Egyptian National Guidelines for Pancreatic Cancer

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- **Abbreviations**

BRPC	Borderline resectable prostatic cancer
CBC	Complete blood count
CRT	Combined chemo radiotherapy
CT	Computed Tomography
EHC	Egyptian Health Council
EUS	Endoscopic ultrasound
KFTs	Kidney function tests
LAPC	Locally advanced pancreatic cancer
LFTs	Liver function tests
LMWH	Low-molecular-weight heparin
MRI	Magnetic resonance imaging
MDT	Multidisciplinary team
PC	Pancreatic cancer
PET/CT	Positron emission tomography/Computed Tomography
PS	Performance Status
SMA	Superior mesenteric artery
ULN	Upper limit of normal

- **Executive Summary**

This guidance provides a data-supported approach to diagnosis, staging, treatment and follow up of patients diagnosed with pancreatic Cancer. This Guideline is intended only for pancreatic adenocarcinoma.

Recommendation	Strength of recommendation
Diagnosis	
• **Labs**	
• Routine labs including LFTs, KFTs, and CBC should be included in the primary diagnosis of pancreatic cancer.	**Good practice statement**
• CA 19-9 can be used as a serum marker to measure disease burden and potentially guide treatment decisions.	**Good practice statement.**
• Cytology in localized pancreatic lesion, preferably by EUS guidance or biopsy from metastatic site "preferred" should be obtained before initiation of chemotherapy.	**Strong**
• **Imaging**	
• Multiphasic contrast-enhanced thoracic-abdominal and pelvic CT, including late arterial phase and portal venous phase, should be used as the first-line imaging modality for suspected PC.	**Strong**
• We recommend imaging before biliary drainage or stenting in case of jaundice due to an obstructive head PC.	**Strong**
• Imaging should be carried out in the 4 weeks before starting treatment.	**Strong**
• Abdominal MRI may be used when CT cannot be carried out, or inconclusive or for pancreatic cystic lesions.	**Conditional**
• We do not recommend PET/CT for diagnosis of primary tumors but may be useful for staging localized tumors and in cases where the presence of distant metastases is uncertain (e.g. Doubtful imaging or high CA 19-9).	**Conditional**

• Hepatic MRI is recommended before surgery to confirm the absence of small liver metastases	**Strong**
Pathology and immunophenotyping	
• CA19-9 (or CK19 according to availability), Chromogranin (or synaptophysin according to availability) are recommended for pathologic diagnosis.	**Conditional**
Staging and Risk assessment	
• MDT discussion in expert centers is required to define a recommended treatment strategy for patients with PC.	**Good clinical practice**
• Tumors should be staged according to the AJCC staging system	**Strong**
• We recommend assessing resectability by anatomical NCCN criteria.	**Strong**
• We prefer staging laparoscopy in patients who meet any of the followings: CA19.9 > 150U/ml, low volume ascites, tumor in the body or tail of pancreas, borderline resectable tumor (after neoadjuvant treatment), or tumor > 3 cm in size.	**Conditional**
Treatment of resectable PC	
• We suggest performing frozen section analysis of pancreatic neck transection and of common bile duct transection margins.	**Conditional**
• Tumour clearance should be defined for all margins identified by the surgeon	**Good clinical practice**
• For adenocarcinomas of the pancreas head and uncinate, a pancreatoduodenectomy (Whipple procedure) should be done.	**Strong**
• For patients with tumours in the body or tail, radical anterograde modular pancreatosplenectomy with dissection of the left hemi-circumference of the SMA to the left of the coeliac trunk is recommended.	**Strong**
• Standard lymphadenectomy is recommended and should involve the removal of $\geq$16 lymph nodes to allow adequate pathological staging of the disease.	**Strong**

