Original Article

Patterns of failure for stage I ampulla of Vater adenocarcinoma: a single institutional experience

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Background: Ampullary adenocarcinoma is a rare malignancy associated with a relatively favorable prognosis. Given high survival rates in stage I patients reported in small series with surgery alone, adjuvant chemoradiotherapy (CRT) has traditionally been recommended only for patients with high risk disease. Recent population-based data have demonstrated inferior outcomes to previous series. We examined disease-related outcomes for stage I tumors treated with pancreaticoduodenectomy, with and without CRT.

Methods: All patients with stage I ampullary adenocarcinoma treated from 1976 to 2011 at Duke University were reviewed. Disease-related endpoints including local control (LC), metastasis-free survival (MFS), disease-free survival (DFS) and overall survival (OS) were analyzed using the Kaplan-Meier method.

Results: Forty-four patients were included in this study. Thirty-one patients underwent surgery alone, while 13 also received adjuvant CRT. Five-year LC, MFS, DFS and OS for patients treated with surgery only and surgery with CRT were 56% and 83% (P=0.13), 67% and 83% (P=0.31), 56% and 83% (P=0.13), and 53% and 68% (P=0.09), respectively.

Conclusions: The prognosis for patients diagnosed with stage I ampullary adenocarcinoma may not be as favorable as previously described. Our data suggests a possible benefit of adjuvant CRT delivery.

Keywords: Ampulla of Vater; patterns of failure; adjuvant therapy

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Background

Ampullary adenocarcinoma is a rare cancer that accounts for less than 1% of all gastrointestinal malignancies (1). Given the location of these tumors, patients often present with relatively early stage disease with symptoms related to biliary obstruction. Given higher potential for surgical resection compared with other hepatobiliary tumors, prognosis is favorable, with multiple studies demonstrating 5-year overall survival (OS) rates ranging from 30% to 60% (2-8). Risk factors adversely impacting prognosis include positive surgical margins, nodal involvement, and tumor differentiation and size (9-11).

The primary treatment modality for ampullary carcinomas is pancreaticoduodenectomy. Despite the relatively favorable prognosis for ampullary tumors, patients with high-risk features often develop locoregional and distant recurrence (12). Due to the rarity of this disease, the benefits of adjuvant therapy have primarily been analyzed through retrospective and institutional series, and the role of adjuvant therapy remains unclear.

Many authors recommend the use of adjuvant chemoradiotherapy (CRT) for patients with nodal involvement, involved margins and advanced tumor stage (8-11,13). Published series advocate the use of adjuvant therapy in advanced tumors (i.e., T3/T4 and node positive disease) based on high locoregional recurrence and low OS rates reported in these patients. With surgery alone, 5-year local control (LC) rates of 33-47% have been reported (8-11). However, most investigators have not advised adjuvant therapy for T1-T2N0 tumors (stage I) given

the more favorable 5-year OS rates ranging from 40-100% (7,8,10,11,14). However, contemporary population-based data from the National Cancer Data Base (Commission on Cancer of the American College of Surgeons and the American Cancer Society) demonstrated poor outcomes with 5-year OS rates of 40-44% for T1-T2N0 tumors (15). We hypothesize that even early stage (T1-T2N0) ampullary tumors may have failure rates high enough to warrant adjuvant therapy. We undertook this study to evaluate patterns of failure and disease-related outcomes for patients with T1-T2N0 tumors undergoing pancreaticoduodenectomy, with or without adjuvant CRT.

Methods

This study was approved by the Duke University Institutional Review Board. The records of all patients evaluated between 1976 and 2011 who were diagnosed with stage I (T1-T2, node negative) ampullary carcinoma were reviewed. Ampullary carcinoma was defined as tumors arising in the ampulla or major papilla. Patients with tumors of the duodenum, bile duct, pancreas or minor papillae on pathologic examination were excluded. Patients who presented with disease metastasis or those who received neoadjuvant CRT were excluded as were patients with positive resection margins. Surgical pathology was staged according to the American Joint Committee on Cancer Guidelines, 7th edition (15).

Surgery

All patients underwent pancreaticoduodenectomy with curative intent. Prior to surgery, patients were evaluated by cross-sectional imaging with abdominal and pelvic computed tomography (CT) or magnetic resonance imaging (MRI), as well as endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography (ERCP). Patients' pathology, including histological stage and grade, as well as perineural (PNI) and lymphovascular (LVI) invasion and margin involvement, were abstracted. For patients whose original pathology did not include information regarding PNI or LVI, the pathology slides were reexamined by the Duke University Pathology department. Both diagnostic biopsy and Whipple specimens were reviewed in some instances given that some stage I tumors were resected at biopsy with minimal or no residual tumor in the Whipple specimen.

