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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

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SYSTEMATIC REVIEWS

Management of distal cholangiocarcinoma with arterial involvement: Systematic review and case series on the role of neoadjuvant therapy

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Abstract

BACKGROUND

The use of neoadjuvant therapy (NAT) in distal cholangiocarcinoma (dCCA) with regional arterial or extensive venous involvement, is not widely accepted and evidence is sparse.

AIM

To synthesise evidence on NAT for dCCA and present the experience of a high-volume tertiary-centre managing dCCA with arterial involvement.

METHODS

A systematic review was performed according to PRISMA guidance to identify all studies reporting outcomes of patients with dCCA who received NAT. All patients from 2017 to 2022 who were referred for NAT for dCCA at our centre were retrospectively collected from a prospectively maintained database. Baseline

characteristics, NAT type, progression to surgery and oncological outcomes were collected.

RESULTS

Twelve studies were included. The definition of "unresectable" locally advanced dCCA was heterogenous. Four studies reported outcomes for 9 patients who received NAT for dCCA with extensive vascular involvement. R0 resection rate ranged between 0 and 100% but without survival benefit in most cases. Remaining studies considered either NAT in resectable dCCA or inclusive with extrahepatic CCA. The presented case series includes 9 patients (median age 67, IQR 56-74 years, male:female 5:4) referred for NAT for borderline resectable or locally advanced disease. Three patients progressed to surgery and 2 were resected. One patient died at 14 months with evidence of recurrence at 6 months and the other died at 51 months following recurrence 6 months post-operatively.

CONCLUSION

Evidence for benefit of NAT is limited. Consensus on criteria for uniform definition of resectability for dCCA is required. We propose using the established National-Comprehensive-Cancer-Network® criteria for pancreatic ductal adenocarcinoma.

Key Words: Cholangiocarcinoma; Neoadjuvant therapy; Arterial involvement; Locally advanced; Systematic review

Core Tip: Use of neoadjuvant therapy in distal cholangiocarcinoma (dCCA) with regional arterial or extensive venous involvement, is not widely accepted and evidence is sparse. This systematic review highlights heterogeneity of definitions and outcome reporting. Consensus on criteria for a uniform definition of resectability for dCCA is required to provide homogenous reporting of pathways and outcomes. We propose the use of the already established National-Comprehensive-Cancer-Network® criteria for pancreatic ductal adenocarcinoma and exemplify this with our case series. Future studies should focus on international observational high-quality studies and prospective registries to account for the rare nature of the disease.

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INTRODUCTION

Distal cholangiocarcinomas (dCCA) are tumours that arise in the common bile duct, below the confluence of the cystic duct and above the ampulla of Vater[1,2], and comprise 30% of all CCA[1,3]. Surgical resection is the only curative treatment for dCCA, though remains limited to early disease only, with just over a third of patients undergoing resection [4]. A combination of gemcitabine and cisplatin is considered first-line systemic treatment for patient with unresectable dCCA[5], with ongoing investigations into concurrent chemoradiotherapy (CRT)[6,7], triple-agent chemotherapy regimens (with added nab-paclitaxel)[8,9], and immunotherapy[10]. Application of these regimens in the neoadjuvant setting may downstage unresectable tumours, otherwise managed with palliative intent, to improve conversion rate to resection with curative intent[11,12].

Use of neoadjuvant therapies (NAT) is now the standard of care for various malignancies, including borderline resectable and locally advanced pancreatic ductal adenocarcinoma (PDAC)[13-15]. NAT tests tumour biology and identifies patients who may be more likely to benefit from resection, offers improved completion rates when contrasted with adjuvant delivery and may downstage the tumour to improve lymph node (LN) positivity and rates of margin negative (R0) resection[16-18], resulting in improvement in overall survival (OS)[14]. The most widely accepted definition of resectablity in PDAC is from the National Comprehensive Cancer Network® (NCCN®) and includes "resectable", "borderline resectable", and 'locally advanced' and is graded on extent vascular involvement (Table 1)[15]. In contrast, these staging terms in the context of dCCA are poorly defined and heterogenous in the literature. Similarly, a common strategy for the management of dCCA with regional arterial or extensive venous involvement is less widely accepted. Their similarities (in anatomy, surgical strategy, and chemotherapeutic response) might permit application of PDAC evidence to the dCCA setting[18], especially considering diagnostic uncertainty, with some reviews suggesting resection criteria are the same[19]. However, dedicated evidence for NAT in dCCA is necessary to define locally advanced disease and optimise management strategy.

Table 1 National Comprehensive Cancer Network Criteria defining resectablity at diagnosis for pancreatic ductal adenocarcinoma

Resectability status	Arterial	Venous
Resectable	No arterial tumour contact (CA, SMA, or CHA)	No tumour contacts with the SMV or PV or ≤ 180° contact without vein contour irregularity
Borderline resectable	Pancreatic head/uncinate process: (1) Solid tumour contact with CHA without extension to the CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction; (2) Solid tumour contact with the SMA of ≤ 180°; and (3) Solid tumour contact with variant arterial anatomy, and the presence and degree of tumour contact should be noted if present, as it may affect surgical planning. Pancreatic body/tail: Solid tumour contact with the CA of ≤ 180°	Solid tumour contact with the SMV or PV of > 180°, contact of ≤ 180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction: Solid tumour contact with the IVC
Locally advanced	Pancreatic head/uncinate process: Solid tumour with > 180° degrees contact with SMA or CA. Pancreatic body/tail: (1) Solid tumour contact > 180° with the SMA or CA; and (2) Solid tumour contact with CA and aortic involvement	Unreconstructible SMV or PV due to tumour involvement or occlusion (thrombus tumour)

CA: Coeliac axis; SMA: Superior mesenteric artery; CHA: Common hepatic artery; SMV: Superior mesenteric vein; PV: Portal vein; IVC: Inferior vena cava.

