Appendiceal Neoplasms

67

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Refer to Algorithm in Fig. 67.1

A. Many tumors of the appendix present acutely, often initially mistaken for acute appendicitis and are only found intra-operatively or following pathology examination. Others present as asymptomatic incidental lesions during a work-up for other symptoms (*i.e.*, CT scan) and allow the opportunity for a more definitive evaluation. Appendiceal tumors can be divided into epithelial (*i.e.*, adenoma, adenocarcinoma), non-epithelial (*e.g.*, carcinoid), and mixed lesions. Other rare lesions include sarcomas, lymphomas, and mixed lesions such as goblet cell carcinoids.

B. Appendiceal neoplasms are rare, with a reported incidence of 1.2 cases per 100,000 people per year in the United States. In general, the history and physical examination are non-specific. Patients are often over 50 years of age, with a mean age of 62–65 years, and there is a slight male predominance. In many cases, patients are asymptomatic, especially in early stage disease. Those patients with symptoms may present with right lower quadrant abdominal pain (mimicking appendicitis), which is classically from obstruction of the lumen by the tumor. As disease progresses, mucin throughout the abdomen (*i.e.*, pseudomyxoma peritonei) may lead to abdominal distension, obstructive symptoms and even a mass. Unfortunately this indicates advanced disease.

C. Radiological evaluation is one of the most important aspects for evaluation. Plain radiographs may be indicated in those patients with a concern for obstruction or perforation, although non-specific. Cross-sectional imaging with CT is useful both in the initial evaluation as well as for surveillance. CT will help in the staging of mucinous adenocarcinoma to evaluate for lymph node and distant metastases. CT will also help with calculation of the peritoneal cancer index (PCI) (Fig. 67.2). Abdominal MRI has been incorporated in several surveillance strategies to follow solid and mucinous peritoneal disease. Both allow for evaluation of the appendix as well as the entire abdomen (Table 67.1). Fluoroscopic studies such as small bowel follow-through and gastrografin enema are seldom indicated as primary studies. PET scans may be helpful for solid tumors to detect recurrence but typically are unreliable for small lesions <1 cm and not helpful for detecting pseudomyxoma peritonei. Somatostatin receptor scan may be used in those patients with carcinoid tumors >1 cm to help detect distant disease.

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S. R. Steele et al. (eds.), *Clinical Decision Making in Colorectal Surgery*,
https://doi.org/10.1007/978-3-319-65942-8_67

