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Research Article

Survival and Recurrence in Pancreatobiliary Versus Intestinal Histology of Ampullary Carcinoma

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ABSTRACT

Background: Ampullary carcinoma is rare with a more favourable prognosis compared to pancreatic ductal adenocarcinoma. The role of histological classification, including pancreatobiliary (PB) and intestinal (INT), on survival and recurrence outcomes in ampullary cancer is still debatable.
Methods: 42 patients were identified between 1996-2010.
Results: Nineteen classic pancreatoduodenectomies (PD) and 23 pylorus-preserving PDs were performed. Pathological review revealed 23, 18 and 1 patients with the PB, INT and mixed histology, respectively. Adjuvant chemoradiation (ACRT), chemotherapy, and radiation were given to 14 (33.3%), 4 (9.5%) and 2 (4.8%) patients, respectively. Recurrence-free survival (RFS) and overall survival (OS) from time of surgery were higher in the PB histological variant compared to INT (p=0.005 and 0.012, respectively). A landmark (LM) analysis found higher survival in the PB variant patients compared to INT (RFS p=0.023; OS p=0.048). There was no difference in RFS between both histological variants for patients who underwent surgery alone (p=0.42). However, the PB had higher RFS compared to the INT histology for patients who underwent ACRT (p=0.008).
Conclusion: Ampullary carcinoma with PB histological variant was associated with significant survival benefit. The PB versus INT survival benefit was seen in the setting of ACRT, but not with surgery alone.

Highlights

- Ampullary carcinoma with pancreatobiliary histology has better survival.
- No survival difference between both histologies for patients who had surgery alone.
- The pancreatobiliary histology has better survival with adjuvant chemoradiation.

Background

Carcinoma of the ampulla of Vater is a rare malignancy, however, it has a better prognosis compared to pancreatic ductal adenocarcinoma [1, 2]. Pancreatoduodenectomy (PD) remains the mainstay of treatment with contemporary improvement of postoperative morbidity and mortality [3, 4]. Five-year survival of resectable ampullary carcinoma is reported to be between 30%-60%, which exceeds the survival rate for patients with resectable pancreatic cancer (20%) [1, 5-8]. The literature is much more robust regarding pancreatic adenocarcinoma, although it is still overwhelmed by conflicting data regarding the best management of patients following the oncological resection of ampullary carcinoma. Many prognostic features have been proposed, although certain "high-risk" elements were indicted to associate with worse prognosis. They include cellular differentiation, histopathological architecture, lympho-vascular and perineural invasion, and loco-regional progression [2, 9, 10]. Two main histological subtypes have been reported: the

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pancreatobiliary (PB) variant which mimics the morphology of pancreatic ductal adenocarcinomas and the intestinal (INT) variant which imitates colorectal adenocarcinoma [11]. The PB variant demonstrates a single layer of cuboidal or columnar cells organized in simple or branching glands in the background of desmoplastic stroma. The tumor cells of the PB subtype are rounder than those of the INT type and lack nuclear pseudostratification (Figures 1a & 1b). On the contrary, the INT subtype is microscopically encompassing simple or cribriform glands that are lined by columnar cells with pseudostratified oval or elongated nuclei (Figures 1c & 1d).

