**Supplemental Table 1: Evidence Table**

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| **Ref #** | **Reference** | **Study Type** | **Patients/Events** | **Study Objective (Purpose of Study)** | **Study Results** | **Study Quality** |
| **1** | Gad MM, Saad AM, Faisaluddin M, et al. Epidemiology of Cholangiocarcinoma; United States Incidence and Mortality Trends. *Clinics and Research in Hepatology and Gastroenterology*. 2020/11/01/ 2020;44(6):885-893. doi:<https://doi.org/10.1016/j.clinre.2020.03.024> | SEER registry retrospective study | 16,189 patients with cholangiocarcinoma, of which 64.4% were intrahepatic. | To investigate trends of incidence and mortality on cholangiocarcinoma in a large nation-wide epidemiologic study. | A total of 13,121 patients died of cholangiocarcinoma during the study period. Cholangiocarcinoma incidence and mortality were 11.977 and 10.295 and were both higher among Asians, males, and individuals older than 65 years. Incidence rates have significantly increased over the study period (APC=5.063%, P<.001), while mortality increased significantly over the study period (APC=5.964%, P<.001), but decreased after 2013 (APC=-25.029, P<.001). | 2 |
| **2** | Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. *Ann Surg*. Jan 1992;215(1):31-8. doi:10.1097/00000658-199201000-00005 | Single institution retrospective study | Curative intent resection was performed in 23 of 122 patients who underwent surgical treatment for hilar cholangiocarcinoma. Local excision of the lesion alone was performed in 10 cases (43%). Hepatic resection for tumor extending to the secondary bile ducts or hepatic parenchyma was performed in 13 cases (57%): extended right hepatectomy (3), right hepatectomy (1), extended left hepatectomy (6), left hepatectomy (2), and left lobectectomy (1). In three other cases, resection by total hepatectomy and liver transplantation was performed, but these were not included in the analysis of results for resection. | To report outcomes for a series of patients who underwent curative intent resections for huilar cholangiocarcinoma | A potentially curative resection, with histologically negative margins and no recurrence to date, was achieved in seven patients using the following procedures: local excision for two type I lesions; left hepatectomy plus excision of segment 1 for two type IIIb lesions and one type IV lesion; right hepatectomy and right hepatectomy plus excision of segment 1 for two type IIIa lesions. These results indicate that improved survival in hilar cholangiocarcinoma can be achieved by resection, with minimal morbidity and zero mortality rates, if histologically free resection margins are obtained. To achieve this, the following procedures were recommended for each type of lesion, based on our experience and on anatomic considerations: local excision for type I; local excision plus resection of segment 1 for type II; local excision, resection of segment 1, and right or left hepatectomy for types IIIa and b; hepatectomy plus liver transplantation for type IV. | 3 |
| **3** | Page MJ, McKenzie JE, Bossuyt PM, et al: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71, 2021 | Methodology | The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, published in 2009, was designed to help systematic reviewers transparently report why the review was done, what the authors did, and what they found. | To present the PRISMA 2020 27-item checklist, an expanded checklist that details reporting recommendations for each item, the PRISMA 2020 abstract checklist, and the revised flow diagrams for original and updated reviews. | The PRISMA 2020 statement replaces the 2009 statement and includes new reporting guidance that reflects advances in methods to identify, select, appraise, and synthesize studies. | NA |
| **3** | Page MJ, Moher D, Bossuyt PM, et al: PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. The BMJ 372, 2021 | Methodology | The methods and results of systematic reviews should be reported in sufficient detail to allow users to assess the trustworthiness and applicability of the review findings. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was developed to facilitate transparent and complete reporting of systematic reviews and has been updated (to PRISMA 2020) to reflect recent advances in systematic review methodology and terminology | To present the explanation and elaboration paper for PRISMA 2020, where we explain why reporting of each item is recommended, present bullet points that detail the reporting recommendations, and present examples from published reviews. | Changes to the content and structure of PRISMA 2020 will facilitate uptake of the guideline and lead to more transparent, complete, and accurate reporting of systematic reviews. | NA |
| **4** | Amin MB, ed AJCC Cancer Staging Manual. In: Cancer AJCo, ed (ed 8th). Chicago, IL: Springer, 2017 | Staging Manual | NA | To include relevant, nonanatomic (including molecular) factors has been foremost, although changes are made only when there is strong evidence for inclusion in current cancer stagin. | The American Joint Committee on Cancer staging manual has become the benchmark for classifying patients with cancer, defining prognosis, and determining the best treatment approaches. Many view the primary role of the tumor, lymph node, metastasis (TNM) system as that of a standardized classification system for evaluating cancer at a population level in terms of the extent of disease, both at initial presentation and after surgical treatment, and the overall impact of improvements in cancer treatment. The rapid evolution of knowledge in cancer biology and the discovery and validation of biologic factors that predict cancer outcome and response to treatment with better accuracy have led some cancer experts to question the utility of a TNM-based approach in clinical care at an individualized patient level. | NA |
| **5** | Coelen RJS, Roos E, Wiggers JK, et al. Endoscopic versus percutaneous biliary drainage in patients with resectable perihilar cholangiocarcinoma: a multicentre, randomised controlled trial. Lancet Gastroenterol Hepatol. 2018;3(10):681-690. | Multi institution randomized prospective study | 54 patients with eligible perihilar ECC were randomly assigned to endoscopic biliary drainage (n=27) or percutaneous transhepatic biliary drainage (n=27). | To investigate the incidence of severe drainage-related complications of endoscopic biliary drainage or percutaneous transhepatic biliary drainage in patients with potentially resectable perihilar cholangiocarcinoma. | The study was prematurely closed because of higher mortality in the percutaneous transhepatic biliary drainage group (11 [41%] of 27 patients) than in the endoscopic biliary drainage group (3; [11%] of 27 patients; relative risk 3·67, 95% CI 1·15-11·69; p=0·03). Three of the 11 deaths among patients in the percutaneous transhepatic biliary drainage group occurred before surgery. The proportion of patients with severe preoperative drainage-related complications was similar between the groups (17 [63%] patients in the percutaneous transhepatic biliary drainage group vs 18 [67%] in the endoscopic biliary drainage group; relative risk 0·94, 95% CI 0·64-1·40). 16 (59%) patients in the percutaneous transhepatic biliary drainage group and ten (37%) patients in the endoscopic biliary drainage group developed preoperative cholangitis (p=0·1). 15 (56%) patients required additional percutaneous transhepatic biliary drainage after endoscopic biliary drainage, whereas only one (4%) patient required endoscopic biliary drainage after percutaneous transhepatic biliary drainage. | 1 |
| 6 | Lin H, Li S, Liu X. The safety and efficacy of nasobiliary drainage versus biliary stenting in malignant biliary obstruction: A systematic review and meta-analysis. Medicine (Baltimore). 2016 Nov. 95 (46):e5253 | Systematic search and meta-analysis | Search of Embase, PubMed and Cochrane Library databases identified 7 studies including 925 patient with malignant biliary obstruction who were treated with nasobiliary drainage or stent. | To compare the safety and efficacy of endoscopic nasobiliary drainage and endoscopic biliary stenting in malignant biliary obstruction in terms of preoperative and postoperative complications | This meta-analysis suggests that ENBD is better than EBS for malignant biliary obstruction in terms of the preoperative cholangitis rate, the postoperative pancreatic fistula rate, the incidence of stent dysfunction, and morbidity. However, a limitation is that there are no data from randomized controlled trials. Endoscopic nasobiliary drainage had reductions in the preoperative cholangitis rate (OR = 0.35, 95% CI = 0.25-0.51, P < 0.0001), the postoperative pancreatic fistula rate (OR = 0.38, 95% CI = 0.18-0.82, P = 0.01), the incidence of stent dysfunction (OR = 0.39, 95% CI = 0.28-0.56, P < 0.0001), and morbidity (OR = 0.47, 95% CI = 0.27-0.82, P = 0.008) compared with patients who had stents. | 3 |
| 7 | Tringali A, Hassan C, Rota M, Rossi M, Mutignani M, Aabakken L. Covered vs. uncovered self-expandable metal stents for malignant distal biliary strictures: a systematic review and meta-analysis. Endoscopy. 50(6):631-641, 2018 06. UI: 29342491 | Systematic review and Meta-analysis | Systematic search of MEDLINE, EMBASE, and the Cochrane Library identified 11 randomized controlled trials including 1,272 patients comparing use of covered and uncovered metal stents for distal malignant biliary strictures | To compare the performance of covered and uncovered self- expanding metal stents in patients with unresectable distal malignant biliary strictures. | Stent failure and patient mortality did not differ significantly between covered and uncovered stents (HR 0.68, 95 % CI 0.40 - 1.17; HR 0.89, 95 %CI 0.76 - 1.05, respectively). However, stent migration and sludge formation were much more common with covered stents (OR 5.11, 95 %CI 1.84 - 14.17; OR 2.46, 95 %CI 1.37 - 4.43). The use of covered stents was associated with a lower rate of tumor ingrowth (OR 0.21, 95 %CI 0.09 - 0.50) but a higher rate of tumor overgrowth (OR 2.00, 95 %CI 1.15 - 3.48) compared with uncovered stents. The rates of procedure-related adverse events were similar in both groups. | M |
| 8 | Xia MX, Pan YL, Cai XB, Wu J, Gao DJ, Ye X, Wang TT, Hu B. Comparison of endoscopic bilateral metal stent drainage with plastic stents in the palliation of unresectable hilar biliary malignant strictures: Large multicenter study. Digestive Endoscopy. 33(1):179-189, 2021 Jan. UI: 32249460 | Multi institution nonrandomized prospective study | 262 consecutive patients (Bismuth classification types II-IV) who underwent either bilateral metal or plastic stenting as primary therapy at 4 tertiary centers. To overcome selection bias, 1:1 propensity score matching was performed. | To compare transpapillary parallel-style bilateral metal stenting with bilateral plastic stenting, and evaluated short- and long-term outcomes. | After propensity score matching, each group comprised 96 patients, with no significant differences in baseline characteristics. The MS was significantly longer in the metal group than in the plastic group (7.2 months [95% CI 6.0-8.5] vs. 4.1 months [95% CI 2.9-5.3]; P = 0.015). The clinical success rates were significantly higher in the metal stenting group than in the plastic stenting group (99.0% vs. 71.9%, respectively; P <  0.001), and lower post-procedure cholangitis incidence (7.3% vs. 26.0%; P < 0.001), longer median symptom-free stent patency (9.2 months [95% CI 7.6-10.6] vs. 4.8 months [95% CI 4.2-5.3]; P < 0.001), and fewer total interventions (1.3  +/- 0.6 vs. 2.0 +/- 1.4; P < 0.001). In multivariate Cox analysis of the OS, metal stenting (HR 0.589, P = 0.002), hilar cholangiocarcinoma (HR 0.419, P = 0.009), and adjuvant treatment (HR 0.596, P = 0.006) were independent predictors of death. | 2 |
| 9 | Sakai Y, Sugiyama H, Kawaguchi Y, Kawashima Y, Hirata N, Nakaji S, Natsui M, Shioji K, Nakahara K, Tsuyuguchi T, Kato N. Uncovered versus covered metallic stents for the management of unresectable malignant distal biliary obstruction: a randomized multicenter trial. Scand J Gastroenterol. 56(10):1229-1235., 2021 Oct | Multi institution randomized trial | 92 patients with distal malignant biliary obstruction were randomized to uncovered stents (48) or covered stents (44). | To compare the efficacies and complication rates of uncovered metal stents and covered metal stents in unresectable malignant distal biliary obstructions at a prospective randomized multicenter trial. | No significant difference was found in the drainage effect between the 2 groups. The number of stent occlusion was significantly greater (*p* = .0467) with uncovered stents (43.8%) comparing with those with covered stents (22.7%). As the cause of stent occlusion, tumor ingrowth was significantly greater (*p* < .001) with uncovered stents group (35.4%) than with covered stents (2.3%). The median stent patency period was significantly longer (*p* = .0112) in the covered stent group (455 days) than for the uncovered stent group (301 days). A significant difference in the MS period was not found between the 2 groups. | 1 |
| 10 | Zhu HD, Guo JH, Huang M, Ji JS, Xu H, Lu J, Li HL, Wang WH, Li YL, Ni CF, Shi HB, Xiao EH, Lv WF, Sun JH, Xu K, Han GH, Du LA, Ren WX, Li MQ, Mao AW, Xiang H, Zhang KX, Min J, Zhu GY, Su C, Chen L, Teng GJ. Irradiation stents vs. conventional metal stents for unresectable malignant biliary obstruction: A multicenter trial. Journal of Hepatology. 68(5):970-977, 2018 05. UI: 29331343 | Multi institution open label single arm randomized Phase III study | 328 patients with unresectable malignant biliary obstruction randomized to undergo placement if irradiation or conventional uncovered self- expanding metal stents | To assess the efficacy of an irradiation stent compared to an uncovered self- expanding metal stents in patients with unresectable malignant biliary obstruction | The first quartile stent patency time (when 25% of the patients experienced stent restenosis) was 212 days for the irradiation stents and 104 days for the conventional stents. Irradiation stents were significantly associated with a decrease in the rate of stent restenosis (9% vs. 15% at 90 days; 16% vs. 27% at 180 days; 21% vs. 33% at 360 days; p=0.010). Median OS for irradiation stent group 202 days vs. 140 days for conventional; p=0.020). No significant results were observed in technical success rate (93% vs. 95%; p=0.499), relief of jaundice (85% vs. 80%; p=0.308), and the incidence of grade 3 and 4 complications (8.5% vs. 7.9%; p=0.841). | 1 |
| 11 | Sha KH, Liu TG, Yang F, Zhang LG, Jiao ZS, Xia FF. Irradiation stent insertion for inoperable malignant biliary obstruction: a meta-analysis of randomized controlled trials. Abdominal Radiology. 46(5):2173-2181, 2021 05. UI: 33156948 | Meta-analysis | Pubmed, Embase, and  Cochrane Library databases were searched and identified 8 randomized controlled trials including 319 patients who had undergone radioactive stent insertion, and 328 who had undergone conventional stent insertion. | To compare the relative clinical efficacies of radioactive stent and conventional  stent insertions for the treatment of patients with malignant biliary obstruction | No significant differences in pooled DELTA total bilirubin values (MD 0.34; P = 0.92), incident rates of cholangitis (P = 0.47), hemobilia (P = 0.60), or pancreatitis (P = 0.89) were detected. The rate of stent dysfunction was significantly lower in the radioactives stent group compared to the conventional stent group (22.2% vs. 37.7%, P = 0.02). The pooled stent patency (P < 0.00001) and OS (P < 0.00001) were significantly longer in the radioactive stent group. Significant heterogeneity was detected in the endpoints of rate of stent dysfunction (I2 = 52%; P = 0.08) and survival  (I2 = 77%; P = 0.0005). Subgroup analysis was performed based on the different radioactive stent types and showed significantly longer  OS based on radioactive stent type. Funnel plot analyses did not detect any evidence of publication bias. | M |
| 12 | Pang Q, Zhou L, Hu XS, Wang Y, Man ZR, Yang S, Wang W, Qian Z, Jin H, Liu HC. Biliary stenting alone versus biliary stenting combined with 125I particles intracavitary irradiation for the treatment of advanced cholangiocarcinoma. Scientific Reports. 9(1):11348, 2019 08 05. UI: 31383886 | Single institution retrospective study | 184 advanced ECC  patients, who received percutaneous transhepatic biliary stenting, of which 113 had 125I particles implantation and 71 did not | To compare the efficacy of percutaneous transhepatic biliary stenting with or without 125I  particles implantation in the treatment of advanced ECC | The jaundice and liver function were significantly improved in all patients, especially in the 125I group. There was no significant difference in the risk of postoperative complications between the 2 groups. However, the risk of biliary re-obstruction significantly reduced in 125I group (19.5% vs. 35.2%, p = 0.017). Kaplan Meier analysis showed that patients in 125I group had a significantly better OS, both for hilar and distal ECC. Univariate analysis demonstrated that preoperative levels of carbohydrate antigen 19-9  (CA19-9), total bilirubin, neutrophil count, lymphocyte count, and different therapeutic method were significant factors for OS. Multivariate analysis further identified the treatment with 125I particles implantation as an independent protective prognostic factor (HR = 0.26, 95% CI: 0.17-0.39, p < 0.001). | 3 |
| 13 | Chen W, Fang XM, Wang X, Sudarshan SKP, Hu XY, Chen HW, Preliminary clinical application of integrated 125I seeds stents in the therapy of malignant lower biliary tract obstruction. Journal of X-Ray Science & Technology. 26(5):865-875, 2018. UI: 30040791 | Single institution randomized controlled trial | 32 patients with malignant lower biliary obstruction were randomized to 2 groups; 13 patients with integrated 125I seed stents and 19 with conventional metal stents. The pre- and post-operative changes in biochemical indices, white blood cell count, IgG level, stent patency, survival time, tumor size and complications were compared between the two groups. RECIST 1.1 (Response Evaluation Criteria In Solid Tumors) was used to evaluate therapeutic effects. | To evaluate the clinical efficacy of percutaneous trans-hepatic integrated 125I seed stents implantation for malignant lower biliary tract obstruction. | The differences between pre- and post-operative (30 days) intragroup biochemical indices had statistically significant difference (P < 0.05), but there were no significant differences (P > 0.05) in leukocyte counts and IgG levels. As to the median time of stent patency and patients' survival, there were significant differences (P < 0.05) between standard stent and 125I seed stents (3.9 months vs. 8.1 months, 139 days vs. 298 days, respectively). After 3 months, the average tumor size was reduced in the 125I seed stent group, but was increased in the standard stent group (P < 0.05). There was no significant difference in the incidence of complications between the two groups. The evaluation results using RECIST 1.1 showed that there were statistically significant differences between the two groups in terms of the rates of remission, control, and progression (chi2 = 17.5, P < 0.05). | 1 |
| 14 | Autorino R, Bisiello S, Pappalardi B, Privitera V, Buwenge M, Piccolo F, Masciocchi C, Tagliaferri L, Macchia G, Curti  CD, Luppatteli M, Cerrotta A, Morganti AG, Valentini V, Mattiucci G. Intraluminal Brachytherapy in Unresectable Extrahepatic Biliary Duct Cancer: An Italian Pooled Analysis. Anticancer Research. 40(6):3417-3421, 2020 Jun. UI: 32487639 | Pooled Analysis from 3 institutions | 73 patients with unresectable ECC;  39 (53%) received CRT treatment with HDR ILBT boost (18 with chemotherapy (gemcitabine or 5-FU during RT), while 28 (38%) were treated with RT (chemotherapy in 26) and 6 (8.2%) with definitive HDR ILBT (2 with chemotherapy). | To evaluate the outcome of patients with unresectable ECC treated with  RT or CRT with or without HDR ILBT boost or with definitive HDR ILBT. | Overall median LC was 16 months and patients who underwent ILBT had a better local control (LC) (p=0.018). | 2 |
| 15 | Boothe D, Hopkins Z, Frandsen J, Lloyd S. Comparison of external beam radiation and brachytherapy to external beam radiation alone for unresectable extrahepatic  cholangiocarcinoma. Journal of Gastrointestinal Oncology. 7(4):580-7, 2016 Aug. UI: 27563448 | SEER registry retrospective study | 1,326 patients with unresectable ECC | To evaluate the benefit of adding HDR ILBT to RT for  unresectable ECC. | Of 1,326 patients with unresectable ECC, 1,188 (92.9%) received RT only, while 91 (7.1%) received both RT and HDR ILBT. Patients receiving combined modality therapy were more likely to be treated prior to the year 2000. Median OS for patients receiving RT and RT plus HDR ILBT was 9 and 11 months, respectively (P=0.04). CSS was 12 months for those receiving RT only, and 15 months for those who received RT + HDR ILBT (P=0.10). Survival analysis performed on patients with locoregional disease only revealed a trend towards prolonged overall survival with those receiving RT + HDR ILBT (P=0.08). Multivariate analysis revealed grade and stage of disease were correlated with both OS and CSS (P<=0.05). | 3 |
| 16 | Taggar AS, Mann P, Folkert MR, Aliakbari S, Myrehaug SD, Dawson LA.  A systematic review of intraluminal high dose rate brachytherapy in the management of malignant biliary tract obstruction and cholangiocarcinoma.  Radiotherapy & Oncology. 165:60-74, 2021 12. UI: 34695521 | Systematic review | Systematic search of PubMed, Cochrane Library, Embase. Pooled analysis included 17 studies including 1 prospective randomized controlled trial, 2 prospective Phase 1/2 trials, 6 prospective cohort series and 8 retrospective series. The time period for all the included studies spanned from 1986 to 2014. A total of 649 patients were included in all studies and 342 underwent ILBT. | To conduct a systematic review evaluating the impact of HDR ILBT in the management of malignant biliary obstruction and cholangiocarcinoma with specific focus on stent patency, clinical outcomes and toxicities. | Significant heterogeneity was observed in treatment regimens, which included surgery, RT, and/or intra-arterial and intravenous chemotherapy in conjunction with ILBT. ILBT appeared to result in longer duration of stent patency: 10 months with ILBT compared to 4-6 months without ILBT. A trend was observed towards prolonged LC and improved complete and partial response rates in patients treated with ILBT with or without  EBRT. Weighted mean overall survival of patients treated with ILBT alone was 11.8 months compared to 10.5 months for those that received EBRT +/- chemotherapy in addition to ILBT. The included studies reported low complication rates and toxicity related to ILBT. | 2 |
| 17 | Huang YY, Xu XJ, Huang XZ, Cheng H. A stent with radioactive seed strand insertion for inoperable malignant biliary obstruction: A meta-analysis. [Review]  Brachytherapy. 20(3):638-644, 2021 May-Jun. UI: 33678600 | Meta-analysis | Relevant articles published as of November 2020 in the Embase, PubMed, and Cochrane Library databases were identified and identified 9 studies with 643 patients (280 with stent placement + RSS and 363 with stent without RSS). Primary study endpoints for this meta-analysis were stent dysfunction, stent patency, and OS. Secondary endpoints were rates of clinical success and complications | To assess the relative clinical effectiveness of stent insertion with or without  RSS insertion in patients suffering from malignant biliary obstruction | No differences were observed in pooled rates of clinical success (p = 0.25), stent dysfunction (p = 0.47), cholangitis (p = 0.97), cholecystitis (p = 0.95), or pancreatitis (p = 0.66). Stent patency duration (p < 0.00001) and patients' OS (p < 0.00001) were significantly increased in patients in the stent + RSS group. No heterogeneity was detected for any of these endpoints, nor did funnel plots yield any publication bias. A subgroup analysis of patients with hilar malignant biliary obstruction similarly exhibited stent + RSS insertion to be associated with longer stent patency and OS as compared with stent insertion alone. | M |