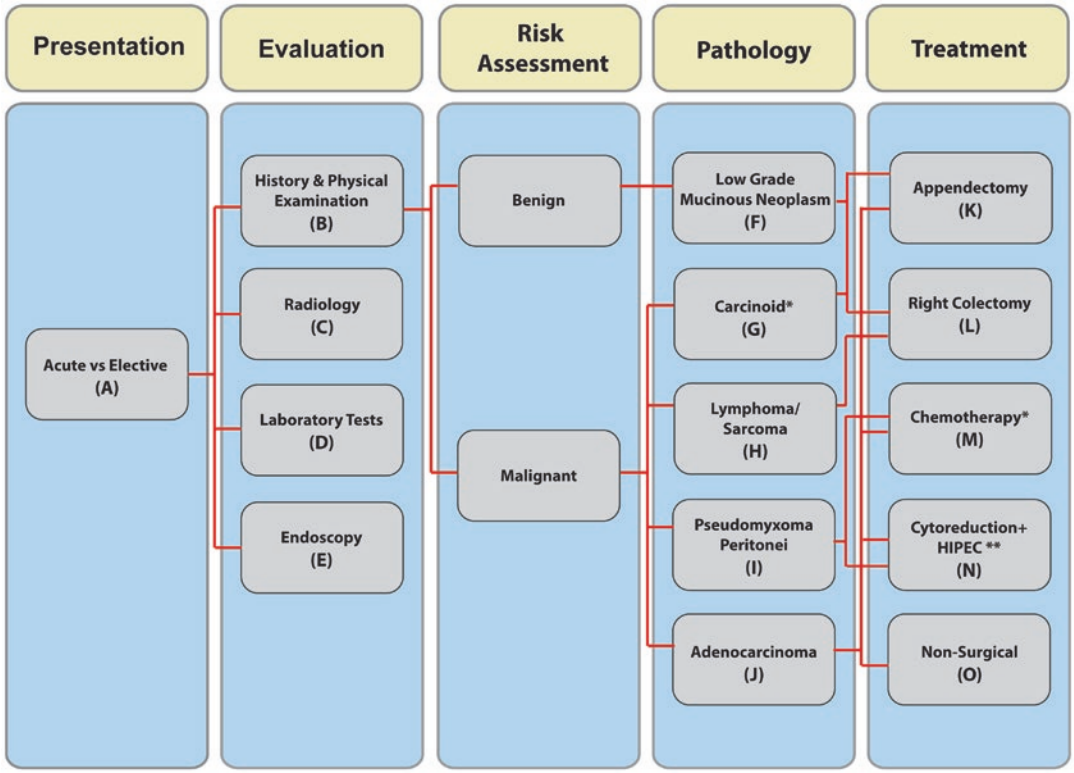
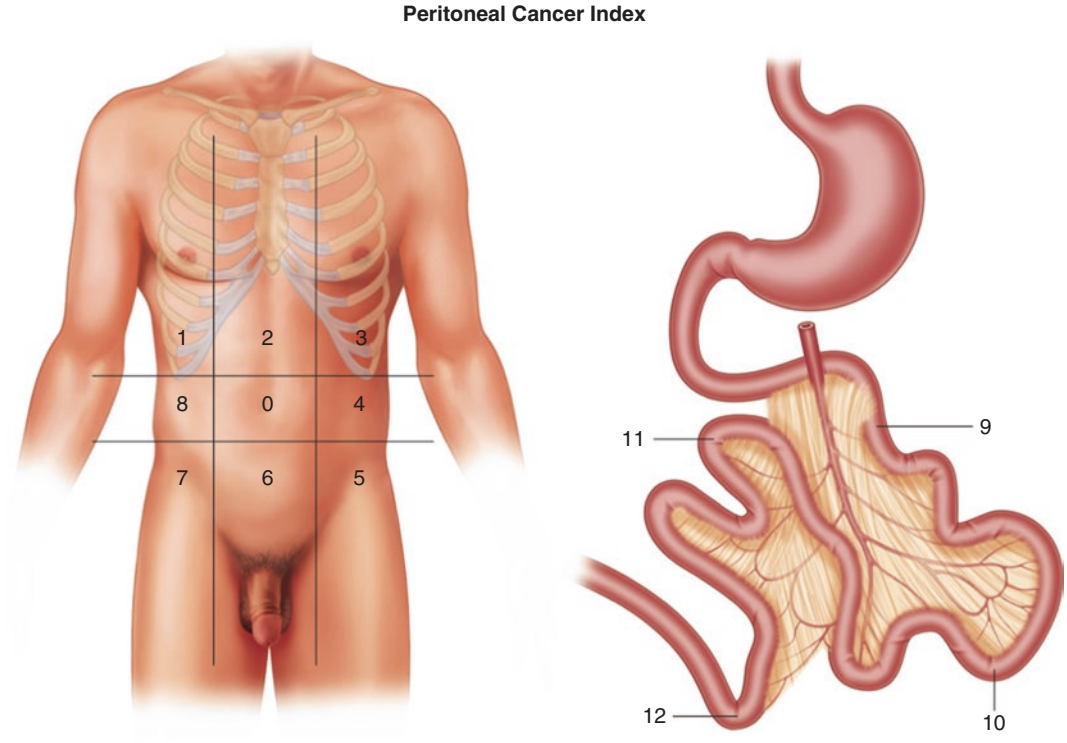


