**Review Article**

# The role of down staging treatment in the management of locally advanced intrahepatic cholangiocarcinoma: Review of literature and pooled analysis

Sivesh Kamarajah[1], Francesco Giovinazzo[1], Keith J. Roberts[1],
Pankaj Punia[2], Robert P. Sutcliffe[1], Ravi Marudanayagam[1], Nikolaos Chatzizacharias[1],
John Isaac[1], Darius F. Mirza[1], Paolo Muiesan[1], and Bobby VM Dasari[1]

*Departments of [1]Hepatobiliary and Pancreatic Surgery, and [2]Oncology, Queen Elizabeth Hospital, Birmingham, UK*

**Backgrounds/Aims:** Approximately 60-80% of patients with intrahepatic cholangiocarcinoma (iCCA) are not suitable for surgical resection due to advanced disease at presentation. This review assesses the role of surgical resection followed by down staging treatment in the management of patients with locally advanced iCCA. **Methods:** A systematic review and pooled analysis were performed of the relevant published studies published between January 2000-December 2018. The primary outcome measure was overall survival. Secondary outcome measures were rates of clinical benefit, margin-negative (R0) resections, overall and surgery-specific complications, and post-operative mortality. **Results:** Eighteen cohort studies with 1880 patients were included in the review. The median overall survival in all patients was 14 months (range, 7-18 months). Patients undergoing resection following down staging had significantly longer survival than those who did not (median: 29 vs. 12 months, $p < 0.001$). The Clinical Benefit Rate with this strategy (complete response+partial response+stable disease) was 64% (244/383), ranging from 33-90%. Thirty-eight percent of the patients underwent resections with a 60% R0 resection rate and 6% postoperative mortality. **Conclusions:** Although the evidence to support the benefits of NAT for iCCA is limited, the review supports the use of down staging treatment and also surgical resection in the cohort with response to NAT in order to improve long-term survival in patients with locally advanced iCCA. **(Ann Hepatobiliary Pancreat Surg 2020;24:6-16)**

**Key Words:** Intrahepatic; Cholangiocarcinoma; Locally advanced; Down staging; Surgery

## INTRODUCTION

The incidence of intrahepatic cholangiocarcinoma (iCCA) is about 0.7 cases per 100,000 adults in the USA.[1] Despite advances in multimodality treatment, long-term survival is only seen in 10-20% of patients due to the advanced stage at presentation.[2] Surgical resection remains the only potentially curative therapy for patients with iCCA; however, only 30-60% of patients are candidates for surgical resection due to locally advanced (large tumors with either hepatic inflow or outflow involvement) or metastatic disease, underlying chronic liver disease, or frailty.[3] In patients undergoing surgical resection, the 5-year survival is 20-40%, and median survival is 25 months.[3]

In patients with unresectable disease, median survival is 12-15 months with a 5-year survival of 5-10%,[4,5] with chemotherapy based on a combination of gemcitabine and platinum salts.[6] There is no established standard treatment for patients with locally advanced biliary cancers. The role of chemotherapy or radiotherapy is considered mainly a palliative in unresectable iCCA. Neoadjuvant therapy (NAT) with a view to downstage has gained popularity in the last decade in the management of hepatobiliary and pancreatic cancers, particularly the latter in patients with borderline resectable and locally advanced (LA) cancers. Pooled analysis by Suker et al.[7] in a systematic review demonstrated NAT with FOLFIRINOX for locally advanced pancreatic cancers had a median overall survival (OS) ranging between 10 and 33 months and resection rates of up to 43%. In resectable oesophageal cancers, NAT has

been demonstrated standard treatment through high-quality randomized controlled trials.[8] A recent network meta-analysis further demonstrated neoadjuvant CRT (chemoradiotherapy) followed by surgery to be the most effective strategy in improving long-term survival of resectable oesophageal cancers.[9]

To date, there is limited consensus for advocating NAT for patients with iCCA to further improve survival and surgical outcomes. For the purpose of the study, this was considered downstaging treatment given to patients with non-metastatic iCCA as NAT, although the intention might have been palliation given the clinical practice during the study period. Hence, the aim of this review is to determine the oncological and surgical outcomes of patients receiving NAT for borderline iCCA.

## METHODS

### Search strategy

A systematic search of PubMed, EMBASE and the Cochrane Library databases were conducted. The search terms used were 'intrahepatic cholangiocarcinoma' or 'cholangiocarcinoma', and 'neoadjuvant therapy or 'neoadjuvant radiotherapy' or 'neoadjuvant chemotherapy' or 'chemotherapy' individually or in combination. Search terms used for this review are presented as shown in Supplementary Table 1. The 'related articles' function was used to broaden the search, and all citations were considered for relevance. A manual search of reference lists in recent reviews and eligible studies was also undertaken.

