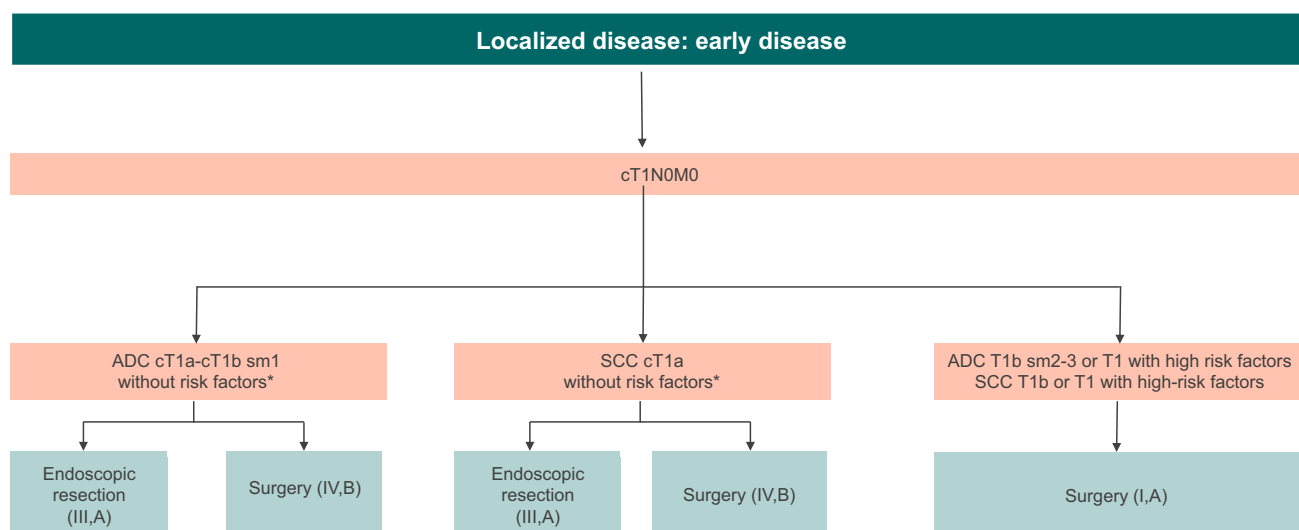


Fig. 1 Localized disease: early disease. *ADC* adenocarcinoma, *SCC* squamous cell carcinoma. *High-risk factors: vascular invasion, ulceration, grade 3, size < 2 cm, positive margin

