

ESOPHAGEAL AND ESOPHAGOGASTRIC JUNCTION CANCER TREATMENT REGIMENS (Part 1 of 7)

Clinical Trials: The National Comprehensive Cancer Network recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are provided only to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Preoperative Chemoradiation¹

Note: All recommendations are category 2A unless otherwise indicated.

Preferred Regimens

REGIMEN	DOSING
Paclitaxel + carboplatin (Category 1)²	Day 1: Paclitaxel 50mg/m ² IV + carboplatin AUC 2mg·min/mL IV. Repeat weekly for 5 weeks (Days 1, 8, 15, 22, and 29).
Cisplatin + 5-fluorouracil (5-FU) (Category 1)^{3,4}	Days 1 and 29: Cisplatin 75–100mg/m ² IV Days 1–4 and 29–32: 5-FU 750–1,000mg/m ² IV continuous infusion over 24 hours on a 35-day cycle. OR Days 1–5: Cisplatin 15mg/m ² IV daily + 5-FU 800 mg/m ² IV continuous infusion over 24 hours. Repeat cycle every 21 days for 2 cycles with radiation.
Oxaliplatin + 5-FU + leucovorin⁵	Day 1: Oxaliplatin 85mg/m ² IV + leucovorin 400mg/m ² + fluorouracil 400mg/m ² IVP followed by: Days 1–2: Fluorouracil 800mg/m ² IV continuous infusion over 24 hours. Repeat cycle every 14 days for 3 cycles with radiation and 3 cycles after radiation.
Cisplatin + capecitabine (Category 1)⁶	Day 1: Cisplatin 30mg/m ² IV Days 1–5: Capecitabine 800mg/m ² orally twice daily Repeat cycle weekly for 5 weeks.
Oxaliplatin + 5-FU (Category 1)⁷	Days 1, 15, and 29: Oxaliplatin 85mg/m ² IV Days 1–33: 5-FU 180mg/m ² /day continuous IV infusion.
Oxaliplatin + capecitabine (Category 1)⁸	Days 1, 15, and 29: Oxaliplatin 85mg/m ² IV Days 1–5: Capecitabine 625mg/m ² orally twice daily for 5 weeks.

Other Regimens

Irinotecan + cisplatin (Category 2B)⁹	Days 1, 8, 22, and 29: Irinotecan 65mg/m ² IV + cisplatin 30mg/m ² IV.
Paclitaxel + 5-FU (Category 2B)¹⁰	Day 1: Paclitaxel 45mg/m ² IV weekly Days 1–5: 5-FU 300mg/m ² /day continuous IV infusion. Repeat cycle weekly for 5 weeks.
Paclitaxel + capecitabine (Category 2B)¹⁰	Day 1: Paclitaxel 45–50mg/m ² IV Days 1–5: Capecitabine 625–825mg/m ² orally twice daily. Repeat cycle weekly for 5 weeks.

Perioperative Chemotherapy (including esophagogastric junction)¹

ECF (epirubicin + cisplatin + 5-FU) (Category 2B)^{11,a}	Day 1: Epirubicin 50mg/m ² IV bolus and cisplatin 60mg/m ² IV Days 1–21: 5-FU 200mg/m ² IV continuous infusion over 24 hours daily. Repeat cycle every 21 days for 3 cycles preoperatively and 3 cycles postoperatively.
ECF modifications (Category 2B)¹²	Day 1: Epirubicin 50mg/m ² IV + cisplatin 60mg/m ² IV Days 1–21: 5-FU 200mg/m ² IV continuous infusion once daily. Repeat cycle every 21 days for 3 cycles preoperatively and 3 cycles postoperatively. OR Day 1: Epirubicin 50mg/m ² IV + oxaliplatin 130mg/m ² IV Days 1–21: 5-FU 200mg/m ² IV continuous infusion over 24 hours. Repeat cycle every 21 days for 3 cycles preoperatively and 3 cycles postoperatively. OR Day 1: Epirubicin 50mg/m ² IV + oxaliplatin 130mg/m ² IV Days 1–21: Capecitabine 625mg/m ² orally twice daily. Cycled every 21 days for 3 cycles preoperatively and 3 cycles postoperatively.
5-FU + cisplatin (Category 1)¹³	Day 1: Cisplatin 100mg/m ² IV Days 1–5: 5-FU 800mg/m ² IV continuous infusion over 24 hours daily. Repeat cycle every 28 days for 2–3 cycles preoperatively and 3–4 cycles postoperatively for a total of 6 cycles.

