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Ampullary cancer of intestinal origin and duodenal cancer - A logical clinical and therapeutic subgroup in periampullary cancer

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Abstract

Periampullary cancers include pancreatic, ampullary, biliary and duodenal cancers. At presentation, the majority of periampullary tumours have grown to involve the pancreas, bile duct, ampulla and duodenum. This can result in difficulty in defining the primary site of origin in all but the smallest tumors due to anatomical proximity and architectural distortion. This has led to variation in the reported proportions of resected periampullary cancers. Pancreatic cancer is the most common cancer resected with a pancreaticoduodenectomy followed by ampullary

(16%-50%), bile duct (5%-39%), and duodenal cancer (3%-17%). Patients with resected duodenal and ampullary cancers have a better reported median survival (29-47 mo and 22-54 mo) compared to pancreatic cancer (13-19 mo). The poorer survival with pancreatic cancer relates to differences in tumour characteristics such as a higher incidence of nodal, neural and vascular invasion. While small ampullary cancers can present early with biliary obstruction, pancreatic cancers need to reach a certain size before biliary obstruction ensues. This larger size at presentation contributes to a higher incidence of resection margin involvement in pancreatic cancer. Ampullary cancers can be subdivided into intestinal or pancreatobiliary subtype cancers with histomolecular staining. This avoids relying on histomorphology alone, as even some poorly differentiated cancers preserve the histomolecular profile of their mucosa of origin. Histomolecular profiling is superior to anatomic location in prognosticating survival. Ampullary cancers of intestinal subtype and duodenal cancers are similar in their intestinal origin and form a logical clinical and therapeutic subgroup of periampullary cancers. They respond to 5-FU based chemotherapeutic regimens such as capecitabine-oxaliplatin. Unlike pancreatic cancers, *KRAS* mutation occurs in only approximately a third of ampullary and duodenal cancers. Future clinical trials should group ampullary cancers of intestinal origin and duodenal cancers together given their similarities and their response to fluoropyrimidine therapy in combination with oxaliplatin. The addition of anti-epidermal growth factor receptor therapy in this group warrants study.

Key words: Periampullary cancer; Pancreatobiliary subtype; Intestinal subtype; Ampullary cancer; Duodenal cancer; Epidermal growth factor receptor; Pancreatic cancer; Chemotherapy; Pancreaticoduodenectomy; *KRAS*

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Core tip: Periampullary cancers include pancreatic, ampullary, bile duct and duodenal cancers. Pancreatic cancer is the most common cancer resected with a pancreaticoduodenectomy followed by ampullary, bile duct and duodenal cancer. Patients with resected duodenal and ampullary cancers have better prognosis compared to pancreatic cancer. Ampullary cancers can be subdivided into intestinal or pancreatobiliary subtype cancers with histomolecular staining. Histomolecular profiling is superior to anatomic location in prognosticating survival. Ampullary cancers of intestinal subtype and duodenal cancers are similar in their intestinal origin and form a logical clinical and therapeutic subgroup. They respond to 5-FU based chemotherapeutic regimens such as capecitabine-oxaliplatin.

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INTRODUCTION

Periampullary cancers are defined as cancers arising within 2 cm of the papilla of Vater and include pancreatic, ampullary, biliary and duodenal cancers^[1]. The region of the ampulla is anatomically complex because it is the area of convergence of the bile duct, pancreatic duct and the duodenum. Conceptually the distinction between pancreatic, biliary, ampullary and duodenal carcinoma is straightforward. The 7th edition 2009 AJCC staging manual states that this distinction is based solely on the presumed anatomical primary site of origin^[2]. However, in practice by the time of presentation, the majority of periampullary tumours have grown to involve the pancreas, bile duct, ampulla and duodenum. Therefore it may be difficult to define the primary site of origin in all but the smallest tumors^[3]. As a result the distinction between many non-pancreatic periampullary cancers arising in this region from pancreatic cancer is inherently difficult and subjective^[4]. This has led to variation in the reported proportions of pancreatic, ampullary, biliary and duodenal cancers resected with a pancreaticoduodenectomy (PD)^[5]. Pancreatic cancers represent the majority of cancers resected with a PD in most series^[6]. There are fundamental genomic and molecular differences in the four cancer subtypes^[7]. There is a need to categorise these cancer subtypes in order to treat them in a way that respects their histological, molecular and behavioural differences.