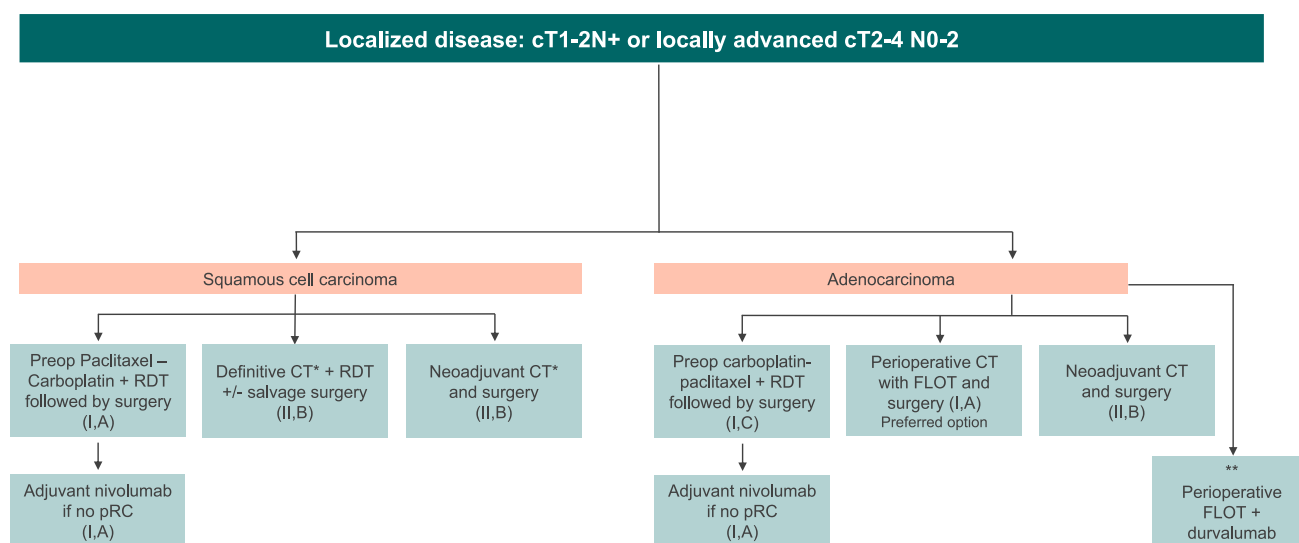


Fig. 2 Localized disease: locally advanced cT2-4 N0-2. *CT* chemotherapy, *FLOT* 5-FU, leucovorin, oxaliplatin, and docetaxel, *pCR* pathologic complete response, *Preop* preoperative, *RDT* radiotherapy. *Platinum doublets. **Adenocarcinoma surpassing the GEJ

physiological reserve. These programs acknowledge a big focus on respiratory exercises, optimization on the hemoglobin levels and the nutritional status, and the stimulation of patient active involvement and physical activity (IIIA).

Pre- and perioperative treatment *Adenocarcinoma*

Two multimodal approaches have been tested for locally advanced resectable adenocarcinoma (cT2–T4 or cN1–3, M0): neoadjuvant CRT and perioperative chemotherapy, with current data supporting the second one.

The benefits of CRT followed by surgery were initially based on results from meta-analyses and some large, randomized trials [22, 23]. The European CROSS phase III trial established a standard of care that has been largely used until 2025. This trial included 363 patients with resectable esophageal or gastroesophageal junction (GEJ) cancer (273 with adenocarcinoma, 86 with SCC). Preoperative CRT using weekly paclitaxel 50 mg/m² plus carboplatin (area under the concentration × time curve [AUC] 2) plus concurrent radiotherapy (41.4 Gy over 5 weeks)

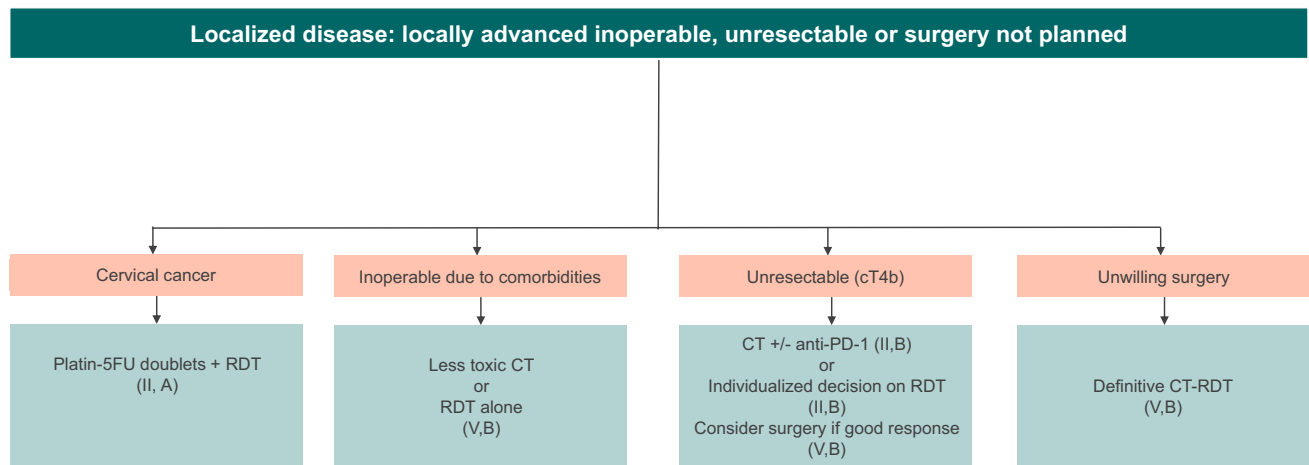


Fig. 3 Localized disease: locally advanced inoperable, unresectable, or surgery not planned. *CT* chemotherapy, *RDT* radiotherapy