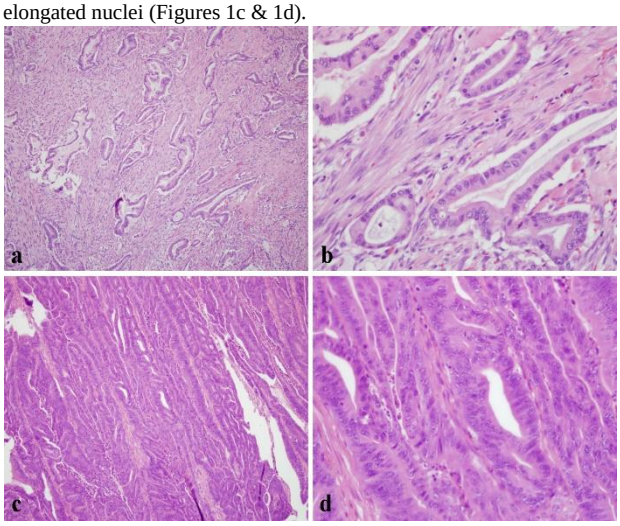

Figure 1: Ampullary carcinoma histological variants. **a)** Pancreatobiliary subtype (10X) - well-formed individual glands in a desmoplastic stroma; **b)** Pancreatobiliary subtype (40X) - single layer of cuboidal/columnar epithelium with round nuclei; **c)** Intestinal subtype (10X) - dense glands demonstrating a cribriform like pattern; **d)** Intestinal subtype (40X) - columnar cells with pseudostratified nuclei.

The use of adjuvant chemoradiotherapy (ACRT) is not a novel approach for ampullary cancer, as this was originally advocated for by the Gastrointestinal Tumor Study Group (GITSG) [12]. On the contrary, the European Organization for Research and Treatment of Cancers (EORTC) showed no improvement in survival with the use of ACRT following resection for pancreatic and ampullary cancer [13]. However, this trial is historical and does not incorporate the recent advancements in radiation oncology. Our study aims to address the survival outcomes of these two different histological variants in the era of multi-modality approach and bring attention to the effect of adjuvant treatment in both subtypes.

Materials and Methods

An institutional database of a National Cancer Institute designated cancer center identified 42 patients with Ampullary carcinoma from 1996-2010 who had undergone Whipple procedure with prolonged follow-up. The registry query was approved by the Fox Chase Cancer Center's Institutional Review Board (IRB). Characteristics studied included age at diagnosis, gender, type of surgical procedure, lymph node yield and metastases, other treatment including chemotherapy and/or radiation therapy, pathological stage (pStage) and histological variant (PB, INT and mixed). Staging was reported utilizing the American Joint Committee on Cancer (AJCC) staging at the time of diagnosis. The pathological and histological examinations were re-reviewed by a senior pathologist. The primary outcomes were overall survival (OS) and recurrence-free survival (RFS).

Statistical Analyses

Patient characteristics were compared by histology variant (PB vs. INT), excluding one mixed variant, using Chi-square tests for categorical variables and t-tests for age and number of lymph nodes harvested. Survival outcomes were examined in two ways: starting at the date of surgery, and also as a landmark analysis starting 9 months after surgery to address immortal time bias between patients who received treatment after surgery and those who did not. The landmark starting point was based on the maximum duration of adjuvant chemoradiation for the cohort. Patients who died or had recurrence prior to the landmark start were excluded from the comparison. One patient who had 'mixed' variant subtype was also excluded from all survival analyses. Overall survival is based on time to death from any cause; recurrence free survival is based on time to first recurrence or death from any cause. Survival outcomes were censored at the date of last patient follow-up. Kaplan Meier methods were used to generate survival curves, which were compared using log-rank tests. Cox proportional hazards regression was utilized to estimate the association of histological variant with survival. The proportional hazards assumption was assessed for the variant and each covariate separately. Due to the small cohort, Cox models were utilized to adjust for one covariate at a time. pStage and adjuvant chemotherapy were correlated, as advanced pStages were more likely to receive adjuvant therapy. In subset analyses, we looked at differences by histological subtype within the surgery only and adjuvant chemoradiation groups. Analyses were performed using SAS statistical software (version 9.4), with $p<0.05$ indicated the presence of a statistically significant association.

Results

The study cohort includes 42 patients with 15 males (36%) and mean age at diagnosis of 65 years. Nineteen classic PDs and 23 pylorus-preserving PDs were performed. The mean number of lymph nodes harvested was 18.3, with 19 patients (45%) having at least one lymph node metastasis. Pathological review revealed 23, 18 and 1 patients with the PB, INT and mixed histological variants, respectively. There were no differences between the PB and INT histological variant groups regarding gender, age, type of procedure, lymph node yield and metastases, and other treatments (Table 1). The TNM pStage distribution was IA 9.5% (n=4), IB 19.1% (n=8), IIA 19% (n=8), IIB 38.1% (n=16), and III 14.3% (n=6), reflecting the AJCC staging system in use at time of surgery. Neoadjuvant chemoradiation was administered to three patients (7.1%). Adjuvant treatment included ACRT, adjuvant chemotherapy, and adjuvant radiation were given to 14 (33.3%), 4 (9.5%) and 2 (4.8%) patients, respectively. Nineteen patients (45.2%) did not receive adjuvant therapy (Table 1).