Fig. 67.1 Algorithm for appendiceal neoplasms. ∗Appendectomy for <1 cm lesions and negative margins; Right colectomy for >2 cm lesions, positive (or questionable) margins, nodal involvement, invasion of mesoappendix >3 mm, or metastases to the liver only; Chemotherapy for diffuse metastases >1 site; $ May require HIPEC and cytoreduction in the setting of diffuse mucinosis; ∗∗ Diffuse mucinosis with PCI <16–20, or perforated primary without pseudomyxoma peritonei; # Diffuse mucin or carcinomatosis with PCI >16–20, diffuse systemic metastases, or carcinomatosis with concomitant metastases

D. There is no diagnostic laboratory test for the majority of the appendiceal tumors. Laboratory testing may include baseline CBC, chemistry and coagulation panels as indicated by appropriate risk stratification. For patients with suspected epithelial lesions, the tumor marker carcinoembryonic antigen (CEA) should be evaluated. Carcinoid lesions may be evaluated with urinary 5-HIAA metabolites and serum chromogranin A.

E. Endoscopy is not classically useful to detect the primary lesion. In some cases, mucin may be visualized extruding from the appendiceal orifice that may suggest the presence of a mucinous neoplasm. More importantly, those patients with an appendiceal neoplasms including carcinomas, carcinoid and neuroendocrine tumors have an ~10–20% risk of concomitant lesions elsewhere in the colon. Prior to any surgical intervention, endoscopic clearance of the colon should be performed.

F. Nomenclature for mucinous neoplasms of the appendix is evolving and contributes somewhat to the confusion regarding the optimal treatment. In general, low-grade mucinous neoplasms encompass serrated or villous adenomas, cystadenoma, or mucinous neoplasms of uncertain behavior. Of note, mucocele is a morphologic term to describe a dilated fluid filled appendix, and does not relate to the biological aggressiveness. They are slow-growing and typically indolent. They may rupture (or iatrogenically ruptured during surgery), leading to mucin throughout the abdomen. Localized tumors may typically be treated with appendectomy



Regions	Lesion size	Lesion size score
0. Central	—	LS 0 No tumor seen
1. Right upper	—	LS 1 Tumor up to 0.5 cm
2. Epigastrium	—	LS 2 Tumor up to 5.0 cm
3. Left upper	—	LS 3 Tumor > 5.0 cm or confluence
4. Left flank	—	
5. Left lower	—	
6. Pelvis	—	
7. Right lower	—	
8. Right flank	—	
9. Upper jejunum	—	
10. Lower jejunum	—	
11. Upper ileum	—	
12. Lower ileum	—	
PCI		

Fig. 67.2 Peritoneal Cancer Index (PCI). This is a collective score with a maximum of 39 points from nine abdominal squares and 4 small bowel segments. Each area is scored between 0 (no disease) to 3 (deposits are >5 cm)

and have good long-term prognosis. If epithelial cells are present outside the appendix in the peritoneum, this may lead to more aggressive behavior and result in pseudomyxoma peritonei **(refer to section I in algorithm in** Fig. 67.1**)**.

G. Carcinoid (Neuroendocrine) tumors of the appendix are derived from hormone-active neuroendocrine cells. While various hormones (growth hormone, calcitonin) may be produced, most commonly they secrete serotonin, which is subsequently metabolized to 5-hydroxyindoleacetic acid (5-HIAA). This metabolite is excreted in the urine and classically used to monitor disease. The majority are located at the tip of the appendix, are less than 1 cm, and when large can be associated with a desmoplastic inflammatory response

