

Therapeutic options for ampullary carcinomas. A review

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Abstract

Ampullary Carcinoma arises from a histologically heterogeneous region where three different epithelia converge. Even though Ampullary Carcinoma has a superior prognosis compared to pancreatic and biliary ductal neoplasms, at least half of the patients turn up at an advanced stage that limits the treatment prospects. In addition to surgery for early-stage disease, several studies have shown that chemoradiotherapy confers additional benefits in the management of Ampullary Carcinoma. Analogously, chemotherapy plays a crucial role in treating advanced Ampullary Carcinoma with distant metastasis/recurrences. Although, stage of the disease, lymph node status, and histo-morphology are three critical prognostic variables, recently much attention is being placed on the genetic landscape of Ampullary Carcinoma. In this review, we have discussed various studies describing the role of chemoradiation and chemotherapy in the treatment of early and advanced stage Ampullary Carcinoma. Also, we have summarized the molecular landscape of Ampullary Carcinoma and the novel therapeutic strategies which could possibly target the genetic alterations involving the tumor cells.

Introduction

Ampullary Carcinoma emerges from the ampulla of Vater complex which lies distal to the ramification of the pancreatic duct and the distal common bile duct. Ampullary Carcinoma roughly constitutes 7 percent of peri-ampullary tumors.¹ Although Ampullary Carcinoma belongs to the subset of peri-ampullary tumors, it is crucial to distinguish Ampullary Carcinoma against a broader group of peri-ampullary tumors because of the treatment and prognostic implications. For example, Primary Ampullary Carcinoma has a better prognosis when compared to other peri-ampullary tumors like pancreatic cancer or extrahepatic cholangiocarcinoma.^{2,3} Adenocarcinoma, which is the majority type of Ampullary carcinoma is predominantly of the intestinal (47 percent) or pancreato-biliary (24 percent) histologic subtypes.⁴ Interestingly, histologic and histo-molecular phenotypes are important prognostic variables.⁵ For example, histo-molecular pancreato-biliary phenotype (CDX- negative, MUC 1-positive) has a poor prognosis when compared to intestinal phenotype (CDX- positive MUC 1-negative).⁵ This understanding might help in making treatment decisions, particularly when using adjuvant therapy. Also, the lymph node status around disease onset is another important prognostic factor. There is no well-framed set of guidelines on when to use adjuvant therapy because of the relative infrequency of disease and paucity of robust clinical studies. Here we try to give an outline of the current treatment strategies and the molecular alterations with their actionable targets specific to Ampullary Carcinoma.

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Staging and survival of ampullary carcinoma

Approximately fifty percent of patients with Ampullary Carcinoma presents at an advanced stage⁶ with the stage at the diagnosis being the critical prognostic factor.⁷ For those who present at an early stage, standard treatment has been complete surgical resection via pancreaticoduodenectomy. However, because the disease presents in older age groups and the risks of surgical resection, approximately only 40 percent of the patients undergo surgical resection.⁸ This understanding has led to the usage of other surgical approaches like endoscopic papillectomy⁹ and trans-duodenal local resection.¹⁰ The above procedures, in contrast to pancreaticoduodenectomy, have lesser peri-operative morbidity and mortality.¹¹ Nevertheless, these interventions have the drawback of patients having poor resection margins and higher chances of recurrence.¹¹

Even though the likelihood of successful resection is higher in early-stage disease, approximately 45 percent of the treated population develops recurrence over time.¹² Therefore, a section of these patients could potentially get benefited from chemoradiation or chemotherapy.

Adjuvant therapy

Most of the evidence data for the use of concurrent chemoradiation in Ampullary Carcinoma is based on retrospective analyses reported from large academic institutions (Table 1¹²⁻²³). A retrospective study at Mayo clinic reported likely benefit with concurrent radiotherapy and 5-fluorouracil 5-FU) chemotherapy following Pancreaticoduodenectomy. However, an improvement in overall survival (median 3.4 years vs 1.6 years) was only demonstrated among patients with positive lymph nodes. This study could not confirm the clinical benefit in patients with negative lymph node status, thereby signifying the role of lymph node status as a crucial predictor of outcome.¹³ In a study from Duke university, Palta *et al.*, showed significant enhancement in three-year local control (88% vs 55%, P=0.001) with an inclination toward improved overall survival (62% vs 46%, P=0.074) and recurrence-free survival (66% vs 48%, P=0.09) with addition of adjuvant chemoradiation over surgery alone.¹⁴ In addition, 28% of patients who received neoadjuvant chemoradiation for inoperable tumors also showed