### Inclusion and exclusion criteria

Inclusion criteria were: (1) studies reporting the use of NAT (by any modality) in human subjects with non-metastatic locally advanced iCCA; (2) published in the English language. Exclusion criteria were: (1) conference abstracts, review articles, and case reports (<5 patients); (2) publications with mixed populations where the outcomes of patients with cancers at another site could not be separated from those of patients with intrahepatic cholangiocarcinoma. After excluding duplicates, two authors (SK, BD) independently reviewed the titles and abstracts of studies identified by the literature search. Where a study was considered to be potentially relevant to the research question a full copy of the publication was ob-

tained for further review. The references of all included studies were hand-searched in order to identify other potentially relevant studies. Any areas of disagreement between the two primary researchers were resolved through discussion. The intention of the NAT in this review might have been palliative treatment when offered to patients but patients have then progressed to surgical pathways where response has been noted. It is therefore important to note the differences in the terminology used in this review to the terms used in standard clinical practice. Patients who progressed to surgery following down staging treatment are considered to have had surgery following NAT, patients who received treatment but not surgery had palliative chemotherapy, and those who did not receive any treatment (no NAT group) were managed by best supportive care.

### Data extraction

Two researchers (SK, BD) independently extracted data on study characteristics, patient demographics, definitions of borderline resection, modality and regimes of NAT, response to and the clinical benefit with NAT, progression to surgery and postoperative outcomes such as overall mortality and morbidity rates such as bile leak, liver failure, where reported.

### Study outcomes

The primary outcome measure was OS in patients receiving NAT with or without subsequent surgical resection. Response to chemotherapy, where reported, was graded as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Secondary outcome measures were rates of overall resection rates and margin-negative (R0) resections, overall complications (Grade I-V) and major complications (>Grade III) reported according to Clavien-Dindo classification, surgery-specific complications (bile leak, intra-abdominal collections), and response to chemotherapy. A pooled analysis of the data was performed to assess the study outcomes and a comparative survival analysis was performed.

**Table 1.** Baseline demographics of included studies

| Study name | Study design | Study country | All patients, n | Duration | Male gender, % | Median age | Tumour number | Tumour size, mm |
|---|---|---|---|---|---|---|---|---|
| Herber et al. 2007[10] | RCS | Germany | 15 | October 2000-June 2006 | 33 | 64 (46-83) | Solitary (8), Multiple (7) | 108±46 |
| Shitara et al. 2008[11] | RCS | Japan | 20 | December 2002-December 2006 | 50 | 75 (43-83) | 3 (1-10) | 78 (30-160) |
| Nehls et al. 2008[12] | PCS | Germany | 18 | February 2002-January 2004 | 44 | 52 (28-74) | NR | NR |
| Chen et al. 2010[13] | RCS | China | 84 | December 1998-December 2008 | 61 | NR | NR | 77±32 |
| Vogl et al. 2012[14] | RCS | Germany | 115 | March 1999-March 2010 | 52 | NR | Solitary (34), Multiple (81) | NR |
| Scheuermann et al. 2013[15] | RCS | Germany | 32 | September 1997-February 2012 | 53 | 64 (44-87) | Solitary (13), Multiple (19) | 87 (20-180) |
| Kim et al. 2013[16] | RCS | Korea | 132 | June 2001-March 2012 | 55 | 58 (26-78) | NR | NR |
| Kato et al. 2013[17] | RCS | Japan | 7 | January 2004-December 2010 | 57 | 68 | NR | NR |
| Yi et al. 2014[18] | RCS | Korea | 176 | January 1995-December 2010 | NR | NR | NR | NR |
| Kato et al. 2015[19] | RCS | Japan | 25 | October 2011-April 2014 | NR | NR | NR | NR |
| Rayar et al. 2015[20] | RCS | France | 45 | January 2008-October 2013 | 38 | 68 (39-79) | NR | NR |
| Konstantinidis et al. 2016[21] | RCS | USA | 167 | January 2000-August 2012 | 41 | 62 (30-88) | Solitary (61), Multifocal (106) | 85 (15-164) |
| Omichi et al. 2017[22] | RCS | USA | 43 | January 2000-September 2015 | 42 | 54 (30-80) | NR | NR |
| Cho et al. 2017[23] | RCS | Korea | 64 | 2000-2012 | 59 | NR | Solitary (37), Multiple (27) | NR |
| Chang et al. 2018[24] | RCS | Taiwan | 844 | January 2006-December 2015 | 61 | 60±10 | NR | NR |
| Sumiyoshi et al. 2018[25] | RCS | Japan | 7 | January 2006-August 2016 | - | NR | NR | NR |
| Lunsford et al. 2018[26] | PCS | USA | 12 | Jan 2010-December 2017 | 25 | 47 (31-63) | NR | NR |
| Le Roy et al. 2018[5] | RCS | France | 74 | January 2000-December 2013 | 54 | 60 (52-68) | NR | NR |