| 18 | Isayama H, Tsujino T, Nakai Y, Sasaki T, Nakagawa K, Yamashita H, Aoki T, Koike K. Clinical benefit of radiation therapy and metallic stenting for unresectable hilar cholangiocarcinoma. World Journal of Gastroenterology. 18(19):2364-70, 2012 May 21.UI: 22654427 | Multi institutional retrospective study | 64 patients with locally advanced hilar ECC including 25 who underwent resection (17 curative and 8 non-curative), 28 treated with RT, and 11 who received best supportive care. The RT group received 50 Gy, 30 fractions, with 11 receiving an additional 24 Gy (4 fractions) HDR ILBT. HDR ILBT was performed using percutaneous transhepatic biliary drainage.  Uncovered metallic stents were inserted into unresected patients with obstructive jaundice, with the exception of 4 patients who received percutaneous transhepatic biliary drainage only. | To determine the efficacy of RT, with or without HDR ILBT  in patients with unresected locally advanced hilar ECC | No statistically significant differences in patient characteristics were found among the resection, RT, and best supportive care groups. 3 patients in the RT group and one in the best supportive care group did not receive stents but received percutanteous biliary drainage alone; cholangitis occurred after endoscopic stenting, and patients were treated with percutaneous drainage.  A total of 16 patients received AC (5-FU-based regimen in 9, S-1 in 6, and gemcitabine in 1). OS varied significantly among groups, with MS of 48.7 mo in the surgery group, 22.1 mo in the RT group, and 5.7 mo in the best supportive care group. Patients who underwent curative resection survived significantly longer than those who were not candidates for surgery (P = 0.0076). Cumulative survival in the RT group was significantly longer than in the best supportive care group (P = 0.0031), but did not differ significantly from those in the unresected group. Furthermore, the MS of patients in the RT group who were considered for possible resection (excluding 7 patients who were not candidates for surgery due to comorbid disease or age) was 25.9 mo. Stent patency was significantly longer in the RT than in the best supportive care group (P = 0.0165). | 3 |
| 19 | Yoshioka Y, Ogawa K, Oikawa H, Onishi H, Kanesaka N, Tamamoto T, Kosugi T, Hatano K, Kobayashi M, Ito Y, Takayama M,  Takemoto M, Karasawa K, Nagakura H, Imai M, Kosaka Y, Yamazaki H, Isohashi F, Nemoto K, Nishimura Y, Japanese Radiation  Oncology Study Group (JROSG). Impact of intraluminal brachytherapy on survival outcome for radiation therapy for unresectable biliary tract cancer: a propensity-score matched-pair analysis. International Journal of Radiation Oncology, Biology, Physics. 89(4):822-9, 2014 Jul 15. UI: 24969796 | Multi institutional retrospective propensity score matched cohort study | 209 patients with unresected BTC, including 153 who underwent RT alone and 56 who received both RT and HDR ILBT. By matching propensity scores, 56 pairs (112 patients) consisting of 1 patient with and 1 patient without ILBT were selected. They were well balanced in terms of sex, age, performance status, clinical stage, jaundice, and addition of chemotherapy. | To determine whether adding HDR ILBT to RT for  unresectable biliary tract cancer has a positive impact on survival outcome. | The 2-year OS rates were 31% for the HDR ILBT group and 40% for the patients who did not receive HDR ILBT (P=.862). The 2-year DSS rates were 42% for the ILBT group and 41% for the patients who did not receive HDR ILBT (P=.288). The 2-year LC rates were 65% for the ILBT group and 35% for the patients who did not receive HDR ILBT (P=.094). Three of the 4 sensitivity analyses showed a significantly better LC for the ILBT group (P=.010, .025, .049), and another showed a marginally better LC (P=.068), and none of the sensitivity analyses showed any statistically significant differences in OS or DSS. | 2 |
| 20 | Hauge T, Hauge PW, Warloe T, Drolsum A, Johansen C, Viktil E, Aabakken L, Buanes T, Konopski Z. Randomised controlled trial of temoporfin photodynamic therapy plus chemotherapy in nonresectable biliary carcinoma—PCS Nordic study. Photodiagnosis & Photodynamic Therapy. 13:330-333, 2016 Mar.UI: 26415549 | Single institution randomized controlled trial | 20 patients with unresectable BTC treated with combination chemotherapy and stent with or without temopofin (Foscan) PDT. 10 in each group | To compare outcomes for patients with unresectable BTC treated with combination chemotherapy and stent with or without PDT | No serious, acute procedure-related complication related to PDT or the treatment combination was seen. The number of patients with cholangitis was equal in both groups. In the PDT group-, 2 patients had cutaneous erythema after sun exposition, one of them with a localized blister. No neutropenic infection was seen. Quality of Life was similar in both treatment groups. Progression free survival was numerically longer in the PDT group. | 1 |
| 21 | Li Z, Jiang X, Xiao H, Chen S, Zhu W, Lu H, Cao L, Xue P, Li H, Zhang D. Long-term results of ERCP- or PTCS-directed photodynamic therapy for unresectable hilar cholangiocarcinoma.  Surgical Endoscopy. 35(10):5655-5664, 2021 10. UI: 33104917 | Single institution retrospective study | 62 patients with unresectable hilar cholangiocarcinoma. 30 received PDT using hematoporphyrin combined with biliary stent placement (PDT+stent group), including (22 ERCP-directed PDT and 8 receiving PTCS-directed PDT). Survival time, quality of life, and postoperative adverse  events were compared to 32 patients receiving biliary stent placement alone | To explore the clinical efficacy and safety  of ERCP or PTCS directed PDT combined with stent placement for unresectable hilar cholangiocarcinoma | MS was significantly longer in the PDT+stent group than the Stent-only group (14.2 vs. 9.8 months, P = 0.003). In the PDT+stent group, the MS was longer in the 6 patients with recurrence after surgical resection than the 24 patients without prior surgical resection (20.0 vs. 13.0 months, P = 0.017). The QOL total scores was significantly higher in the PDT+stent group than the Stent-only group at postoperative 6, 9, and 12 months (P<0.05). There was no significant difference in the incidence of postoperative adverse events between the 2 groups (24 [38.7%] vs. 20 [29.0%], P = 0.239). | 3 |
| 22 | Lu Y, Liu L, Wu JC, Bie LK, Gong B. Efficacy and safety of photodynamic therapy for unresectable cholangiocarcinoma: A meta-analysis. Clinics & Research in Hepatology & Gastroenterology. 39(6):718-24, 2015 Dec. UI: 26070572 | Systematic search and Meta-analysis | Search identified 8 trials (642 patients) comparing PDT with other therapies, 7 of these trials, which compared the result of PDT+stent and stent-only | To compare PDT with stent to biliary stenting alone or other therapies for the treatment of unresectable cholangiocarcinoma | OS was significantly better in patients who received PDT than those who did not [HR=0.49, 95% CI, 0.33~0.73, P=0.0005]. Among the 8 trials, 5 assessed the changes of serum bilirubin levels, and/or Karnofsky performance status, as other indications for improvement. In all, the incidence for phototoxic reaction is 11.11%. The incidence for other events in photodynamic therapy and the stent-only group was 13.64% and 12.79%, respectively. | M |
| 23 | Leggett CL, Gorospe EC, Murad MH, Montori VM, Baron TH, Wang KK. Photodynamic therapy for unresectable cholangiocarcinoma: a comparative effectiveness systematic review and meta-analyses. [Review] Photodiagnosis & Photodynamic Therapy. 9(3):189-95, 2012 Sep. UI: 22959798 | Systematic review and meta-analysis | Search identified 6 prospective studies; 170 participants received PDT and 157 had biliary stenting only. | To determine the effectiveness of biliary stenting with PDT compared to biliary stenting alone in the palliative treatment of cholangiocarcinoma | Compared with biliary stenting, PDT was associated with a statistically significant increase in the length of survival (weighted mean difference 265 days; 95% CI: 154-376; p = 0.01), improvement in Karnofsky scores (weighted mean difference 7.74; 95% CI: 3.73-11.76; p = 0.01), and a trend for decline in serum bilirubin (weighted mean difference -2.92 mg/dL; 95% CI: -7.54 to 1.71; p=0.22). The pooled event rate for biliary sepsis was 15% and was similar between PDT and control groups. | M |
| 24 | Moole H, Tathireddy H, Dharmapuri S, Moole V, Boddireddy R, Yedama P, Dharmapuri S, Uppu A, Bondalapati N, Duvvuri A. Success of photodynamic therapy in palliating patients with nonresectable cholangiocarcinoma: A systematic review and meta-analysis. [Review] World Journal of Gastroenterology. 23(7):1278-1288, 2017 Feb 21. UI: 28275308 | Systematic review and Meta-analysis | Systematic review of MEDLINE, PubMed and EMBASE databases identified 10 studies including 402 patients with unresectable cholangiocarcinoma who received stenting with or without PDT. Pooled proportions were calculated using fixed and random effects model. Heterogeneity among studies was assessed using the I2 statistic. | To perform a systematic review and meta-analysis on clinical outcomes of PDT in non-resectable cholangiocarcinoma. | Pooled odds ratio for successful biliary drainage (decrease in bilirubin level > 50% within 7days after stenting) in PDT vs stent alone group was 4.39 (95%CI: 2.35-8.19). Survival period in  PDT and stent alone groups were 413.04 d (95%CI: 349.54-476.54) and 183.41 (95%CI: 136.81-230.02) respectively. The change in  Karnofsky performance scores after intervention in PDT and stent alone groups were +6.99 (95%CI: 4.15-9.82) and -3.93 (95%CI: -8.63-0.77) respectively. OR for post-intervention cholangitis in PDT vs stent alone group was 0.57 (95%CI: 0.35-0.94). In PDT group, 10.51% (95%CI: 6.94-14.72) had photosensitivity reactions that were self-limiting. Subgroup analysis of prospective studies showed similar results, except the incidence of cholangitis was comparable in both groups. | M |
| 25 | Park DH, Lee SS, Park SE, Lee JL, Choi JH, Choi HJ, Jang JW, Kim HJ, Eum JB, Seo DW, Lee SK, Kim MH, Lee JB. Randomised phase II trial of photodynamic therapy plus oral fluoropyrimidine, S-1, versus photodynamic therapy alone for unresectable hilar cholangiocarcinoma. European Journal of Cancer. 50(7):1259-68, 2014 May. UI: 24485665 | Single institution prospective randomized phase II trial | 21 patients with unresectable hilar ECC received PDT plus S-1 and 22 to receive PDT alone. | To compare PDT plus S-1 and PDT alone for unresectable hilar ECC | PDT plus S-1 showed higher 1-year OS compared with the patients treated with PDT alone (76.2% versus 32%, P=0.003) and prolonged OS (median 17 months, 95% CI: 12.6-21.4, versus 8 months, 95% CI: 6-10, P=0.005, HR 0.36; 95% CI: 0.17-0.75). PDT plus S-1 was associated with prolonged PFS compared with PDT alone (median 10 months [95% CI: 4.1-16] versus 2 months [95% CI: 0.4-3.5], P=0.009 (HR for progression 0.39, 95% CI: 0.19-0.83). There were no differences in the number of PDT sessions, the frequency of cholangitis, overall adverse events or the quality of life in either group. | 1 |
| 26 | Bokemeyer A, Matern P, Bettenworth D, Cordes F, Nowacki TM, Heinzow H, Kabar I, Schmidt H, Ullerich H, Lenze F. Endoscopic Radiofrequency Ablation Prolongs Survival of Patients with Unresectable Hilar Cholangiocellular Carcinoma - A  Case-Control Study. Scientific Reports. 9(1):13685, 2019 09 23. UI: 31548703 | Single institution retrospective case-controlled study | RFA was performed in 32 patients with malignant biliary strictures that were mainly caused by Bismuth III and IV hilar CCCs (66%). 14 received repeated RFA, for a total of 54 procedures. Stents were applied in all patients | To compare outcomes of patients who underwent endoscopic RFA for unresectable hilar ECC and historical controls that received standard treatments of stent application | Adverse events occurred in 18.5% of examinations. Case-control analysis revealed that the median OS of cases with unresectable Bismuth type III and IV hilar ECC (20) treated with combined RFA and stent application significantly increased compared to controls (22) treated with sole stent application (342 +/- 57 vs. 221 +/- 26 days; p = 0.046). | 2 |
| 27 | Yang J, Wang J, Zhou H, Wang Y, Huang H, Jin H, Lou Q, Shah RJ, Zhang X. Endoscopic radiofrequency ablation plus a novel oral 5-fluorouracil compound versus radiofrequency ablation alone for unresectable extrahepatic cholangiocarcinoma. Gastrointestinal Endoscopy. 92(6):1204-1212.e1, 2020 12. UI: 32437711 | Single institution randomized controlled trial | Patients with unresectable ECC were prospectively randomized to 1 of 2 groups: the RFA + S-1 group and the RFA group. Median OS, stent patency time, Karnofsky performance status score, and adverse events rate were analyzed. | To evaluate the clinical efficacy and safety of endoscopic RFA combined with S-1 for the treatment of unresectable locally advanced ECC. | The median OS was longer in the RFA + S-1 group (n = 37) than that in the RFA group (n = 38) (16.0 months [95% CI, 13.1-19.0] vs 11.0 months [95% confidence interval, 9.7-12.3]; P < .001). Stent patency time was significantly longer in the RFA + S-1 group than that in the RFA group (6.6 +/- 1.5 vs 5.6 +/- .1 months, P = .014). Karnofsky performance scores at postoperative month 9 (51.6 +/- 17.0 vs 40.4 +/- 16.4, P = .012) and month 12 (35.2 +/- 18.3 vs 23.9 +/- 11.4,  P = .014) were all higher in the RFA + S-1 group than those in the RFA group (P < .05). The incidence of ERCP-related adverse events was not significantly different between RFA + S-1 and RFA groups (8.1% vs 10.5%, P > .05). | 1 |
| 28 | Knüppel M, Kubicka S, Vogel A, et al. Combination of conservative and interventional therapy strategies for intra- and extrahepatic cholangiocellular carcinoma: a retrospective survival analysis. Gastroenterol Res Pract. 2012;2012:190708. | Single institution retrospective study | 195 patients with intra- (n = 111) or extrahepatic (n = 84) changiocarcinoma, received either chemotherapy or a combination of PDT or TACE chemotherapy. | To compare the effect of the various forms of treatment on morbidity and mortality for patients with cholangiocarcinoma. | Median OS for all patients was 15.6 months, 50.8% were still alive 1 year after diagnosis. Patients, who had previously undergone surgery, survived 17.1 months longer than those without surgical treatment (P < .01). Chemotherapy prolonged the survival by 9.2 months (P = .47). Palliative patients under combination of chemotherapy and PDT survived on average 1.8 months longer (P = .28), with chemotherapy and TACE 9.8 months longer (P = .04) compared to chemotherapy alone. | 3 |
| 29 | Koch C, Franzke C, Bechstein WO, Schnitzbauer AA, Filmann N, Vogl T, Gruber-Rouh T, Zeuzem S, Waidmann O, Trojan J. Poor Prognosis of Advanced Cholangiocarcinoma: Real-World Data from a Tertiary Referral Center. Digestion. 101(4):458-465, 2020. UI: 31129660 | Single institution retrospective study | 220 consecutive patients screened; 105 with unresectable cholangiocarcinoma treated at a tertiary center | To evaluate various outcomes associated with various treatment for patients with unresectable cholangiocarcinoma | Any palliative treatment was beneficial when compared to best supportive care alone; median OS with best supportive care was 10 weeks (vs HAI p = 0.017, HR 0.36; vs. HAI + chemotherapy p < 0.001, HR 0.24; vs. chemotherapy p < 0.001, HR 0.31). Combination of HAI and chemotherapy prolonged overall survival as compared to HAI alone (105 vs. 43 weeks, p = 0.045). | 3 |
| 30 | Goto T, Saito H, Sasajima J, Kawamoto T, Fujinaga A, Utsumi T, Yanagawa N, Hiramatsu K, Takamura A, Sato H, Fujibayashi S, Fujiya M. High Response Rate and Prolonged Survival of Unresectable Biliary Tract Cancer Treated With a New Combination Therapy  Consisting of Intraarterial Chemotherapy Plus Radiotherapy. Frontiers in Oncology. 10:597813, 2020. UI: 33312956 | Single institution retrospective study | 52 patients with unresectable BTC who received HAI chemotherapy + RT (one-shot IAC at the first angiography session, almost 6 months of reservoir HAI chemotherapy (5-FU and cisplatin, q/week) and external radiation with a maximum dose of 50.6  Gy). Included hilar ECC, distal bile duct and gall bladder cancer but not intrahepatic cholangiocarcinoma | To the effectiveness and safety of a new combination therapy consisting of HAI chemotherapy + RT n patient with unresectable BTC | The response rate and disease control rate were 40.4% and 96.2%, respectively, and median OS and PFS were 463 and 431 days. Univariate analysis identified 12 prognostic factors, and a performance status of 2 (HR: 4.82, p=0.02), jaundice (HR: 3.22, p<0.01), peritoneal dissemination (HR: 22.5, p<0.01), number of IAC (HR: 0.35, p=0.01) and response to HAI chemotherapy +RT (HR: 0.23, p<0.01) were significant prognostic factors in multivariate analysis. Grade >=3 AEs occurred: leucopenia (11.5%), neutropenia (1.9%), anemia (15.4%), thrombocytopenia (11.5%), anorexia (3.8%), gastroduodenal ulcer (25.0%), and cholangitis (23.1%). There were no cases of treatment-related death. | 3 |
| 31 | Zheng WH, Yu T, Luo YH, Wang Y, Liu YF, Hua XD, Lin J, Ma ZH, Ai FL, Wang TL. Clinical efficacy of gemcitabine and cisplatin-based transcatheter arterial chemoembolization combined with radiotherapy in hilar cholangiocarcinoma. World Journal of Gastrointestinal Oncology. 11(6):489-498, 2019 Jun 15. UI: 31236199 | Single institution retrospective study | 72 patients with unresectable hilar ECC. According to percutaneous transhepatic biliary angiography and the patients' wishes, stent implantation or biliary drainage tube implantation was used to relieve biliary obstruction. The patients were divided into either a control group (35 patients with biliary drainage tube +/- stent) or a combined treatment group (37 patient treated with HAI and 3D-CRT or IMRT at an average dose of 48.3 Gy after biliary drainage +/- stent. The HAI regimen included gemcitabine and cisplatin, and the embolic agent was iodized oil. | To investigate the clinical efficacy of gemcitabine and cisplatin-based HAI combined with RT in unresectable hilar ECC | MS control group 10.5 mo; MS for patients with stent vs percutaneous biliary drainage was 9.6 mo and 11.4 mo, respectively, not statistically significant. MS of the combined treatment group was 20.0 mo, significantly higher than control group (P < 0.05). Among patients in the combined treatment, MS of patients with stent vs percutaneous biliary drainage before combination therapy was 19.5 mo and 20.1 mo, respectively, not statistically significant. In the combination treatment group, the mean time of median stent patency was 15.6 mo, significantly higher than control group (7.0 mo; P < 0.05). The independent factors affecting survival time included age, combination therapy, percutaneous biliary drainage tube implantation, and Bismuth-Corlette classification as type IV. | 3 |
| 32 | Gou Q, Wu L, Cui W, Mo Z, Zeng D, Gan L, He J, Mai Q, Shi F, Chen M, Sun Z, Liu Y, Wu J, Chen X, Zhuang W, Xu R, Li W,  Cai Q, Zhang J, Chen X, Li J, Zhou Z. Stent placement combined with intraluminal radiofrequency ablation and hepatic arterial infusion chemotherapy for advanced biliary tract cancers with biliary obstruction: a multicentre, retrospective, controlled study.  European Radiology. 31(8):5851-5862, 2021 Aug. [UI: 33585991 | Multi institution retrospective study | 135 patients from 3 centers with advanced BTC and biliary obstruction, 64 underwent intraluminal RFA and HAI; 71 stent only | To evaluate efficacy and safety of stent placement combined with intraluminal RFA and HAI for patients with advanced BTC  and biliary obstruction | The median stent patency time was significantly longer in the combination group (8.2 months, 95% CI: 7.1-9.3) than in the control group (4.3 months, 95% CI: 3.6-5.0; p < 0.001). OS (combination: 13.2 months, 95% CI: 11.1-16.5; control: 8.5 months, 95% CI: 7.6-9.6; p < 0.001).  AEs related to biliary tract operation was not significantly different between the two groups (p > 0.05). The most common AE and serious AE related to HAI were alanine aminotransferase elevation (24/64; 37.5%) and thrombocytopenia (8/64; 12.5%), and there was no death from AEs. | 2 |
| **33** | Burke EC, Jarnigan WR, Hochwald SN, Pisterrs PW, Fong Y, BlumgartLH. Hilar Cholangiocarcioma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. Ann Surg. 1998. Sept; 228(3): 385-394. PMID 9742921. | Single institution retrospective study | 91 patients with hilar cholangiocarcinoma, Disease was staged in 87 patients using extent of ductal tumor involvement, portal vein compromise, and liver atrophy.In 21 patients, disease was deemed unresectable for cure at presentation. In 39 patients, disease was found to be unresectable at laparotomy, 23 secondary to nodal (N2) or distant metastases. Unresectability was the result of metastases in 52% and of locally advanced disease in 28%. Thirty patients (33%) had resection of all gross disease, and 25 of these (83%) had negative histologic margins. | To determine the resectability rate for hilar cholangiocarcinoma, to analyze reasons for unresectability, and to devise a presurgical clinical T-staging system. | 22 patients underwent partial hepatectomy. The 30-day mortality rate was 7%. Projected survival is greater than 60 months in those with a negative histologic margin, with a median follow-up of 26 months. A presurgical T-staging system allows presurgical selection for therapy, predicts partial hepatectomy, and offers an index of prognosis. | 3 |
| **34** | Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunven P, Yamasaki S, Hasegawa H, Ozaki H. Preoperative portal embolization to increase safety aof major hepatectomy for hilar bile duct carcinoa: a preliminary report. Surgery, 107(5): 5210527, 1990. PMID: 2333592 | Single institution retrospective study | To minimize postoperative liver dysfunction, a portal venous branch was embolized before surgery to induce atrophy of the lobe to be resected and hypertrophy of the contralateral lobe in 14 patients with hilar bile duct carcinoma. Bile was drained before surgery in 11 patients with jaundice. | To describe a surgical technique with potential to increase success rates and decrase mortality | Portal embolization did not produce major side effects, and moderate increases of serum transaminase activity or bilirubin returned to baseline values within 1 week. Hepatectomy with bile duct resection and lymphadenectomy was performed 6 to 41 days after embolization, at which time the embolized lobe was atrophied in 12 of the patients. Extended right or left lobectomy or left trisegmentectomy (10, 3, and 1 cases, respectively) with biliointestinal reconstruction was performed. One patient with jaundice and suppurative cholangitis died 30 days after hepatectomy. Another patient died 3 months after surgery of aggravated hepatitis. After surgery, no bile leakage occurred and hyperbilirubinemia was usually moderate and reversible. | NA |
| 35 | Shindoh J, Truty MJ, Aloia TA, Curley SA, Zimmitti G, Huang SY, Mahvash A, Gupta S, Wallace MJ, Vauthey JN. Kinetic growth rate after portal vein embolization predicts posthepatectomyoucomes: toward zero liver-related mortalityin patients with colorectal liver metastases and small ruture liver remnant. J am Coll Surg. 216(2): 201-209, 2013. PMIS: 23219349. | Single institutional retrospective study | Kinetic growth rate (KGR) is defined as the degree of hypertrophy at initial volume assessment divided by number of weeks elapsed after PVE. In 107 consecutive patients who underwent liver resection for colorectal liver metastases with an sFLR volume >20%, the ability of the KGR to predict overall and liver-specific postoperative morbidity and mortality was compared with sFLR volume and degree of hypertrophy. | To describe a surgical technique with potential to increase success rates and decrase mortality | Using receiver operating characteristic analysis, the best cutoff values for sFLR volume, degree of hypertrophy, and KGR for predicting postoperative hepatic insufficiency were estimated as 29.6%, 7.5%, and 2.0% per week, respectively. Among these, KGR was the most accurate predictor (area under the curve 0.830 [95% CI, 0.736-0.923]; asymptotic significance, 0.002). A KGR of <2% per week vs ≥2% per week correlates with rates of hepatic insufficiency (21.6% vs 0%; p = 0.0001) and liver-related 90-day mortality (8.1% vs 0%; p = 0.04). The predictive value of KGR was not influenced by sFLR volume or the timing of initial volume assessment when evaluated within 8 weeks after PVE. | NA |