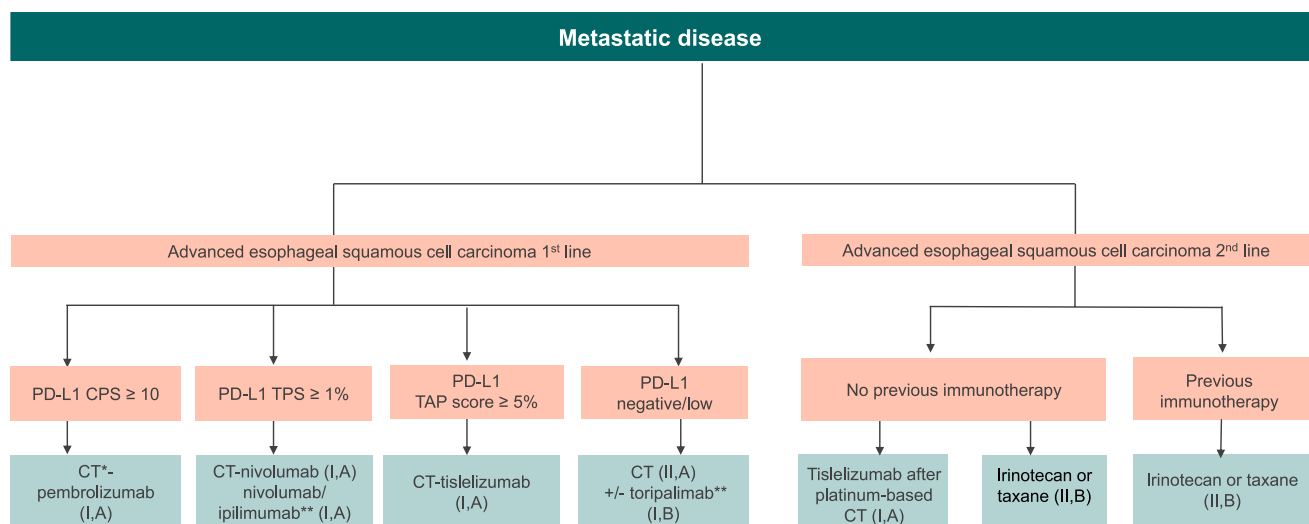


Fig. 4 Metastatic disease: first line and second line for ESCC. *CT consists of platinum doublets. **Pending reimbursement in Spain. *CPS* combined positive score, *CT* chemotherapy, *PD-L1* programmed

death-ligand 1, *SCC* squamous cell carcinoma, *TAP* tumor area positivity, *TPS* tumor proportion score

followed by surgery was compared with surgery alone, and resulted in a significant increase in the R0 resection rate, with a pathologic complete response (pCR) rate of 29% (23% for adenocarcinoma, 49% for SCC). Median OS was significantly better with preoperative CRT (HR for death 0.66, 95% CI 0.49–0.87; HR 0.73, 95% CI 0.52–1 in adenocarcinoma), and this benefit persisted after a 10-year follow-up period (38% vs. 25% in the preoperative CRT and the surgery only arms, respectively; HR for death 0.70, 95% CI 0.55–0.89) [24–26]. Recurrence patterns of this trial showed similar percentages of systemic relapses between the preoperative CRT group and the surgery group, thus translating insufficient systemic control with this preoperative strategy.

Since then, two studies have recently demonstrated the benefit of a better systemic treatment approach, i.e., the Neo-AEGIS trial (2023) and the ESOPEC trial (2025), both of them accounting with patients diagnosed of esophageal adenocarcinomas (not SCCs).

