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SAUDI GASTROINTESTINAL CANCER CLINICAL GUIDELINES

National Cancer Center

(NCC)

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Abstract

Updated guidelines for the evaluation and the medical and surgical management of anal canal cancer established by local experts from all disciplines in the field of gastro-intestinal cancer are presented in this report. The literature was reviewed and recommendations were categorized according to the stage of the disease using the American Joint Committee on Cancer (AJCC) TNM staging system 7th edition. The recommendations took all of the supporting evidence into consideration and were graded accordingly. The guidelines represent the authors' view of the minimum recommendations for the management of anal canal cancer in Saudi Arabia.

According to the Saudi Cancer Registry data, 24 cases of anal cancer were diagnosed in the Kingdom of Saudi Arabia (KSA) in 2013, which accounted for 0.2% of all diagnosed cancers in that year.[1] Several international guidelines have been established for the treatment of all types of cancer. The multi-national culture of the medical community in the KSA has resulted in different treatment strategies that lack documentation of treatment outcomes and sequelae. In addition, the local health authority requires a standardized approach to cancer therapy as many essential cancer medications or treatment approaches are absent in local cancer clinics and centers. Substantial evidence suggests that clinical guidelines aid in standardizing and improving patient care, and that local adaptation of national guidelines provides a cost-effective approach to introducing these guidelines.[2] Data likewise suggest that regional guidelines are more likely to be understood and followed. Accordingly, the Saudi Oncology Society (SOS) aimed to develop national cancer treatment guidelines to improve the standard of care in cancer management across the nation, and to achieve improved disease outcome.

Numerous agencies have published methodologies for guideline development, which have been collected by the Guidelines International Network.[3 3 3] A committee of experts in the medical and surgical treatment of anal canal cancer, chosen according to the recommendations of their oncology department leadership, was established at the request and support of the national cancer center and under the supervision of the national cancer center and SOS. The initial meetings were devoted to planning and establishing the structure, which all agreed should follow the previously published lung cancer guidelines.[4] A draft of the guidelines was commissioned by a working group of the committee and was sent to all committee members for further examination. The guidelines presented, which were developed using a standardized methodology, are the resulting second edition of the SOS guidelines for anal canal cancer.

These guidelines represent the 2016 update of the Saudi Oncology Society (SOS) for anal cancer, which was first published for 2014. The evidence adopted in these guidelines is rated at 3 levels: 1) Evidence level 1 (EL-1; highest level) includes data from phase III randomized trials or meta-analyses; 2) EL-2 (intermediate-level) includes data from good phase II trials or phase III trials with limitations; and 3) EL-3 (low-level) includes retrospective or observational data and/or expert opinion. Ultimately, all anal canal cancer cases are preferably seen or discussed in a multidisciplinary form. This easy-to-follow grading is convenient and allows the reader to accurately assess the applicability of the guidelines in individual patients.[4]

1. Pre-treatment evaluation

1.1 History and clinical examination including inguinal lymph node palpation and rigid anoscopy.
1.2 Blood count and liver and renal function levels.
1.3 Chest X-ray.
1.4 Computed tomography (CT) scan of abdomen and pelvis.
1.5 Magnetic resonance imaging (MRI) of pelvis.
1.6 Fine-needle aspiration (FNA) of inguinal lymph nodes if clinically palpable.
1.7 Human immunodeficiency virus (HIV) testing in selected cases.

2. Staging classification

The 2010 American Joint Committee on Cancer (AJCC) TNM pathological staging system (7th edition) will be used[5] (**Table 1** and **Table 2**).

3. Treatment

3.1. Localized disease (clinical stage T1-4, N0-1): concurrent chemoradiotherapy[6] (EL-2).

3.1.1. Chemotherapy: 5-fluorouracil and mitomycin C[7] (EL-1).

3.1.2. Radiotherapy: 45 Gy given as 1.80 Gy per fraction in 25 fractions to the pelvis and inguinal node area + 5.4-9.0 Gy boost to the tumor bed.[8]

3.2. Localized disease (clinical stage any T, N2-3): concurrent chemoradiotherapy[9]

3.2.1. Chemotherapy: 5-fluorouracil and mitomycin C (EL-1).

3.2.2. Radiotherapy: 45 Gy given as 1.80 Gy per fraction in 25 fractions to the pelvis and inguinal node area + 5.4-9.0 Gy boost to the tumor bed and involved node area.

3.3. Metastatic disease: palliative chemotherapy with 5-fluorouracil and cisplatin[10] (EL-2). Consider palliative radiation to local disease.

3.4. Recurrent disease: Local recurrence or persistent disease post-chemoradiotherapy

3.4.1.1. Persistent disease is defined as a positive biopsy 3 months from the end of chemo radiotherapy.

3.4.1.2. Recurrent disease should be confirmed by biopsy.

3.4.1.3. Anal recurrence: consider abdominoperineal resection[11] (EL-2).

3.4.1.4. Inguinal lymph nodes recurrence: consider groin lymph node dissection (EL-3) or groin irradiation if not performed earlier +/- chemotherapy: 5-fluorouracil and mitomycin C[12] (EL-3).

3.4.2. Distant recurrence: see section 4.3.

3.5. Follow up:

3.5.1. Every 4 months in first year and every 6 months thereafter for 5 years, then annually with digital rectal examination and inguinal palpation (EL-3).

3.5.2. CT scan of abdomen and pelvis annually for the first 3 years (EL-3).

Table 1. TNM AJCC staging for anal canal cancer, 7th edition.

Primary tumor (T)		**Regional lymph nodes (N)**		**Distant metastasis (M)**	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant metastasis
T_{IS}	Carcinoma *in situ* (Bowen disease, high-grade squamous intraepithelial lesion (HSIL), anal intraepithelial neoplasia II-II (AIN- II-III)	N1	Metastasis in perirectal lymph node(s)		
T1	Tumor 2 cm or less in greatest dimension	N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)		
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension	N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes		
T3	Tumor more than 5 cm in greatest dimension				
T4	Tumor of any size invades adjacent organ(s) (e.g., vagina, urethra, bladder); direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4				

Table 2. Stage grouping for anal canal cancer.

Stage grouping	T stage	N stage	M stage
Stage 0	T_{IS}	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T4	Any N	M0
	Any T	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

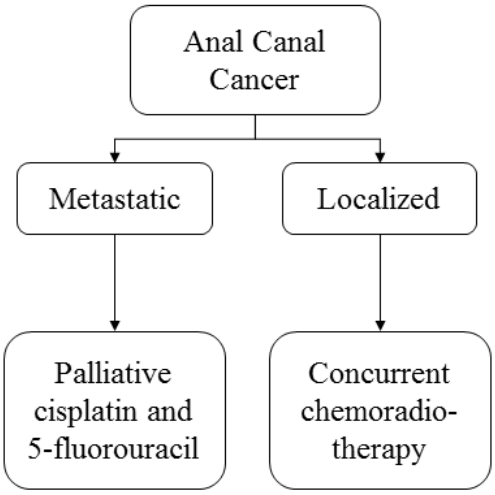

Figure 1. Flow diagram for management of anal canal cancer.

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CHOLANGIOCARCINOMA CLINICAL GUIDELINES

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Abstract

Guidelines for the evaluation and the medical and surgical management of cholangiocarcinoma cancer established by local cancer experts are presented in this report. The literature was reviewed and recommendations were categorized according to the stage of the disease using the American Joint Committee on Cancer (AJCC) TNM staging system 7th edition. The recommendations took all available supporting evidence into consideration and were graded accordingly. The guidelines represent the authors' view of the minimum recommendations for the management of cholangiocarcinoma in Saudi Arabia.

Cholangiocarcinoma (CC) is a rare cancer in Saudi Arabia. CC includes intrahepatic, perihilar, and distal extrahepatic bile duct cancers. Approximately 20% of all cases of CC are intrahepatic, 50–60% are perihilar, and 20% are distal extrahepatic tumors, whereas 5% of CC tumors are multifocal. The extent of perihilar cholangiocarcinoma (CC) can be described by the Bismuth-Corlette classification (Figure 1). All cases of cholangiocarcinoma cancer should be managed in a high-volume treatment center that offers expertise in surgical oncology. Biopsies should not be taken in cases of cholangiocarcinoma that are potentially resectable.

This report represents the first guidelines for CC developed by the Saudi Oncology Society in conjunction with other gastro-intestinal guidelines. The evidence adopted in these guidelines is rated at three levels: 1) Evidence level 1 (EL-1; highest level) includes data from phase III randomized trials or meta-analyses; 2) EL-2 (intermediate-level) includes data from good phase II trials or phase III trials with limitations; and 3) EL-3 (low-level) includes retrospective or observational data and/or expert opinion. This easy-to-follow grading system is convenient and allows the reader to accurately assess the applicability of the guideline in individual patients.[1]

1. **Anatomical classification[1-3] (Figure 1)**
   - 1.1. Type I: below confluence of left and right hepatic ducts.
   - 1.2. Type II: reaching confluence but not involving left or right hepatic ducts.
   - 1.3. Type III: occluding common hepatic duct and either right (IIIa) or left (IIIb) hepatic duct.
   - 1.4. Type IV: multicentric or bilateral intrahepatic segmental involvement or involving confluence and both right and left hepatic ducts.

2. **Pre-treatment evaluation**
   - 2.1. History and clinical examination.
   - 2.2. Blood count and liver and renal function.
   - 2.3. Cancer antigen 19-9 (CA19-9) level.
   - 2.4. Computed tomography (CT) scan of chest, abdomen, and pelvis.
   - 2.5. Magnetic resonance imaging (MRI) of liver when indicated.
   - 2.6. Endoscopic Retrograde Cholangiopancreatography/Magnetic resonance cholangiopancreatography (ERCP/MRCP) when indicated.
   - 2.7. Positron emission tomography (PET) CT scan when indicated.

3. **Surgical pathology report requirement.** The following parameters should be noted in all biliary cancer surgical pathology reports:
   - 3.1. Specimen submitted
   - 3.2. Procedure
   - 3.3. Tumor site
   - 3.4. Tumor size
   - 3.5. Histological type
   - 3.6. Histological grade
   - 3.7. Angiolymphatic invasion
   - 3.8. Perineural invasion
   - 3.9. Margin
   - 3.10. Tumor extent
   - 3.11. Lymph nodes

3.12. Additional findings
3.13. Pathological staging (pTNM)

4. Staging

The 2010 TNM American Joint Committee on Cancer (AJCC) pathological staging system (7th edition) will be used[2-4] (**Tables 1-6**).

5. Treatment (Figure 2)

5.1. Intrahepatic CC is resectable[5, 6]

5.1.1. Surgical resection:
5.1.1.1. Managed by segmental or lobe resection (EL-1).
5.1.1.2. Every effort should be made to achieve a 5-mm free margin.
5.1.2. Adjuvant therapy:
5.1.2.1. Negative margin and node negative disease: observation alone is appropriate[7-20] (EL-3).[7]
5.1.2.2. Microscopic margins (R1) or positive regional nodes: no EL-1 supporting a best approach; chemotherapy or observation are acceptable options (EL-3).

5.2. For perihilar CC, the Bismuth classification is a guide to the extent of surgery required (aim is tumor-free margin of >5 mm).

5.2.1. Surgical treatment is principally as follows[5, 6]:
5.2.1.1. Types I and II: en bloc resection of the extrahepatic bile ducts and gall bladder, regional lymphadenectomy, and Roux-en-Y hepaticojejunostomy (EL-1).
5.2.1.2. Type III: as above plus right or left hepatectomy (EL-2).
5.2.1.3. Type IV: not usually resectable but extended right or left hepatectomy might be feasible, depending on the biliary anatomy (EL-2).
5.2.2. Adjuvant therapy:
5.2.2.1. Negative margin (R0) and node negative disease: observation alone is appropriate (EL-3).[7-20]
5.2.2.2. Positive margin (R1) or positive regional nodes: no level[1] evidence for the best approach; chemotherapy, chemoradiation, or observation are acceptable options (EL-3).[7-20]
5.2.3. Distal CC:
5.2.3.1. Surgical resection.[5, 6]
5.2.3.2. Pancreatoduodenectomy (EL-1)
5.2.3.2.1. Aim to have greater than a 5-mm free margin adjuvant therapy.
5.2.3.2.2. Negative margin (R0) and node negative disease: observation alone is appropriate (EL-2).
5.2.3.2.3. Positive margin (R1) or positive regional nodes: no EL-1 supporting a best approach; chemotherapy, chemoradiation, or observation are acceptable options (EL-3). [7-20]

5.3. Metastatic disease

5.3.1. Palliative chemotherapy for patients with good performance status (PS 0–2) can be offered including gemcitabine and cisplatin combination chemotherapy (EL-1).[20]

5.3.2. No clear consensus exists regarding second-line therapy options including systemic chemotherapy (capecitabine or 5-FU and oxaliplatin or taxane-based therapy) or best supportive care (EL-3).