| 36 | Ethun CG, Lopez-Aguiar AG, Anderson DJ, Adams AB, Fields RC, Doyle MB, Chapman WC, Krasnick BA, Weber SM, Mezrich JD,  Salem A, Pawlik TM, Poultsides G, Tran TB, Idrees K, Isom CA, Martin RCG, Scoggins CR, Shen P, Mogal HD, Schmidt C, Beal E, Hatzaras I, Shenoy R, Cardona K, Maithel SK. Transplantation Versus Resection for Hilar Cholangiocarcinoma: An Argument for Shifting Treatment Paradigms for Resectable Disease. Annals of Surgery. 267(5):797-805, 2018 05. UI: 29064885 | Multi institution retrospective study | 304 patients with suspected hilar ECC, 234 underwent attempted resection and 70 were enrolled in a transplant protocol. Excluding incomplete/R2 resections (43), patients who were enrolled, but did not undergo LT (24), and transplants without confirmed H-CCA diagnoses (5), 191 patients underwent curative-intent resection and 41 curative-intent LT. Compared with resection, LT patients were younger (52 vs 65 years; P < 0.001), and more frequently had PSC; 61% vs 2%; P < 0.001) and received chemotherapy and/or RT (98% vs 57%; P < 0.001). Groups were otherwise similar in demographics and comorbidities. | To investigate the influence of type of surgery (LT vs resection) on OS in  patients with hilar ECC | LT was associated with improved OS compared with resection (3-year: 72% vs 33%; 5-year: 64% vs 18%; P < 0.001). Among patients who underwent resection for tumors <3 cm with lymph-node negative disease, and excluding PSC patients, LT was still associated with improved OS (3-year: 54% vs 44%; 5-year: 54% vs 29%; P = 0.03). LT remained associated with improved OS on intention-to-treat analysis, even after accounting for tumor size, LN status, and PSC (P = 0.049). | 3 |
| 37 | Darwish Murad S, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, Botha JF, Mezrich JD, Chapman WC, Schwartz JJ, Hong  JC, Emond JC, Jeon H, Rosen CB, Gores GJ, Heimbach JK. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology. 143(1):88-98.e3; quiz e14, 2012 Jul. UI: 22504095 | Multi institution retrospective study | 287 patients from 12 centers with perihilar ECC received neoadjuvant therapy followed by LT | To determine the effectiveness neoadjuvant CRT, followed by LT, for perihilar ECC and the appropriateness of the MELD exception. | The patients completed RT (99%), HDR ILBT (75%), CRT (98%), and/or maintenance chemotherapy (65%). 71 patients dropped out before LT (rate, 11.5% in 3 months). Intent-to-treat survival rates were 68% and 53%, 2 and 5 years after therapy, respectively; post-LT and DFS rates were 78% and 65%, respectively. Patients outside the United Network of Organ Sharing criteria (those with tumor mass >3 cm, transperitoneal tumor biopsy, or metastatic disease) or with a prior malignancy had significantly shorter survival times (P < .001). There were no differences in outcomes among patients based on differences in surgical staging or HDR ILBT. Although most patients came from 1 center (193), the other 11 centers had similar survival times after therapy. | 3 |
| 38 | Welling TH, Feng M, Wan S, Hwang SY, Volk ML, Lawrence TS, Zalupski MM, Sonnenday CJ. Neoadjuvant stereotactic body radiation therapy, capecitabine, and liver transplantation for unresectable hilar  cholangiocarcinoma. Liver Transplantation. 20(1):81-8, 2014 Jan. UI: 24115315 | Single institution pilot study | 12 patients with unresectable hilar ECC qualified for neoadjuvant therapy and were treated with SBRT (50-60 Gy in 3-5 fractions over the course of 2 weeks). After 1 week of rest, capecitabine was initiated and continued until LT | To evaluate the use of SBRT followed by capecitabine in LN negative patients with unresectable hilar ECC prior to LT | In this pilot study, neoadjuvant therapy with SBRT, capecitabine, and LT demonstrated acceptable tolerability. There were 35 adverse events in all, with cholangitis and palmar-plantar erythrodysesthesia being the most common. Capecitabine dose reductions were required on 5 occasions. Ultimately, 9 patients were listed for LT, and 6 patients received LT. The explant pathology of hilar tumors showed at least a partial treatment response in 5 patients, with extensive tumor necrosis and fibrosis noted. Additionally, high apoptotic indices and low proliferative indices were measured during histological examinations. Eleven transplant-related complications occurred, and the 1-year OS after LT was 83%. | 2 |
| 39 | Machairas N, Kostakis ID, Tsilimigras DI, Prodromidou A, Moris D. Liver transplantation for hilar cholangiocarcinoma: A systematic review. Transplantation Reviews. 34(1):100516, 2020 01. UI: 31711828 | Systematic review | A systematic search of Medline, Scopus, Google Scholar and ClinicalTrails.gov databases identified 13 studies with 698 patients with inoperable advanced hilar ECC; 74.4% of patients received combination of chemotherapy and RT as a part of neoadjuvant therapy. | To collect and  evaluate long-term outcomes of patients with hilar ECC undergoing LT. | 1-, 3- and 5-year OS ranged greatly among the included studies from 58% to 92%, 31% to 80% and 20% to 74%, respectively. Recurrence rates ranged from 16% to 61%, whilst perioperative mortality ranged from 0% to 25.5%. | 2 |
| 40 | Azad AI, Rosen CB, Taner T, Heimbach JK, Gores GJ. Selected Patients with Unresectable Perihilar Cholangiocarcinoma (pCCA) Derive Long-Term Benefit from Liver Transplantation. Cancers. 12(11), 2020 Oct 27. UI: 33121179 | Single institution retrospective cohort study | 237 patients who underwent LT for perihilar ECC | To compare difference in outcome for subsets of patients with perihilar ECC following LT | Noted 2 distinct patient populations: those with underlying PSC and those without identifiable risk factors termed sporadic or de novo perihilar ECC. Long-term survival after LT is better in PSC patients (74% 5-year OS) than in those with de novo perihilar ECC (58% 5-year OS). | 3 |
| 41 | Tan EK, Rosen CB, Heimbach JK, Gores GJ, Zamora-Valdes D, Taner T. Living Donor Liver Transplantation for Perihilar Cholangiocarcinoma: Outcomes and Complications. Journal of the American College of Surgeons. 231(1):98-110, 2020 07. UI: 32035181 | Single institution retrospective study | 247 consecutive liver donor LT for ECC (30% perihilar ECC with 49 (66.2%) PSC associated perihilar ECC; 70% non perihilar ECC indications) were reviewed, including demographics, donor variables, operative details, and postoperative outcomes. Logistic regression models were used to investigate the relationship between variables and outcomes. | To investigate the incidence of vascular and biliary complication in perihilar ECC compared with non-perihilar ECC indications and their impact on patient and graft survival. | Liver donor LDLT for perihilar ECC was associated with nonstandard arterial (p = 0.001) or portal vein reconstruction (p < 0.001) and Roux-en-Y choledochojejunostomy (p < 0.001). The incidence of early hepatic artery thromboses was similar (5.4% vs 7.6%; p = 0.54). Late hepatic artery (18.9% vs 4.1%; p < 0.001) and portal vein (37.8% vs 8.7%; p < 0.001) complication was more common in the perihilar ECC group.  Anastomotic biliary complications occurred in 39.2% vs 54.1% (p = 0.032) of patients. OS for perihilar ECC at 1, 5, 10 years was 84.9%, 66.5%, and 55.6%, respectively. Cancer recurred in 12.3%. Residual tumor on explant prognosticated inferior survival (hazard ratio 5.69; 95% CI, 1.97 to 16.35) and vascular and biliary complications did not. | 3 |
| 42 | Strijker M, Belkouz A, van der Geest LG, van Gulik TM, van Hooft JE, de Meijer VE, Haj Mohammad N, de Reuver PR, Verheij  J, de Vos-Geelen J, Wilmink JW, Groot Koerkamp B, Klumpen HJ, Besselink MG, Dutch Pancreatic Cancer Group. Treatment and survival of resected and unresected distal cholangiocarcinoma: a nationwide study. Acta Oncologica. 58(7):1048-1055, 2019 Jul. UI: 30907207 | Retrospective cohort study for Netherlands National Cancer Registry | 1,338 patients with distal ECC | To investigate the incidence, treatment and outcomes, including time trends and predictors for survival, in a nationwide cohort of distal ECC. | 1-, 3- and 5-year OS of 46%, 18%, and 11%. Incidence of DCC was 0.55-0.90 per 100.000 per year. Median OS was 10.4 months across all stages; 21.9 months for resected (n = 620, 46.3%), 6.7 months for unresected nonmetastatic (n = 445, 33.3%), and 3.6 months for metastatic DCC (n = 273, 20.4%) (p < .001). After resection, 30-day mortality was 4.8% and 90-day mortality 7.7%. Patients with metastatic DCC who received chemotherapy (n = 78, 28.6%) had a median OS of 8.2 versus 2.8 months for those not treated (p < .001). Over time, resection rates (53.6% to 61.7%, p = .008) and use of palliative chemotherapy in metastatic DCC (22.3% to 32.9%, p = .05) increased, without improvement in OS (10.3 vs 10.6 months, p = .55). Independent poor prognostic factors for OS in resected disease were increasing age, pT3/T4 stage, higher LN ratio, poor differentiation, and R1 resection. | 2 |
| 43 | Kato A, Shimizu H, Ohtsuka M, Yoshidome H, Yoshitomi H, Furukawa K, Takeuchi D, Takayashiki T, Kimura F, Miyazaki M. Surgical resection after downsizing chemotherapy for initially unresectable locally advanced biliary tract cancer: a retrospective single-center study. Annals of Surgical Oncology. 20(1):318-24, 2013 Jan. UI: 23149849 | Single institution retrospective study | 22 patients with initially unresectable locally advanced BTC who received neoadjuvant chemotherapy | To evaluate the effect of downsizing chemotherapy in patients with initially unresectable locally advanced BTC. | Tumor was significantly downsized in nine patients, and surgical resection was performed in 8 (36.4%) of 22 patients. Surgical resection resulted in R0 resection in four patients and R1 resection in four patients. Patients who underwent surgical resection had a significantly longer survival compared with those unable to undergo surgery. | 3 |
| 44 | Kuriyama N, Usui M, Gyoten K, Hayasaki A, Fujii T, Iizawa Y, Kato H, Murata Y, Tanemura A, Kishiwada M, Sakurai H, Mizuno S, Isaji S. Neoadjuvant chemotherapy followed by curative-intent surgery for perihilar cholangiocarcinoma based on its anatomical  resectability classification and lymph node status. BMC Cancer. 20(1):405, 2020 May 11.UI: 32393197 | Single institution retrospective study | 72 consecutive patients with perihilar ECC were classified into three groups: Resectable (29), Borderline resectable (23), and Locally advanced (20), based on the two factors of tumor vascular and biliary extension. Resectable with clinically LN metastasis, borderline resectable, and locally patients received neoadjuvant chemotherapy using gemcitabine plus S-1. | To clarify the long-term outcomes and validation of a new  anatomical resectability classification for patients with localized perihilar ECC and performed  neoadjuvant chemotherapy followed by curative-intent surgery based on its resectability classification and LN status to improve prognosis. | 47 (65.3%) received neoadjuvant chemotherapy: 8 resectable, 21 borderline resectable, 18 Iocally advanced. 59 (68.1%) underwent curative-intent surgery: 26 resectable, 17 borderline resectable, 6 Iocally advanced. 5-year DSS 31.5% (median: 33.0 months): resectable 50.3% (not reached), borderline resectable 30.0% (31.4 months, which were relatively stratified. Among 49 patients with resection, DSS 43.8% (57.0 months): resectable 57.6% (not reached), borderline resectable 41.0% (52.4 months) in BR, locally advanced 0% (49.4 months) compared to 23 patients without resection (17.2 months). Multivariate analysis identified preoperative high carcinoembryonic antigen levels (more than 8.5 ng/ml) and pT4 as independent poor prognostic factor of patients with resection. | 3 |
| 45 | Baltatzis M, Jegatheeswaran S, Siriwardena AK. Neoadjuvant chemoradiotherapy before resection of perihilar cholangiocarcinoma: A systematic review. Hepatobiliary & Pancreatic Diseases International. 19(2):103-108, 2020 Apr. UI: 32147487 | Systematic Review | Systematic review of MEDLINE and EMBASE databases identified 7 studies and 97 patients with hilar ECC and Klatskin tumors who received neoadjuvant chemotherapy or CRT. Data were extracted on demographic profile, disease staging, CRT protocols, complications and outcome. Risks of bias were assessed using Cochrane methodology. | To assess whether there is evidence to justify modern phase II studies of neoadjuvant CRT prior to resection of perihilar ECC. | Interval from completion of neoadjuvant treatment to surgery varied from 3 days to 6 months. Resection was by hepatectomy with three studies reporting an R0 rate of 100%, 24% and 63%, respectively. Three studies reported histopathological evidence of prior treatment response. There were two treatment related deaths at 90 days. Median survival was 19 (95% CI: 9.9-28) months and 5-year survival 20% suggesting potential benefits of treatment on both R0 rate and complete response in resected specimens. | 2 |
| 46 | Matsuyama R, Mori R, Ota Y, Homma Y, Yabusita Y, Hiratani S, Murakami T, Sawada Y, Miyake K, Shimizu Y, Kumamoto T, Endo I. Impact of Gemcitabine Plus S1 Neoadjuvant Chemotherapy on Borderline Resectable Perihilar Cholangiocarcinoma. Annals of Surgical Oncology. 2022 Jan 07.  UI: 34994885 | Therapeutic  Single arm non- randomized Phase II | 60 patients with borderline resectable perihilar cholangiocarcinoma received NAC (gemcitabine/S1) x 3 cycles every 21 days followed by surgery | To evaluate the efficacy and safety of NAC  gemcitabine/S-1 followed by definitive surgery | The overall control rate was  91.3%. MS for the entire cohort was 30.3 months. For all the patients, estimated 3-year OS 44.1%; 5-year OS 30.0%. Resection with curative intent was performed 43/60 patients (71%). R0 resection in 81% resected patients. 41% with Clavien-Dindo grade 3 complications or a higher morbidity. MS for resected patients 50.1 months vs. 14.8 months for unresected patients. Estimated 3-year OS for resected patients 55.8 months vs. 36.4 months for unresected patients. | 2 |
| 47 | Jung JH, Lee HJ, Lee HS, Jo JH, Cho IR, Chung MJ, Park JY, Park SW, Song SY, Bang S. Benefit of neoadjuvant concurrent chemoradiotherapy for locally advanced perihilar cholangiocarcinoma.  World Journal of Gastroenterology. 23(18):3301-3308, 2017 May 14. UI: 28566890 | Multi institution retrospective study | 57 patients who underwent surgical resection with or without neoadjuvant CRT for perihilar  ECC; 12 patients received neoadjuvant CRT and 45 patients did not. Patients with locally advanced perihilar ECC requiring neoadjuvant CRT were defined as follows: (1) a mass involving unilateral branches of the portal vein or hepatic artery with insufficient volume of the anticipated remnant lobe; or (2) an infiltrating mass in the main portal vein that was too long for reconstruction, identified at preoperative staging. | To clarify the role of neoadjuvant CRT followed by surgical resection for localized or locally advanced perihilar ECC | The median DFS for neoadjuvant and non-neoadjuvant CRT groups were 26.0 and 15.1 mo, respectively (P = 0.91). The median OS for neoadjuvant and non-neoadjuvant  CRT groups were 32.9 and 27.1 mo, respectively (P = 0.26). The CRT group showed a downstaging tendency compared to the non-CRT group as compared with the tumor stage confirmed by histological examination after surgery and the tumor stage confirmed by imaging test at the time of diagnosis (P = 0.01). | 3 |
| 48 | Kobayashi S, Tomokuni A, Gotoh K, Takahashi H, Akita H, Marubashi S, Yamada T, Teshima T, Fukui K, Fujiwara Y, Sakon M. A retrospective analysis of the clinical effects of neoadjuvant combination therapy with full-dose gemcitabine and radiation therapy in patients with biliary tract cancer. European Journal of Surgical Oncology. 43(4):763-771, 2017 Apr. UI: 28100416 | Single institution retrospective study | 27 patients with resectable BTC who received neoadjuvant CRT were compared to  79 patients who were treated without neoadjuvant therapy. Hemi-hepatectomy or pancreatoduodenectomy was planned for all of the patients in the study population. CT-based staging was used to adjust for the pre-treatment characteristics | To evaluate survival and the objective response to neoadjuvant CRT (50-60 Gy) with gemcitabine in patients with BTC | Multivariate analysis showed that the absence of arterial invasion on CT, the absence of LNs, and neoadjuvant CRT were independent prognostic factors. The 3-year DFS rates in patients treated with and without neoadjuvant therapy were 78% and 58%, respectively (P = 0.0263). The adjusted OS (determined by the inverse probability of treatment weighting method using the inverse propensity score) was improved by neoadjuvant CRT (P = 0.00187); the hazard ratio was 0.3505. | 3 |
| 49 | Kobayashi S, Tomokuni A, Gotoh K, Takahashi H, Akita H, Marubashi S, Yamada T, Teshima T, Nishiyama K, Yano M, Ohigashi  H, Ishikawa O, Sakon M. Evaluation of the safety and pathological effects of neoadjuvant full-dose gemcitabine combination radiation therapy in patients with biliary tract cancer. Cancer Chemotherapy & Pharmacology. 76(6):1191-8, 2015 Dec. UI: 26547917 | Multi institution prospective phase I trial | 25 patients with resectable BTC received neoadjuvant CRT with full dose gemcitabine (50 to 60Gy to the tumor and regional/paraaortic nodes; average 53.8Gy) | To evaluate the safety of neoadjuvant CRT with full dose gemcitabine in the treatment of BTC and to investigate the pathological effects of neoadjuvant CRT and its impact on survival. | Sixty percent of the patients underwent pancreatoduodenectomy, and 32 % underwent hemi-hepatectomy due to BTC (24) or gall bladder cancer (1). During neoadjuvant  CRT, 21 patients (84 %) suffered from adverse events. The common hematological adverse events were leukopenia (44 %) and thrombocytopenia (32 %). It was necessary to exchange the plastic biliary stent in 11 patients (44 %). An R0 resection was achieved in 96 % of the patients, with pathological LN metastasis noted in 16 %. Moderate or marked histological changes were noted in 32 % of the patients. The 3-year OS after was 74.6 % | 2 |
| 50 | Panjala C, Nguyen JH, Al-Hajjaj AN, Rosser BA, Nakhleh RE, Bridges MD, Ko SJ, Buskirk SJ, Kim GP, Harnois DM. Impact of neoadjuvant chemoradiation on the tumor burden before liver transplantation for unresectable  cholangiocarcinoma. Liver Transplantation. 18(5):594-601, 2012 May. UI: 22140024 | Single institution retrospective analysis | 22 patients with cholangiocarcinoma that underwent neoadjuvant CRT and LT | Top report single institution data for neoadjuvant CRT followed by LT for cholangiocarcinoma patients | Median OS of the cohort was 3.3 years. The 1-, 2-, and 3-year Kaplan-Meier survival probabilities were 90%, 70%, and 63%, respectively, whereas the historical 5-year survival rates were 0% to 18% for intrahepatic CC and 23% to 26% for ECC when patients underwent LT without neoadjuvant therapy. Disease recurrence was significantly associated with a larger residual tumor [6.3 versus 2.0 cm (mean values), P = 0.008] and with a shorter waiting time for LT after CRT [18 versus 56 days (mean values), P = 0.04]. | 3 |
| 51 | Gu J, Bai J, Shi X, Zhou J, Qiu Y, Wu Y, Jiang C, Sun X, Xu F, Zhang Y, Ding Y. Efficacy and safety of liver transplantation in patients with cholangiocarcinoma: a systematic review and meta-analysis. International Journal of Cancer. 130(9):2155-63, 2012 May 01. UI: 21387295 | Systematic review and meta-analysis | Systematic review of in PubMed/Medline, Embase and Cochrane electronic databases identified 14 clinical trials including 605 OLT for BTC | To evaluate the efficacy and safety of OLT in patients with  cholangiocarcinoma | The overall 1-, 3- and 5-year pooled survival rates were 0.73 [95% CI = 0.65-0.80], 0.42 (95% CI = 0.33-0.51) and 0.39 (95% CI = 0.28-0.51), respectively. Of note, preoperative adjuvant therapies resulted in 1-, 3- and 5-year pooled survival rates of 0.83 (95% CI = 0.57-0.98), 0.57 (95% CI = 0.18-0.92) and 0.65 (95% CI = 0.40-0.87). In addition, the overall pooled incidence of complications was 0.62 (95% CI = 0.44-0.78), among which that of neoadjuvant therapy followed by OLT group (0.58; 95% CI = 0.20-0.92) was relatively acceptable compared to those of OLT alone (0.61; 95% CI = 0.33-0.85) and LT with extended bile duct resection (0.78; 95% CI = 0.55-0.94). | M |
| **52** | De Vreede I, Steers JL, Burch PA, Rosen CB, Gunderson LL, Haddock MG, Burgart L, Gores GJ. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. Liver Transpl. 2000 May;6(3):309-16. doi: 10.1053/lv.2000.6143. PMID: 10827231. | Single institution prospective | 19 patients with unresectable cholangiocarcinoma above the cystic duct without intrahepatic or extrahepatic metastases treated with external-beam CRT plus bolus 5-FU, followed by brachytherapy with iridium and concomitant protracted venous infusion of 5-FU. 5-FU was then administered continuously through an ambulatory infusion pump until OLT. | To evaluate the effect of neoadjuvant chemoradiation therapy followed by orthotopic liver transplantation in patients with unresectable cholangiocarcinoma. | 19 patients were treated per protocol, of which 8 did not go on to OLT because of the presence of metastasis at the time of exploratory laparotomy (n = 6), subsequent development of malignant ascites (n = 1), or death from intrahepatic biliary sepsis (n = 1). Eleven patients completed the protocol with successful OLT. Except for 1 patient, all had early-stage disease (stages I and II) in the explanted liver. All patients who underwent OLT are alive, 3 patients are at risk at 12 months or less, and the remaining 8 patients have a median follow-up of 44 months (range, 17 to 83 months; 7 of 9 patients > 36 months). Only 1 patient developed tumor relapse. | 2 |
| **53** | Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Nyberg SL, Ishitani MB, Rosen CB. Liver transplantation for unresectable perihilar cholangiocarcinoma. Semin Liver Dis. 2004 May;24(2):201-7. doi: 10.1055/s-2004-828896. PMID: 15192792. | Single institution prospective | 56 patients with unresectable, stage I and II perihilar cholangiocarcinoma treated with neoadjuvant external beam irradiation, brachytherapy, and 5-fluorouracil and/or oral capecitabine prior to liver transplantation between1993-2003. | To evaluate the effect of neoadjuvant chemoradiation therapy followed by orthotopic liver transplantation in patients with unresectable cholangiocarcinoma. | Of the 56 patients treated per protocol, 4 patients died and 4 had disease progression prior to completion of neoadjuvant therapy. Forty-eight patients underwent operative staging and 14 had findings precluding transplantation. Twenty-eight patients underwent transplantation and 6 patients are awaiting transplantation. Three patients died from perioperative complications, and 4 developed recurrent disease 22 to 63 months after transplantation. Actuarial patient survival was 54% at 5 years for all 56 patients, 64% for 48 operatively staged patients, and 84% for 34 patients with negative staging operations. Actuarial survival was 88% at 1 year and 82 % 5 years after transplantation. | 2 |
| 54 | Duignan S, Maguire D, Ravichand CS, Geoghegan J, Hoti E, Fennelly D, Armstrong J, Rock K, Mohan H, Traynor O. Neoadjuvant chemoradiotherapy followed by liver transplantation for unresectable cholangiocarcinoma: a single-centre national experience. HPB. 16(1):91-8, 2014 Jan. UI: 23600750 | Single institution retrospective study | 27 patients with unresectable cholangiocarcinoma were treated with the neoadjuvant therapy and with possible orthotopic LT. Patients were given HDR ILBT, RT and 5-FU, followed by LT if progression free (20 patients). | To report single institution outcome data for patients undergoing neoadjuvant therapy followed by LT | 20 progression-free patients after neoadjuvant therapy underwent LT. Hospital mortality was 20%. Of the 16 patients who left hospital, survival rates were 94% and 61% at 1 and 4 years. 7 patients developed recurrent disease and died at intervals of 10-58 months after LT, whereas 9 were disease free with a median follow-up of 37 months (18-76). Predictors of disease recurrence were a tumor in explant specimen and high CA 19.9 levels. | 3 |