pathological complete response status. Another recent retrospective study by Krishnan *et al.*, illustrated a notable clinical benefit with chemoradiation when compared to surgery alone among patients with T3/T4 or lymph node (LN) positive disease, with a predilection toward a better overall survival (35.2 vs 16.5 months; P=0.06).¹⁵ Enhanced overall survival on using adjuvant chemoradiation in patients with positive LN has also been reported.¹⁶⁻¹⁸ Furthermore, another retrospective study by Mehta *et al.*, showed significant clinical benefit with chemoradiation among patients with large tumor size or positive LNs.¹⁶

Contrary to the above, few studies have shown a lack of notable advantage on using adjuvant chemoradiation regardless of the LN status and tumor stage. In a single-center retrospective study by Zhou *et al.*, a significant benefit with chemoradiation was not demonstrated, though there was no substantial improvement in median overall survival (OS) (33.4 vs 36.2 months) among patients with positive LN.¹⁷ In another study, 104 patients with aggressive features such as positive lymph nodes, pancreatic infiltration or poor differentiation were either treated with adjuvant chemoradiation (49 patients) or observed due to poor performance status, post-

Table 1. Studies on adjuvant chemoradiotherapy.

Author	N	Type of Malignancy	Treatment group	Treatment group protocol	Control group	Response	Benefit	Study Design
Bhatia ¹³	125	Ampullary Carcinoma	Chemoradiation n=29	RT 50.4 Gy with concurrent 5-FU	Only surgery n=96	OS 3.4 yr vs 1.6 yr in those with positive LN status	Yes (if node +ve)	Retrospective
Sikora ¹²	113 (104 alive r after surgery)	Ampullary Carcinoma	Chemoradiation n=49	RT 50.4 Gy with concurrent 5-FU	Only surgery n=55	No significant OS and median survival difference	No	Retrospective
Palta ¹⁴	137	Ampullary Carcinoma	Chemoradiation Adjuvant n=43	RT 50.4 Gy with concurrent Chemotherapy	Only surgery n=76	LC 88% vs 55%,	Yes	Retrospective
Lee ²⁰	39	Ampullary Carcinoma	Chemoradiation n=13	RT 48.7 Gy with concurrent 5-FU	Only surgery n=26	OS 55% DFS 54%	Yes (if node +ve)	Retrospective
Krishnan ¹⁵	96	Ampullary Carcinoma	Chemoradiation n=54	RT 50.4 Gy with concurrent 5-FU (52%) and Capecitabine (43%)	Only surgery n=42	35.2 months with CRT vs 16.5 months with only surgery	Yes (if T3/T4)	Retrospective
Kim ²¹	118	Ampullary Carcinoma	Chemoradiation n=41	RT 40 Gy with 5-FU split course	Only surgery n=77	Improved LC in ICRT group	Yes (especially if node +ve)	Retrospective
Narang ²²	186	Ampullary Carcinoma	Chemoradiation n=66	RT median dose 50.4 Gy with 5-FU	Only surgery n=120	Median OS 39.9 months	Yes (if node +ve)	Retrospective
Zhou ¹⁷	111	Ampullary Carcinoma	Chemoradiation n=50	Rt median dose 50.4 Gy with 5-FU or Capecitabine	Only surgery n=61	33.4 months median OS with CRT vs 36.2 months with surgery alone (not statistically significant)	No	Retrospective
Willet ²³	17 (high risk features at presentation)	Ampullary Carcinoma	Radiation n=12	na	Only surgery n=5	Improved local control (not statistically significant)	No	Retrospective
Mehta	na	Ampullary Carcinoma	Chemoradiation n=12 (patients with high risk features)	RT median dose 45 Gy with 5-FU	na	Median survival 34 months and Actuarial Overall survival 89%	Yes (if +ve LN status, large tumor size, poor histology, neurovascular invasion)	Retrospective
Al-Jumayli <i>et al.</i> ¹⁸	45	Ampullary Carcinoma	Chemoradiation n=5 Chemotherapy n=13	na	Only surgery n=27	Median overall survival of the cohort is 30 months	No statistically significant difference in PFS and OS between the surgery vs CRT or chemotherapy group	Single-center retrospective

