Current Problems in Diagnostic Radiology 48 (2019) 61–74

Current Problems in Diagnostic Radiology

journal homepage: www.cpdrjournal.com

The Tipping Point: Key Oncologic Imaging Findings Resulting in Critical Changes in the Management of Malignant Tumors of the Gastrointestinal Tract

Jonathan Wu, MS, MBA[b], Lipika Goyal, MD, MPhil[c], Ryan Nipp, MD[c], Jennifer Wo, MD[d], Motaz Qadan, MD, PhD[e], Raul N. Uppot, MD[a,*]

[a] Division of Interventional Radiology, Massachusetts General Hospital, Boston, MA
[b] Department of Radiology, Massachusetts General Hospital, Boston, MA
[c] Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, MA
[d] Department of Radiation Oncology, MGH Cancer Center, Massachusetts General Hospital, Boston, MA
[e] Division of Surgical Oncology, MGH Cancer Center, Massachusetts General Hospital, Boston, MA

A B S T R A C T

Objective: The purpose of this article is to review tumor staging systems for gastrointestinal tumors including pancreatic adenocarcinoma, hepatocellular carcinoma, cholangiocarcinoma, gastric adenocarcinoma, small bowel adenocarcinoma, rectal carcinoma, and anal carcinoma and identify the key imaging findings ("tipping points"), which change patient management based on changes in tumor staging.
Conclusion: For all malignant gastrointestinal tumors, there are key imaging findings ("tipping points") including tumor size, tumor extension, lymphadenopathy, vascular invasion, and distant metastasis that dictate patient management and prognosis, based on changes in tumor stage. In interpreting these imaging studies, radiologists should be cognizant of these "tipping points" to guide patient management.

Introduction

Over the past 10 years, the management of malignant tumors of the gastrointestinal tract has advanced significantly with the introduction of new chemotherapeutic agents, new surgical techniques, new radiation treatment modalities, and the growth of interventional oncology. Critical to this therapeutic advancement is the understanding that imaging not only plays a role in diagnosis, but also drives treatment recommendations. Central to this role is the recognition that, for most tumors, a few key imaging findings can dictate treatment choices and influence prognosis.

Cancer management and prognosis is dependent on the clinical staging of tumors, which describes the extent and severity of the disease. Imaging plays a central role in clinical staging. For all tumors, there are critical imaging findings ("tipping points") that include tumor size, tumor extension, lymphadenopathy, vascular invasion, and distant metastasis. These imaging "tipping points" dictate changes in patient management and prognosis.

The purpose of this article is to focus on staging systems of gastrointestinal tumors including pancreatic adenocarcinoma, hepatocellular carcinoma, cholangiocarcinoma, gastric adenocarcinoma, small bowel adenocarcinoma, rectal carcinoma, and anal carcinoma, and to show how key imaging findings are important in defining treatment choices and prognosis.

*Reprint requests: Raul N. Uppot, MD, Division of Interventional Radiology, Massachusetts General Hospital, 55 Fruit St, Boston, MA.
E-mail address: uppot.raul@mgh.harvard.edu (R.N. Uppot).

https://doi.org/10.1067/j.cpradiol.2017.12.005
0363-0188/

Staging Systems

Each staging system determines prognosis, and is generally defined by tumor size, nodal involvement, or presence of metastasis. The most commonly used staging system as defined by the American Cancer Society is a tumor node metastasis (TNM) staging system. Accepted by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC), the TNM staging is based on the extent of tumor (T), spread to lymph nodes (N), and the presence of distant metastases (M).[1] Most cancers rely on treatment guidelines that drive clinical practice. These guidelines, such as the National Comprehensive Cancer Network (NCCN) guidelines, are based on AJCC staging systems.[2] Alternative staging systems are also employed for some cancers. For example, the Barcelona Clinic Liver Cancer Staging (BCLC) system is frequently used for hepatocellular carcinoma. The following describes specific abdominal tumors, key components of their staging systems, and critical imaging findings that represent points of treatment change or change in prognosis.

Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma is the fourth most common cause of cancer death in the United States.[3] Pancreatic adenocarcinoma arises from the exocrine glands of the pancreas. Depending on the stage, treatment of pancreatic adenocarcinoma can include surgical resection, chemotherapy, or radiation.[4] Although the AJCC staging

TABLE 1
NCCN staging of pancreatic adenocarcinoma and identified "Tipping Points". Published with permission from National Comprehensive Cancer Network NCCN

- Stage grouping for pancreatic cancer is as follows:
  - Resectable
    - Tipping Point → Surgery with or without chemoradiation
  - Borderline Resectable
    - Chemoradiation first, possible surgery
    - Tipping Point
  - Unresectable
    - Chemotherapy Only
- Staging of pancreatic tumors is as follows:
  - Resectable
    - Clear fat plane around celiac, hepatic, and superior mesenteric arteries
    - No superior mesenteric vein/portal vein distortion
  - Borderline Resectable
    - Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery without extension to the CA
    - Tumor abutment of the SMA does not exceed 180 degrees of the circumference of the vessel wall
    - Venous involvement of the SMV or portal vein with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement
  - Unresectable
    - Aortic invasion or encasement
    - Pancreatic head
      - More than 180 degrees SMA encasement, any CA abutment, IVC
    - Pancreatic body/tail
      - SMA or CA encasement greater than 180 degrees
    - Unreconstructible SMV/portal vein occlusion
    - Distant metastases

system exists, it is largely based on pathologic determination. From a practical perspective, pancreatic cancer is categorized as upfront resectable, borderline resectable, locally advanced unresectable, or metastatic, based on radiographic imaging (Table 1).[5] Borderline resectable and locally advanced unresectable are collectively known as locally advanced disease.

Resectable pancreatic tumors are characterized by (1) clear fat planes around the celiac artery (CA), hepatic artery, and superior mesenteric artery (SMA) and (2) <180° venous involvement (Fig 1A and B). Standard treatment traditionally includes pancreaticoduodenectomy (Whipple procedure) or distal pancreatectomy (for body or tail tumors) with consideration of adjuvant chemotherapy alone, or with chemoradiation.

Borderline resectable tumors are characterized by (1) gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery without extension to the CA, (2) tumor abutment of the SMA that does not exceed 180° of the circumference of the vessel wall, and (3) venous involvement of the superior mesenteric vein or portal vein with distortion or narrowing of the vein or occlusion of the vein with suitable proximal and distal vessel landing zones, allowing for safe resection and replacement (Fig 1C). The standard treatment in this setting includes neoadjuvant chemotherapy, often with chemoradiation, and surgery frequently attempted provided that follow-up imaging does not show tumor progression.[6] It is important to note, however, that based on a recent study examining posttreatment changes before operation, that traditional imaging may have difficulty in reliably distinguishing between fibrosis and viable cancer.[7] Therefore, routine exploration with intraoperative frozen biopsy sampling is indicated unless clear progression has been demonstrated.

Some patients have "locally advanced unresectable" disease at presentation. Unresectable tumors are characterized by greater than 180° SMA or celiac axis encasement or with unreconstructible superior mesenteric vein (SMV) or portal vein occlusion secondary to tumor encasement (Fig 1D). In tumors with distant metastatic disease (Fig 1E), surgery is no longer a conventional option and treatment includes chemotherapeutic agents such as fluorouracil-based or gemcitabine-based regimens.[8,9]

Key questions to ask when reviewing images of a patient with pancreatic carcinoma include:

(1) Are there distant metastases?
The presence of distant metastases renders the tumor surgically unresectable and treatment should focus on systemic chemotherapy regimens alone.

(2) Is there any arterial (CA, SMA, and HA) or venous involvement and how much circumferential involvement is there in each tree?

This is important to distinguishing between upfront resectable vs locally advanced disease (including borderline resectable or locally advanced unresectable). It is important to note that there is little difference between borderline resectable and locally advanced unresectable disease for treatment algorithms, as both generally require upfront neoadjuvant therapy followed by surgical exploration if the disease has not progressed, given that stable changes may resemble treatment effect and fibrosis, rather than persistent disease. Minor involvement of the superior mesenteric vein may or may not influence upfront resectability, since some surgeons proceed with surgical resection with repair or reconstruction of the SMV.[10]

Hepatocellular Carcinoma

The incidence of hepatocellular carcinoma (HCC) is increasing in the United States and developing countries.[11,12] The most common risk factors include cirrhosis from alcohol use, chronic hepatitis B and