This systematic review and case series aims to synthesise available evidence on the role of NAT for dCCA and present the experience of a high-volume tertiary centre in the management of dCCA with arterial involvement.

MATERIALS AND METHODS

Design

The review was designed and performed in accordance with the PRISMA guidelines[20]. The PubMed database was searched in December 2023 for published studies reporting on use of NAT in patients with CCA. No date restrictions were used in the primary search. Reference lists of relevant studies were also cross-referenced to identify additional studies. Key terms related to CCA and NAT, were used to complete the search. The initial search was kept broad to ensure all relevant articles were captured and added for full text review. The complete search terms are available in Supplementary material.

Study selection

The aim of the search strategy was to include all articles that described at least a subgroup of patients with dCCA and their outcomes, with precedent for the search strategy from Grendar *et al*[21], who delivered an equivalent review on hilar CCA. The rationale described by Grendar *et al*[21] included studies that detail the use of NAT for any indication (*i.e.*, in resectable patients), with the assumption that the morbidity and mortality profile for resection after NAT will be similar, independent of indication. Therefore, for this review, all studies that included original data on NAT in patients with dCCA (even when grouped as extrahepatic CCA; eCCA) who subsequently underwent surgery were included. Conference abstracts, literature reviews, animal studies, single case reports and articles not in the English language were excluded, along with studies that reported outcomes for all CCA (including intrahepatic) without stratification.

Two reviewers (SG and MB) independently identified the studies for inclusion. Any discrepancies were identified and resolved through discussion and third-party involvement (LH). The PRISMA flow diagram of included studies is shown in Figure 1.

Data extraction

Data extraction points were pre-defined for both quantitative and qualitative elements, and three reviewers (LH, SG, and MB) extracted data to a prepared template. A fourth reviewer assessed the data for completeness (JHS). Study characteristics collected included country of origin, publication year and sample size. Type of NAT, indication for NAT, rate of surgery and R0 resection, and survival outcomes were all collected. Finally, the conclusion of each study was documented to deliver a narrative synthesis of current evidence of NAT for dCCA. Evidence Grade of Recommendations, Assessment, Development and Evaluation (GRADE) was assessed according to the Cochrane GRADE approach[22].

Statistical analysis

Results were summarized in a narrative synthesis and descriptive statistics were provided where indicated.

Case series

All patients from 2017 to 2022 with dCCA with arterial involvement at our centre that were referred for NAT were retrospectively collected from a prospectively maintained database. Baseline characteristics, disease stage, NAT type, progression to surgery and survival data were all collected. Descriptive statistics were used to display demographic variables. Continuous data was expressed as median (interquartile range, IQR), and categorical variables presented as

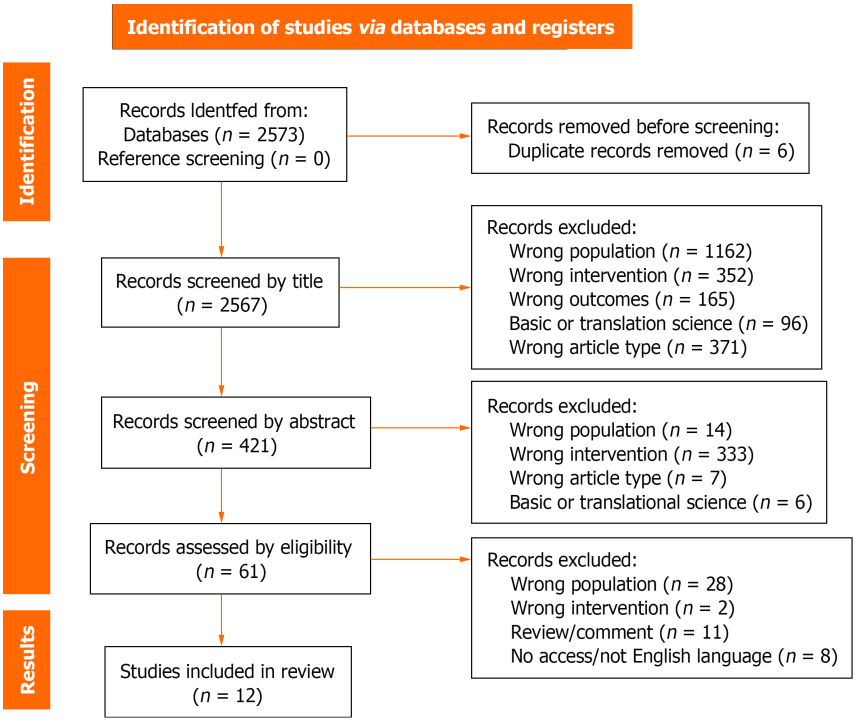

Figure 1 PRISMA flow chart.

numbers and/or percentages. Where conducted, statistical analysis was completed using SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY, United States: IBM Corp).

RESULTS

Review

The systematic literature search yielded 2573 records. Full text screening was performed for 61 records. Twelve studies were included in the final systematic review. The premier study was published in 1997[23], with the latest publications over two decades later in 2023[24]. Eight of twelve studies were from the United States, with two studies from Japan and two from South Korea. Study characteristics are presented in Table 2.

Studies design

Nine of twelve studies were retrospective, with four of these utilising national datasets. The remaining three studies were prospective, with two defined as Phase I trials. Study rationale was heterogenous, with variability in comparator groups (where present), choice of NAT and patient cohort.