Table 67.1 Characteristics of Appendiceal Neoplasms on Cross-Sectional Imaging

Lesion	Appearance
Mucocele	Encapsulated dilated appendix filled with intraluminal mucin ± calcifications
Adenocarcinoma	Mucinous: Soft tissue mass-like lesion with cystic dilation and possible invasion through the wall ± disseminated mucin throughout the abdomen; Non-mucinous: Soft tissue mass-like lesion with cystic dilation with possible invasion through the well± lymphadenopathy ± liver metastases
Carcinomatosis	Mucin or clusters of tumor throughout the peritoneum with involvement of peritoneal surface, parenchyma and/or omentum
Carcinoid	Most commonly normal or with localized inflammation;[a] Occasionally with soft-tissue mass within the appendix or diffused mural thickening
Pseudomyxoma Peritonei	Intra-peritoneal low attenuation mucin (ascites) ± serosal implants

[a]Many lesions may present with localized appendiceal inflammation consistent with acute appendicitis or may be not visualized on cross-sectional imaging

Table 67.2 AJCC (seventh Edition) Staging Systems for Primary Appendiceal Neuroendocrine Carcinoma

AJCC	
Tumor	
T1a	≤1 cm greatest diameter
T1b	1–2 cm greatest diameter
T2	>2 cm but ≤4 cm or invasion of cecum
T3	>4 cm or extension to ileum
T4	Perforates peritoneum or invades other organs
Nodes	
N0	No regional lymph node involvement
N1	Metastasis to regional nodes
Metastasis	
–	–
M0	No distant metastasis
M1	Distant metastasis
Stage	
–	–
I	T1, N0, M0
II	T2/3, N0, M0
III	T4, N0, M0
	Any T, N1, M0
IV	Any T, any N, M1
I	T1, N0, M0

AJCC American Joint Committee on Cancer

in the mesentery. Outcomes correlate with stage, of which size is the primary factor (Table 67.2). While lymph node involvement is rare in lesions <1 cm, up to 30% of carcinoids over 2 cm will have nodal metastases. In general, outcomes are good, with 5-year survival for tumors limited to local and regional disease >80%; though 25–30% for stage IV disease. Goblet cell carcinoid represents a mixed epithelial and neuroendocrine tumor variant that presents with a wide spectrum of biological aggressiveness. Whereas the majority are incidental findings on appendectomy, ~10–15% will present with metastatic disease. Outcomes are typically worse than routine carcinoids with 5-year survival for patients with local/regional disease 45–82%, and those with stage IV disease <20%.

H. Lymphoma and sarcoma represent less common tumors than may be found in the appendix. Lymphoma is more common among these more rare conditions, yet the appendix may be the primary disease site. Patients are commonly 30–40 years old, and commonly present in with symptoms of appendicitis or obstructive symptoms from intussusception or local inflammation. Sarcomas are much rarer, with Kaposi's sarcoma and leiomyosarcoma among the subtypes.

I. Pseudomyxoma peritonei may occur in the setting of appendiceal tumors or those from peritoneal or ovarian sources. This process is describes mucin to varying degrees in the peritoneum as well as strong and mucinous epithelial cells. In the setting of appendiceal neoplasms, it results from a rupture of low-grade mucinous neoplasms. The outcome is directly proportional to the amount of mucin, which is a result of the degree of epithelial cell presence or absence in the mucin. Often this will be confined to the right lower quadrant, but may also present as disseminated peritoneal adenomucinosis or peritoneal carcinomatosis. The former may spread throughout the abdominal cavity, whereas the latter may also infiltrate the abdominal organs.

J. Adenocarcinoma of the appendix may include mucinous and non-mucinous subtypes. These tumors may rupture and lead to seeding of the peritoneal cavity and pseudomyxoma peritonei. These tumors invade the appendiceal wall and may spread by both nodal (less commonly) and peritoneal surfaces. Non-mucinous adenocarcinoma of the appendix closely resemble colonic adenocarcinoma with metastases more commonly to the lymph nodes and hematogenously to the liver. Outcomes correlate to colon cancer and are determined by the stage (Table 67.3). Mucinous subtypes have a comparatively worse prognosis than non-mucinous lesions. A variant of mucinous adenocarcinoma is the signet ring cell subtype that is much more aggressive and tends to lead to diffuse metastases throughout the peritoneal cavity. It characteristically has a very poor prognosis.