Table 1: Patient characteristics by histologic variant.

	All (n=42)		***Histological Variant*****				
			INT (n=18)		***PB (n=23)***		
Characteristic	***N****	***%***	***N***	***%***	***N***	***%***	***p-value******
Gender							0.70
Female	27	64.3	12	66.7	14	60.9	
Male	15	35.7	6	33.3	9	39.1	
Age, Mean (std)	64.8	(14.0)	61.4	(15.5)	66.8	(12.6)	0.22
Age (years)							0.63
29-59	13	31.0	7	38.9	6	26.1	
60-69	14	33.3	5	27.8	9	39.1	
70-87	15	35.7	6	33.3	8	34.8	
PD Procedure							0.093
Classic	19	45.2	11	61.1	8	34.8	
Pylorus-preserving	23	54.8	7	38.9	15	65.2	
LN harvested, Mean (std)	18.3	(8.9)	18.9	(8.8)	18.1	(9.2)	0.78
LN positive							0.83
No	23	54.8	12	52.2	10	55.6	
Yes	19	45.2	11	47.8	8	44.4	
Any Chemotherapy and/or radiation							0.95
No	19	45.2	8	44.4	10	43.5	
Yes	23	54.8	10	55.6	13	56.5	
Type of Chemo/RT							
Neoadj. ChemoRT	3	7.1	1	5.6	2	8.7	
Adj. RT	2	4.8	1	5.6	1	4.3	
Adj. Chemo	4	9.5	1	5.6	3	13.0	
Adj. ChemoRT	14	33.3	7	38.9	7	30.4	

INT: Intestinal; PB: Pancreatobiliary; STD: Standard Deviation; PD: Pancreatoduodectomy; LN: Lymph Node; Chemo: Chemotherapy; RT: Radiation; Neoadj.: Neoadjuvant; Adj.: Adjuvant.

*Columns are N and Percent unless specified otherwise.

**one patient with mixed variant excluded from breakdown by histological variant.

***p-value compares INT vs. PB variants, Chi-square test or t-test, as appropriate.

Of 42 patients, eleven who were alive at last contact have median follow-up of 114.8 months [interquartile range: 53.2-119.2 months]. Thirty-one patients have expired including 11 and 20 with and without recurrence events, respectively (Supplementary Table). The median OS and RFS from date of surgery for all 42 patients are 70.5 (95% CI = 28.9-134.3) months and 68.1 (95% CI = 26.4-129.1) months, respectively. RFS and OS are higher in the PB histological variant (p=0.005 and 0.012, respectively) (Figure 2). To adjust for immortal time bias, landmark analysis was performed, where time to death or recurrence was from 9 months postoperatively. This starting point was based on the maximum interval to complete ACRT in this cohort. Utilizing this criterion, we excluded 5 patients from the analysis due to RFS less than 9 months. They included 2 patients with surgery only, 2 patients with adjuvant chemotherapy, and 1 patient with ACRT. In the landmark cohort of 36 patients, there are differences in RFS based on type of therapy (p=0.005): four patients who received only adjuvant chemotherapy or only adjuvant radiotherapy had poorer RFS, while those in the surgery only, neoadjuvant or adjuvant chemoradiation groups had similar, more favourable RFS (Figure 3). In the landmark cohort, RFS and OS are higher in the PB histological variant group (p=0.023 and p=0.048, respectively), consistent with the differences seen in the initial cohort. Survival differences were seen 36 months after surgery in the PB compared to the INT variant (Figure 4).

