**INTRODUCTION**

Adjuvant therapy in pancreatic and periampullary adenocarcinoma remains a topic of intense investigation. Initial adjuvant treatment efforts grew out of the recognition that overall survival rates remained low despite curative intent resection for early stage disease. The pool of potentially therapeutic options have largely been derived from the metastatic setting, and numerous regimens have been evaluated. Although chemotherapy offers a significant but modest survival benefit over receipt of no treatment, the use of chemoradiation in the adjuvant setting has not demonstrated a clear survival
benefit among the major studies and, as such, its role is less clear. The rarity of peri-
ampullary carcinoma, historically treated similarly to pancreatic adenocarcinoma,
limits its evaluation to retrospective studies or subgroup analyses within larger studies.
In addition, there have not been many studies demonstrating a clear survival benefit of
an adjuvant regimen in this small group, which may be reflective of the histologic het-
erogeneity that exists among these tumors. This article discusses the data that have
led to and support the current standard of care for the adjuvant management of
pancreatic adenocarcinoma and periampullary cancers, which in turn illuminates the
way forward for more effective adjuvant and potentially neoadjuvant treatment
strategies.

PANCREATIC ADENOCARCINOMA
Epidemiology and Rationale for Adjuvant Therapy
Pancreatic adenocarcinoma is the 12th most commonly diagnosed malignancy, but is
the 4th leading cause of cancer-related death with 40,560 patients dying from this dis-
ease in 2015.1 Despite curative intent surgical resection of early stage lesions (stages I
and II), local and systemic recurrence rates are high and overall survival rates are
dismally low. Retrospective surgical studies demonstrate that although perioperative
mortality has improved with surgical advances, overall survival continues to be low,
with 5-year survival rates of 7% to 25% after a curative intent resection.2–6 Criteria
for resectability relate to the degree of arterial and venous tumor involvement as
well as the presence of metastases.7 Given the high recurrence rates after surgical
resection—likely owing to the lingering presence of micrometastatic disease—the
role of adjuvant therapy, specifically chemotherapy, radiation therapy or a combina-
tion of the 2 modalities, has been evaluated for survival benefit.

Adjuvant Chemotherapy
The efficacy of adjuvant chemotherapy alone has been assessed in several clinical tri-
als with initial studies producing mixed results. An early Norwegian study randomized
61 patients with stages I through III pancreatic cancer to adjuvant chemotherapy with
doxorubicin, mitomycin C, and 5-fluorouracil (5-FU) or observation after surgical
resection.8 Median survival in the treatment group was 23 months compared with
11 months in the observation group ($P = .02$); however, there was no significant
improvement in 2-year survival ($P = .10$). Similarly, a Japanese group randomized
508 patients with resected stages II through IV pancreaticobiliary cancers to adjuvant
mitomycin C and 5-FU. Despite a large overall population, only a fraction of patients
with pancreatic cancer underwent curative resection ($n = 92$). Among this subgroup,
no differences were found in 5-year disease-free or 5-year overall survival ($P = .28
and $P = .45$, respectively).9 Although neither of these studies was positive for the use of
adjuvant chemotherapy, the small number of patients undergoing curative resection
in both trials made the results inconclusive.

Historically, 5-FU has been the most extensively studied chemotherapeutic agent of
choice for patients with any stage of pancreatic cancer.10–12 However, the subsequent
success of gemcitabine in metastatic disease changed the adjuvant landscape. Burris
and colleagues13 published a randomized phase III trial conducted in patients with
advanced pancreatic adenocarcinoma, demonstrating that gemcitabine conferred a
superior survival benefit as compared with 5-FU (5.6 vs 4.4 months, respectively;
$P = .0025$). Similar efforts to improve adjuvant therapy led to Charite Onkologie’s
(CONKO) study of gemcitabine in the adjuvant setting. In a randomized controlled
phase III trial, 368 patients with T1-4 N0-1 M0 pancreatic adenocarcinoma were
randomized to either gemcitabine or observation after resection. Median disease-free survival was significant in favor of adjuvant gemcitabine (13.4 vs 6.9 months; \( P < .001 \)). After long-term analysis, patients in the gemcitabine arm were found to have modest benefit in overall survival as well, with a median overall survival of 22.8 months in the treatment group versus 20.2 months in the observation group (\( P = .01 \)). The 5-year survival rate was reported as 20.7% in the treatment group versus 10.4% in the observation group (\( P = .01 \)). These results thus established gemcitabine as a standard treatment approach for the adjuvant management of pancreatic adenocarcinoma.