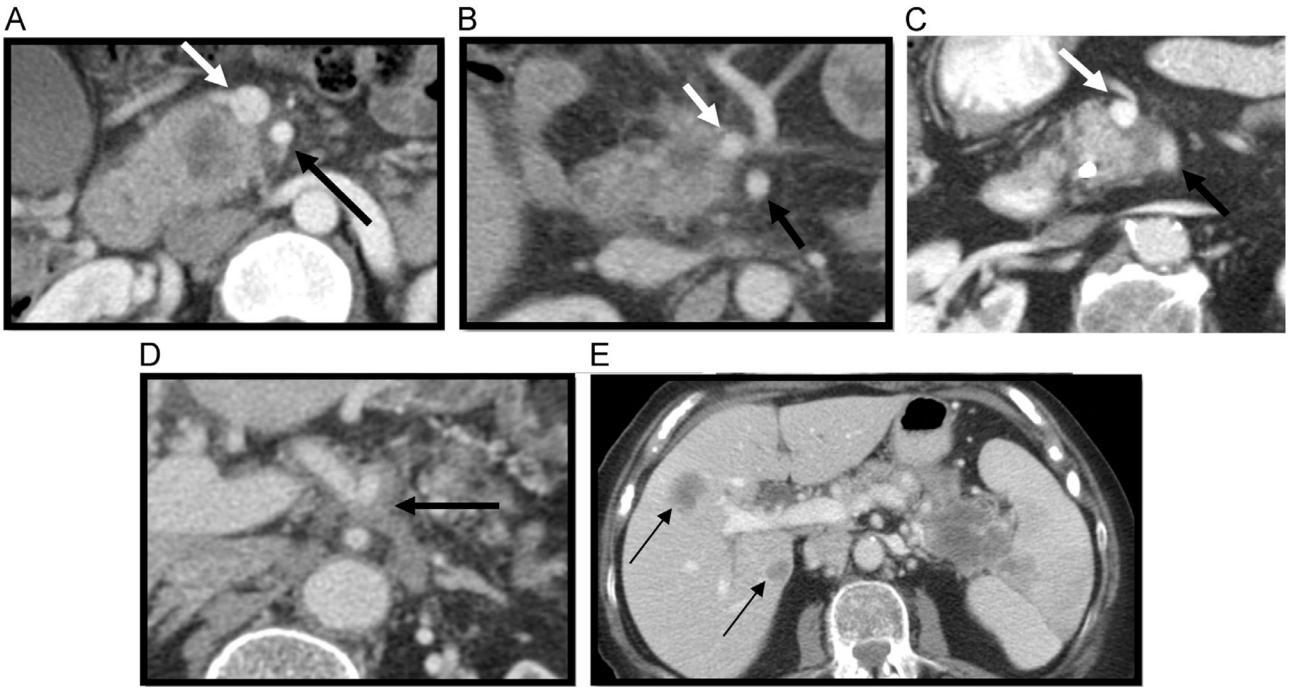

FIG 1. (A) Resectable-Axial CT shows low density pancreatic tumor confined to the pancreas. There is no invasion of SMV (white arrow) or SMA (black arrow). (B) Resectable-Axial CT shows low density pancreatic tumor partially surrounds SMV (white arrow) but spares SMA. (C) Borderline Resectable-Axial CT shows low density pancreatic tumor abuts SMA (black arrow) and at least 25% SMV (white arrow). (D) Unresectable-Axial CT shows low density pancreatic tumor encases celiac artery and branches (arrow). (E) Unresectable-Axial CT shows not only splenic invasion but distant hepatic metastasis (arrows).

C virus infections, and nonalcoholic fatty liver disease. The BCLC, which categorizes patients into 5 stages (0 and A-D), is the most widely used staging system for the management of HCC (Table 2). The treatment of HCC includes liver transplantation, partial hepatectomy, and percutaneous ablation for early stage tumors (0 and A). Transarterial chemoembolization (TACE) or bland transarterial embolization, selective internal radiation therapy (SIRT), and stereotactic body radiation therapy (SBRT) are used for intermediate stage (B), systemic therapy (such as sorafenib, regorafenib, and nivolumab) for advanced stage (C), and best supportive care is provided for terminal stage (D). The imaging tipping points based on treatment changes exist between stages A and B, and B and C.[13,14]

Very early stage (0) HCC is defined as a single tumor less than 2 cm (Fig 2A), and early stage (A) HCC is defined as a single tumor less than 5 cm or 3 nodules no greater than 3 cm (Fig 2B). Treatment can be curative at these stages and includes partial hepatectomy, liver transplantation, or ablation. The Milan criteria, widely used to determine eligibility for transplantation, requires that patients have no evidence of vascular invasion and either have (A) a single tumor ≥2 cm and ≤5 cm or (B) up to 3 lesions that are ≥1 cm and ≤3 cm.[15,16] Ablation may be used to treat tumors that are not suitable operative candidates or as a "bridge" to transplantation. Ablation is most successful in treating tumors <3 cm.[17-19]

The organ procurement and transplant network (OPTN) classification system is used to help determine eligibility and priority for liver transplantation. The OPTN system uses specific imaging criteria to classify nodules seen on imaging into 5 classes. OPTN class 5 meets the radiological criteria for HCC and is further divided into 5A, 5A-g, 5B, 5T, and 5X (Table 3). For radiologists, the most critical item is to identify the 5A or 5B lesion. OPTN class 5A is defined as lesions ≥1 cm and <2 cm measured on late arterial or portal venous phase images that show increased contrast enhancement in late hepatic

TABLE 2
BCLC staging of hepatocellular carcinoma and identified "Tipping Points"

- Stage grouping for Hepatocellular Carcinoma is as follows:
  - Very early stage (0)
  - Early stage (A)
  - Tipping Point
  - Intermediate stage (B)
  - Tipping Point
  - Advanced stage (C)
  - Terminal stage (D)

Transplantation, Partial Hepatectomy, Ablation

Embolization

Systemic Therapy

- Staging of Hepatocellular Carcinoma is as follows:
  - Very early stage (0) – Single <2 cm, carcinoma in situ
  - Early stage (A) – Single or 3 nodules ≤ 3 cm
  - Intermediate stage (B) – Multinodular
  - Advanced stage (C) – Portal invasion, N1, M1
  - Terminal stage (D) – PST > 2, Child-Pugh C

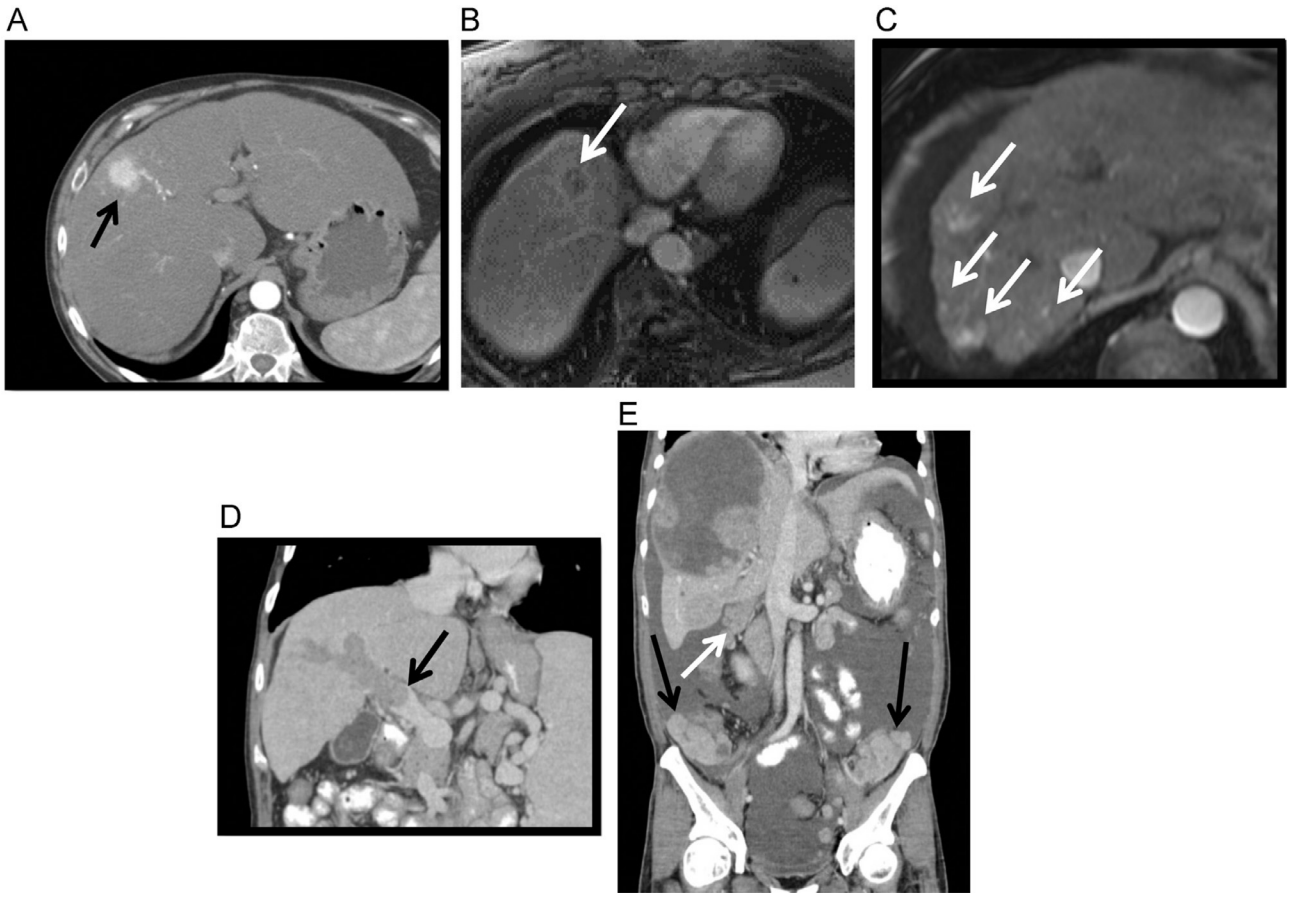

FIG 2. (A) Stage 0 - Axial CT shows single arterially enhancing tumor < 2 cm that does not invade blood vessels (arrow). (B) Stage A - Axial portal venous phase T1-weighted MRI with gadolinium shows 2.1 cm HCC (arrow) with washout. (C) Stage B - T1-weighted MRI with gadolinium shows multiple tumors that do not invade blood vessels (arrows). (D) Stage C - Coronal CT shows tumor invading portal vein (arrow). (E) Coronal CT shows porta hepatis nodal involvement (white arrow) and distant metastasis (black arrows).