RCS, retrospective study; PCS, prospective study; NR, not reported

**Table 2.** Definitions of locally advanced iCCA used in the studies

| Study name | Number of NAT, n | NAT+ resection, % | NAT only, % | Inclusion definition |
|---|---|---|---|---|
| Herber et al. 2007[10] | 15 | 0 | 100 | NR |
| Shitara et al. 2008[11] | 20 | 0 | 95 | NR |
| Nehls et al. 2008[12] | 18 | 0 | 100 | NR |
| Chen et al. 2010[13] | 84 | 0 | 42 | Extensive bilobar involvement of the liver by a large solitary by multiple tumours, or invasion of major blood vessels |
| Vogl et al. 2012[14] | 115 | 0 | 100 | NR |
| Scheuermann et al. 2013[15] | 32 | 0 | 100 | NR |
| Kim et al. 2013[16] | 132 | 0 | 70 | AJCC 7th Edition Stage IVA and IVB tumours |
| Kato et al. 2013[17] | 7 | 57 | 43 | Unreconstructable hepatic artery, portal vein and hepatic vein and extensive hepatic and bile duct invasion not amenable for curative resection |
| Yi et al. 2014[18] | 176 | 0 | 64 | AJCC 6th Edition N1 classification and any T classification or T3/4 and any N classification without distant metastases |
| Kato et al. 2015[19] | 25 | 20 | 80 | Surgical resection could not be achieved even by aggressive surgical procedures, including combined vascular resection |
| Rayar et al. 2015[20] | 45 | 18 | 82 | NR |
| Konstantinidis et al. 2016[21] | 167 | 5 | 95 | Unreconstructable vascular involvement, severe underlying liver parenchymal disease, multifocal tumours and extensive regional nodal disease |
| Omichi et al. 2017[22] | 43 | 100 | 0 | NR |
| Cho et al. 2017[23] | 64 | 13 | 88 | Extensive bilobar involvement of a large tumour, multiple satellite tumours, LN metastasis beyond the porta hepatis (i.e., celiac or retroperitoneal LN), and invasion of major vessels |
| Chang et al. 2018[24] | 844 | 0 | 75 | NR |
| Sumiyoshi et al. 2018[25] | 7 | 71 | 29 | Cancer invasion to bilateral hepatic arteries, portal veins, or hepatic veins that prevented reconstruction, broad infiltration to bilateral bile ducts that prevented the achievement of curative resection, broad extra-hepatic perineural invasion extending around the proper hepatic artery and common hepatic artery |
| Lunsford et al. 2018[26] | 12 | 50 | 50 | Solitary tumour >2 cm in diameter or multifocal disease confined to the liver without radiological evidence of extrahepatic, macrovascular, or lymph node involvement |
| Le Roy et al. 2018[5] | 74 | 53 | 47 | Tumour in contact with the future remaining hepatic or portal veins, or those with contralateral metastases |