Five studies compared NAT to surgery alone and two to surgery with adjuvant chemotherapy. Five studies did not use a comparator. The type of NAT used was variable, broadly split between chemotherapy alone and CRT when reported. The four studies reporting on national data cited inability to define NAT agents used as a limitation. Adam *et al*[25] suggested that there was a "likelihood" that patients with eCCA treated with NAT were initially misdiagnosed as PDAC, and therefore principal agents would be FOLFIRNOX or Gemcitabine/Abraxane.

Selected patient cohort was the most heterogenous aspect of the included studies, largely secondary to vague definitions. Four studies report number of patients with locally advanced/unresectable dCCA who underwent upfront chemotherapy (either with neoadjuvant or palliative intent) and subsequently had resection. A further four report outcomes for patients with any (including resectable) dCCA who received NAT. Remaining studies treated eCCA as a whole cohort, including both hilar and distal disease.

Outcomes

Studies that report outcomes on NAT for unresectable dCCA: Amongst the four studies that report outcomes of patients who received NAT for unresectable dCCA, a total of 19 patients are included[23,26-28]. The definition of unresectability was heterogenous across the four studies. McMasters *et al*[23] reported 4 patients who received NAT for "unresectable disease" and subsequently underwent resection. No formal definition of "unresectability" was given, though grading was based on radiographic imaging or exploratory surgery. All patients had R0 resection, with one shown to have a pathological complete response (PCR). Only minor surgical complications were reported (3 wound infections and 1 arrhythmia). When compared to patients that had upfront resection, there was no difference in OS and the authors state that all NAT patients died "within a relatively short period of time", without specific quantification. Cloyd *et al*[26] report

Table 2 Characteristics of included studies

Ref.	Country	Study type	NAT type	*n* (total)	*n* (distal)	*n* (NAT, distal)	*n* (unresectable, distal, NAT)	*n* (advanced vascular involvement, distal, NAT)	*n* (unresectable, distal, NAT, resected)
McMasters *et al*[23], 1997	United States	Prospective	5-FU CRT	91	28	4	4	4	4
Czito *et al* [27], 2006	United States	Prospective (Phase I)	Eniluracil/5-FU CRT	3	3	3	2	2	1
Nelson *et al* [31], 2009	United States	Retrospective	Fluoropyrimidine-based CRT	45	NR	NR	NR	NR	NR
Kobayashi *et al*[33], 2015	Japan	Prospective (Phase I)	Gem CRT	25	25	15	NR	NR	NR
Cloyd *et al* [26], 2019	United States	Retrospective	Gem or 5-FU Chemotherapy or 5-FU, cap or Gem CRT	45	45	21	9	1	9
Oh *et al*[28], 2021	South Korea	Retrospective	Gem-based	12	4	4	4	2	4
Adam *et al* [25], 2023	United States	Retrospective	NR	2514	2514[1]	157	NR	NR	NR
Fujii *et al* [29], 2022	Japan	Retrospective	Gem CRT	16	16	16	NR	NR	NR
Parente *et al* [30], 2023	United States	Retrospective	NR	9411	1953	271	NR	NR	NR
Toyoda *et al* [32], 2023	United States	Retrospective	NR	6582	NR	NR	NR	NR	NR
Choi *et al* [24], 2023	South Korea	Retrospective	Gem/Cis/nab-P chemotherapy	129	NR	NR	NR	NR	24 (+4)[2]
Silver *et al* [34], 2023	United States	Retrospective	NR	8040	NR	NR	NR	NR	NR

[1]Adam *et al*[25] report on extrahepatic cholangiocarcinoma, in the context of peri-ampullary malignancy, without explicitly defining distal cholangiocarcinoma.

[2]Choi *et al*[24] give a total number of patients with distal (24) and distal + hilar (4) patients who had locally advanced disease, who received NAT, and were then resected, but without giving the individual numbers of each.

NAT: Neoadjuvant therapy; CRT: Chemoradiotherapy; FU: Fluorouracil; Gem: Gemcitabine; Cap: Capecitabine; nab-P: Nab-paclitaxel; NR: Not reported.

outcomes for 25 patients who receive NAT for various indications, of which nine were for "advanced disease" [radiographic evidence of adenopathy (n = 6), locally advanced vascular anatomy (n = 1), markedly elevated carbohydrate antigen 19-9 (CA19-9, n = 1), indeterminate liver lesion (n = 1)]. Other indications included poor performance status (n = 7), misdiagnosis of PDAC (n = 3) and undetermined (n = 2). Ninety-five per cent of patients had an R0 resection, and one patient had a PCR. Median OS was 40.3 [95% confidence interval (95%CI): 0-111.5] months in patients who received NAT, *vs* 50.3 (95%CI: 0-101.8) months after surgery first approach (P > 0.05). Fourteen per cent of patients who received NAT had local recurrence, *vs* 0% patients who proceeded straight to surgery. Czito *et al*[27] reports 2 patients who received NAT for "unresectable" dCCA. Unresectability was defined as "tumour involvement of the superior mesenteric artery or coeliac axis, as well as encasement and/or thrombosis of the superior mesenteric vein or portal vein". One patient experienced a 33% reduction in tumour size and progressed to an R1 resection, the other patient was found to have metastatic disease and did not proceed to surgery. Survival data specific to these patients is not reported.