With the historical use of 5-FU as a standard adjuvant agent for pancreatic adenocarcinoma, the objective of ESPAC (European Study Group for Pancreatic Cancer)-3 was to compare gemcitabine with 5-FU in a randomized trial. ESPAC-3 randomized 1088 patients with resected pancreatic cancer to adjuvant gemcitabine or 5-FU for a total of 6 months. This study demonstrated no difference in median overall survival (23.6 vs 23 months; \( P = .39 \)) between gemcitabine and 5-FU. Although gemcitabine was not deemed superior, it is considered to be better tolerated. Gemcitabine did have significantly higher rates of grade 3 and 4 hematologic toxicity, but 5-FU had significantly higher rates of grade 3 and 4 stomatitis and diarrhea. The ability of a patient to complete the entire course of adjuvant therapy also seems to be important. In an ad hoc analysis of the ESPAC-3 data evaluating whether timing or duration of chemotherapy after surgery influenced survival, patients who received chemotherapy within 8 weeks of surgery did not have a survival benefit over those who began therapy after 8 weeks and up to 12 weeks postoperatively. However, completion of all 6 cycles (24 weeks) was an independent prognostic factor, with a median overall survival in this subgroup of 28 months compared with only 14.6 months in patients completing 1 to 5 cycles (hazard ratio [HR], 0.516; \( P < .001 \)).

The finding of nonsuperiority for either gemcitabine or 5-FU was confirmed in RTOG (Radiation Therapy Oncology Group) 9704, where gemcitabine versus 5-FU as part of an adjuvant chemoradiation regimen were compared. Although this study did include a radiation component, the question being studied was which chemotherapeutic backbone was more favorable. In this study, 451 patients with resected pancreatic cancer were randomized to chemoradiation plus gemcitabine or chemoradiation plus 5-FU. Chemotherapy in both arms was given before and after chemoradiation, and chemotherapeutic radiosensitization with 5-FU was used during radiation in both arms of the study. Of note, the gemcitabine group had a significantly higher number of T3 and T4 tumors than the 5-FU group (81% vs 70%; \( P = .01 \)). As in ESPAC-3, there was no difference in median overall survival between the gemcitabine or 5-FU groups (20.5 vs 16.9 months; \( P = .09 \)). Also similar to ESPAC-3, hematologic toxicities were more commonly seen in the gemcitabine arm. A summary of adjuvant chemotherapy trials is presented in Table 1.

**Adjuvant Chemoradiation**

Based on promising studies in locally advanced disease, combined modality chemoradiation has been evaluated in several randomized controlled trials as an alternative adjuvant option for resected pancreatic adenocarcinoma, however with competing results. The Gastrointestinal Study Group (GITSG) was the first to demonstrate a potential survival benefit in favor of adjuvant chemoradiation. In this trial, 43 patients with pancreatic adenocarcinoma were randomized after curative resection to either chemoradiation or observation. In the treatment group, patients underwent a course of concurrent chemoradiation with weekly 5-FU. After a 2-week interval, this was repeated. 5-FU was then continued as maintenance weekly for 2 years or until...
reurrence. Median overall survival was 20 months in the treatment arm compared with 11 months in the observation arm \((P = .3)\). Median disease-free survival was 11 versus 9 months, respectively \((P = .1)\). The study was terminated prematurely owing to low accrual, and statistical conclusions could not be made; however, it did suggest an underlying survival benefit, which resulted in the use of adjuvant 5-FU and radiation therapy as a standard adjuvant therapy option.