operative complications or patient refusal. The results showed no impact of adjuvant chemoradiation on overall survival or loco-regional recurrences.¹² Most recently, a single center retrospective study on 54 patients with ampullary carcinoma did not show any significant difference in overall survival and progression free survival with either CRT (5 patients) or chemotherapy (13 patients) vs surgery alone (27 patients).¹⁸ However, in this study, sample size is small and the patients who received adjuvant therapy were found to have an advanced stage of disease.¹⁸ The frequently quoted prospective randomized EORTC trial, examining the role of adjuvant chemoradiation, analyzed pancreatic, and peri-ampullary carcinomas separately. However, Ampullary Carcinomas were grouped along with other peri-ampullary carcinomas, making it any meaningful interpretation difficult.¹⁹ In conclusion, there exists an unmet need for a randomized controlled trial as all currently available information on chemoradiation in Ampullary Carcinoma is retrospective in nature and all such analyses are beset with possible selection biases. However, drawing from available information, most centers currently consider chemoradiation for inoperable, incompletely resected or large tumors or patients with positive LN.

Role of chemotherapy in advanced ampullary carcinoma

Chemotherapy does a pivotal job in the treatment of Ampullary Carcinoma, especially in patients who present with distant metastasis/recurrence or unresectable locally advanced disease (Table 2²⁴⁻³⁴). A retrospective study has reported the use of chemotherapy for 12 patients having advanced Ampullary Carcinoma and 14 patients having recurrent Ampullary Carcinoma. In this study,

patients received either 5-FU based regimen or Gemcitabine-based regimen. The patients had poor treatment outcome with progression-free survival of 2.5 and 3.5 months in 5-FU and Gemcitabine group, respectively.²⁴ Apart from the conventional 5-FU or Gemcitabine-based regimen, a study has substantiated usage of XELOX regimen (Oxaliplatin and Capecitabine combined). In this study, 21 patients who were affected by recurrent or metastatic Ampullary Carcinoma were given XELOX regimen and reevaluated over 16.6 months. 7.6 months and 19.7 months were the median time to progression (TTP) and median overall survival (OS), respectively. Also, there was statistically significant longer TTP in intestinal phenotype when compared to pancreatobiliary phenotype.²⁵ Similarly, a phase-II study has delineated the usage of CAPOX (Capecitabine and Oxaliplatin combined) regimen in 30 patients with either advanced Ampullary or small bowel carcinoma. 11.3 months and 20.4 months were the median TTP and median OS, respectively.²⁶ Recently, a case report has also demonstrated a good response to 5-FU in a patient with advanced ampullary adenocarcinoma.²⁷

A retrospective study compiling the data from National cancer database has shown the overall benefit of using adjuvant chemotherapy in patients who underwent pancreatoduodenectomy when compared to observation alone.²⁸ Similarly, ESPAC-3 peri-ampullary cancer trial has showed the advantage of using adjuvant chemotherapy after surgical resection when compared to observation alone. However, only patients with poor prognostic variables like poor tumor differentiation and positive lymph node status have had this advantage.²⁹ Furthermore, a study analyzed 29 patients with advanced Ampullary Carcinoma who were either treated with Cisplatin plus 5-FU or Cisplatin plus Gemcitabine. 4.9 months and 12.5 months were the median TTP and median OS with only a little difference between the two regimens.³⁰

Table 2. Studies on using chemotherapy alone.