Oh *et al*[28] do not use the term NAT, but instead report on rate of "conversion surgery" following palliative chemotherapy for unresectable eCCA. Twelve patients with eCCA were commenced on palliative chemotherapy regimens for unresectable disease; 4 patients had dCCA. Two patients were graded unresectable due to local LN enlargement, and 2 due to extensive vascular involvement (1 due to portal vein and superior mesenteric vein invasion with superior mesenteric artery abutment, and 1 due to portal vein abutment). Three patients received gemcitabine-based chemotherapy, and 1 patient received FOLFIRINOX due to initial misdiagnosis of PDAC. All 4 patients were converted to an R0 resection, 2 were alive at last follow up (12 and 17 months) without evidence of recurrence, and 2 had died at 7 and 24 months, with the former experiencing recurrence at 9 months post-operatively.

Studies that report outcomes on patients commenced on NAT for dCCA of any stage: Two studies report outcomes for patients commenced on NAT for dCCA of any resectability stage[29,30]. Parente *et al*[30], reported data on 271 patients with dCCA who received a resection after NAT from the United States National Cancer Database. No indications on the reasoning for NAT use were reported. Sixty-three (23.2%) patients who received NAT had American Joint Committee on Cancer (AJCC) grade T3 or above. Eighty one percent of patients who received NAT had an R0 resection, *vs* 78% and 67% in surgery alone, and with adjuvant chemotherapy respectively. NAT significantly improved survival [Hazard ratio (HR): 0.65; 95%CI: 0.53-0.78, $P < 0.001$], when compared to upfront resection. OS was 38.1 months, *vs* 21.8 (surgery alone) and 28.0 months (adjuvant chemotherapy). The authors acknowledge that it is likely most patients who received NAT did so due to locally advanced disease, but a definition is not given, and specific numbers cannot be derived.

Fujii *et al*[29] investigated the impact of NAT on body composition and sarcopenia in 16 patients with resectable dCCA. All patients underwent R0 resection. Three-year OS was reported as 100% for patients without sarcopenia *vs* 71% in patient with sarcopenia ($P = 0.115$), and disease-free survival (DFS) was 100% in patients without sarcopenia *vs* 50% ($P = 0.025$) in sarcopenic patients.

Studies that report outcomes on NAT for any eCCA (including distal and hilar disease): Remaining studies report outcomes for all eCCA, including hilar tumours. Three studies stratify by resectability and three report on NAT in all eCCA. Nelson *et al*[31] describe 10 patients who received NAT for locally advanced or borderline resectable disease (assessed radiographically) and 2 patients due to surgeon preference. The authors do not specify the radiological or other criteria used to define locally advanced or borderline resectable disease. Amongst the 12 patients, 91% had an R0 resection; a quarter of patients had a PCR. When compared to patients who had upfront resection with adjuvant chemotherapy, 5-year-OS was 53% (NAT) *vs* 23% (upfront resection/adjuvant chemotherapy). Choi *et al*[24] included 95 patients with locally advanced eCCA who received NAT. Locally advanced disease was defined by the lack of distant metastatic disease and local vessel involvement that however is mainly applicable to hilar CCA. Sixty per cent were considered resectable following NAT and of these, 91.2% had an R0 resection. The authors specify that of the resected patients, 24 had distal disease with 4 patients having PCR in the pathology report. Further outcome data is not specific to distal disease, however.

Toyoda *et al*[32] identified 70 patients with eCCA who received NAT across a decade (2006-2017). The proportion of patients who received NAT for eCCA increased from 1.2% to 2.1% over this time. Overall, there was no significant effect on survival when compared to upfront resection (median OS 26 for NAT *vs* 23 months for upfront resection). However, when patients were stratified according to the disease stage as per AJCC, patients with advanced disease (stage III/IVa) experienced a significant survival benefit (HR: 0.53; 95%CI: 0.30-0.92, $P = 0.02$).

Kobayashi *et al*[33] aimed to assess the safety of NAT in any patient with biliary tract cancer, actively excluding patients with "major vessel involvement". Fifteen patients with dCCA received NAT and 3-year-OS was 75.2%. R0 rate for any patient who received NAT (all biliary tract cancers) was 96%. Adam *et al*[25] looked to describe patterns of NAT use in CCA, comparing outcomes to upfront resection. One hundred and fifty-seven patients with eCCA were identified retrospectively using national data. No included patients had a disease stage greater than AJCC stage II. Eighty-three percent of patients had an R0 resection *vs* 76% who had upfront resection. NAT also improved survival, with median OS of 38.4 (NAT) *vs* 25.6 months (upfront resection).

Silver *et al*[34] also utilised national datasets to explore NAT use in all eCCA. Overall, they report an increase in NAT use from 0.5% in 2004, to 5.8% in 2017. NAT improved rate of R0 resection [Odds ratio (OR): 1.49; 95%CI: 1.10-2.02] and mOS, at 35.1 months *vs* 25.3 months with surgery alone. The authors stratified according to chemotherapy or CRT and found that CRT improved R0 rate (OR: 3.52; 95%CI: 2.11-5.86) and showed longest mOS of 47.8 months.

GRADE scoring

GRADE scoring was completed for all included studies. Three studies were considered "moderate", six "low", and three "very low". A summary of study conclusions with assigned GRADE Score and rationale are shown in Table 3.

Case series

From 2017 to 2023, 9 patients with borderline resectable or locally advanced dCCA received NAT at our centre and are included in the present study (median age 67, IQR 56-74 years, male:female 5:4). The definitions used for radiological staging were the same as the NCCN definitions for PDAC[15]. All cases were discussed in the HPB MDT. Staging investigations included a computed tomography (CT) with contrast of the chest abdomen and pelvis for all patients and a magnetic resonance tomography of the liver. Positron emission tomography and CT (PET-CT) was selectively used if there were concerns for metastatic disease on the CT.