A subsequent study conducted by the European Organization of Research and Treatment of Cancer (EORTC) reported results of a larger prospective trial that did not show survival benefit for the use of adjuvant chemoradiation.\(^{12}\) This study randomized 218 patients with resectable head of the pancreas or periampullary adenocarcinoma postoperatively in a similar fashion as the GITSG study. The treatment arm consisted of radiation given over 2 weeks to a total of 40 Gy, in combination with 24-hour continuous 5-FU (given as a bolus in the GITSG study) given on the first day of radiation. This regimen was given again after a 2-week hiatus, and 5-FU was continued weekly for 2 years until recurrence. The control arm consisted of observation only. Median survival was 24.5 months in the treatment group compared with 19.0 months in the observation group \((P = .208)\). When further stratified by tumor type, patients with pancreatic adenocarcinoma had a median survival of 17.1 months in the treatment arm compared with 12.6 months in the observation arm \((P = .099)\). Of

<table>
<thead>
<tr>
<th>Table 1: Major adjuvant randomized trials</th>
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<tr>
<td><strong>Trial Type</strong></td>
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<tr>
<td>GITSG(^{11})</td>
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<td>EORTC(^{8,12})</td>
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<td>ESPAC-1(^{19})</td>
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<td>CONKO-001(^{15})</td>
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<td>RTOG 9704(^{18})</td>
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<td>ESPAC-3(^{8,16})</td>
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<td>JASPAC(^{23})</td>
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*Abbreviations: 5-FU, 5-fluorouracil; ChemoRT, chemoradiation; CONKO, Charité Onkologie trial; DFS, disease-free survival; EORTC, European Organisation for Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer; GITSG, Gastrointestinal Tumor Study Group; JASPAC, Japan Adjuvant Study Group of Pancreatic Cancer; OS, overall survival; RTOG, Radiation Therapy Oncology Group.

* Denotes studies including both pancreatic adenocarcinoma and ampullary cancers.

Data from Refs.\(^{11,12,15,16,18,19,23}\)
note, the sample size was too small to make a separate conclusion in this subset of patients. This study concluded that adjuvant chemoradiation did not confer a significant survival benefit over observation alone. When taken into consideration alongside results from the GITSG study, the role of chemoradiation in the adjuvant pancreatic cancer setting remains unclear. A summary of trials assessing adjuvant chemoradiation is included in Table 1.

Adjuvant Chemotherapy Versus Adjuvant Chemoradiation

Given the inconclusive data regarding the role for a component of chemoradiation in the adjuvant treatment setting, ESPAC sought to investigate this question in a large randomized controlled trial, ESPAC-1. One of their reported aims was to evaluate whether chemoradiation or chemotherapy alone resulted in an improved survival benefit. A second objective was to determine if chemoradiation followed by chemotherapy (as in GITSG) improved survival. A total of 289 patients were randomized after surgery in a 2 × 2 design; 73 patients were assigned to chemoradiation alone, 75 to chemotherapy alone, 72 to chemoradiation followed by chemotherapy, and 69 to observation. The trial was not powered to compare these 4 groups directly. Survival estimates were based on 145 patients receiving chemoradiation (one-half of the patients also receiving chemotherapy) compared with 144 patients not receiving chemoradiation. Median survival was 15.9 months in patients receiving chemoradiation compared with 17.9 months in those not receiving chemoradiation (P = .05). Similarly, 147 patients received chemotherapy (one-half of them also receiving chemoradiation) and 142 patients did not receive chemotherapy. Median survival was 20.1 months in patients receiving chemotherapy compared with 15.5 months in those not receiving chemotherapy (P = .009). From these results, ESPAC-1 concluded that standard of care should consist of adjuvant chemotherapy, and that adjuvant chemoradiation could actually be detrimental to patient survival, even in patients receiving a component of chemotherapy alone. It should be noted, however, that in this trial the dose of radiation administered was well below the standard of care today—20 Gy in 10 fractions over a 2-week period in ESPAC-1 versus current standard of care consisting of 45 to 46 Gy in 1.8 to 2 Gy fractions over 5 weeks with a possible additional 5 to 9 Gy if clinically appropriate. The fact that the chemoradiation arm was deemed detrimental may be secondary to patients receiving suboptimal radiation dosing in combination with an associated delay in administration of single agent chemotherapy.