PROPORTION OF PERIAMPULLARY CANCER SUBTYPES RESECTED WITH A PD

Pancreatic cancer accounts for the majority of periampullary cancers resected with a PD in most series, followed by ampullary 16%-50%, biliary 5%-39%, and duodenal cancer 3%-17%^[6-8] (Table 1). The wide variation in the reported incidence and proportion of resected periampullary cancers relates partly to difficulties in accurate determination of the primary tissue origin. This is due to close anatomical proximity of the cancer subtypes and architectural distortion at time of presentation.

Review of pathology slides results in reassignment of cancer origin in a significant number of cases and highlights the importance of central pathology review in clinical trials^[9-12]. The Pomianowska *et al*^[13] study of 207 resected periampullary cancers, demonstrated that slide review changed the diagnosis in 27% of cases. Inaccurate subtyping of periampullary cancers or the addition of non-pancreatic cancers to pancreatic cancer studies can distort and may inflate survival data and skew tumour size and stage. Indeed, Verbeke *et al*^[5]

Table 1 Proportion of periampullary cancer subtypes resected in pancreaticoduodenectomy series

Study (Institution, author, yr)	n	Pancreatic cancer	Ampullary cancer	Biliary cancer	Duodenal cancer
Johns Hopkins, United States He <i>et al</i> ^[14] , 2014	2564	66%	16%	12%	6%
Academic Medical Centre, The Netherlands Tol <i>et al</i> ^[8] , 2015	760	46%	30%	20%	4%
Taipei Veterans General Hospital, Taiwan Chen <i>et al</i> ^[15] , 2013	501	34%	50%	10%	5%
Ohio State University, United States Hatzaras <i>et al</i> ^[24] , 2010	346	72%	23%	5%	0
Oslo University Hospital, Norway Pomianowska <i>et al</i> ^[16] , 2013	207	33%	28%	14%	25%
South Australian Pathology Database, Adelaide, Australia Chandrasegaram <i>et al</i> ^[6] , 2015	115	55%	28%	15%	3%
University Medical Center Groningen, The Netherlands Van Roest <i>et al</i> ^[25] , 2008	121	42%	25%	16%	17%
Leeds Teaching Hospitals NHS Trust, United Kingdom Menon <i>et al</i> ^[76] , 2009	83	33%	29%	39%	N/I
Queen Elizabeth Hospital, Birmingham, United Kingdom Jarufe <i>et al</i> ^[28] , 2004	251	53%	35%	12%	N/I
University of California San Diego, United States Katz <i>et al</i> ^[17] , 2004	120	62%	26%	8%	4%

N/I: May not have been included.

proposed that the failure to accurately distinguish the cancer subtypes represented the most important factor in the variation in clinicopathological and survival data in periampullary cancer studies.

DIFFERENCES IN SURVIVAL IN PERIAMPULLARY CANCERS

Pancreatic cancer has the poorest survival amongst periampullary cancers. Reported median survival for each cancer subgroup is outlined in Table 2. He *et al*^[14] study of 2564 patients with resected periampullary cancers from Johns Hopkins, reported that patients with duodenal cancer had the highest estimated 5-year survival (49%), followed by ampullary cancer (45%), distal bile duct cancer (27%), and pancreatic cancer (18%)^[14]. The recent Dutch study by Tol *et al*^[8] of 760 cancer resections reported that duodenal cancer patients had the most favourable survival. In the Taiwanese study of 501 patients with periampullary cancer, Chen *et al*^[15] reported that patients with ampullary cancer formed the majority (76%) of long-term (≥ 5 years) survivors.

DIFFERENCES IN NODAL, NEUROVASCULAR AND MARGIN STATUS IN PERIAMPULLARY CANCERS

The poorer survival seen with pancreatic cancer has been attributed to differences in tumour behavior and invasiveness^[6,16-18]. Pancreatic cancers have a higher incidence of nodal, neural and vascular invasion compared to non-pancreatic periampullary cancers^[19-25]. Pancreatic cancers also tend to have a much higher incidence of margin positivity^[14,22,26,27]. Multiple studies

have demonstrated that resection margin status, neurovascular invasion, lymph node involvement and lymph node ratio > 0.2 are important prognostic factors for survival with periampullary adenocarcinomas^[8,28,29].