The Neo-AEGIS phase III trial compared perioperative chemotherapy (85% of patients receiving ECF; only 15% receiving FLOT) with CROSS-like CRT. While CRT achieved higher pathologic response rates, survival outcomes were similar (non-inferiority not met) [27].

The ESOPEC phase III trial directly compared perioperative FLOT with the CROSS regimen in esophageal and GEJ adenocarcinomas. At 55 months of median follow-up, FLOT showed superiority in all the endpoints, since tumor

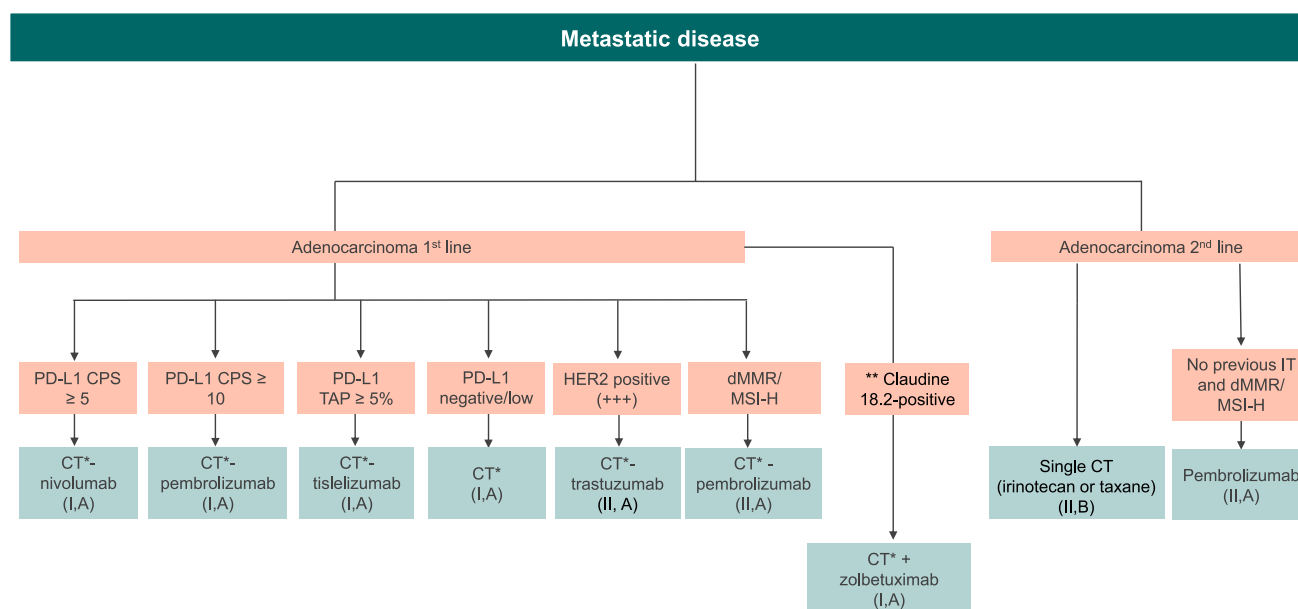


Fig. 5 Metastatic disease: first line and second line for adenocarcinoma. *CT consists of platinum doublets. **Adenocarcinoma surpassing the GEJ. CPS combined positive score, CT chemotherapy, dMMR deficient DNA mismatch repair, GEJ gastroesophageal junction

tion, HER2 human epidermal growth factor receptor 2, IT immunotherapy, MSI-H microsatellite instability high, PD-L1 programmed death-ligand 1, TAP tumor area positivity

response to survival outcomes. FLOT demonstrated superior OS (66 vs. 37 months; HR 0.70, 95% CI 0.53–0.92; $p=0.01$) and PFS (HR 0.66; 95% CI 0.51–0.85). Distant recurrence was significantly reduced (31.5% vs. 47.2%), with similar locoregional control [28–30].

