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REVIEW ARTICLE

Neoadjuvant therapy for downstaging of locally advanced hilar cholangiocarcinoma: a systematic review

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Abstract

Background: Hilar cholangiocarcinoma is a rare but highly lethal type of cancer. A minority of patients present with resectable disease. Surgery remains the only treatment modality offering a chance of long-term survival. Unresectable patients are typically offered palliative treatment. The aim of this systematic review was to summarize the evidence for neoadjuvant therapy followed by surgical resection in patients presenting with hilar cholangiocarcinoma.

Methods: Cochrane databases, Medline, PubMed and EMBASE were systematically searched to identify articles describing neoadjuvant therapy and surgical resection or re-assessment of resectability in patients with hilar cholangiocarcinoma. Included were all articles with original research. Study selection and data extraction were performed separately by two reviewers using a standardized protocol.

Results: From 732 articles 8 full text articles and 2 abstracts met the inclusion criteria. The 2 abstracts and 1 full text article were case reports, 3 articles were retrospective and 4 were prospective studies (2 phase I and 2 phase II studies). Photodynamic therapy, chemotherapy and radiation therapy were used in various indications in populations that included patients with hilar cholangiocarcinoma, some of which were primarily unresectable. Overall quality of articles was limited.

Conclusion: Current evidence suggests that neoadjuvant therapy in patients with unresectable hilar cholangiocarcinoma can be performed safely and in a selected group of patients can lead to subsequent surgical R0 resection. Surgical resection of downstaged patients should be assessed in properly designed phase II studies.

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Background

Cholangiocarcinomas account for approximately 3% of all gastrointestinal malignancies,[1,2] this represents 5000 new patients in the US annually.[2,3] From an anatomical point of view approximately 60–70% are located within 2 cm from the bifurcation of the common bile duct (hilar cholangiocarcinoma, also called Klatskin tumour), extrahepatic cholangiocarcinomas occur in approximately 20–30% of patients and intrahepatic in 5–10%.[2,4] Surgery represents the only chance of long-term survival and cure and the 5-year survival after an R0 resection of hilar cholangiocarcinoma is in the range of 30–50%.[2,5–11]

Unfortunately, the majority of patients who present with hilar cholangiocarcinoma are not resectable owing to the local extent (involvement of vessels or bilateral extension beyond the secondary radicals) or because of the presence of metastatic disease.[2,12,13] This was described in a retrospective review by Jarnagin *et al.*,[8] when 65% of the 225 patients with hilar cholangiocarcinoma treated at MSKCC between 1991 and 2001 had unresectable disease, 32% as a result of metastases and 23% because of locally unresectable disease. Patients with unresectable disease are usually referred only for palliative therapy. It may prolong their life as well as control their symptoms with the use of chemotherapy, radiation or photodynamic therapy (PDT).[14–20] The expected survival

in this patient population is 6–12 months depending on the therapy used.[16]

The outcomes of incomplete R1/R2 resection in spite of the use of adjuvant therapy are comparable with palliative PDT without resection.[21] This makes decision making in marginally resectable patients challenging. The benefit of an aggressive approach if a R0 resection is achieved needs to be weighed against the impact on quality of life without a survival benefit in patients with a R1/R2 resection.

There is no general consensus when it comes to use of neoadjuvant and adjuvant therapy. Multiple guidelines, reviews and opinions describe that these therapies are currently not indicated. They suggest further research as there is lack of sufficient evidence from prospective studies. The only exception is the use of neoadjuvant chemoradiation prior to the liver transplant in a highly selected group of patients with hilar cholangiocarcinomas. It has been extensively studied and neoadjuvant therapy in this setting is currently a requirement.[22–27]

The authors hypothesize that a certain number of patients with locally advanced hilar cholangiocarcinoma, currently only offered palliative therapy, could be rendered resectable with the use of neoadjuvant therapy. Downstaging and subsequent resection could potentially improve their outcome. Similarly, marginally resectable patients might benefit from downstaging of their tumours by increasing their chance for an R0 resection.

The aim of this review is not to compare regimens or to identify the one with the best pathological response. This has been done in the past in great detail[16] and with new emerging chemotherapeutics it will continue to evolve. The aim is to describe clinical relevance of neoadjuvant therapy. Only complete pathological response guarantees clinical significance in terms of subsequent resectability.

Methods

This study was conducted in accordance with the standards of quality for reporting systematic reviews (PRISMA).[28] A formal protocol has not been created on the web for access. The authors did not receive any funding for the systematic review.

The authors sought to answer a question: What is the evidence with regards to the safety and efficacy of downstaging locally advanced hilar cholangiocarcinoma with the use of neoadjuvant therapy and subsequently resecting them?

Search strategy

Using the Cochrane databases, Medline, PubMed and EMBASE a search was performed in October 2012 using either keyword or subject heading (MeSH) 'cholangiocarcinoma' OR 'Klatskin tumor' AND keyword 'neoadjuvant' or subject heading 'neoadjuvant therapy'. Searches were auto exploded and no limits were used. In terms of identification of additional papers during full text reviews, six additional papers were identified and all were added to the full text reviews. The authors kept the initial search terms broad in order to identify all potentially relevant articles.

Study selection

It was very likely that multiple different types of cholangiocarcinomas or even other types of biliary tract cancers were grouped together in some studies. The focus on exclusion of articles that did not contain any patients with specifically hilar cholangiocarcinoma was left for the second stage of the review process. The aim was to include all articles that described at least a subset of patients with hilar cholangiocarcinoma.

Similarly, in spite of a very specific research question in terms of the indication for neoadjuvant therapy, all articles describing safety and efficacy of neoadjuvant therapy followed by resection were included. This would include articles describing the use of neoadjuvant therapy in resectable patients with the aim of improving local control or survival. The rationale for that was a reasonable expectation that resection after neoadjuvant therapy will have a similar morbidity and mortality profile regardless of indication.

As a result, all articles that contained original research regarding any neoadjuvant therapy used for patients with resectable or unresectable hilar cholangiocarcinoma who subsequently underwent either an assessment of resectability or a resection were included. (Fig. 1)

Excluded were all review and expert opinion articles without original data, chemotherapy, radiation or photodynamic therapy in an adjuvant or palliative setting as well as papers describing neoadjuvant therapy followed by an orthotopic liver transplant. Also studies describing only response rates without an assessment of subsequent resectability were excluded because resectability cannot be assumed purely based on overall decreased volume of the tumour.

Two authors (J.G. and P.G.) independently screened titles and abstracts of all studies for inclusion eligibility. Any disagreements were settled by including all of the identified papers in full-text review.

All articles were written either in English or German language, translation from German was performed by the same two authors.

Data extraction

The same two authors then extracted data from included articles; this was again done through independent work. The developed protocol included description of the study method, the number of patients, the reason for unresectability, the type of neoadjuvant regimen, the type of subsequent reassessment of resectability, timing and type of subsequent surgery, outcome after surgery including complications and survival, and the type of conclusion the study suggested.

Results

Trial flow

The search and the whole screening process are described in the flow chart (Fig. 1). Agreement on selected studies was 100%.