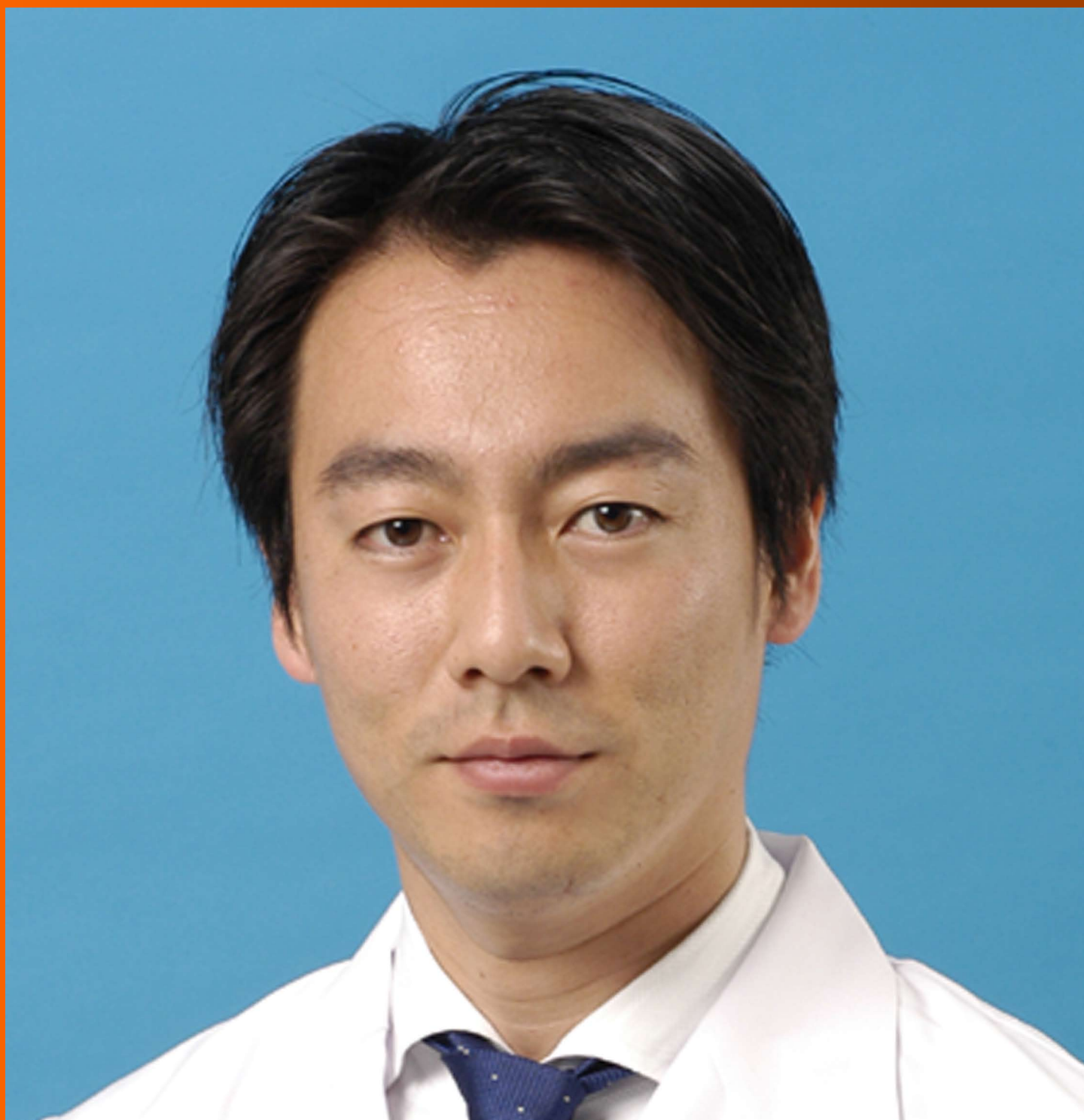


# World Journal of *Gastrointestinal Surgery*

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### MINIREVIEWS

- 660 Goblet cell carcinoids of the appendix: Tumor biology, mutations and management strategies  
*Shenoy S*
- 670 Advances in minimally invasive neonatal colorectal surgery  
*Bandi AS, Bradshaw CJ, Giuliani S*

### ORIGINAL ARTICLE

#### Case Control Study

- 679 Increasing trend in retained rectal foreign bodies  
*Ayantunde AA, Unluer Z*

#### Retrospective Cohort Study

- 685 Incidental non-benign gallbladder histopathology after cholecystectomy in an United Kingdom population: Need for routine histological analysis?  
*Patel K, Dajani K, Iype S, Chatzizacharias NA, Vickramarajah S, Singh P, Davies S, Brais R, Liao SS, Harper S, Jah A, Praseedom RK, Huguet EL*

- 693 Acute appendicitis: Epidemiology, treatment and outcomes-analysis of 16544 consecutive cases  
*Ceresoli M, Zucchi A, Allievi N, Harbi A, Pisano M, Montori G, Heyer A, Nita GE, Ansaloni L, Coccolini F*

#### Retrospective Study

- 700 Peptide-based enteral formula improves tolerance and clinical outcomes in abdominal surgery patients relative to a whole protein enteral formula  
*Liu MY, Tang HC, Hu SH, Chang SJ*

#### Clinical Trials Study

- 706 Phase II study of docetaxel, cisplatin and capecitabine as preoperative chemotherapy in resectable gastric cancer  
*Dassen AE, Bernards N, Lemmens VEPP, van de Wouw YAJ, Bosscha K, Creemers GJ, Pruijt HJFM*

### EVIDENCE-BASED MEDICINE

- 713 Acute pain management in symptomatic cholelithiasis  
*Masudi T, Capitelli-McMahon H, Anwar S*



## Contents

*World Journal of Gastrointestinal Surgery*  
Volume 8 Number 10 October 27, 2016

### ABOUT COVER

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## Goblet cell carcinoids of the appendix: Tumor biology, mutations and management strategies

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### Abstract

Malignant neoplasms of the appendix are rare and represent less than 1% of gastrointestinal cancers. Goblet cell carcinoids (GCC) tumors are a distinctive group of heterogeneous appendiceal neoplasm that exhibit unique clinical and pathologic features. This review focuses on

the current diagnostic procedures, pathogenesis, possible signaling mechanisms and treatment options for GCC. Perspectives for future research are discussed. The tumor likely arises from pluripotent intestinal epithelial crypt base stem cells. Previous findings of Notch signaling as a tumor suppressor in Neuroendocrine tumors may have a similar role in this tumor too. Loss of Notch signaling may be the driver mutation with other successive downstream mutations likely favors them into progressing and behavior similar to poorly differentiated adenocarcinoma with minimal neuroendocrine differentiation. A multi-disciplinary approach is suggested for optimal outcomes. Surgery remains the main treatment modality. Simple appendectomy may be sufficient in early stages while right hemicolectomy is recommended for advanced tumors. Cytoreductive surgery with heated intraperitoneal chemotherapy may improve survival in a select few with metastatic peritoneal disease. These tumors have an unpredictable behavior even in early stages and local recurrence and delayed metastases may be seen. Lifelong surveillance is warranted.

**Key words:** Goblet cell carcinoid of the appendix; Notch-1 signaling; Immunomarkers; Math-1 signaling; Intestinal stem cells; Disease management

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**Core tip:** Goblet cell carcinoids tumors are a distinctive group of heterogeneous appendiceal neoplasm that exhibit unique clinical and pathologic features. The pathogenesis is unclear however the tumor likely arises from pluripotent intestinal epithelial crypt base stem cells. Loss of Notch signaling may be the driver mutation with other successive downstream mutations likely favors them into progressing and behavior similar to poorly differentiated adenocarcinoma with minimal neuroendocrine differentiation. Surgery remains the main treatment modality. We discuss the clinical implications of this cancer focusing on the tumor biology, mutations,

## signaling mechanisms and management.

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## INTRODUCTION

Malignant neoplasms of the appendix are rare and represent less than 1% of gastrointestinal cancers. Studies evaluating data for appendiceal malignancies from seer database between 1973-2001 showed the age-adjusted incidence of cancer of appendix was 0.12 cases per 1 million people per year<sup>[1,2]</sup>. They are further classified into colonic type adenocarcinoma, mucinous tumors, signet ring cell tumors, carcinoids [neuroendocrine tumors (NETs)] and goblet cell carcinoids (GCC). Overall five-year survival is highest for appendiceal carcinoid (83%) and lowest for signet ring cancers (18%)<sup>[1,2]</sup>. This review focuses on GCC of the appendix. The current diagnostic procedures, pathogenesis, signaling mechanisms and possible mutations are presented. Treatment options for this neoplasm are defined and summarized, although evidence-based data are lacking. Surgery remains the treatment mainstay.

GCC tumors are a distinctive group of heterogeneous appendiceal neoplasm that exhibit unique clinical and pathologic features. These hybrid tumors have both glandular and neuroendocrine morphology and are designated with various terminologies: Adenocarcinoids, crypt cell carcinoma, mixed carcinoid-adenocarcinoma and amphicrine tumors. These various terminologies do not reflect consistent morphology, biologic behavior or accepted criteria for the diagnosis. GCC was first described by Gagné *et al*<sup>[3]</sup> in 1969, Subbuswamy *et al*<sup>[4]</sup> subsequently coined the term GCC in 1974. Warner *et al*<sup>[5]</sup> in 1979 suggested a probable origin from crypt based stem cell. Isaacson *et al*<sup>[6]</sup> in 1981 demonstrated presence of IgA, lysozyme in GCC suggestive of possible role of Paneth cells in this tumor<sup>[3-6]</sup>.

GCC exhibits clear distinction when compared to appendiceal NETs or primary adenocarcinoma in terms of demographics, biology and clinical aggressive behavior. The prognoses of GCC lays intermediate between appendiceal NETs and primary appendiceal adenocarcinoma<sup>[1,2]</sup>.

## CLINICAL PRESENTATION

GCC are diagnosed in less than 1% of appendectomy specimens<sup>[7,8]</sup>. Most commonly, patients present with abdominal pain and acute appendicitis (> 50%). They are most often diagnosed incidentally during appendectomy

or ileocecal resection and confirmed by the pathologist in post-surgical specimens. About 27% of patients may present with perforated appendicitis<sup>[9]</sup>. Patients may also present sub-acutely in advanced stages with vague abdominal pain and mass<sup>[7,8]</sup>. Common in Caucasians, there is equal distribution in male and females with the average age of diagnosis in the fifth decade<sup>[1,2]</sup>. Up to 50% of patients present with metastatic disease<sup>[8,10-12]</sup>. Similar to carcinoids a significant number of these patients may harbor a second primary malignancy<sup>[12-14]</sup>.

Morphologically the tumor circumferentially involves the appendiceal wall with transmural extension. Sub-mucosal involvement with mucosal sparing is noted. Most tumors are generally > 2 cm in size. The native appendiceal epithelium may show fibrous obliteration without adenomatous or dysplastic changes<sup>[8,15]</sup>.

GCC display a wide range of histologic patterns both in primary and metastatic sites. Common to all GCC is the presence of mucin containing goblet shaped epithelial cells arranged in clusters in the lamina propria and submucosa. These cells stain positive for mucicarmine, periodic acid-Schiff and alcian blue stains suggestive of goblet cell mucin. Extracellular pools of mucin may also be present. Also seen are cells, which demonstrate focal, inconsistent scattered immunoreactivity for neuroendocrine markers (*i.e.*, chromogranin, synaptophysin)<sup>[8,16]</sup>.

Since GCCs show a submucosal growth pattern, it has a tendency to spread to surrounding bowel. The most common metastatic sites include direct extension into the right colon and ileum, followed by spread to lymph nodes, peritoneum and omentum. The ovaries are common site of metastases in women presenting as Krukenberg tumor. Up to 80 % of women with stage 4 disease present with ovarian metastases<sup>[8,12]</sup>. Solid organ metastases to liver, lung, bones are uncommon<sup>[8]</sup>. A previous study reports the rate of metastases to lymph nodes increases with the T stage of the tumor T2 (0%), T3 (13%), T4 (60%)<sup>[9]</sup>.

Metastatic lesions from GCC are more aggressive tumors and often show poorly differentiated signet ring cell or undifferentiated adenocarcinoma morphology with minimal neuroendocrine features. They may not share features of primary tumor and carry poorer prognosis. Metastatic tumors usually do not stain for chromogranin A or synaptophysin and stain heavily for mucin, suggestive of degeneration into signet ring cell morphology. The population of endocrine cells and Paneth cells seem to decrease in metastatic lesions. Yan *et al*<sup>[17]</sup> in their series of 26 patients reported that nine patients (35%) with metastatic GCC failed to stain for neuroendocrine marker. The explanation for this finding remains elusive<sup>[17-21]</sup>.

## CLASSIFICATION

Currently multiple classification systems exist to describe GCC.

The 2010 World Health Organization (WHO) cla-



ssification for tumors of the appendix, classifies GCC under the category of neuroendocrine neoplasms based on differentiation and histological grading. Grade refers to the proliferative activity measured with mitotic counts and Ki-67 index. They are further sub-classified as low grade: G1 (< 2 mitosis/10 HPF and  $\leq$  2% Ki index), intermediate grade: G2 (2-20 mitosis/10 HPF, 3%-20% Ki index) and high grade: G3 (> 20 mitosis/10 HPF, > 20% Ki index). Differentiation refers to resemblance of tumor cells to the normal neuroendocrine cells. Carcinoids (well differentiated neuroendocrine neoplasm) generally belong to G1 and G2 categories while G3 is considered as a neuroendocrine carcinoma (NEC). Goblet cell tumors are subtyped under mixed adeno-NEC (MANEC). To qualify for this definition at least 30% of tumor should have gland forming epithelial and neuroendocrine components<sup>[22]</sup>.

The 2010 American joint commission on cancer (TNM classification) stages these tumors based on the tumor size, nodal status and metastatic disease into stages (I - IV). Stage I (T1, N0, M0), stage II (T2/T3, N0, M0), stage III (any T/N1, M0), and stage IV (any T /any N/ M1)<sup>[23]</sup>.

Tang *et al*<sup>[8]</sup> in 2008, proposed a system of classification specific for GCC of appendix based on histologic features of the tumor at the primary site. They include the arrangement of the goblet cells, degree of atypia and desmoplasia to label these tumors into three groups. Typical GCC (group A); adenocarcinoma ex GCC, signet ring cell (group B); adenocarcinoma ex GCC, poorly differentiated (group C). Almost all patients in group C presented in advanced stages with wide metastases. This suggests that GCCs display a spectrum of histologic features with the potential to progress to an aggressive adenocarcinoma phenotype<sup>[8]</sup>.

These multiple pathologic definitions and differing terminologies have led to inconsistent reporting and difficult to characterize this disease.

MANEC per the 2010 WHO classification are tumors harboring both epithelial and neuroendocrine components. However based on this definition it requires tumors to have at least 30% representation of each component. In general this is not true for all GCC tumors. Further advanced stages of GCC losses its neuroendocrine differentiation and acquires an aggressive signet ring cell or poorly differentiated morphology.

This tumor may need further investigations to better clarify and define their heterogeneous, molecular profile and classification.

## IMMUNOCHEMISTRY AND MUTATIONAL FINDINGS

GCC specimens demonstrate focal, inconsistent immuno-reactivity for neuroendocrine markers. In contrast diffuse staining is observed in most classic carcinoids of the appendix. Common positive markers are synaptophysin, chromogranin A, serotonin, neuron specific enolase,

pancreatic polypeptide. Ultrastructural immuno- histo-chemistry staining has shown tumor nests resembling normal crypts in the submucosa. Separate goblet cell and neuroendocrine cells are often located in close proximity to each other<sup>[24]</sup> (Table 1).