These findings were supported by the results of the phase III TOPGEAR trial, which demonstrated that the addition of CRT to perioperative chemotherapy only improved pathologic response but not survival in gastric and GEJ tumors [31].

**Special situations

For patients with resectable esophageal adenocarcinoma surpassing the GEJ, perioperative durvalumab in combination with FLOT should be considered based on the recently reported results of the phase III MATTERHORN study [32]. The addition of durvalumab to perioperative FLOT significantly improved event-free survival (HR 0.71) and markedly increased pCR rates (19.2% vs. 7.2%) compared with FLOT alone. The benefit was even greater in patients with higher levels of PD-L1 TAP expression and in dMMR/MSI-H [32]. Importantly, updated results presented at ESMO 2025 demonstrated a statistically significant OS benefit (HR 0.78), supporting a meaningful clinical impact beyond pathologic response and disease control. Despite this level of evidence, perioperative durvalumab is not yet approved nor reimbursed in Europe, and its use should currently be considered in selected patients within an evidence-based, guideline-driven context.

Recommendation

Multimodality treatment should be considered in all patients with locally advanced resectable esophageal cancer [IA]. Perioperative FLOT is the *preferred treatment* for locally advanced resectable adenocarcinoma of the esophagus [IA]. Neoadjuvant CRT (CROSS regimen) remains a potential alternative for patients unsuitable for FLOT [IC]. It should be noted that perioperative FLOT has not been directly compared with the approach of neoadjuvant CRT followed by surgery and adjuvant nivolumab, as evaluated in the CheckMate-577 study, in a broader esophageal cancer population [33]. Therefore, the relative benefit of perioperative FLOT versus CRT plus adjuvant immunotherapy remains unknown.

Squamous cell carcinoma (SCC) Various meta-analyses and two well-designed phase 3 randomized trials support neoadjuvant CRT as the standard of care for patients with locally advanced resectable esophageal SCC [IA].

In the CROSS trial, the median OS for ESCC was 81.6 months in the preoperative CRT group and 21.1 months in the surgery only group (HR, 0.48; $p=0.008$) [25], and this benefit persisted after a 10-year follow-up period (46% vs. 23% in the surgery only arm) [26].

Alternative options include definitive CRT with platinum-based doublets and salvage surgery in selected cases [34]. The traditional standard regimen for definitive CRT is four

cycles of cisplatin 5-FU (or capecitabine) combined with RT to a dose of 50.4 Gy in 28 fractions (or 50 Gy in 25 fractions) [35]. Alternatively, six cycles of folinic acid 5-FU oxaliplatin (FOLFOX) can be considered [36]. Perioperative chemotherapy may be considered in selected ESCC cases, though evidence remains limited [37].

Recommendation

For ESCC, neoadjuvant CRT (carboplatin/paclitaxel + 41.4–50.4 Gy) followed by surgery is standard [IA]. Definitive CRT with planned surveillance and salvage surgery is an alternative for patients' unwilling surgery [IIB].

Adjuvant treatment Adjuvant nivolumab is recommended as standard treatment in patients with residual disease (no pCR) after neoadjuvant CRT and R0 resection, irrespective of histology or PD-L1 status.

This recommendation is based on the CheckMate-577 phase III trial, where 794 patients with residual esophageal cancer after neoadjuvant CRT were randomized to nivolumab vs. placebo. Median DFS was doubled in the nivolumab arm (22.4 vs. 11 months; HR 0.69, 96.4% CI 0.56–0.86; $p < 0.001$), with benefit across all subgroups [33].

The benefit of adjuvant nivolumab after perioperative FLOT remains unclear, as no direct comparison exists [38].

Locally advanced: inoperable, unresectable tumors or surgery not planned

Definitive concomitant CRT with platinum and 5-FU-based regimens without surgery have been shown to be superior to radiotherapy alone [IIB], achieving long-term survival rates of around 30% [35]. This is the only therapeutic option in localized tumors that are in surgically inaccessible regions, such as the cervical esophagus, and in patients with comorbidities that contraindicate surgery even if their tumors were initially resectable. The most used regimen in this context is cisplatin combined with 5-FU [35]. Alternative approaches are folinic acid, 5-FU, and oxaliplatin (FOLFOX) [VB] [36] or carboplatin and paclitaxel [VB]. The standard radiotherapy dose is 45–50.4 Gy; higher doses of radiotherapy are not more effective and result in greater toxicity [IIB] [39, 40].