To clarify the conflicting results of the major adjuvant trials to date, Stocken and colleagues published a metaanalysis to evaluate the efficacy of adjuvant chemoradiation and chemotherapy, especially because some of the studies and subgroup analyses were inadequately powered. This metaanalysis reviewed the data from GITSG, EORTC, Bakkevold and colleagues, Takada and colleagues, and ESPAC-1. Data from an additional group of patients in the ESPAC trial outside of the 2 × 2 factorial design were also included. To evaluate the question of benefit from adjuvant chemoradiation, the trial data from EORTC and ESPAC-1 were reanalyzed. The HR indicated no reduction in the risk of death (HR, 1.09), and no difference in median survival (15.8 vs 15.2 months), 2-year survival (30% vs 34%) or 5-year survival (12% vs 17%) with or without chemoradiation, respectively. To evaluate the question of benefit from adjuvant chemotherapy, a pooled analysis of trial data from Bakkevold and colleagues, Takada and colleagues, and ESPAC-1 was conducted and reported an estimated HR of 0.75, indicating a 25% reduction in the risk of death with chemotherapy compared with no chemotherapy. Within subgroups, chemoradiation seemed to have a benefit in patients with positive resection margins, whereas chemotherapy seemed less beneficial in these situations; however, this was not
powered to be statistically conclusive. The authors noted that their data were dominated by the ESPAC trial data, and came to the similar conclusion that adjuvant chemotherapy should be the standard of care for resected pancreatic cancer. Studies comparing chemotherapy and chemoradiation in the adjuvant pancreatic cancer setting are summarized in Table 1.

**Ongoing Adjuvant Therapy Studies**

With gemcitabine as the adjuvant standard, ongoing studies are evaluating gemcitabine in combination with additional agents. Two active trials, RTOG 0848 and CONKO-005, are evaluating the addition of erlotinib to gemcitabine in the adjuvant setting. Both of these studies draw on the approval of erlotinib, a tyrosine kinase inhibitor, that has a demonstrated survival benefit in advanced pancreatic cancer when given in combination with gemcitabine as compared with gemcitabine alone.\(^{24}\) Combination adjuvant gemcitabine and metformin is also being evaluated. RTOG 0848 also hopes to further define the role of adjuvant chemoradiation. More recently, Nab-paclitaxel was found to have a survival benefit in combination with gemcitabine in advanced pancreatic cancers as compared with gemcitabine alone.\(^{25}\) As such, the role for combination therapy with Nab-paclitaxel and gemcitabine in the adjuvant setting is being addressed in the APACT (Nab-paclitaxel and Gemcitabine vs Gemcitabine Alone as Adjuvant Therapy for Patients With Resected Pancreatic Cancer) trial, which has completed accrual but has pending results. Finally, the role for immunotherapy in pancreatic adenocarcinoma is also under intense investigation with studies assessing vaccine therapies, immune checkpoint inhibitors, and other immunotherapeutic agents. Combination therapy with low dose cyclophosphamide, GVAX (a vaccine composed of a granulocyte-macrophage colony-stimulating factor secreting pancreatic cancer cell line), gemcitabine, and chemoradiation (5-FU based) with or without nivolumab (an immune checkpoint inhibitor) is being assessed based on promising results demonstrated with GVAX in the metastatic pancreatic adenocarcinoma setting.\(^{26}\) The largest completed immunotherapy study conducted in the adjuvant setting (with results still pending) was IMPRESS (Immunotherapy Study for Surgically Resected Pancreatic Cancer), which evaluated the role of algenpantucel-L, a vaccine composed of human pancreatic adenocarcinoma cell lines expressing a murine enzyme that is theorized to mount an immune response against cancer cells. This study was founded on results demonstrated in a phase II trial showing 1-year disease-free survival and 1-year overall survival rates of 62% and 86%, respectively.\(^{27}\) In the pending phase III trial, patients received standard adjuvant therapy with gemcitabine alone or gemcitabine and 5-FU–based chemoradiation then were randomized to receive either vaccine or no vaccine. Table 2 summarizes selected ongoing clinical trials in the adjuvant setting.

