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Review

Routine histological analysis of a macroscopically normal gallbladder – A review of the literature

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HIGHLIGHTS

- Gallbladder specimens are submitted for histology to exclude malignancy.
- There is a significant cost to routine histology.
- Normal macroscopic gallbladder findings at operation may exclude malignancy.

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ABSTRACT

Background: 70,000 cholecystectomies were performed in the United Kingdom in 2011–2012. Currently it is standard practice to submit all gallbladder specimens for routine histology to exclude malignancy. The aim of this systematic review was to establish whether a normal macroscopic appearance to the gallbladder at the time of cholecystectomy is sufficient to rule out malignancy and therefore negate the need for routine histology. **Methods**: Relevant articles that were published between 1966 and January 2013 were identified through electronic databases. **Results**: 21 studies reported on 34,499 histologically analysed specimens. 172/187 (92%) of gallbladder cancers demonstrated intra-operative macroscopic abnormality. Studies that opened the specimens intra-operatively identified all cancers, whereas gross macroscopic visualization resulted in 15 potentially missed cancers ($p = 0.10$). In patients of European ethnicity, gallbladder cancer in a macroscopically normal looking gallbladder was identified in only one study; however all of these patients were above the age of 60. The incidence of gallbladder cancer was significantly raised in ethnic groups from high risk areas ($p = 0.0001$). **Conclusions**: A macroscopically normal gallbladder in patients of European ethnicity under the age of 60 may not require formal histopathology. The best method for intra-operative examination may involve opening the specimen to allow inspection of the mucosa and wall, however this needs further investigation. In the context of the volume of gallbladder surgery being performed there is the potential for significant cost and time savings.

1. Introduction

Gallbladder carcinoma is a relatively rare neoplasm and considered to be a highly lethal disease with 5 year survival rates of approximately 10% [1]. In most cases the tumour is diagnosed on histological examination after elective cholecystectomy for presumed benign disease [2]. Preoperative diagnosis is therefore the exception rather than the rule occurring in less than 20% of patients [3]. The incidence of gallbladder cancer varies from approximately 1% in high risk areas such as India, Japan, Chile and China, to a lower incidence of 0.4% in Europe and United States [4].

Currently in the United Kingdom (UK) it is standard practice to submit all gallbladder specimens for routine histology to exclude malignancy. This has been re-iterated by the 2005 Royal College of Histopathology report [5]. The recommendation was that all gallbladder specimens should be examined as significant

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pathology may be present with normal macroscopic appearance. This statement, although reasonable appeared to suggest the opposite of their reference by Taylor et al. [6]. Current estimates are that between 20 and 40% of all laboratory tests are unnecessary yet nonetheless continue to be carried out in already overworked and understaffed pathology departments [7]. Approximately 70,000 cholecystectomies were performed in the UK in 2011–2012, a substantial rise from 50,000 in 2003–2004 [8]. A number of papers published over the last decade provide evidence to suggest that a more selective policy towards gallbladder histological examination may be safe and effective [9–12]. In the context of the volume of gallbladder surgery being performed there is therefore the potential for significant cost and time savings. The aim of this systematic review was to assess whether it is necessary to send all gallbladder specimens from both open and laparoscopic cholecystectomies for routine histological examination.

2. Material and methods

Relevant articles published between 1966 and January 2013 were identified through Pubmed, MEDLINE, EMBASE, CINAHL, DARE, ACP, LILACS and Cochrane library databases. MeSH and key words used for the searches included: 'laparoscopic cholecystectomy, 'histology', 'specimens', 'cholangiocarcinoma', 'gallbladder, 'open cholecystectomy ', and 'gallbladder cancer'. References cited in these articles were also obtained to prevent missed articles. The criterion was widened further by using the 'related article' function within the search. Abstracts were also included in the literature search and all languages were considered. Retrospective studies that examined intraoperative findings of open and laparoscopic cholecystectomies against histological findings were included in the review.

Having completed the search, two assessors KJ and KR critically evaluated the suitability of each paper for inclusion in this systematic review. Any conflict was resolved by mutual agreement (Fig. 1) [13].

Outcomes assessed in this review included whether a normal macroscopic appearance to the gallbladder intra-operatively is sufficient to rule out malignancy and to assess whether other parameters should be considered when deciding whether or not to send cholecystectomy specimens for routine histology (e.g. age, ethnicity and pre-operative ultrasound findings). We also investigated optimal intra-operative technique for examination of the gallbladder (simple visualization alone or careful open examination of the specimen).