K. As many lesions are incidental findings or originally felt to represent appendicitis, appendectomy is one of the more common "diagnostic" modalities for appendiceal neoplasms. However, appendectomy en bloc with resection of the mucinous lesion may also be curative for localized, non-ruptured benign lesions, carcinoids <1 cm with negative margins, and benign mucoceles. When dealing with the latter, it is important to avoid perforation and spillage to minimize the changes of peritoneal mucinosis. Carcinoids 1–2 cm with otherwise negative features and clear margins may be candidates for therapy with an appendectomy;

Table 67.3 ACJJ staging (8th edition) of mucinous adenocarcinoma of the appendix

Primary tumor (pT)
T stage
• **TX**: primary tumor cannot be assessed
• **T0**: no evidence of primary tumor
• **Tis**: carcinoma in situ, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
• **T1**: tumor invades submucosa (through the muscularis mucosa but not into the muscularis propria)
• **T2**: tumor invades muscularis propria
• **T3**: tumor invades through the muscularis propria into the pericolorectal tissues
• **T4**
– **T4a**: tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
– **T4b**: tumor directly invades or adheres to other adjacent organs or structures
Notes
• Tis and T1
– Tis in the AJCC 8th edition refers only to intramucosal carcinoma, a lesion with invasion into the lamina propria that does not penetrate the muscularis mucosa
– Unlike in the 7th edition, lesions with high grade dysplasia without invasion into the lamina propria are not considered Tis and these lesions have no potential to spread
– Term intraepithelial carcinoma is synonymous to Tis but is rarely used (and may be misleading)
– True intramucosal carcinoma also lacks the potential for metastasis; however, because of the potential for missing invasion beyond the muscularis mucosa due to incomplete sampling, designating these lesions Tis is appropriate
– T1 lesions have invasion into the submucosa
• Carcinoma in a polyp
– Classified according to pT definitions used for colorectal carcinomas; i.e. invasive carcinoma in the muscularis mucosae or lamina propria is pTis and tumor that has entered the submucosa of the polyp's head or stalk is pT1
– If a resected polyp has a clear margin during endoscopic resection, it is a pTis lesion and the nodal and metastatic status is unknown; however, the risk of metastatic disease is very low and lymph node dissection is not indicated
– Several professional societies recommend resection if there is a high grade invasive tumor, the invasive tumor is 1 mm or less from the resection margin or lymphovascular space invasion is present

(continued)

Table 67.3 (continued)

