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GUIDELINE OBSERVATION

Updates of the NCCN guidelines for pancreatic adenocarcinoma

Liu Huang (✉)

Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

Updates in version 2.2018 of the NCCN guidelines for pancreatic adenocarcinoma from version 1.2018

MS-1

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

Updates in version 1.2018 of the NCCN guidelines for pancreatic adenocarcinoma from version 3.2017

General

Changed "narcotic" to "analgesic."

Changed "Locally Advanced Unresectable" to "Locally Advanced."

PANC-1

Workup recommendations have been significantly revised and former PANC-2 was removed.

The following options have been added to the workup:

If no metastatic disease: "Consider genetic counseling and germline testing if diagnosis confirmed."

If metastatic disease: "Consider genetic counseling and germline testing."

Footnote "a" revised: "Multidisciplinary review should ideally involve expertise from diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, and pathology, geriatric medicine, and palliative care. Consider consultation with a registered dietitian. See NCCN Guidelines for Older Adult Oncology, and NCCN Guidelines for Palliative Care."

Footnote "d" added: "PET/CT scan may be considered after formal pancreatic CT protocol in high-risk patients to detect extra pancreatic metastases. It is not a substitute for high-quality, contrast-enhanced CT. See Principles of Diagnosis, Imaging, and Staging (PANC-A)."

Footnote "e" added for stent: "Plastic stent or consider covered metal stent, if clinically indicated."

Footnote "f" revised: ERCP = endoscopic retrograde cholangiopancreatography; PTC = percutaneous transhepatic cholangiography.

Footnote "g" revised: " Consider germline testing for patients with a personal history of cancer, a family history of pancreatic cancer, or if there is a clinical suspicion of inherited susceptibility. See Discussion and see NCCN Guidelines for Genetic/Familiar High Risk Assessment: Breast and Ovarian."

PANC-2

Option added for those with resectable disease: "Consider neoadjuvant therapy in high-risk patients, clinical trial preferred."

Follow-up recommendations added after neoadjvuant therapy: "Repeat pancreatic protocol CT or MRI; Repeat chest/pelvic CT; Post-treatment CA 19-9; Consider stent if clinically indicated."

Footnote "h" added: "If not previously done, consider germline testing for patients with a personal history of cancer, a family history of pancreatic cancer, or if there is a clinical suspicion of inherited susceptibility. See Discussion and see NCCN Guidelines for Genetic/Familial High Risk Assessment: Breast and Ovarian."

Footnote "n" revised: "There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. See PANC-G for acceptable neoadjuvant options. Subsequent chemoradiation is sometimes included (see PANC-F). Most NCCN Member

✉ Correspondence to: Liu Huang. Email: huangliu017@163.com

Institutions prefer neoadjuvant therapy at or coordinated through a high-volume center."

Footnote "k" added: "Stent placement is not routinely recommended prior to planned surgery; however, stent may be considered for symptoms of cholangitis/fever or if surgery is being delayed for any reason. Stent should only be placed if tissue diagnosis is confirmed."

Footnote "l" added: "High-risk features include imaging findings, very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain."

PANC-3

Revised imaging recommendations after neoadjuvant therapy for consistency: "Pancreatic protocol CT or MRI (abdomen); Chest/pelvic CT".

Footnote "s" added: "Core biopsy recommended, if possible, to obtain adequate tissue for possible ancillary studies."

PANC-4

Baseline pretreatment imaging revised: "Pancreas protocol CT (abdomen) and chest/pelvic CT"

Surveillance timing revised: "...every 3–6 mo for 2 years, then every 6–12 mo as clinically indicated."

Surveillance imaging revised: "Consider CT (chest, abdomen, pelvis) with contrast (category 2B)"

Footnote "t" revised: "Adjuvant treatment should be administered to patients who have adequately recovered from surgery; treatment should..."

PANC-5

The following recommendation was moved from the footnotes to the Workup algorithm: "Consider microsatellite instability (MSI) testing and/or mismatch repair (MMR) testing on available tumor tissue (category 2B)." (also on PANC-7).

Stent recommendation revised for those with confirmed adenocarcinoma: "If jaundice, placement of self-expanding metal stent preferably via ERCP."

Footnote "y" revised: "EUS- guided FNA and core biopsy at a center with multidisciplinary expertise is preferred. When EUS-guided biopsy is not feasible, CT-guided biopsy can be done."

PANC-6

Revised first-line therapy for patients with poor performance status (PS): "Palliative and best supportive care and Consider single-agent chemotherapy or palliative RT." (Also on PANC-7).

For patients with good PS and disease progression, removed separate pathways for those previously treated with gemcitabine- versus fluoropyrimidine-based therapy. Refer to the Principles of Chemotherapy (PANC-G) for details about chemotherapy recommendations based on prior therapy. (Also on PANC-7).

Added second-line therapy options for those with poor PS and disease progression after first-line therapy: "Palliative and best supportive care and Consider single-agent chemotherapy or palliative RT." (Also PANC-7).

Added second-line therapy options for those with good PS and disease response after first-line therapy: "Consider resection, if feasible or Observe or Clinical trial." If surgery is done, adjuvant therapy is recommended, if clinically indicated.

Added SBRT as an option for patients with good PS and disease progression after first-line therapy, if not previously given and if primary site is the sole site of progression.

Following second-line therapy for those with disease progression, changed "poor PS" to "declining PS."

