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MINIREVIEWS

Where does chemotherapy stands in the treatment of ampullary carcinoma? A review of literature

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Abstract

Ampullary carcinoma (AC) is a rare gastrointestinal tumor without clear treatment recommendations. The management of this tumor is usually extrapolated from the treatment of pancreatic, biliary duct and intestinal cancers. Few papers have studied the AC as an independent entity and yet succombs to several limitations. These studies were retrospective single institutional experiences with limited sample sizes recruited over a long period of time. Unlike metastatic ACs where chemotherapy is the only recommended option, localized AC once excised may be approached by either chemotherapy alone or concomitant chemoradiation therapy. In this review, we report the overall survival and recurrence factors of more than 1000 patients from all the studies treating exclusively ACs. We also review the medical treatment of this tumor and conclude to the necessity of multi-institutional randomized controlled studies for AC exclusively.

Key words: Ampullary cancer; Prognostic factors; Treatment; Review; Novel therapies

Core tip: This paper is a minireview outlining the actual knowledge concerning the treatment of ampullary carcinoma. After a brief review of the prognostic factors and current treatment options for localized and advanced ampullary carcinoma, we discuss the new molecular targets and report on the potential novel therapies.

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INTRODUCTION

Ampullary carcinoma (AC) is an uncommon tumor accounting for approximately 0.2% of gastrointestinal malignancies and 7% of periampullary tumors[1]. It is continuously increasing in frequency and actually is the second most common of periampullary tumors after pancreatic cancers[1,2]. Adenocarcinomas are the most common tumors of the ampulla and may be subdivided pathologically into intestinal and pancreaticobiliary subtypes for potential prognostic purposes[3]. Few trials have studied the AC as an independent entity. It is frequently seen as a subgroup of pancreatic and biliary tract cancer trials even though ACs have a better prognosis and constitute a confounding factor in these studies. In comparison to pancreatic adenocarcinomas, prognostic factors are in favor of the ampullary tumors. The tumor size and staging at diagnosis, the positivity of lymph nodes (LN), the vascular and neural invasions were lower in ACs[4]. Nevertheless, trials treated ACs as pancreatic cancers. This dilemma probably stands essential for the absence of any guidelines from both the National Care Cancer Network (NCCN) and the European Society for Medical Oncology(ESMO) concerning the treatment of advanced ACs[5,6]. In this paper we report on the recurrence factors and overall survival (OS) of patients with AC. We also review the position of chemotherapy in this setting.

PROGNOSTIC FACTORS IN AC

Although localized AC is known for its high rates of resectability and good long term OS, most of the series report a high proportion of recurrent disease. However, these series are of small numbers which disables any statistical OS analysis[1]. LN spreading and number of resection LV[7-12], the vascular, nervous and pancreatic invasion[7,11-15] along with the unresectability of the tumor and positive margin status after resection[9,10,13,16], and intraoperative transfusions[7,11,17] are the most consistent survival factors throughout the studies of localized AC.

Several studies tried to establish the risk factors for the recurrences of excised ACs. Todoroki *et al*[14] in 2003 did not experience locoregional failure with pancreaticoduodenectomy. Recurrences occurred distally and were affected by lymphatic and venous invasion with a mean time to relapse of 13 mo. Perioperative blood transfusion, LN spreading and pancreatic invasion increased the risk of recurrence[7,11,17].

Very few studies elaborated the prognostic factors of advanced ACs. These factors can be extrapolated from studies of unresectable pancreatic and periampullary cancers. Negative prognostic factors include weight loss, abdominal pain, peritoneal dissemination and liver metastasis. Older age is also a negative prognostic factor except in white younger women characterized by a worse prognosis than older ones[18,19].

EVOLUTION OF TREATMENTS

Tumor resection is the mainstay in the treatment of localized AC. Current surgical options prefer radical pancreaticoduodenectomy over local resection despite its higher morbidity[7]. The conventional local regional resection technique considers a transduodenal approach. The extraduodenal technique is a potential alternative that offers a complete removal of the tumor with concurrent excision of retropancreatic LN[20]. Preoperative endoscopic biliary drainage is not widely acceptable among pancreatic surgeons in view of the increased morbidity and delays of definite treatment[21]. However, the only study involving exclusively AC showed that preoperative biliary drainage reduces postoperative wound infection without influencing mortality[22].

The role of chemotherapy for both local and advanced AC is not yet clearly established in view of the rarity of the disease. The only relevant data is commonly found in series combining patients with small bowel, pancreatic or biliary tract tumors. Tables 1 and 2 report the response rate, time to progression and OS of 10 retrospective single institutional experience of small sample sizes varying between 26 and 186 patients with AC that were recruited over periods ranging from 5 to 33 years.

