

Table S1 Select series of curative-intent radiotherapy for extra-hepatic biliary cancers

Author	Year	N	Disease site	Study design	Concurrent chemotherapy (%)	Median EBRT dose (Gy)	Brachy-therapy (%)	OS	PFS	Grade 3+ acute toxicity	Late toxicity
TakamuraSaito <i>et al.</i> , 2003	1988 to 1998	93	EBC: 100%	Retrospective	0	50	100	mOS: 12 months; OS2: 15%; OS3: 10%; OS5: 4%	–	–	Bowel: G3: 11%; Biliary (including cholangitis) G3: 5%
DeodatoClemente <i>et al.</i> , 2006	1991 to 1997	22	EBC: 100%	Retrospective	95	50.4	55	mOS: 23 months; OS2: 41%; OS3: 18%	–	GI: 0%	Bowel: G3: 9%
BrunnerSchwab <i>et al.</i> , 2004	1994 to 2001	25	EBC: 100%	Retrospective	100	45	16	mOS: 17 months	–	Nausea: 21%; Diarrhea: 0%	–
BowlingGalbraith <i>et al.</i> , 1996	1988 to 1994	28	EBC: 100%	Retrospective	–	30	100	mOS: 10 months	–	–	–
SchleicherStaatz <i>et al.</i> , 2002	1991 to 1999	30	EBC: 100%	Retrospective	80	30	60	mOS: 6 months; EBRT vs. EBRT + brachytherapy: 4 months vs. 9 months (P=0.25)	–	–	–
YoshiokaOgawa <i>et al.</i> , 2014	2000 to 2011	209	EBC: n/a I-CCA: n/a Ampullary cancer: n/a	Retrospective	78	50	27	Brachytherapy yes vs. no: OS2: 31% vs. 33% (P=0.34); DSS2 42% vs. 37% (P=0.079)	–	–	–
TorgesonLloyd <i>et al.</i> , 2017	2004 to 2014	Total 2,966; 1,070 RT	EBC: 73% Ampullary cancer: 27%	NCDB	85	54	–	CRT vs. chemotherapy: mOS: 15 vs. 13 months (P<0.001)	–	–	–
AutorinoMattiucci <i>et al.</i> , 2016	2002 to 2009	27	EBC: 100%	Prospective Phase II	100	50	22	mOS: 14 months; OS2: 27%; OS3: 7%	–	Hematologic: 19%; GI: 19%	–
BiselloBuwenge <i>et al.</i> , 2019	1991 to 2017	76	EBC: 96% I-CCA: 4%	Retrospective	78	50	51	mOS: 14 months; OS2: 26%; OS3: 11%	mPFS: 10 months; PFS2 9%; PFS3 9%	Hematologic: 8%; GI: 13%	–
Ben-DavidGriffith <i>et al.</i> , 2006	1986 to 2004	81 total, 52 unresectable	EBC: 100%	Retrospective	54	60.2	–	mOS: 13 months	mPFS: 8 months	Nausea: 1%; Fatigue: 2%; Cholangitis: 6%	GI bleed: 3%
ElganainyHolliday <i>et al.</i> , 2018	2001 to 2015	80	EBC: 100%	Retrospective	86	50.4 BED: 59.5 Gy10	–	mOS: 19 months, 17 months, (perihilar), 27 months (distal)	–	GI: 11%; Hematologic: 15%; Hospitalization: 33%	GI Bleed: 28%
SandlerVeruttipong <i>et al.</i> , 2016	2008 to 2015	31	EBC: 81% I-CCA: 19%	Retrospective	–	40 (SBRT)	–	mOS: 16 months; OS2: 33%	mPFS: 17 months; PFS2: 34%	–	Overall: 16%; GI ulcer and bleed: 9%; Duodenal Obstruction: 6%
ChenChen <i>et al.</i> , 2015	2001 to 2010	34 total, 16 CRT, 18 RT	EBC: 100%	Retrospective	47	54	–	mOS: 10 months; CRT vs. RT mOS: 14 vs. 7 months (P=0.003)	CRT vs. RT mPFS: 9 vs. 4 months (P=0.005)	–	–
PhelipVendrey <i>et al.</i> , 2014	2006 to 2010	34 total, 18 CRT, 16 Chemo	EBC: 100%	Prospective Randomized Phase II	100 (in CRT arm)	50	–	CRT vs. Chemotherapy 14 vs. 20 months	CRT vs. Chemotherapy mPFS: 6 vs. 11 months	Hospitalization: 74%; CRT vs. Chemotherapy Overall: 47% vs. 75%; Hematologic: 23% vs. 25%; GI: 12% vs. 6%	CRT vs. chemotherapy biliary: 28% vs. 44%