| 55 | Zaborowski A, Heneghan HM, Fiore B, Stafford A, Gallagher T, Geoghegan J, Maguire D, Hoti E. Neoadjuvant Chemoradiotherapy and Liver Transplantation for Unresectable Hilar Cholangiocarcinoma: The Irish Experience of the Mayo Protocol. Transplantation. 104(10):2097-2104, 2020 10. UI: 31972704 | Multi institution retrospective study | 27 patients commenced CRT, 11 were excluded due to disease progression and 26 proceeded to LT. 88% had underlying PSC | To report the experience of the Irish National Liver Transplant Programme with the Mayo neoadjuvant CRT and orthotopic liver  transplant protocol for unresectable hilar ECC | R0 and pathologic complete response rates were 96% and 62%, respectively. Medical OS  53 months and 1-, 3-, and 5-year OS was 81%, 69%, and 55%, respectively. The median OS of  patients achieving a pathologic complete response was 83.8 months compared with 20.9 months in the group with residual disease (P = 0.036). Six patients (23%) developed disease recurrence. Among the patients who developed metastaticdisease during neoadjuvant treatment, median survival was 10.5 months compared with 53 months in patients who proceeded to LT (P < 0.001). | 3 |
| 56 | Loveday BPT, Knox JJ, Dawson LA, Metser U, Brade A, Horgan AM, Gallinger S, Greig PD, Moulton CA. Neoadjuvant hyperfractionated chemoradiation and liver transplantation for unresectable perihilar cholangiocarcinoma in  Canada. Journal of Surgical Oncology. 117(2):213-219, 2018 Feb. UI: 29480952 | Prospective nonrandomized trial | 43 patients <=65 years, brush biopsy-proven unresectable perihlar ECC <3.5 cm diameter received CRT with Capecitabine. Following surgical staging, patients received maintenance Cisplatin and Gemcitabine until transplant or progression. Time to event analyses were performed from start of neoadjuvant therapy. | To determine the dropout rate and survival of patients who entered  a national tri-modality protocol of neoadjuvant CRT followed by LT in patients with unresectable perhilar ECC | Of 43 patients screened, 18 started treatment; median age 53.9 (26.7-62.8) years, tumor diameter 2.7 (2.0-3.4) cm. 11/18 dropped out due to metastatic disease identified during CRT (n = 2), surgical staging (n = 6), or maintenance chemotherapy (n = 3). 6 underwent LT. Median follow up was 17.6 (4.9-57.7) months and OS 16.4 months. 1- and 2-year OS 70.6% and 35.3%, respectively. 1- and 2-year post transplant survival was 83.3% and 55.6%. Median PFS was 11.5 months. | 2 |
| 57 | Cambridge WA, Fairfield C, Powell JJ, Harrison EM, Soreide K, Wigmore SJ, Guest RV. Meta-analysis and Meta-regression of Survival After Liver Transplantation for Unresectable Perihilar Cholangiocarcinoma. Annals of Surgery. 273(2):240-250, 2021 02 01. UI: 32097164 | Systematic review and Meta-analysis | Systematic review of MEDLINE, EMBASE, Scopus, and Web of Science databases identified 20 studies and 428 patients eligible for analysis. No RCTs were retrieved; the majority of studies were noncomparative cohort studies. Meta-regression was used to evaluate perihilar ECC as a confounder affecting survival. | To systematically review studies reporting survival data following neoadjuvant CRT and orthotopic  LT for unresectable perihilar ECC | The pooled 1, 3-, and 5-year overall survival rates following LT without neoadjuvant therapy were 71.2% (95% CI 62.2%-79.4%), 48.0% (95% CI 35.0%-60.9%), and 31.6% (95% CI 23.1%-40.7%). These improved to 82.8% (95% CI 73.0%-90.8%), 65.5% (95% CI 48.7%-80.5%), and 65.1% (95% CI 55.1%-74.5%) if neoadjuvant CRT was completed. Pooled recurrence after 3 years was 24.1% (95% CI 17.9%-30.9%) with neoadjuvant CRT, 51.7% (95% CI 33.8%-69.4%) without. | M |
| **58** | Luterstein E, Cao M, Lamb J, Raldow A, Low D, Steinberg M, Lee P. Clinical Outcomes Using Magnetic Resonance-Guided Stereotactic Body Radiation Therapy in Patients With Locally Advanced Cholangiocarcinoma. Adv Radiat Oncol. 5 (2):189-195, 2019 Oct. doi: 10.1016/j.adro.2019.09.008 | Single institution retrospective study | 17 consecutive patients with locally advanced cholangiocarcinoma (12 with ECC) treated with SBRT (40Gy 5 fractions) using magnetic resonance guidance | To report outcomes of patients with locally advanced cholangiocarcinoma treated with SBRT using magnetic resonance guidance | Median OS 18.5 months, with a 1-year OS of 76% and 2-year OS of 46.1%. Three of the 17 patients progressed locally, yielding a 1-year local control of 85.6% and a 2-year local control of 73.3%. Although 12 of 17 patients experienced an acute grade 1 toxicity, none experienced acute grade 2 toxicities. One patient had an acute grade 3 duodenal ulcer with perforation (6%), and one patient had a late radiation-related toxicity grade 2 gastritis/colitis. | 3 |
| **59** | Sandler K, Veruttipong D, Agopian V, Finn R, Hong J, Kaldas FM, Sadeghi S, Busuttil R, Lee P. Stereotactic body radiotherapy (SBRT) for locally advanced extrahepatic and intrahepatic cholangiocarcinoma. Adv Radiat Oncol. 9 (4):237-243, 2016 Oct. doi: 10.1016/j.adro.2016.10.008 | Single institution retrospective study | 31 consecutive patients with unresectable extrahepatic (n = 25) or intrahepatic (n = 6) cholangiocarcinoma were treated with SBRT; 4 patients underwent liver transplantation, and 1 underwent resection. SBRT was delivered in 5 fractions with a median dose of 40 Gy – 5 fractions | To report outcomes for patients with unresectable cholangiocarcinoma treated with SBRT followed by OLT or surgery | The median follow-up time was 11.5 months. The 1- and 2-year OS rates were 59% and 33%, respectively, with a median survival of 15.7 months. The 1- and 2-year freedom from progression was 67% and 34%, respectively. Median time to progression was 16.8 months. Nine patients had local failure. The actuarial 1- and 2-year local control rates were 78% and 47%, respectively. Among patients who also had OLT, the median OS was 31.3 months. Twenty-four patients (77%) experienced some form of acute grade 1-2 toxicity, most commonly fatigue or pain. Five patients (16%) experienced grade ≥3 toxicity. | 3 |
| 60 | Cereda S, Belli C, Reni M. Adjuvant treatment in biliary tract cancer: To treat or not to treat? World J Gastroenterol. 2012 Jun 7; 18(21):2591-2596 | Review article | Review of literature evaluating various adjuvant therapies for resected biliary cancers | To review literature evaluating the role of adjuvant therapy for resected biliary cancers | Although resection is identified as the most effective and the only potentially curative treatment, there is no consensus on the impact of adjuvant chemotherapy and/or radiotherapy on the high incidence of disease recurrence and on survival. This is mainly due to the rarity of this disease and the consequent difficulty in performing randomized trials. The only two prospectively controlled trials concluded that adjuvant chemotherapy did not improve survival. Most of the retrospective trials, which had limited sample size and included heterogeneous patients population and non-standardized therapies, suggested a marginal benefit of chemoradiotherapy in reducing locoregional recurrence and an uncertain impact on survival. Well-designed multi-institutional randomized trials are necessary to clarify the role of adjuvant therapy. Two ongoing phase III trials may provide relevant information. | 4 |
| 61 | Im JH, Choi GH, Lee WJ, Han DH, Park SW, Bang S, Choi HJ, Seong J. Adjuvant radiotherapy and chemotherapy offer a recurrence and survival benefit in patients with resected perihilar cholangiocarcinoma. Journal of Cancer Research & Clinical Oncology. 147(8):2435-2445, 2021 Aug. UI: 33471185 | Single institution retrospective study | 196 patients with perihilar ECC underwent curative resection. Patients were divided into 4 groups according to adjuvant treatment type: surgery alone (90), surgery + AC (67), surgery + RT radiotherapy (18), and surgery + CRT (21). | To investigate the benefits of various adjuvant treatments for  patients with resected perihilar ECC | 5-year OS 32%. In multivariate analysis, AC and CRT were significant prognostic factors for OS. In subgroup analyses of the R1 resection patients, the CRT group showed better OS than the surgery alone group (p < 0.05). In subgroup analyses of the stage III-IVA patients with a negative resection margin, the AC and CRT groups showed superior OS than surgery alone (p < 0.05). | 3 |
| 62 | Kang MJ, Jang JY, Chang J, Shin YC, Lee D, Kim HB, Kim SW. Actual Long-Term Survival Outcome of 403 Consecutive Patients with Hilar Cholangiocarcinoma. World Journal of Surgery. 40(10):2451-9, 2016 Oct. UI: 27206402 | Single institution retrospective cohort study | 403 consecutive patients with hilar ECC with at least 5-year follow up following surgery. R0 resection rate was 41.2 and 63.8 % among intended curative resection. Adjuvant therapy 48.8 % after curative surgery. | To explore actual long-term survival outcome of hilar ECC after surgical treatment, and to investigate the characteristics of patients with actual long-term survival. | Actual 5-year OS 18.9, and 30.1 % after R0 resection. Actual 5-year DFS 25.8 % after resection. Adjuvant treatment improved prognosis in patients with positive LNs (median OS 21.9 vs. 11.5 months, p = 0.003). Overall RR 55.0 %; DM (39.7 %); LRR (20.8 %). LN metastasis (p = 0.021) and poor histologic grade (p < 0.001) were independent prognostic factors after curative resection. Patients who survived more than 5 years had less LN metastasis (p = 0.025), poor histologic differentiation (p = 0.010), R2 resection (p = 0.040), and recurrence (p < 0.001). | 3 |
| 63 | Nassour I, Mokdad AA, Porembka MR, Choti MA, Polanco PM, Mansour JC, Minter RM, Wang SC, Yopp AC. Adjuvant Therapy Is Associated With Improved Survival in Resected Perihilar Cholangiocarcinoma: A Propensity Matched Study. Annals of Surgical Oncology. 25(5):1193-1201, 2018 May. UI: 29488187 | NCDB retrospective matched study | 1,846 patients who underwent resection for perihilar ECC and received either adjuvant therapy (793; 43%) or observation (1,053; 57%). Patients who received adjuvant therapy were more likely to be younger, have a higher rate of private insurance, have higher T and N stage tumors, and were more likely to have positive resection margins. After 1:1 propensity score matching, 577 observation group patients were compared with 577 adjuvant therapy group patients. | To compared outcomes for patients receiving adjuvant therapy or observation following resection for perihilar ECC | The adjuvant therapy cohort was associated with better overall survival compared with the observation cohort (hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.64-0.83). The median survival was 29.5 and 23.3 months for the adjuvant therapy and observation groups, respectively (P < 0.01). Subgroup analysis demonstrated a survival advantage for adjuvant therapy in disease with positive resection margins (HR 0.53; 95% CI 0.42-0.67). | 2 |
| 64 | Yang H, Zhou J, Wei X, Wang F, Zhao H, Li E. Survival outcomes and prognostic factors of extrahepatic cholangiocarcinoma patients following surgical resection: Adjuvant therapy is a favorable prognostic factor. Molecular & Clinical Oncology. 2(6):1069-1075, 2014 Nov. UI: 25279199 | Single institution retrospective study | 105 patients who underwent surgery for ECC were identified, 32 received adjuvant therapy. 18 received at least 2 cycles combination AC, including gemcitabine/cisplatin (n=8), gemcitabine/oxaliplatin (n=6) and gemcitabine/capecitabine (n=4). 11 received postoperative RT (45–50 Gy, 5 fractions per week, with 1.8 Gy per fraction, including the primary tumor bed as well as the regional LNs). 2 received postoperative RT (45 Gy, followed by single-agent capecitabine). 1 received CRT, (45 Gy/5-FU leucovorin). Patients were stratified into seven risk subgroups and the survival rates were compared within each subgroup between patients who received adjuvant therapy and those who did not. | To investigate prognostic factors for ECC following surgical resection and evaluate the effects of postoperative adjuvant therapy on OS. | Entire cohort MS = 17.6 months, with 1- and 3-year survival rates of 67.9 and 19.5%. On univariate analysis, preoperative cholangitis, non-R0 surgical margins, poor differentiation grade, stage 3/4 and nodal metastasis were identified as adverse prognostic factors. Adjuvant therapy was not significantly associated with improved OS. However, the subgroup analysis revealed that the effect of adjuvant therapy was significant only in the lymphatic metastasis group (MS 21.6 vs. 10.4 months; and 3-year OS, 16.6 vs. 0%, respectively; P=0.02). The survival curves were significantly different only for node-positive patients. The COX regression model identified nodal metastasis, surgical margins and adjuvant therapy as independent prognostic factors for ECC. A negative resection margin may reduce the mortality rate following surgery by 47%. By contrast, LN metastasis was associated with a 2.18-fold higher mortality rate for ECC patients. Postoperative adjuvant therapy contributed to a 0.45-fold mortality rate compared to non-adjuvant ECC patients. | 3 |
| 65 | McNamara MG, Walter T, Horgan AM, Amir E, Cleary S, McKeever EL, Min T, Wallace E, Hedley D, Krzyzanowska M, Moore M,  Gallinger S, Greig P, Serra S, Dawson LA, Knox JJ. Outcome of adjuvant therapy in biliary tract cancers. American Journal of Clinical Oncology. 38(4):382-7, 2015 Aug. UI: 24572429 | Single institution retrospective study | 296 patients who underwent definitive surgery for BTC. Negative or microscopically positive resections were reported in 42% and 14%, respectively, with 44% not reported. LN positivity was reported in 35% patients. Adjuvant therapy was given in 28% with 59% receiving AC and 35% CRT/RT | To evaluate the use and effectiveness of adjuvant therapy (AC +/-RT) in a single institution series. | Disease recurred in 60% patients. Adjuvant therapy was associated with significantly improved OS (HR, 0.41; P=0.02). Compared with R0resection, patients with R1 resection derived significantly increased benefit from adjuvant therapy (P for difference 0.02). In the LN positive population (n=103), adjuvant therapy was associated with significantly improved OS (HR 0.60; 95% CI, 0.38-0.95; P=0.03). | 3 |
| 66 | Krasnick BA, Jin LX, Davidson JT 4th, Sanford DE, Ethun CG, Pawlik TM, Poultsides GA, Tran T, Idrees K, Hawkins WG, Chapman WC, Doyle MBM, Weber SM, Strasberg SM, Salem A, Martin RCG, Isom CA, Scoggins C, Schmidt CR, Shen P, Beal E, Hatzaras I, Shenoy R, Maithel SK, Fields RC. Adjuvant therapy is associated with improved survival after curative resection for hilar cholangiocarcinoma: A multi-institution analysis from the U.S. extrahepatic biliary malignancy consortium. Journal of Surgical Oncology. 117(3):363-371, 2018 Mar. UI: 29284072 | Multi institution propensity matched retrospective study | 249 patients who underwent curative resection for hilar ECC with or without adjuvant therapy. Patients who received adjuvant therapy and those who did not had similar demographic and preoperative features. | To analyze the impact of adjuvant therapy on OS and DFS in patients undergoing curative resection for hilar ECC | In a multivariate Cox regression analysis, adjuvant therapy was associated with improved OS (HR 0.58, P = 0.013), and this was maintained in a propensity matched analysis (HR 0.66, P =  0.033). The protective effect of adjuvant therapy remained significant when node negative patients were excluded (HR 0.28, P = 0.001), while it disappeared (HR 0.76, P = 0.260) when node positive patients were excluded. | 2 |
| 67 | Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. [Review] Journal of Clinical Oncology. 30(16):1934-40, 2012 Jun 01. UI: 22529261 | Meta-analysis | 20 studies involving 6,712 patients with BTC undergoing resection with and without adjuvant therapy | To determine the impact of adjuvant therapy on survival. In patient with BTC undergoing surgery | There was a nonsignificant improvement in OS with any adjuvant therapy compared with surgery alone (pooled OR, 0.74; P = .06). There was no difference between gallbladder and bile duct tumors (P = .68). The association was significant when the two registry analyses were excluded. Those receiving AC or CRT derived statistically greater benefit than RT alone (OR, 0.39, 0.61, and 0.98, respectively; P = .02). The greatest benefit for adjuvant therapy was in those with LN-positive disease (OR, 0.49; P = .004) and R1 disease (OR, 0.36; P = .002). | M |
| 68 | Rangarajan K, Simmons G, Manas D, Malik H, Hamady ZZ. Systemic adjuvant chemotherapy for cholangiocarcinoma surgery: A systematic review and meta-analysis. European Journal of Surgical Oncology. 46(4 Pt A):684-693, 2020 04. UI: 31761507 | Systematic review and meta-analysis | Search of MEDLINE, EMBASE, Cochrane and PubMed databases identified 35 clinical trials including 42,917 patients with ECC and gall bladder cancer patients treated with or without AC | To delineate the effect of adjuvant therapy on overall survival. | There was a significant improvement in OS with any adjuvant therapy after surgery compared with surgery only (HR 0.74; 95% CI, 0.67 to 0.83; P < 0.001). There was a significant benefit for adjuvant therapy in those with margin positive surgery (RR, 0.83; 95% CI, 0.77 to 0.91; P <  0.001) and node-positive disease (RR 0.82; 95% CI 0.76 to 0.89; P < 0.001) | M |
| 69 | Chen X, Meng F, Xiong H, Zou Y.  Adjuvant Therapy for Resectable Biliary Tract Cancer: A Bayesian Network Analysis. Frontiers in Oncology. 11:600027, 2021. UI: 33777744 | Systematic review | Systematic search of PubMed, Cochrane Library, Embase of articles regarding BTC therapy approaches. Pooled analysis included 22 studies and a total of 14,646 patients who received adjuvant therapy following resection for BTC were included | To identify the optimal adjuvant therapy for BTC patients | Adjuvant gemcitabine was considered as the optimal adjuvant therapy for BTC for 5-year OS compared with CRT; HR = 0.59; 95% CI = 0.34-0.97), observation (OB; HR = 0.49; 95% CI = 0.33-0.73), and RT alone (RT; HR = 0.40; 95% CI = 0.22-0.71). Additionally, 5-FU exhibited improved efficacy compared with RT alone (HR = 0.52; 95% CI = 0.29-0.91) and OB (HR = 0.63; 95% CI = 0.43-0.92). 5-FU was more effective than gemcitabine (HR = 1.29). CRT and RT alone prolonged positive resection margin OS (HR = 0.69; 95% CI = 0.49-1.00) and positive LNs OS (HR = 0.22; 95% CI = 0.074-0.66) in BTC patients. DFS and 1-year OS were not statistically significant among different therapeutic interventions. | 2 |
| 70 | Choi HS, Kang KM, Jeong BK, Jeong H, Lee YH, Ha IB, Kim TG, Song JH. Patterns of failure after resection of extrahepatic bile duct cancer: implications for adjuvant radiotherapy indication and treatment volumes. Radiation Oncology. 13(1):85, 2018 May 08. UI: 29739420 | Multi institution retrospective study | 93 patients with ECC who underwent resection without adjuvant RT | To evaluate the indication and treatment volume for adjuvant RT in ECC patients by identifying the prognostic factors for LRR, and analyze the patterns of LRR | 38 (40.9%) patients experienced LRR; With regards to LR recurrence, close or positive resection margin status (p < 0.001) remained statistically significant in the multivariable analysis. The most common LR recurrence sites were the tumor bed (18.3%), and LN stations No. 8 (14.1%), No. 9 (12.7%), No. 12 (12.7%), No. 13 (5.6%), No. 14 (21.1%), No. 16 (14.1%), and No.17 (1.4%). | 3 |
| 71 | Kim MY, Kim JH, Kim Y, Byun SJ. Postoperative radiotherapy appeared to improve the disease-free survival rate of patients with extrahepatic bile duct cancer at high risk of loco-regional recurrence. Radiation Oncology Journal. 34(4):297-304, 2016 Dec. UI: 27951624 | Multi institution retrospective study | 52 patients with ECC underwent surgical resection. Of these, 33 patients did not receive postoperative RT (group I), and 19 patients did (group II). R1 resection was significantly more frequent in group II. The median radiation dose was 50.4 Gy. | To investigate the outcomes of postoperative RT, in patients with ECC by comparing the survival rate between patients undergoing surgery alone or surgery plus postoperative RT, and to identify the prognostic factors affecting survival. | The 3-year OS for group I and group II was 38% and 56%, respectively (p = 0.274). The 3-year DFS rate for group I and group II was 20% and 31%, respectively (p = 0.049), and the 3-year LR DFS) rates were 19% and 58%, respectively (p = 0.002). Multivariate analyses showed that postoperative RT and lymphovascular invasion were independent prognostic factors for DFS and LRFS. Overall, 42 patients (80%) experienced treatment failure. DM was the predominant pattern of failure in group II. | 3 |
| 72 | Kim YJ, Kim K, Min SK, Nam EM. Role of adjuvant radiotherapy for localized extrahepatic bile duct cancer. British Journal of Radiology. 90(1071):20160807, 2017 Mar. UI: 28118028 | Single institution retrospective study | 59 patients who underwent resection for operable ECC included; 36 observation; 23 adjuvant RT were compared. Microscopic residual disease (R1) was in 9 (25%) patients and 5 (22%) patients, and macroscopic residual disease (R2) was in 2 (6%) patients and 6 (26%) patients in the observation and RT groups, respectively. Adjuvant RT was delivered to the tumor bed and regional LNs up to 50.4 Gy (range, 45-61 Gy). | To evaluate the benefit of adjuvant RT after surgical resection for ECC | LR in 10 (28%) and 2 (9%) in the observation and RT groups, respectively. On univariate analysis, the 5-year LR PFS 50% in the observation group and 54% in the RT group (p = 0.401). The 5-year OS 29.3% in the observation group and 26.3% in the RT group (p = 0.602). On multivariable analysis, adjuvant RT significantly improved LR PFS, HR, 0.310; 95% CI, 0.100-0.963; p = 0.043] and had a trend towards increased OS (HR, 0.491; 95% CI, 0.219-1.102; p = 0.085). Resection margin status was also correlated with LR PFS (HR for R1 6.134, 95% CI 2.051-18.344; and HR for R2 18.551, 95% CI 3.680-93.520; p < 0.001) and OS (HR for R1 1.816, 95% CI 0.853-3.867; and HR for R2 3.564, 95% CI 1.175-10.809; p = 0.054). | 3 |
| 73 | Kim YS, Hwang IG, Park SE, Go SI, Kang JH, Park I, Oh SY, Ji JH, Song HN, Park SH, Kim ST, Park JO. Role of adjuvant therapy after R0 resection for patients with distal cholangiocarcinoma. Cancer Chemotherapy & Pharmacology. 77(5):979-85, 2016 05. UI: 27017615 | Multi institutional retrospective study | 56 patients who underwent R0 resection for distal ECC. Adjuvant therapy consisted of AC (27), CRT (20), RT (9) | To analyze the role of adjuvant therapy in R0-resected distal ECC | Patients with advanced TNM stage (P < 0.001), T3/T4 disease (P = 0.009), positive LNs; P = 0.052), and elevated baseline CA19-9 (P = 0.071) were more likely to receive adjuvant therapy. The effect of adjuvant therapy varied according to treatment modality. A multivariable analysis showed a significant improvement in OS after AC HR 0.21, 95 % CI 0.08-0.53, P = 0.001] and CRT (HR 0.25, 95 % CI 0.08-0.83, P = 0.024). However, RT alone was associated with shorter OS (HR 2.38, P = 0.040), along with T3/T4 disease (HR 2.12, P = 0.012) and positive LN (HR 2.30, P = 0.008). DFS benefited from adjuvant treatment with AC (HR 0.34, P = 0.002) and CRT (HR 0.33, P = 0.004), but not with RT alone (HR 1.42, P = 0.361). In the subset analysis according to LN status, adjuvant therapy not including RT alone was associated with a significant OS and RFS advantage in both LN-negative and LN-positive patients. | 3 |