**Neoadjuvant Management**

More recently, the question of whether or not there may be a benefit from administration of neoadjuvant chemotherapy with or without neoadjuvant chemoradiation has been increasingly asked. This is likely owing to the fact that the large majority of patients undergoing what is an intended curative surgical resection develop disease recurrence in a relatively short period of time. As such, administration of neoadjuvant treatment may aid in identifying which patients are more likely to benefit from surgery and which patients may be spared undergoing an unnecessary surgery owing to the rapid development of metastatic disease. By virtue of their questionably resectable status, neoadjuvant therapy has been evaluated most extensively in patients with borderline resectable disease (see Jason W. Denbo and Jason B. Fleming...
### Table 2
Selected active adjuvant and neoadjuvant trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Trial</th>
<th>N</th>
<th>Planned Enrollment Dates</th>
<th>Treatment Arms</th>
<th>Primary Endpoint</th>
</tr>
</thead>
</table>
| RTOG 0848   | Phase II/III  | 950 | 2009–2020                | • Adjuvant gemcitabine for 5 cycles  
• Adjuvant gemcitabine + erlotinib hydrochloride for 5 cycles then
Patients without disease progression are randomized again  
• One more cycle of previous regimen  
• One more cycle of previous regimen followed by chemoRT | OS               |
| NCT01013649 |               |     |                          |                                                                                   |                  |
| NEOPAC      | Phase III     | 350 | 2009–2014                | • Neoadjuvant gemcitabine/oxaliplatin + adjuvant gemcitabine  
• Adjuvant gemcitabine       | PFS              |
| NCT01314027 |               |     |                          |                                                                                   |                  |
| NCT01526135 | Phase III     | 490 | 2012–2018                | • Adjuvant gemcitabine  
• Adjuvant mFOLFIRINOX          | DFS              |
| APACT       | Phase III     | 846 | 2014–2020                | • Adjuvant Nab-paclitaxel followed by gemcitabine  
• Adjuvant gemcitabine         | DFS              |
| NCT01964430 |               |     |                          |                                                                                   |                  |
| NCT02172976 | Phase II/III  | 126 | 2014–2019                | • Neoadjuvant and adjuvant FOLFIRINOX  
• Adjuvant gemcitabine         | OS               |
| NCT02047513 | Phase II      | 166 | 2015–2019                | • Neoadjuvant and adjuvant Nab-paclitaxel and gemcitabine  
• Adjuvant Nab-paclitaxel and gemcitabine | DFS              |
| NCT02005419 | Phase II      | 300 | 2013–2017                | • Adjuvant gemcitabine  
• Adjuvant gemcitabine plus metformin | RFS              |
| SWOG 1505   | Phase II      | 112 | 2015–2019                | • Neoadjuvant and adjuvant mFOLFIRINOX  
• Neoadjuvant and adjuvant Nab-paclitaxel and gemcitabine | OS               |
| NCT02562716 |               |     |                          |                                                                                   |                  |
| NCT02451982 | Phase II/I    | 50  | 2016–2020                | • Neoadjuvant and adjuvant cyclophosphamide/GVAX, gemcitabine and radiation  
• Neoadjuvant and adjuvant cyclophosphamide/GVAX and nivolumab, gemcitabine and radiation | IL-17A expression in resected tumors |
| IMPRESS     | Phase III     | 722 | 2010–2016                | • Adjuvant gemcitabine with or without 5-FU chemoradiation  
• Adjuvant gemcitabine with or without 5-FU chemoradiation plus HyperAcute immunotherapy (Algenpantucel-L) | OS               |
| NCT01072981 |               |     |                          |                                                                                   |                  |

