Ampullary Cancer

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Lawrence Lau, Nicholas Latchana, Shiva Jayaraman, Sean Cleary, and Carol-anne E. Moulton

Introduction

Periampullary neoplasms arise in proximity of the ampulla of Vater (within 2 cm) and can originate from the duodenum, pancreatic head, distal common bile duct, or the ampullary complex. Ampullary tumors are those arising directly from the structures of the ampullary complex distal to the confluence of the bile duct and pancreatic duct and represent roughly 7% of periampullary neoplasms. These rare tumors represent 0.5% of all GI cancers, though a subtle increase of 0.9% per year has been observed in recent decades [1].

Ampullary carcinoma carries a notably more favorable prognosis than other pancreaticobiliary malignancies. This is likely attributed to presentation with early clinical jaundice, and potentially, a more favorable disease biology. Curative-intent resection is possible in 50% of patients presenting with ampullary cancer compared with 10% for patients with pancreatic cancer [2]. Specific risk factors for ampullary cancer have not been identified, but duodenal adenomas and periampullary malignancies are a well-described feature of the familial adenomatous polyposis syndrome.

The large majority of ampullary cancers are adenocarcinoma and are broadly categorized into pancreaticobiliary and intestinal histologic subtypes based on their morphological appearance, immunohistochemical staining pattern, and molecular features. Intestinal-type tumors (CDX2 positive, MUC1 negative) have a more favorable prognosis compared with pancreaticobiliary type (CDX2

L. Lau · N. Latchana · S. Jayaraman · C.-a. E. Moulton (✉)
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: Nicholas.Latchana@mail.utoronto.ca; Shiva.Jayaraman@unityhealth.to; Carol-anne.Moulton@uhn.ca

S. Cleary
Department of Surgery, Mayo Clinic, Rochester, MN, USA
e-mail: Cleary.Sean@mayo.edu

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Table 2.1 Prognosis based on tumor extent at presentation [1, 6, 7]

Presentation	Prognosis 5-year overall survival (OS)
Local	45–67%
Regional	31–55%
Distant	4–14%

negative, MUC1 positive) (~60% vs. ~20% at 5 years; median OS 116 vs. 22 months) [3, 4]. Prognosis is determined by the stage at presentation (Table 2.1). Lymph node positivity is among the strongest prognostic factors and is closely correlated with the size of the primary tumor: <1 cm = 9%, 1–1.5 cm = 25%, and >1.5 cm 40–50% [4]. The recommended staging system is the International Union Against Cancer and American Joint Committee on Cancer (UICC/AJCC) 8th edition [5].

Several factors conspire against the formulation of large prospective randomized studies for ampullary carcinoma: the rarity of the disease, histologic heterogeneity, differentiating from other periampullary tumors preoperatively, and the amalgamation with other pancreaticobiliary cancers. As such, no prospective studies exclusively evaluating ampullary carcinoma have been published, and management recommendations are based largely on extrapolation from the management of pancreatic adenocarcinoma and consensus guidelines (Table 2.2).

Special Notes

- In Ontario, all patients with known or suspected ampullary adenocarcinoma should be referred for management at a high-volume hepatopancreaticobiliary surgical oncology center.
- *Endoscopic resection* of ampullary adenomas is associated with lower morbidity than surgical resection, but has a fivefold increased rate of recurrence [9]. Endoscopic biopsy has a false negative rate of 16–24% for invasive adenocarcinoma [10–12]. The likelihood of coexistent adenocarcinoma increases with adenoma size (>2–3 cm), the presence of high-grade dysplasia, pancreatic duct involvement with dilation >7 mm, and endoscopic signs of malignancy (friability, ulceration, spontaneous bleeding, and firm consistency) [9, 11–13].
- *Role of Frozen Section*: Frozen section is used to confirm metastatic/unresectable disease. In cases where a lesion is not endoscopically resectable, but is amenable to local resection (transduodenal ampullectomy), frozen section is used to determine margin status and to determine the need to proceed to pancreaticoduodenectomy.
- *Laparoscopic Staging*: It has limited use in upstaging ampullary carcinoma since the advent of high-quality multidetector CT. Appropriate in selected patients at increased risk of metastatic disease in the absence of unresectability on preoperative imaging (e.g., elevated CA 19-9, larger tumors [14]).

Table 2.2 Management of resectable periampullary tumors

Clinical scenario	Work-up	Surgical management	Adjuvant therapy	Follow-up (F/U)
Benign adenoma	History and physical exam Labs: Ca 19–9, CEA Staging: CT chest, biphasic CT abdo/pelvis MRI/MRCP +/− EUS to evaluate the extent of local invasion or for biopsy +/− Staging laparoscopy[a] Consider biliary decompression if jaundice present (ERCP or PTC) and immediate resection not available	*Local resection* recommended: endoscopic resection, duodenotomy with polypectomy and/or ampullectomy[a] [8]	No adjuvant therapy indicated	Following local resection surveillance is required with a side-viewing endoscope
In situ disease		*Pancreaticoduodenectomy* should be considered for high-grade dysplasia/in situ disease in young patients and good performance status; otherwise local excision is recommended		CT chest/abdo/pelvis every 3–6 months for the first 2 years, then every 6 months to 1 year thereafter
Invasive disease		*Pancreaticoduodenectomy* recommended [8] Local resection for cT1 disease is associated with R1 resection rate of 25–60% and higher local recurrence. Not recommended for good operative candidates Lymphadenectomy: Routine LN dissection includes peripancreatic, CBD and pyloric nodes Extended LN dissection not indicated as no demonstrated improvement in outcomes	No consensus of optimal therapy Consider: Chemotherapy alone[a] Chemoradiotherapy[a] Observation	