Nine patients were referred for NAT: 1 died before receiving NAT, 4 did not progress to surgery, and 1 was lost to follow up (the patient opted for private treatment at another centre). Of the remaining 3 patients, 2 received 6 cycles of Gemcitabine and Cisplatin and 1 received only 4 cycles. On restaging, these 3 patients demonstrated disease stability with no evidence of metastatic disease and progressed to surgery. One was found to have liver metastases intraoperatively, and the other 2 patients underwent resection. The resections included a pancreaticoduodenectomy with extended right hemi-hepatectomy and a total pancreatectomy with splenectomy, portal vein resection with interposition cadaveric vein graft reconstruction and replaced common hepatic artery resection with end-to-end reconstruction (Figure 2). The first patient had an R1 resection and histology revealed pathological stage T3N2M1 due to positive para-aortic LNs (TNM stage M1). The latter patient had an R0 resection with evidence of partial response to NAT and histology showed T4N2 disease. Severe complications (Clavien-Dindo grade IIIa) were encountered only in the first case, where the patient had a pancreatojejunostomy leak and required CT guided drainage of a collection. Length of stay was 36 and 13 days

Table 3 Summary of study's findings

Ref.	Rationale	Results	Conclusions	GRADE[1]
McMasters *et al*[23], 1997	Premier paper on NAT in eCCA; Initial experience; NAT *vs* UR	4 dCCA received NAT for advanced disease; 100% had R0 resection; 25% had PCR; No survival difference between NAT *vs* UR; 100% died "within relatively short period of time"	NAT is safe; NAT is associated with a high rate of PCR; NAT may improve R0 rate; Encourages further multicentre trials	Moderate: Few patients; No definition of "locally advanced"; Specific to dCCA
Czito *et al* [27], 2006	Dose determination for novel CRT for resectable and unresectable UGI cancers; NAT only	3 dCCA received NAT; 1 (resectable) patient had R0 resection and PCR; 1 (unresectable) had 33% decreased in tumour size, underwent R1 resection; 1 was not resected due to metastatic disease; Survival not reported	No specific conclusion on NAT in dCCA	Very low: Few patients; No comparator group; Trial halted before completion; Offers no conclusion
Nelson *et al* [31], 2009	Evaluation of CRT in neoadjuvant setting for eCCA; NAT *vs* AC	12 eCCA received NAT (hilar and distal); 10 had NAT due to BLR or LA disease, 2 for surgeon preference; 91% had R0 resection and 25% had PCR; 5-year-OS: 53% *vs* 23%, despite more advanced disease in NAT cohort	NAT affords local control and enhances resectablity and survival in eCCA	Low: Few patients; Only includes resected patients; Heterogenous indication for NAT; Includes hilar and distal tumours
Kobayashi *et al*[33], 2015	Assessment of safety of NAT for all BTC; Assessment of pathological effect of NAT for BTC	15 dCCA received NAT (25 total); 96.0% R0 resection rate (total); 3-year-OS 75.2% for dCCA	NAT gemcitabine with RT feasible to improve survival and control regional extension	Very low: Excluded patients with major vessel involvement; Includes hilar and distal tumours
Cloyd *et al* [26], 2019	Pragmatic assessment of NAT use in resected dCCA; NAT *vs* UR	45 dCCA; 21 had NAT; 5/21 chemotherapy only, 10/21 CRT, 6/21 both; Varied indications for NAT; 95.0% had R0 resection; 1/21 had PCR; Median OS: 40.3 months UR *vs* 50.3 months UR; 14.3% NAT had local recurrence *vs* 0% UR	Does not support routine administration but beneficial in advanced disease or in patients with poor PS	Moderate: Only includes resected patients; Specific to dCCA
Oh *et al* [28], 2021	Demonstration of feasibility of conversion surgery after palliative chemotherapy for unresectable eCCA	12 eCCA, 4 dCCA commenced on palliative chemotherapy; 2 patients deemed unresectable due to LN enlargement, 1 due to PV/SMV invasion with SMA abutment, and one due to PV abutment; 3 received Gem-based chemo, and 1 received FOLFIRINOX, 2 also received radiotherapy; All 4 had R0 resection (100%); 2 were alive at last FU (12 and 68 months) and 2 had died (24 and 7 months); Only one patient developed recurrence, 9 months post-operatively (died at 24 months)	Conversion surgery is a feasible and effective treatment strategy in certain unresectable CCAs	Moderate: Few patients; Includes all patients with initially unresectable disease, specifying distal disease; Chemo given with palliative intent, rather than NAT
Adam *et al* [25], 2023	Describe pattern of NAT use in CCA; NAT *vs* UR	157 eCCA received NAT; 24% were T downstaged; 9% were N downstaged; 83% NAT had R0 resection *vs* 76% UR; OS: 38.4 (NAT) months *vs* 25.6 (UR) months	NAT is associated with downstaging, improved R0 resection and survival for eCCA	Very low: Excluded patients with advanced disease; Uses national database with heterogenous data; Includes hilar and distal tumours
Fujii *et al* [29], 2022	Investigate impact of NAT CRT on body composition in patients with dCCA	16 dCCA received NAT CRT, all resectable; 16 progressed to surgery, with 100% R0 rate; 6/16 had significant AEs (grade > 3); 9/16 were sarcopenic pre-NAT, 8/16 after NAT (one patient recovered during NAT); 3-year-OS without sarcopenia: 100% versus 71% with sarcopenia (NS); Patients with sarcopenia had significantly shorter DFS (P = 0.025)	NAT CRT is safe in this cohort and does not significantly affect body composition; Further studies necessary to assess impact of sarcopenia on OS in biliary tract cancer	Low: Few patients; Resectable only and no indication for NAT given
Parente *et al* [30], 2023	Evaluate role of NAT in each subset of CCA, specifically impact on survival; NAT *vs* AC *vs* UR	271 CCA had NAT; 81% R0 resection rate, *vs* 78% (UR) *vs* 67% (AC); Median OS 38.1% (NAT) *vs* 21.8% (UR) 28.0% (AC); NAT significantly improved survival *vs* AC; HR: 0.65 (0.53-0.78), P < 0.001	NAT + resection *vs* UR increased survival, regardless of nodal or margin status; Careful MDT evaluation warranted for NAT incorporation into CCA management; Multicentre trials needed	Low: Included distal tumours only but no indication for NAT given; Only includes resected patients; Uses national database with heterogenous data
Toyoda *et al* [32], 2023	Characterize impact of NAT on eCCA prognosis and establish trends in utilisation; NAT *vs* UR	70 eCCA received NAT; Over a decade, proportion of NAT use increased from 1.2%-2.1%; Median OS 26 months UR *vs* 23 months UR; 5-year-survival 21.5% UR *vs* 25.5% UR; Advanced Stage eCCA OS HR: 0.53 (0.30-0.92), P = 0.02	Use of NAT in CCA remains low but is increasing; No overall benefit, however beneficial in advanced disease	Low: Includes hilar and distal tumours; Uses national database with heterogenous data
Choi *et al* [24], 2023	Assessment of effectiveness of local (improved chance of surgery with curative intent) and systemic disease (reduced risk of metastasis)	95 eCCA had NAT; 60.0% were resectable following NAT; 91.2% had R0 resection; 24 dCCA were resected + 4 distal and hilar; 4 dCCA had PCR	Triplet chemotherapy has acceptable safety profile; Clear downstaging effect in LA disease	Low: Includes hilar and distal tumours