Chemoradiotherapy (CRT)

The decision to deliver adjuvant therapy was based on physicians' preference. Multi-field external beam radiation therapy was used to treat the tumor bed and locoregional lymph nodes, including pancreaticoduodenal, superior mesenteric artery, celiac, and porta hepatis nodal regions. Patients were treated in 1.8 Gy fractions, 5 days consecutively per week. Prior to 1997, radiation plans used 2-dimensional anterior-posterior/posterior-anterior with opposed lateral beams; following 1997, patients underwent 3-dimensional treatment planning. Concurrent chemotherapy regimen was determined by the treating Medical Oncologist and was fluoropyrimidine-based in all cases.

Statistical analysis

All statistical analyses were performed by Duke Cancer Institute's statistics department. Time-to-event endpoints were estimated using the Kaplan–Meier method, calculated from the time of surgery. P values were calculated using the Log-Rank method. LC, disease-free survival (DFS), metastasis-free survival (MFS) and OS were measured. Local failure was defined as recurrence in the initial tumor bed or locoregional lymph node basins. Recurrences outside these regions were designated as distant failures. Patients without local failure were censored either at the time of distant failure, time of death or, if alive, at the last follow-up. DFS was defined as the time to the first instance of a local or distant failure, and was censored at last follow-up if alive or at death if there was no evidence of recurrence. Similarly, MFS was defined as the time to distant failure and was censored at last follow-up if alive or at death if there was no evidence of distant failure. OS was defined as the time between surgery and death and was censored at the last follow-up for patients alive at the time of analysis. Patients returned to clinic for follow-up approximately every 3 months following treatment. Patterns of failure were assessed during follow-up primarily through radiographic imaging with biopsy of the suspected recurrent disease when clinically appropriate. Median follow-up time was calculated using the reverse Kaplan–Meier method (16).

Results

Forty-four patients diagnosed with stage I ampullary cancer underwent pancreaticoduodenectomy. Median patient age

Table 1 Patient/tumor characteristics

Characteristics	Surgery (n=31)	Surgery + CRT (n=13)	P value
Median age [range]	64 [38-79]	67 [50-75]	0.46
Grade, n [%]			
Well	6 [19]	2 [15]	0.71
Moderately	19 [61]	7 [54]	
Poor	6 [19]	4 [31]	
T stage, n [%]			
1	13 [42]	4 [31]	0.48
2	18 [58]	9 [69]	
LVI, n [%]			0.68
Positive	14 [45]	5 [38]	
Negative	16 [52]	8 [62]	
Unknown	1 [3]	0 [0]	
PNI, n [%]			0.23
Positive	2 [6]	0 [0]	
Negative	28 [91]	13 [100]	
Unknown	1 [3]	0 [0]	

CRT, chemoradiotherapy; LVI, lymphovascular; PNI, perineural invasion.

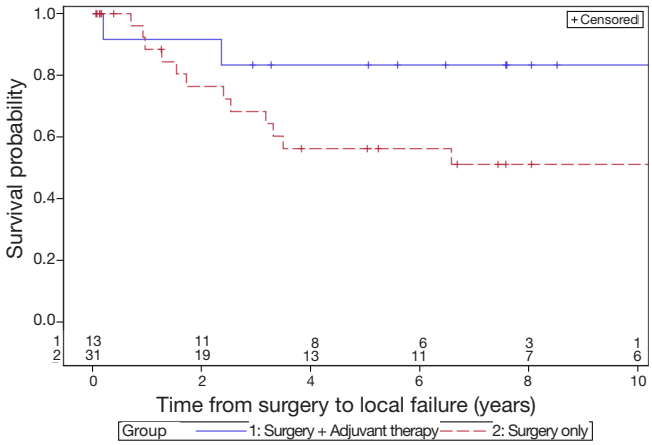

Figure 1 Kaplan-Meier Plot of local control of patients treated with surgery only versus surgery and adjuvant therapy (P=0.13).

