

Supplementary materials:

Role of adjuvant (chemo)radiotherapy for resected extrahepatic cholangiocarcinoma: a meta-analysis

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Table S1 Characteristics of the included studies

| Study (first author) | Format | Publication year | Journal | Study period | Center | Patient number (A(C)RT group vs. control) | Median age (A(C)RT group vs. control) | Male (% A(C)RT group vs. control) | Primary site | NOS score |
|--------------------------|-----------|---------------------|---------------------------------------|------------------------------|--------|---|---|---|----------------------|--------------|
| Gwak HK 2010 | Full text | 2010 | Int J Radiation Oncology Biol | 1997 to 2005 | Korea | 31 vs. 47 | 57 (36–76) vs. 65 (38–85) | 77.4 vs. 68.1 | Perihilar/ distal | 4 |
| Hughes MA 2007 | Full text | 2007 | Int J Radiation Oncology Biol Phys | 1994 to 2003 1970 to 1992 | USA | 34 vs. 30 | 64 (39–90) vs. – | – | distal | 4 |
| Im JH 2016 [#] | Full text | 2016 | Cancer Res Treat | Jan. 2001 to Dec. 2010 | Korea | 49 vs. 168 | 64 (32–90) | 63.3 vs. 70.2 | Perihilar/ distal | 7 |
| Im JH 2016 [#] | Full text | 2016 | Cancer Res Treat | Jan. 2001 to Dec. 2010 | Korea | 29 vs. 168 | 64 (32–90) | 55.2 vs. 70.2 | Perihilar/ distal | 7 |
| Itoh H 2005 | Full text | 2005 | Dig Dis Sci | Apr. 1994 to Mar. 2004 | Japan | 11 vs. 8 | 71 (62–79) | – | Perihilar/ distal | 4 |
| Kim MY 2016 | Full text | 2016 | Radiat Oncol J | Jan. 2000 to Dec. 2013 | Korea | 19 vs. 33 | 67 (46–81) vs. 65 (43–79) | 74.0 vs. 70.0 | Perihilar/ distal | 5 |
| Kim YJ 2017 | Full text | 2017 | Br J Radiol | 1997 to 2015 | Korea | 23 vs. 36 | 65 | 47.8 vs. 58.3 | Perihilar/ distal | 5 |
| Kim YS 2016 [#] | Full text | 2016 | Cancer Chemother Pharmacol | Jan. 2001 to Dec. 2013 | Korea | 20 vs. 102 | 63 (39–78) vs. 68 (48–85) | 62.5 vs. 75.5 | distal | 5 |
| Kim YS 2016 [#] | Full text | 2016 | Cancer Chemother Pharmacol | Jan. 2001 to Dec. 2013 | Korea | 9 vs. 102 | 63 (39–78) vs. 68 (48–85) | 62.5 vs. 75.5 | distal | 5 |
| Matsuda T 2013 | Full text | 2013 | Am J Clin Oncol | Jan. 2000 to Mar. 2010 | Japan | 11 vs. 25 | 74 (60–80) vs. 69 (35–81) | 63.6 vs. 36.0 | Perihilar/ distal | 4 |

| Study (first author) | Histology type | TNM stage | Positive lymphovascular invasion (% A(C)RT group vs control) | Positive perineural invasion (% A(C)RT group vs. control) | Surgery-radiotherapy interval | Radiation therapy dose (Gy) | Fraction dose (Gy) |
|--------------------------|---|-----------|--|---|-------------------------------|-----------------------------|--------------------|
| Gwak HK 2010 | Adenocarcinoma/ adenosquamous | I–III | 35.5 vs. 38.3 | 67.7 vs. 61.7 | – | 50.4 (45.0–54.0) | 1.8 |
| Hughes MA 2007 | Moderate-poor differentiated vs Well-poor differentiated | II–III | – | – | 53 (43–62) days | 50.4 (40.0–54.0) | 1.8–2.5 |
| Im JH 2016 [#] | Well-poor differentiated | I–III | 16.3 vs. 19.6 | 71.4 vs. 55.4 | 4–6 weeks | 50.4 (41.4–54.0) | 1.8 |
| Im JH 2016 [#] | Well-poor differentiated | I–III | 20.7 vs. 19.6 | 65.5 vs. 55.4 | 4–6 weeks | 50.4 (41.4–54.0) | 1.8 |
| Itoh H 2005 | Well-poor differentiated | I–III | – | – | 4–6 weeks | 52.3 (37.8–79.8) | 1.8–2.0 |
| Kim MY 2016 | Well-poor differentiated/ unclear | I–III | 53.0 vs. 58.0 | 63.0 vs. 70.0 | 4–8 weeks | 50.4 (45.0–54.0) | – |
| Kim YJ 2017 | Well-poor differentiated/ unclear | – | – | 65.2 vs. 55.6 | – | 50.4 (45.0–61.0) | 1.8–2.0 |
| Kim YS 2016 [#] | Well-poor differentiated/ unclear | I–III | – | – | – | – | – |
| Kim YS 2016 [#] | Well-poor differentiated/ unclear | I–III | – | – | – | – | – |
| Matsuda T 2013 | Well-poor differentiated | I–IVB | – | – | – | 46.0–60.0 | 1.8–2.0 |