Zenali *et al*^[30], showed that patients with duodenal and ampullary cancer had lower frequencies of nodal metastasis, margin involvement and had improved survival compared to patients with pancreatic cancer. Interestingly such differences were not demonstrated between patients with ampullary and duodenal cancers.

Historically periampullary tumours have been treated as a single group. There is strong evidence that non-pancreatic periampullary cancers require further stratification in future clinical trials^[7,31].

AMPULLARY CANCER SUBTYPES: INTESTINAL AND PANCREATOBILIARY SUBTYPES

The ampulla of Vater is made up of the union of 2 distinct mucosal tissue types, by virtue of its location at the opening of the bile duct into the duodenum. The ampullo-duodenal part of the papilla is lined by intestinal mucosa and the deeper part of the ampulla is lined by pancreatobiliary ductal mucosa. In 1994 Kimura *et al*^[32] classified ampullary cancers into two histological subtypes of either intestinal or pancreatobiliary subtype. Differentiating ampullary cancers into these subtypes is aided by the use of histomolecular staining. This method of subtyping ampullary cancers can overcome difficulties in distinguishing these cancers on the basis of histomorphology alone, as even poorly differentiated cancers preserve the histological marker profile of their mucosa of origin^[33].

Table 2 Median survival of patients following resection of periampullary cancers

Study (Institution, author, yr)	n	Median survival, mo			
		Pancreatic cancer	Ampullary cancer	Biliary cancer	Duodenal cancer
Johns Hopkins, United States He <i>et al</i> ^[14] , 2014	2564	19	47	23	54
Academic Medical Centre, The Netherlands Tol <i>et al</i> ^[8] , 2015	760	19	36	29	Not reached
Taipei Veterans General Hospital, Taiwan Chen <i>et al</i> ^[15] , 2013	501	13.7	28.9	24.4	21.7
Ohio State University, United States Hatzaras <i>et al</i> ^[24] , 2010	346	17.1	44.3	17.9	N/I
Queen Elizabeth Hospital, Birmingham, United Kingdom Jarufe <i>et al</i> ^[28] , 2004	251	13.4	35.5	16	N/I

N/I: Subtype not included or reported.

Transcription factor CDX2 is expressed in the nucleus of intestinal epithelium^[34,35]. Mucin (MUC) 1 is expressed at the apical border of cells of pancreatobiliary ductal origin^[36]. In addition to CDX2 and MUC 1, other markers have been used to subtype ampullary cancers. CDX2, CK 20 and MUC 2 are expressed in intestinal subtype cancers, whereas CK 7, CK 17, MUC 1 and MUC 4 are expressed in pancreatobiliary subtype cancers^[37].

The markers have varying sensitivity and specificity in tissue subtyping and often their reported performance depends more on the gold standard to which they are compared to than the clinical utility of the markers^[38]. For example, if a very rigid definition is applied so that the term ampullary carcinoma only applies to tumours in which there is absolute certainty of origin from the ampullary epithelium (usually very small tumours centred exquisitely on the ampulla of Vater), then ampullary carcinomas can be expected to be essentially uniformly CDX2 positive and MUC 1 negative. That is, the CDX2 positive, MUC 1 negative profile would be highly sensitive for ampullary carcinoma in this subgroup which, are not difficult to classify as ampullary by a conventional anatomic approach. However, if a more liberal interpretation is applied so that larger tumours which probably, possibly or potentially originally arose from the ampullary epithelium are considered ampullary, then the CDX2 positive, MUC 1 negative profile becomes much less specific for ampullary carcinoma both because larger tumours may lose differentiation and because this expanded subgroup must include at least some tumours which originally arose from the pancreas and merely mimic ampullary carcinoma. This is problematic because it is exactly these anatomically difficult to classify tumours in which ancillary markers would be most useful clinically. Therefore a more sensible approach to the investigation of ancillary markers of ampullary status is to not compare their expression to the older anatomical classification (which is known to be flawed) but to compare their expression to outcome or response to therapy.