at diagnosis was 65 (range, 38-79). Patients often presented with obstructive symptoms including abdominal pain, jaundice as well as pancreatitis. Of these patients, 31 were treated with surgery alone, while 13 received surgery and adjuvant CRT. There were no cases of perioperative deaths. Median radiation dose was 4,500 cGy (range, 3,060-5,040 cGy) and chemotherapy was fluorouracil-based (infusional 5-fluorouracil or capecitabine). Seventeen patients had T1 tumors while 27 were found to have T2 disease. The median follow-up time for all patients was 8.0 years. Patient characteristics are summarized in *Table 1*. Patients returned to clinic every 3-6 months with physical examination and CT following treatment completion. Those who demonstrated no evidence of disease after 5 years were then frequently followed by their local physician. The patients that received adjuvant therapy did not exhibit statistically significant differences in age, tumor grade or stage versus surgery-alone patients.

Of the 44 patients, 14 patients (32%) experienced disease recurrence with some component of locoregional failure. Eleven (79%) of these patients demonstrated both local and distant failures. Of these, nine (82%) demonstrated local and distant disease diagnosed synchronously. Of the two patients whose local and distant recurrences were diagnosed metachronously, one exhibited local failure first while the other was diagnosed with distant disease initially. Of the distant failures, 10 patients (91%) developed liver metastases and one patient (9%) lung metastases.

Of the 31 patients undergoing surgery only, 12 patients (39%) developed recurrent disease. Two patients (17%) demonstrated local recurrence only, while 10 (83%) were found to have both local and distant recurrence. Half of these patients initially presented with T1 disease while the other half T2. Six of these patients (50%) had no other adverse pathologic factors, 5 (42%) were found to have LVI, and 1 (8%) to have PNI. Two (15%) of 13 patients receiving adjuvant therapy subsequently experienced disease recurrence. Both patients presented with T2 disease without any other adverse pathologic features and were diagnosed with synchronous local and distant recurrence.

The 5-year LC rates for patients treated with surgery only and surgery with adjuvant therapy were 56.3% and 83.3%, respectively (P=0.13) (*Figure 1*). The 5-year MFS rates for the surgery and adjuvant group were 66.8% and 83.3%, respectively (P=0.31) (*Figure 2*). The 5-year DFS rates for the surgery only and surgery with adjuvant therapy groups were 56.4% and 83.3%, respectively (P=0.13) (*Figure 3*). The 5-year OS rates for the surgery only and surgery with adjuvant therapy groups were 53.4% and 68.4%, respectively (P=0.09) (*Figure 4*), with corresponding 10-year OS rates of 28.8% and 68.4%, respectively. There were no differences observed in disease-related outcomes based on T staging, tumor histology or PNI/LVI.

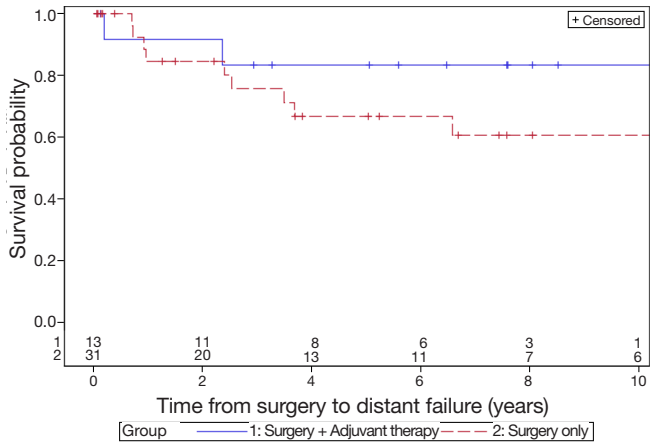

Figure 2 Kaplan-Meier Plot of metastasis-free survival of patients treated with surgery only versus surgery and adjuvant therapy (P=0.31).

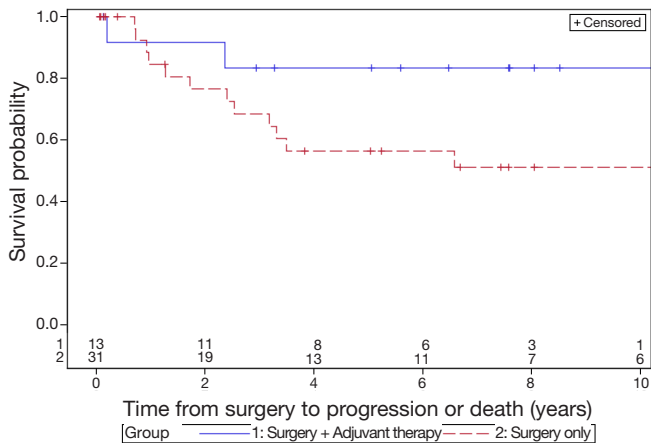

Figure 3 Kaplan-Meier Plot of disease-free survival of patients treated with surgery only versus surgery and adjuvant therapy (P=0.13).