Unresectable tumors Special mention should be made of unresectable T4b tumors. When there is infiltration of large vessels (i.e., aorta or pulmonary arteries) or the trachea, radiotherapy is associated with a high risk of massive bleeding or tracheal esophageal fistulae [41, 42], so its use is discouraged. In this situation, the administration of chemotherapy plus/minus immunotherapy depending on PD-L1 expression is the best option [43], and surgery can be evalu-

ated when response is positive enough to reconsider resection [VB].

Surgery contraindicated due to comorbidities Patients with tumors that are considered inoperable due to their comorbidities, general condition, or age are not usually included in clinical trials, and therapeutic toxicity is usually a more important consideration, particularly for patients receiving more aggressive treatment options. The best approach in these patients may be a less toxic drug or radiotherapy alone [VB].

Surgery not planned For patients with resectable and operable locally advanced disease, but unwilling surgery, definitive CRT can be considered if complete clinical response [VB]. These patients should be submitted to an intensive follow-up, and surgery may be indicated afterward if local relapse. This strategy cannot be upfront recommended but otherwise individualized in those patients with ESCC and always consensual within the multidisciplinary tumor board [IIB] [44].

Recommendation

Then, for inoperable, unresectable, or medically unfit patients, definitive concurrent CRT is the treatment of choice. Standard regimens include.

- Cisplatin + 5-FU (or capecitabine) with radiotherapy (50–50.4 Gy) [35, 45]
- Carboplatin + paclitaxel (CROSS regimen) weekly with radiotherapy, only adopted for patients not tributary to the previous schema, due to its favorable toxicity and comparable efficacy [34, 38].

After definitive CRT, active surveillance is recommended. Despite the encouraging results from the SKY-SCRAPER study with the anti-PDL1 antibody atezolizumab [46], immunotherapy still remains an investigational option, with awaited results from adjuvant immunotherapy in this context during the next years.

Advanced/metastatic disease

First-line chemotherapy Patients with metastatic or inoperable locally advanced esophageal cancer have a poor prognosis, with a median OS of less than 1 year when treated with chemotherapy alone. Despite differences in biology [6], SCC and adenocarcinoma of the esophagus have traditionally been treated with similar chemotherapy combinations, based on a platinum salt (cisplatin or oxaliplatin) and a fluoropyrimidine (5-FU or capecitabine) [47]. The recent introduction of immune checkpoint inhibitors in combina-

tion with chemotherapy has improved outcomes in these patients [48–51].

First-line treatment for esophageal squamous cell cancer The standard first-line chemotherapy treatment in patients with PD-L1-negative tumors is based on a platinum salt and a fluoropyrimidine [IIA]. This recommendation is mainly based on the extrapolation from classical clinical trials conducted in esophageal and gastric adenocarcinoma [47, 52, 53]. Derived from the recent European approval, the combination of toripalimab plus paclitaxel–cisplatin may also be considered in this setting, regardless of PD-L1 expression. The phase III JUPITER-06 trial [54], conducted exclusively in a Chinese population, demonstrated a significant OS benefit (17.0 vs. 11.0 months; HR 0.58, 95% CI 0.43–0.78) and PFS improvement (5.7 vs. 5.5 months; HR 0.58, 95% CI 0.46–0.74) with toripalimab plus paclitaxel–cisplatin versus chemotherapy alone. This regimen is approved in Europe but remains pending reimbursement in Spain.

