

# Resectiver surgery versus palliative care in advanced gallbladder cancer

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## Abstract

### Introduction

Despite multiple advances in medicine, gallbladder cancer remains a disease with poor prognosis. In advanced stages, the main options are surgical management or palliative non-surgical care. However, it is not clear which therapy constitutes a better alternative.

### Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

### Results and conclusions

We identified one systematic review including three primary studies, none of them randomized. We concluded that resective surgery may increase survival rates in patients with advanced gallbladder cancer, but the certainty of the evidence is low.

## Problem

Gallbladder cancer is an uncommon cancer, but it is the most common biliary duct cancer, representing 85-90%<sup>1</sup>. However, diagnosis is frequently done at a late stage, since it does not present with symptoms or signs in earlier stages, and prognosis remains ominous in comparison to other types of cancer. Five-year overall survival is 18%, while in advanced stages it might be as low as 2 to 8 percent<sup>2</sup>. Thus, it is imperative to clarify the best type of treatment, particularly in stages considered incurable.

Traditionally, two distinct forms of treatment have been proposed in advanced stages: resective surgery and palliative non-surgical care. Unlike resective surgery which has curative intent in early stages, in advanced gallbladder cancer the aim is to reduce tumor size, and to improve quality of life and survival.

However, its comparative effectiveness against other palliative alternatives such as chemotherapy, endoscopic therapy, interventional radiology or other medical therapies is still a matter of controversy.

### Key messages

- Resective surgery compared to palliative care may increase survival rate in patients with advanced gallbladder cancer (low certainty of evidence).

### Methods

We searched in Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and re-analyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

## About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	Only one systematic review <sup>3</sup> was found, which included three primary studies <sup>4-6</sup> , none of them a randomized trial.
What types of patients were included*	All primary studies included adult patients with advanced gallbladder cancer. Average participant age ranged from 64 to 68 years. All studies included patients in stages IVA and IVB, according to the American Joint Committee on Cancer (AJCC) classification scale. In one of the studies 78% of patients were classified IVB and 22% IVA <sup>4</sup> . In another study <sup>5</sup> , 88% were IVB and 12% IVA. In the last study, 55% of patients were IVA and 45% IVB <sup>6</sup> .
What types of interventions were included*	All primary studies assessed surgical treatment in comparison to any type of palliative non-surgical treatment. One study <sup>4</sup> assessed resective surgery, palliative chemotherapy and best available supportive care (biliary duct prosthesis, external biliary drain and radiotherapy). Another study <sup>5</sup> evaluated resective surgery and palliative care (chemotherapy and radiotherapy). The last study <sup>6</sup> compared surgical treatment to chemotherapy and other palliative treatments.
What types of outcomes were measured	All studies and the review reported survival as main outcome. Average follow-up was 10.6 years, with a range of seven to 16 years. Only one of them reported the number of patients with R0 borders after surgery.

\* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

## Summary of Findings

Information about the effects of resective surgery on advanced gallbladder cancer is based on three studies, that included 2990 participants overall<sup>4-6</sup>.

All of the studies assessed overall survival rate. The review reported the data were not suitable for incorporation into a meta-analysis, so the information is presented as a narrative synthesis.

The summary of findings is as follows:

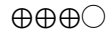
- Resective surgery may increase survival rate in advanced gallbladder cancer (low certainty of evidence)
- No studies were found that assessed quality of life.
- No studies were found that assessed adverse effects.

Resective surgery versus palliative treatment in advanced gallbladder cancer		
<b>Patients</b>	Patients with advanced gallbladder cancer	
<b>Intervention</b>	Resective surgery	
<b>Comparison</b>	Non surgical palliative treatment	
Outcome	Effects	Certainty of evidence (GRADE)
Survival	<p>All studies<sup>4-6</sup> reported better survival in patients that received palliative resective surgery.</p> <p>The first study<sup>4</sup> reported overall survival rate 4.5 times greater (45% vs 10%) in the surgery group compared to those who received palliative chemotherapy (1-year follow-up).</p> <p>The second study<sup>5</sup> reported five-year survival rate of 10% in stage IVB patients who received surgery and 0% in those that received palliative care (5-year follow-up).</p> <p>The third study<sup>6</sup> reported a mean survival rate 2.6 times greater (8 vs 3 months) in patients who received surgery versus those who opted for palliative care (follow-up not specified).</p>	<p>⊕⊕○○<sup>1,2,3</sup> Low</p>
Quality of life	The outcome quality of life was not reported by the systematic review	--
Adverse effects	The outcome adverse effects was not reported by the systematic review	--
<p>GRADE: Evidence grades of the GRADE Working Group (see later).</p> <p><sup>1</sup> Observational studies</p> <p><sup>2</sup> The certainty of the evidence was downgraded one level for risk of selection bias in primary studies reported by the systematic review.</p> <p><sup>3</sup> The certainty of evidence was upgraded in one level for large effect size.</p>		

## About the certainty of the evidence (GRADE)\*



**High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.



**Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.



**Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.



**Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

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\* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

## Other considerations for decision-making

### To whom this evidence does and does not apply

The results presented are applicable to patients with advanced gallbladder cancer, in which conventional therapy with curative intention has been ruled out. All three included studies consider patient with gallbladder adenocarcinoma in stages IVA and IVB of the American Joint Committee on Cancer (AJCC). In absence of direct evidence, it seems reasonable to extrapolate these conclusions to other stages considered incurable such as IIIA or IIIB. It is important to mention that the studies did not report functionality of patients prior to surgery, which should be considered when interpreting the results.