	control using a triplet chemotherapy; Locally advanced CCA			
Silver *et al* [34], 2023	Characterize NAT trends over time in eCCA; Identify factors associated with NAT use; NAT impact on outcomes	417 eCCA received NAT (215 chemo only versus 202 CRT); Increase from 0.5% to 5.8% of NAT use across study time frame (2004-2017); NAT improved R0 resection rate (OR: 1.49; 95%CI: 1.10-2.02) and longer mOS (35.1 months *vs* 25.3 months) *vs* surgery alone; NAT CRT improved R0 rate (OR: 3.52, 95%CI: 2.11-5.86) and showed longest mOS of 47.8 months, with improvement in OS of HR: 0.64, 95%CI: 0.52-0.79 *vs* surgery alone	NAT, especially NAT CRT, is associated with improved post-operative outcomes and increased survival in eCCA	Low: Include distal and hilar tumours; No indication for NAT given; Only includes resected patients; Uses national database with heterogenous data

[1]Cochrane Grade of Recommendations, Assessment, Development and Evaluation (GRADE) approach.
NAT: Neoadjuvant therapy; CRT: Chemoradiotherapy; RT: Radiotherapy; AC: Adjuvant chemotherapy; UR: Upfront resection; dCCA: Distal cholangiocarcinoma; eCCA: Extrahepatic cholangiocarcinoma; BTC: Biliary tract cancer; OS: Overall survival; PCR: Pathological complete response; HR: Hazard ration; LA: Locally advanced.

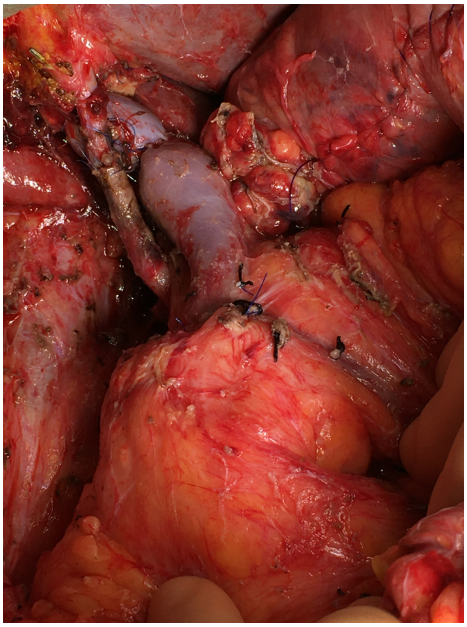

Figure 2 Intraoperative image. Intraoperative image of vascular reconstruction after total pancreatectomy with splenectomy, portal vein resection with interposition cadaveric vein graft, and replaced common hepatic artery resection, with end-to-end anastomosis.

respectively. The former patient died at 14 months from diagnosis (7 months post-operatively), with evidence of recurrence *via* malignant cytology on ascitic drain at 6 months. The latter died at 51-months from diagnosis (36 months post-operatively) following detection of peritoneal metastases at 6 months and evidence of locoregional, soft tissue recurrence at the hilum and lung metastases 21 months post-operatively.

Of the 4 that did not progress to surgery, reasons for failure to progress included: Adverse effects of NAT (n = 2) and failure to achieve disease control (n = 2). The median OS of patients who did not proceed to resection, with the exception of one long survivor (39 months), was 5-months.

DISCUSSION

This study is an exhaustive review of the current landscape of NAT in dCCA. The included case series offers a small addition of a tertiary centre experience, where an appropriate denominator (all patients referred for NAT) is provided. Whilst existing literature defines 9 patients who had resection, for "unresectable" or "advanced" disease due to extensive vascular involvement, this series is unique in reporting, together, a formal denominator and rate of progression to surgery, and a definition of locally advanced disease. To the best of our knowledge, this series is also the first from the United Kingdom.