arterial phase and washout during later phases of contrast enhancement with peripheral rim enhancement (capsule or pseudocapsule). Arterial phase enhancement occurs because the tumor is mainly supplied by a neovascularized chain of vessels arising from the hepatic arteries. There is a "washout effect" because in the portal venous phase, the portal vein which provides most blood supply to the normal hepatic parenchyma, hyperenhances the liver. The tumor, on the other hand, does not have a portal venous supply, and thus appears as hypodense. Incidentally, this perfusion pattern may be grossly distorted in patients with who have Budd Chiari syndrome or a transjugular intrahepatic portosystemic shunt. Class 5B lesions have a diameter ≥2 cm and ≤5 cm. Patients who have 2 OPTN 5A lesions or one OPTN 5B lesion may be eligible for model for end stage liver disease exception points, as designated by United Network for Organ Sharing, to give priority to patients with HCC for transplantation. More specifically, patients with conconmitant hepatocellular malignancy can receive up to 28 MELD points after being listed for 6 months, thus expediting organ procurement than they would have received with their natural MELD score based on liver function assessment alone.

For intermediate stage (B), tumors are multinodular and beyond Milan criteria, but show no evidence of vascular invasion on imaging (Fig 2C). These patients are no longer eligible for transplantation and the standard treatment is TACE or transarterial embolization.[4] Liver-directed SBRT is also being increasingly used for these patients with promising results.[20-22]

Advanced BCLC stage (C) is defined by macrovascular invasion (portal or hepatic vein invasion), lymph node involvement, or distant metastases (Fig 2D and E). Of portal vein, hepatic vein and inferior vena cava involvement, portal vein involvement is most common, and typically seen as thrombosis. Expansion and enhancement of the thrombus suggests tumor thrombus. Lymph node involvement, particularly in the hilar space, can be difficult to diagnose, as cirrhosis itself, independent of the presence of HCC, may result in portal lymphadenopathy in the hepatic hilum. Enlarged nodes in other areas such as peridiaphragmatic or paracardiac are often due to metastatic involvement. Hepatocellular carcinoma typically metastasizes to other sites in the liver and to the lymph nodes, peritoneum, lungs, and bones.

For advanced stage hepatocellular carcinoma, standard treatment includes systemic therapy with sorafenib in the first line, or regorafenib or nivolumab in the second line, in an attempt to control tumor growth.[23] For patients with portal or hepatic vein invasion and no extrahepatic spread, liver-directed therapy with SIRT or SBRT may be also used.[24,25]

Key radiologic findings to make when reviewing imaging in a patient with hepatocellular carcinoma include:

(1) Are there distant metastases?
(2) Are tumors > 2.0 cm?
(3) Are there any single tumors greater than 5 cm or more than 3 tumors greater than 3 cm?
(4) Is there major vascular invasion?

Cholangiocarcinoma

Cholangiocarcinoma is a rare cancer of the intrahepatic and extrahepatic bile ducts, and the incidence of intrahepatic cholangiocarcinoma is rising in the United States.[26] Treatment of cholangiocarcinoma

TABLE 3
OPTN classification system for nodules seen on images of cirrhotic livers[13]

OPTN Class 0—Incomplete or Technically inadequate study
- Repeat study required for adequate assessment; automatic priority MELD points cannot be assigned on basis of an imaging study categorized as OPTN class 0

OPTN Class 1—No evidence of HCC on good quality, appropriate surveillance examination
- Typically, surveillance would continue according to routine practice at the respective transplant center

OPTN Class 2—Benign lesion(s) or diffuse parenchymal abnormality with no dominant focal lesion
- Typically, need for any further imaging would be determined on a clinical basis according to routine practice at the respective transplant center

OPTN Class 3—Abnormal scan, indeterminate focal lesion(s), not currently meeting radiologic criteria for HCC
- Typically, follow-up imaging would be performed in 6-12 months

OPTN Class 4—Abnormal scan, intermediate suspicion for HCC (Meets some radiologic criteria for HCC—could represent HCC)
- Consider short term F/U in 3 months (lesions ≥2 cm maximum diameter) to 6 months (lesions < 2 cm maximum diameter). Imaging follow-up should be considered if biopsy is negative or not possible

OPTN Class 5—Meets radiological criteria for HCC
- May qualify for automatic exception, depending on stage

Class 5A—≥1 cm and <2 cm measured on late arterial or portal venous phase images
- Increased contrast enhancement in late hepatic arterial phase AND washout during later phases of contrast enhancement AND peripheral rim enhancement (capsule or pseudocapsule)

Class 5A-g—Same as Class 5A
- Increased contrast enhancement in late hepatic arterial phase AND growth by 50% or more documented on serial CT or MR images obtained £6 months apart

Class 5B—Maximum diameter ≥2 cm and ≤5 cm
- Increased contrast enhancement in late hepatic arterial phase AND either washout during later contrast phases OR peripheral rim enhancement (capsule or pseudocapsule) OR growth by 50% or more documented on serial CT or MR images obtained 6 months apart (UNOS class 5B-g)

Class 5T—Prior regional treatment for HCC
- Any residual lesion or perfusion defect at site of prior class 5 lesion

Class 5X—Maximum diameter ≥5 cm
- Increased contrast enhancement in late hepatic arterial phase AND either washout during later contrast phases OR peripheral rim enhancement (capsule or pseudocapsule)

UNOS, United Network for Organ Sharing.

includes primary surgical resection, surgical resection after neoadjuvant chemotherapy with or without radiation therapy, adjuvant chemotherapy with or without radiation therapy, and palliative therapy.[4] Staging and management strategies also vary based on location of tumor. Extrahepatic cholangiocarcinoma includes distal, mid, and proximal bile duct tumors, and proximal tumors involving the biliary confluence are otherwise known as Klatskin tumors. In conventional settings, the extrahepatic bile duct anatomy is defined as follows: the proximal bile duct lies anterior to the portal vein and to the right of the hepatic artery. The mid bile duct is behind the duodenum, and the distal bile duct is defined as the portion behind the pancreas.

Distal Cholangiocarcinoma

Practically, with distal cholangiocarcinoma based on imaging, the question is whether the lesion is resectable or not. The imaging tipping points therefore exist between stages IIB and III, and III and IV (Table 4).[1]

Stage 0-IB tumors may range from carcinoma in situ to tumor that has grown beyond the confines of the bile duct, but has not invaded adjacent structures. Treatment options include extrahepatic bile duct surgical resection and Roux-en-Y hepaticojejunostomy with regional lymphadenectomy.[4,27] If the tumor is in the very distal common bile duct, with associated pancreatic head, treatment may likely include Whipple pancreaticoduodenectomy. Stage IIA and IIB tumors represent tumors that have invaded into adjacent structures such as the gallbladder or branches of the portal vein or hepatic artery or regional lymph nodes. Direct invasion can be identified with loss of fat plane betwee the mass and these structures. Regional nodes to evaluate for metastatic involvement include cystic duct and common bile duct nodes. Treatment of stage IIA and IIB is also surgical resection with a plan for neoadjuvant therapy in select cases.

Stage III tumors (T4 disease) invade into major vascular structures such as the celiac axis or SMA. Treatment for stage III disease may include preoperative chemotherapy with or without chemoradiotherapy. Surgery only occurs if the tumor reduces in size and there is a chance of complete (R0) resection off the major vascular structures.

Stage IV tumors include those with distant metastases. Common areas of metastasis include the lymph nodes, peritoneum, liver, and lungs. Involvement of celiac, peripancreatic and superior mesentric nodes also consitutes metastatic disease. The mainstay of treatment is palliative systemic therapy with first line gemcitabine and cisplatin; palliative radiation and surgery can be offered in select cases. Percutaneous biliary drainage and biliary stent placement often help relieve biliary obstruction.