**Table 3.** Treatment regimen used in the included studies and response to treatment

| Study name | Type of NAT | Details of regimes | NAT, n | PD, % | SD, % | PR, % | CR, % | Toxicities, n (%) |
|---|---|---|---|---|---|---|---|---|
| Herber et al. 2007[10] | CT - TACE | Suspension consisting of 10 ml Lipiodol and 10 mg MMC mixed directly before administration. | 15 | 27 | 60 | 7 | 7 | 6 |
| Shitara et al. 2008[11] | CT - TACE | 2 mg MMC and 300 mg DSM infused through a port system placed in hepatic artery | 20 | 10 | 40 | 45 | 5 | 62 |
| Nehls et al. 2008[12] | CT | Capecitabine/oxaliplatin | 18 | 67 | 33 | 0 | 0 | NR |
| Chen et al. 2010[13] | RT | Limited-field EBRT using linear accelerator with 6-or 15-MV photons - full radiation dosage up to 50 to 60Gy. For patients with synchronous LN metastasis, typical EBRT was 40Gy to the Planning Target Volume with 10 to 20Gy delivered to the Gross Tumour Volume as boost fields | 35 | 14 | 49 | 29 | 9 | 74 |
| Vogl et al. 2012[14] | CT - TACE | 8mg/m$^2$ MMC, 1000 mg/m$^2$ Gemcitabine and 35 mg/m$^2$ Cisplatin. Embolization was performed (after drug injection) with a maximum of 10ml Lipiodol, followed by an injection of 200-450 mg of degradable starch microspheres (200 lm) for vessel occlusion | 115 | 34 | 57 | 9 | 0 | NR |
| Scheuermann et al. 2013[15] | CT - TACE | Lipiodol (up to 30 mL and MMC (up to 10 mg) or doxorubicin-eluting beads injected into the supplying artery | 32 | NR | NR | NR | NR | NR |
| Kim et al. 2013[16] | CT or CRT | Chemotherapy-capecitabine+cisplatin, CRT-capecitabine+cisplatin+RT | 92 | 53 | 40 | 4 | 0 | NR |
| Kato et al. 2013[17] | CT | Gemcitabine (5), gemcitabine/cisplatin (2) | 7 | 14 | 57 | 29 | 0 | NR |
| Yi et al. 2014[18] | CT | Active combinations of modulated 5-FU or Gemcitabine. the regimen of 5-FU alone was 1,000 mg/m$^2$/day for 3 successive days during the rest and fth week of radiotherapy. also, geM of 1,000 mg/m$^2$/day by intra- venous infusion over 2 h for consecutive 2 weeks and repeated after 3 weeks | 42 | NR | NR | NR | NR | NR |
| Kato et al. 2015[19] | CT | Gemcitabine (1000 mg/m$^2$) plus cisplatin (25 mg/m$^2$) administered for 2 weeks followed by a 1-week respite, with a single course extending over 3 weeks | 25 | NR | NR | NR | NR | NR |
| Rayar et al. 2015[20] | CT | Systemic chemotherapy was first initiated using gemcitabine and/or platinum salts followed by Ytt-90 radioembolizations administered few weeks after the initiation of the chemotherapy | 45 | NR | NR | NR | NR | NR |

**Table 3.** Continued

| Study name | Type of NAT | Details of regimes | NAT, n | PD, % | SD, % | PR, % | CR, % | Toxicities, n (%) |
|---|---|---|---|---|---|---|---|---|
| Konstantinidis 2016[21] | CT | Systemic chemotherapy with or without hepatic arterial infusion (HAI) chemotherapy consisted of a continuous infusion of floxuridine (FUDR) into the hepatic arterial circulation that was administered through a surgically implanted pump at a predetermined flow rate | 167 | NR | NR | NR | NR | NR |
| Omichi 2017[22] | CT | Gemcitabine regimens (n=39), Fluorouracil regimens (n=2), Other (n=2) | 43 | NR | NR | NR | NR | NR |
| Cho 2017[23] | CRT | RT was three-dimensional-conformal RT (3D-CRT; n=55) or intensity-modulated RT (IMRT) with helical tomotherapy (n=9). Systemic chemotherapy was administered concurrently (n=46) or sequentially (n=18); 5-fluorouracil (5-FU)-based chemotherapy (800 mg/m$^2$ weekly) was administered to 33 patients (51.5%), and gemcitabine (1000 mg/m$^2$ weekly) was administered to 16 patients (25%) as a monotherapy or combined with cisplatin. | 64 | NR | NR | 25 | NR | 55 |
| Chang 2018[24] | CCRT vs CT+RT vs CT vs None | NR | 633 | NR | NR | NR | NR | NR |
| Sumiyoshi 2018[25] | CRT | Chemotherapy - S-1 (n=6) and CDDP & CPT-11 (n=1). Intensity-modulated radiotherapy was administered with a total dose of 50 Gy delivered in 25 fractions over 5 weeks. The gross tumor volume (GTV) was defined as the area of solid macroscopic tumors that was enhanced on MDCT imaging. In patients with broad extra-hepatic perineural invasion, the area around proper hepatic artery and common hepatic artery were also included in the GTV | 7 | 29 | 14 | 57 | 0 | NR |
| Lunsford 2018[26] | CT | 1st line - gemcitabine/cisplatin, 2nd line - erlotinib (n=3); FOLFIRI (folinic acid, uorouracil, and irinotecan; n=1), fluorouracil (n=1) | 12 | NR | NR | NR | NR | NR |
| Le Roy 2018[5] | CT | Gemcitabine/oxaliplatin (n=44), gemcitabine regimens (n=4), gemcitabine alone (n=3), radioembolization/transarterial chemotherapy (n=4), other regimens (n=19) | 74 | 31 | 45 | 24 | 0 | NR |

PD, progressive disease; SD, stable disease; CR, complete response; PR, partial response; CT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy; CCRT, chemoradiotherapy; TACE, transarterial chemoembolisation

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# RESULTS

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### Study characteristics

The literature search identified 18 cohort studies, including 1880 patients with locally advanced iCCA, of which two were prospective cohort studies. Baseline demographics of the included studies are presented in Table 1. Study quality was assessed using NewCastle Ottawa system. Ten studies provided the definitions for locally advanced or inoperable iCCA, and these are detailed in Table 2.