For RFS, the unadjusted hazard ratio for PB vs INT was 0.39 (95% CI=0.17-0.90, p=0.027). With adjustment for potential confounders separately (due to the small sample size), the association of variant with RFS remained statistically significant when adjusting for chemoradiation treatment, age, lymph node metastases, and type of surgery, and borderline significant when adjusting for pStage (Table 2). As an alternative way to control for type of treatment, we looked at the surgery alone group (n=16) and the ACRT group (n=13) separately. There is no difference in RFS between histological variants for patients who underwent surgery alone (p=0.42). However, the PB histological variant demonstrated improved RFS compared to the INT variant for patients who underwent adjuvant chemoradiation (p=0.008) (Figure 5).

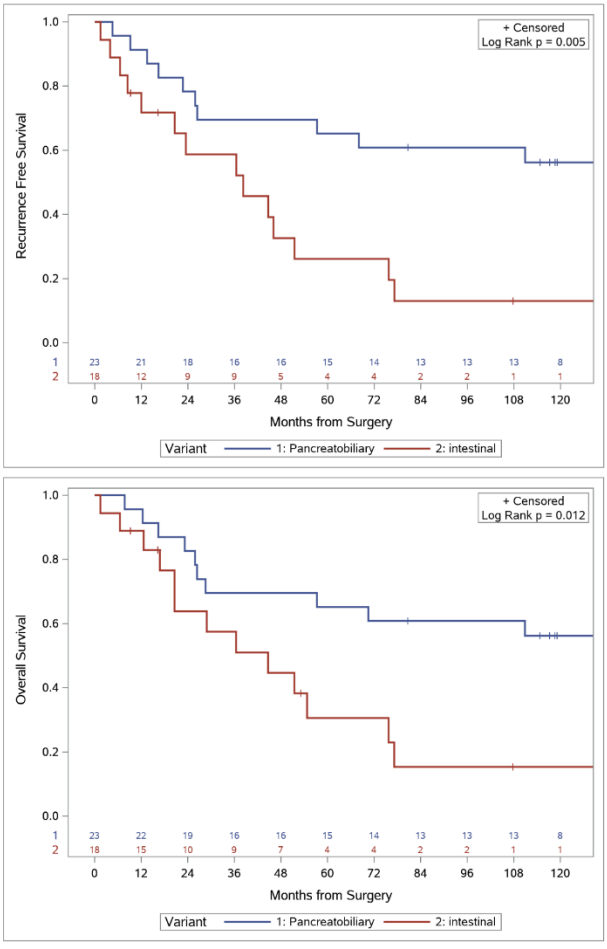

Figure 2: Recurrence-free survival and overall survival from date of surgery stratified by histological variants (p=0.005 and 0.012 respectively).

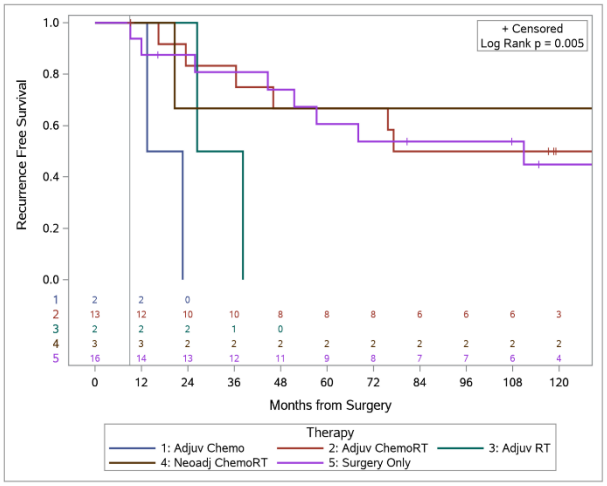

Figure 3: Recurrence-free survival from date of surgery stratified by treatment category for patient with ampullary carcinoma who had at least 9 months of postoperative recurrence-free follow-up (p=0.005). The reference line at 9 months indicates the landmark analysis cut point.