| 74 | Kamarajah SK, Bednar F, Cho CS, Nathan H. Survival benefit with adjuvant radiotherapy after resection of distal cholangiocarcinoma: A propensity-matched National Cancer Database analysis. Cancer. 127(8):1266-1274, 2021 04 15. UI: 33320344 | NCDB review | After propensity score matching of patients who underwent resection for distal ECC – of the 2,162 (34%) adjuvant RT and 4,155 (66%) no RT patients, 1,509 adjuvant RT and 1,509 no RT patients remained in the cohort after matching. | To evaluate the benefit of adjuvant RT following resection of distal ECC | After matching, adjuvant RT was associated with improved median OS (29.3 vs 26.8 months; P < .001), which remained after multivariable adjustment (HR, 0.86; 95% CI, 0.80-0.93; P < .001). Multivariable interaction analyses showed this benefit was seen irrespective of nodal status (N0: HR, 0.77; 95% CI, 0.66-0.89; P < .001; N+: HR, 0.79; 95% CI, 0.71-0.89; P < .001) and margin status (R0: HR, 0.58; 95% CI, 0.50-0.67; P <  .001; R1: HR, 0.87; 95% CI, 0.78-0.96; P = .007). Stratified analyses by nodal and margin status demonstrated consistent results. | 2 |
| 75 | Leng KM, Liu YP, Wang ZD, Zhong XY, Liao GQ, Kang PC, Cui YF, Jiang XM. Results of adjuvant radiation therapy for locoregional perihilar cholangiocarcinoma after curative intent resection. OncoTargets and therapy. 10:2257-2266, 2017. UI: 28461760 | SEER registry retrospective propensity score matching study | 1,917 patients had surgical resection for perihilar ECC, 762 (39.7%) received adjuvant RT. | To define the role of adjuvant RT for patients with curative intent  resection of perihilar ECC | Median OS for patients receiving adjuvant RT compared with those undergoing surgery alone was 23 versus 22 months (P=0.651). Patients who received adjuvant RT were younger (65 vs 68 years, P<0.001), had more regional diseases (86.0% vs 76.7%, P<0.001), and had more positive LNs (43.8% vs 32.2%, P<0.001). In the matched population, adjuvant RT did not show better OS (22 vs 23 months, P=0.978) or cancer-specific survival (CSS) (17 vs 18 months, P=0.554). | 2 |
| 76 | Matsuda T, Fujita H, Harada N, Kunimoto Y, Tanaka T, Kimura T, Kitaoka H, Asano E, Hosono M, Hayashi T, Ogino K. Impact of adjuvant radiation therapy for microscopic residual tumor after resection of extrahepatic bile duct cancer. American Journal of Clinical Oncology. 36(5):461-5, 2013 Oct. UI: 22706178 | Single institution retrospective study | 52 patients with ECC underwent surgery, 36 were subjected to a retrospective analysis. 11 patients received adjuvant RT after resection, which included 9 patients with R1 resection and 2 with para-aortic LN metastasis. Their oncological outcomes were analyzed and compared with those of the 25 patients with R0 resection who did not receive adjuvant RT | To examine the effect of adjuvant RT in ECC patients with microscopic-positive resection margins (R1 resection) | Patients in the surgery + RT group had significantly more advanced disease than those in the surgery alone group. However, there was no significant difference in DFS or OS between the 2 groups. Median survival times for the surgery + RT and the surgery alone groups were 44 and 47 months, respectively, whereas the 5-year survival rates were 38.9% and 46%, respectively (P=0.707). LRR was less frequent in the surgery + RT group as compared with the surgery alone group, but the incidence of distant metastasis was unaffected by the adjuvant RT. | 3 |
| 77 | Ren B, Guo Q, Yang Y, Liu L, Wei S, Chen W, Tian Y. A meta-analysis of the efficacy of postoperative adjuvant radiotherapy versus no radiotherapy for extrahepatic  cholangiocarcinoma and gallbladder carcinoma. Radiation Oncology. 15(1):15, 2020 Jan 15. UI: 31941520 | Meta-analysis | Search of PubMed, EMBASE, Cochrane Library and CNKI databases identified 21 clinical trials including 1,465 ECC and gall bladder cancer patients who received adjuvant RT versus no RT | To determine the impact of adjuvant RT on survival in resected ECC and gall bladder cancer patients | The 5-year OS was higher in the RT group than in the no RT group (OR = 0.63; 95% CI = 0.50-0.81, p = 0.0002). The 5-year OS was significantly higher for those with LN-positive disease (OR = 0.15; 95% CI 0.07-0.35; p < 0.00001) and margin-positive disease (OR = 0.40; 95% CI 0.19-0.85; p = 0.02) in the RT group than in the no RT group. Adjuvant RT associate with a sno-significant trend in 5-year OS of patients with margin-negative disease (OR = 0.57, 95% CI 0.30-1.07, p = 0.08). LR was significantly lower in the RT group than in the no RT group (OR = 0.54; 95% CI = 0.38-0.76, p = 0.0004), and there was no significant difference in DM between the two groups (OR = 1.33; 95% CI = 0.95-1.87, p = 0.10). | M |
| 78 | Shi XQ, Zhang JY, Tian H, Tang LN, Li AL. Role of adjuvant (chemo)radiotherapy for resected extrahepatic cholangiocarcinoma: a meta-analysis. Journal of Zhejiang University SCIENCE B. 21(7):549-559, 2020 Jul. UI: 32633109 | Meta-analysis | PubMed, Embase, and ClinicalTrials databases identified 8 studies including 685 patients with ECC who underwent surgery followed by adjuvant RT or CRT and analyzed OS, DFS, and LR free survival were included. Estimated hazard ratios (HRs) were calculated for OS, DFS, and LR free survival | To investigate the role of adjuvant RT or CRT following resection for ECC | Adjuvant RT/CRT significantly improved OS (HR 0.69, 95% confidence interval (CI) 0.48-0.97, P=0.03), DFS (HR 0.60, 95% CI 0.47-0.76, P<0.0001), and LR free survival (HR 0.27, 95% CI 0.17-0.41, P<0.00001) of ECC overall. In subgroups, patients with microscopically positive resection margin (R1) could achieve a benefit from RT/CRT (HR 0.44, 95% CI 0.27-0.72, P=0.001). No statistically OS difference was observed in negative resection margin (R0) subgroup (HR 0.98, 95% CI 0.30-3.19, P=0.98). Significant OS benefit was found in patients who received concurrent CRT (HR 0.40, 95% CI 0.26-0.62, P<0.0001), while the result of RT without chemotherapy showed no significant benefit (HR 1.14, 95% CI 0.29-4.50, P=0.85). In the distal  cholangiocarcinoma subgroup, no significant difference was seen when CRT and RT were included (HR 0.61, 95% CI 0.14-2.72, P=0.52), but a significant difference was seen when analyzing the concurrent CRT only (HR 0.29, 95% CI  0.13-0.64, P=0.002). | M |
| 79 | Kim K, Yu JI, Jung W, Kim TH, Seong J, Kim WC, Choi JH, Park Y, Jeong BK, Kim BH, Kim TG, Kim JH, Park HJ, Shin HS, Im JH, Heo JS, Park JO, Jang JY, Oh DY, Woo SM, Lee WJ, Chie EK. Role of adjuvant radiotherapy in extrahepatic bile duct cancer: A multicenter retrospective study (Korean Radiation Oncology Group 18-14). European Journal of Cancer. 157:31-39, 2021 11. UI: 34474218 | Multi institution prospective nonrandomized study | 1,475 patients from 14 institutions with ECC who underwent curative resection were accrued: 959 did not receive adjuvant RT and  516 had adjuvant RT with or without chemotherapy. Nodal involvement in 482 (32.7%); resection margin involved in 293 (19.9%). Patients who received adjuvant RT had more patients with proximal tumors, advanced tumors, nodal involvement, perineural invasion, and involved resection margin (all p < 0.001). | To evaluate the role of adjuvant RT after curative resection in patients with ECC | 211 LRR, 307 DM and 322 LRR+DM. On multivariate analysis adjuvant RT was associated with improved OS (HR, 0.74; 95% CI, 0.63-0.86; p < 0.001). When the adjuvant RT group was separated into RT alone, CRT, and CRT followed by chemotherapy, the greatest benefit was observed in patients treated with CRT followed by chemotherapy (HR, 0.52; 95% CI, 0.41-0.68). | 2 |
| 80 | Chang WI, Kim BH, Kang HC, Kim K, Lee KH, Oh DY, Kim H, Kwon W, Jang JY, Chie EK. The Role of Adjuvant Chemoradiotherapy in Nonhilar Extrahepatic Bile Duct Cancer: A Long-Term Single-Institution Analysis. International Journal of Radiation Oncology, Biology, Physics. 111(2):395-404, 2021 10 01. UI: 34029643 | Single institution retrospective review | 383 consecutive patients who underwent surgery for nonhilar ECC. Univariate and multivariate analyses were conducted to identify prognostic factors for  LRR-free survival, DM-free survival, DFS and OS. Subgroup analyses were performed to further identify the role of adjuvant CRT. | To identify the role of adjuvant CRT in nonhilar ECC patients after radical surgery. | 3-year LRRFS, DMFS, DFS, and OS were 63.4%, 59.0%, 53.2%, and 67.5%, respectively. In multivariate analysis, adjuvant CRT was an independent prognostic factor for LRRFS, DMFS, DFS, and OS (P < .05). For patients with nodal involvement, pT3 stage, tumor size >= 5 cm, poorly differentiated tumor, and R1 resection, adjuvant CRT significantly improved DFS (P < .05). | 3 |
| 81 | Kim H, Heo MH, Kim JY. Comparison of the effects of adjuvant concurrent chemoradiotherapy and chemotherapy for resected biliary tract cancer. BMC Gastroenterology. 20(1):20, 2020 Jan 28. UI: 31992208 | Single institution retrospective study | 92 patients who had curatively resected BTC and had received adjuvant CRT or chemotherapy | To compare the effects of adjuvant CRT and AC on resected BTC. | Median DFS for the adjuvant CRT and AC groups were 13.8 and 11.2 months (p = 0.014), respectively. Median OS for the CRT and AC groups were 30.1 and 26.0 months (p = 0.222), respectively. CRT had significantly better RFS and numerically higher OS than did AC. For subgroups with no LN involvement (DFS p = 0.006, OS p = 0.420) or negative resection margins (DFS p = 0.042, OS p =0.098), adjuvant CRT led to significantly longer RFS and numerically higher OS than did chemotherapy. For multivariate analysis, the pattern of adjuvant treatment (AC vs. CRT, p = 0.004, HR 2.351), histologic grade (poor vs. well, p = 0.023, HR 4.793), and LN involvement (p = 0.028, HR 1.912) were the significant prognostic factors for DFS. | 3 |
| 82 | Dover LL, Oster RA, McDonald AM, DuBay DA, Wang TN, Jacob R. Impact of adjuvant chemoradiation on survival in patients with resectable cholangiocarcinoma. HPB. 18(10):843-850, 2016 10. UI: 27542590 | Single institution retrospective study | 95 patients with cholangiocarcinoma following curative resection. 23 (24%) received adjuvant CRT (45Gy to tumor bed and elective nodes) with concurrent 5-FU based chemotherapy and 72 (76%) were observed | To evaluate impact of adjuvant CRT on survival in patients following definitive resection of cholangiocarcinoma | For those receiving adjuvant CRT, median OS was 30.2 months compared with 26.3 months for those observed (p = 0.0695). In a multivariable model controlling for other prognostic factors, adjuvant CRT was associated with improved DFS (HR 0.50, p = 0.03) and OS (HR 0.37, p = 0.004). In multivariable models stratified by margin status, adjuvant CRT was associated with improved overall survival following both margin-negative (HR 0.34, p = 0.035) and margin-positive (HR 0.15, p = 0.003) resections. | 3 |
| 83 | Hoehn RS, Wima K, Ertel AE, Meier A, Ahmad SA, Shah SA, Abbott DE. Adjuvant Chemotherapy and Radiation Therapy is Associated with Improved Survival for Patients with Extrahepatic  Cholangiocarcinoma. Annals of Surgical Oncology. 22 Suppl 3:S1133-9, 2015 Dec. UI: 25976862 | American College of Surgeons Database retrospective study | Patients with pathologic stage I-III who underwent resection for ECC. Three groups were compared: surgery only (5,766), surgery plus AC (450), and surgery plus adjuvant CRT (1,918) | To analyze adjuvant therapy among patients with ECC at a national level. | Patients who received adjuvant treatment were more likely to be younger (median age surgery, 70 years; AC, 65 years; CRT, 63 years), in the highest income quartile (>$46,000: surgery, 38.3 %; AC, 43.4 %; CRT, 44.7 %), and treated at a community cancer center (surgery, 43.0 %; AC, 50.7 %; CRT, 52.9 %) (p < 0.001). These patients also were more likely to have positive LNs (surgery, 34.7 %; AC, 69.6 %; CRT, 63.3 %), positive surgical margins (surgery, 5.9 %; AC, 7.1 %; CRT, 10.7 %), and stage 3 disease (surgery, 21.4 %; AC, 37.8 %; CRT, 37.9 %) (p < 0.001). Multivariate analysis of the entire cohort showed improved survival with CRT (H] 0.82; 95 % CI 0.75-0.91). The survival benefit was independent of margin status (R0: HR 0.88; 95 % CI 0.79-0.97; R1: HR 0.49; 95 % CI 0.38-0.62). | 3 |
| 84 | Zhu GQ, Shi KQ, You J, Zou H, Lin YQ, Wang LR, Braddock M, Chen YP, Zheng MH. Systematic review with network meta-analysis: adjuvant therapy for resected biliary tract cancer. [Review] Alimentary Pharmacology & Therapeutics. 40(7):759-70, 2014 Oct. UI: 25099956 | Systematic review and meta-analysis | Systematic review identified 12 studies including 5-FU, gemcitabine and CRT following resection for BTC | To compare adjuvant therapies including 5-FU, gemcitabine and CRT following resection for BTC in terms of patient survival rates after resection and toxic effects | Gemcitabine improved 5-year OS (HR 2.12, 95% CI, 1.23-4.02, P = 0.01), whereas 5-FU (HR 1.61, 95% CI 0.74-3.67) and CRT (HR 1.55, 95% CI 0.82-3.32) provided a poorer survival outcome compared with gemcitabine after 1 year. Similarly, for 5-year OS, although differing, CRT did not provide a significant improvement in survival (HR 0.46, 95% CI 0.20-0.97) compared with gemcitabine. 5-FU did not appear to provide benefit over gemcitabine (HR 1.56, 95% CI 0.77-3.35). CRT was ranked highest for toxic effects including hematological (HR 5.45, 95% CI 0.01-483.85) and non-hematological (OR 5.77, 95% CI 0.01-3807.40). | M |
| 85 | Ecker BL, Vining CC, Roses RE, Maggino L, Lee MK, Drebin JA, Fraker DL, Vollmer CM Jr, Datta J. Identification of Patients for Adjuvant Therapy After Resection of Carcinoma of the Extrahepatic Bile Ducts: A Propensity Score-Matched Analysis. Annals of Surgical Oncology. 24(13):3926-3933, 2017 Dec. UI: 28952140 | NCDB retrospective propensity matched analysis | 4,872 patients who underwent resection for ECC were identified (2,461; 49.6% received AC, often in conjunction with RT 1,555; 64.4%). Cox regression identified covariates associated with overall survival (OS). Adjuvant therapy and surgery alone cohorts were matched (1:1) by propensity scores based on the survival hazard in Cox modeling. OS was compared by Kaplan-Meier estimates. | To identify Patient subsets most likely to benefit from adjuvant therapy following resection of ECC | AC with or without RT was used increasingly for cases with higher T classification [reference: T1-2; T3: 1.36; 95% CI, 1.19-1.55; T4: 1.77; 95% CI 1.38-2.26], nodal positivity [OR, 1.26; 95% CI 1.01-1.56], lymphovascular invasion (OR 1.21; 95% CI 1.01-1.46), or margin-positive resection (OR 1.85; 95% CI 1.61-2.12), and was associated with significant improvements in OS for each high-risk subset in the propensity score-matched cohort. Adjuvant therapy was associated with improved median OS for hilar tumors (40.0 vs 30.6 months; p = 0.025) but not distal tumors (33.0 vs 30.3 months; p = 0.123). CRT was associated with superior outcomes compared with AC alone in the subset of margin-positive resection [HR 0.63; 95% CI 0.42-0.94]. | 2 |
| 86 | Lee J, Kang SH, Noh OK, Chun M, Oh YT, Kim BW, Kim SW. Adjuvant concurrent chemoradiation therapy in patients with microscopic residual tumor after curative resection for extrahepatic cholangiocarcinoma. Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico. 20(8):1011-1017, 2018 Aug. UI: 29256155 | Multi institution retrospective study | 84 patients treated with curative resection for ECC; 52 with negative resection margins did not receive any adjuvant treatments (R0 + S group); 32 patients with microscopically positive resection margins received either adjuvant CRT (R1 + CRT group, n = 19) or adjuvant RT alone (R1 + RT group, n = 13). | To investigate the role of adjuvant CRT in patients with a  microscopically positive resection margin (R1) after curative resection for ECC | 2-year LR PFS, DFS, and OS were: 81.8, 62.6, and 61.5% for R0 + S group; 71.8, 57.8, and 57.9% for R1 + CRT group; and 16.8, 9.6, and 15.4% for R1 + RT group, respectively. Multivariate analysis revealed that the R1 + CRT group did not show any significant difference in survival rates compared with the R0 + S group. The R1 + RT group had lower LR DFS [hazard ratio (HR) 3.008; p = 0.044], DFS (HR 2.364; p = 0.022), and OS (HR 2.417; p = 0.011) when compared with the R0 + S and R1 + CRT group. | 3 |
| 87 | Park HJ, Kim K, Chie EK, Jang JY, Kim SW, Han SW, Oh DY, Im SA, Kim TY, Bang YJ, Ha SW.  Chemoradiotherapy for extrahepatic bile duct cancer with gross residual disease after surgery. Anticancer Research. 34(11):6685-90, 2014 Nov. UI: 25368275 | Single institution retrospective study | 30 patients with ECC who underwent CRT after palliative resection (R2 resection). Postoperative RT was delivered to the tumor bed including residual tumor and regional LNs (range=40-55.8 Gy). Most patients underwent CRT concurrently with 5-FU or gemcitabine. | To analyze the outcome of CRT for ECC patients with gross residual disease after surgical resection. | The 2-year LR PFS, DM PFS, and OS rates were 33.3%, 42.4% and 44.5%, respectively. High radiation dose>=50 Gy had a marginally significant impact on superior LR PFS compared to 40 Gy (p=0.081). One patient developed grade 3 late gastrointestinal toxicity. | 3 |
| 88 | Sugiura T, Uesaka K, Okamura Y, Ito T, Yamamoto Y, Ashida R, Ohgi K, Asakura H, Todaka A, Fukutomi A. Adjuvant chemoradiotherapy for positive hepatic ductal margin on cholangiocarcinoma.  Annals of Gastroenterological Surgery. 4(4):455-463, 2020 Jul. UI: 32724890 | Single institution retrospective study | 340 patients who underwent resection for ECC. Hepatic ductal margin was negative in 296 and positive in 44. Of these 44 patients, 22 received postoperative CRT,22 no adjuvant therapy | To evaluate the effects of postoperative adjuvant CRT for positive hepatic ductal margin in patients undergoing surgery for ECC | Hepatic stump recurrence occurred in 19 patients. The incidence was significantly higher with positive hepatic ductal margin (20%, 9/44) than in those with negative hepatic ductal margin (3%, 10/296) (P < 0.001). Among the patients with positive hepatic ductal margin the incidence similar in patients who received adjuvant CRT compared to those who did not: 23% (5/22) in no CRT and 18% (4/22) in + CRT patients (P = 0.999). The median OS was 49 months in patients with negative hepatic ductal margin (no CRT) and 43 months in patients with positive hepatic ductal margin without CRT, and 49 months in patients with positive hepatic ductal margin with CRT. The differences were not significant among the groups. A multivariate analysis revealed CA 19-9 >= 300 U/mL, combined vascular resection, histologic grade G2/G3, and LN metastasis to be significant prognostic factors. | 3 |
| 89 | Ben-Josef E, Guthrie KA, El-Khoueiry AB, Corless CL, Zalupski MM, Lowy AM, Thomas CR Jr, Alberts SR, Dawson LA, Micetich  KC, Thomas MB, Siegel AB, Blanke CD. SWOG S0809: A Phase II Intergroup Trial of Adjuvant Capecitabine and Gemcitabine Followed by Radiotherapy and Concurrent Capecitabine in Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma. Journal of Clinical Oncology. 33(24):2617-22, 2015 Aug 20. UI: 25964250 | Multi institutional Cooperative Group prospective nonrandomized phase II trial | 79 patients with resected ECC treated with this AC gemcitabine and capecitabine x 4 cycles followed by capecitabine-based CRT (45 Gy to regional lymphatics; 54 to 59.4 Gy to tumor bed) | To estimate 2-year OS and after R0 or R1 resection, pattern of relapse, and toxicity in patients with resected ECC treated with AC gemcitabine/ capecitabine x 4 cycles followed by capecitabine-based CRT | For all patients, 2-year survival was 65% (95% CI, 53% to 74%); it was 67% and 60% in R0 and R1 patients, respectively. Median OS was 35 months (R0, 34 months; R1, 35 months). Local, distant, and combined relapse occurred in 14, 24, and nine patients. Grade 3 and 4 adverse effects were observed in 52% and 11% of patients, respectively. The most common grade 3 to 4 adverse effects were neutropenia (44%), hand-foot syndrome (11%), diarrhea (8%), lymphopenia (8%), and leukopenia (6%). There was one death resulting from GI hemorrhage. | 2 |
| 90 | Ebata T, Hirano S, Konishi M, Uesaka K, Tsuchiya Y, Ohtsuka M, Kaneoka Y, Yamamoto M, Ambo Y, Shimizu Y, Ozawa F, Fukutomi A, Ando M, Nimura Y, Nagino M, Bile Duct Cancer Adjuvant Trial (BCAT) Study Group. Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. British Journal of Surgery. 105(3):192-202, 2018 02. UI: 29405274 | Multi institution Phase III Randomized Controlled Trial | 225 patients with resected bile duct cancer were randomized to (117 gemcitabine (117), or observation (108). Baseline characteristics were well balanced between the gemcitabine and observation groups. | To test the hypothesis that adjuvant gemcitabine would improve survival probability in resected bile duct cancer | There were no significant differences in OS (median 62.3 vs 63.8 months respectively; HR 1.01, 95% CI 0.70 to 1.45; P = 0.964) and DFS (median 36.0 vs 39.9 months; HR 0.93, 0.66 to 1.32; P = 0.693). There were no survival differences between the two groups in subsets stratified by LN status and margin status. Although hematological toxicity occurred frequently in the gemcitabine group, most toxicities were transient, and grade 3/4 non-hematological toxicity was rare. | 1 |
| 91 | Edeline J, Benabdelghani M, Bertaut A, Watelet J, Hammel P, Joly JP, Boudjema K, Fartoux L, Bouhier-Leporrier K, Jouve  JL, Faroux R, Guerin-Meyer V, Kurtz JE, Assenat E, Seitz JF, Baumgaertner I, Tougeron D, de la Fouchardiere C, Lombard-Bohas C, Boucher E, Stanbury T, Louvet C, Malka D, Phelip JM. Gemcitabine and Oxaliplatin Chemotherapy or Surveillance in Resected Biliary Tract Cancer (PRODIGE 12-ACCORD  18-UNICANCER GI): A Randomized Phase III Study. Journal of Clinical Oncology. 37(8):658-667, 2019 03 10. UI: 30707660 | Multi institution open label Phase III Randomized Controlled Trial | 33 centers, 196 patients randomly assigned (1:1) within 3 months after R0 or R1 resection of a localized BTC to receive either gemcitabine and oxaliplatin or  surveillance | To assess whether gemcitabine and oxaliplatin chemotherapy would increase DFS while maintaining HRQOL in patients who undergo resection. | There was no significant difference in DFS between the two arms (median, 30.4 months in AC arm v 18.5 months in observation arm B; HR, 0.88; 95% CI, 0.62 to 1.25; P = .48). There was no difference in time to definitive deterioration of global HRQOL (median, 31.8 months in AC arm v 32.1 months in observation arm; HR, 1.28; 95% CI, 0.73 to 2.26; log-rank P = .39). Overall survival was not different (median, 75.8 months in AC arm v 50.8 months in observation arm; HR, 1.08;  95% CI, 0.70 to 1.66; log-rank P = .74). Maximal adverse events were grade 3 in 62% (AC) versus 18% (observation) and grade 4 in 11% versus 3% (P < .001). | 1 |
| 92 | Primrose JN, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D, Anthony A, Corrie P, Falk S, Finch-Jones M, Wasan H, Ross  P, Wall L, Wadsley J, Evans JTR, Stocken D, Praseedom R, Ma YT, Davidson B, Neoptolemos JP, Iveson T, Raftery J, Zhu S,  Cunningham D, Garden OJ, Stubbs C, Valle JW, Bridgewater J, BILCAP study group. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. Lancet Oncology. 20(5):663-673, 2019 05. UI: 30922733 | Multi institution randomized controlled phase III trial | 447 Patients with resected BTC; 223 were randomly assigned to the capecitabine group and 224 to the observation group | To determine whether adjuvant capecitabine improved overall survival compared with observation following surgery for  BTC | Intention-to-treat analysis, median OS 51.1 months (95% CI 34.6-59.1) for capecitabine  compared with 36.4 months (29.7-44.5) for observation (adjusted HR] 0.81, 95% CI 0.63-1.04;  p=0.097). In a protocol-specified sensitivity analysis, adjusting for minimisation factors and nodal status, grade, and gender, the OS HR was 0.71 (95% CI 0.55-0.92; p=0.010). In the prespecified per-protocol analysis (210 patients in the capecitabine group and 220 in the observation group), median OS was 53 months (95% CI 40 - not reached) capecitabine and 36 months (30-44) observation (adjusted HR 0.75, 95% CI 0.58-0.97; p=0.028). In the intention-to-treat analysis, median DFS was 24.4 months (95% CI 18.6-35.9) capecitabine and 17.5 months (12.0-23.8) observation. In the per-protocol analysis, median DFS was 25.9 months (95% CI 19.8-46.3) capecitabine and 17.4 months (12.0-23.7) observation. Adverse events were measured in the capecitabine group only, and of the 213 patients who received at least one cycle, 94 (44%) had at least one grade 3 toxicity, the most frequent of which were hand-foot syndrome in 43 (20%) patients, diarrhea in 16 (8%) patients, and fatigue in 16 (8%) patients. One (<1%) patient had grade 4 cardiac ischemia or infarction. Serious adverse events were observed in 47 (21%) of 223 patients in the capecitabine group and 22 (10%) of 224 patients in the observation group. No deaths were deemed to be treatment related. | 1 |