In addition GCC do not exhibit mutations as conventional colorectal adenocarcinoma. These tumors are negative for KRAS, SMAD4 and BRAF mutations<sup>[25]</sup>. They show negative staining for nuclear  $\beta$ -catenin and for p53. MUC2 expression is preserved<sup>[8]</sup>. Normal colorectal and appendicular epithelium expresses MUC2 only. GCC show strong carcinoembryonic antigen, caudal type homeobox transcription factor 2, cytokeratin 7 (CK7), CK20 expression suggestive of intestinal epithelial origin while these markers remain negative in classic carcinoids<sup>[26]</sup>. A single study showed allelic loss in chromosomes 11q, 16q, and 18q in GCC similar to ileal carcinoids<sup>[25]</sup>.

The proliferative Ki67 index remains low in typical GCC but rises with advanced stages (Tangs group C). The significance remains unknown as some groups have shown worsening survival rates with rising Ki67 index<sup>[19,27]</sup> while other have shown no correlation<sup>[9,28,29]</sup>. Positive staining for p53 and MUC1 with loss of MUC2 expression is suggestive of transformation to adenocarcinoma phenotype similar to colorectal adenocarcinoma<sup>[8]</sup>. This also correlates with the rising Ki67 index as reported with Tangs *et al*<sup>[8]</sup>'s classification.

In general patients with GCC do not present with carcinoid syndrome and urinary 5HIAA levels are within normal range<sup>[16]</sup>. Unlike classic midgut carcinoids, serum chromogranin A levels are normal and have no value in detecting and monitoring GCC. Somatostatin expression is sparse and erratic and therefore functional scans such as 111-Indium pentetreotide scintigraphy (Octreoscan) and Gallium 68-octreotide positron emission tomography (PET) scans are usually normal in patients with GCC, and thus are of limited use<sup>[11,19]</sup>. Fluorodeoxyglucose PET scan may be useful in advanced disease to detect peritoneal metastatic disease<sup>[7,27,30]</sup>.

GCC also express transcription factor Math-1 and HD5 (Defensins) a known marker for Paneth cells<sup>[26]</sup>. Math-1 is a basic helix-loop-helix transcription factor essential for development of the pluripotent stem cell towards secretory stem cell lineage and may play a role in pathogenesis of GCC.

## PATHOGENESIS

The pathogenesis of GCC remains unclear. Unlike adenocarcinomas of the GI tract which arises through an adenoma-carcinoma sequence GCC is thought to arise from pluripotent intestinal epithelial crypt base stem cells<sup>[6,26]</sup>.

An understanding of the embryological origin and signaling pathways associated with development of small bowel and appendix may provide clues and explain the origin and progression of GCC. The epithelial lining of

**Table 1 Immunomarkers and mutations for appendiceal goblet cell carcinoids, typical neuroendocrine tumors and adenocarcinoma**

Markers	Goblet cell carcinoid	Typical carcinoid	Adenocarcinoma
CEA	+	-	+
CK7	+	-	+
CK20	+	-	+
CDX2	+	-	+
CD56	+/-	++	-
CAM5.2	+	-	+
Synaptophysin	+/-	++	-
Chromogranin A	+/-	++	-
B-Catenin (nuclear)	-	-	+
p53	+/-	-	++
Ki67%	+/-	+/-	++
MUC1	-	-	++
MUC2	++	-	+/-
E-cadherin expression	N	N	U
MATH-1 expression	+	+	-
KRAS mutation	-	-	+
SMAD4 mutation	-	-	+
Notch signaling inhibition	U	+	-
MMR (MSH2, MSH6, MLH1, PMS2)	-	-	+/-

(+): Present; (-): Absent; (+/-): Present sometimes. CEA: Carcinoembryonic antigen; CK: Cytokeratin; CDX2: Caudal type homeobox transcription factor 2; CD56: Neural cell adhesion molecule; CAM 5.2: Antibody against CK8; p53: Tumor protein 53; Ki-67: Cellular proliferative marker; MUC: Mucin; Math-1: Protein atonal homolog 1 (a basic helix-loop-helix family of transcription factors); KRAS: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; SMAD4: Mothers against decapentaplegic homolog 4, transcription factors in the TGF pathway; MMR: Mismatch repair genes; N: Normal expression; U: Unknown.

small gut consists of a single layer of columnar cells. This differentiated epithelium arises from the crypts and projects up as villi into the lumen forming the absorptive lining of the gut (Figure 1). Villi begin to form by embryonic day 15 and crypt form by invagination of intervillus pockets at post-natal day 7<sup>[31,32]</sup>. The four main types of differentiated cells are absorptive enterocytes, goblet cells, neuroendocrine and Paneth cells. The crypt thus forms the proliferative stem cell compartment, where these cells originate, differentiate, amplify and move up into the villi akin to a system of conveyor belt in an assembly line<sup>[33]</sup>. Paneth cells which also originate from the crypt in an exception and migrates downward into the base of the crypt. These four cell types are the main differentiated cell types found in the epithelial lining of the small intestine.

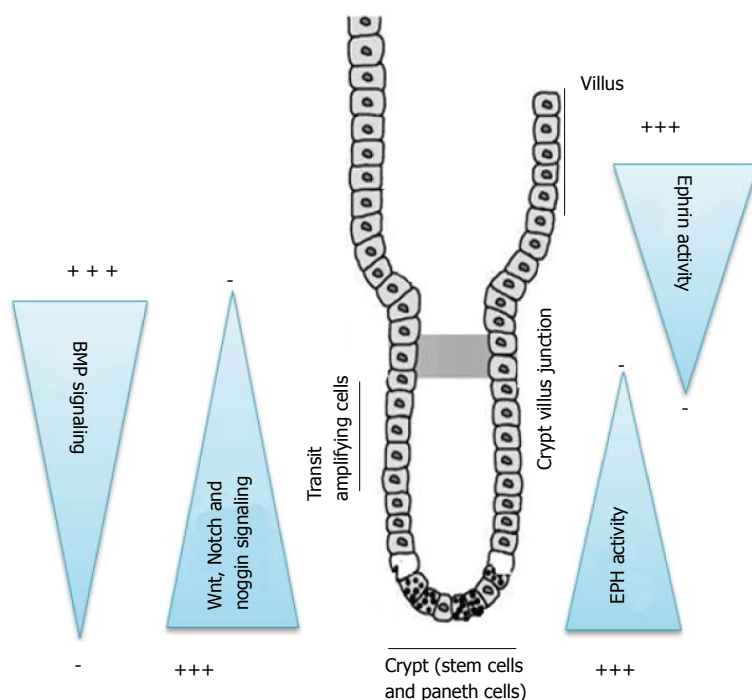
How is the stem cell niche created and defined? What molecular signaling mechanisms keep the niche intact and regulated? Information on these fundamental questions comes from mouse studies. Advances in development and stem cell biology have also occurred to generate complex three dimensional human intestinal tissues *in vitro* through directed differentiation of human pluripotent stem cells. These human intestinal organoids called mini-gut have expanded our ability to study development, genetics, intestinal pathogens and metabolic disease and cancer<sup>[34]</sup>. Cheng and Leblond<sup>[35,36]</sup> in 1974 were first to characterize crypt based columnar cells as intestinal stem cells. Barker *et al*<sup>[37]</sup> identified a marker Lgr5/GPR49, a leucine rich orphan G-protein coupled receptor that labels these stem cells. Tritiated radioactive thymidine labelling experiments have confirmed that these Lgr5 cells are the multipotent stem

cells. Stem cell division occurs every 24 h and these cells are localized to the crypts. Subsequently cells migrate up from the crypt to the villus in 3-5 d<sup>[34,38]</sup>. These stem cells by itself are not terminally differentiated and can divide without a limit. The daughter cells have to choose between committing to terminal differentiation or remain as a stem cell. The rapidly dividing groups of cells derived from the crypt stem cells that have committed to differentiation are known as transit amplifying cells. As they migrate further up the crypt they amplify according to their prospective destined fate and differentiate as enterocyte, goblet cell, neuroendocrine and Paneth cell. They cease to divide further once they reach the neck of the crypt at the crypt villous junction<sup>[31,33]</sup>.

Thus this slim, columnar crypt based Lgr5 positive stem cells along with the post mitotic Paneth cells form the stem cell niche through which begins the growth and renewal of all the differentiated cells of the small intestinal epithelium.

There are two major groups of cell signaling mechanisms which govern the crypt-villus axis (Figure 1). The first is an epithelial-epithelial cell communication. The key mediators of these mechanisms are Wnt, Notch, Eph-ephrin and Math 1 signaling pathways. Together and sequentially they are primarily responsible for maintaining the gut stem cells in a proliferative state, differentiation into secretory or absorptive lineage and establish boundaries between these clones of cells. Mutation in these critical pathways has been implicated with excessive uncontrolled, ectopic crypt formation, adenomas, excessive goblet cell or neuroendocrine cells and other risks for colorectal malignancies.

The second major group of cellular signaling comprises



**Figure 1 Schematic diagram of crypt-villus axis.** The initial signaling mechanisms in a crypt-villus axis begin with Wnt and Notch pathways. The Wnt pathways maintain the gut stem cell compartment. The Paneth cell which constitutes part of the stem cell niche generates Wnt signals that act over a short range and keep cells in the crypt in a proliferative state. There exists a gradient in Wnt, Notch and noggin signaling which is highest in the crypt base and diminishes towards the crypt-villus junction. BMP signaling is low in the crypt and higher in the crypt villus junction. A definitive gradient exists for Eph-ephrin pathways too. The cells acquiring a differentiated fate switch off the expression of Eph-B and switch on the expression of Ephrin B ligands which progressively increases as they migrate up the axis.

of epithelial-mesenchymal (EMT) communications and the mediators in these pathways consist of hedgehog, BMP and PDGAF signaling pathways. The essential function of EMT pathways is to maintain a proper spacing between one crypt and the next. They are negative regulators of crypt formation. Hedgehog signaling increases the expression of BMP in the mesenchyme which further represses the Wnt signaling. Noggin, a BMP inhibitor is expressed in the crypts to maintain unsuppressed Wnt activity in the crypt epithelium (Figure 1). Mutation in these pathways or inhibition of BMP signaling by overexpression of its inhibitors, Noggin or inactivation of its receptor BMPRIA lead to excessive and ectopic crypt formation as seen with juvenile polyposis syndrome due to BMP knock out mutations<sup>[39]</sup>.

We will limit our discussion to the epithelial-epithelial signaling mechanisms which may hold clues to the pathogenesis of GCC.

The initial signaling mechanisms in a crypt-villus axis begin with Wnt and Notch pathways in the crypts (Figure 1). Both the development of small intestine and its homeostasis require canonical Wnt signaling. The Wnt pathways maintain the gut stem cell compartment. The Paneth cell which constitutes part of the stem cell niche generates Wnt signals that act over a short range and keep cells in the crypt in a proliferative state<sup>[31,33]</sup>. There exists a gradient in Wnt signaling which is highest in the crypt base and diminishes towards the crypt-villus junction (Figure 1). Wnt signaling further drives the expression of Notch pathway. Notch pathway through its ligands such as Delta and jagged and effectors such as Hes and NF- $\kappa$ B transcription factors mediate lateral inhibition within the Wnt activated cell population thus driving cells towards different fates. Delta expressing cells escape Notch activation (Wnt<sup>+</sup>, Notch<sup>-</sup>) and commit to secretory

fate through the downstream Math-1 signaling pathways and exit into a committed fate<sup>[32,33,40]</sup>. Meanwhile (Wnt<sup>+</sup>/Notch<sup>+</sup>) cells continue to migrate up the crypt and divide, generating daughter cells and diversify till they lose Wnt activation as they move up the villus and differentiate as absorptive enterocytes. Inactivation of Notch pathway by deletion of Hes 1 or nonsense mutation of Delta ligands leads to excessive formation of goblet cells and neuroendocrine cells<sup>[32,33,40]</sup>. Further studies have shown that inhibiting transcription factors in the Notch pathways by deletion of RBP-jk or by use of  $\gamma$ -secretase inhibitors prevents proteolytic cleavage and the release of notch intracellular domain complex. This result in epithelial cells composed exclusive of goblet cells<sup>[41]</sup>. Conversely experiments have shown that increased Notch activity results in severe reduction of differentiated secretory cells, suggesting a tumor suppressor role of Notch signaling in neuroendocrine tumors<sup>[42]</sup>.

In addition to Wnt-Notch signaling another significant pathway in the crypt-villus axis known to play a role in maintaining cellular boundaries, segregation and establish migratory path are the Eph-ephrin molecules (Figure 1). Expression of Eph B receptors and the Ephrin-B ligands within the intestine is regulated *via* the  $\beta$ -catenin-TCF transcription complex through the Wnt pathway. A definitive gradient exists with proliferative cells in the crypt expressing higher density of Eph-B receptors and progressively decreases at the crypt villus axis. The cells acquiring a differentiated fate switch off the expression of Eph-B and switch on the expression of Ephrin B ligands which progressively increases as they migrate up the axis. Paneth cells express only Eph receptors and therefore remain at the crypt base. In general cells expressing Eph receptors are repelled by contact with cells expressing ephrins on their surface.

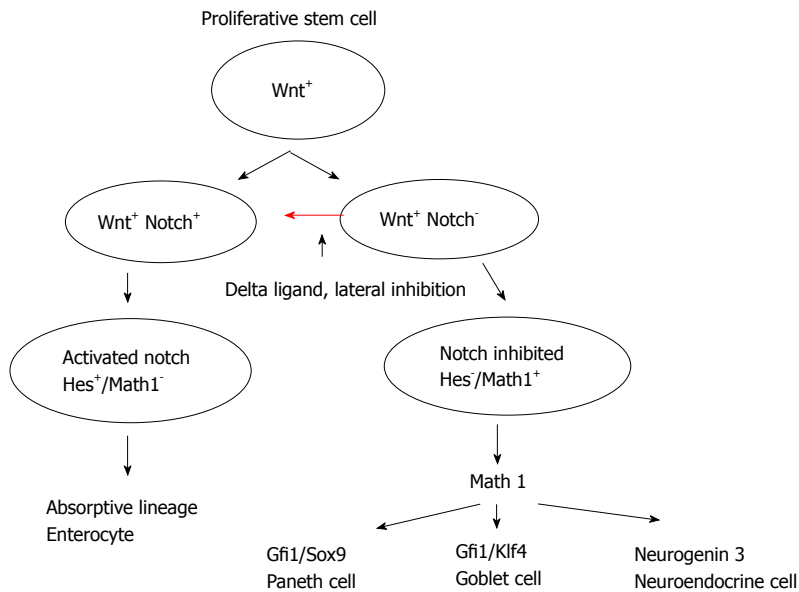


Figure 2 Intestinal stem cell signaling (Wnt, Notch, Math-1 pathways, lateral inhibition).

These mechanisms keep the cells segregated in their respective niches. Dysregulation of the eph-ephrin axis leads to cellular derangement with proliferating cells are not restricted to the bottom of the crypt and abnormally scattered along the crypt-villus axis<sup>[33]</sup>. Eph B mediated compartmentalization restricts the spreading of Eph B expressing tumor cells into ephrin B1-positive territories *in vitro* and *in vivo*. Loss of EphB-mediated compartmentalization may lead to invasiveness of the tumor cells<sup>[43]</sup>.