MakitaNakamura <i>et al.</i> , 2014	2009 to 2011	28	EBC: 43% Lymph node recurrence: 36% I-CCA: 21%	Retrospective	11	68.2	–	OS1: 49%	PFS1: 30%	Biliary: 4%	Duodenal ulcer: 7%; Gastric ulcer: 4%; GI Bleed: 7%; Duodenal stenosis: 7%
ValekKysela <i>et al.</i> , 2007	to	42 total, 21 Stent, 21 Stent + RT	EBC: 100%	Prospective RCT	–	50	100	Stent + RT vs. Stent: 13 months vs. 10 months (P<0.05)	–	–	–
Alden and Mohiuddin 1994	1984 to 1990	48 total, 24 RT, 24 no RT	EBC: 100%	Retrospective	79	46	67	RT vs. no RT 12 months vs. 6 months (P=0.01); OS2: 30% vs. 17%	–	–	Biliary infection: 56%; Biliary obstruction: 17%
Moureau-ZabottoTurrini <i>et al.</i> , 2013	1995 to 2008	30	EBC: 100%	Retrospective	60	48.25	–	mOS: 12 months; OS3: 15% RT vs. CRT; OS1: 28% vs. 67% (P=0.15)	mPFS: 9 months; PFS3: 16%; RT vs. CRT PFS1: 29% vs. 44% (P=0.3)	Overall: 30%; Nausea: 13%; Cholangitis: 17%	–
GhafooriNelson <i>et al.</i> , 2011	1992 to 2006	37	EBC: 100%	Retrospective	86%	45	38	mOS: 14 months; OS2: 22%	–	Overall: 14%	–
TsujinoLandry <i>et al.</i> , 1995	1979 to 1993	27	EBC: 100%	Retrospective	15	45	74	mOS: 13 months; OS2: 9%	–	–	Cholangitis: 61%; Gastric outlet obstruction: 9%
CraneMacdonald <i>et al.</i> , 2002	1957 to 2000	52	EBC: 100%	Retrospective	73	30–85	6	mOS: 10 months; OS2: 13%	–	Overall: ~21%; Hospitalization: 21%	–
KozakToesca <i>et al.</i> , 2020	2003 to 2017	40	I-CCA: 62% EBC: 38%	Retrospective	–	40 (SBRT)	–	mOS: 23 months I-CCA vs. Perihilar: 23 months vs. 10 months (P=0.018)	–	Non-hepatobiliary: 3%; Hepatobiliary: 40%	Non-hepatobiliary: 3%; Hepatobiliary: 43%
KasuyaTerashima <i>et al.</i> , 2019	2005 to 2016	56	EBC: 52% I-CCA: 48%	Retrospective	2	76	–	mOS: 15 months; OS2: 41% Perihilar only; mOS: 13 months; OS2: 26%	mPFS: 9 months; PFS2: 32%	–	Liver: 2%
FooGunderson <i>et al.</i> , 1997	1980 to 1991	24	EBC: 100%	Retrospective	38	50.4	100	mOS: 13 months; OS2: 19%; OS5: 14%	PFS5: 13%	Hospitalization: 8%	Cholangitis: 50%; GI ulcer with bleeding: 42%
LeeYi <i>et al.</i> , 2016l	2007 to 2011	18	EBC: 100%	Prospective Pilot	100	45	0	mOS: 10 months	mPFS: 7 months	Thrombocytopenia: 33%; Anemia: 11% Neutropenia: 6%; Non-hematologic: 6%	–
TanZhu <i>et al.</i> , 2015	2007 to 2013	38 total, 13 Stent, 25 Stent + RT	EBC: 100%	Retrospective	–	37–40.7	–	mOS: 12 months	–	–	–
IsayamaTsujino <i>et al.</i> , 2012	1986 to 2008	39 total, 11 Stent, 28 Stent + RT	EBC: 100%	Retrospective	0	54	39%	Stent vs. Stent + EBRT 6 months vs. 22 months (P=0.0031)	–	–	GI ulcer and bleed: 18%

EBRT, external beam radiotherapy; OS, overall survival; PFS, progression-free survival; EBC, extrahepatic biliary cancer; mOS, median overall survival; G3, grade 3 or higher; I-CCA, intra-hepatic cholangiocarcinoma; DSS, disease-specific survival; NCDB, national cancer database; CRT, chemoradiotherapy; GI, gastrointestinal; mPFS, median progression-free survival; BED, biologically effective dose; SBRT, stereotactic body radiotherapy; RT, radiotherapy