| 93 | Park J, Kim M-H. Kim K-P, Park DH, Moon S-H, Song TJ, Eum J, Lee SS, Seo DW, Lee SK. Natural History and Prognostic Factors of Advanced Chalangiocarsinoma without Surgery, Chemotherapy, or Radiotherapy: A Large Scale Observational Study. | Single institution retrospective study | Of the 1,377 cases reviewed, 330 patients complied with the inclusion criteria and were thus eligible to participate in this study; 203 had intrahepatic cholangiocarcinoma and 127 had hilar cholangiocarcinoma. | To evaluate survival time and prognostic factors in patients with advanced unresectable cholangiocarcinoma who have not received surgery, chemotherapy, or radiotherapy. | The overall survival time of the entire cohort (n=330) was median 3.9 months (range; 0.2 to 67.1). The survival time was significantly shorter in the intrahepatic cholangiocarcinoma group (3.0+/-5.3 months) than in the hilar cholangiocarcinoma group (5.9+/-10.1 months; Kaplan-Meier survival analysis). Multivariate analysis revealed that distant metastasis was a poor prognostic factor for intrahepatic cholangiocarcinoma (p< 0.001), baseline serum albumin >3.0 g/dL was a favorable prognostic factor (p=0.02), and baseline serum carcinoembryonic antigen level >30 ng/mL was a poor prognostic factor for hilar cholangiocarcinoma (p=0.01). | 3 |
| 94 | Pollom EL, Alagappan M, Park LS, Whittemore AS, Koong AC, Chang DT. Does radiotherapy still have a role in unresected biliary tract cancer? Cancer Medicine. 6(1):129-141, 2017 01.UI: 27891822 | SEER database retrospective propensity matched analysis | 2,343 patients with inoperable BTC were identified. 452 (19%) received RT within 4 months of diagnosis. Multivariate logistic regression was used to evaluate factors associated with treatment selection, and multivariate Cox regression and propensity score matching to evaluate treatment selection in relation to subsequent survival. | To evaluate the impact of RT on survival in patients with unresectable BTC using the SEER-Medicare database. | The use of RT declined over time, and was influenced by receipt of chemotherapy and patient age, race, marital status, poverty status, and tumor stage and type. Median OS was 9.3 (95% CI 8.7-9.7) months among patients who did not receive RT and 10.0 (95% CI 9.1-11.3) months among those who received RT, conditional on having survived 4 months. In patients who received chemotherapy (n = 1053), receipt of RT was associated with improved OS, with an adjusted HR of 0.82 (95% 0.70-0.97, P = 0.02). In patients who did not receive chemotherapy (n = 1290), receipt of RT was not associated with improved OS, with an adjusted HR of 1.09 (95% 0.91-1.30, P = 0.34). Propensity-scored matched analyses showed similar results. Despite the survival benefit associated with the addition of  RT to chemotherapy, the use of RT for unresectable biliary tract cancers has declined over time. | 2 |
| 95 | Chen SC, Chen MH, Li CP, Chen MH, Chang PM, Liu CY, Tzeng CH, Liu YM, Yen SH, Chao Y, Huang PI. External beam radiation therapy with or without concurrent chemotherapy for patients with unresectable locally advanced hilar cholangiocarcinoma. Hepato-Gastroenterology. 62(137):102-7, 2015 Jan-Feb. UI: 25911877 | Single institution retrospective study | 34 patients with unresectable locally advanced hilar ECC. 18 received RT and 16 patients received CRT. Survivals and multivariate analyses were performed to explore potential variables affecting survivals. | To evaluate the efficacy of CRT compared to RT for  unresectable, locally advanced hilar ECC | Median OS was 10.4 months (95% CI, 6.7-13.5) with the 1-year survival rates of 41%. The median OS and PFS were 13.5 months and 8.8 months for patients receiving CRT as compared to 6.7 months and 4.4 months for patients receiving RT alone (p = 0.003 and p = 0.005, respectively). On multivariate analysis demonstrated that Karnofsky performance status >= 80 (p = 0.001), pretreatment CA 19-9 200 U/ml (p = 0.045) and CRT were prognostic factors for OS and PFS. | 3 |
| 96 | Torgeson A, Lloyd S, Boothe D, Cannon G, Garrido-Laguna I, Whisenant J, Lewis M, Kim R, Scaife C, Tao R. Chemoradiation Therapy for Unresected Extrahepatic Cholangiocarcinoma: A Propensity Score-Matched Analysis. Annals of Surgical Oncology. 24(13):4001-4008, 2017 Dec. UI: 29043526 | NCDB retrospective propensity matched analysis | 2,996 patients with unresectable ECC who received chemotherapy or CRT. Uni- and multivariate Cox regression analyses were used to compare characteristics related to survival. Propensity score matching and shared frailty analysis were undertaken to correct for baseline differences between the two groups. Additional analyses were performed to compare survival for the minority of patients who underwent surgery and advanced-stage patients. | To compare outcomes for patients with unresectable ECC treated with chemotherapy or CRT | CRT was associated with better survival (MS], 14.5 months; HR 0.84; p < 0.001) than chemotherapy alone (MS, 12.6 months). Induction chemotherapy before CRT was associated with a trend toward decreased risk of death compared with concurrent CRT (HR 0.81; p = 0.051). For the patients able to undergo surgery after initial treatment, MS was 24.5 months (HR 0.38; p < 0.001) versus 12.2 months for those who had no surgery. For these patients, CRT also was associated with better survival (MS, 31.2 months; HR 0.66; p = 0.001) than CT (MS, 22.1 months). Positive margins at surgery yielded survival equivalent to that with no surgery. | 2 |
| 97 | Autorino R, Mattiucci GC, Ardito F, Balducci M, Deodato F, Macchia G, Mantini G, Perri V, Tringali A, Gambacorta MA, Tagliaferri L, Giuliante F, Morganti AG, Valentini V. Radiochemotherapy with Gemcitabine in Unresectable Extrahepatic Cholangiocarcinoma: Long-term Results of a Phase II Study. Anticancer Research. 36(2):737-40, 2016 Feb. UI: 26851032 | Single institution prospective phase II study | 27 patients underwent weekly gemcitabine during 3D-CRT (50.4 Gy to the tumor and 39.6 Gy to the nodes). 6 patients (22%) received a boost of HDR ILBT with 192Ir (4 patients received 15 Gy and 2 patients 20 Gy) | To evaluate the outcome of patients affected by unresectable ECC treated with  RT and concurrent gemcitabine-based chemotherapy with or without HDR ILBT | 2-year LC for the entire group was 29% (median=12 months), 2-year and 3-year OS were 27% and 7% respectively, with a median of 14 months. Toxicities were acceptable. Median OS in patients treated with HDR ILBT boost was 21 months versus 14 months for the group treated with gemcitabine-based CRT only; 2-year LC was 53% versus 25%, respectively. | 2 |
| 98 | Engineer R, Mehta S, Kalyani N, Chaudhari S, Dharia T, Shetty N, Chopra S, Goel M, Kulkarni S, Shrivastava SK. High dose chemoradiation for unresectable hilar cholangiocarcinomas using intensity modulated external beam radiotherapy: a single tertiary care centre experience. Journal of Gastrointestinal Oncology. 8(1):180-186, 2017 Feb.  UI: 28280622 | Single institution retrospective study | 68 consecutive patients were treated. 50 (group 1) with HDR ILBT (14 Gy) followed by RT (45 Gy). 22 (group 2) with previously biliary drainage and RT (57 Gy). All patients  received concurrent Gemcitabine | To report results of patients diagnosed with unresectable hilar ECC treated with high dose  RT and concurrent chemotherapy. | 29 patients in group 1 and 22 patients in group 2 completed the treatment. 26 (55%) patients achieved complete radiological response, 16 (64%) of group 1 and 8 (44%) of group 2 (P=0.05). The median OS was 17.5 and 16 months for group 1 and 2 respectively (P=0.07). The 1- and 2-year OS was 63%, and 18% for group I and 61% and 22% for group II respectively. The median OS was 5 months and 1 year survival was 14% for patients receiving HDR ILBT only. Median OS was significantly better after complete response (P=0.001). | 3 |
| 99 | Jethwa KR, Sannapaneni S, Mullikin TC, Harmsen WS, Petersen MM, Antharam P, Laughlin B, Mahipal A, Halfdanarson TR, Merrell KW, Neben-Wittich M, Sio TT, Haddock MG, Hallemeier CL.  Chemoradiotherapy for patients with locally advanced or unresectable extra-hepatic biliary cancer. Journal of Gastrointestinal Oncology. 11(6):1408-1420, 2020 Dec. UI: 33457010 | Single institution retrospective cohort study | 48 patients with unresectable ECC, including extra-hepatic cholangiocarcinoma (41, 85%) or gallbladder cancer (7, 15%) deemed inoperable treated with RT. The median RT dose was 50.4 Gy in 28 fractions and 94% received concurrent 5-fluorouracil. | To report the efficacy and  AEs associated with CRT for patients with locally advanced and unresectable ECC | MS = 12.0 months [95% CI: 2.3-73.2 months]. The 2-, 3-, and 5-year OS were 33% (95% CI: 22-50%), 20% (95% CI: 11-36%), and 7% (95% CI: 2-20%), respectively. The 2-year PFS, LR, LRR, and DM were 21% (95% CI: 12-36%), 27% (95% CI: 17-44%), 31% (95% CI: 20-48%), and 33% (95% CI: 22-50%), respectively. On univariate analysis, biologically effective dose (BED) >59.5 Gy10 was associated with improved OS [HR: 0.40, 95% CI: 0.18-0.92, P=0.03] and PFS (HR: 0.37, 95% CI: 0.16-0.84, P=0.02) and primary tumor size (per 1 cm increase) was associated with worsened PFS (HR: 1.29, 95% CI: 1.02-1.63, P=0.04). BED >59.5  Gy10 remained associated with PFS on multivariate analysis (HR: 0.34, 95% CI: 0.15-0.78, P=0.01). Treatment-related grade 3+ acute and late gastrointestinal AEs occurred in 13% and 17% of patients, respectively. | 3 |
| 100 | Elganainy D, Holliday EB, Taniguchi CM, Smith GL, Shroff R, Javle M, Raghav K, Kaseb A, Aloia TA, Vauthey JN, Tzeng CD, Herman JM, Koong AC, Krishnan SX, Minsky BD, Crane CH, Das P, Koay EJ. Dose escalation of radiotherapy in unresectable extrahepatic cholangiocarcinoma. Cancer Medicine. 7(10):4880-4892, 2018 10. UI: 30152073 | Multi institution retrospective nonrandomized study | Consecutive cohort of 80 patients with unresectable ECC underwent RT. Demographic, tumor, treatment, toxicity, and laboratory variables were collected. The maximal RT doses ranged from 30 to 75 Gy (median 50.4 Gy, at 1.8-4.5 Gy/fraction). Gross tumor volume coverage by maximal dose in escalated RT dose group ranged from 38% to 100%. Kaplan-Meier method was used to estimate OS, FFLP, and FFDP. Univariate and multivariate Cox regression models were analyzed. | To evaluate the effect of escalated dose RT (defined as doses >50.4 Gy in 28 fractions [59.5 Gy BED]) on OS, FFLP, and FFDP of patients with unresectable ECC | Median OS, FFLP, and FFDP were 18.7, 22.6, and 24.3 months, respectively. There was no significant difference in OS or FFLP between patients who received escalated RT dose to portions of the GTV and patients who did not. On multivariate analysis, bigger gross tumor volume, age, and ECOG performance status were independently associated with shorter OS. LF on chemotherapy prior to RT was independently associated with shorter FFLP. High baseline neutrophil/lymphocyte ratio (>5.3) was independently associated with shorter FFDP. Toxicity grades were similar in the dose escalated group and lower doses except lymphopenia which was higher in dose escalated group (P = 0.053). Escalated RT to selective portions of the GTV may not benefit patients with unresectable EHCC despite having  acceptable toxicity | 3 |
| 101 | Hung SP, Huang BS, Hsieh CE, Lee CH, Tsang NM, Chang JT, Chen JS, Chou WC, Tseng JH, Hong JH. Clinical Outcomes of Patients With Unresectable Cholangiocarcinoma Treated With Proton Beam Therapy. American Journal of Clinical Oncology. 43(3):180-186, 2020 03. UI: 31764017 | Multi institutional retrospective study | 30 patients with unresectable cholangiocarcinoma who received PBT. The median tumor size was 7 cm. Seventeen patients (56.7%) had regional LN metastases. The median RT dose was 72.6 cobalt gray equivalents, and 23 patients (76.7%) received concurrent chemotherapy. | To investigate the clinical outcomes and failure patterns of patients with unresectable cholangiocarcinoma  (CC) who had been treated with PBT | The 1-year LC, regional control, and DM-free rates were 88%, 86%, and 68%, respectively. The median OS and PFS were 19.3 and 10.4 months, respectively. The median jaundice-free survival was 13 months, with a 1-year biliary tract infection-free rate of 58%. Patients who received concurrent chemotherapy had a better median PFS (12.1 vs. 4.7 mo). The most common form of acute toxicity from PBT was acute skin reactions which were rarely severe (grade III: 7% of patients). 3band 2 patients had grade  III-IV toxicities and radiation-induced liver disease. There were no deaths caused by PBT or concurrent chemotherapy. | 3 |
| 102 | Dang YZ, Huang SG, Lu WL, Wu FW, Wang QY. Curative effect of stereotactic body radiotherapy on hepatic hilar carcinoma. Molecular & Clinical Oncology. 2(6):1135-1138, 2014 Nov.  UI: 25279211 | Single institution prospective single arm study | 63 patients with unresectable hilar tumors treated with SBRT 45Gy (range 44 – 48 Gy) at 3 – 6 Gy per fraction administered 9 – 12 times, 2 – 5 times per week. Patients were evaluated at 1 and 3 months for response | To investigate the effect of SBRT on hepatic hilar tumors. | At 1 month, CR = 15 (23.8%), PR = 34 (54.0%), SD = 11 (17.5%) and PD = 3 (4.7%). At 3 months, CR = 22 (34.9%), PR = 32 (50.8%), SD = 3 (4.8%) and PD = 6 (9.5%). CR + PR = 85.7% (54/63). Response for tumor diameter of <=5 cm CR = 13 (72.2%), PR = 4 (22.2%), SD = 1 (5.6%) and PD = 0 (0.0%). Response for tumor diameter of >5 cm CR = 9 (20.0%), PR = 28 (62.2%), SD = 6 (13.3%) and PD = 2 (4.5%). The 1-year OS for those with tumor diameter >5 cm was 71.4% (45/63) and the 2-year survival rate was 42.9% (27/63). | 2 |
| 103 | Baak R, Willemssen FEJA, van Norden Y, Eskens FALM, Milder MTW, Heijmen BJM, Koerkamp BG, Sprengers D, van Driel LMJW, Klumpen HJ, den Toom W, Koedijk MS, IJzermans JNM, Mendez Romero A. Stereotactic Body Radiation Therapy after Chemotherapy for Unresectable Perihilar Cholangiocarcinoma: The STRONG Trial, a Phase I Safety and Feasibility Study.  Cancers. 13(16), 2021 Aug 07.  UI: 34439146 | Single institution Phase 1 feasibility study | 6 patients with unresectable perihilar ECC stage T1-T4N0-N1M0, ECOG 0-1, having finished 6-8 cycles of cisplatin and gemcitabine without disease progression received SBRT was planned in 15 fractions of 4 Gy. | To investigate the feasibility and  safety of adding SBRT after chemotherapy in patients with unresectable perhilar ECC | No SBRT-related DLT was observed. The most common grade >= 3 toxicity was cholangitis (n = 5). The median follow-up was 14 months. The 12-month local control rate was 80%. No substantial changes in quality of life observed. | 3 |
| 104 | Valle JW, Wasan H, Palmer D, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira S, Roughton M, Bridgewater J, ABC-02 Trial Investigators. Cisplatin plus gemcitabinee versus gemcitabine for biliary tract cancer. N Engl J Med Apr 8; 362(14): 1272-1281, 2010. PMID: 20375414 DOIL 10.1056/NEJMoa0908721 | Randomized phase III prospective trial | 410 patients with metastatic or locally advanced BTC (cholangiocarcinoma, gallbladder cancer, or ampullary cancer) randomly assigned to gemcitabine alone (n=206), or gemcitabine plus cisplatin (n=204). The study was initially a randomized, phase 2 study involving 86 patients to compare cisplatin plus gemcitabine with gemcitabine alone. Afteran improvement in PFS was demonstrated, the trial was extended to the phase 3 trial | To evaluate the efficacy and safety cisplatin-gemcitabine in patients with locally advanced or metastatic biliary tract cancer. | After a median follow-up of 8.2 months and 327 deaths, the median OS was 11.7 months among the 204 patients in the cisplatin-gemcitabine group and 8.1 months among the 206 patients in the gemcitabine group (HR, 0.64; 95% CI, 0.52 to 0.80; P<0.001). The median PFS was 8.0 months in the cisplatin-gemcitabine group and 5.0 months in the gemcitabine-only group (P<0.001). In addition, the rate of tumor control among patients in the cisplatin-gemcitabine group was significantly increased (81.4% vs. 71.8%, P=0.049). Adverse events were similar in the two groups, with the exception of more neutropenia in the cisplatin-gemcitabine group; the number of neutropenia-associated infections was similar in the two groups. | 1 |
| 105 | Sahai V, Catalano PJ, Zalupski MM, Lubner SJ, Menge MR, Nimeiri HS, Munshi HG, Benson AB 3rd, O'Dwyer PJ. Nab-Paclitaxel and Gemcitabine as First-line Treatment of Advanced or Metastatic Cholangiocarcinoma: A Phase 2 Clinical Trial. JAMA Oncology. 4(12):1707-1712, 2018 12 01. UI: 30178032 | Multi institution single arm 2 stage Phase II Cooperative Group Trial | 74 patients with advanced or metastatic cholangiocarcinoma without prior chemotherapy received gemcitabine plus nanoparticle albumin-bound (nab)-paclitaxel. Previous surgery, radiation, or liver-directed therapies were permitted. | To evaluate whether gemcitabine plus nanoparticle albumin-bound (nab)-paclitaxel is safe and effective for treatment of advanced or metastatic cholangiocarcinoma | The trial did not meet primary endpoint in improvement in 6 month PFS. Observed 6-month PFS rate of 61% (95% CI, 48%-73%) did not favor the alternative hypothesis. Median PFS was  7.7 (95% CI, 5.4-13.1) months, median OS was 12.4 (95% CI, 9.2-15.9) months, and median time to progression was 7.7 (95% CI, 6.1-13.1) months. The confirmed best overall response rate and disease control rate were 30% and 66%, respectively. | 2 |
| 106 | Moehler M, Maderer A, Schimanski C, Kanzler S, Denzer U, Kolligs FT, Ebert MP, Distelrath A, Geissler M, Trojan J, Schutz M, Berie L, Sauvigny C, Lammert F, Lohse A, Dollinger MM, Lindig U, Duerr EM, Lubomierski N, Zimmermann S, Wachtlin D, Kaiser AK, Schadmand-Fischer S, Galle PR, Woerns M, Working Group of Internal Oncology. Gemcitabine plus sorafenib versus gemcitabine alone in advanced biliary tract cancer: a double-blind placebo-controlled multicentre phase II AIO study with biomarker and serum programme. European Journal of Cancer. 50(18):3125-35, 2014 Dec. UI: 25446376 | Multi institution prospective double blinded randomized controlled phase II study | 102 unresectable or metastatic BTC patients with histologically proven BTC, Eastern Cooperative Oncology Group 0-2 were randomized to gemcitabine plus sorafenib or placebo. | To evaluate first-line gemcitabine plus sorafenib in patients with advanced BTC | Gemcitabine plus sorafenib was generally well tolerated. 4 and 3 patients achieved partial responses in the sorafenib and placebo groups, respectively. There was no difference in the primary end-point, median PFS for gemcitabine plus sorafenib versus gemcitabine plus placebo (3.0 versus 4.9 months, P=0.859), and no difference for median OS (8.4 versus 11.2 months, P=0.775). Patients with liver metastasis after resection of primary BTC survived longer with sorafenib (P=0.019) compared to placebo. Patients who developed hand-foot syndrome showed longer PFS and OS than patients without HFS. Two sorafenib targets, VEGFR-2 and c-kit, were not expressed in BTC samples. VEGFR-3 and Hif1alpha were associated with LN metastases and T stage. Absence of PDGFRbeta expression correlated with longer PFS. | 1 |
| 107 | Arima S, Shimizu K, Okamoto T, Toki M, Suzuki Y, Okano N, Naruge D, Kawai K, Kobayashi T, Kasuga A, Kitamura H, Takasu A, Nagashima F, Sugiyama M, Furuse J. A Multicenter Phase II Study of Gemcitabine plus S-1 Chemotherapy for Advanced Biliary Tract Cancer. Anticancer Research. 37(2):909-914, 2017 02. UI: 28179351 | Multi institution single arm nonrandomized phase II study | 38 patients with histologically-proven BTC, unresectable or recurrent disease, ECOG performance status 0-1 regardless of previous treatment, received gemcitabine and S-1 chemotherapy. 7 patients had a previous history of first-line or AC after surgery. | To evaluate the efficacy and safety of gemcitabine plus S-1 in patients with advanced BTC. | Partial response in 6 (15.8%) and as stable disease in 18 (47.4%). The median PFS and OS were 5.8 and 15.9 months, respectively. The toxicity was generally mild, and the most common grade 3/4 toxicities were leukopenia  (31.6%), neutropenia (36.8%), nausea/vomiting (2.6%), and diarrhea (2.6%). There was one treatment-related death due to interstitial pneumonia. | 2 |
| 108 | Oh DY, He AW, Qin S, Chen L-T, Okusaka T, Vogel A, Kim JW, Suksombooncharoen T, Lee MA, Kitano M, Burris H, Bouattour M, Tanasanvimon S, Zaucha R, Avallone A, Cundom J, Rokutanda N, Xiong J, Cohen G, Valle J. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. 2022 ASCO GI Cancers Symposium Abstract 378. JCO 40(4) suppl, 2022. DOI: 10.1200/JCO.2022.40.4\_suppl.378 | Multi-institutional randomized phase 3 study | Double-blind study including 685 previously untreated unresectable locally advanced, recurrent, or metastatic BTC randomized 1:1 to receive durvalumab or placebo + GemCis for up to 8 cycles, followed by durvalumab or placebo until disease progression or unacceptable toxicity. Randomization was stratified by disease status (initially unresectable, recurrent) and primary tumor location (intrahepatic, ECC, gallbladder cancer). | To assess OS, PFS and response for patients with previously untreated unresectable BTC who receive durvalumab | 685 pts were randomized to durvalumab + GemCis (n=341) or placebo + GemCis (n=344; Table). Durvalumab + GemCis significantly improved OS vs placebo + GemCis (HR 0.80; 95%; CI 0.66–0.97; p=0.021). PFS was also significantly improved with durvalumab vs placebo (HR, 0.75; 95%; CI, 0.64–0.89; p=0.001). Overall response rate was 26.7% with durvalumab and 18.7% with placebo. Grade 3/4 treatment-related adverse events occurred in 62.7% of pts receiving durvalumab and 64.9% of pts receiving placebo. TRAEs led to discontinuation of any study medication in 8.9% of pts receiving durvalumab and 11.4% of pts receiving placebo. | 1 |
| 109 | Lamarca A, Palmer DH, Wasan HS, Ross P, Ma YT, Arora A, Falk S, Gillmore R, Wadsly J, Patel K, Anthoney A, Maraveyas A, Iveson T, Waters J, Hobbs C, Barber S, Ryder WD, Ramage J, Davies LM, Bridgewater JA, Valle JW. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol 2021 May;22(5): 690-701.doi: 10.1016/S1470-2045(21)00027-9. | Multi-institutional phase 3 open-label randomized trial | 162 patients with locally advanced or metastatic BTC (including cholangiocarcinoma, gallbladder or ampullary carcinoma) with radiological progression to first-line cisplatin and gemcitabine and Eastern Cooperative Oncology Group performance status of 0-1 were randomly assigned (1:1) to active symptom control plus FOLFOX (n=81) or active symptom control alone (n=81). | To determine the benefit derived from second-line FOLFOX chemotherapy in advanced BTC | OS was significantly longer in the FOLFOX group, with a median OS of 6·2 months (95% CI 5·4-7·6) in the FOLFOX group versus 5·3 months (4·1-5·8) in the active symptom control alone group (HR 0·69 [95% CI 0·50-0·97]; p=0·031). The OS rate in the active symptom control alone group was 35·5% (95% CI 25·2-46·0) at 6 months and 11·4% (5·6-19·5) at 12 months, compared with 50·6% (39·3-60·9) at 6 months and 25·9% (17·0-35·8) at 12 months in the FOLFOX group. | 1 |
