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Guideline Obeservation

Updates in version 2.2018 of the NCCN guidelines for esophageal and esophagogastric junction cancers

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Comment

Preferred Regimens provide by expert group were adjusted: (1) Fluorouracil and cisplatin was no longer the Preferred Regimen for Preoperative Chemoradiation and Perioperative Chemotherapy (recommended as the other regimens); (2) DCF modifications were no longer the Preferred Regimens for First-Line Therapy (recommended as the other regimens); (3) Pembrolizumab (For second-line or subsequent therapy for MSI-H or dMMR tumors) was recommended as the Preferred Regimen for Second-Line or Subsequent Therapy; (4) Ramucirumab for adenocarcinoma (category 1 for EGJ adenocarcinoma; category 2A for esophageal adenocarcinoma) was no longer the Preferred Regimen for Second-Line or Subsequent Therapy. Survivors who underwent esophagectomy are at particular risk for clinically relevant long-term health issues, especially GI-related issues, such as malnutrition, dysphagia, dumping syndrome, delayed gastric emptying, reflux, and fatigue, which have been shown to negatively impact survivors' quality of life. This update proposes the following specific management and monitoring solutions for esophageal cancer survivors: Weight monitoring and the nutritional status in patients with esophageal cancer who underwent surgery are important. Intervention by nutrition specialists is recommended. Treatment of postoperative complications, such as delayed gastric emptying, dumping syndrome, esophageal bile reflux, and dysphagia should be carefully considered, and nursing advice should also be provided. In patients who previously had hypertension, the blood pressure condition may be improved after weight loss. Therefore, blood pressure should be monitored, and the original antihypertensive regimen adjusted as appropriate. Patients who previously had diabetes and hyperlipidemia may also need similar adjustments. Complications caused by chemoradiotherapy, such as radiation-induced heart injuries and chemotherapy-induced neuropathy, should be managed. Patient's psychological and physical states should be evaluated. Healthy lifestyle: Specific advice on dietary habits, living habits, physical activities, smoking cessation, and alcohol abstinence is necessary.

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Updates in version 2.2018 from version 1.2018

ESOPH-F principles of systemic therapy

The NCCN Categories of Preference has been applied to all of the suggested treatment regimens.

The regimen and dosing schedule pages were updated to reflect the changes noted above.

ESOPH-J principles of survivorship

This is a new section that provides recommendations for survivorship including Management of long-term sequelae of disease or treatment, Counseling regarding health behaviors, Cancer screening recommendations (for average risk survivors), and Survivorship care planning and coordination.

MS-1

The Discussion section has been updated to reflect the changes in the algorithm.

Updates in version 1.2018 from version 4.2017

Workup

PET/CT evaluation , from skull base to mid-thigh, if no evidence of M1 disease.

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Adenocarcinomas

Primary Treatment Options for Medically Fit Patients: For cT4b the following option was added, "Consider chemotherapy alone in the setting of invasion of trachea, great vessels, or heart".

For patients who have received preoperative chemoradiation or chemotherapy, if R1 resection: Added "Observation until progression"as an option.

"Chemotherapy if received preoperatively" was removed.

Squamous cell carcinoma and adenocarcinoma

Management of non-surgical candidates: cT1b-T4a N0–N+ or cT4b (unresectable); able to tolerate chemoradiation: "Definitive chemoradiation (50–50.4 Gy of RT + concurrent chemotherapy), removed "Fluoropyrimidine- or taxane-based".

Follow-up / Surveillan

"Imaging studies and Upper GI endoscopy and biopsy as clinically indicated".

Palliative management

"Locoregional recurrence: Prior esophagectomy, no prior chemoradiation" pathway: Revised, still recommend "Concurrent chemoradiation" , but deleted the recommendation of Fluoropyrimidine- or taxane-based regimen.

Principles of pathologic review and biomarker testing

Title revised as "Principles of Pathologic Review and Biomarker Testing"

This section was extensively revised and includes new recommendations for "Microsatellite Instability (MSI) or Mismatch Repair (MMR)Testing" and "PD-L1 Testing."