| Study (first author) | Concurrent chemotherapy used in A(C)RT group | CRT patient number in A(C)RT group | Resection margin status | R0 resection margin (% A(C)RT group vs. control) | LN status | Positive lymph nodes (% A(C)RT group vs. control) | Median follow-up time (month) | Median OS (month) (A(C)RT group vs. control) | Median DFS (month) (A(C)RT group vs. control) |
|--------------------------|--|------------------------------------|-------------------------|---|-----------|--|-------------------------------|---|--|
| Gwak HK 2010 | 5-FU based | 16/31 | R0/R1 | 35.5 vs. 42.6 | N(+)/N(-) | 45.2 vs. 44.7 | 19.5 | 26 vs. 19 | - |
| Hughes MA 2007 | 5-FU based | 34/34 | R0/R1/R2 | 74.0 vs. 93.0 | N(+)/N(-) | 82.0 vs. 37.0 | 41 | 36.9 vs. 22 | - |
| Im JH 2016 [#] | 5-FU/gemcitabine based | 49/49 | R0/R1/R2 | 38.8 vs. 86.3 | N(+)/N(-) | 42.9 vs. 23.8 | 63 | 42.9 vs. 43.2 | 30.3 vs. 39.1 |
| Im JH 2016 [#] | NO | 0/29 | R0/R1/R2 | 34.5 vs. 86.3 | N(+)/N(-) | 41.4 vs. 23.8 | 63 | 47.6 vs. 43.2 | 44.0 vs. 39.1 |
| Itoh H 2005 | NO | 0/11 | R0/R1/R2 | 42.1 | N(+)/N(-) | 57.9 | 32 | 17 vs. 16 | - |
| Kim MY 2016 | 5-FU/gemcitabine based | 12/19 | R0/R1 | 26.0 vs. 70.0 | N(+)/N(-) | 42.0 vs. 27.0 | 24 | 37 vs. 26 | - |
| Kim YJ 2017 | 5-FU/gemcitabine based | 15/23 | R0/R1/R2 | 52.2 vs. 69.4 | N(+)/N(-) | 34.8 vs. 41.7 | 19 | - | - |
| Kim YS 2016 [#] | 5-FU/capecitabine/ gemcitabine based | 20/20 | R0 | 100 vs. 100 | N(+)/N(-) | 39.3 vs. 24.5 | 33.7 | - | - |
| Kim YS 2016 [#] | NO | 0/9 | R0 | 100 vs. 100 | N(+)/N(-) | 39.3 vs. 24.5 | 33.7 | - | - |
| Matsuda T 2013 | - | 5/11 | R0/R1 | 18.2 vs. 100 | N(+)/N(-) | 54.5 vs. 32.0 | - | 44 vs. 47 | 40 vs. 29 |

A(C)RT: adjuvant (chemo)radiotherapy; TNM: tumor-node-metastasis; 5-FU: 5-fluorouracil; CRT: concurrent chemoradiotherapy; R0: negative resection margin; R1: microscopic positive resection margin; R2: macroscopic positive resection margin; LN: lymph node; -: not reported. [#] Two articles contained three groups, comparing ACRT vs. surgery alone and ART vs. surgery alone; thus, they were calculated respectively (Im et al., 2016; Kim YS et al., 2016). * Data are expressed as median (range)