For example, Chang *et al*^[12] subdivided anatomical

periampullary cancers based on protein expression and immunohistochemistry to distinct cancer subtypes. In their study of 208 ampullary cancers, 74% were intestinal subtype (CDX2 +ve, MUC1-ve), and 22% were pancreatobiliary subtype (CDX2 -ve, MUC 1 +ve).

The Chang study demonstrated that patients with pancreatobiliary subtype cancers have poorer survival compared with those with intestinal subtype cancers consistent with historical studies^[39-41]. The Schueneman *et al*^[42] study of 163 ampullary cancers validated the prognostic role of the histomolecular results of Chang *et al*^[12], using MUC 1 and CDX2. In their study, 25% of their patients had pancreatobiliary subtype tumours. These patients had significantly poorer median overall survival of 21.1 mo compared to patients with intestinal subtype tumours, 108.3 mo ($P < 0.0001$)^[42].

In the Schiergens retrospective study of their prospective database, patients with pancreatobiliary subtype cancers receiving adjuvant gemcitabine had improved overall survival (32 mo vs 13 mo, $P = 0.013$) unlike patients with intestinal subtype cancers who tended to have poorer survival with gemcitabine (35 mo vs 112 mo, $P = 0.193$)^[39]. This suggests patients with pancreatobiliary subtype cancers may benefit from gemcitabine.

Similarly Leo *et al*^[3] demonstrated significantly higher pathological stage and worse overall survival in pancreatic compared to intestinal phenotype ampullary carcinomas. In a more recent study of 510 patients undergoing PD, histopathologic phenotype was superior to tumour anatomic location in prognosticating survival. There was no difference in survival between pancreatobiliary subtype cancers and pancreatic cancer (33.3 mo vs 31.4 mo, $P = 0.66$)^[43].

Whilst these studies emphasize the clinical outcome differences between pancreatobiliary phenotype and intestinal phenotype ampullary carcinomas, at the genomic level these tumours show both similarities and differences. Yachida *et al*^[44] reported whole exome sequencing in a cohort of Japanese and American patients with ampullary cancers. While ampullary cancers were found to be similar to colorectal cancers, and pancreatobiliary subtype cancers

similar to pancreatic cancer, the two subtypes also share similar mutational patterns and signatures differentiating them from colorectal and pancreatic cancers. The authors found tumour suppressor gene *ELF3*, to be a significant driver of ampullary cancers present in both histological subtypes^[44].

Gingras *et al*^[45] evaluated 98 ampullary adenocarcinomas, comparing these to 44 distal bile duct and 18 duodenal adenocarcinomas. Mutations in the WNT signaling pathway occurred in approximately half and *ELF3* approximately 10% of patients across all three tumour types^[45].

A LOGICAL SUBGROUP: AMPULLARY CANCERS OF INTESTINAL SUBTYPE AND DUODENAL CANCERS

Ampullary cancers of intestinal subtype and duodenal cancers are similar in their intestinal origin and form a logical clinical and therapeutic subgroup of periampullary cancers. While *KRAS* mutation occurs in over 90% of pancreatic cancers, both these cancers have a much lower incidence of *KRAS* mutation^[7,46].

Valsangkar *et al*^[11] reported the incidence of *KRAS* mutation in 75 patients with ampullary cancer was 33%. This was supported by the Kwon *et al*^[47] study of 62 ampullary cancers revealing a similar 31% incidence of *KRAS* mutation.

Mikhitarian *et al*^[48] analysed the incidence of *KRAS* mutation by ampullary cancer subtype. They reported that 52% of 25 intestinal subtype cancers and 42% of 24 pancreatobiliary subtype cancers had *KRAS* mutation. In the Hechtman *et al*^[49] study of 18 pancreatobiliary subtype cancers and 14 intestinal subtype cancer, there was an increased frequency of *KRAS* mutation in the pancreatobiliary subtype cancers (61% vs 29%).

While small bowel cancers are rare, the duodenum represents the most common site (56%) for adenocarcinoma of the small bowel, followed by the jejunum (16%) and ileum (13%)^[50,51].

As with ampullary cancers, the incidence of *KRAS* mutation is much lower in duodenal cancers compared to pancreatic cancer. Fu *et al*^[52] reported the incidence of *KRAS* mutations to be 35% in 78 duodenal cancers.