An audit of histological data from our center was compared with the literature. A retrospective analysis of operation notes and histological examination of all gallbladder specimens from 2004 to 2011 was carried out.

Statistical analysis was performed using SPSS (Statistical Package for The Social Science). The data was analysed with using Chi Squared Test.

3. Results

After exclusion of unsuitable papers from our search we analysed 20 papers [6,7,9–12,14–27]. When combined with data from our own hospital there were a total of 34,499 histologically analysed gallbladder specimens from which 187 cancers were identified (0.54%).

The incidence of gallbladder cancer in the various countries studied was sub-divided in to high and low risk areas for gallbladder carcinoma. We found that the difference between the high and low risk areas to be 0.56% (95% CI: 0.36–0.78, $p < 0.0001$)

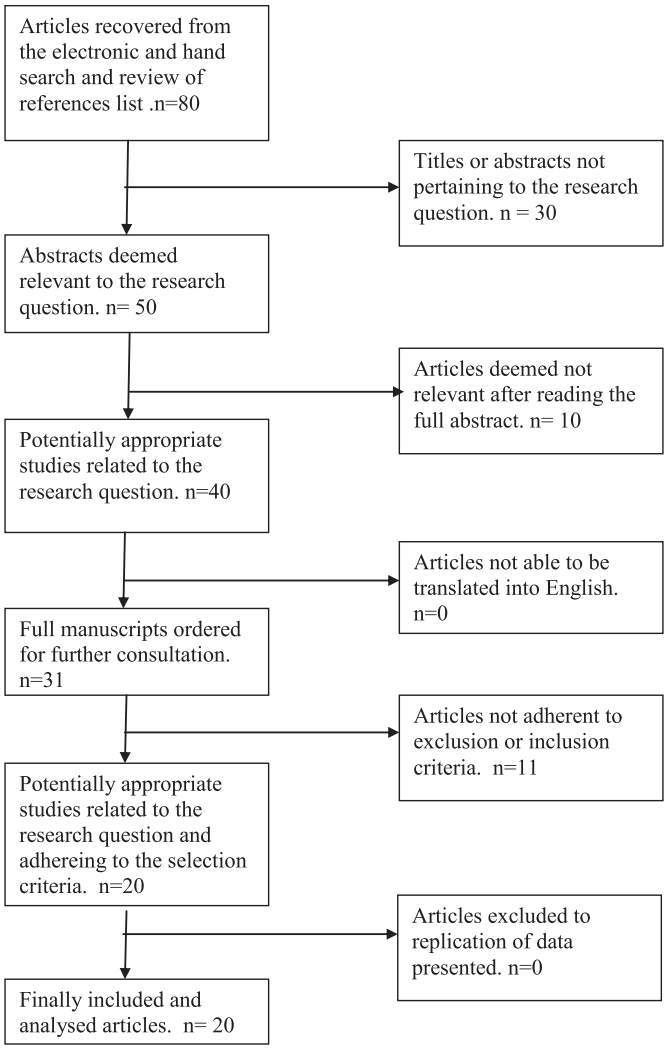

Fig. 1. QUOROM Flow Chart.

(Table 1). The analysis of specimens found to have gallbladder cancer within each study is shown in Table 2. It is sub-divided in to studies that performed a detailed intra-operative examination of the gallbladder versus a crude macroscopic assessment alone. We identified a difference of 10.85% (95% CI: −0.76 to 17.53, $p = 0.10$) between the 2 groups.

Out of a total of 187 gallbladder cancers identified in this systematic review, 172 (92%) demonstrated an abnormal macroscopic intra-operative appearance. 15 cancers with normal intra-operative findings are detailed in Table 3 [12,14,18,25].

For early tumours (T1a and Tis) it is widely accepted that simple cholecystectomy alone is likely to be curative [28–32]. Of the remaining carcinomas of clinical relevance, apart from the missed T2 cancer from the paper by Tantia et al, all of the cancers that would have altered surgical management came from the Greek Study by Antonakis et al. They reported 7 macroscopically normal gallbladder cancers (T_2 (2), T_3 (5)) out of 5539 specimens all occurring in patients above the age of 60. This study was the only one in the systematic review to not diagnose a macroscopic abnormality in a T3 cancer [17]. We were unable to explain this as a T3 tumour by definition has penetrated the gallbladder wall. 95% of cholecystectomy specimens were also reported as macroscopically normal which is higher than reported rates [17]. Most studies quote