Perihilar Cholangiocarcinoma

Perihilar, or Klatskin, tumors occur at the bifurcation of the common hepatic duct. They account for 25% of all cholangiocarcinomas.[28] Many times the tumor mass is ill-defined and not fully appreciated

TABLE 4
TMN staging of distal cholangiocarcinoma and identified "Tipping Points"

- Stage grouping for Cholangiocarcinoma is as follows:
  - Stage 0 – Tis, N0, M0
  - Stage IA - T1, N0, M0
  - Stage IB - T2, N0, M0
  - Stage IIA - T3, N0, M0
  - Stage IIB – T1, T2,or T3, N1, M0
  - Stage III - T4, Any N, M0
  - Stage IV - Any T, Any N, M1

Surgery

Tipping Point

Surgery only after chemotherapy w/o chemoradiation

Tipping Point

Palliative Treatment

- Staging of Cholangiocarcinoma is as follows:
  - Tumor (T)
    - Tis - Carcinoma in situ
    - T1 – Tumor is confined to the bile duct
    - T2 – Tumor has grown through the bile duct but has not reached adjacent structures.
    - 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 celiac axis, or the superior mesenteric artery
  - Regional lymph nodes (N)
    - N0 – No lymph node involvement
    - N1 - Regional lymph node metastasis
  - Distant metastasis (M)
    - M0 - No distant metastasis
    - M1 - Distant metastasis

by computed tomography (CT) or magnetic resonance imaging (MRI). The only indication may be intrahepatic bile duct dilation toward the mass. Most perihilar cholangiocarcinomas present late and are unresectable. In addition, most resections are extended right hepatectomies since the left bile duct is longer with more space to work.

Based on the treatment changes, the imaging tipping points therefore exist between stages IIIB and IVA and stage IVA and IVB (Table 5).

Stage 0-IIIB tumors may range from carcinoma in situ to tumor that has grown beyond the confines of the bile ducts into the hepatic parenchyma and involves unilateral branches of the portal vein or hepatic

TABLE 5
TMN staging of perihilar cholangiocarcinoma and identified "Tipping Points"

- Stage grouping for Cholangiocarcinoma is as follows:
  - Stage 0 – Tis, N0, M0
  - Stage I - T1, N0, M0
  - Stage II - T2a or T2b, N0, M0
  - Stage IIIA - T3, N0, M0
  - Stage IIIB – T1, T2, or T3, N1, M0
  - Stage IVA - T4, N0 or 1, M0
  - Stage IVB - Any T, Any N, M1

Surgery

Tipping Point

Chemotherapy w/o chemoradiation, surgery only if tumor shrinks

Tipping Point

Palliative Treatment

- Staging of Cholangiocarcinoma is as follows:
  - Tumor (T)
    - Tis - Carcinoma in situ
    - T1 – Tumor is confined to the bile duct, with extension up to muscle layer or fibrous tissue
    - T2a – Tumor invades beyond the wall of the bile duct 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 main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement
  - Regional lymph nodes (N)
    - N0 – No lymph node involvement
    - N1 - Regional lymph node metastasis
  - Distant metastasis (M)
    - M0 - No distant metastasis
    - M1 - Distant metastasis

TABLE 6
TMN staging of intrahepatic cholangiocarcinoma and identified "Tipping Points"

- Stage grouping for Cholangiocarcinoma is as follows:
  - Stage 0 – Tis, N0, M0
  - Stage I - T1, N0, M0
  - Stage II - T2, N0, M0
  - Stage III - T3, N0, M0
  - Stage IVA - T4, N0, M0 or Any T, N1, M0 ← Tipping Point
  - Stage IVB - Any T, Any N, M1

Surgery, radiation, or TACE

Palliative Treatment

- Staging of Cholangiocarcinoma is as follows:
  - Tumor (T)
    - Tis - Carcinoma in situ
    - T1 – Solitary tumor without vascular invasion
    - T2a – Solitary tumor with vascular invasion
    - T2b – Multiple tumors, with or without vascular invasion
    - T3 – Tumor perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion
    - T4 – Tumor with periductal invasion
  - Regional lymph nodes (N)
    - N0 – No lymph node involvement
    - N1 - Regional lymph node metastasis
  - Distant metastasis (M)
    - M0 - No distant metastasis
    - M1 - Distant metastasis

artery, but has not invaded the main portal vein or common hepatic artery. Treatment options include extended surgical resection with Roux-en-Y hepaticojejunostomy (often multiple) and regional portal lymphadenectomy.[4,27] Neoadjuvant chemotherapy or chemoradiotherapy can be considered in select cases of locally advanced disease.

Stage IVA tumors represent tumors that have invaded into the main portal vein or common hepatic artery and have regional lymph node metastasis. There can either be direct invasion of the tumor into these stuctures or associated trombosis. Treatment involves chemotherapy or chemoradiotherapy, and surgical resection is only considered with great response to therapy.

Stage IVB tumors include those with distant metastases or nonregional node involvement (nodes beyond porta hepatis) with similar sites of involvement as distal cholangiocarcinoma. The mainstay of treatment is again palliative systemic therapy with first-line gemcitabine and cisplatin; palliative radiation and surgery can be offered as needed. When necessary, biliary drainage and stent placement can help to relieve biliary obstruction.

Overall, for perihilar cholangiocarcinoma, surgery is reserved for patients with no T4 disease, distant lymphadenopathy, or distant metastasis.

Intrahepatic Cholangiocarcinoma

Based on the treatment changes, the imaging tipping points therefore exist between IVA and IVB (Table 6).

Stage 0-II tumors may range from carcinoma in situ to multiple tumors with or without vascular invasion (Fig 3A and B). The mainstay of curative therapy is surgical resection; if a patient is not a good surgical candidate, alternative treatments include liver-directed stereotactic body radiotherapy, TACE, or systemic chemotherapy.

Stage III tumors perforate the visceral peritoneum or extend into the extrahepatic structures by direct invasion (Fig 3C and D). Thickening, stranding, or nodularity of the adjacent visceral peritoneum suggest perforation into the peritoneum, and extrahepatic structures that can be involved include the gallbladder, colon, stoamch, and pancreas. If the tumor invades the bile ducts or involves regional lymph nodes, such as the portal or hepatoduodenal lymph nodes, this is a Stage IVA tumor. The mainstay of treatment for Stage III and IVA disease is surgical resection, although neoadjuvant therapy is frequently considered in attempts to downsize the tumor and reduce the extent of the operative resection. For patients with intrahepatic cholangiocarcinoma who are not suitable surgical candidates due to underlying cirrhosis, other comorbidities, or extensive involvement of local structures, radiation may be an option based on data from a phase II study showing that proton beam radiation offered a local control rate of >90% at 2 years in patients with intrahepatic cholangiocarcinoma.[25]

Stage IVB tumors involve distant lymph nodes or metastastic sites in a pattern similar to extrahepatic cholangiocarcinoma (Fig 3E). First-line palliative gemcitabine and cisplatin is again the standard of care, with palliative radiation and surgery used as needed.

In reviewing cases of cholangiocarcinoma (all locations) key imging findings to identify include:

(1) Are there distant metastases?
(2) Is the tumor distal, perihilar or intrahepatic?
(3) Is there invasion into main portal vein or common hepatic artery?
(4) Is there invasion of celiac artery or SMA?

In addition, there are considerations beyond tumor staging that determines whether surgery is an option. These include:

(1) Future liver remnant has to be greater than 20% for healthy, 30% for fatty, and 40% for cirrhotic.
(2) Jaundice has to be drained and stented in future liver remnant if less than 30% remnant anticipated with no active cholangitis infection.
(3) Patient has to be a healthy and active physical specimen with few comoribidities.

Gastric Adenocarcinoma

Approximately, 28,000 individuals in the United States are diagnosed with gastric adenocarcinoma annually.[3] Treatment options for the management of gastric adenocarcinoma include primary surgical resection, surgical resection following neoadjuvant chemotherapy, and palliative