continued

ESOPHAGEAL AND ESOPHAGOGASTRIC JUNCTION CANCER TREATMENT REGIMENS (Part 2 of 7)

Perioperative Chemotherapy (including esophagogastric junction)¹ (continued)

REGIMEN	DOSING
Fluoropyrimidine + oxaliplatin^c	<p>Day 1: Oxaliplatin 85mg/m² IV + leucovorin 400mg/m² IV + fluorouracil 400mg/m² IVP followed by:</p> <p>Days 1-2: Fluorouracil 1200mg/m² continuous IV infusion over 24 hours. Repeat cycle every 14 days.³²</p> <p>OR</p> <p>Day 1: Oxaliplatin 85mg/m² IV + leucovorin 200mg/m² IV + fluorouracil 2600mg/m² continuous IV infusion over 24 hours. Repeat cycle every 14 days.²⁶</p> <p>OR</p> <p>Day 1: Oxaliplatin 130mg/m² IV</p> <p>Days 1-14: Capecitabine 1000mg/m² orally twice daily. Repeat cycle every 14 days.³³</p>

Definitive Chemoradiation (Nonsurgical)¹

Preferred Regimens

Cisplatin + 5-FU (Category 1)¹⁴	<p>Day 1: Cisplatin 75–100mg/m² IV</p> <p>Days 1–4: 5-FU 750–1,000mg/m²/day continuous IV infusion over 24 hours daily. Repeat cycle every 28 days for 2–4 cycles for 2 cycles with radiation followed by 2 cycles without radiation.</p>
Oxaliplatin + 5-FU (Category 1)^{7,15}	<p>Days 1, 15, and 29: Oxaliplatin 85mg/m² IV for 3 doses</p> <p>Days 1–33: 5-FU 180mg/m² IV daily.</p> <p>OR</p> <p>Day 1: Oxaliplatin 85mg/m² IV</p> <p>Day 1: Leucovorin 400mg/m² IV</p> <p>Day 1: 5-FU 400mg/m² IVP</p> <p>Days 1 and 2: 5-FU 800mg/m² continuous IV over 24 hours daily. Repeat cycle every 14 days for 3 cycles with radiation followed by 3 cycles without radiation.</p>
Cisplatin + capecitabine (Category 1)⁶	<p>Day 1: Cisplatin 30mg/m² IV</p> <p>Days 1–5: Capecitabine 800mg/m² orally twice daily. Repeat cycle weekly for 5 weeks.</p>
Oxaliplatin + capecitabine (Category 1)⁸	<p>Days 1, 15, and 29: Oxaliplatin 85mg/m² IV</p> <p>Days 1–5: Capecitabine 625mg/m² orally twice daily for 5 weeks.</p>
Paclitaxel + carboplatin²	<p>Day 1: Paclitaxel 50mg/m² IV and carboplatin 2mg·min/mL IV once weekly for 5 weeks.</p>

Other Regimens

Paclitaxel + cisplatin¹⁶	<p>Days 1, 8, 15, and 22: Paclitaxel 60mg/m² IV</p> <p>Day 1: Cisplatin 75mg/m² IV given for 1 cycle.</p>
Docetaxel + cisplatin^{17,18}	<p>Days 1 and 22: Docetaxel 60mg/m² IV</p> <p>Days 1 and 22: Cisplatin 60–80mg/m² IV given for 1 cycle.</p> <p>OR</p> <p>Day 1: Docetaxel 20–30mg/m² IV</p> <p>Day 1: Cisplatin 20–30mg/m² IV given for weekly for 5 weeks.</p>
Irinotecan + cisplatin (Category 2B)⁹	<p>Days 1, 8, 22, and 29: Irinotecan 65mg/m² IV</p> <p>Days 1, 8, 22, and 29: Cisplatin 30mg/m² IV.</p>
Paclitaxel + 5-FU (Category 2B)¹⁰	<p>Day 1: Paclitaxel 45mg/m² IV weekly</p> <p>Days 1–5: 5-FU 300mg/m² IV continuous infusion daily. Repeat cycle weekly for 5 weeks.</p>
Paclitaxel + capecitabine (Category 2B)¹⁰	<p>Day 1: Paclitaxel 45–50mg/m² IV</p> <p>Days 1–5: Capecitabine 625–825mg/m² PO twice daily. Repeat cycle weekly for 5 weeks.</p>