### Chemotherapy and radiotherapy regimes

NAT regimes and tumor responses are presented in Table 3. Eleven studies reported the use of neoadjuvant chemotherapy, of which four[10,11,14,15] reported the use of transarterial chemoembolization (TACE) with mitomycin C (MMC). One study[14] used gemcitabine and cisplatin in addition to MMC for TACE. Eight studies[5,12,17-20,22,26] evaluated combinations of chemotherapy (gemcitabine/capecitabine and platinum-based regimes). Of the remaining studies, one reported use of RT,[13] three reported use of chemoradiotherapy (CRT),[16,23,25] and one compared concurrent CRT, chemotherapy and RT, chemotherapy, and no treatment.[24]

### Response rates and the definitions of response

Eleven studies reported the criteria used to assess tumour response [RECIST (n=9),[10,11,14,16,17,19,21,23,25] mRECIST (n=1),[5] and WHO (n=1)].[12] Nine studies[5,10-14,16,17,25] (n=383 patients) provided response rates as the presence of progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR). The rates of PD were 36%, ranging from 10 to 67%. The Clinical Benefit Rate (CBR=CR+PR+SD) was noted in 64% (244/383) of the patients going for NAT, ranging from 33 to 90%.

### Resectability rates

Of the nine studies[5,10-14,16,17,25] (383 patients) where response rates were provided, 64% (244/383) showed a clinical benefit for NAT. None of the studies provided the number of patients who were explored for but failed to proceed to resection following NAT. Of the studies[5,17,19-22,25,26] where post-NAT resection rates were reported, 135/354 patients (38%) underwent resections. Of these, 60% of the patients had R0 resections (82/135 patients), 40% were reported to have R1 resection, and R2 resection was performed in 1/135 patients.

### Overall survival

The OS of the entire cohort was 14 months (range, 7-18 months). OS was significantly longer in patients receiving NAT with resection (median: 29 months; range: 18-37 months) compared to NAT alone (median: 12 months; range: 5-43 months) or no NAT (median: 8 months; range: 5-11 months) ($p < 0.001$) for locally advanced iCCA. In patients receiving chemotherapy only, the OS of the entire cohort was 18 months (range, 5-20 months). OS was significantly longer in patients receiving NAT with resection (median, 36 months; range, 18-37 months) compared to NAT alone (median, 12 months; range, 5-43 months, $p=0.02$). In patients receiving CRT only, the OS of the entire cohort was 12 months (range, 9-15 months). OS was longer in patients receiving NAT with resection (median, 21 months; range, 18-24 months) compared to NAT alone (median: 11 months; range: 9-43 months, $p=0.8$) (Table 4).

### Postoperative outcomes

Overall post-surgical complications were reported in eight studies.[5,17,19-22,25,26] The overall rate of postoperative mortality was 6% (8/135 patients) on pooled analysis. The rate of major complications was 15.5% (21/135 patients). Bile leaks (four patients), post-hepatectomy liver failure (four patients), intraabdominal collections (four patients), ascites (three patients), post-operative bleeding (one patient), pleural effusion (one patient), and acute kidney injury (one patient) were the reported complications (Table 5).

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# DISCUSSION

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Over the last decade, the long-term survival of patients diagnosed with iCCA has been relatively poor, with a small proportion of patients undergoing curative surgical resection and a median survival of 20-30 months in the resected group.[3] NAT for iCCA is an appealing option for suitable candidates to select the patient with less aggressive tumor biology, downstage the disease, increase

**Table 4.** Overall survival among the patients in the all the treatment pathways

| Study name | All patients, n | OS entire cohort, months | OS NAT+ resection, months | OS NAT only, months | OS no NAT, months |
|---|---|---|---|---|---|
| Herber et al. 2007[10] | 15 | 21 (9-33) | - | 21 (9-33) | NR |
| Shitara et al. 2008[11] | 20 | 14 | - | 14 | NR |
| Nehls et al. 2008[12] | 18 | NR | - | NR | NA |
| Chen et al. 2010[13] | 84 | 7±1 | - | 10±1 | 5±1 |
| Vogl et al. 2012[14] | 115 | 13 | - | 13 | NA |
| Scheuermann et al. 2013[15] | 32 | NR | - | 11 | NR |
| Kim et al. 2013[16] | 132 | 9 | - | 9 | NR |
| Kato et al. 2013[17] | 7 | 13 | 29 | 13 | NA |
| Yi et al. 2014[18] | 176 | NR | - | 43 (34-51) | 11 (7-16) |
| Kato et al. 2015[19] | 25 | NR | NR | NR | NR |
| Rayar et al. 2015[20] | 45 | NR | 16 (4-41) | NR | NR |
| Konstantinidis et al. 2016[21] | 167 | 20 (1-120) | 37 (10-92) | NR | NR |
| Omichi et al. 2017[22] | 43 | NR | NR | NA | NA |
| Cho et al. 2017[23] | 64 | NR | NR | NR | NR |
| Chang et al. 2018[24] | 844 | NR | - | NR | NR |
| Sumiyoshi et al. 2018[25] | 7 | NR | NR | NR | NR |
| Lunsford et al. 2018[26] | 12 | NR | 36 | NR | NR |
| Le Roy et al. 2018[5] | 74 | 18 | 36 | 11 | NA |