MRCP magnetic resonance cholangiopancreatography, *ERCP* endoscopic retrograde cholangiopancreatography, *PTC* percutaneous transhepatic cholangiography, *EUS* endoscopic ultrasound, *LN* lymph node
[a]See Special Notes

- *Medical Oncology*: No consensus exists regarding optimal systemic therapy for ampullary carcinoma [6]. The largest RCT evaluating adjuvant chemotherapy for resected periampullary cancers (ESPAC-3 trial, n = 297 ampullary) showed a statistically nonsignificant improvement in overall survival with gemcitabine or 5-FU over observation alone [15]. The role of molecular targeted agents remains to be evaluated in ampullary cancer. Treatment approaches follow guidelines established for pancreatic cancer regardless of subtype [16]. Patients should be referred for discussion of adjuvant therapy.

Table 2.3 Management strategy for duodenal polyps in patients with familial adenomatous polyposis [22]

Stage	Size (mm)	Histology	Management
1	0	Normal	EGD q 5 years
2	1–2	Adenoma	EGD q 3 years
3	2.1–10	Adenoma	EGD q6 months
4	2.1–10 >10	HGD Adenoma	Endoscopic or surgical resection
5	Any	Adenocarcinoma	Radical surgery (e.g., pancreaticoduodenectomy)

EGD esophagoduodenoscopy (with side-viewing scope), *HGD* high-grade dysplasia

- *Radiotherapy*: The role of adjuvant radiation is controversial. Several observational studies suggest improved survival with chemoradiation (CRT) for tumors with adverse features (node positive, poorly differentiated, T3/T4) [17–20]. The only prospective RCT evaluating CRT for resected pancreatic and periampullary cancers failed to demonstrate a survival benefit for the subgroup of mixed periampullary tumors (n = 104) [21].

Special Case: Familial Adenomatous Polyposis (FAP)

- 50–90% of patients diagnosed with FAP have duodenal adenomas.
- Overall lifetime risk of duodenal cancer is ~5%.
- Duodenal cancer in FAP has a later onset than colorectal cancer (median age 52).
- FAP patients require regular side-viewing duodenoscopy and biopsy of suspicious lesions, starting at 25 years.
- A practical and effective surveillance strategy for upper GI malignancies in FAP patients has been developed at the University of Toronto (Table 2.3).

Landmark Trials

Prospective RCTs regarding the management of ampullary carcinoma are few, due to the relative rarity of the disease and inclusion in pancreatic adenocarcinoma trials. As such, treatment protocols have largely been extrapolated from trials evaluating periampullary malignancies that included subsets of ampullary carcinoma [15, 21]. Surgical management is largely dictated by consensus statements [8].

Referring to Multidisciplinary Cancer Conference (MCC)

1. High-risk features (R1 resection, poorly differentiated, T3/T4, node positive, pancreaticobiliary histology).
2. Locally advanced disease.
3. Unresectable disease (Table 2.4).

Table 2.4 Management of unresectable/metastatic ampullary adenocarcinoma

Criteria of unresectability	Management
Metastatic disease: Liver, lung, peritoneum, and distant lymph nodes (celiac, SMA nodes, tail of pancreas)	Radical resection not indicated Consider nonoperative palliation interventions (e.g., stent/PTC placement)
Patient factors: Prohibitive comorbidities or functional status	Consider surgery for palliation only
Anatomical factors: Criteria similar to those applied to pancreatic head cancers, e.g., arterial encasement, portal vein involvement which precludes reconstruction	Improved PFS and median survival have been demonstrated with platinum + anti-metabolite regimens [23, 24] Consider radiotherapy

SMA superior mesenteric artery, *PTC* percutaneous transhepatic cholangiography/catheter, *PFS* progression-free survival

Toronto Pearls

- Biliary obstruction associated with ampullary lesions can be intermittent (ball-valve effect).
- Lesions with high-grade dysplasia or carcinoma in situ on endoscopic biopsies have high rate of invasive cancer on final pathology. Formal resection (pancreaticoduodenectomy) or intraoperative frozen section at ampullectomy should be considered in these patients.
- Formal pancreaticoduodenal resection should be considered for malignant ampullary lesions.
- Pylorus-preserving pancreaticoduodenectomy is generally not advised for ampullary lesions.
- Luminal obstruction by ampullary lesions can be palliated by endoscopic resection and/or endoluminal stent placement.

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