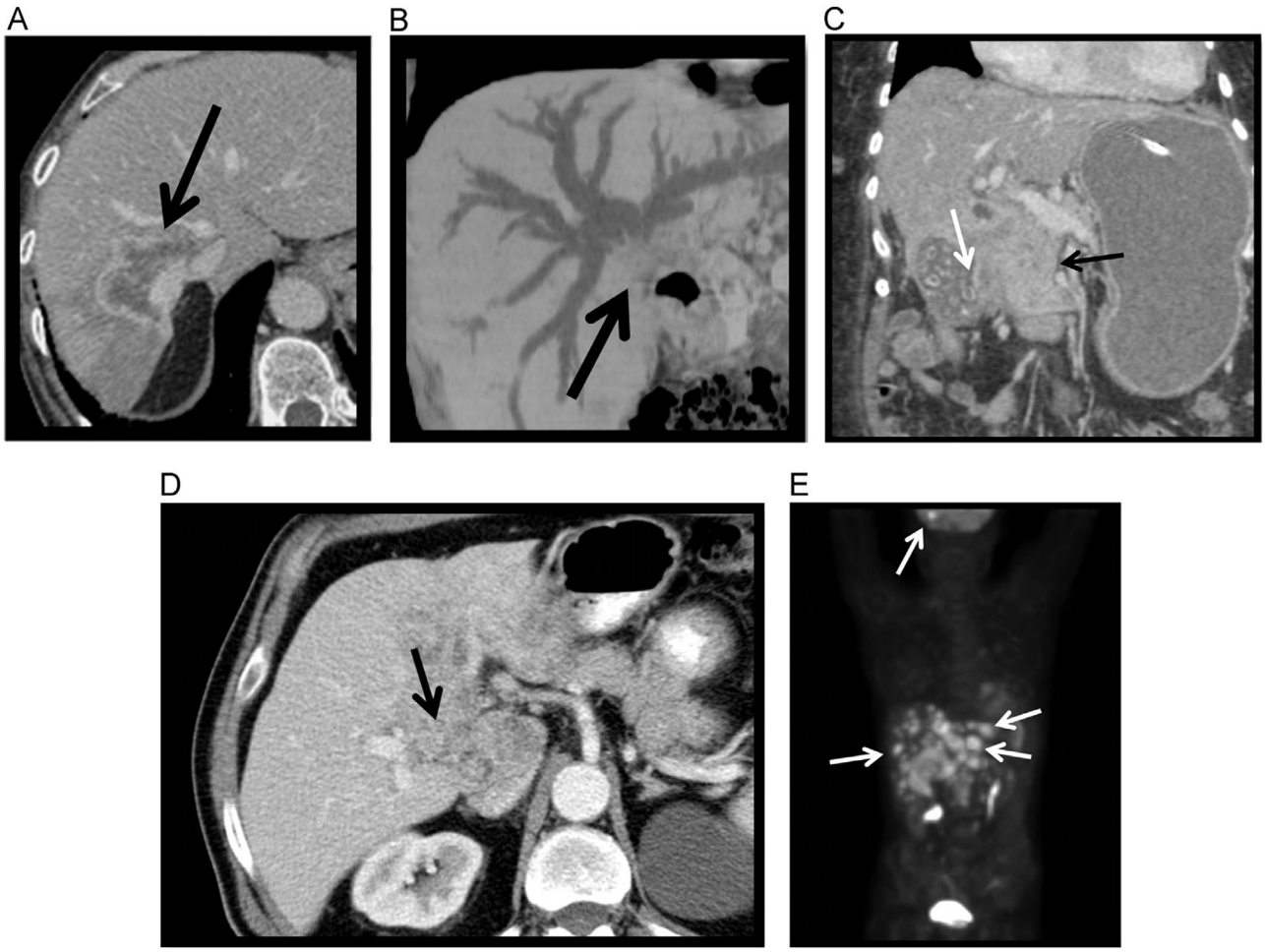

FIG 3. (A) Stage 0-I - Axial CT shows mass with irregular margins in the right hepatic ducts (arrow). (B) Stage 0-I - Coronal CT shows central tumor with dilation of right and left ducts (arrow). (C) Stage II - Coronal CT shows local invasion into liver (black arrow) and gallbladder (white arrow). (D) Stage III - Axial CT shows invasion of main portal vein (arrow). (E) Stage IV - Coronal PET showing abdominal and right cerebellar uptake (arrows) consistent with distant metastasis.

treatment with chemotherapy. Proper staging often requires computed tomography-positron emission tomography, diagnostic laparoscopy, and endoscopic ultrasound for investigations. In reviewing cross-sectional images of a patient with gastric cancer, it is important to identify gastroesophageal junction tumors as they may be treated differently with esophagectomy and mediastinal lymph node dissection from a thoracic approach.[29] Gastric cancer is generally divided into 3 categories from a practical perspective, including early gastric cancer, locally advanced cancer, and metastatic gastric cancer. Early gastric cancer (T1/T2/N0) is treated with upfront surgical resection (Fig 4A). Locally advanced gastric cancer (T3/T4/N+) is treated with neoadjuvant chemotherapy and then surgical resection (Fig 4B). Metastatic disease conventionally precludes surgical resection (Fig 4C). Based on treatment changes, the imaging tipping points exist between stages IA/IB and IIA, and between stage IIIC and IV (Table 7).[1]

Therefore, key questions to ask in the imaging evaluation of a patient with known gastric carcinoma include:

(1) Where the location of the lesion?
Proximal lesions (upper third) are treated with total gastrectomy with possible esophagectomy. Distal lesions (lower two-thirds) are treated with subtotal or distal gastrectomy.

(2) Is there lymphadenopathy?
Findings of multiple nodes may prompt the oncology team to consider treatment with neoadjuvant chemotherapy with or without chemoradiation.

(3) Are there distant metastases?
The presence of distant metastasis or more than 15 lymph nodes may focus the treatment paradigm on palliative options.

(4) Is there gastric outlet obstruction?
May require palliative surgery or procedure to decompress the stomach in the interim while the patient is being considered for the treatment modalities above.

(5) Is there vessel involvement?
Invasion of the aorta or encasement or occlusion of the hepatic artery or celiac axis/proximal splenic artery preclude resectio.

(6) Is there adjacent organ involvement?

Does not preclude surgery but changes the type of surgery, that is, invasion into pancreas, warrants a Whipple.

Small Bowel Adenocarcinoma

Small bowel adenocarcinoma is rare. The American Cancer Society estimated that about 10,190 people were diagnosed with small bowel cancer in 2017.[3] Roughly, 37% are adenocarcinomas and the remaining 63% are sarcomas, carcinoid, tumors, gastrointestinal stromal tumors, and intestinal lymphomas.[30] Risk factors for small bowel adenocarcinoma include Crohn's disease, hereditary nonpolyposis colorectal cancer, and familial adenomatous polyposis.[31] Treatment for small bowel adenocarcinoma includes surgical resection for localized disease. Adjuvant chemotherapy or

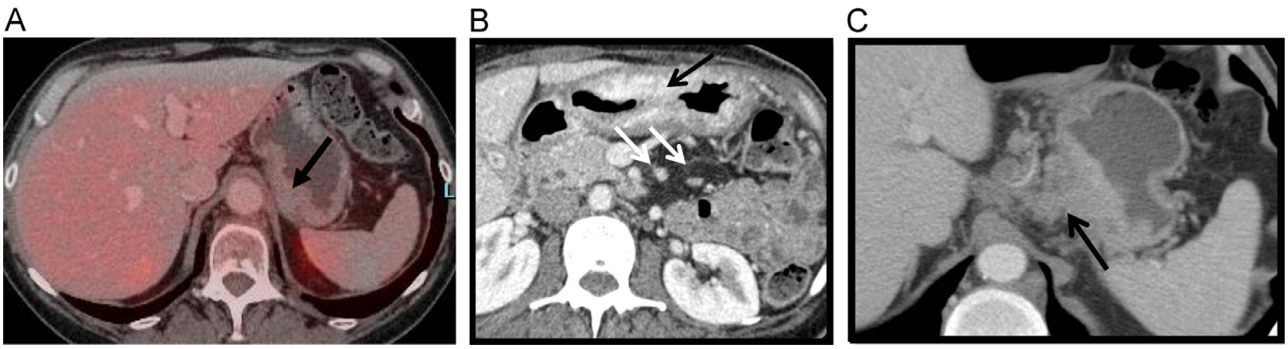

FIG 4. (A) Stage 0-I - Axial PETCT showed tumor in the posterior wall of the stomach. No FDG uptake was noted in the area of the tumor (arrow). There was no adenopathy. (B) Stage II-III - Axial CT show gastric wall thickening (black arrow) and multiple mesenteric nodes (white arrows). (C) Stage IV - Axial CT shows gastric tumor invading the left adrenal gland (arrow).

chemoradiation may also be considered for localized disease. Adenocarcinomas should be differentiated from carcinoids tumors, as they are managed differently. Based on the treatment changes, the imaging tipping point of small bowel adenocarcinoma exists between stage III and IV (Table 8).

Small bowel adenocarcinomas from stage 0-III can range from mucosal lesions to tumors that extend to nearby organs and nodes (Fig 5A and B). The treatment in tumors without distant metastasis usually entails surgical resection and lymph node dissection. Even if the entire tumor cannot be resected, palliative resection, small bowel bypass, or bowel stent placement may be performed to help manage bowel obstruction.[32] Special consideration is paid to periampullary tumors, which are often treated similarly to pancreaticobiliary tumors.

Stage IV small bowel adenocarcinomas are defined by distant metastasis (Fig 5C). Attempts at palliative resection, surgical bypass, or stent placement may be necessary at times. Chemotherapy may be an option to help with palliation for patients with metastatic small bowel adenocarcinoma. Chemoradiation may help for local control, and palliative radiation be used to treat pain or bleeding.