**Table 5.** Post-operative outcomes following resection surgery, where reported

| | Numbers received NAT | Numbers proceeded to resection | R0 resection | R1 resection | Post-op mortality | Major morbidity |
|---|---|---|---|---|---|---|
| Kato et al. 2015[19] | 39 | 10 | 7 | 3 | - | - |
| Kato et al. 2013[17] | 22 | 8 | 4 | 4 | - | - |
| Rayar et al. 2015[20] | 45 | 10 | 10 | 0 | 2 | 3 |
| Konstantinidis et al. 2016[21] | 104 | 8 | 5 | 3 | 2 | |
| Sumiyoshi et al. 2018[25] | 15 | 11 | 9 | 2 | - | 3 |
| Omichi et al. 2017[22] | 43 | 43 | 30 | 13 | - | 5 |
| Lunsford et al. 2018[26] | 12 | 6 | 5 | 1 | - | 1 |
| Le Roy et al. 2018[5] | 74 | 39 | 12 | 27 | 4 | 9 |
| Total | 354 | 135 (38.1%) | 82 (60.7%) | 53 (39.2%) | 8 (6%) | 21 (15.5%) |

the resectability rates, and improve the OS in the locally advanced iCCA. NAT therapy in iCCA lags behind other gastrointestinal cancers, such as oesophageal and pancreatic cancers, where this approach has shown significant improvement in long term-survival and increased the number of ongoing clinical trials.[7,9] The present review highlights that current evidence for NAT in iCCA is limited to cohort studies, specifically retrospective case series. This review further highlights that NAT followed by resection has a superior survival rate than patients receiving NAT alone or no surgery in the group of patients deemed unresectable because of locally advanced disease. Le Roy et al.[5] reported no significant difference in the patients who had primarily resectable and downstaged un-

resectable lesions in terms of postoperative complications, but despite the higher R1 resection rates (p=0.004), the OS was similar (HR 1.23, 0.77−1.97; p=0.391) between the two groups. The current review does not differentiate the outcomes of R1 and R0 resections but together the OS was significantly better in the cohort that proceeded for surgery following downstaging NAT.

iCCAs are usually peripherally located, away from the hilum and are usually dealt with by anatomical, non-anatomical resections based on the position of the lesion. When the lesions are larger or located centrally, the inflow or (more often) the outflow of the liver could be infiltrated. Such vascular or biliary involvement on the contralateral side of resection are usually considered the

limiting factor for upfront resection.[25] The group of patients with iCCA that is not suitable for surgical resections are usually put through a palliative pathway or best supportive care. Factors such as micro or macro vascular invasion, presence of lymph node metastases, and presence of satellite nodules represent poor pathological prognostic factors. The influence of pathological factors on their outcomes is not clear from this review. However, this study has shown a variable median OS in the group of patients receiving NAT (with or without curative resection) with an encouraging survival benefit. There is a lack of a definition for locally advanced iCCA, which might reflect the lack of consensus about the patients suitable for NAT and type of treatment in the context of multimodal treatment options (Table 2). We propose that the HPB surgical community should aim to obtain consensus for the definition of borderline resectability and selection of iCCA patients for NAT. In this group of patients, NAT might be able to increase resectability rates, with acceptable morbidity, mortality, and prolonged survival.