Table S2 Newcastle-Ottawa Scale (NOS) for quality assessment of non-randomized studies in the meta-analysis (cohort studies)

| Author (year) | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts | Total score |
|----------------|--|-------------------------------------|---------------------------|--|---|-----------------------|---|----------------------------------|-------------|
| Gwak HK 2010 | ★ | ★ | ★ | ☆ | ★☆ | ☆ | ☆ | ☆ | 4 |
| Hughes MA 2007 | ★ | ★ | ★ | ☆ | ☆☆ | ☆ | ☆ | ★ | 4 |
| Im JH 2016 | ★ | ★ | ★ | ☆ | ★★ | ☆ | ★ | ★ | 7 |
| Itoh H 2005 | ★ | ★ | ★ | ☆ | ☆☆ | ☆ | ☆ | ★ | 4 |
| Kim MY 2016 | ★ | ★ | ★ | ☆ | ★★ | ☆ | ☆ | ☆ | 5 |
| Kim YJ 2017 | ★ | ★ | ☆ | ☆ | ★★ | ☆ | ☆ | ★ | 5 |
| Kim YS 2016 | ★ | ★ | ★ | ☆ | ★★ | ☆ | ☆ | ☆ | 5 |
| Matsuda T 2013 | ★ | ★ | ★ | ☆ | ☆☆ | ☆ | ☆ | ★ | 4 |

Table S3 Toxicities (CTCAE Version 3.0) reported in the selected studies

| Study | <i>n</i> | Median follow-up time (month) | Radiation therapy (fraction) dose (Gy) | G3 toxicity (<i>n</i> and type) | Other toxicity (<i>n</i> , grade and type) |
|----------------|----------|----------------------------------|---|---|--|
| Gwak HK 2010 | 31 | 19.5 | 45–54 (1.8) | 0 | Majority G1 anorexia 11 G2 abdominal pain |
| Kim MY 2016 | 19 | 24 | 45–54 | 2 duodenal ulcer | 14 G1 abdominal pain and anorexia |
| Kim YJ 2017 | 23 | 19 | 45–61 | 1 severe nausea and vomiting 1 decreased PLT and WBC count | – |
| Matsuda T 2013 | 11 | – | 46–60 (1.8–2.0) | 0 | 5 G1 anorexia 1 G2 duodenal ulcer |

G1–3: Grade 1–3, PLT: platelet, WBC: white blood cell, -: not reported

References

- Gwak HK, Kim WC, Kim HJ, et al., 2010. Extrahepatic bile duct cancers: surgery alone versus surgery plus postoperative radiation therapy. *Int J Radiat Oncol Biol Phys*, 78(1):194-198.
<https://doi.org/10.1016/j.ijrobp.2009.07.003>
- Hughes MA, Frassica DA, Yeo CJ, et al., 2007. Adjuvant concurrent chemoradiation for adenocarcinoma of the distal common bile duct. *Int J Radiat Oncol Biol Phys*, 68(1):178-182.
<https://doi.org/10.1016/j.ijrobp.2006.11.048>
- Im JH, Seong J, Lee IJ, et al., 2016. Surgery alone versus surgery followed by chemotherapy and radiotherapy in resected extrahepatic bile duct cancer: treatment outcome analysis of 336 patients. *Cancer Res Treat*, 48(2):583-595.
<https://doi.org/10.4143/crt.2015.091>
- Itoh H, Nishijima K, Kurosaka Y, et al., 2005. Magnitude of combination therapy of radical resection and external beam radiotherapy for patients with carcinomas of the extrahepatic bile duct and gallbladder. *Dig Dis Sci*, 50(12): 2231-2242.
<https://doi.org/10.1007/s10620-005-3040-8>
- Kim MY, Kim JH, Kim Y, et al., 2016. Postoperative radiotherapy appeared to improve the disease free survival rate of patients with extrahepatic bile duct cancer at high risk of loco-regional recurrence. *Radiat Oncol J*, 34(4):297-304.
<https://doi.org/10.3857/roj.2016.01879>
- Kim YJ, Kim K, Min SK, et al., 2017. Role of adjuvant radiotherapy for localized extrahepatic bile duct cancer. *Br J Radiol*, 90(1071):20160807.
<https://doi.org/10.1259/bjr.20160807>
- Kim YS, Hwang IG, Park SE, et al., 2016. Role of adjuvant therapy after R0 resection for patients with distal cholangiocarcinoma. *Cancer Chemother Pharmacol*, 77(5): 979-985.
<https://doi.org/10.1007/s00280-016-3014-x>
- Matsuda T, Fujita H, Harada N, et al., 2013. Impact of adjuvant radiation therapy for microscopic residual tumor after resection of extrahepatic bile duct cancer. *Am J Clin Oncol*, 36(5):461-465.
<https://doi.org/10.1097/COC.0b013e31825494ab>