All three secretory cell types derive from a precursor expressing Math-1 (mouse atonal homologue 1), also known as Atoh1, Hath-1 (humans) (Figure 2). As explained earlier Delta expressing cells escape Notch activation (Wnt<sup>+</sup>, Notch<sup>-</sup>) and commit to secretory fate through the downstream Math-1 signaling pathways<sup>[32,33,40]</sup>. It is a basic helix-loop-helix transcription factor that is required for secretory cell lineage through downstream Neurogenin 3 for neuroendocrine cells, Gfi1 and Klf4 for goblet cells,  $\beta$ -catenin and sox9 for Paneth cells and subsequent cell cycle exit<sup>[31,32,44,45]</sup>. Mice deficient in Math1 lack goblet cells and the epithelial cells continue to maintain their proliferative state<sup>[32,40]</sup>. Overexpression of Math1 results in ectopic secretory cells<sup>[46]</sup>. The immunohistochemical expression of Math-1 in GCC suggests that this transcription factor is essential for normal development of the pluripotent stem cell towards secretory stem cell lineage and may play a role in its pathogenesis. Possible somewhere along its differentiation a mutation occurs with altered signaling pathways which causes excessive clones of goblet cells and neuroendocrine cells and may explain the hybrid nature of this tumor<sup>[18,26]</sup>.

NETs including GCC appear to be heterogeneous group of tumors with varying signaling mechanisms and gene expressions in different tissue of origin. A number of questions remain to be answered. Is there a Notch signaling dysfunction or inhibition leading to loss of Hes regulated inhibition of Math-1? Studies have confirmed

the potential oncogenic role of Notch signaling and its transcription factor in certain solid organ abdominal, lung, breast, and genitourinary, neural and hematological malignancies<sup>[47]</sup>. However Notch signaling also appears to have a tumor suppressor role in gastrointestinal, thyroid and pulmonary neuroendocrine tumors<sup>[42,48,49]</sup>. In another recent study of 31 ileal carcinoids, Notch signaling was uniformly absent in ileal neuroendocrine tumors suggestive of loss of tumor suppressive role<sup>[50]</sup>. Is the loss of Notch signaling, the driving mutation and occurs after the first stem cell division at the level of transit amplifying cells with subsequent progeny showing dysfunction? Could there be a concurrent Eph-ephrin pathway mutation along with loss of notch signaling, leading to loss of compartmentalization of cells and portending invasiveness<sup>[43]</sup>?

Why does metastatic GCC show minimal neuroendocrine expression and more of signet ring cell and poorly differentiated morphology? Are there further successive mutations downstream in the Math-1 signaling pathway? Are there subsequent epigenetic modifications, chromatin remodeling and inactivation of tumor suppressor genes which further amplify the carcinogenesis?

Further investigations at these levels are needed that may lead to our understanding of the pathogenesis of these tumors and may have therapeutic implications. Targeted therapies to activate Notch signaling with varying concentrations for metastatic GCC may have potential benefits. The origin of goblet cells carcinoid and its transformation from typical GCC and to advanced signet ring cell, poorly differentiated adenocarcinoma could be due to spontaneous, sporadic mutation in the mentioned crypt-villus architecture and or the surrounding mesenchyme and is yet to be successfully identified. Characterizing the levels of expression of Notch pathway components in tumor samples from patients with GCC could serve as a tumor marker. This reinforces the need to further investigate the presence of these mutations in larger cohorts and in institutions

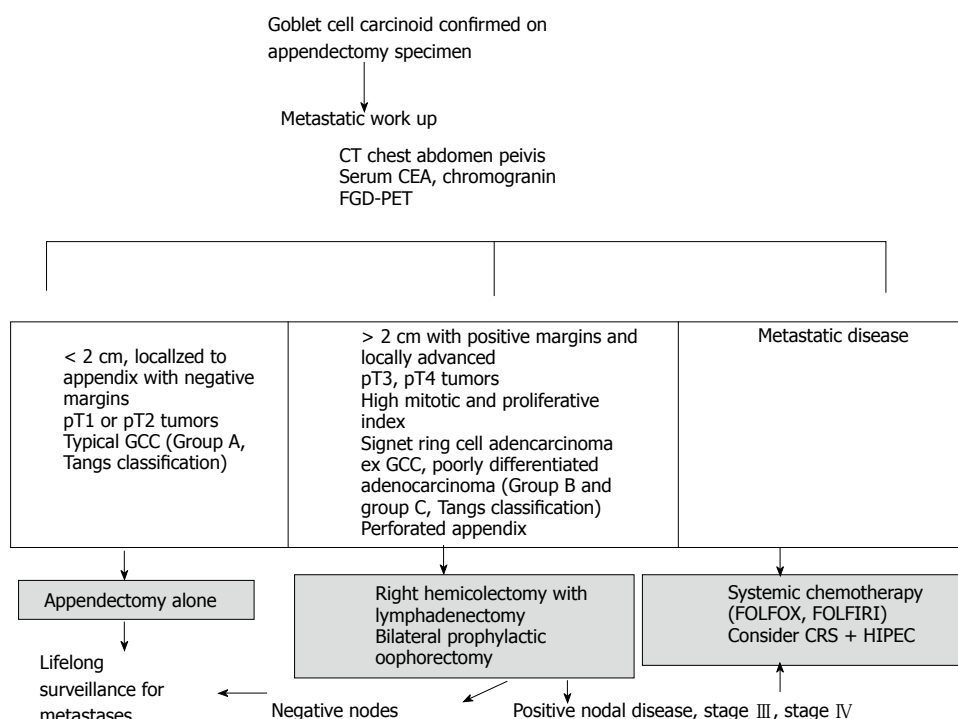


Figure 3 Treatment algorithm for goblet cell carcinoid. FDG-PET: Fluorodeoxyglucose positron emission tomography; GCC: Goblet cell carcinoids.

treating patients with GCC and appendiceal NETs.

## TREATMENT

Most patients typically present with acute appendicitis and undergo appendectomy. The dilemma arises after GCC is diagnosed and confirmed, whether simple appendectomy is adequate or further oncologic resection is required (Figure 3). A multi-disciplinary evaluation is recommended for the optimal treatment. Both European and North American Neuroendocrine tumor societies guidelines recommend right hemicolectomy after appendectomy due to the high rate of metastases and its impact on prognosis<sup>[30,51]</sup>. However other authors have argued against right hemicolectomy in their series<sup>[8,13,52,53]</sup>. In a meta-analysis evaluating 13 studies with 100 patients, the authors concluded no benefits of right hemicolectomy in all patients. Selective criteria were recommended<sup>[53]</sup>. In another recent retrospective analysis of a larger number of appendiceal NETs, GCC and signet ring cell adenocarcinoma from seer database showed a benefit of right hemicolectomy and statistically improved survival only for signet ring cell cancer when compared to appendectomy alone ( $P = 0.01$ ). There was no significant difference in survival for typical NETs ( $P = 0.21$ ) or GCC ( $P = 0.94$ ) based on type of surgery<sup>[54]</sup>. Based on Tangs classification the histology of the tumor in the appendectomy specimens and not the size of the tumor should determine the extent of oncologic resection<sup>[8]</sup>. In patients who fulfill all the following criteria: Tumor less than 2 cm localized to appendix with negative margins, pT1 or pT2 tumors, and typical GCC histology group A (Tang *et al*<sup>[8]</sup> classification) tumors, an

appendectomy alone may be sufficient as the definitive treatment<sup>[13]</sup>. Right hemicolectomy is recommended in tumors greater than two centimeters, locally advanced, positive margins, T3, T4 tumors and histology suggestive of group B, group C (Tangs classification) in the appendectomy specimens<sup>[8,11,12,55]</sup>.

The impact of perforated appendicitis in patients with GCC remains unclear. In a meta-analysis of 18 cases of GCC diagnosed upon perforated appendicitis showed no impact on survival and prognosis<sup>[56]</sup>. In another retrospective series of 20 GCC patients with perforated appendicitis, a lower rate of peritoneal metastases was observed in the perforated group (15%) compared to the non-perforated group (42%) with no difference in peritoneal relapse between the two groups<sup>[9]</sup>.

A complication of GCC of the appendix is their propensity to spread to the ovaries. GCC of the appendiceal origin express elevated MUC2 and MUC5AC. In contrast mucinous tumors arising from ovarian primaries express only MUC5AC<sup>[57]</sup>. This could be of benefit in differentiating the origin of these tumors in females with primary ovarian mucinous malignancy<sup>[58]</sup>. In postmenopausal female patients with GCC prophylactic bilateral oophorectomy, although not evidence based should be considered<sup>[7,8,12]</sup>. In female patients with mucinous ovarian and pelvic malignancies an appendectomy should always be performed in staging laparotomy as these may represent metastatic GCC<sup>[12,19,57]</sup>.

Adjuvant systemic chemotherapy is prescribed for stage III and stage IV diseases and disease recurrence. Due to rarity of GCC a randomized control trial cannot be accomplished. Data is available from scattered anecdotal reports and small series of GCC and therefore guidelines



for choice of chemotherapy is lacking. Since metastatic GCC shows clinical and histological resemblance to colorectal adenocarcinoma and not metastatic carcinoids the choice of adjuvant therapy in GCC is similar to colorectal adenocarcinoma. 5-fluorouracil (5-FU) and leucovorin based FOLFOX (5-FU, leucovorin, oxaliplatin) and FOLFIRI (5-FU, folic acid, irinotecan) chemotherapy are standard regimens recommended<sup>[11,30]</sup>.

With locally advanced or recurrent peritoneal disease, cytoreductive surgery with hyperthermic intraperitoneal mitomycin and systemic chemotherapy (CRS+ HIPEC) may improve median survival<sup>[11,12,17,59,60]</sup>. In a recent study of 45 patients with GCC and peritoneal metastases who received CRS+ HIPEC, the therapy was successfully completed in 71% of patients and 3 years, overall survival (OS) was 63.4 %<sup>[60]</sup>. Another study on 26 patients report median survival of 51 mo and an overall five-year survival of 43%<sup>[17]</sup>. However a recent retrospective study on 25 patients who received CRS plus HIPEC therapy reports no reduction in relapse rates or improvement in disease free survival in either stage I and II compared to stage III and IV<sup>[9]</sup>.

The other treatment options generally available for metastatic carcinoids such as interferon, somatostatin analogues (octreotide), targeted agents such as everolimus and sunitinib and radionuclide targeted therapy is not useful for metastatic GCC due to the absence of adequate uptake on Octreoscan or Gallium 68 PET scan and no confirmed mechanistic target of rapamycin or vascular endothelial growth factor pathway dysregulation.

## PROGNOSIS

The overall disease specific survival for all GCC subtypes is 40%-80% depending on different series<sup>[7-9,11,12,54]</sup>. The five-year survival for localized, regional and distant metastatic disease based on Tang's classification of group A, B, C are 100%, 36% and 0% respectively. This correlates with the AJCC (TNM) staging system where reported five-year survival with stage I (100%), stage II (76%), stage III (22%), stage IV (14%), respectively.

## CONCLUSION

GCC are a separate entity from carcinoids and adenocarcinoma. The pathogenesis is unclear however the tumor likely arises from pluripotent intestinal epithelial crypt base stem cells. Successive mutations likely favor them into progressing and behavior similar to poorly differentiated adenocarcinoma with minimal neuroendocrine differentiation. Metastatic lesions differ from the primary appendiceal site in terms of histology and tumor aggressiveness. A multidisciplinary approach is suggested for optimal outcomes. Surgery remains the main treatment modality. Due to its heterogeneity, this tumor should not be classified according to a single system and a combination of size of the tumor (T classification), grade and mitotic index (WHO classification) and arrangement of the goblet cells, degree of atypia

and desmoplasia (Tang *et al*<sup>[8]</sup>'s histopathologic classification) should dictate further definitive therapy. Simple appendectomy may be sufficient in early stages while right hemicolectomy is recommended for advanced tumors. CRC with HIPEC may improve survival in a select few with metastatic peritoneal disease. These tumors have an unpredictable behavior even in early stages and local recurrence and delayed metastases may be frequently seen. Therefore lifelong surveillance is warranted.

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## Advances in minimally invasive neonatal colorectal surgery

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### Abstract

Over the last two decades, advances in laparoscopic surgery and minimally invasive techniques have

transformed the operative management of neonatal colorectal surgery for conditions such as anorectal malformations (ARMs) and Hirschsprung's disease. Evolution of surgical care has mainly occurred due to the use of laparoscopy, as opposed to a laparotomy, for intra-abdominal procedures and the development of trans-anal techniques. This review describes these advances and outlines the main minimally invasive techniques currently used for management of ARMs and Hirschsprung's disease. There does still remain significant variation in the procedures used and this review aims to report the current literature comparing techniques with an emphasis on the short- and long-term clinical outcomes.

**Key words:** Neonatal surgery; Laparoscopy; Anorectal malformation; Colorectal surgery; Hirschsprung's disease

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**Core tip:** This review describes the recent evolution of neonatal colorectal surgery. It details the advances and current techniques since the introduction of laparoscopic surgery and minimally invasive approaches to the surgical management of anorectal malformations and Hirschsprung's disease. This review focuses on the various surgical options available and the benefits of these different techniques, outlining the current literature reporting the short- and long-term outcomes for these procedures.

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### INTRODUCTION

The application of minimal access techniques within



paediatric surgery has evolved considerably in the last thirty years since the advent of laparoscopic surgery in the late 1980s. Advances in laparoscopic techniques and the development of new entirely transanal procedures has transformed the operative management of paediatric colorectal conditions, in particular Hirschsprung's disease and anorectal malformations (ARMs). Improving technology and refinement of techniques over the last decade has allowed these minimally invasive approaches to be used in increasingly challenging cases.

## ARMs

### *History and evolution of technique*

The posterior sagittal anorectoplasty (PSARP), a perineal approach to the correction of ARMs, has been standard practice since it was first described by Peña in the 1980s<sup>[1]</sup>. Laparoscopy in the operative management of ARMs was first described in 1998. The laparoscopic-assisted anorectal pull-through (LAARP) was popularised in 2000<sup>[2]</sup>. Proponents advocated this approach to avoid a laparotomy to ligate a high fistula and aimed to reduce post-operative pain and recovery time.

The LAARP is beneficial for recto-bladder neck fistulae and it may facilitate clear identification of the levator muscles so the surgeon can be sure of the correct position of the anus, avoiding the risks of sagittal dissection<sup>[3]</sup>. It was hoped this small perineal wound, opening only in the centre of the muscle complex, would improve functional outcomes by its relative preservation of the sphincter muscles<sup>[4]</sup>.

Indications and use of laparoscopy initially expanded rapidly due to the benefit of avoiding extensive perineal dissection which was postulated to reduce soft tissue rectal scarring and lead to improved rectal compliance. However, the management of low anorectal malformation in males (recto-perineal and retro-bulbar fistulae) *via* a laparoscopic approach has resulted in an increased risk of urethral injury due to a difficult and extensive pelvic dissection as well as injury to the rectal nerves and pelvic plexus. This results in poor bowel function and therefore laparoscopy in these cases is unwarranted<sup>[5,6]</sup>.

## CURRENT TECHNIQUES

### *Single or staged laparoscopic procedure?*

ARMs with a recto-urethral fistula have been traditionally managed with colostomy formation in the newborn period, followed by definitive anorectoplasty at a later stage. Good positioning of the colostomy is vital to avoid problems in mobilizing the rectum<sup>[3]</sup>. There is an argument in favour of the use of laparoscopy for stoma formation to ensure that it is appropriately sited and also to allow for fistula assessment and consideration of primary repair<sup>[7]</sup>. Laparoscopy has therefore allowed surgeons to treat patients with recto-

bladder neck fistula ARMs with a single procedure without an initial colostomy. Small case series have shown that this is feasible and without the presumed difficulties of abdominal distension when the patient is operated within 48 h after birth<sup>[7]</sup>. Though the rectum may be dilated with meconium, it has been shown to be feasible with laparoscopic manipulation to perform the dissection safely. Initial concerns about handling of friable bowel leading to injuries have not been seen in the published series reporting this technique<sup>[7]</sup>.

### **LAARP**

We prefer a three stage operation in case of high ARMs with or without fistula. Following stoma formation, a colostogram is performed to identify the presence and level of fistula<sup>[4]</sup>. Laparoscopic assisted pull-through is usually performed at 3 mo of age<sup>[4]</sup>.