Table 1. TNM AJCC staging for perihilar cholangiocarcinoma, 7th edition.

Primary Tumor (T)		**Regional Lymph Nodes (N)**		**Distant Metastasis (M)**	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant metastasis
T_{IS}	Carcinoma *in situ* (intraductal tumor)	N1	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)		
T1	Tumor confined to the bile duct and extends up to the muscle layer or fibrous tissue	N2	Metastasis to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes		
T2a	Tumor invades beyond the bile duct wall to surrounding adipose tissue				
T2b	Tumor invades adjacent hepatic parenchyma				
T3	Tumor invades unilateral branches of the portal vein or hepatic artery				
T4	Tumor invades the main portal vein or its branches bilaterally, the common hepatic artery, the second-order biliary radicals bilaterally, the unilateral second-order biliary radicals with contralateral portal vein, or invasion includes hepatic artery involvement				

Table 2. Stage grouping for perihilar cholangiocarcinoma.

Stage grouping	**T stage**	**N stage**	**M stage**
Stage 0	T_{IS}	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
Stage IVB	Any T	Any N	M0

Abbreviations: T-stage, tumor stage; N-stage, node stage; M, metastases

Table 3. TNM AJCC staging for intrahepatic cholangiocarcinoma, 7th edition.

Primary Tumor (T)		**Regional Lymph Nodes (N)**		**Distant Metastasis (M)**	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant metastasis
T_{IS}	Carcinoma *in situ* (intraductal tumor)	N1	Regional lymph node metastasis		
T1	Solitary tumor without vascular invasion				
T2a	Solitary tumor with vascular invasion				
T2b	Multiple tumors, with or without vascular invasion				
T3	Tumor perforates the visceral peritoneum or involves local extrahepatic structures by direct invasion				
T4	Tumor with periductal invasion				

Table 4. Stage grouping for intrahepatic cholangiocarcinoma.

Stage grouping	**T stage**	**N stage**	**M stage**
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
	Any T	N1	M0
Stage IVB	Any T	Any N	M1

Abbreviations: T-stage, tumor stage; N-stage, node stage; M, metastases

Table 5. TNM AJCC staging for distal cholangiocarcinoma, 7th edition.

Primary Tumor (T)		**Regional Lymph Nodes (N)**		**Distant Metastasis (M)**	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant metastasis
T_{IS}	Carcinoma *in situ* (intraductal tumor)	N1	Regional lymph node metastasis		
T1	Tumor histologically confined to the bile duct				
T2	Tumor invades beyond the bile duct wall				
T3	Tumor invades the gallbladder, pancreas, duodenum, or other adjacent organs without involvement of the celiac axis or the superior mesenteric artery				
T4	Tumor involves the celiac axis or the superior mesenteric artery				

Table 6. Stage grouping for distal cholangiocarcinoma.

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

Abbreviations: T-stage, tumor stage; N-stage, node stage; M, metastases

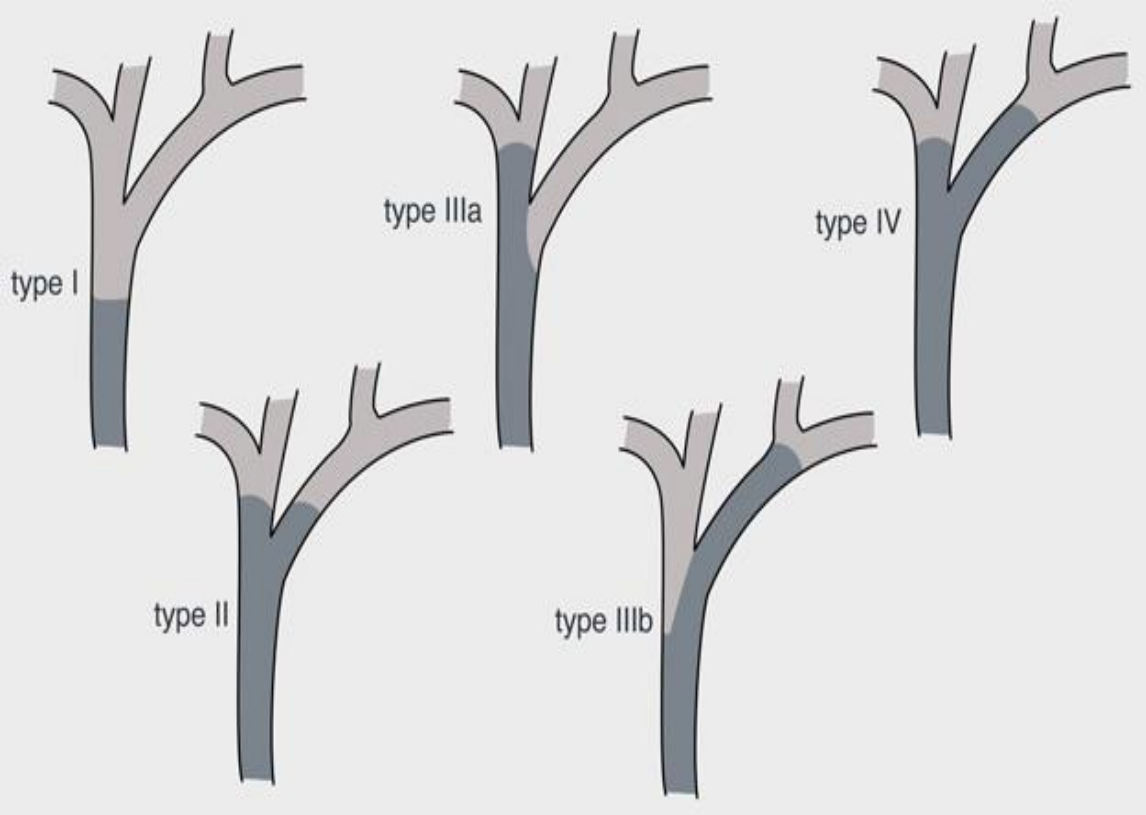

Figure 1. Bismuth-Corlette classification for perihilar cholangiocarcinoma.

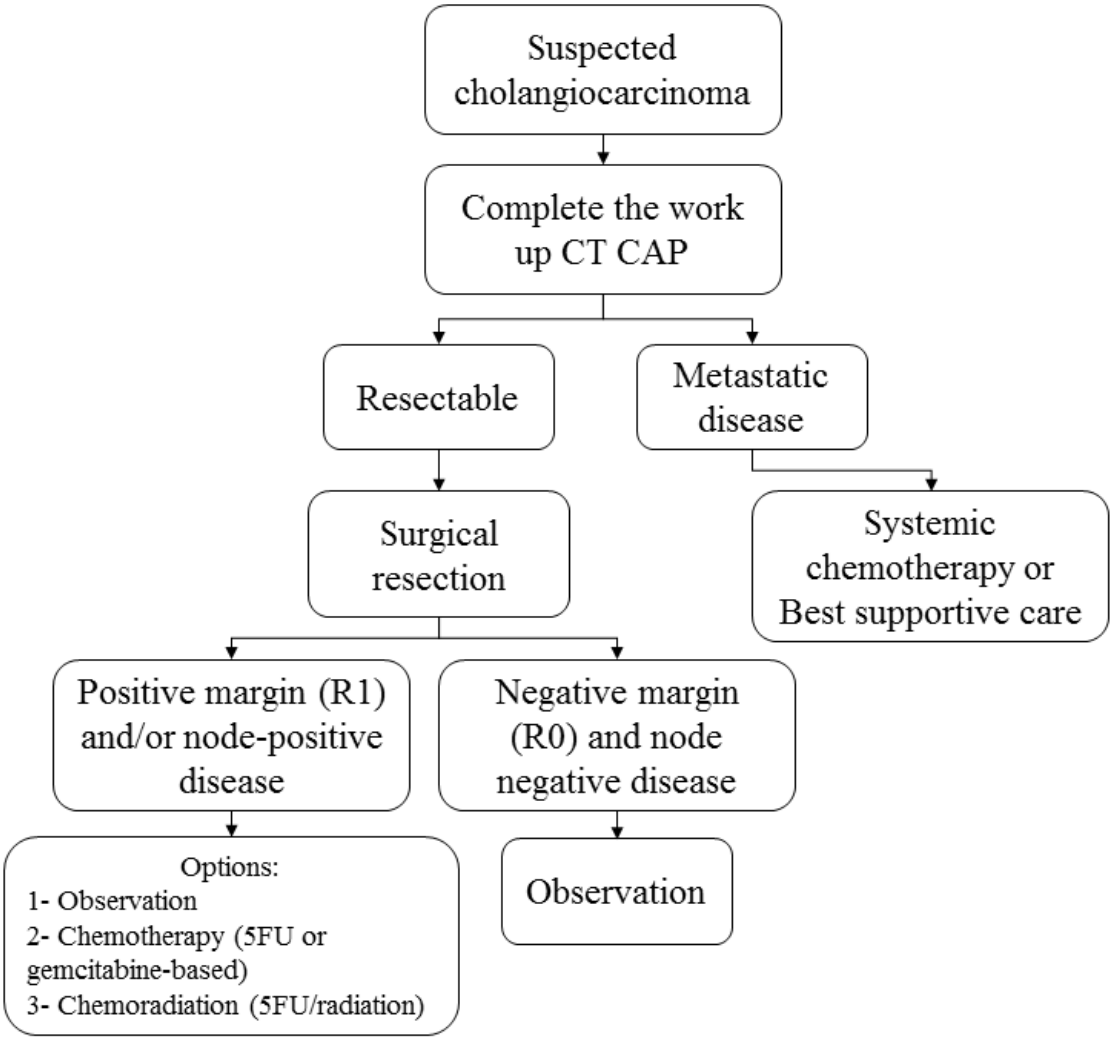

Figure 2. Flow diagram for the management of cholangiocarcinoma.
Abbreviations: CT: computed tomography; CAP: chest, abdomen, and pelvis, 5FU: 5-fluorouracil

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Abstract

Guidelines for the evaluation and the medical and surgical management of colorectal cancer established by local experts in all disciplines related to the field of colorectal cancer are presented in this report. The literature was reviewed and recommendations were categorized according to the stage of the disease using the American Joint Committee on Cancer (AJCC) TNM staging system 7th edition. The recommendations took all of the supporting evidence into consideration and were graded accordingly. The guidelines represent the authors' view of the minimum recommendations for the management of colorectal cancer in Saudi Arabia.

There were 1,387 cases of colorectal cancer accounting for 11.9% of all newly diagnosed cancer cases in year 2013 in Saudi Arabia. This cancer ranked the first among male and the third among female. It affected 736 (53.1%) males and 651 (46.9%) females with a male to female ratio of 113:100. The ASR males was 11.7/ 100,000 and for females 10.1/100,000.[1]

These guidelines represent the first update of the SOS guidelines developed initially in 2014, this time developed in conjunction with the Saudi Society for colon and rectal surgery. The evidence adopted in these guidelines is rated at three levels: 1) Evidence level 1 (EL-1; highest level) includes data from phase III randomized trials or meta-analyses; 2) EL-2 (intermediate-level) includes data from good phase II trials or phase III trials with limitations; and 3) EL-3 (low-level) includes from retrospective or observational data and/or expert opinion. This easy-to-follow grading system allows the reader to accurately assess the applicability of the guidelines in individual patients.[2] All colorectal cancer cases are preferably seen or discussed in a multidisciplinary form.