Postoperative Chemoradiation (for adenocarcinoma or gastroesophageal junction only)¹

5-FU + leucovorin (Category 1)^{18,19}	<p>Days 1–5: 5-FU 425mg/m²/day IV and leucovorin 20mg/m²/day IV, followed by chemoradiotherapy beginning 4 weeks after the start of the initial cycle of chemotherapy.</p> <p>Chemoradiotherapy: 4,500cGy of radiation at 180cGy/day, 5 days/week for 5 weeks, with 5-FU 400mg/m²/day IV and leucovorin 20mg/m²/day IV on the first 4 and the last 3 days of radiotherapy.</p> <p>At 1 month following completion of radiotherapy, two 5-day cycles of 5-FU 425mg/m²/day IV and leucovorin 20mg/m²/day IV; given 1 month apart.</p> <p>NOTE: The NCCN panel acknowledges that the Intergroup 0116 Trial formed the basis for postoperative adjuvant chemoradiation strategy. However, the panel does not recommend the above specified doses or schedule of cytotoxic agents because of concerns regarding toxicity. The panel recommends one of the following modifications instead:</p>
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ESOPHAGEAL AND ESOPHAGOGASTRIC JUNCTION CANCER TREATMENT REGIMENS (Part 3 of 7)

Postoperative Chemoradiation (for adenocarcinoma or gastroesophageal junction only)¹ (continued)

REGIMEN	DOSING
Capecitabine ^{20,21}	Days 1–14: Capecitabine 750–1000mg/m ² orally twice daily; cycled every 28 days; 1 cycle before and 2 cycles after chemoradiation.
5-FU + leucovorin ²²	Days 1, 2, 15, and 16: Leucovorin 200mg/m ² IV as 2-hour infusion followed by 5-FU 400mg/m ² IV push and a 22-hour infusion of 5-FU 600mg/m ² .
5-FU with radiation ²³	Days 1–5 OR Days 1–7: 5-FU 200–250mg/m ² IV continuous infusion over 24 hours daily, once weekly for 5 weeks.
Capecitabine with radiation ⁶	Days 1–5 OR Days 1–7: Capecitabine 625–825mg/m ² orally twice daily, once weekly for 5 weeks.

Postoperative Chemotherapy

Capecitabine + Oxaliplatin ^{58,d}	Day 1: Oxaliplatin 130mg/m ² IV Days 1–14: Capecitabine 1000mg/m ² orally twice daily. Repeat cycle every 21 days.
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Metastatic or Locally Advanced Cancer (where local therapy is not indicated)¹

First-line therapy

Trastuzumab + chemotherapy (for HER2-neu malignancies) ²⁴	Day 1: Trastuzumab 8mg/kg IV loading dose (Cycle 1 only) followed by trastuzumab 6mg/kg IV every 3 weeks, plus chemotherapy (Category 2B). OR Day 1: Trastuzumab 6mg/kg IV loading dose (Cycle 1 only) followed by trastuzumab 4mg/kg IV every 14 days.
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Preferred Regimens