**Abbreviations:** 5-FU, 5-fluorouracil; APACT, Nab-paclitaxel and Gemcitabine vs Gemcitabine Alone as Adjuvant Therapy for Patients With Resected Pancreatic Cancer; chemoRT, chemoradiation; DFS, disease-free survival; ESPAC, European Study Group for Pancreatic Cancer; GVAX, a vaccine composed of a granulocyte-macrophage colony-stimulating factor secreting pancreatic cancer cell line; IMPRESS, Immunotherapy Study for Surgically Resected Pancreatic Cancer; mFOLFIRINOX, modified 5-fluorouracil irinotecan and oxaliplatin; NEONAX, Neoadjuvant Plus Adjuvant or Only Adjuvant Nab-Paclitaxel Plus Gemcitabine for Resectable Pancreatic Cancer; NEOPAC, Adjuvant Versus Neoadjuvant Plus Adjuvant Chemotherapy in Resectable Pancreatic Cancer; OS, overall survival; PFS, progression free survival; RFS, recurrence free survival; RTOG, Radiation Therapy Oncology Group; SWOG, Southwest Oncology Group.
article, “Definition and Management of Borderline Resectable Pancreatic Cancer”, in this issue). This is in an effort to both convert these patients to a resectable status and to identify patients who are unlikely to be surgical candidates. For this patient population, despite the lack of category 1 evidence, it is the current recommendation of the National Comprehensive Cancer Center\textsuperscript{20} Pancreatic Adenocarcinoma Clinical Practice Guidelines in Oncology panel that this patient population receive neoadjuvant treatment with either of the 2 most standardly used metastatic regimens—FOLFIRINOX (folinic acid, 5-FU, irinotecan, and oxaliplatin) or gemcitabine and abraxane.\textsuperscript{28} This further begs the question as to whether these same regimens should be used in a resectable patient population. In a retrospective review of 69 patients with resectable pancreatic adenocarcinoma who received neoadjuvant treatment (chemotherapy, radiation, or both) followed by surgical resection, 60 of the initial 69 patients were able to undergo surgical resection and achieved a median overall survival of 44.9 months; the median overall survival for all 69 patients was 32 months.\textsuperscript{29} This reported median overall survival is superior to what has been reported previously for stage IA and IIB pancreatic cancer patients, which ranges from 12.7 to 24.1 months.\textsuperscript{30} In light of this, active neoadjuvant trials are evaluating similar regimens to those being investigated in the adjuvant setting. NEOPAC (Adjuvant Versus Neoadjuvant Plus Adjuvant Chemotherapy in Resectable Pancreatic Cancer) is studying neoadjuvant gemcitabine and oxaliplatin plus adjuvant gemcitabine in comparison with adjuvant gemcitabine alone. Neoadjuvant plus adjuvant Nab-paclitaxel and gemcitabine will be compared with adjuvant only Nab-paclitaxel and gemcitabine in the NEO-NAX (Neoadjuvant Plus Adjuvant or Only Adjuvant Nab- Paclitaxel Plus Gemcitabine for Resectable Pancreatic Cancer) trial. Neoadjuvant plus adjuvant FOLFIRINOX is being compared with current standard adjuvant gemcitabine. Finally, SWOG 1505 is comparing neoadjuvant plus adjuvant FOLFIRINOX with neoadjuvant plus adjuvant Nab-paclitaxel and gemcitabine. Full trial details of ongoing neoadjuvant trials are summarized in Table 2.

\textbf{Surveillance}

There is not good evidence for surveillance after the completion of adjuvant therapy. Given the high incidence of relapse and poor prognosis, the National Comprehensive Cancer Network panel recommends symptom assessment, CA 19-9, and computed tomography scans every 3 to 6 months for the first 2 years, then annually.\textsuperscript{20} However, the data do not show that routine surveillance computed tomography scans offers any survival benefit.\textsuperscript{31}

\textbf{PERIAMPELLARY CARCINOMA}

\textit{Epidemiology and Histologic Classification}

Periampullary carcinomas comprise a rare and heterogeneous group, making them challenging to evaluate for effective therapy. Any neoplasm in the vicinity of the ampulla of Vater is considered periampullary, and can arise from pancreatic, duodenal, biliary, or ampullary epithelia. Pancreatic cancers account for the majority of periampullary cancers, which has resulted in many of the treatment recommendations for these tumors arising from the pancreatic cancer trials. From a series of 242 resected periampullary cancers from Johns Hopkins, 62\% were pancreatic, 19\% were ampullary, 12\% arose from the distal bile duct, and 7\% were duodenal.\textsuperscript{32} True ampullary cancers have an incidence of 4 to 6 cases per million and account for 0.2\% of all gastrointestinal cancers.\textsuperscript{33,34} Ampullary cancers themselves have 2 distinct histologic subtypes—pancreaticobiliary and nonpancreaticobiliary (also known as
The distinction among the subtypes comprising periampullary carcinomas carries prognostic significance with implications for different therapeutic strategies.

**Survival and Prognostic Factors**

Patients with periampullary cancers have a better prognosis compared with those with pancreatic cancer. Among the periampullary cancers, tumor origin carries prognostic significance, with pancreatic cancers not surprisingly conferring the poorest outcomes. From a Johns Hopkins series of 890 periampullary patients with long-term follow-up, the 5-year survival of the entire cohort was 23%. Duodenal cancers carried the best prognosis with a 5-year survival rate of 51% (n = 47). True ampullary cancers had the next best 5-year survival rate of 37% (n = 135), followed by distal bile duct cancers at 23% (n = 144), and pancreatic cancers at 17% (n = 564).