1. **Pre-treatment evaluation**
    - 1.1 Clinical examination, including rigid proctosigmoidoscopy for rectal cancer
    - 1.2 Blood count and liver and renal function tests
    - 1.3 Chest X-ray
    - 1.4 Carcinoembryonic antigen (CEA) level
    - 1.5 Computed tomography (CT) scan of abdomen and pelvis (including the chest in rectal cancer cases)
    - 1.6 Full length colonoscopy
    - 1.7 Transrectal ultrasound and magnetic resonance imaging (MRI) for rectal cancer

    Rectal cancer will be defined as tumors within 15 cm of the anal verge on rigid proctosigmoidoscopy or below the sacral promontory on a CT scan.
2. **Surgical pathology report requirements.** The following parameters should be mentioned in all surgical pathology reports of colorectal cancer:[3]
    - 2.1 Specimen
    - 2.2 Procedure
    - 2.3 Specimen length
    - 2.4 Tumor site
    - 2.5 Tumor size
    - 2.6 Macroscopic tumor perforation
    - 2.7 Macroscopic intactness of mesorectum
    - 2.8 Histological type
    - 2.9 Histological grade
    - 2.10 Histological features suggestive of microsatellite instability
    - 2.11 Microscopic tumor extension
    - 2.12 Margins
    - 2.12 Treatment effect (applicable to carcinomas treated with neoadjuvant therapy)
    - 2.12 Vascular (large vessel) invasion (V)
    - 2.13 Lymphatic (small vessel) invasion (L)

2.14 Discontinuous extramural extension (irregular tumor nodules in pericolorectal adipose tissue without histologic evidence of residual lymph node)
2.15 Perineural invasion
2.16 Type of pre-existing polyp from which and invasive carcinoma arose
2.17 Pathological staging (pTNM)
2.18 RAS gene mutation in patients with metastatic disease

3. Staging

The 2010 American Joint Committee on Cancer (AJCC) TNM pathological staging system (7th edition) will be used[4] (**Table 1**).

4. Treatment

5. Clinically localized resectable colon cancer (Figure 1):

5.1.1. Surgical resection according to location:

5.1.1.1. Right colonic cancer includes tumors in the cecum, ascending colon, and hepatic flexure, and is treated with a right hemicolectomy (EL-3).

5.1.1.2. Left colonic cancer includes tumors in the transverse colon, splenic flexure, and descending colon, and is treated with a left partial/left hemicolectomy (EL-2).

5.1.1.3. Sigmoid colon cancer includes tumors located in the totally peritonealized aspect of the colon between the descending colon and the sacral promontory and is treated with a sigmoid colectomy (EL-2).

5.1.1.4. Laparoscopic-assisted resection is equivalent to open resection[5] (EL-1).

5.1.1.5. A proximal and distal 5 cm margin is needed for colonic cancer colectomies[6] (EL-2).

5.1.1.6. Surgery should be performed by a colorectal surgeon.

5.1.2. Stage I: no adjuvant therapy required.

5.1.3. Stage II (Node negative): treatment will depend on risk group:

5.1.3.1. High risk stage II (presence of one or more risk factors): consider administering adjuvant chemotherapy with fluoropyrimidine for 6 months

5.1.3.2. Average risk stage II: adjuvant chemotherapy is not recommended

5.1.3.3. There is a lack of adequate evidence to support routine mismatch repair (MMR) testing

High risk factors:

- T4 lesion
- Less than 12 lymph nodes removed
- Lymphovascular or perineural invasion
- Obstruction
- Perforation
- Poorly differentiated histology
- Positive margin (if not considered for re-resection)

5.1.4. Stage III (Node positive): Adjuvant FOLFOX-6 for 6 months (12 cycles)[7] (EL-1), or alternatively eight cycles of XELOX regimen (EL-1).[8] Elderly patients and those with a performance status (PS) of 3 can be offered single-agent capecitabine for 6 months.[9]

5.1.5. Follow up: clinical examination and CEA level evaluation every 6 months for 5 years. CT scan annually for the first 3 years in node positive patients (EL-3). A colonoscopy is recommended within 6 months if not performed preoperatively and again after 3 years, then again every 5 years if normal.

5.2. Clinically localized resectable rectal cancer (Figure 2):

5.2.1. The surgical resection procedure will depend on the location of the tumor (anterior resection *vs* abdominoperineal resection). The following should be ascertained:

- **5.2.1.1.** Rectal cancer includes tumors between the dentate line in the anal canal and the sacral promontory.
- **5.2.1.2.** Surgery should be done by a colorectal surgeon.
- **5.2.1.3.** Total mesorectal excision should be performed.[10]
- **5.2.1.4.** For upper third rectal tumors, a distal mesorectal margin of 5 cm should be excised (however, 2 cm distal margin is needed for lower third rectum)[11] (EL-1).
- **5.2.1.5.** Intraoperative margins of less than 2 cm dictate the need for frozen sections to confirm negative status.
- **5.2.1.6.** The distal doughnut is not considered part of the 2-cm distal margin in rectal cancer.
- **5.2.1.7.** Patients with a compromised lumen (does not allow intubation by 20 mm rigid proctosigmoidoscope) should have an elective stoma (outside the radiation field) prior to starting pre-operative radiation.

5.2.2. Endo-anal or transsacral resection will be offered to selected patients exhibiting *all* of the following factors:[12]

- **5.2.2.1.** Tumor up to 8 cm from anal verge. For tumors located more than 8 cm, trans-anal endoscopic microsurgery is feasible.
- **5.2.2.2.** Tumor less than 3 cm in maximum diameter.
- **5.2.2.3.** Freely mobile tumors.
- **5.2.2.4.** T1 on endoscopic ultrasound or MRI.
- **5.2.2.5.** Node negative on MRI +/- endoscopic ultrasound.
- **5.2.2.6.** Well or moderately differentiated tumors.
- **5.2.2.7.** Absence of lymphovascular or perineural invasion.
- **5.2.2.8.** A 3-mm negative margin.

In the event that any of the above are not present, surgery should be offered. If surgery is not an option, adjuvant chemoradiotherapy should be offered (EL-3).

5.2.3. All clinically T3–4 or N positive lesions will receive concurrent pre-operative chemoradiotherapy. The irradiation will consist of 5040 cGy in 28 fractions and the chemotherapy will consist of capecitabine or infusional 5-Fluorouracil[13] (EL-1). Surgery will be performed 6–8 weeks after the end of radiation therapy. Short course radiation of 2500 cGy in five fractions with surgical resection after 1 week can be considered if sphincter saving is not an option[14] (EL-1).

5.2.4. Patients with pre-operative clinical stage T3 or 4 and or node positive disease who received pre-operative chemoradiotherapy will receive post-operative adjuvant chemotherapy according to the pathological stage as follows:
5.2.4.1. Pathological stage ypT0–2 N0: No adjuvant chemotherapy[15] (EL-1).
5.2.4.2. Pathological stage ypT3–4 or N+: 6 cycles of adjuvant XELOX or eight cycles of adjuvant FOLFOX can be considered (EL-1).[16, 17]

5.2.5. Adjuvant therapy for early stage rectal cancer (for individuals who did not receive pre-operative treatment) will be as follows:
5.2.5.1. T2 tumor: no further therapy.
5.2.5.2. T3–4 or positive nodes will receive adjuvant chemoradiotherapy (same as pre-op) followed by adjuvant chemotherapy with either single-agent capecitabine, infusional 5-Fluorouracil and leucovorin[18] (EL-1), or XELOX/FOLFOX for 4 months[19, 20] (EL-3).

5.2.6. Follow up: will be the same as for colon cancer.

5.3. Locally advanced unresectable or metastatic colon or rectal cancer (Figure 3):

5.3.1. Surgery:
5.3.1.1. Patients with locally advanced or metastatic colon or rectal cancer and a compromised colonic lumen should have a colonic stent (for colon cancer), a stoma, or resection (for colon or rectal cancer) prior to treatment (EL-3).
5.3.1.2. Patients with liver-only metastasis or lung-only metastasis can be considered for resection (metastasectomy) up front or after a period of pre-operative chemotherapy if initially unresectable. The decision for resectability will be made by the operating surgeon (EL-2). Following resection of metastatic liver or lung lesions, patients should receive adjuvant chemotherapy with FOLFOX or XELOX for a total of 6 months (including pre-operative).[21] Pre-operative chemotherapy options if metastases are unresectable include:
5.3.1.2.1. FOLFIRI + cetuximab[22] (EL-1) or FOLFOX + panitumumab[23] if RAS wild type (EL-1).
5.3.1.2.2. FOLFOXIRI (regardless of RAS status)[24] (EL-1).
5.3.1.2.3. FOLFOX, FOLFIRI, or XELOX (+ bevacizumab) if RAS mutant.[25]

5.3.2. Palliative chemotherapy:
5.3.2.1. Patients with locally advanced unresectable rectal tumors can be offered palliative systemic chemotherapy (see below) followed by chemoradiotherapy and surgery if the tumor becomes potentially resectable (EL-3).
5.3.2.2. Patients with unresectable metastatic disease will be treated with chemotherapy with palliative intent**.** The option of chemotherapy will depend on multiple factors including patient age, performance status, co-morbid conditions, and RAS mutational status.
5.3.2.3. Palliative chemotherapy options for patients with good performance status (PS 0–2) include one of the following:
5.3.2.3.1. FOLFOX, FOLFIRI, or XELOX (+ bevacizumab)[26-29] (EL-1) regardless of RAS status (EL-1).

5.3.2.3.2. FOLFIRI or FOLFOX + cetuximab (for wild type RAS tumors)[22, 29] (EL-1).

5.3.2.3.3. FOLFOX + panitumumab[30] (EL-1).

5.3.2.3.4. Patients who might not tolerate oxaliplatin- or irinotecan-containing regimens can be considered for single-agent capecitabine +/- bevacizumab.[31]

5.3.3. Duration of palliative therapy: patients can continue chemotherapy until disease progression or until indication of unacceptable toxicity. It is preferable to have patients on an oxaliplatin-containing regimen stop oxaliplatin after 6 cycles and continue with another medication (LV5FU2 or capecitabine + bevacizumab). Chemotherapy-free intervals (chemotherapy holidays) can also be considered[32-34] (EL-1)**.**

5.3.4. Second-line therapy: patients who progress on first-line chemotherapy and exhibit good PS will receive second-line therapy depending on the first-line agents used with the following options:

5.3.4.1. Re-introduction of oxaliplatin if the patient is on maintenance capecitabine or LV5FU2 +/- bevacizumab[34] (EL-1).

5.3.4.2. FOLFIRI or single-agent irinotecan if the first-line therapy was oxaliplatin-based[26, 35] (EL-1).

5.3.4.3. FOLFOX/XELOX if the first-line therapy is irinotecan-based[26, 36] (EL-1).

5.3.4.4. Consider adding one of the following targeted therapies to the above chemotherapy:

5.3.4.4.1. Cetuximab or panitumumab if FOLFIRI or single-agent irinotecan is used in a tumor with wild type RAS status[37, 38] (EL-1).

5.3.4.4.2. Bevacizumab to any of the above chemotherapy regimens regardless of RAS status[39] (EL-1).

5.3.4.4.3. Aflibercept or ramucirumab if FOLFIRI is used as a second-line therapy and regardless of the RAS status[40] (EL-1).

5.3.5. Third-line therapy: patients failing second-line therapy and those who have good PS and a wild type RAS tumor can be offered cetuximab and irinotecan, cetuximab alone, or panitumumab alone if the drugs were not previously administered[41-43] (EL-1).

5.3.6. Fourth-line therapy: patients who progress despite receiving oxaliplatin, irinotecan, fluoropyrimidine, bevacizumab, and cetuximab, or panitumumab have the option of best supportive care or regorafenib and BSC[44] (EL-1).

Table 1. TNM AJCC staging for colorectal cancer, 7th edition.