In recto-bladder neck fistula, the fistula is located approximately 2 cm below the peritoneal reflection, and the rectum communicates with the urinary tract in a T fashion, which means that there is a minimal common wall between the distal part of the rectum and the urinary tract. The laparoscopic approach provides an excellent view of the peritoneal reflection, the ureters and the vas deferens, which must be visualised to prevent injury when dividing a recto-bladder neck fistula<sup>[2]</sup>.

The operation is begun by dividing the peritoneum around the distal rectum to create a plane of dissection to be followed distally. The dissection should occur on the rectal wall. The rectum rapidly narrows as it reaches its communication with the bladder neck. Dividing the fistula as close to the urinary tract as possible is required to prevent the formation of a diverticulum in the future<sup>[8]</sup>. This can be confirmed by noting that the rectum has narrowed sufficiently to allow the 3 mm Maryland laparoscopic instrument to completely clamp across the fistula. A suture with 3/0 PDS is used to ligate the fistula. A submucosal dissection plane to create a mucosal tube of the distal rectum has been advocated as this facilitates easier ligation, further limiting the amount of fistula tissue left attached to the urethra<sup>[9]</sup>. Initial reports described clip or endoloop ligation of the fistula but later studies have shown that simple sharp ligation flush with the bladder is the best technique<sup>[10,11]</sup>.

The distal rectum is then mobilized by dividing feeding vessels until there is enough length to pull the rectum comfortably down to the perineum. If the colostomy was created too distal in the sigmoid it may prevent this mobilisation.

The pubococcygeus muscle is then identified by inspection of the pelvic floor. A hiatus is located along the anterior surface of the two muscle bellies just posterior to the urethra which is the anatomical landmark where the rectum will be delivered from the pelvic side of the dissection<sup>[2,5]</sup>.

Various techniques have been described for creation



of the pull-through channel at the optimal site. The laparoscopic Peña electrostimulator has been used to identify accurately the centre of the muscle complex in the perineum<sup>[10,12]</sup>. This can be particularly useful in cases of immature and unclear levator muscles<sup>[3,13]</sup>. The positioning of the channel can be further guided with perineal and endoscopic ultrasound which can also serve as a useful tool for ensuring that the dissection is not risking injury to genitourinary structures<sup>[14,15]</sup>.

Entry into the pelvis from below can be facilitated under laparoscopic vision with a Verres needle and serial dilatation until a 10-12 mm trocar can be placed to allow the bowel to be pulled through and the anoplasty completed<sup>[4,9]</sup>.

Robotic assistance has been used to perform these operations in a limited series. The increased range of movement added with 3D vision technology aims to make the pelvic dissection easier for the surgeon. Currently this is hampered by the size of these infants but, as these technology advances, robotic assistance may prove a valuable tool in minimally invasive pull-through surgery for ARMs<sup>[16]</sup>.

As with other laparoscopic procedures, surgeons aiming for improved cosmesis have reported successful completion of LAARP using single-port techniques but such techniques are not commonplace due to the technical challenges and cosmetic benefits<sup>[17]</sup>.

## OUTCOMES FOR LAPAROSCOPIC REPAIR OF ARMS

### Short-term outcomes

Anal stenosis is a significant complication following PSARP and remains so in case series of LAARP. Ischaemia of the pull-through and tension on the anastomosis are causes of stenosis but it can also result from non-compliance with the postoperative dilatation regimes<sup>[10]</sup>.

Initial pitfalls encountered with the laparoscopic approach have been bladder/urethral injuries, bladder/urethral diverticulum and rectal prolapse but as the technique has become more established these problems do not appear to be encountered any more frequently in this group<sup>[18]</sup>.

There is evidence of reduced operating times, post-operative stay and blood loss in the LAARP group compared with open PSARP for high ARMs but again in these case series no clinical outcome difference was found<sup>[19,20]</sup>.

### Long-term outcomes

It has been well documented that constipation is a major problem for patients that have undergone corrective surgery for high ARMs<sup>[21]</sup>. Reviews have indicated a 80%-100% constipation rate following corrective surgery for recto-vesical fistulae<sup>[22,23]</sup>. Some degree of soiling has been shown to occur in 42%-63% of cases of recto-vesical fistula<sup>[23]</sup>. It has been noted that the majority of these patients experience resolution of constipation

by the time they have progressed through puberty<sup>[24]</sup>. Long term follow up suggests that approximately half of patients managed with PSARP for high anorectal malformation have an excellent functional result by adulthood<sup>[25]</sup>. It remains to be seen whether LAARP will improve this figure.

Outcome data for patients that have had LAARP remains limited to small series with relatively short follow up. The incidence of the most commonly described outcomes after PSARP and LAARP are shown in Table 1. These rates are calculated from pooled data used in a meta-analyses<sup>[26]</sup>. An increase in preserved recto-anal relaxation reflex has been shown in patients undergoing LAARP compared to PSARP by performing follow up anorectal manometry<sup>[27]</sup>. MRI imaging has revealed less peri-rectal fibrosis and sphincter asymmetry in these patients. However, neither of these measures has shown a correlation with a significant clinical improvement in the studies to date<sup>[26-29]</sup>.

It has been shown that the objective feedback using a continence evaluation questionnaire is significantly better at 3-4 years post-op in the LAARP group compared to PSARP, however this significance did not persist in patients that had been followed up for 5 years or more<sup>[30]</sup>. The possible significance of this data remains limited by its small numbers.

Currently the main benefit of the laparoscopic approach is to replace the laparotomy in cases of recto-bladder neck and recto-prostatic urethra fistula. Other potential benefits remain to be confirmed<sup>[18,31]</sup>. Attempts to review and combine the data of existing studies to ascertain if there are significant benefits have been unsuccessful due to the lack of standardisation of outcome measures reporting between paediatric surgical centres<sup>[26,29]</sup>.

## HIRSCHSPRUNG'S DISEASE

### History and evolution of technique

The surgical management of Hirschsprung's disease has evolved since the basic principles of repair described by Swenson *et al*<sup>[32]</sup> in 1948. Progression occurred from a two- or three-stage procedure to a primary operation in the early 1980s<sup>[33]</sup>. In the single stage primary operation, a laparotomy is used to mobilise the colon followed by an endorectal pull-through. Three main endorectal pull-through techniques are popularly used: Swenson, Soave and Duhamel.

The laparoscopic-assisted primary pull-through was first described by Georgeson *et al*<sup>[34]</sup> in 1995. Following this, surgeons quickly began to replace the laparotomy for the transabdominal portion of each of the different pull-through procedures with laparoscopy<sup>[35,36]</sup>. Subsequently, the entirely transanal endorectal pull-through emerged in 1998<sup>[37]</sup>.

More recent technical advances have also been described in conjunction with the pull-through procedure. Single-incision laparoscopic surgery has been used safely

**Table 1 Comparison of outcomes of the open posterior sagittal anorectoplasty and the laparoscopic-assisted anorectal pull-through for management of anorectal malformations, subdivided into high and low malformations**

	Open PSARP			LAARP		
	High	Low	All	High	Low	All
Short-term outcomes						
Mucosal prolapse (%)	10.7	21.2	16.4	9.8	2.9	6.2
Long-term outcomes						
Defecation dysfunction (%)	33.3	41.8	40.3	36.4	27	29.2
Rectoanal inhibitory reflex positive (%)	-	-	57.4	-	-	72.7

Rates extrapolated from pooled data from a meta-analysis comparing the different techniques<sup>[26]</sup>. PSARP: Posterior sagittal anorectoplasty; LAARP: Laparoscopic-assisted anorectal pull-through.

to compliment the transanal endorectal pull-through and the Duhamel's procedure<sup>[38-40]</sup>. One series used robotic assistance for the Swenson pull-through in 7 cases. They hypothesize that the increased dexterity as compared to laparoscopic surgery may improve the accuracy of the endorectal dissection and thus improve future outcomes, however this is as yet unproven<sup>[41]</sup>.

### Main current techniques

The majority of patients with Hirschsprung's disease are suitable for a definitive primary procedure, using either the laparoscopic-assisted or the primary transanal approach<sup>[42]</sup>. Both of these techniques can be performed at any age and are routinely performed within the first few months of life<sup>[43,44]</sup>.

Relative contraindications for a primary procedure include severe dilatation of the proximal bowel, significant clinical deterioration due to enterocolitis or long segment Hirschsprung's disease<sup>[42]</sup>. These patients may be more appropriately managed with an initial levelling colostomy, which can be achieved with a laparoscopic approach, and a definitive pull-through procedure performed at a later stage. Laparoscopy offers the advantage of visualising the entire bowel, allowing for identification of the transition zone and biopsies prior to creating a stoma at the appropriate level.

Long segment Hirschsprung's disease is defined as a transition zone proximal to the mid-transverse colon. The most common type is total colonic aganglionosis, which can involve a portion of the terminal ileum. Although any of the three pull-through techniques can be used, the laparoscopic assisted Duhamel's procedure is favoured in these patients.

### Laparoscopic-assisted endorectal pull-through

Laparoscopy is first used to take intra-operative frozen section levelling biopsies in order to identify normal ganglionated bowel. The bowel is inspected to identify the transition zone. A seromuscular biopsy is taken from above the transition zone in what appears to be normal bowel. Any perforation or bleeding at this site can be closed with a braided suture (Figure 1). If ganglion cells are absent or there is evidence of thickened nerve fibres then biopsies should be continued proximally until

normal ganglionated colon is identified. No dissection of the mesentery or rectum should be started until the level of normal bowel has been confirmed.

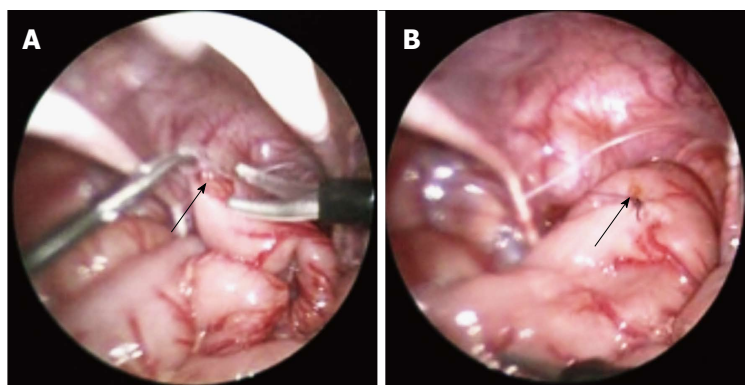
At this stage, in those patients found to have a long Hirschsprung's segment, it may be preferred to create a stoma above the suspected transition zone and delay the definitive procedure to a later stage, in order to await formal histology results.

Once the proximal level of the pull-through has been established, mobilisation of the colon with dissection of the mesocolon and mobilisation of the rectum below the peritoneal reflection can be continued laparoscopically (Figure 2). This is usually achieved with hook diathermy or the harmonic scalpel in older children. The trans-anal dissection of the surgeon's choice then follows. This involves a trans-anal endorectal dissection of the rectum starting 2-3 mm above the dentate line until the rectum and colon is completely free. In a Soave procedure, the first part of the dissection includes only the mucosa and submucosa, leaving a muscular cuff of aganglionated rectum. The posterior wall of this cuff should be incised in order to prevent stenosis. At this stage the pneumoperitoneum can be re-instated, using the laparoscope to visualise the mobilised aganglionic rectum and colon as it is pulled through. This ensures that the bowel has not been kinked or rotated during this process and there is sufficient mobilisation of the colon to prevent tension on the anastomosis. The mesenteric defect or window should then be closed to prevent the risk of an internal hernia. The aganglionated segment is excised and anastomosis of the colon to the rectal mucosa is performed, followed by closure of the laparoscopic port sites<sup>[45]</sup>.

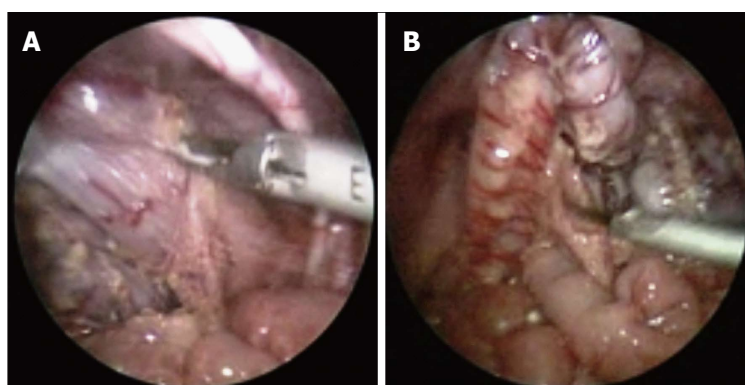
### Laparoscopic Duhamel procedure

The procedure for the initial levelling biopsies for the laparoscopic Duhamel procedure is the same as for the laparoscopic-assisted endorectal pull-through, as described above.

After the level of normal ganglionated bowel has been identified, the colon needs to be mobilised adequately and the mesentery of the distal aganglionated bowel can be divided. Once dissection has reached the peritoneal reflection, the rectum is closed to create the rectal



**Figure 1** Photographs demonstrating a laparoscopic colonic biopsy taken in the sigmoid colon. A: Maryland grasper holding the sigmoid colon, while scissors are used to take the biopsy specimen; B: The biopsy site is then sutured closed. Arrow indicates the biopsy site.



**Figure 2** Photographs demonstrating the laparoscopic mobilisation of the colon and rectum using a harmonic scalpel. A: Mobilisation of the rectum at the peritoneal reflection; B: Division of the sigmoid colon mesentery.

pouch, either by oversewing the bowel or using an automatic stapler. Following this, the posterior rectum is then incised transanally, approximately 1 cm proximal to the dentate line. This creates an opening for the pull-through. A tunnel behind the rectum is created with a smooth dissector and dilated up to an adequate size with Hegar dilators. The proximal colon is pulled through the tunnel using a traction suture under laparoscopic vision. The colon is then anastomosed to the posterior wall of the rectum at the incision site. This can be completed with an automatic stapler to remove the wall between the rectal stump and the colon. Correct positioning of the pulled-through colon, without twisting or tension, is then confirmed using the laparoscopic view prior to closure<sup>[46,47]</sup>.

#### **Primary trans-anal endorectal pull-through**

The totally trans-anal endorectal pull-through was derived from the laparoscopic-assisted endorectal pull-through. It excludes the initial biopsies and proceeds directly to the trans-anal endorectal dissection, assuming that if the infant is responding to rectal wash-outs there is a classic Hirschsprung's disease, with the transition zone at the recto-sigmoid colon. Either a lonestar retractor or retracting sutures are placed between the perianal skin and the dentate line. The rectal mucosa dissection begins 2-3 mm above the dentate line. In a Soave procedure, the dissection then proceeds submucosally until the peritoneal reflection at the level of the pouch of Douglas is reached. At this point the bowel can be dissected full-thickness after separating the sero-muscular plane 360

degrees. The muscular cuff should be vertically split posteriorly to avoid stenosis. The dissection continues along the rectal wall until a clear difference in calibre is noted, representing the transition zone. Alternatively in the Swenson procedure, the dissection of the rectum is full thickness from the beginning, leaving no muscular cuff. Once the peritoneal reflection has been reached the colon will be pulled through and the mesentery is divided trans-anally. Care must be taken to avoid rotating the bowel as the dissection progresses. Biopsies can be taken and sent as frozen section during the procedure to confirm the level of the transition zone. Once normal bowel has been reached the aganglionic segment can be excised and the anastomosis performed<sup>[37,44]</sup>.

The trans-anal pull-through has gained popularity due to its simplicity. It avoids the intra-peritoneal dissection and the need for laparoscopic expertise and equipment, which may be particularly important in low-income countries. However, in cases where the transition is proximal to the sigmoid colon mobilisation of the descending colon is usually required in order to perform an anastomosis without tension. This can be achieved laparoscopically if necessary.