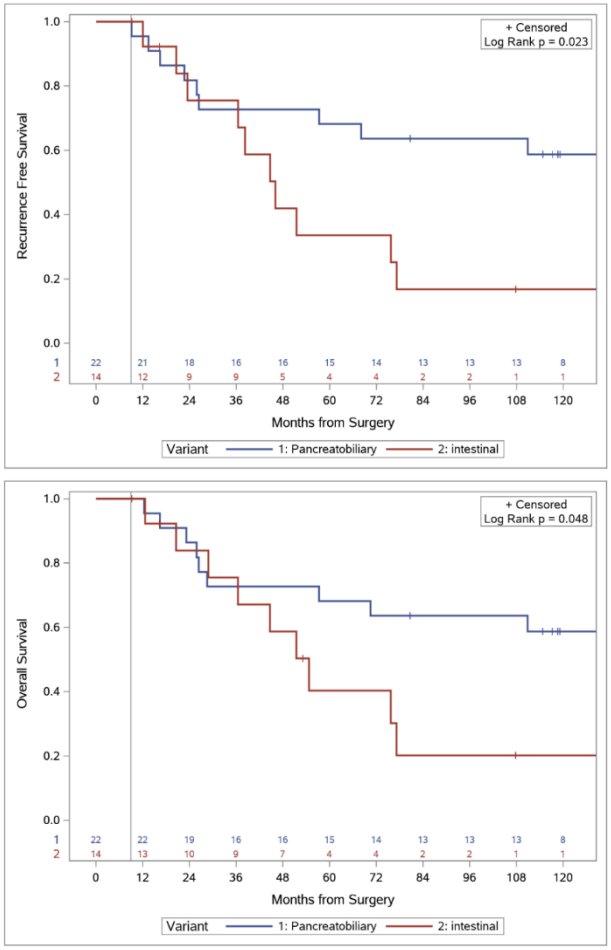

Figure 4: Landmark analyses demonstrating recurrence-free survival and overall survival from date of surgery, stratified by histological variants (p=0.023 and 0.048 respectively). Survival differences are seen after 36 months postoperatively. The reference line at 9 months indicates the landmark analysis cut point.

Table 2: Association of histological variant with time to recurrence or death, with adjustment for each covariate separately. Results of 6 Cox models, landmark analysis, starting at 9 months postoperative, with 36 patients with 26 events.

	Histological Variant (PB vs INT)		
Covariates included with Variant	**HR**	**95% CI**	**p-value**
Variant only (no covariates)	0.39	0.17-0.90	0.027
Variant plus ChemoRT*	0.36	0.15-0.88	0.025
Variant plus Age (continuous)	0.37	0.16-0.87	0.022
Variant plus LN positivity (Yes vs No)	0.39	0.17-0.93	0.033
Variant plus Pathological Stage**	0.45	0.18-1.14	0.091
Variant plus PD (Classic vs. pylorus-preserving)	0.40	0.17-0.93	0.034

INT: Intestinal; PB: Pancreatobiliary; LN: Lymph Node; HR: Hazard Ratio; CI: Confidence Intervals; PD: Pancreatoduodectomy.

*ChemoRT included in model as: None, Adjuvant ChemoRT, Neoadjuvant ChemoRT, and single adjuvant treatment (Chemo or RT).