TABLE 7
TMN staging of gastric cancer and identified "Tipping Points"

- Stage grouping for gastric cancer is as follows:
  - Stage 0 – Tis, N0, M0
  - Stage IA - T1, N0, M0
  - Stage IB – T1, N1, M0, OR T2, N0, M0

Surgical Resection

Tipping Point

  - Stage IIA – T1, N2, M0 OR T2, N1, M0 OR T3, N0, M0
  - Stage IIB – T1, N3, M0 OR T2, N2, M0, OR T3, N1, M0 OR T4a, N0, M0
  - Stage IIIA – T2, N3, M0 OR T3, N2, M0 OR T4a, N1, M0
  - Stage IIIB – T3, N3, M0 OR T4a, N2, M0, T4b, N1, M0 OR T4b, N0, M0
  - Stage IIIC – T4a, N3, M0 OR T4b, N3, M0 OR T4b, N2, M0

Surgery/Neoadjuvant Chemotherapy

Tipping Point

  - Stage IV – Any T, Any N, M1

Palliative Therapy

- Staging of gastric cancer is as follows:
  - Tumor (T)
    - TX – Tumor cannot be assessed
    - T0 – No evidence of a main tumor
    - Tis – Carcinoma in situ
    - T1 – Tumor invades lamina propria, muscularis mucosae, or submucosa
      - T1a – tumor invades lamina propria or muscularis mucosae
      - T1b – tumor invades submucosa
    - T2 – tumor invades muscularis propria
    - T3 – Tumor invades the subserosa
    - T4 - Tumor invades serosa or nearby organs (spleen, intestines, pancreas, kidneys or major vessels)
      - T4a – tumor invades serosa (visceral peritoneum)
      - T4b – tumor invades adjacent structures
  - Regional lymph nodes (N)
    - NX – Regional nodes cannot be assessed
    - N0 - No regional lymph node metastasis
    - N1 - Spread to 1-2 nodes
    - N2 – Spread to 3-6 nodes
    - N3 – Spread to > 7 nodes
      - N3a – spread to 7-15 regional lymph nodes
      - N3b – spread in > 16 regional lymph nodes
  - Distant metastasis (M)
    - MX – Distant metastasis cannot be determined
    - M0 – No distant metastasis
    - M1 – Distant metastasis

TABLE 8
TMN staging of small bowel cancer and identified "Tipping Points"

- Stage grouping for small bowel cancer is as follows:
  - Stage 0 – Tis, N0, M0
  - Stage I - T1, N0, M0 OR T2, N0, M0
  - Stage IIA – T3, N0, M0
  - Stage IIB – T4, N0, M0
  - Stage IIIA – Any T, N1, M0
  - Stage IIIB – Any T, N2, M0
  - Stage IV – Any T, Any N, M1

Surgical Resection

Tipping Point

Chemotherapy, may try surgery

- Staging of small bowel cancer is as follows:
  - Tumor (T)
    - TX – Tumor cannot be assessed
    - T0 – No evidence of primary tumor
    - Tis – Carcinoma in situ
    - T1a – Tumor invades lamina propria
    - T1b – Tumor invades submucosa
    - T2 – Tumor invades muscularis propria
    - T3 – Tumor invades through the muscularis propria into the subserosa or into the nonperitonealized perimuscular tissue with extension 2 cm or less
    - T4 - Tumor extends through the wall and invades nearby organs or vessels
  - Regional lymph nodes (N)
    - NX – Regional nodes cannot be assessed
    - N0 - No regional lymph node metastasis
    - N1 - Spread to 1-3 regional lymph nodes
    - N2 – Spread to > 4 regional lymph nodes
  - Distant metastasis (M)
    - MX – Distant metastasis cannot be determined
    - M0 – No distant metastasis
    - M1 – Distant metastasis

Therefore, key questions to ask in the evaluation of a patient with known small bowel adenocarcinoma include:

(1) Is this an adenocarcinoma or carcinoid tumor?
More than 50% of all cases of small bowel adenocarcinoma are duodenal tumors.[31] Surgical treatment becomes a Whipple procedure rather than a primary resection and reanastomosis, but depends on if the tumor is in the first or second part vs third or fourth part of the duodenum.

(2) Can the tumor be resected?
Assessment is made by the surgeon in reviewing films with the radiologist. If the tumor cannot be resected then palliative treatment may include intraluminal stent to prevent obstruction, with discussion of the risks and benefits of palliative chemotherapy and chemoradiation.

(3) Are there distant metastasis?

If so, the primary treatment is chemotherapy. Surgical resection and radiation may be used for palliative purposes. Radiation is also used to manage bleeding, pain from nonbone lesions, and in rare instances, palliation of brain metastasis.

Rectal Carcinoma

Rectal cancer is the second most common cause of cancer deaths in men and third most common in women in the United States.[3] Treatment options for rectal adenocarcinoma include primary surgical resection, radiation therapy, and chemotherapy.[33-35] Although the staging system for rectal and colon tumors is the same, management of these tumors varies, particularly for T3 or higher (extension through the muscularis propria) or node positive disease. For locally advanced rectal tumors (T3-4, or node positive), patients undergo preoperative (neoadjuvant) chemoradiation, usually with fluorouracil-based

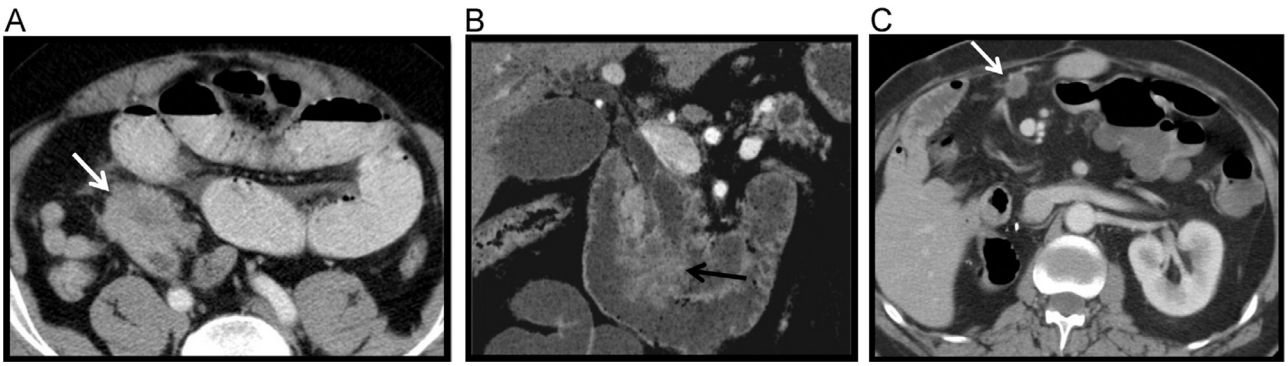

FIG 5. (A) Stage 0-III - Axial CT shows small bowel tumor extending from jejunal loops (arrow) in the right lower quadrant. (B) Stage 0-III Coronal CT show peri-ampullary soft tissue mass (arrow) causing common bile duct dilation. (C) Stage IV - Axial CT shows anterior peritoneal nodule (arrow) in a patient with duodenal adenocarcinoma.

TABLE 9
TMN staging of rectal cancer and identified "Tipping Points"

- Stage grouping for rectal cancer is as follows:
  - Stage 0 – Tis, N0, M0
  - Stage I - T1-2, N0, M0
  - Stage IIA – T3, N0, M0
  - Stage IIB – T4a, N0, M0
  - Stage IIC – T4b, N0, M0
  - Stage IIIA – T1-2, N1/N1c, M0 OR T1, N2a, M0
  - Stage IIIB – T1-2, N2b, M0 OR T2-3, N2a, M0 OR T3-T4a, N1/N1c, M0
  - Stage IIIC – T4a, N2a, M0 OR T3-4a, N2b, M0 OR T4b, N1-2, M0
  - Stage IVA – Any T, Any N, M1a
  - Stage IVB – Any T, Any N, M1b

Local excision/Colectomy

Tipping Point

Pre-operative chemoradiation for rectal tumors. Adjuvant chemotherapy for stage IIB colon cancer

Tipping Point

Chemotherapy

- Staging of rectal cancer is as follows:
  - Tumor (T)
    - TX - Primary tumor cannot be assessed
    - T0 – No evidence of primary tumor
    - Tis – Carcinoma in situ
    - T1 – Tumor invades submucosa
    - T2 - Tumor invades muscularis propria
    - T3 - Tumor invades through the muscularis propria into the pericolorectal tissues
    - T4a - Tumor penetrates to the surface of the visceral peritoneum
    - T4b – Tumor directly invades or is adherent to other organs or structures
  - Regional lymph nodes (N)
    - NX - Regional lymph nodes cannot be assessed
    - N0 - No regional lymph node metastasis
    - N1 - Spread to 1-3 nearby nodes
      - N1a – Spread to 1 regional lymph node
      - N1b – Spread to 2-3 regional lymph nodes
      - N1c – Tumor deposit in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
    - N2 - Spread to 4 or more nearby lymph nodes
      - N2a – Spread to 4-6 regional lymph nodes
      - N2b – Spread to > 7 regional lymph nodes
  - Distant metastasis (M)
    - MX - Distant metastasis cannot be assessed
    - M0 - No distant metastasis
    - M1 - Distant metastasis
      - M1a – metastasis confined to one organ or site (eg, liver, lung, ovary, nonregional node)
      - M1b – metastases in more than one organ/site of the peritoneum

regimens followed by surgical resection, with consideration of adjuvant chemotherapy for 4-6 months (Table 9).[1]

Another issue to address when evaluating patients with rectal cancer is the need to determine if tumor is within the rectum or whether it is within the colon (including sigmoid), as it carries implications for determining if the tumor should be treated as a primary rectal vs primary colon cancer, as detailed above. Although anatomically, the rectosigmoid junction is defined as being 15 cm above the anal verge, controversy exists as to the external bony landmarks that may be used to distinguish the rectosigmoid junction. One group has favored using a line drawn from the sacral promontory to the pubic symphysis as the line identifying the rectosigmoid junction.[36]

Stage 0-I tumors are limited to the mucosa with no extension through the muscularis propria (Fig 6A). Treatment varies from local excision or polypectomy to surgical resection. Imaging cannot distinguish between stage 0 and stage I. For high rectal tumors (upper two-third of the rectum) patients may undergo low anterior resection. For low rectal tumors (lower one-third of the rectum), patients may receive abdominoperineal resection. This distinction is important, as it has implications for the need for an ostomy postoperatively.

