Adjuvant Treatment for Ampullary Cancer
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Summary
Ampullary cancer is an uncommon tumor and tends to have a better prognosis than pancreatic cancer. However, one half of patients will die from recurrent disease suggesting the need for effective adjuvant therapy. Currently, there is lack of randomized trials to guide the use of adjuvant therapy in ampullary cancer. At the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting, the largest trial (Abstract #4006) evaluating adjuvant treatment of ampullary cancer was presented.

What Did We Know Before the 2011 American Society of Clinical Oncology (ASCO) Annual Meeting?
Ampullary adenocarcinoma is a rare gastrointestinal neoplasm. It accounts for up to a quarter of all periampullary malignancies [1]. Periampullary cancers are described as carcinomas arising from structures near the pancreas, common bile duct, duodenum, or the ampulla of Vater itself. Pancreatectoduodenectomy (Whipple procedure) is the preferred treatment modality for this cancer and is the only option for long term survival. However, even with surgery 5-year survival is only approximately 40% [2, 3]. Despite a relatively favorable outcome compared to pancreatic adenocarcinoma following resection, 32-44% of patients will relapse either locally or distantly making adjuvant treatment relevant in this disease [4]. Currently the role of adjuvant chemotherapy in patients with ampullary cancer is unknown, and no standard adjuvant treatment has been established.

There are many uncontrolled series suggesting potential benefit from adjuvant chemoradiotherapy, including the largest series from Mayo, suggesting that overall survival was superior in the arm receiving adjuvant treatment compared to the control arm [4, 5]. The only randomized phase III trials that included substantial number of periampullary cancer failed to show benefit of adjuvant chemoradiotherapy [6]. In this trial 104 patients with periampullary cancer were enrolled and there was no difference in the two-year survival rate (67% versus 63%) or locoregional reoccurrence. Another large retrospective study from Europe, which included 104 patients with periampullary cancer, also did not show any benefit from adjuvant chemoradiotherapy [7].

There is much less data on the benefit of adjuvant chemotherapy for ampullary cancer. In pancreas cancer there is clear benefit of adjuvant treatment with gemcitabine in terms of disease free survival and overall survival [8]. However, in ampullary cancer there have been no randomized trials. The largest reported series which included 56 patients with ampullary cancer failed to demonstrate a survival benefit of adjuvant chemotherapy (5-year survival: 28% versus 34% for controls) [9]. In this trial, patients were randomized to receive postoperative adjuvant therapy with mitomycin C and 5-fluorouracil (5-FU) versus surgery alone (control arm).

Prior to the 2011 ASCO Annual Meeting there was no level I evidence supporting benefit from adjuvant treatment in ampullary cancer. Even National Comprehensive Cancer Network (NCCN) or European Society for Medical Oncology (ESMO) have not published guidelines in ampullary cancer. Commonly, resected ampullary cancer patients have been treated very similarly to resected pancreatic cancer.

What Did We Learn at the 2011 ASCO Annual Meeting?
Ampullary cancer European Study Group for Pancreatic Cancer (ESPAC)-3 (v2) trial: a multicenter, international, open-label, randomized controlled phase
III trial of adjuvant chemotherapy versus observation in patients with adenocarcinoma of the ampulla of Vater. (Abstract #LBA4006) [10].

Neoptolemos et al. examined effects of adjuvant treatment on overall survival in resected ampullary or periampullary cancer. In this trial, patients were randomized to either 5-FU/leucovorin (leucovorin at a dose of 20 mg/m² i.v. bolus then 5-FU at a dose of 425 mg/m², i.v. bolus, 1-5 days every 28 days) versus gemcitabine (1,000 mg/m² i.v. infusion days 1, 8, and 15 every 4 weeks) versus observation. A total of 304 patients were enrolled. The final outcome of the trial demonstrated lack of a benefit of adjuvant chemotherapy overall. Median overall survival for chemotherapy (57.1 months) versus no chemotherapy (43.0 months) gave an HR of 0.85 (95% CI: 0.61-1.18; P=0.323). For R0 patients median overall survival for chemotherapy (58.4 months) versus no chemotherapy (45.1 months) gave an HR of 0.78 (95% CI: 0.55-1.11; P=0.173). Independent prognostic factors were tumor diameter and grade, lymph node status and R0/R1 status. A Cox proportional hazards analysis also failed to show a survival benefit with chemotherapy in the overall population. However, there was a survival outcome benefit from chemotherapy in the subset of patients with R0 resection using multiple regression with an HR of 0.73 (P=0.048). Regarding the type of chemotherapy administered, no significant survival differences were noted with gemcitabine compared with 5-FU/leucovorin, although gemcitabine was better tolerated. The authors concluded that the trial suggests a benefit for adjuvant monochemotherapy in patients with clear resection margins.

**Discussion**

Neoptolemos et al. presented the largest randomized trial in resected ampullary cancer by a wide margin. This is the current gold standard study in this disease. From the trial it is once again clear that periampullary cancers differ from pancreatic cancer in many aspects of their biology, but nodal and margin status remain important markers of outcome. Overall the trial did not meet its endpoint as adjuvant chemotherapy did not significantly improve survival in resected ampullary cancer. There was a trend toward better 5-year overall survival but the P value was non-significant. However, as the authors point out, in the subset of patients with R0 resection, there is better survival when using multiple regression. The pattern of recurrence (local vs. systemic) or histology of the tumor (pancreaticobiliary vs. intestinal) was not reported in the abstract.

In conclusion, the trial showed a trend toward an improvement in survival with adjuvant chemotherapy that was potentially underpowered to show statistical significance. A future adjuvant treatment study should focus on R0 patients with combination chemotherapy or possibly with conjunction with radiation in R1 patients. It may also be important to consider potential differences between the pancreaticobiliary and intestinal types.

**Conflict of interest** The authors have no potential conflict of interest.

**References**