Best oncological outcomes in cancers of the biliary tract are achieved by a combination of resectional surgery and systemic treatment. Negative surgical resection margins are associated with improved oncological outcomes[35] hence the debate on the management of tumours that involve regional vessels whether upfront surgery with concomitant vascular resection followed by adjuvant treatment or NAT followed by resection offers better results. NAT offers the

opportunity to test the disease biology[19] and is the standard of care in such cases of PDAC (borderline resectable and locally advanced)[15]. In PDAC, as well as other cancers, NAT has been proven to confer a survival advantage, improve the rate of negative resection margins and LN involvement[14]. Nonetheless, similar evidence in dCCA is scarce. To complicate the situation further, in contrast to PDAC, in dCCA there are no widely accepted or used definitions to radiologically stage the disease as borderline resectable or locally advanced. Other cited indications, such as initial misdiagnosis of PDAC, also skew any findings[26], while dCCA-specific conclusions are also difficult to draw, as outcomes are often reported by broad anatomical groups (*i.e.*, eCCA)[24,31-33].

Definition of resectability

Our review demonstrated that unresectability in dCCA was rarely defined and where it was, a variety of definitions were used. Cloyd *et al*[26] reported a combination of radiological (adenopathy, indeterminate liver lesions or advanced vascular involvement) and elevated CA19-9 to define unresectability. Czito *et al*[27] defined advanced disease as "tumour involvement of the superior mesenteric artery or coeliac axis, as well as encasement and/or thrombosis of the superior mesenteric vein or portal vein". Choi *et al*[24] defined locally advanced disease with a pentad of criteria, three of which specific to extensive radiological vascular involvement, but are mainly applicable in cases of hilar CCA. Oh *et al*[28] report the use of extensive vascular involvement and LN enlargement to individualise staging in their reported series. Whilst the authors of these studies did not specify a validated classification system; the definitions used are comparable to the NCCN criteria in PDAC[15]. Nelson *et al*[31] stated NAT was given for locally advanced or borderline resectable disease, which was assessed radiographically, but do not define or cite criteria, and McMasters *et al*[23] do not give a definition of "unresectable". Remaining studies did not cite advanced disease as an indication for NAT. With such heterogeneity, or indeed absence, of definition, drawing conclusions on benefit of NAT in advanced dCCA is difficult. In contrast to dCCA, the anatomical criteria for non-resectable disease in the most common periampullary malignancy, PDAC, are very clearly defined[16] though there remains room for debate[36]. In our series, we consistently used these criteria to define locally advanced dCCA and utilised NAT for these cases. Since the anatomical constraints and inter-operative challenges are similar in dCCA and PDAC, we propose the use of the PDAC NCCN staging criteria in preoperative staging of dCCA. This will improve consistency in results reporting and generalisability of outcomes and conclusions in the management of an advanced stage of this rare malignancy. It could be argued that regional LN involvement and biological criteria, such as elevated CA19-9, should also be included in the definition. Both may be used surrogate markers of advanced disease where NAT may be utilised, however neither determine resectability.

The majority of the data on the results of systemic treatment in CCA are reported in the adjuvant or palliative setting. The landmark BILCAP study included all biliary tract cancers and demonstrated a survival benefit of adjuvant capecitabine among resected patients, especially after adjusting for high risk factors[37]. The ABC-02 study was a phase 3 trial on advanced biliary tract cancer, whose results form the basis of the first-line recommendation of the combination of gemcitabine and cisplatin for unresectable CCA, with mOS 11.7 months, *vs* 8.1 months with gemcitabine monotherapy [5]. With median OS limited to less than one year even in patients receiving combination regime, further trials investigated triplet therapy (Gemcitabine/cisplatin and nab-paclitaxel) and immunotherapy[8,9]. The TOPAZ-1 study demonstrated a survival advantage (HR: 0.80; 95%CI: 0.66-0.97; P = 0.021) when durvalumab (a PD-L1 inhibitor) was given with Gemcitabine/cisplatin *vs* Gemcitabine/cisplatin and placebo to patients with unresectable, locally advanced, recurrent, or metastatic biliary tract cancer[10]. The KEYNOTE-966 study showed a similar survival advantage (HR: 0.83; 95%CI: 0.72-0.95, P = 0.0034), when pembrolizumab was added to the doublet chemotherapy[38]. Ulusakarya *et al*[39] report a single-centre experience of NAT with FOLFIRINOX in advanced and metastatic biliary tract cancers (all types) and 6 (14%) patients were converted to either R0 or R1 resection, with prospective trials are ongoing[40]. Whilst results are promising for systemic therapy, specific data on their benefit in the neoadjuvant setting must be expanded.