While reviewing the localized AC studies, most of the series used a pancreatic cancer chemotherapy regimen that consisted of fluorouracil and radiotherapy to treat ACs[23-29]. Regimens also combined gemcitabine and radiotherapy after the introduction of the first in 1997[30]. The ESPAC-3 trial by Neoptolemos *et al*[31] in 2012 included the largest sample of AC patients; 297 of the 428 patients enrolled in this trial had AC. Participants were divided into three subgroups: The control group consisted of 144 patients, the fluorouracyl and the gemcitabine subgroups contained 143 and 141 patients respectively. Overall, the increase in median OS in the chemotherapy group was not statistically significant (43.1 mo *vs* 35.2 mo; $P = 0.25$)[31]. By analyzing exclusively AC data, the median OS of the gemcitabine and the fluorouracyl subgroups were 71 mo and 57.8 mo respectively in comparison to the 41 mo of the control arm group[31]. In opposition, Jiang *et al*[30] in 2013 showed a trend toward increased OS in the fluorouracyl group.

Papers reporting treatments of advanced ACs are fewer, only two papers were published to date[32,33]. The first introduced in 2010 platinum for the first time in the treatment of AC; the regimens consisted of a combination of cisplatin with either gemcitabine or

Table 1 Response rate, time to progression and survival in patients with localized ampullary carcinoma

Ref.	*n*	Patient characteristics	Protocols	OS	RR/TTP
Lee *et al*[23]	39	1988-1997 33% CRT	RT (48.7 Gy) with continuous/ concurrent infusion of 5-FU	3 yr: 55%	3 yr: 54% DFS
Sikora *et al*[24]	113	1989-2000 104 patients remained alive after surgery	RT (50.4 Gy) with concurrent 5-FU	OS: 30 mo 1 yr: 79% 3 yr: 43% 5 yr: 33%	NC
Bhatia *et al*[25]	125	1977-2005	29 patients: RT (50.4 Gy) with 5-FU 96 surgery	3.4 yr 1.6 yr	NC
Krishnan *et al*[26]	96	1990-2006 56% CRT	RT (45 Gy preop or 50.4 Gy postop) with 5-FU (42%) or capecitabine (43%)	25.2 mo in patients with CRT *vs* 16.5 mo in control arm	NC
Kim *et al*[27]	118	1991-2002 35% CRT	RT (40 Gy) with 5-FU (day 1, 3) every split course	5 yr: 52.8% *vs* 66.9% in the control arm	NC
Narang *et al*[28]	186	1992-2007	RT with 5-FU	39.9 mo 2 yr: 62.4% 5 yr: 39.1%	NC
Palta *et al*[29]	137	1976-2009	61 CRT 43 adjuvant 18 neoadjuvant	3 yr: 62% in CRT and 46% in adjuvant	Neoadjuvant: 28% pCR
Jiang *et al*[30]	64	1992-2009	5-FU-based *vs* gemcitabine based	5-FU trend toward benefit for OS (P = 0.007)	5-FU significant improvement for TTP

CRT: Chemoradiotherapy; NC: Not calculated; OS: Overall survival; RT: Radiotherapy; TTP: Time to progression.

Table 2 Response rate, time to progression and survival in patients with advanced

Ref.	*n*	Patient characteristics	Protocols	OS	RR/TTP
Kim *et al*[32]	29	2003-2008	31% Cis + Gem 69% Cis + 5-FU	12.5 mo (no significant difference between the two groups)	NC
Shoji *et al*[33]	26	1997-2010	5-FU-based gemcitabine-based 5-FU based gemcitabine-based	OS = 9.1 mo 8 mo 12.3 mo	RR = 7.7%

Cis: Cisplatin; Gem: Gemcitabine; NC: Not calculated; OS: Overall survival; RR: Response rate; TTP: Time to progression.

fluorouracyl but failed to establish any OS difference between the two protocols[32]. In opposition, Shoji *et al*[33] showed more OS benefit in the gemcitabine group. This study reported 26 advanced AC patients receiving chemotherapy without tumor resection. The fluorouracil and gemcitabine based protocols had a response rate of 7.7% and an OS of 9.1 mo (OS = 9 and 12.3 mo respectively). It is of particular importance to note a phase Ⅱ trial by Overman *et al*[34] that recruited 30 patients among which 40% had advanced AC. Patients received a treatment with capecitabine and oxaliplatin (CAPOX) and had an overall response rate of 33% (95%CI: 10%-65%)[34].

TREATMENT MODALITIES IN LOCALIZED AC

In the absence of solid data, neither NCCN nor ESMO established standard chemotherapy regimens for patients with ACs[5,6]. Effectively, the Americans approach this tumor differently than the Europeans (Figure 1)[35].