Similarly, among the true ampullary cancers, the pancreaticobiliary histologic subtype confers a worse prognosis than the intestinal subtype. In retrospective studies, histologic subtypes were found to be independent predictors of survival. Chang and colleagues further delineated these subtypes with histopathologic and molecular criteria, using immunostains for MUC1 to identify pancreaticobiliary cancers, and CDX2 to identify nonpancreaticobiliary cancers. Using this stratification, the pancreaticobiliary histomolecular phenotype was found to be an independent adverse prognostic variable compared with the intestinal histomolecular phenotype (median survival, 16 vs 115 months; \( P < .001 \)). Despite these findings, tumor histology is still not used as a standard to drive treatment decisions.

Other factors predicting survival and outcomes after resection of periampullary cancers include nodal metastases as well as neural and lymphovascular invasion. Negative margins and tumor size do not seem to be independent prognostic variables. Predictive factors did, however, vary among cancers of different tumor origins. Prognostically, this has clinical implications for more tailored therapeutic strategies based on the stratification of periampullary cancers into types of tumor origin and histologic phenotype; however, this is not included as part of any treatment guideline.

**Adjuvant Therapy**

Owing to the rarity of periampullary cancers, current standards of adjuvant therapy are based on retrospective studies and subgroup analyses of larger prospective studies that included both pancreatic cancer and periampullary cancers. As a result, adjuvant chemoradiation and/or chemotherapy alone have not been shown definitively to provide significant survival benefit in this specific group of patients. The use of chemoradiation is largely extrapolated from the adjuvant pancreatic trials. After the EORTC group published its prospective study on chemoradiation with 5-FU in pancreatic and periampullary cancers, several groups retrospectively examined the efficacy of similar chemoradiation regimens in ampullary cancers. Bhatia and colleagues published one of the largest series from the Mayo Clinic, suggesting a benefit for chemoradiation in high-risk patients, defined as locally advanced T3 and T4 disease, positive lymph nodes, or high-grade tumor. There was no difference in median overall survival between patients receiving adjuvant chemoradiation (n = 29) and those being observed (n = 96; 5.6 vs 3.5 years; \( P = .64 \)). The presence of positive lymph nodes, however, was found to be a negative prognostic factor, and adjuvant chemoradiation was found to confer a survival benefit in this subgroup (median overall survival of 3.4 years in the chemoradiation group vs 1.6 years in the observation group; \( P = .01 \)). Despite these findings, this study is inconclusive because it is limited by its retrospective nature and small number of patients in each of the subgroups.
<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Trial</th>
<th>Types of Cancer</th>
<th>N</th>
<th>Treatment Arms</th>
<th>Results</th>
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<tbody>
<tr>
<td>Klinkenbijl et al, 12</td>
<td>1999</td>
<td>Pancreas, periampullary</td>
<td>93</td>
<td>ChemoRT with 5-FU</td>
<td>No difference in median OS ($P = .208$)</td>
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<td>EORTC</td>
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<td>ChemoRT with 5-FU</td>
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<td></td>
<td>Observation</td>
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<tr>
<td>Chakravarthy et al, 50</td>
<td>2000</td>
<td>Pancreas, periampullary</td>
<td>16</td>
<td>ChemoRT with 5-FU /DPM/MMC</td>
<td>Trend toward survival benefit</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Observation</td>
<td></td>
</tr>
<tr>
<td>Lee et al, 43</td>
<td>2000</td>
<td>Ampullary</td>
<td>39</td>
<td>ChemoRT with 5-FU</td>
<td>No difference in 3-y OS rate ($P = .132$), suggestive of benefit in high-risk patients ($P = .032$)</td>
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<td>2005</td>
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<td>113</td>
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<td>No difference in median survival ($P = .3$)</td>
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<tr>
<td>Bhatia et al, 42</td>
<td>2006</td>
<td>Ampullary</td>
<td>125</td>
<td>ChemoRT with 5-FU</td>
<td>No difference in median OS ($P = .64$), suggestive of benefit in patients with positive LNs ($P = .01$)</td>
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<td>Krishnan et al, 45</td>
<td>2008</td>
<td>Ampullary</td>
<td>96</td>
<td>ChemoRT with 5-FU or capecitabine</td>
<td>No difference in 5-y OS rate ($P = .53$), trend toward benefit in T3/T4 tumors ($P = .06$)</td>
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<td>2009</td>
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<td>ChemoRT with 5-FU</td>
<td>No difference in 5-y OS rate ($P = .22$)</td>
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<td>2009</td>
<td>Ampullary</td>
<td>111</td>
<td>ChemoRT with 5-FU or capecitabine</td>
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<td></td>
<td>Observation</td>
<td></td>
</tr>
<tr>
<td>Palta et al, 48</td>
<td>2012</td>
<td>Ampullary</td>
<td>137</td>
<td>ChemoRT</td>
<td>No difference in median OS ($P = .074$)</td>
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<td>Observation</td>
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<tr>
<td>Neoptolemos et al, 49</td>
<td>2012</td>
<td>Periampullary</td>
<td>434</td>
<td>5-FU</td>
<td>No difference in median OS ($P = .25$) between chemotherapy groups and observation; statistically significant benefit after adjusting for prognostic variables ($P = .03$)</td>
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<td>ESPAC-3</td>
<td></td>
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<td>Gemcitabine</td>
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<td>Observation</td>
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**Abbreviations:** 5-FU, 5-fluoracil; DPM, dipyridamole; EORTC, European Organization of Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer; LNs, lymph nodes; MMC, mitomycin C; OS, overall survival.

