Chapter 2
Ampullary Cancer

Gareth Eeson, Sean Cleary, Carol-anne E. Moulton, and Paul F. Ridgway

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 tumours proper 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 favourable prognosis than other pancreaticobiliary malignancies. This is likely attributed to an earlier stage of disease at clinical presentation and a potentially more favourable 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 peri-ampullary malignancies are a well-described feature of the familial adenomatous polyposis syndrome.
The large majority of ampullary cancers are adenocarcinoma and are broadly categorised as (1) pancreaticobiliary and (2) intestinal histologic subtypes based on their epithelial origin. Intestinal-type tumours have a more favourable prognosis compared with pancreaticobiliary type (~60% vs. ~20% at 5 years; median OS 116 vs. 22 months) [3, 4]. Lymph node positivity is among the strongest prognostic factors and is closely correlated with the size of the primary tumour: >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) 7th edition [5].

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Prognosis 5-year overall survival (OS) [1]</th>
</tr>
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<tbody>
<tr>
<td>Local</td>
<td>45%</td>
</tr>
<tr>
<td>Regional</td>
<td>31%</td>
</tr>
<tr>
<td>Distant</td>
<td>4%</td>
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Several factors conspire against the formulation of large prospective randomised studies for ampullary carcinoma including the rarity of the disease, histologic heterogeneity 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.
Management

Resectable Ampullary Adenocarcinoma

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Work-up</th>
<th>Surgical management</th>
<th>Adjuvant therapy</th>
<th>Follow-up (F/U)</th>
</tr>
</thead>
</table>
| 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  
|                   | • 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 [6] | • No adjuvant therapy indicated | • Following local resection surveillance is required with a side-viewing endoscope |
| In situ disease   | • CT chest/abdo/pelvis every 3–6 months for the first 2 years, then every 6 months to 1 year thereafter | • **Pancreatectoduodenectomy** should be considered for high-grade dysplasia/in situ disease in young patients and good performance status; otherwise local excision is recommended |  |  |
| Invasive disease  | • **Pancreatectoduodenectomy** recommended [6]  
|                   |   – 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 peri-pancreatic, CBD and pyloric nodes  
|                   |     – Extended LN dissection not indicated as no demonstrated improvement in outcomes | • No consensus of optimal therapy  
|                   |   • Consider:  
|                   |     – Chemotherapy alone  
|                   |     – Chemoradiotherapy  
|                   |     – Observation |  |  |

*MRCP* magnetic resonance cholangiopancreatography, *ERCP* endoscopic retrograde cholangiopancreatography, *PTC* percutaneous transhepatic cholangiography, *EUS* endoscopic ultrasound, *LN* lymph node

*aSee Special Notes*
Special Notes

- In Ontario, all patients with known or suspected ampullary adenocarcinoma should be referred for management at a high-volume hepatopancreaticobiliary surgical oncology centre.
- **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** 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 pre-operative imaging (e.g. elevated CA 19-9, larger tumours [7]).
- **Medical Oncology**: No consensus exists regarding optimal systemic therapy for ampullary carcinoma. The largest RCT evaluating adjuvant chemotherapy for resected peri-ampullary cancers \( n=297 \) ampullary showed a statistically non-significant improvement in overall survival with gemcitabine or 5-FU over observation alone. The role of molecular targeted agents remains to be evaluated in ampullary cancer. Patients should be referred for discussion of adjuvant therapy.
- **Radiotherapy**: The role of adjuvant radiation is controversial. Several observational studies suggest improved survival with chemoradiation (CRT) for tumours with adverse features (node positive, poorly differentiated, T3/T4) [8–11]. The only prospective RCT evaluating CRT for resected pancreatic and peri-ampullary cancers failed to demonstrate a survival benefit for the subgroup of mixed peri-ampullary tumours \( n=104 \) [12].

Special Case: Familial Adenomatous Polyposis

- 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 and is described below [13].

<table>
<thead>
<tr>
<th>Stage</th>
<th>Size (mm)</th>
<th>Histology</th>
<th>Management</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>Normal</td>
<td>EGD q 5 years</td>
</tr>
<tr>
<td>2</td>
<td>1–2</td>
<td>Adenoma</td>
<td>EGD q 3 years</td>
</tr>
<tr>
<td>3</td>
<td>2.1–10</td>
<td>Adenoma</td>
<td>EGD q6 months</td>
</tr>
<tr>
<td>4</td>
<td>2.1–10 &gt;10</td>
<td>HGD Adenoma</td>
<td>Endoscopic or surgical resection</td>
</tr>
<tr>
<td>5</td>
<td>Any</td>
<td>Adenocarcinoma</td>
<td>Radical surgery (e.g. pancreaticoduodenectomy)</td>
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</tbody>
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*EGD* esophagoduodenoscopy (with side-viewing scope), *HGD* high-grade dysplasia
Unresectable/Metastatic Ampullary Adenocarcinoma

<table>
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<th>Criteria of unresectability</th>
<th>Management</th>
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<tr>
<td>• Metastatic disease:</td>
<td>• Radical resection not indicated</td>
</tr>
<tr>
<td>– Liver, lung, peritoneum and distant lymph</td>
<td>• Consider non-operative palliation interventions (e.g. stent/PTC</td>
</tr>
<tr>
<td>nodes (celiae, SMA nodes, tail of pancreas)</td>
<td>placement)</td>
</tr>
<tr>
<td>• Patient factors:</td>
<td>• Consider surgery for palliation only</td>
</tr>
<tr>
<td>– Prohibitive co-morbidities or functional status</td>
<td>• Improved PFS and median survival have been demonstrated with</td>
</tr>
<tr>
<td>• Anatomical factors:</td>
<td>platinum + anti-metabolite regimens [14, 15]</td>
</tr>
<tr>
<td>– Criteria similar to those applied to pancreatic</td>
<td>• Consider radiotherapy</td>
</tr>
<tr>
<td>head cancers, e.g. arterial encasement, portal</td>
<td></td>
</tr>
<tr>
<td>vein involvement which precludes</td>
<td></td>
</tr>
<tr>
<td>reconstruction</td>
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SMA superior mesenteric artery, PTC percutaneous transhepatic cholangiography/catheter, PFS progression-free survival

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 peri-ampullary malignancies that included subsets of ampullary carcinoma [12, 16]. Surgical management is largely dictated by consensus statements [6].

Referring to Medical Oncology

1. Consider for all patients.
2. High-risk features (R1 resection, poorly differentiated, lymphovascular or perineural invasion, T3/T4, node positive, pancreaticobiliary histology).
3. Unresectable disease.

Referring to Radiation Oncology

1. High-risk features (R1 resection, poorly differentiated, lymphovascular or perineural invasion, T3/T4, node positive, pancreaticobiliary histology).
2. Palliative patients for consideration of symptomatic control.
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.

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.

References

Surgical Oncology Manual
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