The main benefit of using the laparoscopic-assisted approach over the primary trans-anal approach is early identification of the transition zone prior to dissection of the mesentery so that long segment Hirschsprung's can be identified and dealt with appropriately. Laparoscopy also allows full mobilisation of the colon on a mesocolic pedicle to minimise tension on the anastomosis, and reduces the risk of rotational abnormalities during the

**Table 2** Comparison of short-term and long-term outcomes of various approaches to the pull-through procedure for Hirschsprung's disease

	Open pull-through		Laparoscopic-assisted pull-through		Transanal endorectal pull-through
	Swenson/soave	Duhamel	Endoanal	Duhamel	
Short-term outcomes					
Length of stay (d)	12.5	9.8	7.8	7.3	5.1
Enterocolitis (%)	26	15	28	10	25
Long-term outcomes					
Constipation (%)	12	23	15	30	11
Faecal incontinence (%)	26	11	35	4	20

Rates taken from pooled data from meta-analyses comparing the different techniques<sup>[52,57,60]</sup>.

pull-through<sup>[48]</sup>. Additionally, it reduces the need for a lengthy trans-anal dissection resulting in less dilatation of the anal sphincter, a factor that may be associated with faecal incontinence in the long-term<sup>[49]</sup>.

## OUTCOMES

### Short-term outcomes

Quoted benefits of laparoscopic surgery over traditional open techniques include reduced post-operative pain, quicker recovery of bowel function, shorter length of stay and improved cosmesis<sup>[43,46,50]</sup>. On the contrary, the disadvantage is thought to be a longer operative time<sup>[46,50]</sup>. Reported operative time for the open approach ranges from 91.3-297 min, laparoscopic approach from 150-257 min, and trans-anal approach from 43.5-258 min. Meta-analyses directly comparing these techniques demonstrated a shorter operating time in laparoscopic procedures and trans-anal procedures<sup>[51,52]</sup>. Reported length of stay for open procedures range from 6.9 to 18.7 d, laparoscopic-assisted procedures from 3.6 to 10.4 d and trans-anal endorectal procedures from 2.6 to 9.8 d. Two studies comparing laparoscopic vs open procedures showed a significantly shorter average length of stay with laparoscopic procedures; 4 d following the laparoscopic endorectal pull-through, 7 d with the laparoscopic Duhamel pull-through and 10 d after an open Duhamel pull-through<sup>[46,53]</sup>. When compared to the transabdominal approach, both the laparoscopic-assisted pull-through and the trans-anal endorectal pull-through have been shown to have a shorter length of stay<sup>[51,52]</sup>.

Conversion of a laparoscopic to an open procedure usually occurs for technical reasons and conversion rates range between 1%-2.5%<sup>[39,43,54]</sup>.

Recognised early post-operative complications of the pull-through procedure for Hirschsprung's disease include bleeding, anastomotic leak, perforation, adhesive bowel obstruction and post-operative enterocolitis. Late complications include anastomotic stenosis, enterocolitis, need for re-do surgery. These have all been described in association with the minimally-invasive techniques<sup>[39,43,54-56]</sup>. Rates of these post-operative complications are comparable in laparoscopic and open approaches and may favour laparoscopic procedures. Although no individual comparative study has shown any

significant difference in complication rates, pooled data from a meta-analysis demonstrated fewer complications in the laparoscopic operations<sup>[51]</sup>. A meta-analysis comparing laparoscopic vs open Duhamel procedure showed lower rates of further surgery in the laparoscopic group, with 14% compared to 25% of patients after the open procedure. The incidence of post-operative enterocolitis is 10% after the laparoscopic Duhamel's procedure and 15% after the open procedure, however this did not reach significance<sup>[57]</sup>.

A large cohort study investigating the transanal endorectal pull-through suggested lower rates of early complications compared to the transabdominal approach<sup>[58]</sup>. The reported incidence of enterocolitis following the transanal endorectal pull-through ranges from 4.6%-54%, with a systematic review suggesting an incidence of 10.2%<sup>[59]</sup>. Comparison with both the transabdominal approach and laparoscopic-assisted approaches have not demonstrated any difference in the rates of post-operative enterocolitis<sup>[52,60]</sup>.

### Long-term outcomes

Functional outcomes after surgery for Hirschsprung's disease relate to impaired bowel function. Both severe constipation and faecal incontinence are experienced by these patients even into adulthood, although bowel function has been demonstrated to improve with increasing age<sup>[61]</sup>. The rate of severe constipation does decrease by young adulthood<sup>[62]</sup>. Additionally, faecal incontinence, impacting on quality of life, was reported less frequently with longer follow-up. It seems that puberty is the critical age for this improvement as bowel function in late adolescence and adulthood remains similar<sup>[63]</sup>.

Investigation of the long-term outcomes of Hirschsprung's disease managed with minimally invasive techniques has been carried out, with on average up to 5 years of follow-up. There have been 3 meta-analyses undertaken comparing different techniques; laparoscopic to open Duhamel procedure, trans-anal endorectal approach to transabdominal approach, and trans-anal endorectal approach to laparoscopic endoanal approach<sup>[52,57,60]</sup>. Unfortunately, the data has a significant degree of heterogeneity, both in terms of the actual surgical techniques used and in how



the outcomes, constipation and faecal incontinence, were defined. The incidence of the most commonly described outcomes across the different techniques is demonstrated in Table 2. These rates are calculated from pooled data used in the meta-analyses.

Meta-analysis comparing the laparoscopic Duhamel to the open Duhamel procedure indicated that the incidence of faecal incontinence seems to be significantly lower with the laparoscopic approach (4% and 11% respectively;  $P = 0.02$ ), while the incidence of severe constipation does not seem differ (30% and 23% respectively;  $P = 0.12$ )<sup>[57]</sup>. Another study suggested lower constipation rates and better continence at 1-year follow-up for the laparoscopic-assisted endoanal pull-through over the Duhamel procedure<sup>[53]</sup>.

Initial early evidence with the transanal endorectal pull-through raised concerns about higher rates of faecal incontinence<sup>[49]</sup>. This was hypothesized to be related to overstretching of the anal sphincter muscles during the neonatal procedure. Recently comparison of the transanal endorectal approach to the trans-abdominal approach suggested reduced rates of incontinence and constipation<sup>[52]</sup>. While a comparison between the transanal endorectal approach to the laparoscopic-assisted endoanal approach demonstrated no difference in outcome<sup>[60]</sup>.

Currently it remains too early to fully evaluate the longer term outcomes into adulthood of minimally invasive techniques vs the traditional open procedures<sup>[63]</sup>.

## CONCLUSION

Over the past two decades, there has been significant evolution in the surgical management of neonatal colorectal conditions. Advances in the technology and understanding of minimally invasive surgery have allowed these techniques to be adapted for use in small infants for correction of ARMs and Hirschsprung's disease. Laparoscopy and minimally invasive techniques are now safely and routinely used in the management of these major congenital anomalies. As experience grows, these techniques will be used for increasingly complex and challenging cases.

Benefits of minimally invasive surgery have been demonstrated, in terms of shorter hospital stay and improved cosmesis, and other potential benefits are hypothesized. Major improvements in functional outcomes remain as yet unproven. Significant variation does still exist in the specific operative techniques. High quality data investigating different techniques and comparing both short-term and long-term outcomes is still needed to determine which procedures are most effective for our patients.

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## Case Control Study

## Increasing trend in retained rectal foreign bodies

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## Abstract

## AIM

To highlight the rising trend in hospital presentation of foreign bodies retained in the rectum over a 5-year period.

## METHODS

Retrospective review of the cases of retained rectal foreign bodies between 2008 and 2012 was performed. Patients' clinical data and yearly case presentation with data relating to hospital episodes were collected. Data analysis was by SPSS Inc. Chicago, IL, United States.

## RESULTS

Twenty-five patients presented over a 5-year period with a mean age of 39 (17-62) years and M: F ratio of 2:1. A progressive rise in cases was noted from 2008 to 2012 with 3, 4, 4, 6, 8 recorded patients per year respectively. The majority of the impacted rectal objects were used for self/partner-eroticism. The commonest retained foreign bodies were sex vibrators and dildos. Ninety-six percent of the patients required extraction while one passed spontaneously. Two and three patients had retrieval in the Emergency Department and on the ward respectively while 19 patients needed examination under anaesthesia for extraction. The mean hospital stay was 19 (2-38) h. Associated psychosocial issues included depression, deliberate self-harm, illicit drug abuse, anxiety and alcoholism. There were no psychosocial problems identified in 15 patients.

## CONCLUSION

There is a progressive rise in hospital presentation of impacted rectal foreign bodies with increasing use of different objects for sexual arousal.

**Key words:** Rectal foreign bodies; Rigid sigmoidoscopy;

Eroticism; Examination under anaesthesia; Psychosocial issues

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**Core tip:** There is a progressive rising incidence of retained rectal foreign bodies with increasing use of different designed and improvised objects for sexual arousal. The clinicians in the emergency settings must be well informed about the approach to the care of the patients with foreign bodies retained in the rectum.

Ayantunde AA, Unluer Z. Increasing trend in retained rectal foreign bodies. *World J Gastrointest Surg* 2016; 8(10): 679-684 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i10/679.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i10.679>

## INTRODUCTION

Hospital presentation with foreign bodies retained in the rectum is no longer rare although concrete epidemiological data are still lacking<sup>[1,2]</sup>. The earliest report of rectal foreign body dates back to the sixteenth century<sup>[3]</sup>. There have been recent reports to suggest an increasing incidence and hospital presentations with foreign bodies retained within the rectum<sup>[1-6]</sup>. Our prediction is that it is very much likely that such increasing hospital presentations shall continue to rise with the use of different objects for anal sexual fantasy. Objects retained in the rectum are mainly encountered in the adults following either intentional or non-intentional insertion. Occasionally, the retained objects may result from accidental or deliberate ingestion which had travelled through the whole of the gastrointestinal tract only to be impacted in the rectum<sup>[1-3,6,7]</sup>.

These patients usually present to the Emergency Department (ED) due to anorectal, pelvic or lower abdominal pain<sup>[1,4]</sup>. Typically, the patients have delayed hospital presentation after several failed attempts at retrieving the object<sup>[1-7]</sup>. The delayed presentation, particularly due to the perceived shame and/or associated embarrassment, presents both diagnostic and management challenges to the emergency staff<sup>[1,2]</sup>. The fact that significant numbers of these patients are often reluctant to volunteer the truth about the circumstances surrounding their presentation in the ED further contributes to the diagnostic delay. Therefore, the care of the patients with foreign bodies retained within the rectum requires a methodical approach for diagnosis, retrieval of the foreign body and post-extraction clinical observation<sup>[1,2]</sup>. The desired ultimate outcome for every case is a safe and successful per anum extraction of foreign body, in a manner as to respecting the patients' right to dignity, privacy and confidentiality.

We present our experience with retained rectal

foreign bodies to highlight a rising trend in presentation over a 5-year period and the approach to management.

## MATERIALS AND METHODS

We retrospectively reviewed the cases of all retained rectal foreign bodies that were managed in our hospital over a 5-year period, 2008 to 2012. Patients coded on the hospital Patient Administrative System (PAS) with a diagnosis of rectal foreign bodies were identified. Patient and clinical related data were collected from the hospital records right from the ED presentation through to the admission episode until discharge. Data collected relate to patients' demography, clinical presentation, types of the objects, circumstance relating to insertion, the time from insertion to presentation, physical examination findings, investigations and treatment offered. The yearly case presentation, types of retained rectal foreign bodies, length of hospital stay, associated complications and psychosocial problems were recorded.

## RESULTS

A total of 25 patients presented to our ED and treated for retained rectal foreign bodies over the 5 years study period. The mean age was 39 (17-62; SD 13.98) years with 17 males and 8 females giving a gender ratio of 2 to 1. We noted a progressive rise in the number of cases that presented per year from 2008 to 2012 with 3 recorded cases in 2008 and rising to the highest level of 8 cases in 2012 (Figure 1). Various objects impacted in the rectum and the reasons for insertion are shown in Tables 1 and 2 respectively. The presenting complaint were anorectal pain<sup>[4]</sup>, failure to self-retrieve the object, persistent vibration and anorectal pain<sup>[2]</sup>, anorectal pain and failure to retrieve the object<sup>[3]</sup> and anorectal pain and rectal bleeding<sup>[2]</sup>. The mean period between rectal object insertion and the visit to the ED was 14 (1-72; SD 14.6) h. Fifty-two percent (13/25) of the patients volunteered having had previous anorectal insertion of the same object ranging from 2 to 5 episodes with no problem.

Physical examination findings were completely normal in 11 while elicited clinical findings were tender lower abdomen in 3, palpable rectal foreign bodies on digital rectal examination (DRE) in 10 and blood in the rectum with palpable object in 1. Plain abdominal and pelvic X-ray were performed in all patients and erect chest X-ray was selectively performed only in 4 cases where indicated to exclude any free peritoneal gas under the diaphragm. Plain X-ray film confirmed the presence of retained rectal foreign objects in all cases but in one patient with apple in the rectum where it was not so obvious on the plain film. There was no specific indication for computerised tomography (CT) scan in any these patients and therefore this investigation was not done.

Extraction of the retained rectal objects was required



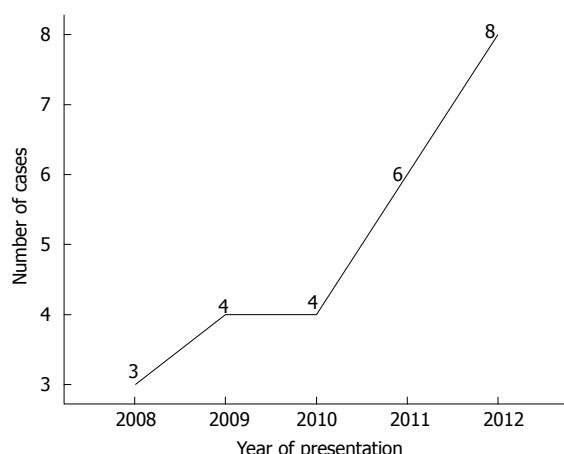


Figure 1 Line chart showing progressive rise in the number of cases over a 5-year period.

in 24 of the 25 patients. One patient passed the object spontaneously while waiting to be taken to the operating theatre. Two patients whose retained foreign bodies were easily palpable had the objects retrieved in the ED by digital manipulation and discharged. Three patients underwent digital removal of the retained rectal foreign bodies on the surgical assessment ward and were kept for a period of observation. Nineteen patients needed examination under anaesthesia (EUA) and extraction of retained foreign bodies in the operating theatre. Of the 19 patients, 15 had the objects extracted with grasping forceps with the aid of a proctoscope and/or a rigid sigmoidoscope, 2 were retrieved using small Keilland's forceps, 1 was digitally removed and one patient with impacted apple in the rectum was broken down and removed piecemeal. Rigid sigmoidoscopy was performed in 19 of 25 patients post extraction to exclude anorectal injury with the status of the anal sphincters assessed and recorded in each case. Two patients sustained anorectal mucosal tear, one of which developed significant bleeding per rectum post extraction; in one patient the sex toy had broken in ano; otherwise there was no complication recorded in 22 patients. There was no evidence of perforation identified in any of our patients in this series either during the EUA and/or following the period careful in hospital clinical observation.

The mean length of hospital stay was 19 (2-38; SD 9.56) h. All our patients had successful per anum extraction of the object with no one requiring a laparotomy or laparoscopy. Identified psychosocial issues in some of the patients included depression and deliberate self-harm in 3, illicit drug abuse in 2, anxiety in 2, depression in 1 and excess alcohol consumption in 2. There were no psychosocial problems identified in 15 patients. There was no correlation between the presence of psychosocial issues and either repeat insertion or number of previous insertions of rectal foreign bodies.