Primary tumor (T)		**Regional lymph nodes (N)**		**Distant metastasis (M)**	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant metastasis
Tis	Carcinoma in situ; intraepithelial or invasion of lamina propria	N1	Metastasis in 1-3 regional lymph nodes	M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, non-regional node
T1	Tumor invades submucosa	N1a	Metastasis in 1 regional lymph node	M1b	Metastases in more than one organ/site or the peritoneum
T2	Tumor invades muscularis propria	N1b	Metastasis in 2-3 regional lymph nodes		
T3	Tumor invades through the muscularis propria into the pericolorectal tissues mesenteric artery	N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis		
T4a	Tumor penetrates to the surface of the visceral peritoneum	N2	Metastasis in 4 or more lymph nodes		
T4b	Tumor directly invades or is adherent to other organs or structures	N2a	Metastasis in 4-6 regional lymph nodes		
		N2b	Metastasis in 7 or more regional lymph nodes		

Table 2. Stage grouping for colorectal cancer.

Stage grouping	**T stage**	**N stage**	**M stage**
Stage 0	T_{IS}	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
Stage IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
	T4b	N1-N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

Abbreviations: T-stage, tumor stage; N-stage, node stage; M, metastases

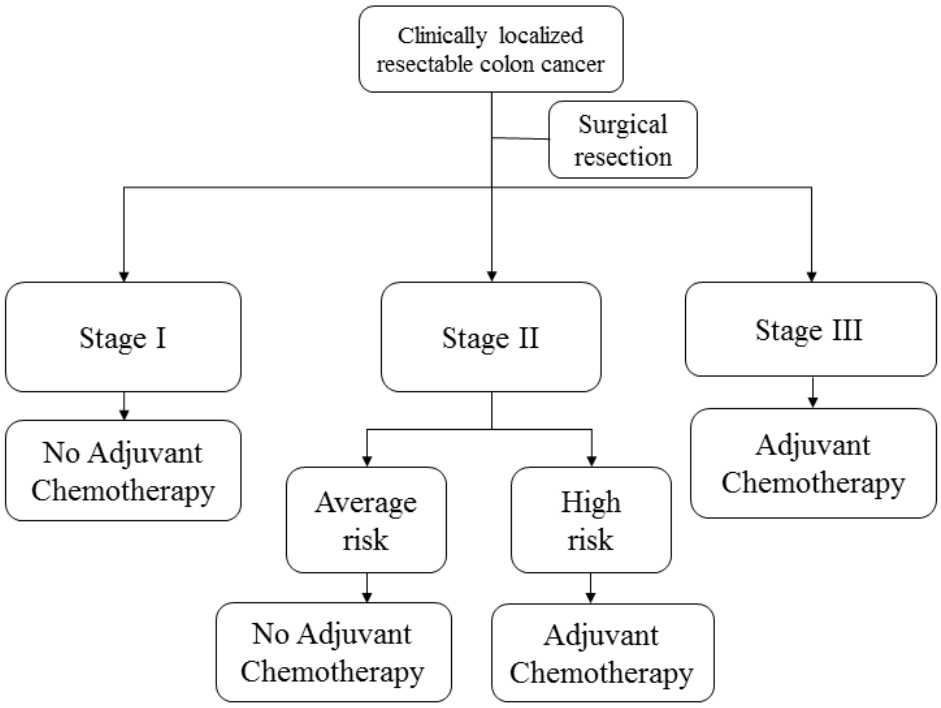

Figure 1. Flow diagram for management of clinical localized resectable colon cancer.

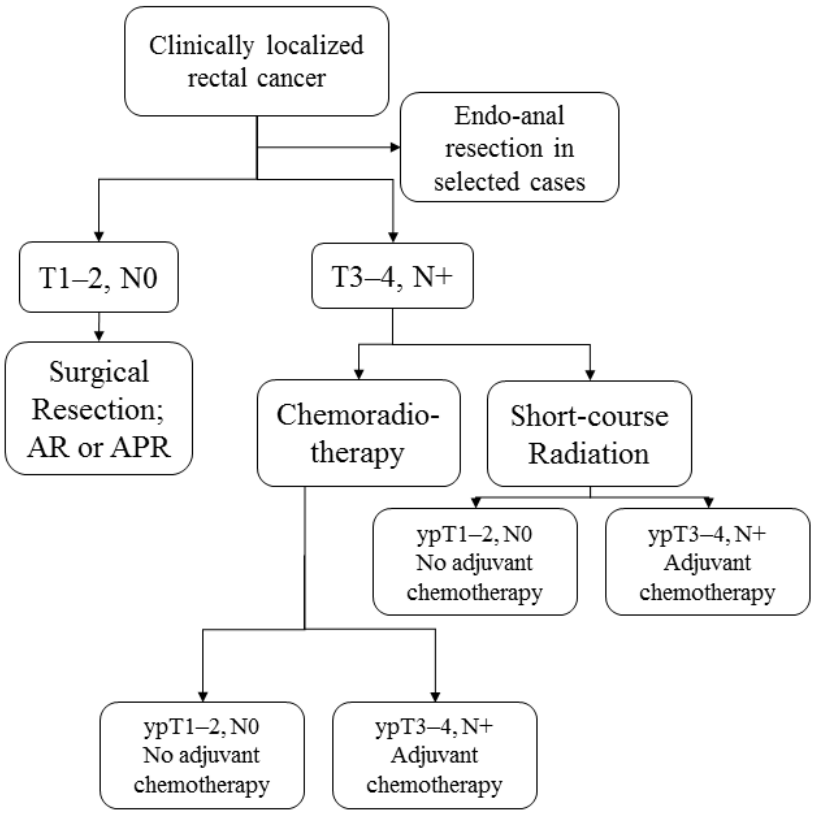

Figure 2. Flow diagram for management of clinically localized rectal cancer.
Abbreviations: AR: Anterior resection; APR: Abdominoperineal resection

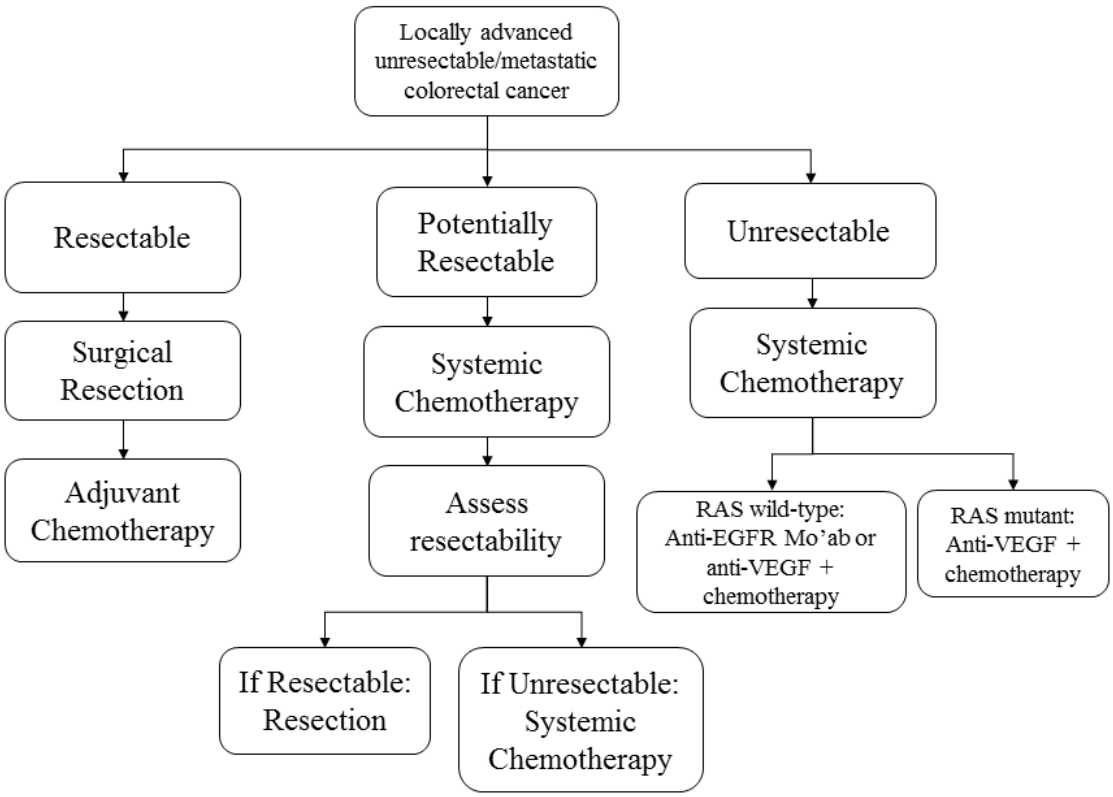

Figure 3. Flow diagram for management of locally advanced unresectable/metastatic colorectal cancer.

Abbreviations: Mo'ab: monoclonal antibodies; Anti-EGFR: anti- epidermal growth factor receptors; Anti-VEGF: anti-vascular endothelial growth factor

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ESOPHAGEAL CANCER CLINICAL GUIDELINES

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Abstract

The following guidelines for the treatment of esophageal cancer include all of the most recent information regarding esophageal cancer and are presented in a multidisciplinary manner. All valid trial data and supporting evidence has been discussed by the gastrointestinal tract oncology group. Additionally, an emphasis is placed on the pathological distinction between squamous cell carcinomas and adenocarcinoma as well as on the location of the cancer. The radiotherapy dose, especially in cervical squamous cell carcinoma of the esophagus, is also discussed and is included in the guidelines. Finally, additional targeted therapies are included in the guidelines and a distinction is made between the salvageable recurrences in the follow-up.

In 2013, 115 case of esophageal cancer were diagnosed in Saudi Arabia, accounting for 1% of all cancers for that year.[1] The age-standardized incidence rate was 1.1/100,000 for males and 0.8/100,000 for females.[1] A committee of experts in the medical and surgical treatment of esophageal cancer was established under the supervision of the Saudi Oncology Society (SOS). The evidence adopted in these guidelines is rated at three levels: 1) Evidence level-1 (EL-1; highest level includes data from phase III randomized trials or meta-analyses; 2) EL-2 (intermediate-level) includes data from good phase II trials or phase III trials with limitations; and 3) EL-3 (low-level) includes retrospective or observational data and/or expert opinion. This easy-to-follow grading system is convenient and allows the reader to accurately assess the applicability of the guidelines in individual patients.[2] Ultimately, all esophageal cancer cases are preferably seen or discussed in a multidisciplinary form.

1. **Pre-treatment evaluation**
    - 1.1. Clinical examination.
    - 1.2 Blood count and liver and renal function tests.
    - 1.3 Barium swallow test and surgeon opinion.
    - 1.4 Upper gastrointestinal (GI) endoscopy and biopsy. Multiple biopsies are preferred.
    - 1.5 Computed tomography (CT) scan of the chest, abdomen, and pelvis.
    - 1.6 Endoscopic ultrasound (EUS) ± biopsy.
    - 1.7 Positron emission tomography (PET) CT in patients who lack evidence of distant metastasis on CT scan.
    - 1.8 Bronchoscopy: preoperative bronchoscopy with biopsy and brush cytology for patients with locally advanced non-metastatic tumors that are located at or above the level of the carina.
    - 1.9 Laparoscopy (optional): if no evidence of metastatic (M1) disease is noted following radiological examination and the tumor is at the gastroesophageal (GE) junction. Biopsy confirmation is mandatory.
    - 1.10 Human epidermal growth factor receptor 2 (Her-2) testing if metastatic adenocarcinoma is documented.
    - 1.11 Nutritional assessment (in preoperative setting): consider nasogastric tube or J tube (percutaneous endoscopic gastrostomy is not recommended).

2. **Surgical pathology report requirement.** The following parameters should be mentioned in all surgical pathology reports of esophageal cancer:[3]
    - 2.1 Clinical history
    - 2.2 Esophagus: endoscopic resection, esophagectomy, or esophagogastrectomy
    - 2.3 Specimen
    - 2.4 Procedure
    - 2.5 Tumor site
    - 2.6 Relationship of tumor to esophagogastric junction
    - 2.7 Tumor size
    - 2.8 Histological type
    - 2.9 Histological grade
    - 2.10 Microscopic tumor extension
    - 2.11 Margins
    - 2.12 Treatment effect

2.13 Lymph-vascular invasion
2.14 Perineural invasion
2.15 Pathological staging (pTNM)
2.16 Additional pathological findings
2.17 Ancillary studies (Her-2 testing if metastatic adenocarcinoma is documented)

3. Staging

The 2010 Union for International Cancer Control (UICC)/American Joint Commission on Cancer (AJCC) pathological staging system will be used[4] (**Tables 1–4**).