DCF (docetaxel + leucovorin + cisplatin + 5-FU) ²⁵	Day 1: Docetaxel 40mg/m ² IV + leucovorin 400mg/m ² IV + 5-FU 400mg/m ² IV, plus Days 1 and 2: 5-FU 1000mg/m ² IV continuous infusion over 24 hours (total 2000mg/m ²), followed by Day 3: Cisplatin 40mg/m ² IV. Repeat cycle every 14 days.
Modified DCF (docetaxel + oxaliplatin + leucovorin + 5-FU) ²⁶	Day 1: Docetaxel 50mg/m ² IV + leucovorin 200mg/m ² IV + oxaliplatin 85mg/m ² IV + 5-FU 2600mg/m ² IV continuous infusion over 24 hours. Repeat cycle every 14 days.
Modified DCF (docetaxel + oxaliplatin + 5-FU) ²⁷	Day 1: Docetaxel 50mg/m ² IV + oxaliplatin 85mg/m ² IV Days 1 and 2: 5-FU 1200mg/m ² IV continuous infusion over 24 hours. Repeat cycle every 14 days.
Modified DCF (docetaxel + carboplatin + 5-FU) (Category 2B) ²⁸	Day 1: Docetaxel 75mg/m ² IV Day 2: Carboplatin AUC 6mg·min/mL IV Days 1–3: 5-FU 1200mg/m ² IV continuous infusion over 24 hours daily. Repeat cycle every 21 days.
Fluoropyrimidine and cisplatin (5-FU + cisplatin) (Category 1) ^{29b}	Day 1: Cisplatin 100mg/m ² IV Days 1–4: 5-FU 1,000mg/m ² IV continuous infusion over 24 hours daily doses of 250mg/m ² IV over 60 minutes.
Fluoropyrimidine and cisplatin (5-FU + cisplatin + leucovorin) (Category 1) ^{26,30b}	Day 1: Cisplatin 50mg/m ² IV Day 1: Leucovorin 200mg/m ² IV Day 1: 5-FU 2,000mg/m ² IV continuous infusion over 24 hours. Repeat cycle every 14 days.
Fluoropyrimidine and cisplatin (capecitabine + cisplatin) (Category 1) ³¹	Day 1: Cisplatin 80mg/m ² IV Day 1–14: Capecitabine 1,000mg/m ² orally twice daily. Repeat cycle every 3 weeks
Fluoropyrimidine and oxaliplatin (oxaliplatin + leucovorin + 5-FU) ^{31,32}	Day 1: Oxaliplatin 85mg/m ² IV + leucovorin 400mg/m ² IV + 5-FU 400mg/m ² IVP Days 1 and 2: 5-FU 1200mg/m ² IV continuous infusion over 24 hours daily. Repeat cycle every 14 days. OR Day 1: Oxaliplatin 85mg/m ² IV + leucovorin 200mg/m ² IV + 5-FU 400mg/m ² IVP plus 5-FU 2600mg/m ² IV continuous infusion over 24 hours daily. Repeat cycle every 14 days.
Fluoropyrimidine and oxaliplatin (oxaliplatin + capecitabine) ³³	Day 1: Oxaliplatin 130mg/m ² IV Days 1–14: Capecitabine 1000mg/m ² orally twice daily. Repeat cycle every 21 days.

continued

ESOPHAGEAL AND ESOPHAGOGASTRIC JUNCTION CANCER TREATMENT REGIMENS (Part 4 of 7)

Metastatic or Locally Advanced Cancer (where local therapy is not indicated)¹ (continued)