• The total number of lymph nodes examined and lymph node ratio (number of involved lymph nodes as a proportion of the number of lymph nodes examined) should be reported in the pathological analysis.	**Strong**
• Patients undergoing surgery should receive perioperative thromboprophylaxis with either unfractionated heparin or low-molecular-weight heparin (LMWH), unless contraindicated.	**Strong**
• If the bilirubin level is >14 mg/l (250 mmol/l), endoscopic drainage is recommended for those planned to receive neoadjuvant treatment or those in whom surgery will be delayed for longer than 2 weeks.	**Strong**
• Neoadjuvant therapy is not recommended for resectable PC.	**Conditional**
• Following resection of PC, completion of 6 months of adjuvant Chemotherapy is strongly recommended.	**Strong**
• Adjuvant mFOLFIRINOX is recommended for patients with resected PC and ECOG PS 0-1.	**Strong**
• In patients who are not candidates for mFOLFIRINOX (age >75 years, ECOG PS 2 or contraindication to mFOLFIRINOX), we recommend gemcitabine-capecitabine as an alternative option.	**Strong**
• Adjuvant gemcitabine or 5-FU-LV should be limited to frail patients.	**Strong**
• Adjuvant CRT is not recommended and should not be given to patients following surgery.	**Strong**
Treatment of borderline resectable tumors (BRPC)	
• Patients with BRPC have a high probability of an R1 resection and should be considered for induction treatment.	**Strong**
• A period of induction chemotherapy (FOLFIRINOX) followed by CRT on a case-by-case basis and subsequent surgery, is recommended according to MDT recommendations	**Strong**
• Gemcitabine combined with oxaliplatin or capecitabine may be considered, when FOLFIRINOX is not feasible.	**Strong**
• CRT with capecitabine may be considered after induction Chemotherapy.	**Conditional**
	Strong

• Following induction therapy, medically fit patients without disease progression and with a decrease in CA 19-9 should undergo surgical exploration, unless contraindicated.	
Treatment of locally advanced pancreatic cancer (LAPC)	
• A conversion surgery strategy utilizing the standard of care of up to 6 months of combination Chemotherapy (e.g. FOLFIRINOX) should be chosen.	**Strong**
• Arterial resection after induction therapy is not recommended but can be considered as a possibility in experienced centers on a case-by-case basis in selected patients according to MDT recommendations.	**Conditional**
Treatment of advanced pancreatic cancer	
First-line treatment	
• **Options to treat patients with metastatic PC should be dependent on PS:** o In patients with ECOG PS 0-1 and bilirubin level ≤1.5 times the ULN, the regimen FOLFIRINOX should be considered. **Strong recommendation, high grade evidence (34)** o For patients with ECOG PS 2, Karnofsky PS (KPS) ≥70 and bilirubin level ≤1.5 times the ULN, gemcitabine-cisplatin can be considered. **Strong recommendation, high grade evidence (34).** o For patients with ECOG PS 2, KPS ≤70 and/or bilirubin level ≥1.5 times the ULN, gemcitabine monotherapy should be considered. **Strong recommendation, high grade evidence (34).** o For patients with ECOG PS 3-4, symptom-directed and palliative care should be considered **Strong recommendation, high grade evidence (34).**	**Strong**
• The efficacy of treatment should be typically evaluated every 8-12 weeks and should be based on clinical status, CA 19-9 trajectory and imaging.	**Strong**
Second-line treatment	

• After FOLFIRINOX treatment, gemcitabine alone may be offered to patients with ECOG PS 0-1 and a favorable comorbidity profile.	**Conditional**
• Oxaliplatin-based second-line treatment (mFOLFOX6 or OFF) may be considered as an alternative in patients with ECOG PS 0-2 if not given previously.	**Conditional**
• For patients with ECOG PS 3-4, symptom directed, and palliative care is recommended.	**Strong**
• Maintenance therapy with capecitabine (after discussion with patient) may be indicated till disease progression or unacceptable toxicity on a case- by case basis according to MDT recommendations.	**Conditional**

➢ Introduction

Pancreatic cancer is a malignancy with high mortality, and the overall prognosis is poor. The growing trend of pancreatic cancer cases is expected to continue for the next two decades and beyond. In Egypt, there was an estimated 3349 new cases of pancreatic cancer and 3186 deaths occurred because of this disease based on GLOBOCAN 2022.

➢ Purpose and scope

These guidelines are developed to improve the quality of care for pancreatic cancer via providing a uniform standard of care across the country to help in early diagnosis, treatment and follow up for pancreatic cancer so more optimal treatment options and improved clinical outcomes.

➢ Target audience

Clinicians who are involved in the care and treatment of patients with pancreatic cancer, include medical oncologists, radiation oncologists, clinical oncologist, gastroenterologists, surgeons, clinical dietrition interventional radiologists, radiologists, pathologists, and palliative care specialists.