With T3 tumors there is extension beyond the muscularis propria (Fig 6B and C). As the T category increases, the risk of lymph node involvement also increases. For patients with clinically T3 or node positive rectal cancer, the treatment for rectal cancer includes preoperative chemoradiation and total mesorectal excision, followed by 4-6 months of adjuvant 5-FU based chemotherapy.

Stage IV tumors are defined by distant metastasis (8D). Treatment includes chemotherapy, palliative local tumor resection, as well as resection of liver and lung metastasis in selected cases. Patients who are not surgical candidate or those with too many metastasis may undergo ablation or SIRT.[37] Rectal MRI is also useful to detect extramural vascular invasion, which has been associated with a 4-fold increased risk of distant metastasis.[38]

Therefore, key questions to ask in reviewing the imaging of a patient with rectal cancer include:

(1) Are there distant metastasis?
Patients with liver or lung metastasis may sometimes have the option of surgical resection or stereotactic radiation therapy or ablation. In addition, patients with metastatic rectal cancer should discuss the option of chemotherapy and palliative local resection.

(2) In what portion of the rectum do you see the tumor?
Although not related to staging, the exact location of the tumor can determine the type of treatment: preoperative chemoradiation of

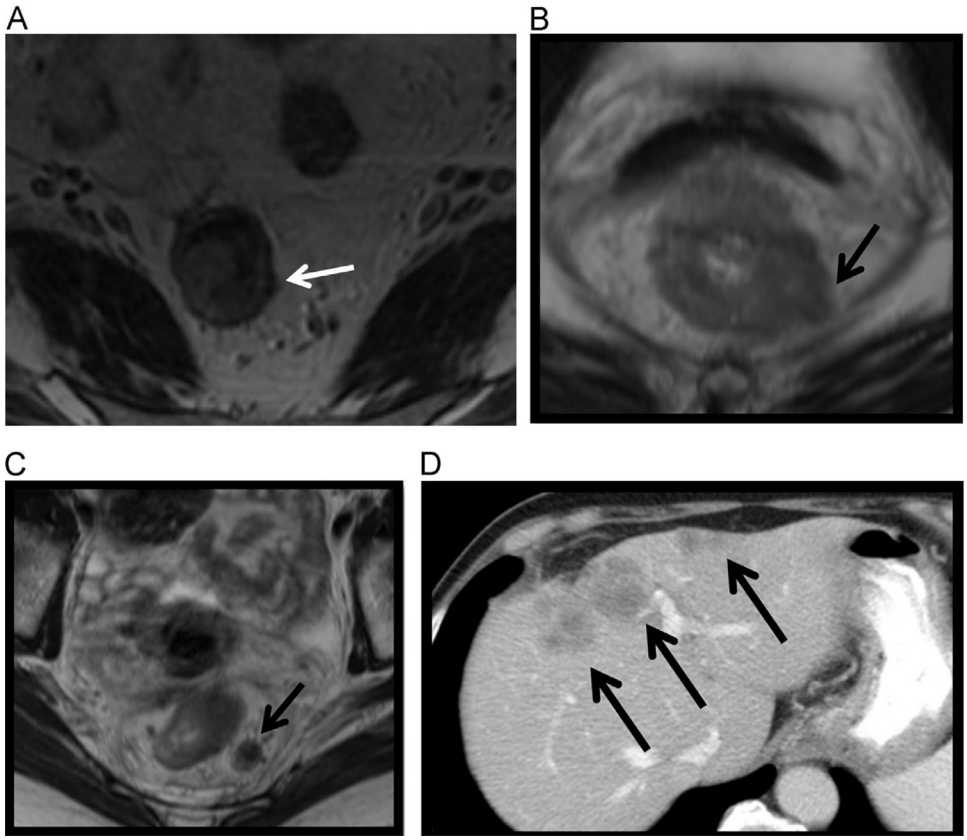

FIG 6. (A) Stage 0 – IIA - Axial MRI confirm rectal tumor confined to the mucosa/wall (arrow). (B) Stage IIB-III -Axial T1-weighted MRI scans show extension of rectal tumor beyond serosa on posterior left (arrow). (C) Stage IIB- III - Axial T1-weighted MRI shows a left perirectal node. (D) Stage IV - Axial CT shows multiple hepatic metastasis from rectal cancer (arrows).

TABLE 10
TMN staging of anal cancer and identified "Tipping Points"

- Stage grouping for anal cancer is as follows:
  - Stage 0 – Tis, N0, M0
  - Stage I – T1, N0, M0,
  - Stage II – T2-3, N0, M0

  Chemoradiation

  - Stage IIIA – T1-3, N1, M0, OR T4, N0, M0
  - Stage IIIB – T4, N1, M0 OR Any T, N2-3, M0

  Tipping Point ←

  - Stage IV – Any T, Any N, M1

  Palliative chemotherapy

- Staging of anal cancer is as follows:
  - Tumor (T)
    - TX - Primary tumor cannot be assessed
    - Tis – Carcinoma in situ
    - T1 – Tumor ≤ 2
    - T2 - Tumor > 2 ≤ 5 cm
    - T3 - Tumor > 5 cm
    - T4 - Tumor extension into nearby organs vagina, urethra, or bladder
  - Regional lymph nodes (N)
    - NX - Regional lymph nodes cannot be assessed
    - N0 - No regional lymph node metastasis
    - N1 - Spread to lymph nodes near the rectum
    - N2 - Spread lymph nodes one one side of the groin or pelvis
    - N3 – Spread to lymph nodes near the rectum and in the pelvis or groin OR to both sides of the groin or pelvis
  - Distant metastasis (M)
    - MX - Distant metastasis cannot be assessed
    - M0 - No distant metastasis
    - M1 - Distant metastasis

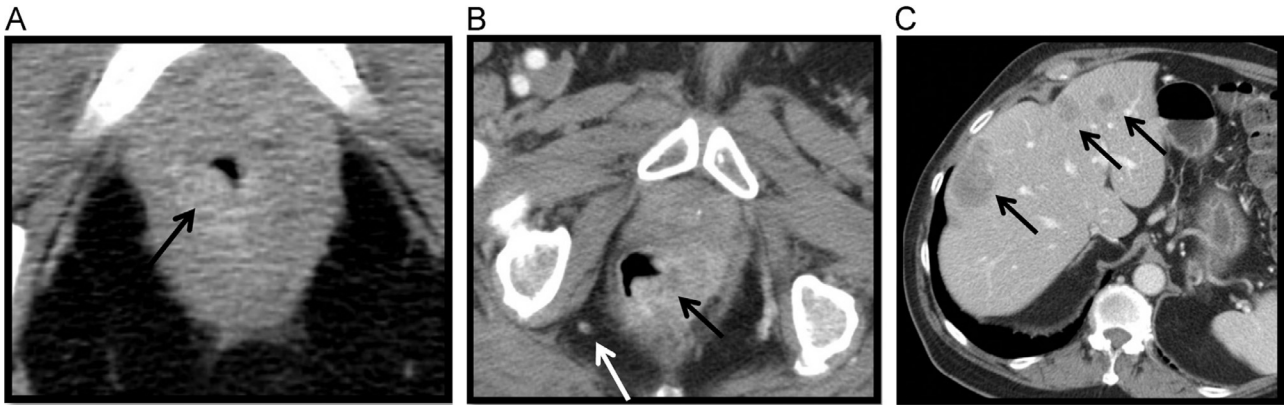

FIG 7. (A) Stage 0-IIIB - Axial CT shows right posterior anal wall thickening (arrow) consistent with known anal carcinoma. (B) Stage 0-IIIB - Axial CT shows large left posterior anal wall mass (black arrow) consistent with known anal carcinoma. A small adjacent node is also visualized (white arrow). (C) Stage IV - Axial CT shows multiple hepatic metastasis (arrows) in a patient with anal carcinoma.

T3-T4 rectal cancer, right hemicolectomy vs left hemicolectomy, and low anterior resection vs abdominoperineal resection.

(3) Is there extension through the wall of the muscularis propria? Is there adjacent adenopathy?
Extension through the wall of the muscularis propria or adjacent adenopathy may result in preoperative chemoradiation before surgical resection for patients with rectal cancer.

(4) Is there extramural vascular invasion on MRI?

Extramural vascular invasion, which has been associated with a 4-fold increased risk of distant metastasis.