Other Regimens

REGIMEN	DOSING
Paclitaxel + cisplatin or carboplatin ³⁴⁻³⁶	<p>Day 1: Paclitaxel 135–200mg/m² IV Day 2: Cisplatin 75mg/m² IV Repeat cycle every 21 days.</p> <p>OR</p> <p>Day 1: Paclitaxel 90mg/m² IV + cisplatin 75mg/m² IV Repeat cycle every 14 days.</p> <p>OR</p> <p>Day 1: Paclitaxel 200mg/m² IV + carboplatin 5mg·min/mL. Repeat cycle every 21 days.</p>
Docetaxel + cisplatin ^{37,38}	<p>Day 1: Docetaxel 70–85mg/m² IV + cisplatin 70–75mg/m² IV. Repeat cycle every 21 days.</p>
Docetaxel + irinotecan (Category 1) ³⁹	<p>Days 1 and 8: Docetaxel 35mg/m² IV + irinotecan 50mg/m² IV. Repeat cycle every 21 days.</p>
Fluoropyridimine ⁴⁰⁻⁴²	<p>Day 1: Leucovorin 400mg/m² IV + 5-FU 400mg/m² IVP Days 1 and 2: 5-FU 1200mg/m² IV continuous infusion over 24 hours daily. Repeat cycle every 14 days.</p> <p>OR</p> <p>Days 1–5: 5-FU 800mg/m² IV continuous infusion over 24 hours daily. Repeat cycle every 28 days.</p> <p>OR</p> <p>Days 1–14: Capecitabine 1000–1250mg/m² orally twice daily. Repeat cycle every 21 days.</p>
Taxane ⁴³⁻⁴⁵	<p>Day 1: Docetaxel 75–100mg/m² IV. Repeat cycle every 21 days.</p> <p>OR</p> <p>Day 1: Paclitaxel 135–250mg/m² IV. Repeat cycle every 21 days.</p> <p>OR</p> <p>Days 1, 8, 15, and 22: Paclitaxel 80mg/m² IV once weekly. Repeat cycle every 28 days.</p>
ECF (epirubicin + cisplatin + 5-FU) (Category 2B) ^{46,47}	<p>Day 1: Epirubicin 50mg/m² IV bolus + cisplatin 60mg/m² IV Days 1–21: 5-FU 200mg/m² IV continuous infusion over 24 hours daily. Repeat cycle every 21 days.</p>
ECF modifications (epirubicin + oxaliplatin + 5-FU) (Category 2B) ⁴⁷	<p>Days 1: Epirubicin 50mg/m² IV + oxaliplatin 130mg/m² IV Days 1–21: 5-FU 200mg/m² IV continuous infusion over 24 hours. Repeat cycle every 21 days.</p>
ECF modifications (epirubicin + cisplatin + capecitabine) (Category 2B) ⁴⁷	<p>Day 1: Epirubicin 50mg/m² IV + cisplatin 60mg/m² IV Days 1–21: Capecitabine 625mg/m² IV orally twice daily. Repeat cycle every 21 days.</p>
ECF modifications (epirubicin + oxaliplatin + capecitabine) (Category 2B) ⁴⁷	<p>Day 1: Epirubicin 50mg/m² IV + oxaliplatin 130mg/m² IV Days 1–21: Capecitabine 625mg/m² IV orally twice daily. Repeat cycle every 21 days.</p>
5-FU and irinotecan (irinotecan + leucovorin + 5-FU) ^{40,48,49}	<p>Day 1: Irinotecan 80mg/m² IV + leucovorin 500mg/m² IV + 5-FU 2000mg/m² IV continuous infusion over 24 hours, weekly for 6 weeks followed by 1 week off treatment OR weekly for 6 weeks followed by 2 weeks off treatment.</p> <p>OR</p> <p>Day 1: Irinotecan 180mg/m² IV + leucovorin 400mg/m² IV + 5-FU 400mg/m² IVP Day 1–2: 5-FU 1200mg/m² IV continuous infusion over 24 hours. Repeat cycle every 14 days.</p>

Second-line or Subsequent Therapy¹

Preferred Regimens

Ramucirumab + paclitaxel (for adenocarcinoma) (Category 1 for EGJ adenocarcinoma; Category 2A for esophageal adenocarcinoma) ⁵⁰	<p>Days 1 and 15: Ramucirumab 8mg/kg IV Days 1, 8, and 15: Paclitaxel 80mg/m² IV. Repeat cycle every 28 days.</p>
Ramucirumab (for adenocarcinoma) (Category 1 for EGJ adenocarcinoma; Category 2A for esophageal adenocarcinoma) ⁵¹	<p>Days 1 and 15: Ramucirumab 8mg/kg IV. Repeat cycle every 28 days.</p>

continued

ESOPHAGEAL AND ESOPHAGOGASTRIC JUNCTION CANCER TREATMENT REGIMENS (Part 5 of 7)

Second-line or Subsequent Therapy¹ (continued)

Preferred Regimens (continued)