- **Methodology**

A comprehensive search for guidelines was undertaken to identify the most relevant guidelines to consider for adaptation.

Inclusion/exclusion criteria followed in the search and retrieval of guidelines to be adapted:

- Selecting only evidence-based guidelines (guidelines must include a report on systematic literature searches and explicit links between individual recommendations and their supporting evidence). - Selecting only national and/or international guidelines.
- Specific range of dates for publication (using Guidelines published or updated 2015 and later).
- Selecting peer reviewed publications only.
- Selecting guidelines written in English language.
- Excluding guidelines written by a single author not on behalf of an organization to be valid and comprehensive, a guideline ideally requires multidisciplinary input.
- Excluding guidelines published without references as the panel needs to know whether a thorough literature review was conducted and whether current evidence was used in the preparation of the recommendations.

All retrieved Guidelines were screened and appraised using AGREE II instrument (www.agreetrust.org) by at least two members. the panel decided a cutoff point or rank the guidelines (any guideline scoring above 50% on the rigor dimension was retained)

The ESMO, NCCN, and NICE guidelines are the main sources used while formulating the national guidelines for pancreatic cancer (1-3).

- **Evidence assessment**

According to WHO handbook for Guidelines we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations. Detailed information on GRADE is available through the on the following sites:

. GRADE working group: http://www.gradeworkingroup.org

. GRADE online training modules: http://cebgrade.mcmaster.ca/

. GRADE profile software: http://ims.cochrane.org/revman/gradepro

Table 1: Quality of evidence in GRADE

Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Table 2: Significance of the four levels of evidence

Quality	Definition	Implications
High	The guideline development group is very confident that the true effect lies close to that of the estimate of the effect	Further research is very unlikely to change confidence in the estimate of effect
Moderate	The guideline development group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect	Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate
Very low	The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	Any estimate of effect is very uncertain

Table 3: Factors that determine How to upgrade or downgrade the quality of evidence

Downgrade in presence of	Upgrade in presence of
Study limitations -1 Serious limitations -2 Very serious limitations	Dose-response gradient +1 Evidence of a dose-response gradient
Consistency -1 Important inconsistency	Direction of plausible bias +1 All plausible confounders would have reduced the effect
Directness -1 Some uncertainty -2 Major uncertainty	Magnitude of the effect +1 Strong, no plausible confounders, consistent and direct evidence
Precision -1 Imprecise data	+2 Very strong, no major threats to validity and direct evidence
Reporting bias -1 High probability of reporting bias	

- **The strength of the recommendation**

The strength of a recommendation communicates the importance of adherence to the recommendation:

Strong recommendations: With strong recommendations, the guideline communicates the message that the desirable effects of adherence to the recommendation outweigh the undesirable effects. This means that in most situations the recommendation can be adopted as policy.

Conditional recommendations: These are made when there is greater uncertainty about the four factors above (Table 2) or if local adaptation must account for a greater variety in values and preferences, or when resource use makes the intervention suitable for some, but not for other locations. This means that there is a need for substantial debate and involvement of stakeholders before this recommendation can be adopted as policy.

When not to make recommendations; when there is lack of evidence on the effectiveness of an intervention, it may be appropriate not to make a recommendation.

- **Recommendations**

Diagnosis

- **Labs**
  - Routine labs including LFTs, KFTs, and CBC should be included in the primary diagnosis of pancreatic cancer.

Good practice statement

- CA 19-9 can be used as a serum marker to measure disease burden and potentially guide treatment decisions in patients with normal bilirubin.

Good practice statement.

- Cytology in localized pancreatic lesion, preferably by EUS guidance or biopsy from metastatic site "preferred" should be obtained before initiation of chemotherapy.

Strong recommendation, low grade evidence (1).

- **Imaging**
  - Multiphasic contrast-enhanced thoracic-abdominal and pelvic CT, including late arterial phase and portal venous phase, should be used as the first-line imaging modality for suspected PC "Pancreatic protocol".

Strong recommendation, low grade evidence (2).

- We recommend imaging before biliary drainage or stenting in case of jaundice due to an obstructive head PC.

Strong recommendation, very low grade evidence (3).