The response rates of iCCA to chemotherapy are variable and limited. Currently, there is no standard treatment for locally advanced cholangiocarcinoma, either in a NAT or palliative set up. The ABC-02 trial compared doublet therapy with gemcitabine and cisplatin to gemcitabine as a single agent in 410 patients with locally advanced or metastatic biliary tract cancer.[6] After a median follow-up of 8.2 months, the combination group had a significantly improved OS (11.7 vs. 8.1 months). Similar results with combination chemotherapy were also reported by studies with a 70% response rate or stable disease and OS of up to 15 months.[27] The results of ABC06 trial for 2nd line chemotherapy with FOLFOX regime are awaited but the unpublished results are promising.[28] Other treatment options, such as chemoradiotherapy, TACE, and external beam RT, have also been associated with longer progression-free survival and OS than chemotherapy alone in a palliative setting for patients with unresectable advanced iCCA.[29] Shitara et al.[11] reported a 50% response rate and a median survival of 14.1 months with hepatic arterial infusion chemotherapy for unresectable iCCA. The review also reflects the variations in the NAT regimes used by the included studies, although the majority of studies used a gemcitabine-based chemotherapy regime and only one study used a standardized regime (gemcitabine/oxaliplatin)

in all patients. Other limitations to this study include significant heterogeneity of the included studies with no clear definitions of locally advanced iCCA. Not all of the reported studies reported the survival data, and well-defined post-operative complications, limiting the quality of the meta-analysis to reliably analyze the impact of NAT in patients with and without surgical resection. However, the current study provides the base to plan future studies that would be of useful in the management of this group of patients.

In conclusion, although the evidence to support the benefits of NAT for iCCA is limited, the data from this review is very promising in improving the outcomes of patients with iCCA. International efforts are required to standardize the definitions and treatment regimens targeting locally advanced iCCA through randomized controlled trials.

## ORCID

Sivesh Kamarajah: https://orcid.org/0000-0002-2748-0011
Francesco Giovinazzo: https://orcid.org/0000-0002-3392-9292
Keith J. Roberts: https://orcid.org/0000-0003-1799-9829
Pankaj Punia: https://orcid.org/0000-0002-4578-6428
Robert P. Sutcliffe: https://orcid.org/0000-0002-1881-7655
Ravi Marudanayagam: https://orcid.org/0000-0002-0640-3535
Nikolaos Chatzizacharias: https://orcid.org/0000-0002-4864-189X
John Isaac: https://orcid.org/0000-0002-7946-1277
Darius F. Mirza: https://orcid.org/0000-0002-7531-9089
Paolo Muiesan: https://orcid.org/0000-0002-7389-6691
Bobby VM Dasari: https://orcid.org/0000-0003-2375-1141

## AUTHOR CONTRIBUTIONS

Writing - review &amp; editing: BD, FG, KJR, RPS, PP, RM, NC, JI, DFM, PM.

# REFERENCES

1. Yao KJ, Jabbour S, Parekh N, Lin Y, Moss RA. Increasing mortality in the United States from cholangiocarcinoma: an analysis of the National Center for Health Statistics Database. BMC Gastroenterol 2016;16:117.

2. Kamarajah SK. Evaluation of the AJCC 8th edition staging system for pathologically versus clinically staged intrahepatic cholangiocarcinoma (iCCA): a time to revisit a dogma? A Surveillance, Epidemiology, and End Results (SEER) analysis. J Gastrointest Cancer 2019;50:392-399.

3. Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 2008;248:84-96.

4. Nathan H, Pawlik TM. Staging of intrahepatic cholangiocarcinoma. Curr Opin Gastroenterol 2010;26:269-273.

5. Le Roy B, Gelli M, Pittau G, Allard MA, Pereira B, Serji B, et al. Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. Br J Surg 2018;105:839-847.

6. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al.; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273-1281.

7. Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta analysis. Lancet Oncol 2016;17:801-810.

8. Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, et al.; Trans-Tasman Radiation Oncology Group; Australasian Gastro-Intestinal Trials Group. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol 2005;6:659-668.

9. Pasquali S, Yim G, Vohra RS, Mocellin S, Nyanhongo D, Marriott P, et al. Survival after neoadjuvant and adjuvant treatments compared to surgery alone for resectable esophageal carcinoma: a network meta-analysis. Ann Surg 2017;265:481-491.

10. Herber S, Otto G, Schneider J, Manzl N, Kummer I, Kanzler S, et al. Transarterial chemoembolization (TACE) for inoperable intrahepatic cholangiocarcinoma. Cardiovasc Intervent Radiol 2007;30:1156-1165.

11. Shitara K, Ikami I, Munakata M, Muto O, Sakata Y. Hepatic arterial infusion of mitomycin C with degradable starch microspheres for unresectable intrahepatic cholangiocarcinoma. Clin Oncol (R Coll Radiol) 2008;20:241-246.

12. Nehls O, Oettle H, Hartmann JT, Hofheinz RD, Hass HG, Horger MS, et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: a prospective multicentre phase II trial. Br J Cancer 2008;98:309-315.

13. Chen YX, Zeng ZC, Tang ZY, Fan J, Zhou J, Jiang W, et al. Determining the role of external beam radiotherapy in unresectable intrahepatic cholangiocarcinoma: a retrospective analysis of 84 patients. BMC Cancer 2010;10:492.