• T4
– Separation of T4 into two categories (T4a and T4b) is based on different outcomes in expanded datasets
– T4a tumors directly invade the serosal surface (visceral peritoneum)
This includes tumors with perforation where the tumor cells are continuous with the serosal surface through inflammation
Some but not all studies indicate that tumors that are under 1 mm from the serosal surface show a higher risk for peritoneal relapse; if so, multiple levels and additional sampling should be performed and if serosal surface involvement is not found, the tumor should be considered pT3
pT4a should not be used in nonperitonealized portions of the colorectum (posterior aspects of ascending and descending colon, lower rectum)
Regional lymph nodes (pN)
• **NX**: regional lymph nodes cannot be assessed
• **N0**: no regional lymph node metastasis
• **N1**: metastasis in 1–3 regional lymph nodes
– **N1a**: metastasis in 1 regional lymph node
– **N1b**: metastasis in 2–3 regional lymph nodes
– **N1c**: no regional lymph nodes are positive but there are tumor deposits in the subserosa, mesentery or nonperitonealized pericolic or perirectal / mesorectal tissues
• **N2**: metastasis in 4 or more regional lymph nodes
– **N2a**: metastasis in 4 - 6 regional lymph nodes
– **N2b**: metastasis in 7 or more regional lymph nodes
Notes
• Minimum of 12 lymph nodes must be recovered for lymph node staging to be considered accurate in curative resections
• Number of recovered nodes has been reported to correlate with better prognosis, likely due to more accurate staging
• Metastasis to nonregional lymph nodes outside of the drainage area of the tumor, i.e. those not found along vascular arcades of the marginal artery or pericolonic, perirectal or mesorectal nodes should be considered distant metastasis (M1a)
• A lymph node metastasis that in other sites would be considered a micrometastasis is recorded as a "typical" metastasis
– Research is ongoing as to the possible significance of micrometastasis or metastasis only found with keratin staining
• N1c tumor deposits are discrete tumor nodules of any shape, contour or size that lack associated lymph node tissue, vascular structures or neural structures found within the lymph drainage area of the primary carcinoma
– These deposits are associated with poor overall survival
– In cases with lymph node metastasis, the number of tumor deposits is NOT added to the number of positive lymph nodes
Distant metastasis (pM)
• **M0**: no distant metastasis by imaging; no evidence of tumor in other sites or organs (this category is NOT assigned by pathologists)
• **M1**: distant metastasis
– **M1a**: metastasis confined to 1 organ or site without peritoneal metastasis
– **M1b**: metastasis to 2 or more sites or organs is identified without peritoneal metastasis
– **M1c**: metastasis to the peritoneal surface is identified alone or with other site or organ metastases
Notes
• Metastasis to nonregional lymph nodes outside of the drainage area of the tumor, i.e. those not found along vascular arcades of the marginal artery or pericolonic, perirectal or mesorectal nodes should be considered distant metastasis (M1a)
• Multiple metastases in an organ, even paired organs (ovaries, lungs), are still M1a disease
• Pathologist should not assign the global designation pM0, as metastasis unknown to the pathologist may be present

Table 67.3 (continued)

Prefixes
• **y**: preoperative radiotherapy or chemotherapy
• **r**: recurrent tumor stage
• **a**: cancer discovered incidentally during autopsy
Grading of quality and completeness of the mesorectum in a total mesorectal excision
• **Complete**: intact and smooth mesorectum, defects if present are no deeper than 5 mm, there is no coning and the circumferential resection margin is smooth and regular
• **Nearly complete**: mesorectum is moderately bulky and irregular, defects on muscularis propria are visible, there is moderate coning and an irregular circumferential resection margin
• **Incomplete**: mesorectum has little bulk, the muscularis propria is visible through defects, there is moderate to marked coning and an irregular circumferential resection margin
• See **J Clin Pathol 2007;60:849**
Tumor regression after neoadjuvant therapy
Modified Ryan scheme for tumor regression score (only performed on primary tumor)
• **0 (complete response)**: no viable cancer cells
• **1 (near complete response)**: single cells or rare small groups of cancer cells
• **2 (partial response)**: residual cancer with evident tumor regression but more than single cells or rare small groups of cancer cells
• **3 (poor or no response)**: extensive residual cancer with no evident tumor regression
• See **CAP: Cancer Protocol Templates [Accessed 29 November 2017]**
Notes
• In rectal cancer, the pathologic response to preoperative radiotherapy, chemoradiation or chemotherapy in colon or rectal cancer is important prognostically
• Acellular mucin is considered to represent completely eradicated tumor and should not be used to assign pT category or be considered positive lymph nodes

T stage			
Stage 0	Tis	N0	M0
Stage I	T1–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
Stage IIIC	T4a	N2a	M0
	T3–T4a	N2b	M0
	T4b	N1–N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

however, this is controversial due to the risk of lymph node metastases.