Anal Cancer

Although anal cancer is less common than rectal cancer, an estimated 8200 individuals will be diagnosed with anal cancer in 2017.[3] Most anal cancers are squamous cell carcinomas. Treatment options for the management of anal cancer include definitive chemoradiation.[39] Surgery is reserved for patients with recurrent or residual disease after chemoradiotherapy. Based on the treatment options, the imaging tipping points of anal cancer exist between stages IIIB and IV (Table 10).[1]

Stage 0-II can be up to 5 cm with no extension to nearby organs (Fig 7A). Concurrent chemoradiotherapy is the appropriate treatment for these patients with localized disease. In patients with locally advanced disease (stage IIIA-IIIB) where there is extension to nearby organs such as the vagina, urethra, or bladder, or spread to regional nodes, combined chemoradiotherapy remains the preferred treatment (Fig 7B). Patients with distant metastases (Stage IV) should receive systemic chemotherapy (Fig 7C).[40]

Therefore, key questions to address when examining the images of a patient with known anal cancer include:

Are there distant metastases?

The presence of distant metastasis results in a discussion with the patient about the options of chemotherapy as standard therapy, consideration of palliative radiation therapy, or clinical trials with novel therapies.

Conclusion

Oncological staging is useful to help guide discussions about management and prognosis for patients with cancer. In reviewing the staging system and treatment through radiographic imaging alone, several caveats should be considered: (1) imaging findings such as adenopathy or even capsular extension may not always correspond to pathological findings (the advent of positron emission tomography-computed tomography and other molecular imaging agents, which assesses for metabolic as well as anatomical changes, will aid in better defining these imaging findings); (2) standard staging often also relies on nonimaging clinical findings including, intraoperative appearance and pathological results; and (3) treatments options identified in this article can vary by institution and will change over time.

Examining the cancer staging system through the lens of radiographic imaging can provide radiologists with a useful roadmap in deciding what is important in interpreting oncological imaging studies. Universal adoption of these “tipping points” may also allow for incorporation of these guidelines into dictation macros, thereby encouraging pertinent oncological findings to be more standardized for each tumor type and ensuring that the proper information is more readily and accurately conveyed to the oncology team.

References

1. Edge S, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th Edition. Springer. ⟨doi:10.1007/978-1-4757-3656-4⟩.
2. National Comprehensive Cancer Network NCCN Practice Guidelines for Pancreatic Cancer, Version 1. ⟨Http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf⟩. Published 2013. Accessed November 20, 2017.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67(1):7–30, https://doi.org/10.3322/caac.21387.
4. Alberts SR, Gores GJ, Kim GP, et al. Treatment Options for Hepatobiliary and Pancreatic Cancer. Mayo Clin Proc 2007;82(5):628–37, https://doi.org/10.4065/82.5.628.
5. 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(1):248–60, https://doi.org/10.1148/radiol.13131184.
6. Moertel CG, Reitemeier RJ, Childs DS, et al. Combined 5-fluorouracil and supervoltage radiation therapy of locally unresectable gastrointestinal cancer. Lancet 2017;294(7626):865–7, https://doi.org/10.1016/S0140-6736(69)92326-5.
7. Ferrone CR, Marchegiani G, Hong TS, et al. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 2015;261(1):12–7, https://doi.org/10.1097/SLA.0000000000000867.
8. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364(19):1817–25, https://doi.org/10.1056/NEJMoa1011923.
9. VHD D, Thomas E, AF P, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369(18):1691–703, https://doi.org/10.1056/NEJMoa1304369.
10. Bold RJ, Charnsangavej C, Cleary KR, et al. Major vascular resection as part of pancreaticoduodenectomy for cancer: Radiologic, intraoperative, and pathologic analysis. J Gastrointest Surg 1999;3(3):233–43, https://doi.org/10.1016/S1091-255X(99)80065-1.
11. Ryerson AB, Eheman CR, Altekruse SF, et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. Cancer 2016;122(9):1312–37, https://doi.org/10.1002/cncr.29936.
12. Hashim D, Boffetta P, La Vecchia C, et al. The global decrease in cancer mortality: trends and disparities. Ann Oncol Off J Eur Soc Med Oncol 2016;27(5):926–33, https://doi.org/10.1093/annonc/mdw027.
13. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: The BCLC staging classification. Semin Liver Dis 1999;19(3):329–38, https://doi.org/10.1055/s-2007-1007122.

14. Liver EA for the S of the, Cancer EO for R and T of. EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2017;56(4):908–43, https://doi.org/10.1016/j.jhep.2011.12.001.
15. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334(11):693–9, https://doi.org/10.1056/NEJM199603143341104.
16. Ikai I, Arii S, Kojiro M, et al. Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. Cancer 2004;101(4):796–802, https://doi.org/10.1002/cncr.20426.
17. Livraghi T, Goldberg SN, Lazzaroni S, et al. Small hepatocellular carcinoma: Treatment with radio-frequency ablation versus ethanol injection. Radiology 1999;210(3):655–61, https://doi.org/10.1148/radiology.210.3.r99fe40655.
18. Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology 2017;129(1):122–30, https://doi.org/10.1053/j.gastro.2005.04.009.
19. Heckman JT, deVera MB, Marsh JW, et al. Bridging locoregional therapy for hepatocellular carcinoma prior to liver transplantation. Ann Surg Oncol 2008;15(11):3169–77, https://doi.org/10.1245/s10434-008-0071-3.
20. Keane FK, Hong TS. Role and future directions of external beam radiotherapy for primary liver cancer 107327481772924 Cancer Control 2017;24(3), https://doi.org/10.1177/1073274817729242.
21. Bush DA, Smith JC, Slater JD, et al. Randomized clinical trial comparing proton beam radiation therapy with transarterial chemoembolization for hepatocellular carcinoma: Results of an interim analysis. Int J Radiat Oncol Biol Phys 2016;95(1):477–82, https://doi.org/10.1016/j.ijrobp.2016.02.027.
22. Skinner HD, Hong TS, Krishnan S. Charged-particle therapy for hepatocellular carcinoma. Semin Radiat Oncol 2011;21(4):278–86, https://doi.org/10.1016/j.semradonc.2011.05.007.
23. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(4):378–90, https://doi.org/10.1056/NEJMoa0708857.
24. Culleton S, Jiang H, Haddad CR, et al. Outcomes following definitive stereotactic body radiotherapy for patients with Child-Pugh B or C hepatocellular carcinoma. Radiother Oncol 2014;111(3):412–7, https://doi.org/10.1016/j.radonc.2014.05.002.
25. Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2016;34(5):460–8, https://doi.org/10.1200/JCO.2015.64.2710.
26. Saha SK, Zhu AX, Fuchs CS, Brooks GA. Forty-year trends in cholangiocarcinoma Incidence in the U.S. Intrahepatic disease on the rise. Oncologist 2016;21(5):594–9, https://doi.org/10.1634/theoncologist.2015-0446.
27. Singh P, Patel T. Advances in the diagnosis, evaluation and management of cholangiocarcinoma. Curr Opin Gastroenterol 2006;22(3).
28. Kanne JP, Rohrmann CA, Lichtenstein JE. Eponyms in radiology of the digestive tract: historical perspectives and imaging appearances. Part 2. Liver, biliary system, pancreas, peritoneum, and systemic disease. Radiographics 2006;26(2):465–80, https://doi.org/10.1148/rg.262055130.
29. Gee DW, Rattner DW. Management of gastroesophageal tumors. Oncology 2007;12(2):175–85, https://doi.org/10.1634/theoncologist.12-2-175.
30. Bilimoria KY, Bentrem DJ, Wayne JD, et al. Small bowel cancer in the united states: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg 2009;249(1).
31. Kummar S, Ciesielski TE, Fogarasi MC. Management of small bowel adenocarcinoma. Oncology (Williston Park) 2002;16(10):1364–9.
32. Bauer RL, Palmer ML, Bauer AM, et al. Adenocarcinoma of the small intestine: 21-year review of diagnosis, treatment, and prognosis. Ann Surg Oncol 1994;1(3):183–8. ⟨http://www.ncbi.nlm.nih.gov/pubmed/7842287⟩ Accessed November 6, 2017.
33. Lacy AM, García-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: A randomised trial. Lancet 2002;359(9325):2224–9, https://doi.org/10.1016/S0140-6736(02)09290-5.
34. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC Trial. J Clin Oncol 2009;27(19):3109–16, https://doi.org/10.1200/JCO.2008.20.6771.
35. MacFarlane JK, Ryall RDH, Heald RJ. Mesorectal excision for rectal cancer. Lancet 1993;341(8843):457–60, https://doi.org/10.1016/0140-6736(93)90207-W.
36. Bagla N, Schofield JB. Rectosigmoid tumours: Should we continue sitting on the fence? Color Dis 2007;9(7):606–8, https://doi.org/10.1111/j.1463-1318.2007.01329.x.
37. Welsh JS, Kennedy AS, Thomadsen B. Selective internal radiation therapy (SIRT) for liver metastases secondary to colorectal adenocarcinoma. Int J Radiat Oncol Biol Phys 2017;66(2):S62–73, https://doi.org/10.1016/j.ijrobp.2005.09.011.
38. Smith NJ, Barbachano Y, Norman AR, et al. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. Br J Surg 2008;95(2):229–36, https://doi.org/10.1002/bjs.5917.
39. Clark MA, Hartley A, Geh JI. Cancer of the anal canal. Lancet Oncol 2004;5(3):149–57, https://doi.org/10.1016/S1470-2045(04)01410-X.
40. Glynne-Jones R, Nilsson PJ, Aschele C, et al. Anal cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(suppl_3):iii10–20.