*As compared with historical control.*

_Data from Refs._ 12,42–50
Several other retrospective studies were similarly inconclusive in regard to a survival benefit derived from adjuvant chemoradiation in periampullary cancers.\textsuperscript{43–48}

The data on adjuvant chemotherapy in periampullary cancers are also mixed. The largest prospective trial to date, ESPAC-3, compared adjuvant gemcitabine versus 5-FU versus observation in 434 patients after surgical resection.\textsuperscript{49} Investigators found there was no difference in overall survival between chemotherapy and observation. Only after the data were adjusted for prognostic variables including age, bile duct cancer, poor tumor differentiation, and positive lymph nodes, was there a survival benefit in favor of chemotherapy (as compared with observation; HR, 0.75; $P = .03$). Subgroup analysis was only hypothesis generating given the small number of patients in each subset. Interestingly, the authors distinguished only between ampullary and bile duct tumor origins, with 35 remaining patients described as “other.” They also noted no significant survival benefit of chemotherapy when ampullary cancers were further stratified to pancreaticobiliary and intestinal subtypes; however, the number of patients in these subgroups was very small. Table 3 provides a summary of prospective and retrospective studies assessing chemotherapy and/or chemoradiation in periampullary cancers.

Given the data from the pancreatic trials, and the added toxicity of radiation without proven benefit, the standard of care for periampullary cancers remains adjuvant chemotherapy. The difficulty in achieving survival benefit with adjuvant regimens is likely owing to their underlying histologic heterogeneity. There are no data to guide therapy based on histologic subtype (intestinal type vs pancreaticobiliary type). However, given the activity of 5-FU in the management of both pancreatic adenocarcinoma as well as intestinal cancers, it may be reasonable to use a fluoropyrimidine-based regimen for tumors with an intestinal histology and a gemcitabine-based regimen for tumors with a pancreaticobiliary histology. Therapy for this malignancy should be discussed in a multidisciplinary setting.

**SUMMARY**

- The rationale for adjuvant therapy in resectable pancreatic cancer is based on high local and systemic recurrence rates and poor overall survival despite curative-intent surgical resection.
- Data regarding the role of adjuvant chemoradiation in resectable disease are conflicting.
- Adjuvant chemotherapy results in a survival benefit after surgical resection with the current standard being administration of adjuvant gemcitabine for 6 cycles (months), beginning up to 12 weeks after surgery.
- Ongoing studies are evaluating new adjuvant regimens, as well as the role for neoadjuvant therapy for resectable disease.
- There are no convincing data for surveillance after resection; however, current guidelines suggest measurement of the CA 19-9 tumor marker every 3 to 6 months for the first 2 years, then annually for up to 5 years. Computed tomography imaging may also be included, but there is no definitive recommendation.
- Periampullary cancers are a rare and heterogeneous group of tumors in terms of site of origin and histologic subtype with an overall better survival rate compared with pancreatic adenocarcinomas; however, the pancreaticobiliary histology among these cancers carries the worst prognosis.
- Data for adjuvant therapy, and hence current treatment standards, for periampullary cancers are derived from subgroup analyses within prospective trials for pancreatic cancer.
REFERENCES