Principles of systemic therapy

Perioperative chemotherapy revisions: "Fluoropyrimidine and oxaliplatin" changed to a referred option; "Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) (category 1)" added as an option with corresponding footnote, "Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit".

The following regimens were removed: ECF (epirubicin, cisplatin, and fluorouracil) (category 2B); ECF modifications (category 2B for all modifications)

– Epirubicin, oxaliplatin, and fluorouracil
– Epirubicin, cisplatin, and capecitabine
– Epirubicin, oxaliplatin, and capecitabine

The regimen and dosing schedule pages were updated to reflect the changes on ESOPH-F 2 of 12, for exzample, added regimen of Fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT).

Fluorouracil 2600 mg/m^2 IV continuous infusion over 24 h on Day 1; Leucovorin 200 mg/m^2 IV on Day 1; Oxaliplatin 85 mg/m^2 IV on Day 1; Docetaxel 50 mg/m^2 IV on Day 1; Cycled every 14 days for 4 cycles preoperatively and 4 cycles postoperatively for a total of 8 cycles.

Principles of surveillance

First bullet revised: "The surveillance strategies after successful local therapy for esophageal and EGJ cancers remain controversial, with no high-level evidence to guide development of algorithms that balance benefits and risks (including cost) within this cohort."

T1b, Any N; Esophagectomy: Revised recommendation, "Imaging (CT chest/abdomen with contrast unless contraindicated) should be considered starting every 12 months for up to 3 years if the patient is likely to tolerate additional curative-intent therapy for recurrence. EGD as

PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

Microsatellite Instability (MSI)* or Mismatch Repair (MMR)* Testing

- **MMR or MSI testing should be considered on locally advanced, recurrent, or metastatic esophageal adenocarcinoma or EGJ,[12] in patients who are candidates for treatment with PD-1 inhibitors. The testing is performed on formalin-fixed paraffin-embedded tissue and results are interpreted as MSI-high or mismatch protein repair-deficient in accordance with guidelines for colorectal cancer specimens. See NCCN Guidelines for Genetic/Familial High-risk Assessment: Colorectal. MMR or MSI testing should be performed only in CLIA-approved laboratories.**

PD-L1 Testing

- **PD-L1 testing may be considered on locally advanced, recurrent, or metastatic esophageal adenocarcinoma in patients who are candidates for treatment with PD-1 inhibitors. An FDA-approved companion diagnostic test for use on formalin-fixed paraffin-embedded tissue is available as an aid in identifying gastroesophageal junction adenocarcinoma patients for treatment with PD-1 inhibitors. PD-L1 testing should be performed only in CLIA-approved laboratories.**
- **Assessment of PD-L1 Protein Expression in Esophageal and Esophagogastric Junction Cancers**
  - **This is a qualitative immunohistochemical assay using anti-PD-L1 antibodies for the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) tissues from esophageal or EGJ adenocarcinoma. A minimum of 100 tumor cells must be present in the PD-L1–stained slide for the specimen to be considered adequate for PD-L1 evaluation. A specimen is considered to have PD-L1 expression if the Combined Positive Score (CPS) ≥ 1. CPS is the number of PD-L1 staining cells (ie, tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.**

needed....".

T2–T4, N0–N+, T4b; Bimodality therapy (definitive chemoradiation): Revised recommendation, "Imaging studies (CT chest/abdomen with contrast unless contraindicated) should be considered every 6 months for up to 2 years if the patient is likely to tolerate additional curative-intent therapy for recurrence.

T2–T4, N0–N+, T4b; Trimodality therapy: Recommendation revised, "Imaging studies (CT chest/abdomen with contrast unless contraindicated) should be considered every 6 months for up to 2 years if the patient is likely to tolerate additional curative-intent therapy for recurrence.

Staging

The AJCC 7th Edition Cancer Staging Tables were updated to the 8th edition.

T4a: Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum, of which, azygos vein and peritoneum was added new.

T4b: Tumor invades other adjacent structures, such as the aorta, vertebral body, or airway, of which, use "airway" instead of "trachea , etc."

Definition of Histologic Grade (G) of adenocarcinoma is the same with that of squamous cell carcinoma.