| 110 | Boscoe A, Rolland C, Kelley RK. Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. J Gastrointestinal Oncol. 2019 Aug; 10(4): 751–765. DOI: 10.21037/jgo.2019.03.10 | Systematic Review and Meta-Analysis | A total of 46 publications met the inclusion criteria and were included in the systematic review; 45 tirals reported the frequency of mIDH1 among a total sample of 5,393 patients | To investigate the prevalence of isocitrate dehydrogenase 1 (IDH1) mutations (mIDH1) in patients with CC, the possible clinical and prognostic significance of mIDH1, and the presence of co-mutations in tumors with mIDH1. | mIDH1 was enriched in intrahepatic CC , with 552 (13.1%; 95% CI, 12.1–14.2) of the 4,214 patients with ICC having the mutation compared with 9 (0.8%; 95% CI, 0.4–1.5%) of the 1,123 patients with ECC. The percentage of females with mIDH1 CC (66.2%; 95% CI, 57.7–73.7%) was higher than in the overall CC population (44.4%). The frequency of mIDH1 in patients with ICC reported in individual studies ranged from 4.5–55.6%, and a significantly higher frequency was reported in non-Asian centers compared with Asian centers (weighted mean, 16.5% vs. 8.8%; P<0.001). The prevalence of mIDH1 in patients with ICC at USA centers was 18.0% (95% CI, 16.4–19.8%). 11 publications reported the prevalence of co-mutations in patients with mIDH1 ICC, with the most frequent being AT-rich interactive domain-containing protein 1A (ARID1A) (22.0%), BRCA1-associated protein 1 (BAP1) (15.5%), and PBRM1 (13.3%). 8 publications investigated the possible prognostic significance of mIDH1. None of the studies reported a statistically significant association between mIDH1 and OS, PFS, or time to progression. | 2 |
| 111 | Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, Paulson AS, Borad M, Gallison D, Murphy AG, Oh D-Y, Dotan E, Catenacci AV, Van Cutsem E, Ji T, Lihou CF, Zhen H, Feliz L, Vogel A. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study Lancet Oncol. 2020 May;21(5):671-684.   doi: 10.1016/S1470-2045(20)30109-1. | Multi institutional phase 2 study | Open-label, single-arm, multicohort, phase 2 study (FIGHT-202), cholangiocarcinoma with disease progression following at least one previous treatment including 146 patients from 146 academic or community-based sites in the USA, Europe, the Middle East, and Asia. Patients were assigned to one of three cohorts: patients with FGFR2 fusions or rearrangements, patients with other FGF/FGFR alterations, or patients with no FGF/FGFR alterations. All enrolled patients received a starting dose of 13·5 mg oral pemigatinib once daily (21-day cycle; 2 weeks on, 1 week off) until disease progression, unacceptable toxicity, withdrawal of consent, or physician decision. | To evaluate the safety and antitumour activity of pemigatinib in patients with previously treated, locally advanced or metastatic cholangiocarcinoma with and without FGFR2 fusions or rearrangements. | Patients included 107 with FGFR2 fusions or rearrangements, 20 with other FGF/FGFR alterations, 18 with no FGF/FGFR alterations, and one with an undetermined FGF/FGFR alteration. The median follow-up was 17·8 months (IQR 11·6-21·3). 38 (35·5% [95% CI 26·5-45·4]) patients with FGFR2 fusions or rearrangements achieved an objective response (three complete responses and 35 partial responses). Overall, hyperphosphataemia was the most common all-grade adverse event irrespective of cause (88 [60%] of 146 patients). 93 (64%) patients had a grade 3 or worse adverse event (irrespective of cause); the most frequent were hypophosphataemia (18 [12%]), arthralgia (nine [6%]), stomatitis (eight [5%]), hyponatraemia (eight [5%]), abdominal pain (seven [5%]), and fatigue (seven [5%]). 65 (45%) patients had serious adverse events; the most frequent were abdominal pain (seven [5%]), pyrexia (seven [5%]), cholangitis (five [3%]), and pleural effusion (five [3%]). Overall, 71 (49%) patients died during the study, most frequently because of disease progression (61 [42%]); no deaths were deemed to be treatment related. | 2 |
| 112 | Salama AKS, Li S, Macrae ER, Park J-I, Mitchell E, Zwiebel JA, Chen HX, Gray RJ, McShane LM, Rubenstein LV, Patton D, Williams PM, Hamilton SR, Armstrong DK, Conley BA, Arteaga CL, Harris LN, O’Dwyer PJ, Chen AP, Flaherty KT. Dabrafenib and Trametinib in Patients With Tumors With *BRAF V600E* Mutations: Results of the NCI-MATCH Trial Subprotocol H. J Clin Oncol. 2020 Nov 20;38(33):3895-3904.  doi: 10.1200/JCO.20.00762 | Multi institutional single arm study | Open-label single arm study with 35 patients with solid tumors (including BTC) enrolled and 29 included in final analysis, 45% of the patients had received ≥ 3 lines of therapy | To investigate the selective BRAF inhibitor dabrafenib and the MEK1/2 inhibitor trametinib in patients with solid tumors, lymphomas, or multiple myeloma whose tumors harbored a *BRAFV600* mutation | The confirmed ORR was 38% (90% CI, 22.9% to 54.9%) with *P* < .0001 against a null rate of 5%, and PFS was 11.4 months (90% CI, 8.4 to 16.3 months); responses were seen in 7 distinct tumor types. Seven patients had a duration of response of > 12 months, including 4 patients with a duration of response of > 24 months. An additional 8 patients had a PFS > 6 months. The median overall survival was 28.6 months. Reported adverse events were comparable to those noted in previously reported profiles of dabrafenib and trametinib. | 3 |
| 113 | Marabelle A, Le DT, Ascierto PA, Di Giaxomo AM, De Jesus-Acosta A, Delord J-P, Geva R, Gottfried M, Penel N, Hansen AR, Piha-Paul SA, Doi T, Gao B, Chung HC, Lopex-Martin J, Bang Y-J, Frommer RS, Shah M, Ghori R, Joe AK, Pruitt SK, Diaz LJ. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. J Clin Oncol. 2020 Jan 1;38(1):1-10.  doi: 10.1200/JCO.19.02105. | Multi Institutional prospective phase 2 study | 233 enrolled patients with histologically/cytologically confirmed MSI-H/dMMR advanced noncolorectal cancer who experienced failure with prior therapy received pembrolizumab 200 mg once every 3 weeks for 2 years or until disease progression, unacceptable toxicity, or patient withdrawal. Radiologic imaging was performed every 9 weeks for the first year of therapy and every 12 weeks thereafter (including endometrial, gastric, cholangiocarcinoma, and pancreatic cancers) | To evaluate the ORR per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by independent central radiologic review in patients with previously treated, advanced noncolorectal MSI-H/dMMR cancer treated with pembrolizumab | Objective response rate was 34.3% (95% CI, 28.3% to 40.8%). Median PFS survival was 4.1 months (95% CI, 2.4 to 4.9 months) and median overall survival was 23.5 months (95% CI, 13.5 months to not reached). Treatment-related adverse events occurred in 151 patients (64.8%). Thirty-four patients (14.6%) had grade 3 to 5 treatment-related adverse events. Grade 5 pneumonia occurred in one patient; there were no other treatment-related fatal adverse events. | 2 |
| 114 | Jung W, Park Y, Kim K, Park HJ, Kim BH. Patterns of Regional Failure after Pancreaticoduodenectomy in Patients with Distal Extrahepatic Cholangiocarcinoma: Suggestion of the Clinical Target Volume for Elective Nodal Irradiation. Clinical Oncology (Royal College of Radiologists). 34(1):e45-e51, 2022 Jan. UI: 34598842 | Retrospective study from 4 institutions | Review of medical records from 1991-2015 identified 72 patients with distal ECC who underwent resection. 30 received AC, 14 underwent RT with or without chemotherapy and 28 received no treatment. After reviewing CT or MRI images, the sites of LRR were identified and mapped to the corresponding locations on the representative CT images. | To identify an optimal target volume for elective nodal irradiation following surgery in patients with distal ECC. | 136 LRRs were observed. LR at 44 sites (32.4%): tumor bed in 15, choledochojejunostomy in 25 and pancreaticojejunostomy in 4. RR at 92 sites (67.6%); the most common site was the portal vein area (n = 18), followed by the para-aortic region (n = 17). Based on the mapped plots of RR, a clinical target volume covering 90% of RR was generated using the appropriate margin for the vascular structures of the portal vein, celiac axis, superior mesenteric artery, left gastric artery and aorta which may be used to assist with RT target delineation for patients with distal ECC following resection. | 3 |
| 115 | Koo TR, Eom KY, Kim IA, Cho JY, Yoon YS, Hwang DW, Han HS, Kim JS. Patterns of failure and prognostic factors in resected extrahepatic bile duct cancer: implication for adjuvant radiotherapy. Radiation Oncology Journal. 32(2):63-9, 2014 Jun. UI: 25061574 | Single institution retrospective study | 97 patients with resected ECC 26 proximal and 71 distal, using the junction of the cystic duct and common hepatic duct as the dividing point. Locoregional failure sites were categorized as follows: the hepatoduodenal ligament and tumor bed, the celiac artery and superior mesenteric artery, and other sites. | To analyze the patterns of failure and evaluate prognostic factors of LRR after curative resection without adjuvant treatment to find the applicability of adjuvant radiotherapy for ECC. | 3-year LR PFS, PFS, and OS rates were 50%, 42%, and 52%, respectively. Initial LRR 79% proximal and 81% distal. The most common site was the hepatoduodenal ligament and tumor bed. On multivariate analysis, perineural invasion was associated with poor LR PFS (p = 0.023) and PFS (p = 0.012); and elevated postoperative CA19-9 (>=37 U/mL) did with poor LR PFS (p = 0.002), PFS (p < 0.001) and OS (p < 0.001). | 3 |
| 116 | Ghiassi-Nejad Z, Tarchi P, Moshier E, Ru M, Tabrizian P, Schwartz M, Buckstein M. Prognostic Factors and Patterns of Locoregional Failure After Surgical Resection in Patients With Cholangiocarcinoma  Without Adjuvant Radiation Therapy: Optimal Field Design for Adjuvant Radiation Therapy.  International Journal of Radiation Oncology, Biology, Physics. 99(4):805-811, 2017 11 15. UI: 29063849 | Single institution retrospective study | 189 patients who underwent surgical resection for cholangiocarcinoma were evaluated for LR (102 intrahepatic; 43 hilar/distal ECC). LR was defined as recurrence in a theoretical reasonable postoperative RT volume. This includes the cut surface of liver, biliary anastomosis, hilum, portal nodes, celiac nodes, peri-pancreatic nodes, gastro-hepatic nodes, and retroperitoneal nodes. Patients receiving adjuvant RT excluded. | To identify prognostic factors and patterns of LR in patients with cholangiocarcinoma after surgical resection in the absence of RT for optimal definition of target volumes encompassing the  majority of local recurrences | 86 (59%) had a documented recurrence, of whom 44 (51%) had a LRR component. Among patients who had a recurrence, 23 (27%) had a recurrence at the biliary anastomosis and/or cut liver surface. 28 (32.6%) had LRR in regional LNs, most prevalent in the portal (16.3%) and retroperitoneal (17.4%) LNs. Univariable analysis identified tumor size, vascular invasion, presence of satellites, stage/nodal status, and receipt of chemotherapy as significant prognostic factors of overall recurrence among intrahepatic patients. Presence of satellites, and stage 3/Nx status remained statistically significant in multivariable modeling. | 3 |
| 117 | Kim BH, Chie EK, Kim K, Jang JY, Kim SW, Oh DY, Bang YJ, Ha SW. Impact of radiation dose in postoperative radiotherapy after R1 resection for extrahepatic bile duct cancer: long term results from a single institution.  Oncotarget. 8(44):78076-78085, 2017 Sep 29. UI: 29100449 | Multi institution retrospective study | 251 patients with ECC who underwent curative resection followed by AC, 86 patients had either invasive carcinoma (n = 63) or carcinoma in situ (n = 23) at the resected margin. 54 conventional RT dose (40-50.4 Gy); 32 escalated RT dose (54-56 Gy). | To evaluate the impact of RT dose after margin involved resection in patients  with ECC | Escalated RT dose was associated with improved LC (5yr, 73.8% vs. 47.1%, p = 0.069), but not DFS (5yr, 43.4% vs. 32.6%, p = 0.490) and OS (5yr, 40.6% vs. 29.6%, p = 0.348). In multivariate analysis for LC, invasive carcinoma at the margin (HR 2.957, p = 0.032) and escalated RT dose (HR 0.394, p = 0.047) were independent prognostic factors. No additional GI toxicity was observed in escalated dose group. | 3 |
| 118 | Ebata T, Watanabe H, Ajioka Y, Oda K, Nimura Y. Pathological appraisal of lines of resection for bile duct carcinoma. Br J Surg. 2002 Oct;89(10):1260-7. doi: 10.1046/j.1365-2168.2002.02211.x. PMID: 12296893. | Single institution retrospective | A retrospective review was carried out of 253 resected specimens of extrahepatic bile duct carcinoma. Carcinomas were classified histologically as invasive or non-invasive in addition to assessment of the resection margin. | To determine adequate surgical margin upon gross tumor for extrahepatic bile duct carcinoma | Tumour was present microscopically at the resection margin in 80 (31.6 per cent) of 253 cases, with 46 showing marginal involvement by non-invasive carcinoma, 20 showing invasive carcinoma at a margin, and 14 showing both. Involvement of the resection margin by invasive carcinoma was encountered only when the margin was shorter than 10 mm, whereas non-invasive carcinoma was encountered even when the margin length reached 40 mm. The observed length of microscopic extension of invasive carcinoma beyond the macroscopically evident tumour mass was limited to 10.0 mm. Median microscopic extension of non-invasive carcinoma beyond the mass was 10 mm (75th percentile 19.5 and 14.5 mm in proximal and distal directions respectively; maximum 52 mm). Margins of 20 mm could be assured to be negative proximally in 89.0 per cent of cases and distally in 93.8 per cent. | 3 |
| 119 | Chang YR, Lee KB, Jang JY, Lim CS, Kang MJ, Kwon W, Jung WH, Kim SW. Analysis of microscopic tumor spread patterns according to gross morphologies and suggestions for optimal resection margins in bile duct cancer. J Gastrointest Surg. 2014 Jun;18(6):1146-54. doi: 10.1007/s11605-014-2518-0. Epub 2014 Apr 19. PMID: 24748341. | Single institution retrospective  study | A total of 79 patients with EHBD cancers who underwent curative resection at Seoul National University Hospital between 2007 and 2010 were reviewed. Pathologic findings were reviewed by a single specialized pathologist. | To analyze the patterns of microscopic tumor spreads and their lengths according to gross morphology and to suggest optimal resection margins for EHBD cancer. | Mucosal and mural/perimural spreads were seen in 37.3 and 62.3 %, respectively. The mean length of tumor spreads in the papillary (n = 13), nodular/nodular infiltrative (n = 43), and sclerosing types (n = 23) were 4.5 ± 6.3, 1.8 ± 6.4, and 6.4 ± 6.7 mm, respectively. Spread patterns correlated with gross morphologies (P < 0.001). The lengths of tumor spreads at the 90th percentile were 15.6, 10.0, and 15.6 mm, respectively. | 3 |
| 120 | Kozak MM, Toesca DAS, von Eyben R, Pollom EL, Chang DT. Stereotactic Body Radiation Therapy for Cholangiocarcinoma: Optimizing Locoregional Control With Elective Nodal Irradiation. Adv Radiat Oncol. 2019 Aug 21;5(1):77-84. doi: 10.1016/j.adro.2019.08.003. PMID: 32051893; PMCID: PMC7004929. | Single institution retrospective | A total of 40 patients with intrahepatic (n = 25) or perihilar (n = 15) cholangiocarcinoma treated with SBRT were retrospectively reviewed. SBRT was delivered in 1 to 5 fractions with median dose of 40 Gy. | To report efficacy and toxicity associated with SBRT for patients with intra-hepatic or peri-hilar cholangiocarcinoma | The median follow-up time was 18 months. The 1-year incidence of local in-field, local out-of-field, regional, and distant failure was 8%, 23%, 13%, and 22%, respectively. Median OS was 23 months and 1- and 2-year OS rates were 69% and 39%, respectively. Patients with perihilar tumors had a 1-year incidence of regional failure of 24% and worse OS (P = .013). Patients with regional failure were more likely to develop distant metastases, 32% versus 19% at 1 year (P = .11). Acute grade 3 + hepatobiliary toxicity developed in 15 patients (36%). | 3 |
| 121 | Habermehl D, Lindel K, Rieken S, Haase K, Goeppert B, Buchler MW, Schirmacher P, Welzel T, Debus J, Combs SE. Chemoradiation in patients with unresectable extrahepatic and hilar cholangiocarcinoma or at high risk for disease recurrence after resection: Analysis of treatment efficacy and failure in patients receiving postoperative or primary  chemoradiation. Strahlentherapie und Onkologie. 188(9):795-801, 2012 Sep. UI: 22526232 | Single institutional retrospective study | 25 patients with nonmetastasized ECC and Klatskin tumors were treated with adjuvant RT and CRT (10 patients, 9 patients with R1 resections) or in case of unresectable disease (15 patients).  45 Gy in both patient groups. | To determine efficacy, toxicity, and patterns of recurrence after CRT in patients with ECC and Klatskin tumors following incomplete resection or unresectable disease. | Patients at high risk (9 times R1 resection, 1 pathologically confirmed lymphangiosis) for tumor recurrence after curative surgery had a median time to progression of 8.7 months and an estimated mean OS of 23.2 months. Patients undergoing CRT in case of unresectable primary tumors experienced PFS of 7.1 months and a median OS of 12.0 months. The main site of progression was systemic (liver, peritoneum) in both patient groups. | 3 |
| 122 | Hayashi K, Isohashi F, Ogawa K, Oikawa H, Onishi H, Ito Y, Takemoto M, Karasawa K, Imai M, Kosaka Y, Yamazaki H, Yoshioka Y, Nemoto K, Nishimura Y, JAPANESE RADIATION ONCOLOGY STUDY GROUP (JROSG). Postoperative External Irradiation of Patients with Primary Biliary Tract Cancer: A Multicenter Retrospective Study. Anticancer Research. 35(11):6231-7, 2015 Nov. UI: 26504056 | Multi institution retrospective study | 187 patients who received postoperative RT following surgical resection for BTC with median RT dose 50.4Gy | To assess clinical outcomes of postoperative radiotherapy for BTC | 2-year actuarial OS and LC rates were 56% and 68%, respectively. In multivariate analysis, macroscopic residual tumor (R2) and irradiated doses <54 Gy were significant indicators of poor  LC prognosis. For patients with complete resection (R0) or microscopic residual tumor (R1), 2-year LCs were 71% for <54 Gy and 83% for >=54 Gy; doses >=54 Gy were associated with high long-term LCs. There was no significant difference in acute adverse event rates between <54 Gy and >=54 Gy. | 3 |
| 123 | Kim K, Chie EK, Jang JY, Kim SW, Han SW, Oh DY, Im SA, Kim TY, Bang YJ, Ha SW. Adjuvant chemoradiotherapy after curative resection for extrahepatic bile duct cancer: a long-term single center experience. American Journal of Clinical Oncology. 35(2):136-40, 2012 Apr. UI: 21325937 | Single institution retrospective analysis | 86 patients who underwent resection for ECC followed by adjuvant CRT (40G, 20 fractions to the tumor bed and regional LN with concurrent 5-FU) | To analyze the outcome of adjuvant CRT for patients with ECC and to identify the prognostic factors for these patients. | 48 patients failed the treatment: LRR in 20, DM in 38, and both LRR and DM in 10 patients. 5-year LR DFS rate was 70.3%. On multivariate analysis, resection margin status was the only significant prognosticator (P=0.0299). 5-year DM DFS was 53.6%. 3 or more involved LN had an adverse impact on DM DFS P=0.0334). 5-year OS was 44.7%, and poorly differentiated tumor was associated with inferior OS (P=0.0297). | 3 |
| 124 | Mukai Y, Matsuyama R, Koike I, Kumamoto T, Kaizu H, Homma Y, Takano S, Sawada Y, Sugiura M, Yabushita Y, Ito E, Sato M,  Endo I, Hata M. Outcome of postoperative radiation therapy for cholangiocarcinoma and analysis of dose-volume histogram of remnant liver. Medicine. 98(31):e16673, 2019 Aug. UI: 31374045 | Single institution retrospective observational study | 32 patients received postoperative RT following partial hepatectomy for cholangiocarcinoma. "Liver reduction rate" was calculated by contouring liver volume at CT just before surgery and at CT for planning the RT. To evaluate late toxicity, the radiation-induced hepatic toxicity was determined by the common terminology criteria for adverse events toxicity grade of bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase, and albumin, and was defined from 3 months after RT until liver metastasis. The radiation-induced liver disease was also evaluated. Tumor stages were distributed as follows: I:  1, II: 8, IIIA: 1, IIIB: 6, IIIC: 14, IVA: 2. Median prescribed total dose was 50 Gy | was to analyze DVH of the remnant liver for postoperative  cholangiocarcinoma patients, to find toxicity rates, and to confirm efficacy of postoperative RT | 2-year OS: 72.4%, DFS: 47.7%, local control: 65.3%, median OS 40 months. The median "liver reduction rate" was 21%. The OS had statistically significant difference in nodal status (P = .032) and "liver reduction rate" >30% (P = .016). In the association between >=grade 2 radiation induced hepatic toxicity and DVH, there were significantly differences in V30 and V40 (P = .041, P = .034), respectively. Grade >=2 radiation induced hepatic toxicity rates differ also significantly by sex (P = .008). Two patients (6.2%) were suspected of radiation induced liver toxicity. V30 and V40 RT for remnant liver should be considered to prevent radiation-induced liver dysfunction. | 3 |
| 125 | Lee HC, Lee JH, Lee SW, Lee JH, Yu M, Jang HS, Kim SH. Retrospective analysis of intensity-modulated radiotherapy and three-dimensional conformal radiotherapy of postoperative treatment for biliary tract cancer. Radiation Oncology Journal. 37(4):279-285, 2019 Dec. UI: 31918466 | Single institution retrospective study | 57 patients of BTC treated with curative surgery followed by postoperative 3D-CRT (27) or IMRT (30) | To compare the outcome of 3D-CRT) and IMRT for the postoperative treatment of BTC | 2-year DFS higher in IMRT arm than 3D-CRT arm with a marginal significance (25.9% vs. 47.4%; p = 0.088). 2-year LR DFS (64.3% vs. 81.7%; p = 0.122) and 2-year DM DFS (40.3% vs. 55.8%; p = 0.234) not significantly different. In the multivariate analysis, ECC, poorly-differentiated histologic grade, and higher stage were significant poor prognostic factors for survival. Severe treatment-related toxicity was not significantly different between 2 arms. | 3 |
| 126 | Liu MY, Lo CH, Lin CS, Chao HL, Yang JF, Lin KT, Fan CY, Su YF, Huang WY. Stereotactic ablative radiotherapy for patients with unresectable or medically inoperable cholangiocarcinoma. Tumori. 103(3):236-241, 2017 May 12.UI: 28058710 | Single institution retrospective study | 15 patients with medically inoperable cholangiocarcinoma with 17 lesions were included in this study. The lesions included 14 intrahepatic, 1 hilar, and 2 distal bile duct tumors. Three patients were classified as medically inoperable because of old age or multiple comorbidities. Tumors measured 0.8-13 cm (median, 3.6 cm). The median prescribed dose was 45 Gy delivered over 5 consecutive days. | To examine the efficacy and safety of SBRT in patients with medically inoperable cholangiocarcinoma | Objective responses were observed for 10 of  17 tumors (58.8%), including 3 complete responses (17.6%). The median survival duration was 12.6 months, and the 1- and 2-year OS were 50.3% and 14.4%, respectively. The 1- and 2-year in-field failure-free rates were 61.5% and 30.8%, respectively. For patients with BEDs exceeding 75 Gy10, the 1- and 2-year OS were 58.3% and 33.3%, respectively, compared to 20.0% and 0%, respectively for those with BEDs lower than 75 Gy10. Radiation-induced liver disease did not develop in any patient. Acute toxicities were generally mild and tolerable. | 3 |
| 127 | Lee J, Yoon WS, Koom WS, Rim CH  Efficacy of stereotactic body radiotherapy for unresectable or recurrent cholangiocarcinoma: a meta-analysis and systematic review. Strahlentherapie und Onkologie. 195(2):93-102, 2019 Feb. UI: 30206644 | Systematic review and Meta-analysis | Systematic review of Embase, PubMed, MEDLINE, and Cochrane library databases identified 11 studies and 226 patients who underwent SBRT for unresectable or recurrent cholangiocarcinoma | To examine the efficacy of SBRT for unresectable or recurrent cholangiocarcinoma | The pooled 1-year LC rate was 81.8% (95% CI 69.4-89.9%) in the studies using an EQD2 >=71.3Gy2 and 74.7% (95% CI 57.1-86.7%) in the studies using an EQD2 <71.3Gy2. The median OS was 13.6 (range 10-35.5) months. The pooled 1-year OS rate was 53.8% (95% CI 44.9-62.5%) and the pooled 1-year LC rate was 78.6% (95% CI 69.0-85.8%). Most common toxicity was duodenal ulcer and gastric ulcer in available studies, with the acute incidence of grade >=3 of less than 10% and the late incidence of 10-20%. | M |