## DISCUSSION

Rectal insertion of objects and retention are commonly

Table 1 Table showing types of retained rectal foreign bodies

Retained rectal objects	Frequency	Percentage (%)
Apple fruit	1	4
Glass jar	2	8
Nail vanish bottle	1	4
Sex toy (dildo)	5	20
Sex vibrator	12	48
Denture (accidentally ingested and retained in the rectum)	1	4
Roll on deodorant bottle	2	8
Ceramic candle holder	1	4

Table 2 Reasons for retained rectal foreign bodies

Reasons for insertion of retained rectal foreign body	Frequency	Percentage (%)
Self erotism	9	36
Partner erotism	13	52
Self-massage of rectal prolapse	1	4
Self-harm	1	4
Accidental ingestion of denture	1	4

seen in the adults. These are either used in the majority of cases for anal sexual stimulation or sometime for criminal intent<sup>[1-9]</sup>. Occasionally, retained rectal foreign body may have resulted from self-treatment of anorectal conditions, attempts at concealment of illicit drugs or weapons and accidental ingestion of objects which eventually get impacted in the anorectum as in one of our patients<sup>[1,2,4,8,10-13]</sup>. There is a wide range of objects finding their ways into the rectum and we and other authors have previously predicted a possible rise in the incidence and presentations in the ED following the of various objects for erotic fantasy<sup>[1-4,6,8]</sup>.

The current study shows a progressive increase in the number of cases that presented over a 5-year period from 2008 through to 2012 from a single centre. This outlook confirmed what we and some other authors have predicted previously<sup>[1-4,6,8]</sup>. This most recent study has demonstrated a significant rise in the number of cases per year compared with studies by Safioleas *et al*<sup>[5]</sup> who reported 34 patients over a 25-year period, Coskun *et al*<sup>[6]</sup> with a report of 15 patients over a 10-year study period (1999-2009), Rodríguez-Hermosa *et al*<sup>[7]</sup> with 30 patients over an 8-year period (1997-2004) and our previous report of 16 cases over a 4-year period (2001-2004)<sup>[8]</sup>. We can only expect a continuing rise in the hospital presentations of impacted foreign bodies within the rectum given the increasing fantasy with a wide variety of improvised household and designed objects. Table 3 summarises the trend in the published literature over the last few decades. The sudden surge in the incidence reported by Lake *et al*<sup>[4]</sup> covering a 10 year study period was a data from a very large United States population and stands as the largest published data on this subject in the literature. The current data and our previous report<sup>[8]</sup> have shown a rising trend in the ED cases of objects impacted in the rectum.



**Table 3** Table showing published trend in retained rectal foreign body

Ref.	Study years	No of cases	Average cases per year	M:F ratio
Huag <i>et al</i> <sup>[14]</sup>	1979-2000 (21 yr)	10	0.48	10:00
Lake <i>et al</i> <sup>[4]</sup>	1993-2002 (10 yr)	87	8.7	17:01
Clarke <i>et al</i> <sup>[13]</sup>	1995-2005 (10 yr)	13	1.3	13:00
Rodríguez-Hermosa <i>et al</i> <sup>[7]</sup>	1997-2004 (8 yr)	30	3.75	15:01
Ayantunde <i>et al</i> <sup>[8]</sup>	2001-2004 (4 yr)	16	4	15:01
Safioleas <i>et al</i> <sup>[5]</sup>	1971-2006 (25 yr)	34	1.36	6:1
Coskun <i>et al</i> <sup>[6]</sup>	1999-2009 (10 yr)	15	1.5	15:00
Ayantunde <i>et al</i> <sup>[8]</sup>	2008-2012 (5 yr)	25	5	2:1

This study also affirmed the persistent male preponderance as it was variously reported in the published literature although there seems to be a slightly higher female population in the current study than previously reported<sup>[1-10]</sup>. The gender ratio showed that the male population was only twice affected as female gender in the current study. This reduced male to female ratio may have been due to a significant increase in the group of female gender using objects for partner-erotism in this cohort than previously reported. The majority of our patients were young adults who were using the retained objects for either self-erotism or partner-erotism. Eighty eight percent of our patient population were using the foreign bodies for erotic stimulation and this is in agreement with the previous published reports<sup>[1-4,7-10]</sup>. The changing pattern with increasing female gender and predominantly younger population than previously reported may likely be the emerging trend in the presentations of retained rectal foreign bodies.

Our previous work<sup>[8]</sup> and that of Cohen *et al*<sup>[9]</sup> have shown objects used for sexual interaction accounted for more than three-quarter of the cases impacted foreign bodies in the rectum presenting to hospitals. One patients in this study inserted an apple fruit for self-harm. This patient disclosed that he was abused as a child and became very depressed after the loss of his wife. One patient was using the object for self-massage of rectal mucosal prolapse in an attempt to reduce it while one accidentally swallowed their dentures, which later became impacted in the rectum prompting the presentation to the ED. We did not encounter any patient in the current series with retained rectal foreign bodies with history of sexual rape or other violent sexual practices as previously reported by some authors<sup>[1,2,8,14,15]</sup>.

Generally speaking, patients with rectal foreign bodies do not attend the ED early unless attempts have been made to retrieve the objects by the patient or their partners because of the perceived embarrassment and shame<sup>[1-4,7,8,12-14]</sup>. The majority of our patients attended the ED because of failure to retrieve the foreign bodies after several attempts while few others presented with anorectal pain and/or bleeding. Two of our patients in particular presented because of persistent vibration of the powered sex toys causing them significant anorectal and lower abdominal pain. The delay in presentation may be due to the hope of a spontaneous passage of the foreign objects by the patient and the eventual failure to

pass against their expectation leads to some measure of anxiety<sup>[1]</sup>.

The initial evaluation at presentation should include a careful history, abdominal and digital rectal examinations (DRE) including the assessment of the status of the perianal region and anal sphincters with the findings clearly documented before and after the extraction of the foreign body in the clinical notes<sup>[1-4,8,14-16]</sup>. Confirmation of the type, size, number and location of the objects should be by biplanar plain abdominal and pelvic films<sup>[1-3,8,14]</sup>. Biplanar plain X-rays in this study showed the foreign objects in all but one of our patients. The one patient with retained apple fruit was not so obvious on the plain films. Erect chest X-ray and CT scan should only be selectively performed where indicated. Plain erect chest radiograph is recommended to exclude the presence of free peritoneal gas under the diaphragm indicating rectosigmoid perforation<sup>[1]</sup>. There was no patient in this series with any specific indication requiring a CT scan evaluation. CT scan where indicated is excellent for localization of non-opaque foreign bodies, detection of perforation or obstruction and diagnosis of pelvic abscess<sup>[1]</sup>.

The basic approach to the management of patients with retained foreign bodies include achieving a safe per anum extraction, direct visualisation of the rectosigmoid mucosal to exclude bowel injury and a period of close clinical observation in the hospital for early detection of complications<sup>[1-4,8,16]</sup>. Extraction of impacted rectal foreign bodies should be achieved under direct vision where possible using an anoscope or sigmoidoscope to avoid iatrogenic anorectal injury<sup>[1-4,8,14,16]</sup>.

Generally speaking, the determination of level of the retained foreign bodies in the rectosigmoid segment is important and useful for the purpose of management. Most low-lying rectal foreign objects are reachable by the examining finger and can be removed per anum whereas those higher up in the sigmoid colon can prove to be difficult to retrieve<sup>[1,2,7,13,14]</sup>. Foreign bodies that are impacted above the rectum are usually not easily visualized and therefore transanal retrieval is difficult<sup>[1,2,7,13,14]</sup>. Generally speaking, a foreign body located below the rectosigmoid junction that is easily palpable by the clinician's examining finger can be extracted in the ED. However, an uncooperative and anxious patient with associated anal sphincter muscles contractions will make ED extraction undesirable. The

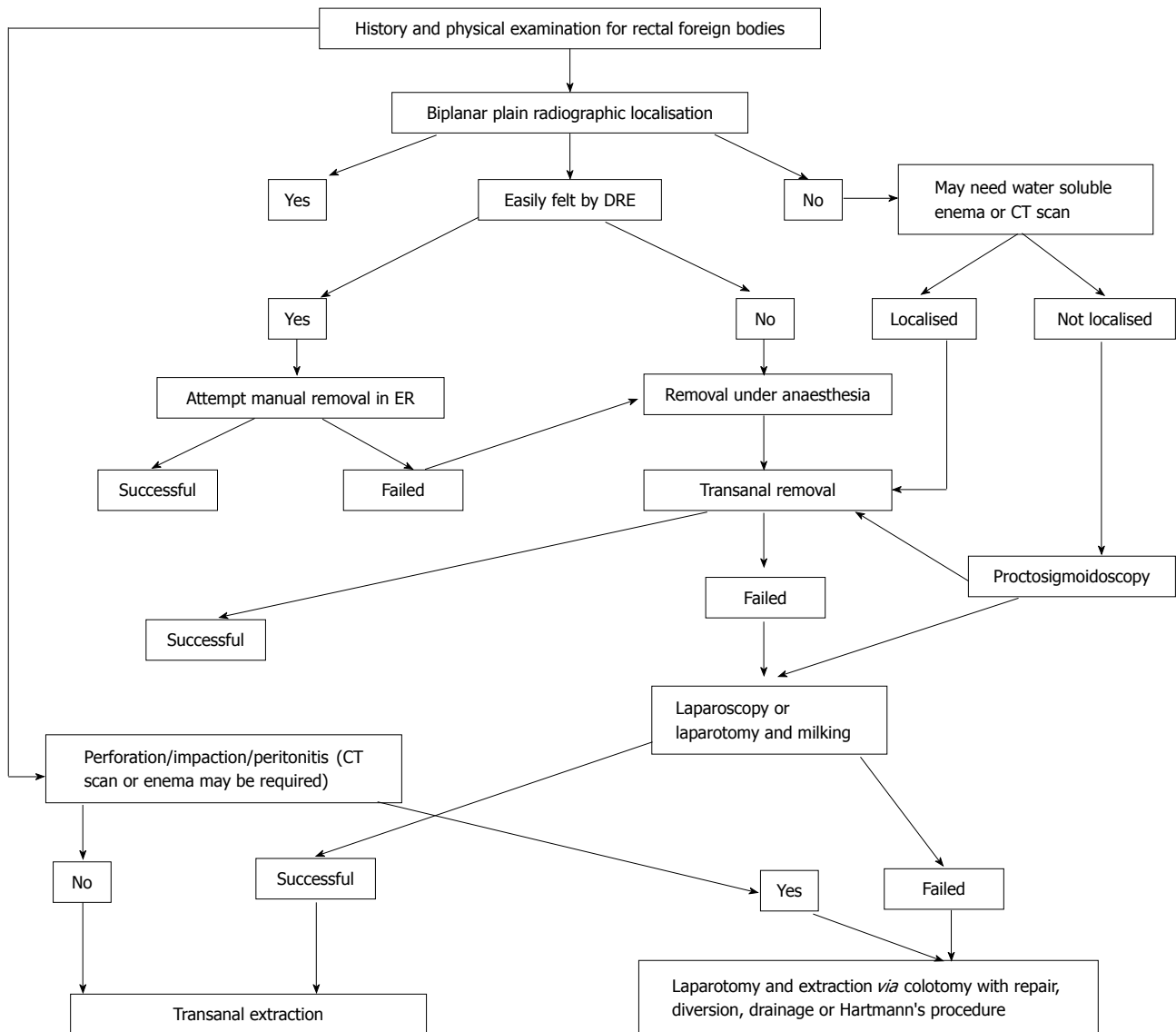


Figure 2 Algorithm for management of retained rectal foreign bodies.

use of anaesthesia in the treatment of these patients reduces anal sphincter muscles spasm and therefore improves direct visualization and good exposure with a successful chance of extraction per anum<sup>[1,8]</sup>.

There has been a significant evolution addressing the various management challenges of wide spectrum of different types of objects impacted in the rectum over the last few years<sup>[1,2,4,8,10,14,16]</sup>. The majority of retained low-lying foreign bodies can be removed with a guided grasping forceps or a clamp introduced a proctosigmoidoscope. This approach can be aided by an initial examining finger manoeuvre to disengage the impacted object from the oedematous anorectal mucosa<sup>[1,8]</sup>. The majority of our patients in this study required their retained rectal objects to be removed in the operating theatre under direct vision with proctosigmoidoscope using a grasping forceps or a small Keilland's forceps. All of them underwent successful transanal retrieval with no need for laparoscopy or laparotomy.

The failure of transanal retrieval of impacted foreign bodies in the rectum can be predicted preoperatively. Lake *et al*<sup>[4]</sup> in their experience cited several factors responsible for failure of transanal removal including the impaction of a an object longer than 10 cm, hard or sharp objects, objects that have migrated upward into the sigmoid colon and those that have been impacted for more than 2 d. There are specific indications for the use of emergency laparotomy for extraction of impacted objects including failure of attempts at transanal removal, presence of perforation and/or peritonitis<sup>[1,2,4,8,16]</sup>. The use of minimally invasive operative techniques for impacted rectosigmoid foreign bodies has been described which is a combination of laparoscopic downward milking of the object followed by per anal extraction<sup>[1,2,17-19]</sup>. This approach however is only recommended for smooth foreign bodies and if successful, avoids the need for a full laparotomy and provides the benefit of early discharge from the hospital<sup>[1,2,17-19]</sup>. Figure 2 is adapted from reference 1.

In conclusion, this study confirms a rising trend in the

number of patients with retained rectal foreign bodies with hospital presentations and most of these objects were used for erotic stimulation. There was also a slightly higher female population in the current study than previously reported and this may be the emerging trend of this entity. It is very much likely that the increasing trend would be encountered in most hospitals and therefore, the clinicians in the emergency settings need to be well informed about the approach to the care of patients with retained rectal foreign bodies.

## COMMENTS

### Background

Hospital presentation with retained rectal foreign bodies is no longer rare although concrete epidemiological data are still lacking. They are usually encountered in the adults and are either inserted intentionally or non-intentionally. The delay in the presentation and the associated patient's vague history usually lead to significant diagnostic and management challenges.

### Research frontiers

There are recent anecdotal reports suggesting an increasing trend in the hospital presentations with impacted foreign bodies in the rectum. The present authors' and other authors' prediction from the previous published reports was a likelihood of an increasing presentation with the use of different objects for anorectal eroticism. Therefore, the clinicians in the emergency settings should be well familiar with the approach and the principles of care of these patients.

### Innovation and breakthroughs

The authors predict that from the current study and the paucity of the available published epidemiological data that there is likely going to be an increasing trend in the incidence and presentations with the retained objects in the rectum.

### Applications

The diagnosis and treatment patients presenting to hospital rectal foreign bodies should be orderly and methodical including safe retrieval and post-extraction period of observation. The desired ultimate outcome for every case is a safe and successful per anum extraction of foreign body, in a manner respecting the patients' right to dignity, privacy and confidentiality.

### Terminology

Retained lower GIT foreign bodies may be located low or high based on their positions relative to the rectosigmoid junction. Most low-lying rectal foreign objects are easily reachable by the examining finger and can be removed per anum whereas those higher up in upper rectum or sigmoid colon may be difficult to reach and retrieved.

### Peer-review

This is an interesting case series of rectal foreign bodies.

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Retrospective Cohort Study

# Incidental non-benign gallbladder histopathology after cholecystectomy in an United Kingdom population: Need for routine histological analysis?

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## Abstract

### AIM

To analyse the range of histopathology detected in the largest published United Kingdom series of cholecystectomy specimens and to evaluate the rational for selective histopathological analysis.

### METHODS

Incidental gallbladder malignancy is rare in the United Kingdom with recent literature supporting selective histological assessment of gallbladders after routine cholecystectomy. All cholecystectomy gallbladder specimens examined by the histopathology department at our hospital during a five year period between March 2008

and March 2013 were retrospectively analysed. Further data was collected on all specimens demonstrating carcinoma, dysplasia and polypoid growths.