Progression to surgery

In every NAT approach, an essential parameter is the number of patients who progressed to surgery after treatment. Reporting this rate allows understanding of NAT tolerability, demonstrates feasibility of delivery and efficacy in systemic disease control or even downstaging advanced disease for subsequent resection. Of the four studies that specifically reported outcomes for NAT in unresectable dCCA, McMaster *et al*[23] report all patients who were commenced on NAT, progressed to surgery. However, Cloyd *et al*[26] and Oh *et al*[28], only included patients who were resected, therefore the number of patients that had disease progression or otherwise did not progress to surgery is unknown. Czito *et al*[27] only includes 2 patients with unresectable dCCA who received NAT, and 1 progressed to resection (R1). Although not specific to dCCA, rate of progression to surgery was reported by Choi *et al*[24], who report 60% were successfully downstaged with NAT, where NAT was given for advanced disease. The authors used the number of patients who were commenced on NAT as the denominator; with 73 of 129 (56.6%) patients progressing to surgery. A conversion rate of patients who progress to surgery provides a broader picture of the treatment sequencing, and the concept was first introduced in the context of resection following palliative chemotherapy in gastric cancer[41]. Further work reported it as an outcome in pancreatic cancer[42-44] and even intrahepatic CCA[45]. Choi *et al*[24] contrast their rate of progression to surgery with a previous study[8], that had a rate of only 20%. Two explanations are given by the authors: First, the included study included only locally advanced patients, whilst the previous study also included patients with distant metastasis. Second, in the previous study only 15.0% of patients had eCCA, whilst Choi *et al*[24], 73.6% patients had eCCA. Other studies corroborate a higher rate of progression to surgery for eCCA than intrahepatic CCA in the NAT setting[9]. In our case series, only 3 patients progressed to surgery and 2 had a resection following NAT. The 33% rate of progression to surgery (22% to resection) in our series is markedly lower than the 56% reported by Choi *et al*[24]. Such disparity is likely secondary to Choi *et al*[24] including all locally advanced eCCA, rather than just dCCA and the difference in definitions of resectability. The difference in reported rates in the literature would be made more comparable if a unifying definition

of resectability is used and outcomes on the management of dCCA are reported independently.

R0 resection rate for studies reporting on NAT for unresectable dCCA ranged between 0% and 100%[23,26-28]. Amongst the other included studies, R0 rate was reported to be between 81% and 96% following NAT, though this is inclusive of hilar tumours, as well as resectable disease[24,25,30,31]. Once again, due to the heterogeneity in reporting it is impossible for safe conclusion to be drawn.

Oncological outcomes

Included studies cannot provide definite oncological outcomes for advanced disease, specific to dCCA. Of those the four studies that reported oncological outcomes for unresectable or locally advanced dCCA, Cloyd *et al*[26] report a median OS of 40.3 months for patients who received NAT and progressed to surgery, with 3 patients developing local recurrence and 8 developing distant recurrent disease. The DFS was not specified. Oh *et al*[28] reported the oncological outcomes for 4 patients with initially unresectable dCCA, with median OS of 18.0 months and DFS of 7.5 months following resection, with 1 patient experiencing recurrence 9.0 months post-operatively. Amongst studies reporting outcomes for NAT in eCCA, independent of a defined indication, median OS was between 26-38 months[25,30,32,34]. Kobayashi *et al*[33] report a 3-year survival of 75% and Nelson *et al*[31] reported a 5-year survival of 53%. With 2 resected patients amongst our own cohort, 1 patient survived fourteen months from diagnosis, and the other 51 months. Both patients experienced recurrence at 6 months post-operatively. Considering the latter patient, such prolonged survival contrasts with an early recurrence. Possible reasons may include misdiagnosis of recurrence on imaging follow-up or likely a favourable disease biology. Amongst studies that compared oncological outcomes in patients receiving NAT and surgery, *vs* chemotherapy alone, Oh *et al*[28] reported a median OS of 28 months for all included patients and stated that this is longer than previous studies where patients received chemotherapy only, but do not offer a comparison within their own data. Choi *et al*[24], however, highlighted a significantly longer survival for patients who progressed to surgery, than those who only received chemotherapy, citing a 2-year overall rate of 45% *vs* 19% respectively (P = 0.032). In our own series, of the patients who did not progress to surgery, median OS was only 5 months (with the exception of a lone, long survivor at 39 months).

Limitations

The main limitation is the lack of a widely accepted and commonly used definition on resectability of dCCA and the pooling of data and outcomes for the management of locally advanced dCCA with all biliary tract cancers of any stage. This may be explained by the rarity of CCA and the sparsity of evidence on the role of NAT in this type of cancer. Nonetheless, it is the main reason for the inability to draw safe conclusions, as specific management pathways and outcomes for the management of locally advanced dCCA cannot be derived from the literature. Most studies were of single-centre and retrospective design and limited by small numbers, while larger retrospective studies using national data were heterogenous and offer little insight into the pre-operative resectability definition and the indications and specific outcomes of NAT.

Another group in which dCCAs are often reported within, as the least common subgroup[46], are peri-ampullary malignancies, due to their similar presentation and operative management. The comparison of dCCA and PDAC is especially important in the context of NAT, as misdiagnosis can occur due to difficulties and limitations in interpretation of imaging and diagnostic cytology. A definitive rate of such misdiagnosis is not available in the literature, however across 2 included studies, 4 patients with dCCA received NAT due to a misdiagnosis of PDAC[28,31].

Whilst the presented case series is limited by its single-centre nature and the small numbers reported, the clear definition of locally advanced disease with appropriate MDT validation is rarely identified in the existing literature. Additionally, due to the rare nature of the disease, our cohort is an important and substantial contribution to the very limited number of reported cases of locally advanced dCCA treated with NAT.

CONCLUSION

From our own series and included studies that report on NAT for dCCA with extensive vascular involvement, evidence for the benefit of NAT is limited. Consensus on the criteria for a uniform definition of resectability for dCCA is required, which will provide homogeneity in reporting of pathways and outcomes. We propose the use of the already established NCCN criteria for PDAC. Due to the rare nature of the disease and thus the difficulty in conducting randomised trials, future studies should focus on international observational high-quality studies and prospective registries to investigate the value and other indications for possible use of NAT, such as LN involvement or CA19-9; agents used, including biological agents; and pathway outcomes, such as failure to progress to surgery.

FOOTNOTES

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