Discussion

Ampullary cancer is a rare malignancy which tends to have better prognosis than pancreatic adenocarcinomas (17,18). Willett *et al.* demonstrated 5-year OS of 55% for "high risk" disease (≥T3, poorly differentiated histologic findings, involved surgical margins or lymph nodes) and 80% survival for "low risk" disease (T1/T2 tumors without high risk features) (10). Similarly, several subsequent retrospective series reported similar survival, with 5-year OS of small patient subsets with T1-T2 disease, ranging from 40% to 100% (*Table 2*) (7,8,11,13,14). However, it is important to

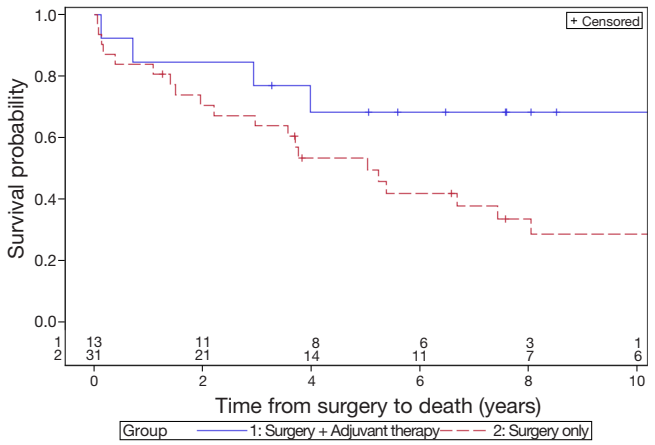

Figure 4 Kaplan-Meier Plot of overall survival of patients treated with surgery only versus surgery and adjuvant therapy (P=0.09).

note that almost all of these studies included lymph node positive patients, with authors reporting outcomes based solely on T-staging without indication of nodal status or other adverse histologic features for these particular subsets. Despite the inclusion of these patients, the favorable outcomes relative to more advanced disease prompted the authors to recommend adjuvant therapy only for advanced tumors or select high risk features (10).

Based on the results of these studies, adjuvant CRT has not been usually recommended for patients with T1/T2N0 disease (8,10,13). However, updated data from the National Cancer Data Base (Commission on Cancer of the American College of Surgeons and the American Cancer Society) from 1998-2002 reported 5-year OS of only 40% and 44% for T1N0 and T2N0 tumors, respectively (15). In addition, a recent randomized European study suggested a possible survival benefit for chemotherapy versus observation following surgery for periampullary tumors, although specific impact on patterns of relapse were not described (21). While this possible benefit was seen on secondary endpoint multivariate analysis (correcting for prognostic variables), approximately 47% of patients in this trial were diagnosed with T1/T2 tumors, and 41% were lymph node negative, although specific analysis of stage I patients was not pursued. The poor disease-related outcomes may potentially be explained by persistent locoregional/nodal disease outside the surgical resection field as demonstrated by Palta *et al.* (5). In the present analysis of early stage patients from a larger group of patients, we hypothesized that adjuvant CRT may lead to improvements in LC and possibly OS, even in patients with relatively early stage tumors.

Table 2 Summary of reported series that designate survival outcomes for patients with T1/T2 tumors

