Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis

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CRD summary
The authors concluded that their analyses supported additional therapy after surgery, for high-risk patients with biliary tract cancers. These conclusions appear to reflect the evidence, but the scope of the search was unclear, reviewer and publication bias were possible, variability was insufficiently assessed, and quality was not assessed, so the reliability of the authors’ conclusions is unclear.

Authors' objectives
To determine the impact, of additional therapy for biliary tract cancer, on survival.

Searching
PubMed, EMBASE, and three oncology databases, were searched for eligible studies up to November 2010. Some key search terms were reported. The reference lists of identified records were checked for eligible studies. Searches were restricted to studies published in English.

Study selection
Only studies comparing add-on therapy versus curative surgery alone were eligible for inclusion. Eligible therapies were chemotherapy, radiotherapy, or both, administered after curative surgery. Curative surgery was defined as surgery that left no gross disease. Studies had to include patients with biliary tract cancer, including tumours of the gallbladder or intrahepatic, perihilar, or distal bile ducts. Studies of ampullary tumours were excluded, as were those in which patients receiving curative surgery could not be separated from those receiving non-curative surgery.

About three quarters of the included studies were of patients with cancer of the bile duct, and the other quarter were of patients with cancer of the gallbladder. The earliest start date for a study was 1962, and the latest completion date was 2008. Almost half of the studies were conducted in the USA, just over a quarter were conducted in Japan, and the remaining studies were conducted in Europe. In just under half of the studies patients were treated with radiation alone. Most of the other studies were of chemotherapy and radiotherapy, and a few studies investigated chemotherapy alone. One study included patients with intrahepatic cancer. The surgical procedures and disease stage of the included patients varied across studies; details were reported in supplementary material.

The number of reviewers who were involved in study selection was not reported.

Assessment of study quality
No quality assessment was reported.

Data extraction
For the assessment of the efficacy of additional therapy, the median survival and three- and five-year survival were extracted to calculate odds ratios, with 95% confidence intervals. Relevant missing data were requested from study authors.

Two reviewers extracted the data and another two were consulted to resolve any discrepancies.

Methods of synthesis
Study data were synthesised using a random-effects meta-analysis, calculating odds ratios, with 95% confidence intervals. The inverse-variance approach was used. Analyses were conducted separately for gallbladder cancers and for bile duct cancers.

Subgroup analyses for node-positive or margin-positive disease (including studies where 50% or more of the participants were node- or margin-positive) were planned. It was planned to repeat analyses, without any registry
studies, to investigate their impact on the overall results.

Results of the review

One randomised controlled trial (230 participants), two studies using data from the Surveillance Epidemiology and End Results (SEER) database (5,671 participants), and 17 institutional case series (811 participants) were included in the review. The total number of participants was 6,712 (range 20 to 4,180). Details of the study methods were not provided. All studies reported five-year survival.

Efficacy of adjuvant therapy: For gallbladder and biliary tract cancers (20 studies), gallbladder cancers (six studies), and biliary tract cancers (16 studies) there were no statistically significant differences, in overall survival, between participants receiving surgery alone and participants receiving surgery plus adjuvant therapy. The difference in survival between gallbladder cancer and bile duct cancer patients was not statistically significant. When the two registry studies were removed from the analysis, there was a statistically significant difference, in overall survival, favouring adjuvant therapy (OR 0.53, 95% CI 0.39 to 0.72; 18 studies).

Treatment modality: Compared with surgery alone, adjuvant chemotherapy (OR 0.39, 95% CI 0.23 to 0.66) and adjuvant chemotherapy with radiotherapy (OR 0.61, 95% CI 0.38 to 0.99) were associated with statistically significant improvements in survival. There were no statistically significant differences in survival between surgery alone and adjuvant radiotherapy alone. The differences between these subgroups were significant (p=0.02). The exclusion of the study of patients with intrahepatic cancer had no effect on the overall odds ratio for combined chemotherapy and radiotherapy, but the confidence interval widened and the result was not statistically significant.

Margin and node positivity: Patients with node-positive (OR 0.49, 95% CI 0.30 to 0.80; five studies) or margin-positive cancer (OR 0.36, 95% CI 0.19 to 0.68; six studies) benefited in survival with adjuvant therapy, compared with surgery alone. All patients included in these analyses received chemotherapy alone or chemotherapy and radiotherapy. Further subgroup analyses were reported.

Authors’ conclusions

The authors concluded that their analyses supported the use of adjuvant therapy after surgery, for high-risk patients with biliary tract cancers.

CRD commentary

The review question and inclusion criteria were clear. Relevant sources were searched, but few search terms were reported, so the scope of the search is unknown. The search was restricted to studies published in English, so relevant unpublished studies and studies in other languages, may have been missed. The risk of publication bias was not assessed. Two people extracted the data independently, which limits the risk of reviewer error and bias, but it was unclear if similar processes were used for study selection.

The methods of synthesis were appropriate, but heterogeneity was not assessed and not taken into consideration in the analyses. The authors stated that the studies were reasonably similar and could be combined in meta-analysis, and that sensitivity analyses were used to explore heterogeneity, but this did not assess the heterogeneity in individual analyses. The comparability of the studies remains unclear. As no quality assessment was reported it is impossible to know the risk of bias associated with each study, and the impact this could have on the analyses. The reliability of the results is unclear. Few demographic details of the included patients were provided, so the generalisability of findings is limited.

The authors’ conclusions appear to reflect the evidence presented, but their reliability is unclear, due to the unclear scope of the search, the unclear potential for publication bias, possible bias and error in the review process, the insufficient assessment of heterogeneity, the lack of patient details, and the lack of quality assessment.

Implications of the review for practice and research

Practice: The authors stated that their findings supported the usual practice for adjuvant therapy in patients with biliary tract cancer.

Research: The authors noted a lack of randomised evidence and encouraged international collaboration to support and develop further research. They recommended that the findings of their review should be used to inform the research.
Funding
Supported by the Princess Margaret Hospital, and the University of Toronto, Canada.

Bibliographic details

PubMedID
22529261

DOI
10.1200/JCO.2011.40.5381

Original Paper URL
http://jco.ascopubs.org/content/30/16/1934.abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Bile Duct Neoplasms /surgery /therapy; Chemotherapy, Adjuvant; Combined Modality Therapy; Gallbladder Neoplasms /surgery /therapy; Humans; Radiotherapy, Adjuvant

AccessionNumber
12012036894

Date bibliographic record published
26/11/2012

Date abstract record published
03/05/2013

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.