- Imaging should be carried out in the 4 weeks before starting treatment.

Strong recommendation, low grade evidence (3).

- Abdominal MRI may be used when CT cannot be carried out, or inconclusive or for pancreatic cystic lesions.

Conditional recommendation, very low grade evidence (4).

- We do not recommend PET/CT for diagnosis of primary tumors but may be useful for staging localized tumors and in cases where the presence of distant metastases is uncertain (e.g. Doubtful imaging or high CA 19-9).

Conditional recommendation, low grade evidence (5).

- Hepatic MRI is recommended before surgery to confirm the absence of small liver metastases

Strong recommendation, low grade evidence (4).

Pathology and immunophenotyping

- CA19-9 (or CK19 according to availability), Chromogranin (or synaptophysin according to availability) are recommended for pathologic diagnosis.

Conditional recommendation, low grade evidence (6).

Staging and Risk assessment

- MDT discussion in expert centers is required to define a recommended treatment strategy for patients with PC.

Good clinical practice

- Tumors should be staged according to the AJCC staging system.

Strong recommendation, low grade evidence (7).

- We recommend assessing resectability by anatomical NCCN criteria

Strong recommendation, low grade evidence (8)

- We prefer staging laparoscopy in patients who meet any of the followings:
  CA19.9 > 150U/ml, low volume ascites, tumor in the body or tail of pancreas, borderline resectable tumor (after neoadjuvant treatment), or tumor > 3 cm in size.

Conditional recommendation, low grade evidence (9)

Treatment of resectable PC

- We suggest performing frozen section analysis of pancreatic neck transection and of common bile duct transection margins.

Conditional recommendation, very low grade evidence (10)

- Tumour clearance should be defined for all margins identified by the surgeon.

Good clinical practice

- For adenocarcinomas of the pancreas head and uncinate, a pancreatoduodenectomy (Whipple procedure) should be done.

  Strong recommendation, very low grade evidence (11)

- For patients with tumours in the body or tail, radical anterograde modular pancreatosplenectomy with dissection of the left hemi-circumference of the SMA to the left of the coeliac trunk is recommended.
  Strong recommendation, very low grade evidence (12, 13)

- Standard lymphadenectomy is recommended and should involve the removal of ≥16 lymph nodes to allow adequate pathological staging of the disease.
  Strong recommendation, very low grade evidence (14).

- The total number of lymph nodes examined and lymph node ratio (number of involved lymph nodes as a proportion of the number of lymph nodes examined) should be reported in the pathological analysis.

  Strong recommendation, very low grade evidence (14)

- Patients undergoing surgery should receive perioperative thromboprophylaxis with either unfractionated heparin or low-molecular-weight heparin (LMWH), unless contraindicated.

  Strong recommendation, high grade evidence (15, 16).

- If the bilirubin level is >14 mg/l (250 mmol/l), endoscopic drainage is recommended for those planned to receive neoadjuvant treatment or those in whom surgery will be delayed for longer than 2 weeks.

  Strong recommendation, high grade evidence (17).

- Neoadjuvant therapy is not recommended for resectable PC.

  Conditional recommendation, moderate grade evidence (18-20).

- Following resection of PC, completion of 6 months of adjuvant Chemotherapy is strongly recommended.
  Strong recommendation, high grade evidence (21-23).

- Adjuvant mFOLFIRINOX is recommended for patients with resected PC and ECOG PS 0-1.

Strong recommendation, high grade evidence (23-25)

- In patients who are not candidates for mFOLFIRINOX (age >75 years, ECOG PS 2 or contraindication to mFOLFIRINOX), we recommend gemcitabine-capecitabine as an alternative option.
  Strong recommendation, high grade evidence (23-25)

- Adjuvant gemcitabine or 5-FU-LV should be limited to frail patients.

  Strong recommendation, high grade evidence (23-25)

- Adjuvant CRT is not recommended and should not be given to patients following surgery (in R0 cases).
  Strong recommendation, high grade evidence (26).

Treatment of borderline resectable tumors (BRPC)

- Patients with BRPC have a high probability of an R1 resection and should be considered for induction treatment.

  Strong recommendation, high grade evidence (18-20)

- A period of induction chemotherapy (FOLFIRINOX) followed by CRT on a case-by-case basis and subsequent surgery, is recommended according to MDT recommendations

  Strong recommendation, low grade evidence (20, 27).