**Article Key:**

Of the 127 (all) references cited in the ARS Appropriateness Criteria Esophageal Adenocarcinoma document found through the search strategy, 124 are categorized as therapeutic references including 40 well-designed studies (Phase II randomized and III), 8 moderately well- designed studies that account for most common biases (matched cohort and phase II studies), 62 studies with design limitations (retrospective reviews), and 14 references that are meta-analysis studies. The authors added 23 citations from bibliographies, websites, or books, not found in the new literature search.

**ARS Appropriateness Criteria Evidence Table Key:**

**Study Quality Category Definitions**

*Category 1* The study is well-designed and accounts for common biases.

*Category 2* The study is moderately well-designed and accounts for most common biases.

*Category 3* There are important study design limitations.

*Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);

b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;

c) the study is an expert opinion or consensus document.

*Category M* The study is a meta-analysis and has not been rated for quality because the method is designed to evaluate individual studies only.

**Abbreviations Key***:*

3D-CRT = three-dimensional conformal radiotherapy

5-FU = 5-fluorouracil

AC = adjuvant chemotherapy

AEs = adverse events

BED = biologic effective dose

BTC = biliary tract cancer

CART = chimeric antigen receptor T-cell

CI = confidence interval

CR = complete response

CRT = chemoradiation

CSS = cause specific survival

CT = computed tomography

DFS = disease free survival

DM = distant metastases

DSS = disease specific survival

DVH = dose-volume histogram

ECC = extrahepatic cholangiocarcinoma

EGFR = epidermal growth factor receptor

EQD2 = equivalent dose in 2 Gy per fraction

ERCP = endoscopic retrograde cholangiopancreatography

FFDP = freedom from distant progression

FFLP = freedom from local progression

HC = hilar cholangiocarcinoma

HDR ILBT = high dose rate intraluminal brachytherapy

HAI = hepatic artery intra-arterial infusion

HIFUA = high-intensity focused ultrasound ablation

HR = hazard ratio

HR QOL = health related quality of life

IAC = intraarterial chemotherapy

IMRT = intensity modulated radiotherapy

ISGLS = International Study Group of Liver Surgery

LC = local control

LN = lymph node

LR = local recurrence

LR PFS = locoregional progression-free survival

LRR = local regional recurrence

LT – liver transplantation

MRI = magnetic resonance imaging

MS = median survival

NAC = neoadjuvant chemotherapy

NCDB = National Cancer Database

NCRT = neoadjuvant chemoradiation

OR = odds ratio

OS = overall survival

PBT = proton beam therapy

PD = progressive disease

PDT = photodynamic therapy

PFS = progression-free survival

PR = partial response

PSC = primary sclerosing cholangitis

PTCS = percutaneous transhepatic cholangioscopy

RFA endoscopic radiofrequency ablation

RR = regional recurrence

RT = radiotherapy

RSS = radioactive seed strand

SBRT = stereotactic body radiotherapy

SD = stable disease

VEGF = vascular endothelial growth factor