In discordance with the European treatment regimens that extrapolate chemotherapy protocols from pancreatic tumor trials[30,31,36], the American treatment regimen is supported by the result of RTOG 9704 trial[37]. As of stage IB of AC, the treatment approach is identical to resectable pancreatic adenocarcinomas with a sequence of gemcitabine and concurrent infusional fluorouracyl and radiotherapy. Though the optimal sequencing is not clear, an acceptable protocol includes gemcitabine 1000 mg/m^2 for 3 weekly followed by conformal radiotherapy with concurrent infusional fluorouracyl 250 mg/m^2 daily, and after 3 to 5 wk gemcitabine is reintroduced at 1000 mg/m^2 for 3 of every 4 wk for 3 mo[38]. As with pancreatic cancer, the infusion protocol of fluorouracil is not clear yet.

CHEMOTHERAPY REGIMENS TREATMENTS IN ADVANCED AC

As with localized AC, the optimal chemotherapy is not yet elucidated. The concurrent chemotherapy regimen recommended in advanced AC is an association of

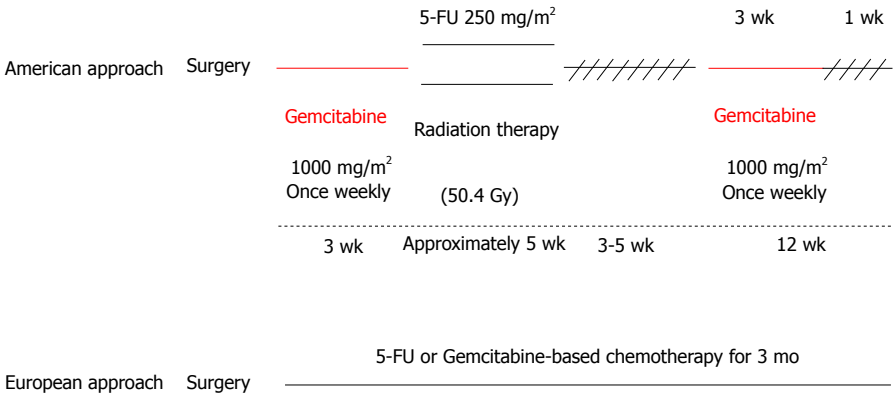

Figure 1 Concurrent American and European approach for the treatment of localized ampullary carcinoma[35]. 5-FU: 5-fluorouracil.

cisplatin and gemcitabine[38]. Other acceptable regimens adopted from the pancreatic chemotherapy treatment panel are fluorouracyl or gemcitabine associated with oxaliplatin[37-40]. An interesting approach in this context considers the pathologic subtype as an indicator for a potential chemotherapy regimen where fluorouracyl-based therapy is used for intestinal ACs and gemcitabine-based therapy for pancreaticobiliary ACs[34].

NOVEL THERAPIES

Given the rarity of the disease, the performance of well-powered randomized controlled clinical trials is very difficult. Multiple phase Ⅱ trials including targeted therapies are actually ongoing among which a combination of CAPOX and bevacizumab (NCT01208103), CAPOX and panitumumab (NCT01202409), gemcitabine-oxaliplatin (GEMOX) and erlotinib (NCT00832637). The only study ongoing in the adjuvant setting is evaluating the role of high volume washing of the abdomen in increasing survival after surgery in patients with pancreatic and peripancreatic tumors (NCT02757859).

The ongoing studies seem promising but recruit also other peripancreatic tumors besides AC. A recent-genomic sequencing study of AC identified severe genetic aberrations with deleterious mutations and deletions in KRAS, SMAD4 and PTEN. This genomic profile suggests that the oncogensis of ACs differs from both biliary tract and pancreatic cancers. The combination of these genomic aberrations suggests a therapeutic approach by mTOR/PI3K inhibition for patients with AC[41]. Moreover, another genomic analysis revealed mutations in the WNT signaling pathway with high frequency inactivating mutations of ELF3 and a high rate of microsatellite instability. Such findings coupled with small-molecule inhibitors of β-catenin would be of particular interest to be evaluated in clinical trials[42]. The only ongoing genetic analysis-guided dosage treatment study of patients with advanced gastroinstestinal cancer include a combination of nab-paclitaxel, fluorouracyl, leucovorin and irinotecan (FOLFI RABAX) (NCT02333188).

CONCLUSION

Given the rarity of the ACs, the published literature lacks well-powered randomized controlled trials. Effectively, the published data is limited to single institutional retrospective studies with small sample sizes. These studies recommend gemcitabine monotherapy or in combination with conformal radiotherapy for the treatment of localized AC and the combination of gemcitabine and cisplatin for the treatment of advanced AC. While analyzing these data, one should be aware to the selection bias of retrospective studies. Moreover, the results of single institutional studies are not to be extrapolated to community hospitals where the surgeons are less experienced in the management of this rare disease. Any effort for future therapeutic development should consider multi-institutional randomized controlled studies recruiting exclusively AC.

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