**Pathological stage included in model as: IA/IB, IIA, IIB and III.

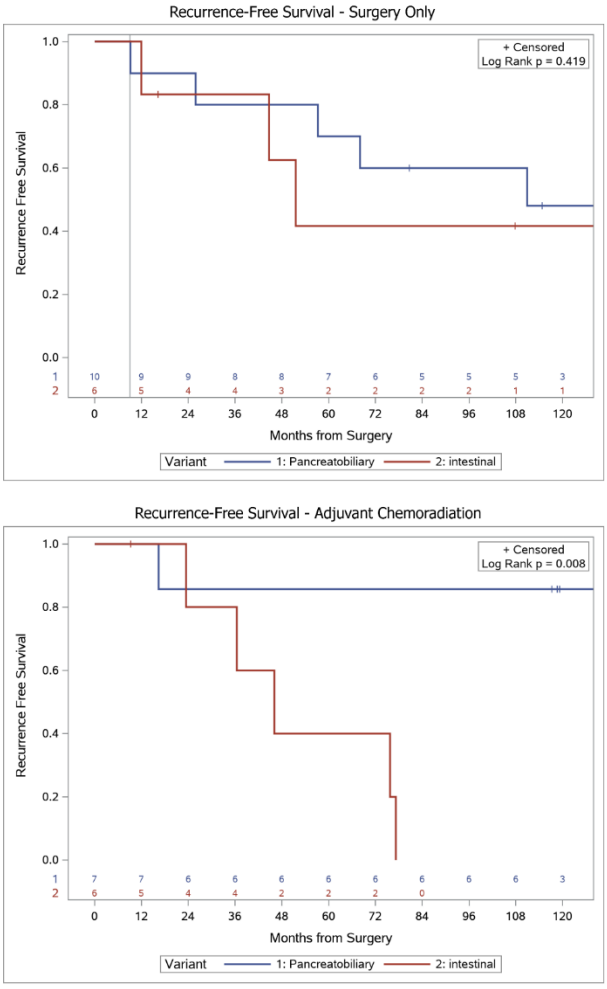

Figure 5: Landmark analyses demonstrating recurrence-free survival in the surgery only and adjuvant chemoradiation groups (p=0.42 and 0.008 respectively), stratified by histological variants. The reference line at 9 months indicates the landmark analysis cut point.

Discussion

Ampullary carcinoma, in spite of its rarity, has historically adopted a better behaviour and further a favourable prognosis compared to both pancreatic ductal adenocarcinoma and cholangiocarcinoma [2, 14]. Halsted performed the first local excision of an ampullary carcinoma in 1898 [15]. Since then, surgery remains the mainstay of treatment for ampullary and periampullary malignancies. Although ampullary carcinoma shares the same anatomic profile and symptomology with pancreatic head cancer, its early presentation and tumor biology have designated at least 80% of patients as candidates to intention-to-cure surgical resection compared to 20% with pancreatic cancer [4]. The literature lacks adequate data when it comes to this disease compared to other gastrointestinal tract malignancies, which is likely related to its relative scarcity [14]. Of all comers, recurrence after surgical resection has been reported to occur in almost half of cases with five-year survival averaged around 35% [2, 7]. In our series, 11 of 42 (24%) patients remained alive, with a median of 115 months of follow-up. Neoadjuvant therapy has been considered in patients with aggressive tumor biology, undergoing preoperative optimization for comorbidities that delays surgery, or labelled "high risk" for postoperative complications that might hinder adjuvant treatment [16]. Complete pathologic response was documented in 14% of cases without increase in postoperative morbidity and mortality or even OS [16].

Literature demonstrated improved survival in patients with ampullary carcinoma and moderately or well-differentiated carcinoma, early T stage, absence of perineural and lympho-vascular invasion, negative lymph node involvement, negative margins, and/or the absence of perioperative blood transfusion [7, 9, 14, 17-21]. High risk patients have worse overall survival (30% versus 80% at 3 years) [22]. Both perineural and/or lympho-vascular invasion predicts worse prognosis and promotes lymph node metastasis [14]. Adequate lymph node harvesting is mandatory as it is irrelevant to the T stage, for example T1 carcinoma is associated with 28% lymph metastasis [14]. In fact, lymph node involvement worsens median overall survival to one third that of patients without nodal metastasis (23% versus 73% at 3 years) [14, 22]. There have been many studies addressing the role of histological prognostic factors that can be validated in foregut and pancreatic carcinoma to predict the need for adjuvant therapy. Palta *et al.* reported that patients with poorly differentiated histology have been historically more inclined to receive adjuvant therapy [2]. According to Willet *et al.*, patients with high-risk features (including poor differentiation, lymph node metastasis and invasion of the pancreas) who received adjuvant radiotherapy demonstrated better loco-regional control, but no survival benefit due to subsequent distant metastases [21]. Lee *et al.* demonstrated 3-year OS and RFS of 55% and 54%, respectively. In their cohort, patients with advanced T and N stages who underwent adjuvant chemoradiation were found to have less loco-regional recurrences [22]. You *et al.* reported 3-year OS of 28% and 8% in patients with positive nodes with and without adjuvant chemoradiotherapy, respectively [23].