Author	N	Type of malignancy	Treatment regimen	Response	Study design
Shoji <i>et al.</i> ²⁴	26 (advanced ampullar carcinoma n=12, recurrent ampullary cancer n=14)	Ampullary Carcinoma	5-FU based vs Gemcitabine based	Median OS 9.1 months. Median progression free survival 3.2 months	Retrospective
Senatore <i>et al.</i> ²⁷	na	Ampullary Carcinoma	5-FU based	Good response	Case report
Kim HS <i>et al.</i> ²⁵	21	Recurrent or metastatic Ampullary Carcinoma	Capecitabine + Oxaliplatin	Median OS 19.7 months Median TTP 7.6 months	Retrospective
Overman <i>et al.</i> ²⁶	30	Ampullary+ Small bowel carcinoma	Capecitabine+ Oxaliplatin	Median OS 20.4 months. Median TTP 11.3 months	Phase II
Nassour <i>et al.</i> ²⁸	880	Ampullary Carcinoma	Na	Median OS 47.2 months Good response	Retrospective
Neoptolemos <i>et al.</i> ²⁹	428	Ampullary+ Bileduct+ other cancers	5-FU and Gemcitabine groups	Median OS 43.1 months	Phase III RCT
Kim ST <i>et al.</i> ³⁰	29	Ampullary Carcinoma	Cisplatin+ Gemcitabine/ 5-FU/Capecitabine	Median OS 12.5 months Median TTP 4.9 months	Phase II
Cereda <i>et al.</i> ³¹	37	Biliary tract+ Ampullary Carcinoma	Cisplatin+ Epirubicin+ Gemcitabine+ 5-FU.	Median OS 12.1 months Median PFS 7.9 months	Phase II
Andre <i>et al.</i> ³²	56	Biliary tract + Ampullary Carcinoma	Gemcitabine + Oxaliplatin	Median OS 7.6-15.4 months	Phase II
Gibson <i>et al.</i> ³³	38	Small Bowel+ Ampullary Carcinoma	5FU+Doxorubicin+ Mitomycin	Median OS 8 months.	Phase II
Valle <i>et al.</i> ³⁴	410	Biliary tract + Ampullary Carcinoma	Gemcitabine+ Cisplatin	Median OS 11.7 months.	Phase III

Molecular alterations in ampullary carcinoma

As discussed earlier, histologic and histo-molecular phenotypes are important prognostic factors. However, as Ampullary Carcinoma emerges from an anatomical site where three different epithelia intestinal/pancreatic ductal/biliary converge defining its histomorphology is susceptible to interobserver variability, which reduces the prognostic reliability.³⁵ So recently, molecular landscape and mutations involving Ampullary Carcinoma have been brought up into clinical practice for better defining the prognosis, response to treatment, and finding the actionable targets.

Chromosomal alterations were the first molecular alterations described in various studies on the genetic landscape of Ampullary carcinoma. To start with, a study has shown that chromosome 5q loss of heterozygosity as one of the foremost events in the evolution of Ampullary Carcinoma.³⁶ Similarly, another study has shown a chromosome 17p loss as an indication for poor prognosis and helps to decide if the patients need adjuvant therapy in addition to surgery.³⁷ Furthermore, molecular alterations involving the genes TP53, K-RAS, APC, ELF-3,³⁸ have been increasingly identified in Ampullary Carcinoma.³⁵ Studies have shown that APC gene is a frequently mutated gene in the intestinal subgroup of Ampullary Carcinoma, in contrast to pancreatobiliary type where there is a predominant presence of TP53 and K-RAS mutations.³⁵ Even though certain genetic alterations are more often found in specific histological types of Ampullary Carcinoma, there is still a huge heterogeneity between morphologic and molecular levels.

In addition to the above, molecular alterations involving the WNT, PI3K, and ERBB2 have also been described.³⁹ Recently, Pinto *et al.* and Mandelker *et al.* described pathogenic germline alteration (PGA) involving BRCA2 gene in Ampullary Carcinoma.^{40,41} Also, germline alterations involving ATM, RAD50, and somatic alterations involving BRAF and ELF3 have been identified most recently.⁴² Applying the molecular profile of Ampullary Carcinoma toward better defining the prognosis and finding actionable therapeutic targets is gaining importance. For example, P53 and K-RAS mutations have been identified as poor prognostic factors.⁴³ Moreover, the presence of BRCA2 and ATM mutations in Ampullary Carcinoma gives an opportunity to synthetically target the tumor cells with platinum agents and poly ADP(adenosine diphosphate-ribose) polymerase (PARP) inhibitors.⁴² In a similar fashion, trastuzumab and PD-L1 inhibition could be used in patients with mutations involving ERBB2 amplification and DNA mismatch repair, respectively.⁴²

Conclusions

In conclusion, chemoradiotherapy plays a crucial role in early Ampullary Carcinoma after surgical resection, especially in node-positive disease. In contrast, few studies have shown no meaningful benefit of chemoradiation irrespective of node status and tumor stage. Nevertheless, chemoradiation should be considered in patients with poor prognostic factors given the high risk of recurrence and local failure with surgery alone. For advanced tumors, owing to the rarity of these tumors, currently, the data is limited on the choice of a chemo regimen. Therefore no consensus regarding optimal management as these tumors were assessed in combined series including pancreatic and small bowel cancers. Treatment with a combination of gemcitabine and cisplatin or treating in lines of pancreatic cancer seems reasonable. Also combining molecular data with histomorphology may define the prognosis and aid in treatment selection.

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