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#### **Review**

# Routine extra-hepatic bile duct resection in gallbladder cancer patients without bile duct infiltration: A systematic review



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#### ABSTRACT

Aim: The optimal treatment for advanced gallbladder cancer, in particular T2 stage cancer, is unclear. The use of "radical cholecystectomy" or more extended procedures with extrahepatic bile duct resection are matter of debate.

Due to the lack of consensus regarding the oncological significance of routine extrahepatic bile duct (EBD) resection for gallbladder carcinoma, we decided to perform a systematic review investigating the real benefit of this procedure focusing on the primary outcomes of overall survival and disease-free survival.

Methods: A systematic literature search was performed using PubMed, EMBASE, Scopus and the Cochrane Library Central according to the PRISMA statement guidelines for conducting and reporting systematic reviews. Multiple primary and secondary outcomes were analyzed.

Results: The selected articles included 424 patients who underwent routine EBD resection without bile duct infiltration. Only two papers discussed the number of dissected lymph nodes during EBD resection for gallbladder carcinoma. Four of the seven included papers reported on tumor involvement in lymph nodes at rates ranging between 39% and 83%. All of the studies included in this systematic review reported on results of overall survival. In general, 5-years OS rate of the EBD-resected patients was not significantly different than that of the EBD-preservation group, while the mobility was significantly higher in the EBD resection group.

Conclusions: Routine EBD resection in gallbladder cancer patients without bile duct infiltration is not associated with improved overall survival, improved lymph-node harvesting or with minor recurrence rate, but it is associated with higher morbidity rates.

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#### Introduction

Gallbladder cancer (GBC) represents the fifth most-common gastrointestinal cancer in the US and the most common biliary tract malignancy, reaching an incidence of 2.5 per 100 000 persons. As reported in a systematic review issued in 1978, this disease is related to a dismal prognosis due to the very low rate of patients eligible for a potentially curative surgical treatment; furthermore only 16.5% of patients undergoing surgery for GBC survive 5 years. However, due to medical and technical improvements, the surgical treatment is now associated with cure in a higher number of cases depending on the stage presentation. While it is well known that in cases of incidental T1 gallbladder cancer, simple cholecystectomy is considered to be a curative procedure, the optimal treatment for advanced gallbladder cancer, in particular T2 stage cancer, is still debated.

The so-called "radical cholecystectomy" represented the standard surgery for advanced GBC since its introduction in 1950.<sup>5</sup> However, the results of this procedure have not always been radical, which led to the proposal of more extended procedures and additional resections, such as major hepatectomies, extra-hepatic bile duct resection and/or pancreaticoduodenectomy (PD), especially when jaundice and direct invasion of the hepatoduodenal ligament is present.<sup>6–8</sup> In recent years, with the improvements in diagnostic imaging methods, patients are being diagnosed with GBC at an earlier stage, raising the question of whether the performance such invasive procedures in these patients is justified.

Besides the resection required because of direct invasion and jaundice, routine resection of the extra-hepatic bile duct (EBD) has been performed with varying frequency among centers. <sup>9,10</sup> The rationale behind this approach is that host cancer cells may spread to small vessels in the submucosal layer of the EBD, as well as to the large lymphatic vessel commonly resected during lymphadenectomy. <sup>11</sup> Furthermore, it has been reported that a complete lymph-node dissection in the hepatoduodenal ligament could compromise the EBD by devascularization. <sup>12</sup> In other series, EBD resection was found to be related to enhanced nodal dissection. <sup>13,14</sup>

However, no clear results indicating improved survival are available, in contrast, there are some reports of increased mortality and morbidity associated with EBD resection.<sup>13</sup>

Due to the lack of consensus regarding the oncological significance of routine EBD resection for gallbladder carcinoma, we decided to perform a systematic review investigating the real benefit of this procedure by reviewing the available literature and considering only patients without direct infiltration of the bile duct by the tumor and without jaundice. We decided to focus our research on the primary outcome of survival, specifically overall survival (OS) and disease-free survival (DFS). Furthermore, the following secondary outcomes were investigated: number and rate of lymph nodes harvested, number and rate of lymph nodes involved by the tumor, mortality and morbidity rate, and R0 resection rate.

#### Materials and methods

#### Literature search

PRISMA statement guidelines for conducting and reporting systematic reviews were followed. The research protocol was registered at the International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO) with the following registration number: CRD42015017811.

A systematic literature search was performed independently by two of the manuscript's authors (GB and GN) using PubMed, EMBASE, Scopus and the Cochrane Library Central. The search was limited to studies in humans and to those reported in the English language. No restrictions were set for the type of publication, date or publication status. Participants of any age and sex who had undergone surgical resection for gallbladder carcinoma were considered. The search strategy was based on different combinations of words for each database. For the PubMed database, the following combination was used: (gallbladder cancer OR gallbladder adenocarcinoma) AND (extrahepatic OR extra hepatic OR extra-hepatic) AND (bile duct OR choledochus) AND (surgical treatment OR resection OR surgery). The same key words were inserted in the search manager fields of Scopus, EMBASE and the Cochrane Library Central (Appendix). Extensive crosschecking of the reference lists of all retrieved articles that fulfilled the inclusion criteria further broadened the search. For all of the databases, the last search was run on February 28, 2015.

#### Study selection

The same two authors independently screened the titles and abstracts of the primary studies that were identified in the electronic search. Duplicate studies were excluded. The following criteria were set for inclusion in this systematic review: 1) Studies reporting extra-hepatic bile duct resection for patients with gallbladder carcinoma in every stage of disease; 2) Original studies reporting outcomes of EBD resection in patients without tumor involvement of the bile duct; 3) Studies reporting at least one perioperative or long-term outcome; and 4) If more than one study was reported by the same institute, only the most recent or the highest quality study was included.

The following exclusion criteria were set: 1) Original studies reporting EBD resection for patients with suspected or documented tumor involvement of the bile duct or presenting with jaundice; 2) Studies in which a specification whether the bile duct was involved by the tumor was not reported; 3) Studies reporting pancreaticoduodenectomy for patients with advanced gallbladder carcinoma. 4) Original articles not reporting a separate analysis of patients without suspected or documented bile duct infiltration that underwent a routine EBD resection. 5) Review articles, letters, comments and case reports; and 6) Studies in which it was impossible to retrieve or calculate data of interest.

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