Footnote "z" revised: "Defined as ECOG 0-1, with good biliary drainage and adequate nutritional intake, and ECOG 0-2 if considering gemcitabine + albumin-bound paclitaxel."

Footnote "aa" revised: "Serial imaging as indicated to assess disease response. See Principles of Diagnosis, Imaging, and Staging #10 (PANC-A)."

Updated reference in footnote "dd": Hammel P, Huguet F, van Laethem JL, *et al*. Effect of chemoradiotherapy vs chemotherapy on survival in patients with locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: The LAP07 randomized clinical trial. Jama 2016; 315(17):1844-1853. (Also PANC-G).

Footnotes removed:

"Patients with a significant response to therapy may be considered for surgical resection."

"Best reserved for patients who maintain a good performance status."

PANC-8

Changed the heading from "Second-line Therapy" to "Recurrence Therapy."

For local recurrence in the pancreas only, added recommendations for multidisciplinary review.

For recurrence in the pancreatic bed:

Added the following to the systemic chemotherapy option: "(See options below for ≥6 or <6 mo from completion of primary therapy)".

Removed the following option: "Consider induction chemotherapy followed by SBRT (if RT not previously done)" (Also on PANC-F, 6 of 9).

Revised the following options for recurrence ≥6 mo from completion of primary therapy:

"Repeat systemic therapy as previously administered"; "Systemic therapy not previously used".

Revised the following options for recurrence less than

6 mo from completion of primary therapy:

"Switch to gemcitabine-based systemic chemotherapy (if fluoropyrimidine-based therapy previously used)"; "Switch to fluoropyrimidine-based systemic chemotherapy (if gemcitabine-based therapy previously used)".

PANC-A (1 of 8)

#3:

Clarified "...dedicated pancreatic CT of abdomen (preferred)..."

Removed bullet: "MR cholangiopancreatography (MRCP) without IV contrast should not be utilized in the staging of pancreatic cancer, except in cases of renal failure or other contraindications to administration of gadolinium intravenous contrast."

PANC-B

Bullet removed under Arterial for Unresectable disease in the Head/uncinate process: "Solid tumor contact with the first jejunal SMA branch."

PANC-C (1 of 2)

First three paragraphs have been added. Content regarding frozen section analysis of the pancreatic neck and bile duct was moved to this section from PANC-D.

Under Whipple technique, the last line of the second bullet has been revised: "Data support an aggressive approach to partial or complete vein excision if tumor infiltration is suspected.

PANC-C (2 of 2)

Heading revised: "Distal pancreatectomy with en-bloc splenectomy"

Line added: "Plane of dissection anterior to adrenal gland or en bloc resection of left adrenal gland with plane of dissection posterior to Gerota's fascia recommended as clinically indicated."

New section added on the management of neck lesions with the following references:

Hirono S, Kawai M, Okada K, *et al*. Pancreatic neck cancer has specific and oncologic characteristics regarding portal vein invasion and lymph node metastasis. Surgery, 2016, 159 (2): 426–440.

Strasberg SM, Sanchez LA, Hawkins WG, *et al*. Resection of tumors of the neck of the pancreas with venous invasion: the "Whipple at the Splenic Artery (WATSA)" procedure. J Gastrointest Surg, 2012, 16: 1048–1054.

PANC-D (1 of 4)

Under Margins, in the fifth and sixth sub-bullets, revised: "...true margins facing up down so that the initial section into the block..." (Also on PANC-D, 2 of 4 under distal pancreatectomy margins).

PANC-E

Added recommendations for treatment of bleeding from the primary tumor site.

PANC-G

5-FU/cisplatin + concurrent RT has been removed from the chemoradiation options for neoadjuvant therapy, adjuvant therapy, first-line therapy for locally advanced, second-line and subsequent therapy for locally advanced, metastatic, and recurrent disease.

Everywhere gemcitabine + cisplatin is included as an option, the indications have been changed to: "(Only for known BRCA1/2 mutations)."

PANC-G (1 of 6)

Added to General Principles: "To optimize the care of older adults, see NCCN Guidelines for Older Adult Oncology."

Revised the following neoadjuvant therapy recommendation: "If neoadjuvant therapy is recommended , treatment with at or coordinated through a high-volume center is preferred, when feasible."

PANC-G (3 of 6)

Footnote "f" added and revised: "FOLFIRINOX should be limited to those with ECOG 0-1. Gemcitabine + albumin-bound paclitaxel is reasonable for patients with ECOG 0-2. 5-FU + leucovorin + liposomal irinotecan is a reasonable second-line option for patients with ECOG 0-2."

PANC-G (4 of 6)

Clarified the "preferred options" for metastatic disease versus the "other options."

PANC-G (5 of 6)

Added 5-FU + leucovorin + irinotecan (FOLFIRI) as a second-line therapy option for patients previously treatment with gemcitabine-based therapy if locally advanced/metastatic disease and good performance status.

Recommendations for recurrent disease have been revised to reflect the changes in the algorithm on PANC-8.

Second-line therapy options have been added for those with poor performance status.

ST-1

Staging tables have been updated based on the AJCC 8th edition.

Table 1. **Definitions for T, N, M**
American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (8th ed., 2017)

T	Primary Tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 cm and <1 cm in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size

N	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assesseds
N0	No regional lymph node metastases
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

M	Distant Metastasis
M0	No distant metastases
M1	Distant metastasis

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

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