Study	N	5-year OS	CRT recommendation
Lee *et al*. 2000 (U Penn) (13)[1,2]	38: T1: 21 [4]; T2: 17 [6]	T1/T2N0: 83%	Adjuvant for ≥T3 or node positive
Beger *et al*. 1999 (Tokyo) (19)[2]	48: T1: 18; T2: 30	T1/T2: 79%	None stated
Bhatia *et al*. 2006 (Mayo) (9)[1,2]	87: T1: 48; T2: 39	T1/T2: 53%	Adjuvant for node positive
Bottger *et al*. 1997 (Germany) (20)[2]	21: T1: 8; T2: 13	T1: 100%; T2: 50%	None stated
Chareton *et al*. 1996 (France) (1)	T1/T2: 5	T1/T2: 85%	None stated
Hsu *et al*. 2007 (Taiwan) (6)[2]	76: T1: 17; T2: 59	T1: 84%; T2: 59%	None stated
Kim *et al*. 2009 (Korea) (11)[1,2]	78: T1: 43 [37]; T2: 35 [20]	T1: 76%; T2: 63%	Consider adjuvant therapy, especially node positive
Krishnan *et al*. 2008 (MDACC) (8)[1,2]	62: T1: 29 [12]; T2: 33 [18]	T1/T2: 77%	Adjuvant for T3+, node positive, or involved surgical margins
Willett *et al*. 1993 (MGH) (10)[1,3]	T1/T2: 12[3]	T1/T2N0: 80%[3]	Adjuvant for T3+, poorly differentiated, node positive, or involved surgical margins
Showalter *et al*. 2011 (Thomas Jefferson) (14)[1]	T1/T2: 33	T1/T2: 65%	Consider clinical trials of adjuvant therapy for T3+ tumor using optimized RT strategies or novel compounds
Zhou *et al*. 2009 (Johns Hopkins) (7)[1,2]	62: T1: 18 [2]; T2: 44 [17]	T1/T2: S only, 40%; CRT, 48%	No benefit of adjuvant therapy

[1], contains a portion of patients treated with adjuvant therapy. (number in parentheses if adjuvant number specified); [2], study contained lymph node positive patients and did not specify number of T1/T2N0 patients; [3], patients were also LN negative, R0, with well or moderately differentiated tumors. OS, overall survival; CRT, chemoradiotherapy.

Our study demonstrated a surprisingly high locoregional failure rate (39%) for the surgery only cohort compared to patients receiving combined modality therapy (15%) for these early stage patients. Similarly, we witnessed trends towards higher MFS and OS in the patients treated with adjuvant CRT. While not statistically significant, given small number of patients treated with combined modality, our data suggests potential benefit from adjuvant CRT. Zhou *et al.*, demonstrated 5-year OS of 40% and 48% for T1/2 tumors treated with surgery only and combined modality therapy, respectively, and recommended no adjuvant treatment based on the negligible survival improvement from additional therapy (7). However, the median follow-up time in this study was 19.3 months, compared with 8.0 years in this series, and patients with nodal involvement were also included in their analysis. We believe that the long-term follow-up and exclusion of node positive patients in our study allows a more accurate assessment of possible benefit of CRT in patients with early stage ampullary cancers.

Given that 39% of patients who received surgery alone experienced locoregional failure, we believe there is a clinically significant risk of residual subclinical disease following radical resection, even for early tumors. These findings are consistent with a previous study suggesting that local resection for early ampullary tumors is inadequate in preventing disease recurrence (22). In our series, the addition of adjuvant CRT appeared to reduce local failure rates, although not statistically significant, given small patient numbers. Additionally, there appeared to be a large number of patients who developed distant metastases, most commonly in the liver. Given most distant metastases occurred synchronously with local recurrence, it is possible that these tumors were more biologically aggressive or that the development of locoregional failure facilitates distant metastases development (23-25). This concept suggests that improved LC, through addition of radiation therapy, may potentially prevent both local and subsequent distant recurrences. It is also likely that the ability to detect local recurrences with contemporary imaging techniques is suboptimal, likely underestimating local recurrence rates, notably given that local recurrences may be overlooked once distant metastases have developed. Surprisingly, we did not notice any significant differences in disease outcomes based on tumor size nor pathologic grade. Additionally, while

almost half of the patients presented with LVI, this did not appear to have any effect on disease-related outcomes on outcomes analysis.

Our study is limited by several factors, including its retrospective nature, relatively small patient numbers and small number of patients receiving adjuvant treatment. Consequently, although the survival curves depicted differences at the 5- and especially 10-year time points, our outcomes only trended towards significance due to limited power. Given the rarity of this disease and lack of randomized prospective studies evaluating adjuvant CRT, these analyses remain instructive. To our knowledge, this is the largest reported non-population-based series specifically reporting outcomes for patients with stage I (T1/T2N0) ampullary cancers, notably those receiving adjuvant CRT.

Conclusions

Our data suggest that LC and OS for stage I ampullary carcinomas may not be as favorable as previously described. Patients who receive adjuvant CRT may derive a benefit in LC and potentially other disease-related outcomes. Based on our experience, we recommend adjuvant CRT for selected patients with resected stage I ampullary carcinoma.

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