Therefore, adjuvant chemotherapy or chemoradiation has been advocated, although the European Study Group for Pancreatic Cancer (ESPAC)-3 and EORTC-40891 trials have not shown survival benefits for adjuvant chemotherapy and chemoradiotherapy, respectively [13, 24, 25]. However, subsequent analysis adjusted for poor prognostic factors showed a statistically significant survival advantage for postoperative chemotherapy, particularly for those who received Gemcitabine based regimen [24]. This argument also holds true for those with pancreatic adenocarcinoma, although the survival rates are justifiably worse. Thus, ampullary carcinoma should be addressed as a systemic disease, even when it is amenable to adequate oncological resection. Kwon *et al.* performed a systematic review and meta-analysis that showed improved OS in patients with positive lymph nodes who received adjuvant chemoradiation [26]. The utilization of adjuvant therapy in patients with poorly differentiated, node-positive, invasive disease is not a novel concept; nonetheless whether other histopathological sub-classifications play a prognostic role and the subsequent need for adjuvant therapy is not well documented in the literature. Our study is looking into the PB and INT histological variants of ampullary carcinoma which was initially introduced to literature by Albores-Saavedra [11]. Westgaard *et al.* reported the PB histological variant as an adverse predictor of survival in patients with periampullary and ampullary carcinomas [27]. They demonstrated similar survival outcomes of the PB subtype among cancers of the ampulla, duodenum, biliary tree and pancreas, while adjusting to tumor size and lymph node metastasis [28]. In essence, they

postulated that adjuvant treatment considerations should be based on tumor biology, rather than anatomic location. Contrary to the previously reported outcomes and in our cohort, the PB histological variant demonstrated improved RFS and OS compared to the INT variant, and in a separate examination of the ACRT setting. RFS did not differ between the PB and INT histological variants for patients who underwent surgery alone.

These results suggest the beneficial role of chemoradiation in ampullary carcinoma, particularly when final pathology demonstrates PB histological variant. Our study reiterates the importance of reporting these histological subtypes in the pathology report and including them during tumor board discussion for multi-modality treatment approach. Despite the long follow-up and patient-tailored multi-disciplinary management of ampullary cancer at a single institution, this study has limitations: its retrospective nature, possible selection bias, the small sample size including those who received adjuvant therapy, and immortal time bias. As we adjusted for the latter using landmark survival analysis, the results are based on those who survived at least 9 months after surgery, to make the ACRT and surgery only groups more comparable.

Conclusion

Ampullary carcinoma with PB histological variant is associated with significant survival benefit compared to the INT variant, especially in the setting of ACRT. However, this benefit is not appreciated in the surgery alone group. Despite the limitations of this study, histopathology should be considered when discussing the role of adjuvant treatment in the setting of ampullary carcinoma. Further randomized trials are warranted to address both histological variants with the emerging advances in chemotherapy regimens and radiation modalities.

Author Contributions

Study Concept and Design: Maitham Moslim, Karen Ruth and Sanjay Reddy; Acquisition of Data: Maitham Moslim, Hailan Liu, Max Lefton, Rajeswari Nagarathinam and Harry Cooper; Statistical Analysis: Karen Ruth; Analysis and Interpretation of Data: Maitham Moslim and Karen Ruth; Drafting of the Manuscript: Maitham Moslim and Sanjay Reddy; Critical Revision of the Manuscript for Important Intellectual Content: Maitham Moslim, Karen Ruth and Sanjay Reddy; Final Approval of the Submitted Version: Sanjay Reddy.

Conflicts of Interest

None.

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None.

Supplementary Table: Summary of recurrence and all-cause mortality events, by histological variants.

		Histological Variant (n)		
Events	**All**	PB	INT	Mixed
No Recurrence, No Death	10	7	3	0
Recurrence, No Death	1	0	1	0
No Recurrence, Death	20	10	9	1
Recurrence and Death	11	6	5	0
Total	42	23	18	1

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