Definition of histologic grade (G)

G	G definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated, undifferentiated

Squamous Cell Carcinoma: Definition of Location (L) is new, and the Location is defined by the position of the epicenter of the tumor in the esophagus.

Location category	Location criteria
X	Location unknown
Upper	Cervical esophagus to lower border of azygos vein
Middle	Lower border of azyos vein to lower border of inferior pulmonary vein
Lower	Lower border of inferior pulmonary vein to stomach, including gastroesophageal junction

Note: Location is defined by the position of the epicenter of the tumor in the esophagus

PROGNOSTIC STAGE GROUPS of Clinical Staging (cTNM), Pathological (pTNM), Postneoadjuvant Therapy (ypTNM) are widly revised.

For Squamous Cell Carcinoma

Clinical staging (cTNM)

	c T	c N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0–1	M0
Stage II	T2	N0–1	M0
	T3	N0	M0
Stage III	T3	N1	M0
	T1–3	N2	M0
Stage IVA	T4	N0–2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

Pathological (pTNM)

	p T	p N	M	G	Location
Stage 0	Tis	N0	M0	N/A	Any
Stage IA	T1a	N0	M0	G1	Any
	T1a	N0	M0	GX	Any
Stage IB	T1a	N0	M0	G2–3	Any
	T1b	N0	M0	G1–3	Any
	T1b	N0	M0	GX	Any
	T2	N0	M0	G1	Any
Stage IIA	T2	N0	M0	G2–3	Any
	T2	N0	M0	GX	Any
	T3	N0	M0	Any	Lower
	T3	N0	M0	G1	Upper/middle
Stage IIB	T3	N0	M0	G2–3	Upper/middle
	T3	N0	M0	GX	Any
	T3	N0	M0	Any	Location X
	T1	N1	M0	Any	Any
Stage IIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
Stage IIB	T2	N2	M0	Any	Any
	T3	N1–2	M0	Any	Any
	T4a	N0–1	M0	Any	Any
Stage IVA	T4a	N2	M0	Any	Any
	T4b	N0–2	M0	Any	Any
	Any T	N3	M0	Any	Any
Stage IVB	Any T	Any N	M1	Any	Any

Postneoadjuvant therapy (ypTNM)

	yp T	yp N	M
Stage I	T0–2	N0	M0
Stage II	T3	N0	M0
Stage IIIA	T0–2	N1	M0
Stage IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
Stage IVA	T4a	N1–2	M0
	T4a	NX	M0
	T4b	N0–2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

For Adenocarcinoma

Clinical staging (cTNM)

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N0	M0
Stage III	T2	N1	M0
	T3	N0–1	M0
	T4a	N0–1	M0
Stage IVA	T1–4a	N2	M0
	T4b	N0–2	M0
	Any T	N3	M0
Stage IVB	any T	Any N	M1

Pathological (pTNM)

	p T	p N	M	G
Stage 0	Tis	N0	M0	N/A
Stage IA	T1a	N0	M0	G1
	T1a	N0	M0	GX
Stage IB	T1a	N0	M0	G2
	T1b	N0	M0	G1–2
	T1b	N0	M0	GX
Stage IB	T1	N0	M0	G3
	T2	N0	M0	G1–2
Stage IIA	T2	N0	M0	G3
	T2	N0	M0	GX
Stage IIB	T1	N1	M0	Any
	T3	N0	M0	Any
Stage IIIA	T1	N2	M0	Any
	T2	N1	M0	Any
Stage IIIB	T2	N2	M0	Any
	T3	N1–2	M0	Any
	T4a	N0–1	M0	Any
Stage IVA	T4a	N2	M0	Any
	T4b	N0–2	M0	Any
	Any T	N3	M0	Any
Stage IVB	Any T	Any N	M1	Any

Postneoadjuvant therapy (ypTNM)

	yp T	yp N	M
Stage I	T0	N0	M0
Stage II	T3	N0	M0
Stage IIIA	T0-2	N1	M0
Stage IIIB	T3	N1	M0
	T0-3	N2	M0
	T4a	N0	M0
Stage IVA	T4a	N1–2	M0
	T4a	NX	M0
	T4b	N0–2	M0
	Any T	N3	M0
Stage IVB	Any T	Any N	M1

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