## RESULTS

The study included 4027 patients. The majority (97%) of specimens exhibited gallstone or cholecystitis related disease. Polyps were demonstrated in 44 (1.09%), the majority of which were cholesterol based (41/44). Dysplasia, ranging from low to multifocal high-grade was demonstrated in 55 (1.37%). Incidental primary gallbladder adenocarcinoma was detected in 6 specimens (0.15%, 5 female and 1 male), and a single gallbladder revealed carcinoma *in situ* (0.02%). This large single centre study demonstrated a full range of gallbladder disease from cholecystectomy specimens, including more than 1% neoplastic histology and two cases of macroscopically occult gallbladder malignancies.

## CONCLUSION

Routine histological evaluation of all elective and emergency cholecystectomies is justified in a United Kingdom population as selective analysis has potential to miss potentially curable life threatening pathology.

**Key words:** Gallbladder; Incidental; Cholecystectomy; Histopathology; Carcinoma

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**Core tip:** The selective use of histopathological examination of gallbladders removed during routine cholecystectomy has been advocated by several authors in the literature. We present a large single centre study demonstrating a full range of gallbladder disease from cholecystectomy specimens, including more than 1% neoplastic histology and two cases of microscopic gallbladder malignancies in macroscopically normal gallbladders. On this basis, routine histological evaluation of all elective and emergency cholecystectomies is justified in an United Kingdom population as selective analysis has potential to miss potentially curable life threatening pathology.

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## INTRODUCTION

Cholecystectomy is among the most commonly performed surgical procedures worldwide, principally indicated in patients with symptomatic gallstone-associated disease. Approximately 5.5 million people in the United Kingdom

have gallstones<sup>[1]</sup>, with 70000 undergoing operative intervention each year in the United Kingdom<sup>[2]</sup>. The indication for cholecystectomy is usually benign disease, though the histology can reveal incidental premalignant or malignant gallbladder pathology warranting appropriate further surgical resection.

Incidental gallbladder malignancies are rare in the United Kingdom with reported rates between 0.17%-0.81% of cholecystectomy resected specimens<sup>[3-6]</sup>. Further revision surgery with curative intent is generally indicated in those without metastatic disease and tumour staging worse than T1a. Potentially curative resection may be offered in up to 50% of patients with incidental gallbladder malignancy post-cholecystectomy, however, some of these patients are ultimately found to have unresectable or metastatic disease at the time of laparotomy<sup>[7,8]</sup>.

Recognised premalignant conditions leading to gallbladder carcinoma include gallbladder dysplasia and those arising from adenomatous polyps<sup>[9]</sup>. Dysplastic changes are often difficult to predict pre-operatively due to absence of macroscopic abnormalities detectable on imaging, hence emphasizing need to histologically examine all gallbladders resected<sup>[9]</sup>. Strategies for gallbladder polyp surveillance and indications for operative management have been previously recommended, however this remains a controversial topic with widely varied practice in reality<sup>[10,11]</sup>.

Some authors have advocated selective, rather than routine, histopathological analysis of resected gallbladders, primarily due to rarity of incidental disease, financial implications and time burden on histopathology departments<sup>[4-6,12]</sup>. Others have suggested macroscopic examination of resected gallbladders intra-operatively, to determine whether further histological analysis is required depending on presence of suspicious macroscopic lesions or significant patient risk factors for gallbladder cancer<sup>[4]</sup>.

The primary aim of this study was to review the range of histopathology detected in the largest United Kingdom series of routine cholecystectomy specimens from a single centre teaching hospital, in particular pre-malignant and malignant pathology. Secondary aims were to further analyse patients with incidental gallbladder malignancy, dysplasia and polyps and to make recommendations for future practice and necessity of routine histological examination of gallbladder specimens.

## MATERIALS AND METHODS

This descriptive study was designed as a retrospective review of a database of all gallbladder specimens histopathologically examined at Cambridge University Hospital (Cambridge, United Kingdom) during a five year period between March 2008 and March 2013. This hospital is a tertiary referral centre for management of hepatopancreatobiliary malignancies. Exclusion criteria included gallbladders resected as part of another procedure (e.g., Whipple's resection) and instances where malignancy was strongly suspected pre-



**Table 1 Summary of histopathological findings**

Histology	Subgroup	No (n = 4027)	% Total
Normal		182	4.50%
Cholecystitis		3480	86.3%
Acute		45	
Chronic	Gangrenous	3435	
	Empyema	29	
	Follicular	6	
	Xanthogranulomatous	3	
		5	
Cholesterosis		246	6%
Polypoidal Lesion		44	10%
	Cholesterol-based	42	
	Hyperplastic	1	
	Adenoma	1	
Metaplasia		13	0.3%
Dysplasia		55	1.4%
	Focal LGD*	40	
	Multi-Focal LGD	9	
	Focal HGD	2	
	Multi-focal HGD	4	
	(Multi-focal HGD + AC)	(2)	
Carcinoma <i>in situ</i>		1	0.02%
Adenocarcinoma		6	0.15%

LGD: Low grade dysplasia; HGD: High grade dysplasia; AC: Adenocarcinoma.

operatively, including ultrasonographically suspicious lesions or polyps greater than 1 cm in size. Histology reports were retrospectively analysed for presence of gallbladder disease, including benign and malignant pathology.

Further information was obtained on gallbladders demonstrating incidental gallbladder malignancies, dysplastic changes and polypoid structures including patient demographics, pre-operative symptoms and imaging, operative details, tumour histology and post-operative clinical outcomes. In patients with incidental malignancies, extensive data was collected on staging, tumour type, further resectional surgery and survival time. Survival times were calculated from time of cholecystectomy to date of death or latest follow up. In those with detected dysplasia, additional data were collected, including type of dysplasia, presence of tumour foci and associated risk factors (*e.g.*, primary sclerosing cholangitis). For gallbladder specimens containing polyps, further information was obtained including uptake into our gallbladder surveillance programme, polyp type, size and number, preoperative ultrasonography findings and indications for surgery. Hospital electronic medical records and patient hard copy notes were used to extract relevant data.

Statistical analysis were performed using Statistical Package for the Social Sciences (SPSS Windows Version 22.0, Chicago, IL, United States) with a *P*-value less than 0.05 representing statistical significance. Continuous data analysed was described with median values accompanied with ranges [Median (range)].

## RESULTS

A total of 4027 resected gallbladders from elective and emergency cholecystectomies were examined by the histopathology department at Addenbrooke's Hospital in the 5 years period studied. Overall, we report an incidental gallbladder invasive adenocarcinoma rate of 0.15% (6/4027) and one gallbladder demonstrating carcinoma-*in-situ* (0.02%, 1/4027). The majority of resected specimens exhibited gallstone or cholecystitis related disease. Table 1 displays the range of histopathological findings demonstrated from our patient sample.

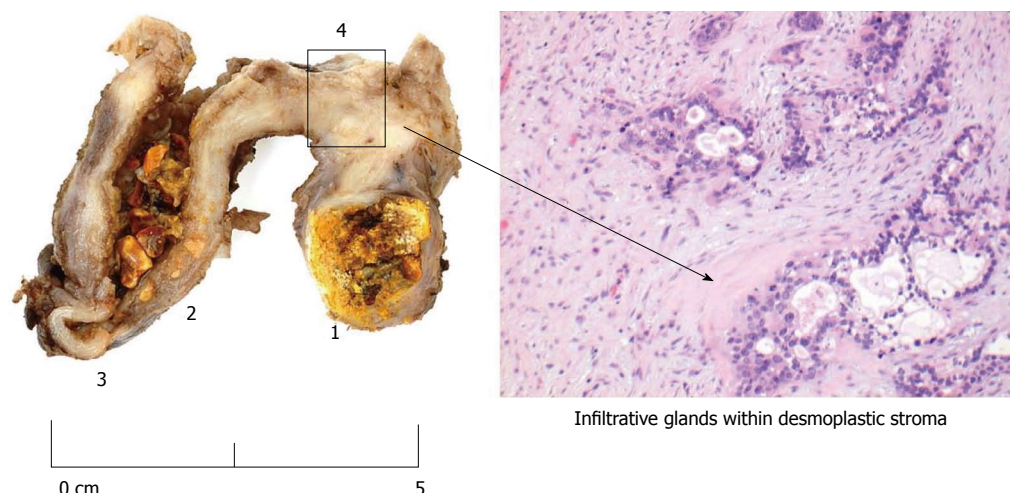
### Gall bladder carcinoma

Primary invasive gallbladder adenocarcinoma was identified in 6 patients with a median age of 66.5 years (range 45-71) and a female majority (5/6) (Figure 1 is an illustration of typical macroscopic and microscopic appearances of a gallbladder cancer specimen). All but one patient (5/6) had co-existing cholelithiasis on pre-operative ultrasonography, while half (3/6) had ultrasonography evident thickened gallbladder walls consistent with cholecystitis. All patients were symptomatic with right upper quadrant pain pre-operatively, however none presented with a palpable mass, clinical jaundice or weight loss. In none of these patients was gallbladder malignancy considered a potential differential diagnosis on decision to perform a cholecystectomy. Surgery in 4 of these of these cases were reported as more challenging than usual, but not in the other 2, which were both reported as macroscopically normal from histopathological examination, but microscopic examination revealed T1 disease, one T1a and the other T1b. Otherwise, tumour staging varied significantly with T3 disease the most advanced. To present date, 3 patients have died from progressive metastatic disease with a post-cholecystectomy mean survival time of 20.6 mo.

A single case of carcinoma-*in-situ* (0.02%, 1/4027) was identified in a 66-year-old gentleman with known gallstones. No lesion was identified on macroscopic examination, however microscopic analysis revealed foci of adenocarcinoma within surrounding extensive high grade dysplasia. Further details of all carcinoma patients including operation details and clinical outcome postoperatively are depicted in Table 2.

### Gall bladder dysplasia

The overall incidence rate of gallbladder dysplasia was 1.37% (55/4027) with a wide spectrum of dysplastic changes as illustrated in Table 1. Median age was 53 years (range 22-82) with the majority of patients being female (85.5%, 47/55). From all 55 cases of dysplasia, 47.3% (26/55) had co-existing gallstone disease on final histology. Primary sclerosing cholangitis was pre-existent in 3.6% (2/55) patients. Four gallbladders exhibited multifocal high grade dysplasia from which half



**Figure 1** Typical macroscopic and microscopic appearances of gallbladder cancer. 1: Cholesterol gallstones, impacted; 2: RA sinuses containing impacted stones; 3: Chronic cholecystitis; 4: Ruptured gallbladder carcinoma.

**Table 2** Pre- and post-operative characteristics of cases with incidental gallbladder adenocarcinoma

Age	Sex	Pre-operative imaging	Operation details	Operative findings	Tumour type/staging	Further management	Survival (mo)
71	F	USS: Multiple gallstones	Lap	Smooth GB wall with multiple calculi	T1a N0 M0, Adenocarcinoma	No further operation, surveillance CT scans	Alive (64)
68	F	USS: Multiple stones, dilated CBD; CT: Multiple stones, no mass seen	Open	Large GB calculi, no CBD stones on CBD exploration	T2 N0 M0, Adenocarcinoma (MD)	Not fit for further resection (known chronic leukaemia – already on chemotherapy)	Alive (22)
45	F	USS: Stones, thickened GB wall; CT: Inflammatory changes on GB wall	Lap converted to open	Small abscess on GB bed, gross GB wall thickening	T3 N1 M0, Adenocarcinoma (PD)	Revision operation – abandoned as nodules on umbilical port and peritoneum, palliative chemotherapy	12
70	F	USS: Grossly thickened GB wall and multiple gallstones	Lap	Thick dense adhesions with fistulous communication between GB tumour and transverse colon	T3 N1 M1, Adenocarcinoma (PD)	Chemotherapy	12
65	F	USS: Stones, cholecystitis; CT: Marked GB wall thickening, ?cholecystitis	Lap	GB wall inflamed, disintegrated with biliary spillage++	T2 N0 M0, Adenocarcinoma (MD)	Not medically fit for revision surgery; developed nodal disease but not fit for chemo; palliative therapy	37
65	M	USS: Sludge and gallstones (pancreatitis patient)	Lap	Mildly inflamed GB with calculi	T1b N0 M0, Adenocarcinoma (PD)	Revision surgery and lymphadenectomy, chemotherapy	Alive (36)
66	M	USS: Multiple small gallstones	Lap	Smooth GB wall with calculi	Tis N0 M0	No further management	Alive (54)

USS: Ultrasonography; CT: Computed tomography; GB: Gallbladder; MD: Moderately differentiated; PD: Poorly differentiated.

(2/4) exhibited foci of adenocarcinoma, both previously mentioned in our cancer cohort (Table 2). One gallbladder (1.8%, 1/55) demonstrated a tubular adenoma with surrounding focal high grade dysplastic changes. No gallbladder specimen revealed evidence of dysplasia at the cystic duct resection margin.

### Gall bladder polyps

Gallbladder polyps were identified in 1.09% (44/4027). The median age was 51 years (range 28–84). Pre-operative imaging identified 77.3% (34/44) of these polyps, with a measured median size of 7.4 mm (range

2–13 mm). All but three polyps were cholesterol in nature (93.2%, 41/44). The other three polyps varied in histology including one hyperplastic polyp, one xanthomatous polyp and one tubular adenomatous polyp. None of these polyps exhibited malignant features.

### DISCUSSION

This study is the largest United Kingdom series to date evaluating range of histopathology demonstrated from cholecystectomy resected gallbladder specimens. Our main findings include observed overall rates of 0.17%

incidental gallbladder adenocarcinomas and 1.37% incidental premalignant gallbladder dysplasia. The most common histology reported in our study was chronic cholecystitis (85.3%).

Incidental gallbladder malignancy identified in cholecystectomy specimens make up the majority of all diagnosed gallbladder cancers<sup>[12]</sup>. There is a well-documented heterogeneity in the incidence of gallbladder cancer, varying according to various patient demographic factors including worldwide location, ethnicity and age<sup>[13]</sup>. Along with most of Europe, the United Kingdom is considered a low risk area with an associated low rate of incidental gallbladder malignancies when compared to high risk areas such as India and Japan<sup>[14]</sup>. Previous United Kingdom studies have reported incidence rates between 0.17%-0.81%, however some of these studies have included gallbladders in which tumour was suspected on preoperative imaging<sup>[3-6]</sup>. Our study observed a 0.17% rate of incidental gallbladder malignancies. This relatively low incidence may reflect the ethnicity of our study population with a strong European-Caucasian representation as only one patient from all carcinoma and dysplasia-revealing gallbladders was non-Caucasian in ethnicity (Indian). Furthermore, those patients in whom gallbladder malignancy was strongly suspected on pre-operative imaging were strictly excluded from our study and this may have contributed further to the low incidence rate.

Chronic gallstone-related irritation is a known significant risk factor for dysplastic changes and development of carcinoma<sup>[15]</sup>. Increased gallstone weight, number and volume have also been associated with an increased risk of gallbladder cancer<sup>[16]</sup>. In this study, 6 out of the 7 carcinoma patients had co-existing gallstones.

In contrast, only 47.3% of dysplastic gallbladders demonstrated final histology cholelithiasis, perhaps implying other pathogenesis factors involved in development of gallbladder dysplasia. In this regard, 2 patients exhibiting high grade dysplasia had a pre-operative diagnosis of primary sclerosing cholangitis, a known risk factor for gallbladder malignancy with previous reports of up to 30% of resected gallbladders displaying dysplasia/carcinoma pathology<sup>[17]</sup>. Consistent with this, our policy is to adopt a low threshold in recommending cholecystectomy in patients with primary sclerosing cholangitis presenting with clinical or radiological evidence of gallbladder pathology.