The results are not applicable to patients presenting with gallbladder cancer in early stages, in which treatment with curative intent is an option, being cholecystectomy or hepatic wedge in accordance with staging. Similarly, these results are not applicable to with other histological types or to incidental diagnosis of gallbladder cancer after cholecystectomy, which are usually eligible for curative treatment.

### About the outcomes included in this summary

The outcome included by the systematic review and reported as main outcome by the primary studies is overall survival. The authors of this summary agree this outcome corresponds to the critical outcome for decision making. Additionally, the authors agree that it is necessary to consider other outcomes at the time of making decisions, such as quality of life after either intervention and adverse effects associated with them. These are not reported by the systematic review. The authors agree that in cases of poor prognosis histology, such as advanced gallbladder cancer, one-year survival rate usually is more relevant for decision-making, however, the studies report the outcomes differently, two of them dichotomously<sup>4,5</sup> and one as extra months of survival<sup>6</sup>.

### Balance between benefits and risks, and certainty of the evidence

In relation to the comparison between resective surgery and non-surgical palliative care in patients with advanced gallbladder cancer, there is a substantial lack of information. Furthermore, the analysis of the little data available is troublesome given the impossibility of conducting a meta-analysis. Considering the former, and the high risk of bias of

the studies presented in this review, the quality of the evidence is considered to be low in accordance with GRADE working group criteria.

Considering that surgical treatment may have better results regarding survival rate in patients with advanced gallbladder cancer, it is necessary to evaluate risks and complications associated with surgery, considering the patient's underlying conditions and the accessibility to existing alternative treatments. In any case, the authors agree that any decision and evaluation must be made in conjunction with the patient.

### Resource considerations

The systematic review analysed does not report costs associated to the surgical treatment versus non-surgical palliative care in advanced stage gallbladder cancer. Given the current uncertainty about the survival benefit, and the lack of data on other relevant outcomes, it is not possible to estimate the balance between costs and benefits.

### What would patients and their doctors think about this intervention

The generalized clinical opinion about gallbladder cancer treatment is frequently biased by the ominous prognosis of this disease, which is greater in advanced stages, where prognosis is poor regardless of the treatment strategy. Whether there are clinically significant benefits associated with resective surgery despite not achieving negative margins (R0) is a matter of unresolved controversy, therefore, most clinicians choose to dismiss the possibility of surgical treatment when curative intention is not possible, especially considering the risks and complications of surgery in the fragile condition of most patients. This approach might disregard the potential benefits on survival for patients with residual disease after surgery. In relation to the opinion of patients at the moment of choosing between treatments, there should be great variability depending on the underlying values and preferences. Notwithstanding, it is common to find patients agreeing with the surgical option after a clear explanation about the aim of the surgery, in terms

of survival and quality of life, particularly among younger patients. There is a special group of patients whom, given their baseline condition, cannot opt for surgical treatment. In this group, palliative treatment plays a fundamental role in their care.

### **Differences between this summary and other sources**

In general, the results presented in this summary, agree with those presented in the systematic review<sup>3</sup>. However, given the lack of information regarding other critical outcomes, new primary studies and systematic reviews are needed. We found three guidelines regarding treatment of advanced gallbladder cancer. The first<sup>7</sup> reached a similar conclusion, recommending that all TNM classified cancers in stage T2 or over should be treated with extended cholecystectomy including hepatic wedge or segmentectomy of segments IVB/V, associated or not to lymph node dissection or resection of bile duct, based on a low-certainty evidence. On the other hand, the other two guidelines<sup>8,9</sup>, state that in cases where curative treatment is not an option or resectability has not been evaluated, surgical treatment is not recommended and palliative care based on chemotherapy and/or radiotherapy is preferred.

### **Could this evidence change in the future?**

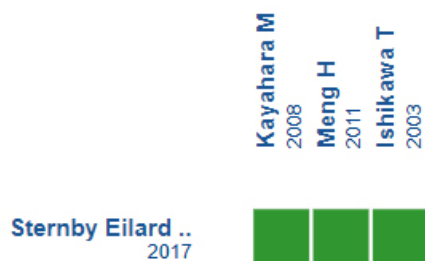
The results in relation to survival presented in this summary are likely to change with future, evidence, considering the limited certainty of the existing evidence.

We found three primary studies relevant for this question<sup>10-12</sup>, which were not included in any systematic review. All of them evaluated survival in patients with gallbladder cancer. One<sup>10</sup> evaluated surgery with curative intent compared to other non-surgical palliative therapies. Other<sup>11</sup> cytoreductive surgery associated with radiotherapy in relation to palliative chemotherapy. The last one<sup>12</sup> compared non-surgical palliative treatment and aborted surgery.

We did not identify ongoing trials or systematic reviews in the International Clinical Trials Registry Platform of the World Health Organization, or the PROSPERO database respectively.

## How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



An evidence matrix is a table that compares systematic reviews that answer the same question.  
Rows represent systematic reviews, and columns show primary studies.  
The boxes in green correspond to studies included in the respective revisions.  
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version**: [Resective surgery versus palliative care in advanced gallbladder cancer](#)

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## Notes

The upper portion of the matrix of evidence will display a warning of “new evidence” if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (<http://dx.doi.org/10.5867/medwave.2014.06.5997>)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

[www.epistemonikos.org](http://www.epistemonikos.org).

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