4. Treatment (Figure 1)

4.1 Clinically localized resectable disease. Treatment will depend on the clinical status of the patient and the resectability of the tumor.

4.1.1 Medically fit and resectable disease:

4.1.1.1 Stage T_{IS} (*in situ*), N0: Endoscopic mucosal resection or ablation[5] (EL-3).

4.1.1.2 Stage T1a, N0: Endoscopic mucosal resection[6] (EL-2) or esophagectomy[7] (EL-2).

4.1.1.3 Stage T1b, N0: Esophagectomy (for non-cervical esophagus) (EL-1) and chemoradiation[8, 9] (for cervical esophagus) with higher doses of radiotherapy is recommended.

4.1.1.4 For stage T2 or higher (except T4b): Any N or stage T1-4aN+: options are:

4.1.1.4.1 Preoperative chemoradiotherapy with 41.4–50.4 Gy of external beam radiotherapy and concurrent chemotherapy (EL-1) [regimen options include two courses of cisplatin and 5-fluorouracil (5-FU) and 50.4 Gy of radiotherapy[10] or low-dose weekly carboplatin plus paclitaxel regimen and 41.4 Gy].[11]

4.1.1.4.2 Preoperative/perioperative chemotherapy for adenocarcinoma of distal esophagus or gastroesophageal junction (GEJ; EL-1) [regimen options include epirubicin, cisplatin, and fluorouracil (ECF) chemotherapy, the equivalent used in The Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial,[12] infusional 5-FU plus cisplatin, or the equivalent used in the Federation Nationale des Centres de Lutte contre le Cancer/Federation Francophone de Cancerologie Digestive trial].[13]

4.1.1.4.3 Esophagectomy with postoperative adjuvant chemoradiotherapy for patients with adenocarcinoma, node-positive disease or a T2 or higher primary tumor stage[14] (EL-3). Adjuvant chemotherapy alone can also be used if radiotherapy is contraindicated.[15]

4.1.1.4.4 Definitive chemoradiation (for cervical cancer).[16] If local disease persists, perform a salvage esophagectomy if possible.

4.1.2 Options for patients that are medically unfit for surgery or have unresectable T4 (T4b) disease include:

4.1.2.1. Definitive concurrent chemoradiotherapy.[16] The radiation dose is 45–50.4 Gy with a preference for 50.4 Gy.

4.1.2.2. Palliative chemotherapy (see metastatic disease).

4.1.2.3. Palliative radiotherapy if patient cannot tolerate chemotherapy.

4.1.2.4. Best supportive care if patient cannot tolerate chemotherapy or radiotherapy.

4.1.3 Radiation technique: 3D conformal/intensity-modulated radiation therapy (IMRT)/Volumetric Arc Therapy (VMAT) techniques should be used for modern treatment planning to minimize toxicities to adjacent vital organs (heart, lung, spinal cord, or liver).[17]

4.1.4 Surgical approach:

4.1.4.2 The surgical approach should be based upon the anatomic tumor location.

4.1.4.3 Patients with Siewert type I tumors are not candidates for a transabdominal approach to surgical resection. The standard surgical approach is a transthoracic *en bloc* esophagectomy and partial gastrectomy with 2-field lymphadenectomy.[18]

4.1.4.4 For the majority of Siewert type II and III tumors, total gastrectomy with a transabdominal/transhiatal resection of the distal esophagus with lymphadenectomy of the lower mediastinum and the abdominal D2 nodal compartment is adequate.[19]

4.1.4.5 The surgical therapy does not differ in patients who have or have not undergone induction therapy. For most thoracic esophageal cancer resections, a total thoracic esophagectomy with cervical esophagogastrectomy, radical 2-field lymph node dissection, and jejunostomy feeding tube placement is suggested.[20] (EL-2)

4.1.4.6 A tri-incisional approach is preferred because it consists of an initial right posterolateral thoracotomy (or a thoracoscopic approach for the mobilization of the intrathoracic portion of the esophagus and node dissection in centers with expertise in these techniques) followed by laparotomy to obtain complete esophageal dissection and to mobilize the gastric conduit, en bloc resection of both the mediastinal and the upper abdominal lymph nodes, and a left neck incision and cervical anastomosis.[21]

4.1.4.7 A minimally invasive esophagectomy is considered a second option if expertise is available, the tumor is small, and adequate oncological resection is possible[22] (EL-2).

4.2 Advanced unresectable or metastatic disease. Treatment will consist of palliative chemotherapy:

4.2.1 Docetaxel, cisplatin,[23] and infusional 5-FU (DCF),[24] or epirubicin, oxaliplatin and capecitabine (EOX)[25] combinations are the standard regimens for first-line treatment (EL-1). Alternative regimens include:

4.2.2 Cisplatin/capecitabine[26] or cisplatin/5FU.[27]

4.2.3 Leucovorin and oxaliplatin (FOLFOX) regimen and 5-FU.[28]

4.2.4 The addition of trastuzumab to any of the above regimens (except ECF/EOX) in GEJ adenocarcinoma with a positive Her-2 test (defined by 3+ immunohistochemical staining or florescent *in-situ* hybridization positivity)[29] (EL-1).

4.2.5 For the elderly, options include single agent capecitabine, leucovorin modulated fluorouracil, or best supportive care[30] (EL-3).

4.2.6 Second-line chemotherapy: There is no standard approach for second-line therapy after failure of the first-line regimen. For patients who retain an adequate performance status, utilization of other active agents not used in the first-line

regimen is a reasonable approach, either in combination or as serial single agents. Quality of life and minimization of side effects are key considerations when choosing the therapeutic approach. Options include single agent irinotecan or taxanes.[31]

4.3. Patients who are fit enough can receive ramucirumab plus weekly paclitaxel, but ramucirumab monotherapy is an acceptable alternative for metastatic GEJ.[32]

4.4 Follow-Up. For those patients who are potential candidates for an early 'salvage surgery' after (failing) endoscopic resection or definitive chemoradiation, follow-up is indicated. However, there is no evidence that regular follow-up after initial therapy will impact the outcome. In general, follow-up visits should concentrate on symptoms, nutrition, and psycho-social support (EL-3).

Table 1. TNM AJCC staging of esophageal squamous cell cancer (SCC), 7th edition.

Primary tumor (T)*		**Regional lymph nodes (N)Δ**		**Distant metastasis (M)**		**Histological grade (G)**	
TX	Primary tumor cannot be assessed	NX	Regional lymph node(s) cannot be assessed	M0	No distant metastasis	GX	Grade cannot be assessed - stage grouping as G1
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant metastasis	G1	Well differentiated
T_{IS}	High-grade dysplasia¶	N1	Metastasis in 1–2 regional lymph nodes			G2	Moderately differentiated
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa	N2	Metastasis in 3–6 regional lymph nodes			G3	Poorly differentiated
T1a	Tumor invades lamina propria or muscularis mucosae	N3	Metastasis in seven or more regional lymph nodes			G4	Undifferentiated - stage grouping as G3 squamous
T1b	Tumor invades submucosa						
T2	Tumor invades muscularis propria						
T3	Tumor invades adventitia						
T4	Tumor invades adjacent structures						
T4a	Resectable tumor invading pleura, pericardium, or diaphragm						
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.						

Note: cTNM is a clinical classification and pTNM is a pathological classification.
* = At least the maximal dimension of the tumor must be recorded and multiple tumors require the T(m) suffix
Δ = Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastasis

¶ = High-grade dysplasia includes all noninvasive neoplastic epithelia that were formerly called carcinoma *in situ*, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.

Table 2. Stage grouping for esophageal squamous cell carcinoma.◊

Stage	**T**	**N**	**M**		**Tumor location** §
Stage 0	Tis (HGD)	N0	M0	1, X	Any
Stage IA	T1	N0	M0	1, X	Any
Stage IB	T1	N0	M0	2-3	Any
	T2-3	N0	M0	1, X	Lower, X
Stage IIA	T2-3	N0	M0	1, X	Upper, middle
	T2-3	N0	M0	2-3	Lower, X
Stage IIB	T2-3	N0	M0	2-3	Upper, middle
	T1-2	N1	M0	Any	Any
Stage IIIA	T1-2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
Stage IIIB	T3	N2	M0	Any	Any
Stage IIIC	T4a	N1-2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
Stage IV	Any	Any	M1	Any	Any

◊ = Or mixed histology including a squamous component or NOS

§ = The location of the primary cancer site is defined by the position of the upper (proximal) edge of the tumor in the esophagus

American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.

Table 3. TNM AJCC staging of esophageal and esophagogastric junction (EGJ) adenocarcinoma, 7th edition.

Primary tumor (T)*		**Regional lymph nodes (N)Δ**		**Distant metastasis (M)**		**Histological grade (G)**	
TX	Primary tumor cannot be assessed	NX	Regional lymph node(s) cannot be assessed	M0	No distant metastasis	GX	Grade cannot be assessed - stage grouping as G1
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant metastasis	G1	Well-differentiated
Tis	High-grade dysplasia¶	N1	Metastasis in 1–2 regional lymph nodes			G2	Moderately differentiated
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa	N2	Metastasis in 3–6 regional lymph nodes			G3	Poorly differentiated
T1a	Tumor invades lamina propria or muscularis mucosae	N3	Metastasis in seven or more regional lymph nodes			G4	Undifferentiated - stage grouping as G3 squamous
T1b	Tumor invades submucosa						
T2	Tumor invades muscularis propria						
T3	Tumor invades adventitia						
T4	Tumor invades adjacent structures						
T4a	Resectable tumor invading pleura, pericardium, or diaphragm						
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.						

Note: cTNM is a clinical classification and pTNM is a pathological classification.

* = At least the maximal dimension of the tumor must be recorded and multiple tumors require the T(m) suffix

¶ = High-grade dysplasia includes all noninvasive neoplastic epithelia that was formerly called carcinoma *in-situ*, which is a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract
Δ = The total number of regional nodes sampled and total number of reported nodes with metastasis must be recorded
American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.

Table 4. Stage grouping for esophageal and esophagogastric adenocarcinoma.

Stage	T	N	M	Grade
Stage 0	T_{IS} (HGD)	N0	M0	1, X
Stage IA	T1	N0	M0	1-2, X
Stage IB	T1	N0	M0	3
	T2	N0	M0	1-2, X
Stage IIA	T2	N0	M0	3
Stage IIB	T3	N0	M0	Any
	T1-2	N1	M0	Any
Stage IIIA	T1-2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
Stage IIIB	T3	N2	M0	Any
Stage IIIC	T4a	N1-2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
Stage IV	Any	Any	M1	Any