Based on the phase III KEYNOTE-590 trial [49], the addition of pembrolizumab to a platinum-doublet chemotherapy regimen should be recommended for patients with a PD-L1 CPS ≥ 10 [IA]. In patients with PD-L1 tumors with TPS of $\geq 1\%$, the addition of nivolumab to platinum-doublet chemotherapy [IA] or first-line nivolumab plus ipilimumab [IA] is also recommended, based on the CheckMate 648 trial [51]. It should be noted that although the combination of nivolumab plus ipilimumab is approved in Europe, it is not currently reimbursed in our setting.

Furthermore, the global phase III RATIONALE-306 trial demonstrated that adding tislelizumab to the investigator's choice of cisplatin–fluoropyrimidine or cisplatin–paclitaxel significantly improved both OS (median 16.8 vs. 9.6 months; HR 0.64, 95% CI 0.51–0.80) and PFS (7.2 vs. 5.5 months; HR 0.56, 95% CI 0.45–0.70), with durable responses and manageable safety [55]. Based on these results, tislelizumab in combination with chemotherapy is approved and reimbursed in our setting for patients with a PD-L1 TAP score $\geq 5\%$. The alternative chemotherapy regimen used in this study may offer potential benefits to those patients with contraindication for the standard platinum–fluoropyrimidine chemotherapy doublet.

Two additional phase III studies conducted exclusively in Chinese populations, the ESCORT-1st with camrelizumab [50] and the ORIENT-15 with sintilimab [56], both combining these agents with cisplatin–paclitaxel, also demonstrated improvements in OS and PFS; however, these regimens are not approved in our setting.

First-line treatment for esophageal adenocarcinoma The standard first-line chemotherapy is a platinum salt (cisplatin or oxaliplatin) plus a fluoropyrimidine (5-FU or capecit-

abine) [IA]. Oxaliplatin can substitute cisplatin (often better tolerated), and capecitabine can replace 5-FU when there is no dysphagia [47, 52, 53].

For patients with a PD-L1 CPS ≥ 10 , adding pembrolizumab to cisplatin–fluoropyrimidine is recommended [IA], based on the KEYNOTE-590 study, which showed an OS benefit in the adenocarcinoma cohort with CPS ≥ 10 [49]. In patients with PD-L1 CPS ≥ 5 , the addition of nivolumab to oxaliplatin–fluoropyrimidine chemotherapy is recommended [IA], supported by the CheckMate 649 trial, which showed improved OS versus chemotherapy alone in gastric/GEJ/esophageal adenocarcinoma with CPS ≥ 5 [48]. In those cases of esophageal adenocarcinoma surpassing the GEJ, tislelizumab plus chemotherapy (XELOX or cisplatin/5-FU) according to the RATIONALE-305 trial [57] may also be used in HER2-negative disease. This trial ($n=997$; $\sim 20\%$ GEJ) showed significant OS improvement both in PD-L1 TAP $\geq 5\%$ (median 17.2 vs 12.6 months; HR 0.74; $p=0.006$) and all comers (15.0 vs 12.9 months; HR 0.80; $p=0.001$), with PFS benefit (TAP $\geq 5\%$ HR 0.67; ITT HR 0.78) and manageable safety. This indication is approved and reimbursed in our setting for PD-L1 TAP $\geq 5\%$ gastric/GEJ adenocarcinoma [IA].

***Special situations*

Considering the biological overlap within gastroesophageal adenocarcinomas, there are two special populations that merit a distinct approach [6]. First, the HER2-positive cases, for which the addition of trastuzumab can be recommended, based on the results of the phase III ToGA trial [58] (VA). Second, the dMMR/MSI cases are highly sensitive for immunotherapy agents and for which strategies combining chemotherapy plus anti-PD1 antibodies should be eagerly considered [48].

Furthermore, for those cases of adenocarcinomas invading de GEJ, zolbetuximab, an anti-claudin 18.2 antibody, could be added to the first line regimen based on the results on SPOTLIGHT and GLOW trials [59] (IA).