REGIMEN	DOSING
Docetaxel (Category 1) ⁴³	Day 1: Docetaxel 75–100mg/m ² IV. Repeat cycle every 21 days.
Paclitaxel (Category 1) ^{43,44,52}	Day 1: Paclitaxel 135–250mg/m ² IV. Repeat cycle every 21 days. OR Day 1: Paclitaxel 80mg/m ² IV once weekly. Repeat cycle every 28 days. OR Days 1, 8, and 15: Paclitaxel 80 mg/m ² IV. Repeat cycle every 28 days.
Irinotecan (Category 1) ^{52–54}	Day 1: Irinotecan 250–350mg/m ² IV. Repeat cycle every 21 days. OR Day 1: Irinotecan 150–180mg/m ² IV. Repeat cycle every 14 days. OR Days 1 and 8: Irinotecan 125mg/m ² IV. Repeat cycle every 21 days.
Fluorouracil + irinotecan (if not previously used in first-line therapy; only for adenocarcinoma)	Day 1: Irinotecan 180mg/m ² IV + leucovorin 400mg/m ² IV + fluorouracil 400mg/m ² IVP followed by: Days 1–2: Fluorouracil 1200mg/m ² IV continuous infusion over 24 hours daily. Repeat cycle every 14 days.

Other Regimens

Irinotecan + cisplatin ^{32,55}	Days 1 and 8: Irinotecan 65mg/m ² IV + cisplatin 25–30mg/m ² IV. Repeat cycle every 21 days.
Irinotecan + fluoropyridimine (Category 2B) ⁵⁶	Day 1: Irinotecan 250mg/m ² IV Days 1–14: Capecitabine 1000mg/m ² PO BID daily. Repeat cycle every 21 days.
Docetaxel + irinotecan (Category 2B) ³⁹	Days 1 and 8: Docetaxel 35mg/m ² IV plus irinotecan 50mg/m ² IV. Repeat cycle every 21 days.
Pembrolizumab ^{59,e} (for MSI-H or dMMR tumors)	Day 1: Pembrolizumab 200mg IV. Repeat cycle every 21 days.

Principles of Systemic Therapy¹

- Systemic therapy regimens recommended for advanced esophageal and esophagogastric junction (EGJ) adenocarcinoma, squamous cell carcinoma of the esophagus, and gastric adenocarcinoma may be used interchangeably (except as indicated).
- Regimens should be chosen in the context of performance status, comorbidities, and toxicity profile.
- Trastuzumab should be added to chemotherapy for HER2 overexpressing metastatic adenocarcinoma.
- Two-drug cytotoxic regimens are preferred for patients with advanced disease because of lower toxicity. Three-drug cytotoxic regimens should be reserved for medically fit patients with good PS and access to frequent toxicity evaluation.
- Modifications of category 1 regimen or use of category 2A or 2B regimens may be preferred (as indicated), with evidence supporting more favorable toxicity profile without compromising efficacy.
- Doses and schedules for any regimen that is not derived from category 1 evidence is a suggestion, and subject to appropriate modifications depending on the circumstances.
- Alternate combinations and schedules of cytotoxics based on the availability of the agents, practice preferences, and contraindications are permitted.
- Preoperative chemoradiation is the preferred approach for localized adenocarcinoma of the thoracic esophagus or EGJ. Perioperative chemotherapy is an alternative option for distal esophagus and EGJ.
- In the adjuvant setting, upon completion of chemotherapy or chemoradiation, patients should be monitored for any long-term treatment-related complications.

a Modified regimens substituting oxaliplatin and/or capecitabine are also acceptable.

b May be coupled with cetuximab administered as an initial dose of cetuximab 400 mg/m² IV on Day 1 over 120 minutes; followed by weekly doses of 250 mg/m² IV over 60 minutes.

c The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.

d Cisplatin may not be used interchangeably with oxaliplatin in this setting.

e For second-line or subsequent therapy for MSI-H/dMMR tumors; for third-line or subsequent therapy for PD-L1-positive esophageal and EGJ adenocarcinoma.

continued

ESOPHAGEAL AND ESOPHAGOGASTRIC JUNCTION CANCER TREATMENT REGIMENS (Part 6 of 7)

References

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