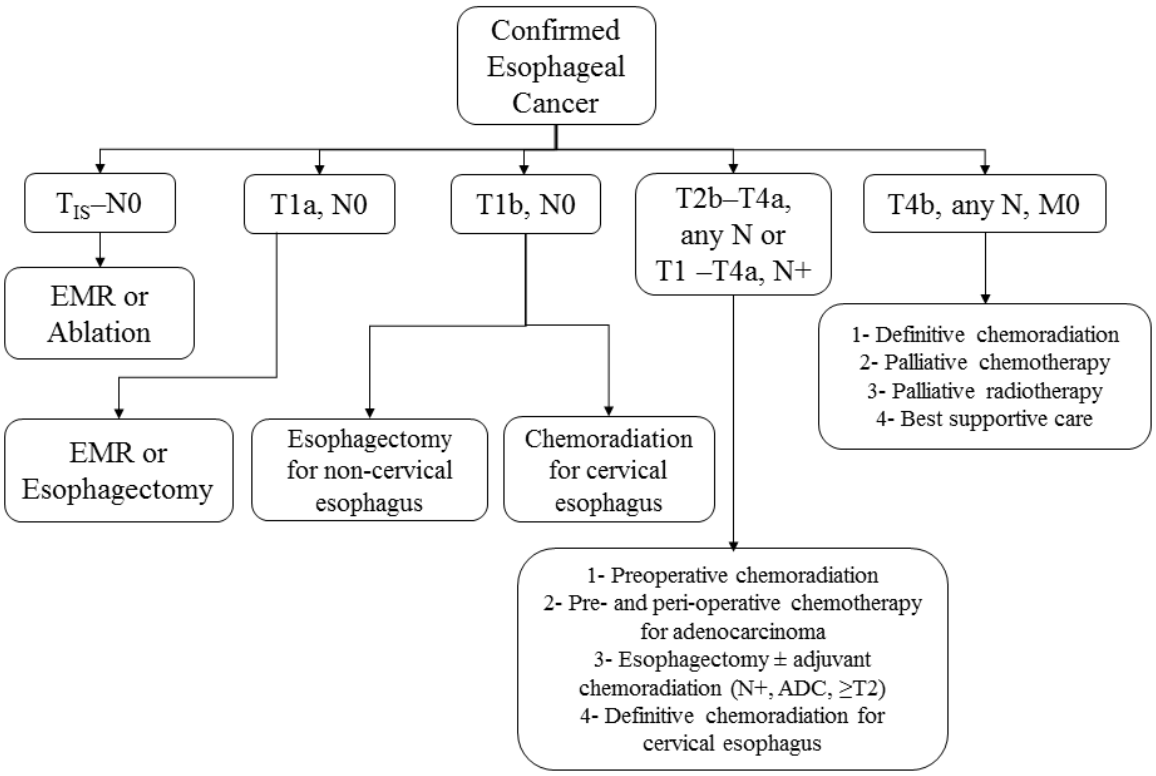

Figure 1. Flow diagram for the management of esophageal cancer.
Abbreviations: EMR: Endoscopic mucosal resection; ADC: adenocarcinoma

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Abstract

Guidelines for the evaluation and the medical and surgical management of gallbladder cancer established by local experts in the field of gallbladder cancer are presented in this report. The literature was reviewed and recommendations were categorized according to the stage of the disease using the American Joint Committee on Cancer (AJCC) TNM staging system 7th edition. The recommendations took all of the supporting evidence into consideration and were graded accordingly. The guidelines represent the authors' view of the minimum recommendations for the management of gallbladder cancer in Saudi Arabia.

Gallbladder cancer is a rare cancer in Saudi Arabia, with an annual incidence rate in 2013 of 1.7/100,000 in female patients (median: 60 years, total: 97 cases) and a 1.3 /100,000 incidence rate (median: 70 years, total: 77 cases) in males.[1] All gallbladder cancer cases should be managed in a high volume center that offers expertise in surgical oncology and potentially resectable gall bladder masses should not be biopsied.

This report represents the first guidelines for gallbladder cancer developed by the Saudi Oncology Society in conjunction with other gastro-intestinal guidelines. The evidence adopted in these guidelines is rated at three levels: 1) Evidence level-1 (EL-1; highest level) involves data from phase III randomized trials or meta-analyses; 2) EL-2 (intermediate-level) involves data from good phase II trials or phase III trials with limitations; 3) EL-3 (low-level) involves retrospective or observational data and/or expert opinion. This easy-to-follow grading system is convenient and allows the reader to accurately assess the applicability of the guidelines in individual patients.

1. **Pre-treatment evaluation**

1.1 History and clinical examination.
1.2 Blood count and liver and renal function.
1.3 Cancer antigen 19-9 (CA19-9) level.
1.4 Computed tomography (CT) scan of chest, abdomen, and pelvis.
1.5 Magnetic resonance imaging (MRI) of liver, if indicated.
1.6 Endoscopic retrograde cholangiopancreatography (ERCP)/Magnetic resonance cholangiopancreatography (MRCP), if indicated.
1.7 Positron emission tomography (PET) scan, optional.

2. **Surgical pathology report requirement.** The following parameters should be mentioned in all surgical pathology reports of biliary cancer[2]:
   2.1 Specimen submitted
   2.2 Procedure
   2.3 Tumor site
   2.4 Tumor size
   2.5 Histological type
   2.6 Histological grade
   2.7 Angiolymphatic invasion
   2.8 Perineural invasion
   2.9 Margins
   2.10 Tumor extent
   2.11 Lymph nodes
   2.12 Additional findings
   2.13 Pathological Staging

3. **Staging**

The 2010 TNM American Joint Committee on Cancer (AJCC) pathological staging system will be used (**Table 1** and **Table 2**).

4. Treatment (Figure 1)

a. If gallbladder cancer (GBC) is suspected pre-operatively and the tumor is clinically localized resectable

i. Surgical resection:

1. For stage pT_{IS} and pT1a GBC, simple cholecystectomy is recommended (EL-1).[3-11]
2. For stage pT1b, extended cholecystectomy is recommended (EC; EL-2). EC includes cholecystectomy with *en bloc* limited hepatic resection (2–3 cm wedge resection or segment IVb and V) and lymphadenectomy with or without bile duct excision.[12-14]
3. For stage T2, extended cholecystectomy is recommended (EL-1).[15, 16]
4. For stage T3 and T4 or positive N disease, extended cholecystectomy and wedge resection or segment IVb and V resection of the liver or major hepatic resection might be considered (extended right hepatectomy or central hepatectomy ± caudate lobectomy), common bile duct resection, or duodenum, colon, or omentum resection might be required in advanced GBC and will need to be assessed on an individual basis.[17-22]

ii. Adjuvant therapy:

1. For stage pT_{IS} and pT1a GBC resected with negative margin, patients should go on observation (EL-1).
2. For stage pT1b or greater, no level one evidence for the best approach; however, chemotherapy, chemoradiation, or observation are acceptable options (EL-3).[19, 23-44]

b. Disease identified incidentally at pathological review of the cholecystectomy specimen

i. For patients with Tis-1aN0M0 disease identified incidentally during pathological review of a cholecystectomy specimen with negative margin, no further therapy is necessary (EL-1).

ii. For patients with IB or greater, radical re-resection (after a complete staging including laparoscopy demonstrating resectability) with resection of the laparoscopic port sites (EL-2).

iii. Adjuvant therapy:

1. No level evidence for the best approach; however, chemotherapy, chemoradiation, or observation are acceptable options (EL-3).

c. Metastatic disease

i. Palliative chemotherapy for patients with good performance status (PS 0-2) can be offered including gemcitabine and cisplatin combination chemotherapy (EL-1).[45]

ii. There is no clear consensus regarding second-line therapy options, which include best supportive care or systemic chemotherapy (EL-3).

Table 1. TNM AJCC staging for gallbladder cancer, 7th edition.

Primary Tumor (T)		**Regional Lymph Nodes (N)**		**Distant Metastasis (M)**	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor	N0	No regional lymph node metastases	M1	Distant metastasis
T_{IS}	Carcinoma *in situ*	N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein		
T1	Tumor invades lamina propria or muscular layer	N2	Metastases to periaortic, pericaval, superior mesentery artery, and/or celiac artery lymph nodes		
T1a	Tumor invades lamina propria				
T1b	Tumor invades muscular layer				
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver				
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or another adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts				
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures				

Table 2. Stage grouping for gallbladder cancer.

Stage grouping	**T stage**	**N stage**	**M stage**
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	N2	Any M
	Any T	Any N	M1

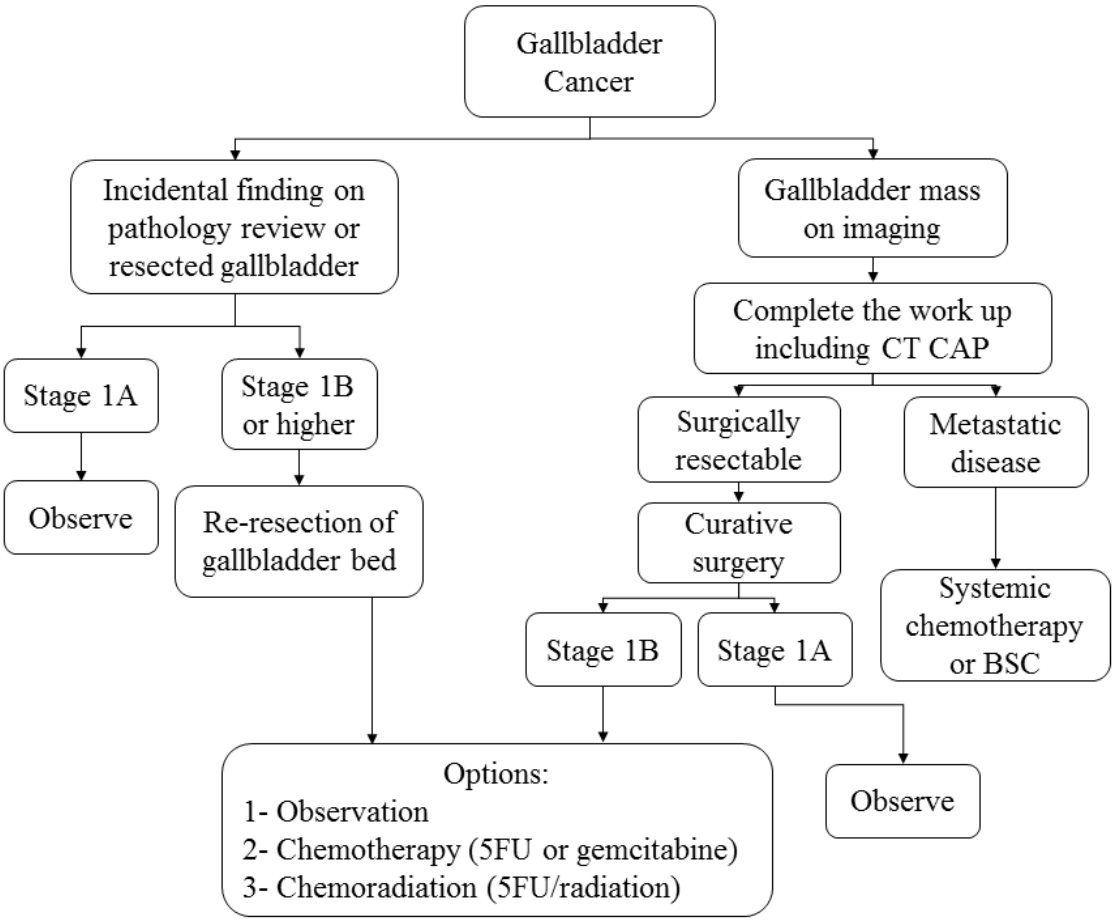

Figure 1. Flow diagram for the management of gallbladder cancer.
Abbreviations: BSC: best supportive care; CT: computed tomography; CAP: chest, abdomen, and pelvis; 5-FU: 5-Fluorouracil

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Abstract

Updated guidelines for the evaluation and the medical and surgical management of gastric cancer are presented in this report. The guidelines are categorized according the stage of the disease using the Union for International Cancer Control (UICC)/American Joint Commission on Cancer (AJCC) staging system 7th edition. The recommendations are accompanied by supporting evidence, and information regarding adjuvant treatments and follow-up are updated.

According to the Saudi Cancer Registry data, 316 cases of stomach cancer, which accounts for 2.7% of all diagnosed cancers and ranks 9th among the male and 12th among female population, were diagnosed in 2013 in the Kingdom of Saudi Arabia.[1] The overall age-standardized incidence rate was 2.7/100,000, with a rate of 3.1/100,000 for males and 2.3/100,000 for females. The median age at diagnosis was 65 years for males (range 4–94 years) and 60 years for females (range 23–100 years).

A committee of experts in the medical and surgical treatment of colorectal cancer was established under the supervision of the Saudi Oncology Society (SOS). The evidence adopted in these guidelines is rated at three levels: 1) Evidence level 1 (EL-1; highest level) includes data from phase III randomized trials or meta-analyses; 2) EL-2 (intermediate-level) includes data from good phase II trials or phase III trials with limitations; and 3) EL-3 (low-level) includes retrospective or observational data and/or expert opinion. This easy-to-follow grading system is convenient and allows the reader to accurately assess the applicability of the guidelines in individual patients.[2] Ultimately, all gastric cancer cases are preferably seen or discussed in a multidisciplinary form. For the purposes of these guidelines, the term "esophagogastric junction tumor" includes lower esophageal adenocarcinoma, junctional tumors, and cancer of the cardia. The Siewert classification is used to subdivide esophagogastric junction tumors into type I, II, and III[3], and covers the area 5 cm to either side of the gastroesophageal junction.