- Gemcitabine combined with oxaliplatin or capecitabine may be considered, when FOLFIRINOX is not feasible.

  Strong recommendation, low grade evidence (20,22).

- CRT with capecitabine may be considered after induction Chemotherapy.

  Conditional recommendation, low grade evidence (19)

- Following induction therapy, medically fit patients without disease progression and with a decrease in CA 19-9 should undergo surgical exploration, unless contraindicated.

  Strong recommendation, strong grade evidence (28).

Treatment of locally advanced pancreatic cancer (LAPC)

- A conversion surgery strategy utilizing the standard of care of up to 6 months of combination Chemotherapy (e.g. FOLFIRINOX) should be chosen.
  Strong recommendation, strong grade evidence (29-31).

- Arterial resection after induction therapy is not recommended but can be considered as a possibility in experienced centers on a case-by-case basis in selected patients according to MDT recommendations.
  Conditional recommendation, very low grade evidence (32,33).

Treatment of advanced pancreatic cancer
First-line treatment

- **Options to treat patients with metastatic PC should be dependent on PS:**
  - In patients with ECOG PS 0-1 and bilirubin level $\leq$1.5 times the ULN, the regimen FOLFIRINOX should be considered.

  Strong recommendation, high grade evidence (34)

  - For patients with ECOG PS 2, Karnofsky PS (KPS) $\geq$70 and bilirubin level $\leq$1.5 times the ULN, gemcitabine-cisplatin can be considered.

  Strong recommendation, high grade evidence (34).

  - For patients with ECOG PS 2, KPS $\leq$70 and/or bilirubin level $\geq$1.5 times the ULN, gemcitabine monotherapy should be considered.

  Strong recommendation, high grade evidence (34).

  - For patients with ECOG PS 3-4, symptom-directed and palliative care should be considered

  Strong recommendation, high grade evidence (34).

- The efficacy of treatment should be typically evaluated every 8-12 weeks and should be based on clinical status, CA 19-9 trajectory and imaging.
  Strong recommendation, high grade evidence (35).

Second-line treatment

- After FOLFIRINOX treatment, gemcitabine alone may be offered to patients with ECOG PS 0-1 and a favorable comorbidity profile.
  Conditional recommendation, low grade evidence (36-39).

- Oxaliplatin-based second-line treatment (mFOLFOX6 or OFF) may be considered as an alternative in patients with ECOG PS 0-2 if not given previously.
  Conditional recommendation, low grade evidence (36-39).

- For patients with ECOG PS 3-4, symptom directed, and palliative care is recommended.

  Strong recommendation, low grade evidence (36-39).

- Maintenance therapy with capecitabine (after discussion with patient) may be indicated till disease progression or unacceptable toxicity on a case- by case basis according to MDT recommendations.
  Conditional recommendation, low grade evidence (36-39).

➢ Clinical indicators for monitoring

For patients newly diagnosed with pancreatic cancer:

- laboratory evaluation (CBC, LFT, and KFT)
- imaging
- tissue biopsy for pathological confirmation &IHC

➢ Research gaps

- Systematic inclusion of cost-benefit analyses in clinical trials with collection of health economic analysis such as incremental cost effectiveness ratio in order to facilitate clinical decision-making.
- Predictive biomarkers: response to specific systemic targeted therapies and immunotherapy.
- Improve models for pre-clinical testing of novel drugs.
- Search for tools to assess quality of life and in clinical trials.
- Dietary supplements, nutritional counselling, physical activity recommendations and psychological support as part of an integrative healthcare approach to care for people with pancreatic cancer.

➢ Update of this guideline

- This guideline will be updated whenever there is new evidence.

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- **Annexes**

NCCN resectability Criteria

Resectability Status	Arterial	Venous
Resectable	• No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	• No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[b]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180°. • Solid tumor contact with variant arterial anatomy (eg, accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180°.	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Locally Advanced[b,c]	Head/uncinate process: • Solid tumor contact >180° with the SMA or CA. Pancreatic body/tail: • Solid tumor contact of >180° with the SMA or CA. • Solid tumor contact with the CA and aortic involvement.	• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus).

Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014;270:248-260.

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 assessed
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 metastasis
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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