Given ampullary and duodenal cancers have a much lower incidence of *KRAS* mutation compared to pancreatic cancer, the addition of anti-epidermal growth factor receptor (EGFR) treatment in the metastatic and advanced disease may well be a fruitful area of study on the basis of the morphological and biological similarity to *KRAS* wild type colorectal adenocarcinoma where the benefits of this treatment are well proven^[53,54].

ADJUVANT STUDIES IN PERIAMPULLARY CANCERS

Historically, non-pancreatic periampullary cancers have

been included in trials of pancreatic cancer^[55]. In a summary of eleven of the most important randomized controlled trials of adjuvant trials in pancreatic cancer, 4 studies deliberately included non-pancreatic cancers. In most studies, shortcomings in pathological assessment and the lack of standardized pathology to determine the tissue of origin of these cancers may have led to the unintentional inclusion of non-pancreatic cancers^[56].

In the ESPAC-3 periampullary cancer trial, 428 patients with periampullary cancer; 297 with ampullary cancers, 96 with bile duct cancers, and 35 with other cancers were randomized to either observation ($n = 144$) or 6 mo of 5-FU and Folinic acid ($n = 143$) or gemcitabine ($n = 141$). There was no survival benefit from adjuvant treatment. However, after adjusting for age, bile duct cancer, poor tumour differentiation and lymph node involvement, on multiple regression analysis there was a survival benefit for chemotherapy compared to observation with a HR of 0.75 (95%CI: 0.57-0.98, $P = 0.03$)^[57].

A recent meta-analysis of 1671 patients reported no survival benefit for adjuvant chemotherapy or chemoradiotherapy in the management of periampullary cancer^[58]. The median 5-year survival was 40.0% with adjuvant treatment vs 37.5% in the control group with a HR of 1.08 (95%CI: 0.91-1.28; $P = 0.067$).

Interestingly, the recent UK BILCAP study has shown a benefit for adjuvant capecitabine in bile duct cancers. Of the 447 patients in the study, 156 (35%) had extrahepatic bile duct cancers which would include distal bile duct cancers resected with a PD. In the per-protocol analysis, median survival with capecitabine was 53 mo (95%CI 40-not reached) compared to 36 mo with observation (95%CI: 30-44), HR = 0.75 (95%CI: 0.58-0.97, $P = 0.028$)^[59].

Duodenal cancer studies are often reported with other small bowel cancers, including those arising from the jejunum and ileum. Halfdanarson *et al*^[60] in a retrospective review of 491 small bowel adenocarcinomas (57% duodenum; 29% jejunum, 10% ileum) reported a median overall survival of 20.1 mo. Adjuvant therapy did not improve survival in their study. In the Khan *et al*^[61] study of 48 resected small bowel adenocarcinomas (63% duodenum, 21% jejunum, 15% ileum), 56% received adjuvant chemotherapy. Adjuvant therapy again did not improve survival in their study.

In the study by Overman *et al*^[62] of 54 resected small bowel adenocarcinomas (67% duodenum, 20% jejunum, ileum 13%) although there was no improvement in overall survival with adjuvant chemotherapy, on multivariate analysis, adjuvant therapy improved disease-free survival (HR = 0.27; 95%CI: 0.07-0.98, $P = 0.05$)^[62].

In a more recent National Cancer Database study (NCDB), patients with resected small bowel adenocarcinoma who received adjuvant chemotherapy ($n = 1674$) were compared to those undergoing surgery alone ($n = 3072$). This study found that adjuvant chemotherapy improved survival in patients with AJCC stage III disease (Median OS 42.4 mo vs 26.1 mo; $P <$

0.001)^[63]. The addition of radiotherapy did not improve survival in another adjuvant NCDB study of duodenal adenocarcinoma patients^[64].

The role of adjuvant chemotherapy in small bowel adenocarcinomas will be investigated in the international phase III study (the BALLAD study) promoted by the International Rare Cancer Initiative^[65].

SYSTEMIC CHEMOTHERAPY IN ADVANCED AND METASTATIC AMPULLARY AND DUODENAL CANCER

Several studies have investigated the role of chemotherapy in the advanced or metastatic setting^[66-68]. Response rates in ampullary and small intestinal cancers with chemotherapy alone vary between 10%-50%.