1. Tumor Classification

1.1 Type I - the center of the cancer or more than two-thirds of the identifiable tumor mass is located >1 cm proximal to the anatomical gastroesophageal junction.

1.2 Type II - the center of the cancer or the tumor mass is located in an area extending 1 cm proximal and 2 cm distal to the gastroesophageal junction.

1.3 Type III - the center of the tumor or more than two-thirds of the identifiable tumor mass is located >2 cm below the gastroesophageal junction.

1.4 The Barrett's esophagus is identified as an esophagus in which the normal squamous lower esophageal epithelium has been replaced by intestinal type mucosa, which is visible macroscopically.

Type I will be treated as esophageal cancer and types II and III will be treated as gastric cancer.

2. Pre-treatment Evaluation

2.1. Clinical and physical examination.

2.2 Blood count and renal and hepatic function tests.

2.3 Tumor markers (optional: carcinoembryonic antigen, CA-19-9).

2.4 Flexible upper gastrointestinal endoscopy is recommended as the diagnostic procedure of choice
in patients with suspected esophageal or gastric cancer.[4]

2.5 Biopsy: all biopsy pathologic reports should include the following checklist:[5]

2.5.1 Histological type

2.5.2 Histological grade
2.5.3 Ancillary studies: Human epidermal growth factor receptor 2 (HER-2) immunoperoxidase studies (in accredited labs or with external quality control) and HER-2 fluorescent *in situ* hybridization (FISH) for patients with an immunoscore of 2+ (in accredited labs or with external quality control).

2.6 Computed tomography (CT) scan of the chest, abdomen, and pelvis to assess the local, nodal, and distant spread. The limitations include: low sensitivity for detecting peritoneal metastasis <5 mm and the underestimation of the depth of wall invasion[6-9] (EL-2).

2.7 Barium studies (optional for defining the extent of surgery).[10]

2.8 Endoscopic ultrasonography (optional)[11-15] (EL-2).

2.9 Staging laparoscopy: recommended for gastric tumors being considered for surgery in which full-thickness gastric wall involvement is suspected, T3-4 or N positive (EL-2).[16-20]

3. Surgical pathology report requirements:[5, 21]

3.1 Specimen
3.2 Procedure
3.3 Tumor site (select all that apply)
3.4 Tumor size
3.5 Histological type
3.6 Histological grade
3.7 Microscopic extent of tumor
3.8 Margins (select all that apply)
3.9 Treatment effect (applicable to carcinomas treated with neoadjuvant therapy)
3.10 Lymph-vascular invasion
3.11 Perineural invasion
3.12 Pathological staging (pTNM)
3.13 TNM descriptors (required only if applicable)
3.13.1 M (multiple primary tumors)
3.13.2 R (recurrent)
3.13.3 Y (post-treatment)
3.14 Additional pathological findings-ancillary studies:
3.14.1 HER2 immunoperoxidase studies (accredited laboratory or external quality control)
3.14.2 HER2 *in situ* hybridization studies/fluorescent *in situ* hybridization (immunoscore 2+) (accredited laboratory or external quality control)

4. Staging

The 2010 Union for International Cancer Control/American Joint Commission on Cancer (UICC/AJCC) 7th edition pathological staging system will be used (**Table 1** and **Table 2**).[21]

5. Treatment (Figure 1)

5.1 Indicators of unresectability: presence of distant metastases, invasion of a major vascular structure, such as the aorta, or disease encasement or occlusion of the hepatic artery or celiac axis/proximal splenic artery.

5.2 Treatment of stage T_{IS} (*in situ*), T1a, and N0M0: Endoscopic mucosal resection of early gastric cancer meeting all of the following (EL2)[22]:

- 5.2.1 Well or moderately differentiated type adenocarcinoma.
- 5.2.2 Superficial, elevated, or depressed (<1 cm) macroscopic appearance (types I, IIa, and IIc).
- 5.2.3 No ulceration.
- 5.2.4 Diameter of the lesion <30 mm.
- 5.2.5 No apparent invasive findings.

5.3 Treatment of stage T1b-T4, N0-2, and M0: Medically fit and potentially resectable patient should be given one of the following options:

- 5.3.1 Perioperative neoadjuvant/adjuvant chemotherapy using epirubicin/cisplatin/5-FU (ECF) chemotherapy regimen, (EL-1) or its modifications (EL-2), based on the Cunningham/Medical Research Council Adjuvant Gastric (MAGIC) trial[23] (EL-1), or Cisplatin/5-Fluorouracil as per the Federation Nationale des Centres de Lutte Contre le Cancer/Federation Francophone de Cancerologie Digestive (FNLCC/FFCD) trial[24] (EL-1).
- 5.3.2 Gastrectomy followed by adjuvant concurrent chemoradiotherapy using 5-fluorouracil and leucovorin as per inter-group 0116 protocol[23] [EL-1 or modifications[23-26] (EL-2)]. The radiotherapy dose is 45 Gy delivered in 25 daily 1.8 Gy fractions 5 days a week to the stomach bed and the draining high-risk nodal regions.[25-28]
- 5.3.3 Gastrectomy to be followed by the post-operative adjuvant XELOX for eight cycles[29] (EL1) or Cisplatin/Capecitabine for six cycles (EL1).[30]

5.4 Surgical management:

- 5.4.1 Gastrectomy.[31-36] Total gastrectomy should be carried out for proximal and mid-body gastric tumors with a Roux-en-Y reconstruction to avoid alkaline reflux esophagitis. Distal subtotal gastrectomy is recommended for distal gastric tumors (EL-2) with a wide macroscopically negative margin of 5 cm, along with the *en bloc* resection of lymph nodes (D2 lymphadenectomy, EL-1)[37-39] and adherent surrounding organs. The spleen and pancreas are spared (EL-2). If a splenectomy is anticipated preoperatively due to tumor adherence revealed by CT, pneumococcal polysaccharide, meningococcal, and *Haemophilus influenzae* vaccines are administered before surgery.
- 5.4.2 Lymphadenectomy.[37-39] Resection of the lymph nodes in gastric cancer surgery can be carried out at three levels: 1) D1, which involves the removal of all nodal tissue within 3 cm of the primary tumor (perigastric lymph nodes); 2) D2, which involves D1 plus clearance of the hepatic, splenic, celiac, and left gastric lymph nodes; and 3) D3, which involves D2 plus omentectomy, splenectomy, distal pancreatectomy, and the clearance of the porta hepatic lymph nodes

and the para-aortic lymph nodes.

5.5 Post-operative management of residual disease: This will depend on the degree of residual disease as follows:

5.5.1 R1 (microscopic residual disease): treat with post-operative chemoradiation or chemotherapy.

5.5.2 R2 (macroscopic residual disease): treat as a metastatic disease.

5.6 Treatment of stage T4M0 or N3 medically fit and unresectable; Treat as a metastatic disease (M1) and reassess for resectability.

5.7 Treatment of stage M1 disease: This will depend on the patient performance status:

5.7.1 Patients with performance status (PS) 0–2: palliative chemotherapy with any of the following options: ECF modifications[40] (EL-1), docetaxel, cisplatin, and 5-FU (DCF) (EL1)/DCF modifications[41, 42] (EL-2), 5-FU, leucovorin, and oxaliplatin 6 (FOLFOX 6)[43], (EL-2) or capecitabine and oxaliplatin (XELOX)[44] (EL-2). Add trastuzumab to cisplatin/fluoropyrimidine if Her-2/neu is +3 on immunohistochemistry or FISH positive[45] (EL-1).

5.7.2 Patients with a PS of 3: administer single agent chemotherapy or best supportive care

5.7.3 If the disease progresses after first line chemotherapy, consider a second-line combination of paclitaxel-ramucirumab[46] or single agent irinotecan, taxane, or ramucirumab[47, 48] when appropriate in patients with a good performance status (EL-1).

6. Follow-up

6.1 For operable gastric cancer, regular follow-up every 3 months for the first 2 years then every 6 months up to 5 years might allow the investigation and treatment of symptoms, psychological support, and early detection of recurrence (EL-3), although there is no evidence that it improves survival outcomes.[49, 50] Patients who undergo gastric resection should be monitored for vitamin B12 and iron deficiency.

6.2 In advanced disease, regular follow-up is recommended to detect symptoms of disease progression before significant clinical deterioration according to patients' clinical condition (EL-3).

Table 1. TNM AJCC staging for gastric cancer, 7th Edition.[21]

Primary tumor (T)	**Regional lymph nodes (N)**	**Distant metastasis (M)**
TX: Primary tumor cannot be assessed	NX: Regional lymph node(s) cannot be assessed	MX: Distant metastasis cannot be assessed
T0: No evidence of primary tumor	N0: No regional lymph node metastasis	M0: No distant metastasis
T_{IS}: Carcinoma *in situ*: intraepithelial tumor without invasion of the lamina propria	N1: Metastasis in one to two regional lymph nodes	M1: Distant metastasis or positive peritoneal cytology
		cytolog
T1a: Tumor invades lamina propria or muscularis mucosae	N2: Metastasis in three to six regional lymph nodes	
T1b: Tumor invades submucosa	N3: Metastasis in seven or more regional lymph nodes	
T2: Tumor invades muscularis propria		
T3: Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures[a]		
T4a: Tumor invades serosa (visceral peritoneum)[b]		

[a]T3 tumors also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures.
[b]Adjacent structures include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine and retroperitoneum.

Table 2. Stage grouping for gastric cancer.

Stage grouping	T stage	N stage	M stage
Stage 0	T_{IS}	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage IIA	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIB	T1	N3	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIIA	T2	N3	M0
	T3	N2	M0
	T4a	N1	M0
Stage IIIB	T3	N3	M0
	T4a	N2	M0
	T4b	N0-1	M1
Stage IIIC	T4a	N3	M0
	T4b	N2-3	M0
Stage IV	Any T	Any N	M1

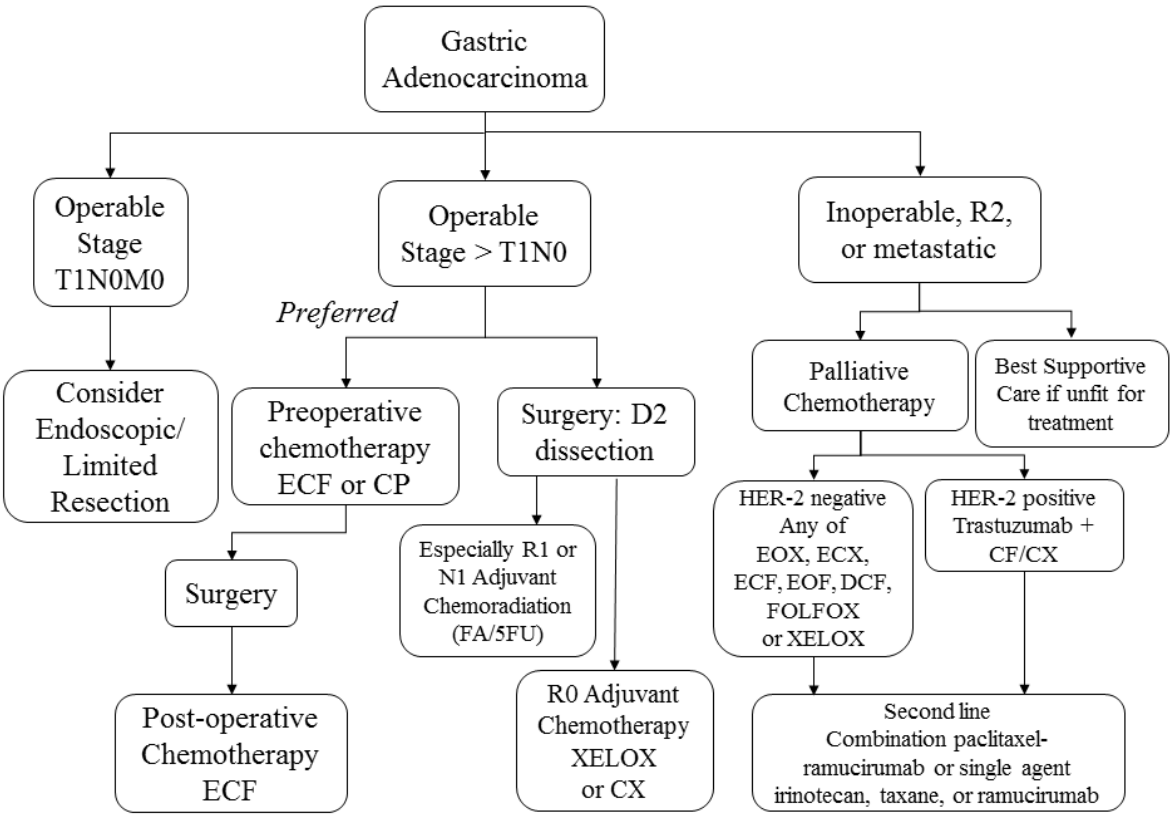

Figure 1. Flow diagram for the management of gastric cancer.