L. Right colectomy is reserved for patients with adenocarcinoma of the appendix and larger carcinoids (>2 cm; >1 cm with high-risk features; positive margins). Goblet cell appendiceal carcinoids have a 20–40% risk of lymph node metastases therefore a right hemicolectomy is recommended regardless of primary tumor size. For patients with low-grade mucinous neoplasms of the appendix in the setting of pseudomyxoma peritonei, there remains controversy. Whereas the traditional teaching has been right colectomy, more recently the shift has been towards appendectomy only and cytoreductive surgery ± HIPEC (see below). This is due, in part, to the fact that lymph node disease is a rare

entity and the peritoneal disease is the primary driver of patient outcomes.

M. Chemotherapy alone is typically for patients with metastatic disease who cannot undergo a complete cytoreduction. Certain patients will have an excellent response and may have the opportunity to subsequently undergo cytoreduction and HIPEC after downstaging. Some argue that even after complete cytoreduction and HIPEC, recurrence of these mucinous lesions is common, and adjuvant systemic chemotherapy is warranted. However, low-grade lesions are not classically responsive to systemic chemotherapy, and it is typically not recommended routinely. Conversely, chemotherapy may be considered for high-grade lesions and has some data to suggest improved progression-free survival.

N. Complete cytoreduction with HIPEC has become the preferred treatment for appendiceal lesions with concomitant peritoneal involvement (carcinomatosis, pseudomyxoma peritonei). Complete cytoreduction involves removal of all gross disease or reduction of tumor deposits to ≤2.5 mm in thickness. This is performed in conjunction with heated intraperitoneal chemotherapy (HIPEC). In addition, some surgeons perform an omentectomy, peritoneal and diaphragm stripping, and even removal of Glisson's capsule when involved. Bilateral oophorectomy may also be performed, especially in post-menopausal women. Tumor deposits on the small bowel may be resected or fulgurated. Intraperitoneal chemotherapy may be performed via an open or closed technique (Fig. 67.3). Mitomycin C (MMC) at a dose of 40 mg in 3 L of perfusate at 41–43 °C for 90 min (30 mg for 60 min with an additional 10 mg during 30 min). Floxuridine and 5-fluorouracil have also been used, but have demonstrated no benefit to date. Non-heated intraperitoneal chemotherapy (EPIC) for up to 7 days postoperatively via an implanted subcutaneous port may also be included. Recurrent disease is most often treated with repeat debulking or complete cytoreduction with additional HIPEC and has been reported result in long-term survival.

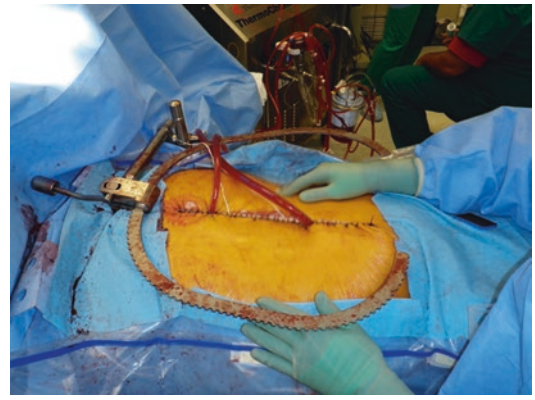


Fig. 67.3 Intraoperative photograph of heated intraperitoneal chemotherapy

O. Surgery is the primary treatment for most appendiceal neoplasms. Normally, only poor operative candidates, those with advanced or metastatic disease, or patients with a high PCI (*i.e.*, >20) who are not likely to undergo successful cytoreduction and HIPEC therapy are treated non-operatively. Somatostatin may be useful for metastatic carcinoid tumors, often with extensive liver involvement for symptomatic relief. Adjuvant chemotherapy may include 5-FU-based therapy alone or in combination with oxaliplatin or the monoclonal antibodies such as bevacizumab or cetuximab. While they play a role for epithelial neoplasms, they generally result in limited improvement in progression-free survival **(refer to section N in algorithm)**. Radiation therapy is rarely used in the treatment of appendiceal neoplasms.

Suggested Reading

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