14. Vogl TJ, Naguib NN, Nour-Eldin NE, Bechstein WO, Zeuzem S, Trojan J, et al. Transarterial chemoembolization in the treatment of patients with unresectable cholangiocarcinoma: results and prognostic factors governing treatment success. Int J Cancer 2012;131:733-740.

15. Scheuermann U, Kaths JM, Heise M, Pitton MB, Weinmann A, Hoppe-Lotichius M, et al. Comparison of resection and trans-arterial chemoembolisation in the treatment of advanced intrahepatic cholangiocarcinoma--a single-center experience. Eur J Surg Oncol 2013;39:593-600.

16. Kim YI, Park JW, Kim BH, Woo SM, Kim TH, Koh YH, et al. Outcomes of concurrent chemoradiotherapy versus chemotherapy alone for advanced-stage unresectable intrahepatic cholangiocarcinoma. Radiat Oncol 2013;8:292.

17. Kato A, Shimizu H, Ohtsuka M, Yoshidome H, Yoshitomi H, Furukawa K, et al. Surgical resection after downsizing chemotherapy for initially unresectable locally advanced biliary tract cancer: a retrospective single-center study. Ann Surg Oncol 2013;20:318-324.

18. Yi SW, Kang DR, Kim KS, Park MS, Seong J, Park JY, et al. Efficacy of concurrent chemoradiotherapy with 5-fluorouracil or gemcitabine in locally advanced biliary tract cancer. Cancer Chemother Pharmacol 2014;73:191-198.

19. Kato A, Shimizu H, Ohtsuka M, Yoshitomi H, Furukawa K, Takayashiki T, et al. Downsizing chemotherapy for initially unresectable locally advanced biliary tract cancer patients treated with gemcitabine plus cisplatin combination therapy followed by radical surgery. Ann Surg Oncol 2015;22 Suppl 3:S1093-S1099.

20. Rayar M, Sulpice L, Edeline J, Garin E, Levi Sandri GB, Meunier B, et al. Intra-arterial yttrium-90 radioembolization combined with systemic chemotherapy is a promising method for downstaging unresectable huge intrahepatic cholangiocarcinoma to surgical treatment. Ann Surg Oncol 2015;22:3102-3108.

21. Konstantinidis IT, Groot Koerkamp B, Do RK, Gönen M, Fong Y, Allen PJ, et al. Unresectable intrahepatic cholangiocarcinoma: systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. Cancer 2016;122:758-765.

22. Omichi K, Cloyd JM, Yamashita S, Tzeng CD, Conrad C, Chun YS, et al. Neutrophil-to-lymphocyte ratio predicts prognosis after neoadjuvant chemotherapy and resection of intrahepatic cholangiocarcinoma. Surgery 2017;162:752-765.

23. Cho Y, Kim TH, Seong J. Improved oncologic outcome with chemoradiotherapy followed by surgery in unresectable intrahepatic cholangiocarcinoma. Strahlenther Onkol 2017;193:620-629.

24. Chang WW, Hsiao PK, Qin L, Chang CL, Chow JM, Wu SY. Treatment outcomes for unresectable intrahepatic cholangiocarcinoma: nationwide, population-based, cohort study based on propensity score matching with the Mahalanobis metric. Radiother Oncol 2018;129:284-292.

25. Sumiyoshi T, Shima Y, Okabayashi T, Negoro Y, Shimada Y, Iwata J, et al. Chemoradiotherapy for initially unresectable locally advanced cholangiocarcinoma. World J Surg 2018;42:2910-2918.

26. Lunsford KE, Javle M, Heyne K, Shroff RT, Abdel-Wahab R, Gupta N, et al.; Methodist-MD Anderson Joint Cholangiocarcinoma Collaborative Committee (MMAJCCC). Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. Lancet Gastroenterol Hepatol 2018;3:337-348.

27. Eckmann KR, Patel DK, Landgraf A, Slade JH, Lin E, Kaur H, et al. Chemotherapy outcomes for the treatment of unresectable intrahepatic and hilar cholangiocarcinoma: a retrospective analysis. Gastrointest Cancer Res 2011;4:155-160.

28. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. ABC-06 | a randomised phase III, multi-centre, open-label study of active symptom control (ASC) alone or ASC with ox-

aliplatin / 5-FU chemotherapy (ASC+mFOLFOX) for patients (pts) with locally advanced / metastatic biliary tract cancers (ABC) previously-treated with cisplatin/gemcitabine (CisGem) chemotherapy. J Clin Oncol 2019;37(Suppl 15):4003.

29. Currie BM, Soulen MC. Decision making: intra-arterial therapies for cholangiocarcinoma-TACE and TARE. Semin Intervent Radiol 2017;34:92-100.