Second-line chemotherapy and beyond Treatment selection depends on ECOG performance status, histologic type, symptom burden, first-line therapy, and biomarker profile. For patients with pMMR, single-agent chemotherapy with drugs not used previously (weekly paclitaxel, docetaxel, or irinotecan) remains an option [IIB], whereas combination regimens (e.g., FOLFIRI, taxane-based doublets) may be considered only in selected patients with high symptom burden or a need for rapid tumor shrinkage [IIB].

The RATIONALE-302 phase III trial evaluated tislelizumab versus investigator's choice chemotherapy in patients with advanced/metastatic ESCC who had progressed after first-line platinum-based therapy [60]. Tislelizumab significantly improved OS, with a median OS of 8.6 vs 6.3 months (HR 0.70, 95% CI 0.57–0.85; $p=0.0001$), ORR (20.3% vs

9.8%), with lower incidence of grade ≥ 3 treatment-related adverse events (18.8% vs 55.8%). Based on these data, tislelizumab is now approved and reimbursed in our setting for second-line ESCC, regardless PD-L1 expression [IA].

Evidence from previous phase III trials also supports nivolumab (ATTRACTION-3) and camrelizumab (ESCORT) in predominantly Asian populations with ESCC, with both agents showing OS benefit compared with chemotherapy [61, 62]. Pembrolizumab (KEYNOTE-181) demonstrated OS benefit in patients with PD-L1 CPS ≥ 10 , particularly in the SCC subgroup [63]. However, these immunotherapy regimens (nivolumab, pembrolizumab, camrelizumab) are not reimbursed in our setting. For patients previously exposed to immunotherapy in the first-line setting, single-agent taxane or irinotecan chemotherapy remains the preferred option [IIB].

For patients with esophageal adenocarcinoma with dMMR or MSI-H that have not been treated with a first-line regimen, including immunotherapy, treatment with pembrolizumab should be recommended, based on the results of the KEYNOTE trials [64, 65] (IIA).

Follow-up, long-term survivorship, and complications

Most relapses (90%) occur within the first 2 years after completion of local therapy [66]. Follow-up visits should concentrate on symptoms, nutrition and psychosocial support [VA]. In patients with complete response to definitive CRT, a careful follow-up based on endoscopy, biopsies, and PET-CT findings may be recommended to detect early recurrence, especially during the first two years [IVB].

Conclusion

These updated guidelines provide evidence-based recommendations for the diagnosis, staging, treatment, and follow-up of patients with esophageal cancer, incorporating the most recent clinical data available as of 2025. While the standard of care remains largely unchanged in many areas, two scenarios have been changed. First, for locally advanced resectable esophageal adenocarcinoma, for which perioperative FLOT and surgery is nowadays the new standard of care. Second, the addition of anti-PD1 agents in the first-line metastatic setting, either for ESCC and adenocarcinomas, particularly those with PD-L1-positive disease.

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Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed during the study.

Declarations

Conflict of interest AF-M has received speaker fees and had attended an advisory board for Pierre Fabre and AstraZeneca; has received speaker fees from Lilly, Servier, Amgen, MSD and Seagen; and has attended an advisory board for Bayer and Mundipharma. JA has received speaker fees from Amgen, Merck and Servier and congress support from Amgen, Merck, Takeda, and MSD. ABC has received speaker fees from AstraZeneca, Lilly, Novartis, and Ipsen and has attended an advisory board for BMS, MSD, BeOne, and Astellas. JGP has received speaker and other fees and has attended an advisory board for Eli Lilly; received other fees and has attended an advisory board for BMS and Servier; and has attended an advisory board for MSD. FR has received speaker fees and has attended an advisory board for Roche, BMS, Sanofi, Amgen, Merck-Serono, and Lilly; has received speaker fees and grants; and has attended an advisory board for MSD, Servier, and AstraZeneca. MA has received speaker fees and has attended an advisory board for BMS, MSD, Lilly, and Servier and has received speaker fees from Amgen and Roche. LFF, CGM, and PR have nothing to disclose.

Ethical approval Not applicable.

Informed consent The manuscript does not contain clinical studies or patient data.

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