A retrospective study of 905 resected periampullary cancers, reported fluoropyrimidine-based chemotherapy was superior to gemcitabine-based chemotherapy in prolonging time to progression in metastatic ampullary cancer suggesting it is a more appropriate first-line approach for ampullary cancers^[69].

Overman *et al*^[70] achieved an overall response rate (complete response and partial response) of 50% (95%CI: 31%-69%) in their phase II study of capecitabine and Oxaliplatin (CAPOX) for advanced or metastatic ampullary and small intestinal adenocarcinoma^[70]. Patients with intestinal adenocarcinoma ($n = 18$) had a response rate of 61% (95%CI: 36-83%) and those with ampullary adenocarcinoma ($n = 12$) a response rate of 33% (95%CI: 10%-65%). The poorer response rates in the ampullary compared to the intestinal cancers in this study was thought to be due to the inclusion of ampullary adenocarcinomas of pancreatobiliary origin which may be less responsive to CAPOX.

In the study by Khan *et al*^[61], 46/59 (78%) patients received systemic chemotherapy for relapsed, unresectable or metastatic small bowel adenocarcinoma (68% duodenum, 19% jejunum, 14% ileum). Of these, 40 were evaluable for response with a response rate of 50% (1 Complete response, 19 Partial response). The overall 1 year survival was better with chemotherapy 60.9% (95%CI: 45.8-76.0) vs 27.3% ($P = 0.042$). Of the 23 patients who received triplet chemotherapy, 13 received EOX (Epirubicin, Oxaliplatin and Capecitabine) and 4 received ECF (Epirubicin, Cisplatin and 5-FU). Of the 18 patients on doublet chemotherapy, 6 received CAPOX, 4 received FOLFOX (5-FU and oxaliplatin), 3 received FOLFIRI (5-FU and irinotecan) and 3 received capecitabine with Mitomycin C^[61].

In a large multicentre retrospective series of different chemotherapy regimens in small bowel cancers, 38 patients received FOLFOX with a tumour response rate of 34% and 11 patients received FOLFIRI with a response rate of 9%. The authors concluded that FOLFOX is the most effective platinum-based chemotherapy for small bowel cancers^[71].

From these studies, the combination of a fluoro-

pyrimidine-regimen and oxaliplatin such as FOLFOX or CAPOX appears to be an active regimen in both ampullary and small bowel cancer (*i.e.*, duodenal cancer) suggesting this is a logical treatment regimen in this subgroup of periampullary cancers.

ANTI-EGFR TREATMENT

The lower incidence of *KRAS* mutation in both ampullary and duodenal cancer suggest a potential role for anti-EGFR therapy trials in this subgroup^[72]. In the phase II study of panitumumab in *KRAS* wild-type metastatic adenocarcinoma of the small bowel and ampulla, 9 patients (1 ampullary - pancreatobiliary subtype, 3 duodenal, 5 jejunal/ileal) received panitumumab with minimal clinical activity. This was thought to relate to these tumours being of foregut origin, given the recent findings of less benefit with anti-EGFR therapy in right sided colon cancers compared to left sided cancers^[73].

Santini *et al*^[74] reported the use of anti-EGFR treatment with Cetuximab in advanced duodenal ($n = 2$) and jejunal ($n = 2$) cancers. Cetuximab was associated with CPT-11-based chemotherapy in first-line (2 patients) or second-line (2 patients) therapy for metastatic disease. The patients previously treated had progressed on Folfiri. One patient had a complete response, 2 patients had a partial response and one had stable disease.

While targeted therapy against anti-EGFR pathway is not established in advanced small intestinal cancers, studies are currently evaluating the safety and efficacy of these targeted therapies in this group^[75,76].

CONCLUSION

Ampullary and duodenal cancer form a significant proportion of cancers resected with a PD. A strong argument can be made that future clinical trials should group ampullary cancers of intestinal origin and duodenal cancers together given their similarities and their response to fluoropyrimidine therapy in combination with oxaliplatin. Furthermore, treatment response should be compared to both established (CDX2 and MUC1) and more investigational biomarkers. The addition of anti-EGFR therapy in this group warrants further study.

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