Abbreviations: FA: folinic acid; 5FU: 5-fluorouracil; CF: cisplatin, 5-fluorouracil; CP: paclitaxel, carboplatin; CX: cisplatin capecitabine; DCF: docetaxel, cisplatin, 5-fluorouracil; ECF: epirubicin, cisplatin, 5-fluorouracil; ECX: epirubicin, cisplatin, capecitabine; EOF: epirubicin, oxaliplatin, 5-fluorouracil; EOX: epirubicin, oxaliplatin, capecitabine; FOLFOX: folinic acid, 5-fluorouracil, oxaliplatin; XELOX: capecitabine, oxaliplatin.

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PANCREATIC CANCER CLINICAL GUIDELINES

National Cancer Center

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Saudi Oncology Society clinical management guidelines for pancreatic cancer 2017

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Abstract

Guidelines for the evaluation and the medical and surgical management of pancreatic cancer are presented in this report. The following guidelines are general recommendations intended to aid physicians in selecting the best therapy for their patients. However, physicians may opt to deviate from these guidelines for sound medical or other reasons. Ultimately, each patient should be treated according to his/her specific condition.

According to the Saudi Cancer Registry data, 233 cases of pancreatic cancer were diagnosed in the Kingdom of Saudi Arabia in 2013, which accounted for 1.7% of all diagnosed cancers for that year[1]. Further, pancreatic cancer ranked 16th among males and 19th among females in regards to cancer diagnoses. Unfortunately, pancreatic ductal adenocarcinoma is associated with poor outcomes and both incidence and mortality are rising. In fact, over the next 10–15 years, pancreatic adenocarcinoma is expected to become the second leading cause of cancer-related mortality in the US.

The evidence adopted in these guidelines is rated at three levels: 1) Evidence level 1 (EL-1; highest level) includes data from phase III randomized trials or meta-analyses; EL-2 (intermediate-level) includes data from good phase II trials or phase III trials with limitations; EL-3 (low-level) includes retrospective or observational data and/or expert opinion. This easy-to-follow grading system is convenient and allows the reader to accurately assess the applicability of the guideline in individual patients.[2] Ultimately, all pancreatic cancer cases are preferably seen or discussed in a multidisciplinary form.

1. Pre-treatment evaluation

1.1. Clinical examination, including age, performance status, and weight loss.
1.2. Blood count and liver and renal function.
1.3. Tumor marker: Cancer antigen 19-9 (CA19.9) level.
1.4. CT scan of chest, abdomen, and pelvis (preferably triple phase, spiral; EL-1).
1.5. Endoscopic ultrasound (EUS- optional) +/- FNA (EL-2).
1.6. Endoscopic Retrograde Cholangiopancreatography (ERCP; EL-2).
1.7. Positron emission tomography (PET) scan (optional; EL-2).
1.8. Laparoscopy in resectable cases (optional; EL-2).

2. Surgical pathology report requirement. The following parameters should be mentioned in all surgical pathology reports of pancreatic cancer:

2.1 Specimen type
2.2 Tumor size
2.3 Histological grade (G)
2.4 Primary tumor extent of invasion (T)
2.5 Regional lymph node (N)
    2.5.1 Number of nodes recovered
    2.5.2 Number of nodes involved
2.6 Metastasis (M)
2.7 Margins: surgical clearance (in mm)
2.8 Whipple's resection
    2.8.1 SMA margin
    2.8.2 Post margin
    2.8.3 Portal vein margin
    2.8.4 Pancreatic neck margin
    2.8.5 Enteric margin
2.9 Lymphatic invasion (L)
2.10 Vascular invasion (V)
2.11 Perineural invasion (P)
2.12 Final Stage: G, T, N, M, L, V, P

3. Staging classification

The 2010 American Joint Committee on Cancer (AJCC) TNM (7th edition) pathological staging system will be used (**Table 1** and **Table 2**).

4. Treatment (Figure 1)

4.1 Assessment of resectability

4.1.1. Tumors will be considered resectable if there are clear fat planes around the celiac trunk and superior mesenteric artery[3] (SMA) and have a clear superior mesenteric vein (SMV) and portal vein.[4]

4.1.2. Tumors will be considered unresectable if there is invasion of the celiac trunk and SMA or if the SMV or portal vein is occluded. Invasion of the superior mesenteric or portal vein is no longer considered an absolute contraindication.[5] These veins can be partially resected with as much as 50% narrowing of the lumen.

4.1.3. Tumors will be considered borderline resectable if there is a high likelihood of an incomplete resection[6] (R1 or R2).

4.2. Management of resectable pancreatic cancer

4.2.1. Laparotomy and pancreatoduodenectomy[7] (including splenectomy for body and tail) should be performed in a tertiary care facility. A pre-operative biopsy is not required. Routine pre-operative biliary drainage can increase the rate of complications.

4.2.2. Adjuvant chemotherapy for 6 months[8] is offered to all patients with pathological stage T1-T4, N0-N1, or R0-R1 resection. Treatment consists of a cycle of single agent gemcitabine at a dose of 1000 mg/m^2 on days 1, 8, and 15, which is repeated every 28 days for a total of six cycles (EL-1). An alternative option is 5FU/LV.[9]

4.3. Options for the management of borderline resectable pancreatic cancer include:

4.3.1. Planned upfront resection: further therapy will depend on surgical findings.

4.3.1.1. If found resectable, perform pancreaticoduodenectomy followed by adjuvant chemotherapy[4, 7, 8] (see Item 4.2.2; EL-1).

4.3.1.2. If found unresectable, obtain biopsy and consider performing bypass surgery and celiac plexus block. Post operatively, patients are offered chemotherapy (see item 4.4.2; EL-2).

4.3.2. When upfront neoadjuvant therapy is planned, patients should have a confirmatory tissue biopsy followed by either chemotherapy (EL-2) or chemoradiotherapy (EL-2).[10] Patients with a major response can be considered for re-exploration and possible resection.

4.4. The management of patients with locally advanced, unresectable pancreatic cancer and metastatic disease should include the following:

4.4.1. Tissue biopsy.

4.4.2. Palliative chemotherapy with one of the following options:

4.4.2.1. A cycle of single agent gemcitabine[8] at a dose of 1000 mg/m^2 on days 1, 8, and 15 that is repeated every 28 days until progression (EL-1).

4.4.2.2. Gemcitabine-based combinations[11] (gemcitabine and fluoropyrimidines or gemcitabine and cisplatin; EL-1).

4.4.2.3 Gemcitabine and Nab-Paclitaxel[12] (EL-1).

4.4.2.4 FOLFIRINOX[13] combination chemotherapy (combination of 5-Fluorouracil, leucovorin, oxaliplatin, and irinotecan) in young patients with performance status 0–1 according to the Eastern Cooperative Oncology

Group ECOG scale (EL-1). Chemotherapy is given until disease progression or unacceptable toxicity.

4.4.3 Patients not fit for chemotherapy should be given best supportive care. This includes, but is not restricted to, pain management (including nerve block of celiac plexus, stenting for biliary obstruction, and duodenal obstruction).

4.5 Options for the management of locally recurrent disease:

4.5.1 Palliative chemotherapy (EL-1),

4.5.2 Concurrent gemcitabine and radiotherapy.[10, 14, 15] (EL-1).

4.5.3 Best supportive care in unfit patients.

4.6 Second-line therapy: with oxaliplatin, folinic acid, and fluorouracil in fit patients progressing on gemcitabine-based on the Conko 003 trial (EL-1).[16]

4.7 Follow-up: There is no evidence that regular follow-up after initial therapy with curative intent is of value.

Table 1. TNM AJCC staging for pancreatic cancer, 7th edition.

Primary tumor (T)		**Regional lymph nodes (N)**		**Distant metastasis (M)**	
TX	Primary tumor cannot be assessed	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M1	Distant metastasis
Tis	Carcinoma in situ*	N1	Regional lymph node metastasis		
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension				
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension				
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery				
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)				

Table 2. Stage grouping for pancreatic cancer.

Stage grouping	**T stage**	**N stage**	**M stage**
Stage 0	T_{IS}	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4a	N0	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Abbreviations: T-stage, tumor stage; N-stage, node stage; M, metastases

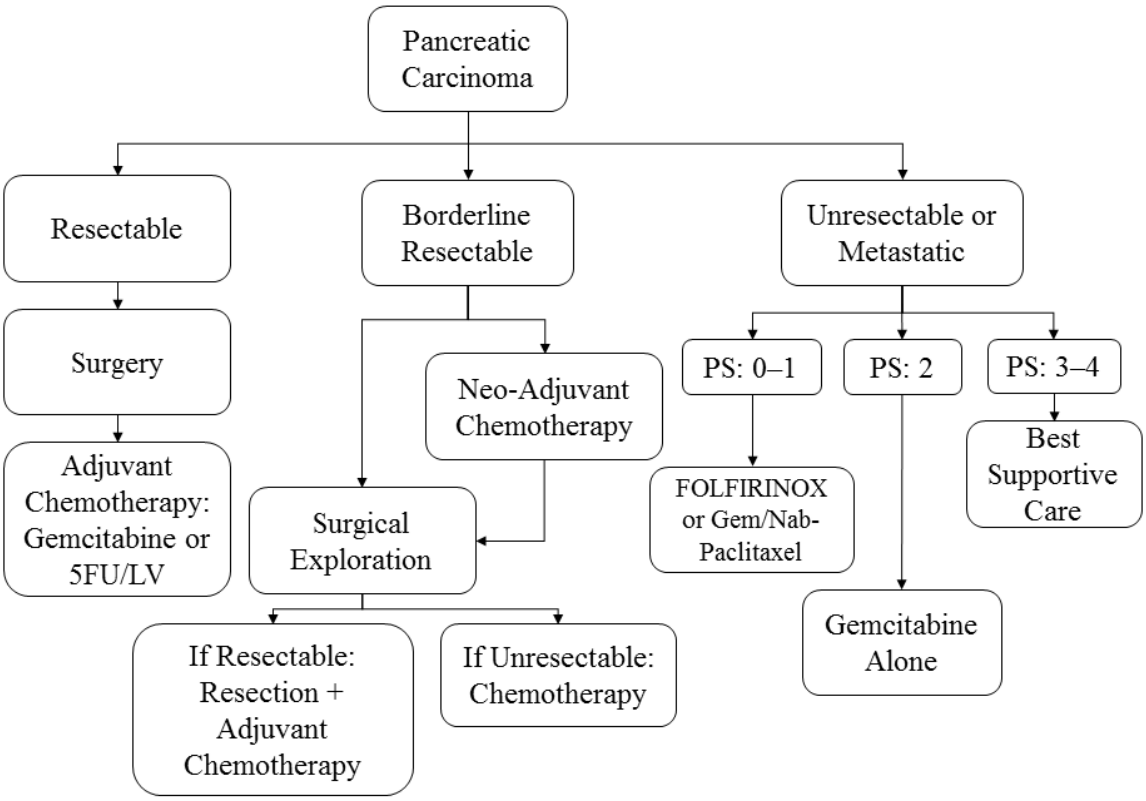

Figure 1. Flow diagram for the management of pancreatic cancer.
Abbreviations: 5FU/LV: 5-fluorouracil, leucovorin; FOLFIRINOX: 5-fluorouracil, leucovorin, irinotecan, oxaliplatin; Gem: gemcitabine; PS: performance status

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