In our institution, routine pre-operative investigations for patients presenting with symptomatic biliary pathology includes the assessment of liver function tests alongside ultrasonographic assessment of the gallbladder and biliary tree. Should these provide any suspicious features then further assessment with cross sectional imaging (CT scan or MRCP) and endoscopic ultrasound are performed, followed by discussion in the regional multi-disciplinary meeting where decision on further management is made.

Six patients in our cohort were identified as having

gallbladder carcinoma on post-operative histology (Table 2), with a median age of 66.5 years. The youngest patient was a 45-year-old female who was found to have T3N1 disease which progressed rapidly with peritoneal spread. None of these were suspected pre-operatively. In 2 of the 6 cases, the pre-operative ultrasound identified gallstones within a thin walled gallbladder with the absence of any worrying features to necessitate further investigations. Operative findings for these 2 cases were of thin walled gallbladders (macroscopically normal) and hence gallbladder cancer was not suspected. Post-operative histology described early gallbladder carcinoma (T1a and T1b respectively), despite these microscopic findings, the histopathological examination reported these specimens as macroscopically normal looking. The remaining 4 cases, were identified on pre- and intra-operative examinations as having macroscopic abnormalities. In 3 of these cases, further pre-operative investigations with cross sectional imaging (CT scan) were performed. The CT findings were reported as inflammatory, with the absence of a mass lesion and abnormal lymphadenopathy. Operative findings were of thickened gallbladder walls, while one had an associated abscess in the gallbladder fossa. The clinical suspicion here was of severe inflammatory changes. Although the presence of gallbladder cancer in such cases is always a possibility, the clinical suspicion was low and hence standard cholecystectomy was performed. Post-operative histology identified T2 disease in 2 cases and T3 N1 disease in the remaining case.

The final case was of a 70-year-old female with pre-operative ultrasonography describing a thickened and inflamed gallbladder with calculi; at the time of surgery she was found to have dense adhesions a thickened shrunken gallbladder, as well as a fistulous communication between the gallbladder and the transverse colon. These findings were thought to be inflammatory in nature, however, the diagnosis of gallbladder carcinoma is regarded as a possibility in such cases. An intra-operative decision on whether a simple cholecystectomy or a more radical should be taken. The majority of such cases will ultimately prove to be benign and inflammatory in aetiology. Factors such as pre-operative co-morbidities and the potential stage of disease, should this turn out to be malignant, are taken into account. If clinical suspicion of cancer is high, co-morbidities are limited and the patient is suitable for a potentially curative resection, then frozen section may be performed to confirm the diagnosis and the surgical plan amended as deemed necessary. However, if the patient or tumour factors render potentially curative surgical intervention impossible then a standard cholecystectomy to achieve a tissue diagnosis may be deemed appropriate.

Several United Kingdom papers have recommended selective histopathological analysis of cholecystectomy resected specimens<sup>[4-6,14]</sup>. This recommendation is based on the assumption that incidental gall bladder malignancy is associated with macroscopic lesions which can be identified on examination of the resected gall bladder

in the operating theatre. Our study, the largest United Kingdom series to date and the only one with over 3000 patients, demonstrates that this assumption is not reliable, as evidenced by the finding of gallbladder malignancy in macroscopically normal gallbladders, including T1b disease for which revision surgery is generally advocated, on account of published data showing a survival benefit of 3.4 years from radical resection over simple cholecystectomy<sup>[18]</sup>. The patient with T1b disease underwent further liver segmental resection with lymphadenectomy and is disease free three years later to this day. This is the first United Kingdom series to report a patient with macroscopically occult incidental gallbladder malignancy with no preoperative or intra-operative suspicion of carcinoma who subsequently underwent successful R0 resectional surgery.

A systematic review in 2014 by Jamal *et al*<sup>[14]</sup> examined 20 previous studies, including 6 United Kingdom studies, evaluating the necessity of routine histological analysis in macroscopically normal gallbladders. The authors concluded that in gallbladders deemed normal from macroscopic examination by the operating surgeon, selective histological analysis was feasible in the "low risk" European ethnicity under the age of 60<sup>[14]</sup>. However, the systematic review did not include a recent histopathology paper by Hayes *et al*<sup>[19]</sup> examining gallbladder specimens sent for histology after cholecystectomy. This study reported a striking 50% (5/10) of incidental invasive gallbladder malignancies presenting with no macroscopic abnormalities on histopathologist examination with a mean age of 54.6 years. This proportion of macroscopically occult malignancies in a "low risk" population of that age range challenges the recommendations from Jamal *et al*<sup>[14]</sup> recent systematic review. In addition, United Kingdom Royal College of Pathologists 2005 recommendations state that all gallbladders removed for presumed benign disease warrant histological examination in order to ensure no significant subtle pathology is missed from macroscopic examination<sup>[20]</sup>.

Solaini *et al*<sup>[3]</sup> in 2014 reported almost 3% incidental neoplastic findings from cholecystectomy gallbladders with inclusion of dysplastic changes and is one of few United Kingdom papers supporting routine histological analysis of all gallbladder specimens. The authors reported dysplasia rates of 2.3% (18/771) with a median age of 45 years in a population with strong Asian ethnicity representation (66%). Our study observed lower rates of dysplastic changes at 1.37% (55/4027) with a higher median age of 53 years, perhaps partly explained by the lack of representation of the Asian population in our study group<sup>[21]</sup>.

Whether the finding of dysplasia is of clinical significance may be debated, but our opinion is that this is not merely academic. Positive cystic duct margins and gross high grade dysplastic changes can indicate further potential pancreatobiliary disease, with further operative exploration warranted in certain circumstances. Bickenbach *et al*<sup>[22]</sup> in 2011 reported five cases of high

grade dysplasia at the cystic duct resectional margin following cholecystectomy, all of whom subsequently underwent further resectional surgery, either with excision of cystic duct remnant or excision of extrahepatic bile duct. Of these, one patient was found to have adenocarcinoma within the resected cystic duct remnant. No gallbladders in our study demonstrated cystic duct margin positive disease, however half our cases of multifocal high grade dysplasia had associated foci of adenocarcinoma. In our practice, the finding of high grade dysplasia on the cystic duct margin would warrant further surgical exploration and frozen section of cystic duct margin to ascertain whether further radical resection would be required to ensure R0 resection.

Gallbladder polyps are common with a reported incidence rate in a recent multi-ethnic United Kingdom series of 3.3%, with higher rates observed in the Asian ethnic groups<sup>[23]</sup>. Our series reports a 1.09% (44/4027) incidence of polypoid lesions of the gallbladder, however we excluded all polyps reported as sonographically suspicious of malignancy or more than 1 cm in size pre-study in order to focus on incidental gallbladder pathology. Our largely Caucasian study population may also reflect the observed lower polyp incidence rate. All but one polyp demonstrated benign pseudotumour characteristics, predominantly cholesterol in nature (41/44). We did however observe one true polyp adenoma (1/44, 2.3%) occurring in a 67-year-old male and of 3mm in size, which had been reported as a gallstone on preoperative sonography with biliary colic as indication for surgery. Cairns *et al*<sup>[24]</sup> in 2013 examined a large cohort of gallbladder polyps in a United Kingdom population and observed a similar 2.2% incidence rate of adenomas as well as 0.7% adenocarcinoma rate. Although adenomas are histologically benign, there is a well-recognised adenoma-carcinoma path of carcinogenesis to gallbladder malignancy<sup>[21]</sup>. This has led to polyp surveillance implementation in HPB centres with indications to operatively remove gallbladders displaying polypoid lesions above 1 cm, rapidly growing in size or symptomatic in nature<sup>[24]</sup>. Marangoni *et al*<sup>[10]</sup> surveyed United Kingdom surgeons regarding their practice of gallbladder polyp surveillance with indications for operative management and revealed significant variation and identified a need for formal national guidelines to tackle this area of conflicting opinions. Although polyp surveillance was not analysed in further detail as part of this study, it is our practice to actively monitor polyps with ultrasonography particularly with recent literature to support it is cost effective<sup>[24]</sup>.

In conclusion, our study has demonstrated a broad spectrum of histopathology from examination of cholecystectomy resected gallbladders for preoperatively diagnosed benign gallbladder disease. This is the largest United Kingdom series within the literature and observed 0.17% incidence of primary adenocarcinoma and 1.37% gallbladder dysplasia. The study is the first United Kingdom study to report cases of macroscopically normal gallbladders harbouring adenocarcinoma lesions



with subsequent successful R0 resection. We also report a single case of adenocarcinoma in a patient aged 45 years. With over 1% rate of pre-malignant and malignant disease, we conclude that routine histological evaluation of all elective and emergency cholecystectomies is justified in a United Kingdom population and that selective histological evaluation has the potential to miss life threatening gallbladder pathology amenable to subsequent curative surgery.

## COMMENTS

### Background

Cholecystectomy is among the most commonly performed surgical procedures worldwide. Routine histopathological examination of the resected specimens is usually performed. However, selective histopathological analysis has been proposed in the literature, primarily due to rarity of incidental disease (0.17%-0.81% in the United Kingdom), financial implications and time burden on histopathology departments.

### Research frontiers

The authors aimed to analyse the range of histopathology detected in the largest published United Kingdom series of cholecystectomy specimens and to evaluate the rational for selective histopathological analysis.

### Innovations and breakthroughs

This large single centre study demonstrated a full range of gallbladder disease from cholecystectomy specimens, including more than 1% neoplastic histology and two cases of macroscopically occult gallbladder malignancies.

### Applications

Routine histological evaluation of all elective and emergency cholecystectomies is justified in a United Kingdom population as selective analysis has potential to miss potentially curable life threatening pathology.

### Peer-review

The authors described an incidental non-benign gallbladder histopathology after cholecystectomy in a United Kingdom population. More than 4000 cases of resected gallbladder specimens were analyzed histopathologically. Although several reports regarding incidental gallbladder cancer have been already published from high prevalence areas, studies from infrequent area such as the United Kingdom are worth publishing.

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## Retrospective Cohort Study

# Acute appendicitis: Epidemiology, treatment and outcomes-analysis of 16544 consecutive cases

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## Abstract

### AIM

To investigate the epidemiology, treatment and outcomes of acute appendicitis (AA) in a large population study.

### METHODS

This is a retrospective cohort study derived from the administrative dataset of the Bergamo district healthcare system (more than 1 million inhabitants) from 1997 to 2013. Data about treatment, surgery, length of stay were collected. Moreover for each patients were registered data about relapse of appendicitis and hospital admission due to intestinal obstruction.

### RESULTS

From 1997 to 2013 in the Bergamo district we collected 16544 cases of AA, with a crude incidence rate of 89/100000 inhabitants per year; mean age was  $24.51 \pm 16.17$ , 54.7% were male and the mean Charlson's comorbidity index was

0.32 ± 0.92. Mortality was < 0.0001%. Appendectomy was performed in 94.7% of the patients and the mean length of stay was 5.08 ± 2.88 d; the cumulative hospital stay was 5.19 ± 3.36 d and 1.2% of patients had at least one further hospitalization due intestinal occlusion. Laparoscopic appendectomy was performed in 48% of cases. Percent of 5.34 the patients were treated conservatively with a mean length of stay of 3.98 ± 3.96 d; the relapse rate was 23.1% and the cumulative hospital stay during the study period was 5.46 ± 6.05 d.

## CONCLUSION

The treatment of acute appendicitis in Northern Italy is slowly changing, with the large diffusion of laparoscopic approach; conservative treatment of non-complicated appendicitis is still a neglected option, but rich of promising results.

**Key words:** Acute appendicitis; Conservative treatment; Epidemiology; Laparoscopic appendectomy; Intestinal obstruction

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**Core tip:** Acute appendicitis is the most common surgical emergency around the world. In the Bergamo district, northern Italy its incidence is 89/100000 inhabitants per year with a negative trend during the last years. Percent of 95 patients were treated with appendectomy, 48% of whom laparoscopically; 1.3% of operated patients had an intestinal obstruction during the follow-up. Conservative treatment resulted in a reduced length of stay but 23% of patients had a relapse during follow up. Cumulative length of stays during the study period was similar for the two treatment option.

Ceresoli M, Zucchi A, Allievi N, Harbi A, Pisano M, Montori G, Heyer A, Nita GE, Ansaloni L, Coccolini F. Acute appendicitis: Epidemiology, treatment and outcomes-analysis of 16544 consecutive cases. *World J Gastrointest Surg* 2016; 8(10): 693-699 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i10/693.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i10.693>

## INTRODUCTION

Acute appendicitis is probably the most common surgical emergency worldwide. Since its first accurate description by Fitz<sup>[1]</sup> in 1886 and the first appendectomy performed by Treves<sup>[2]</sup> in England, appendectomy became the preferred treatment of acute appendicitis. Although appendicitis is a very common disease, nowadays it has a still poorly understood etiology, with a very heterogeneous clinical pattern of presentation, varying from simple uncomplicated appendicitis to generalized peritonitis due to perforation. For each clinical pattern the proposed treatment is the same: Appendectomy.

This results in an overtreatment with a described rate of negative appendectomy (a histopathological diagnosis of normal appendix) ranging from 6% to 20%<sup>[3,4]</sup>. Appendectomy has also a complication rate ranging from 8% to 11%, depending on the surgical technique<sup>[5]</sup>. Several reports described spontaneous resolution of uncomplicated appendicitis without the need of an operation and, since the high rate of negative appendectomy and the significative complications rate, some authors proposed and advised conservative management for uncomplicated appendicitis<sup>[6,7]</sup>. Conservative management for appendicitis has been described in 1930 by the "Ochsen-Sherren delayed<sup>[8]</sup> treatment", which consisted of resting and fasting followed by delayed elective appendectomy; nowadays, a conservative approach based on antibiotic therapy is gaining popularity, as documented by several randomized studies and meta-analyses that analyze this peculiar issue<sup>[9-17]</sup>. Conservative treatment has been shown to be safe and effective as primary treatment compared to surgical treatment with a significative reduction in morbidity, even with a considerable one year recurrence rate of 23%<sup>[17]</sup>.

Despite this positive evidence, great uncertainty and skepticism remain concerning conservative treatment among surgeons.

The aim of the study was to describe the epidemiology of acute appendicitis in a large population study during the last seventeen years in order to analyze the evolution of the treatment throughout the years - appendectomy or conservative treatment, open or laparoscopic surgery - and to study the long term follow up of patients, in order to investigate the relapse rate of acute appendicitis in conservatively-treated patients and the incidence of intestinal occlusion after surgery.

## MATERIALS AND METHODS

This is a retrospective analysis of patients discharged from the hospital between 1997 and 2013 with a diagnosis of acute appendicitis. Data were extracted from the administrative health care database of Bergamo's district, a large area (2723 km<sup>2</sup>) in Northern Italy with 1094062 inhabitants. This database collects all discharge records for each citizen of the district from any hospital, public and private, intra and extra-district. On the basis of this register, patients are assigned to the respective DRG, and reimbursements are supplied to the hospitals from the regional health care system.

Patients were retrieved on the basis of the concomitant presence of an unplanned hospital admission, with a ICD9-CM code of AA (ICD9-CM code 540.X, 541.X, 542.X, 543.X) in the first three diagnostic fields and with an Italian DRG code of Acute Appendicitis.

For each patient tracked, data regarding age, sex, Charlson's comorbidity index, surgical procedures (ICD9-CM code 47.X), length of hospital stay, time intervals between admission and operation and mortality were



**Table 1** Distribution of patients among age categories and sex

Age category	Sex		Total	
	F	M	n	Among total
0-1	1	0	1	0.01%
1-6	239	369	608	3.68%
7-13	1673	2322	3995	24.15%
14-17	1314	1119	2433	14.71%
18-25	1904	1628	3532	21.35%
26-35	1167	1556	2723	16.46%
36-45	529	889	1418	8.57%
46-55	255	514	769	4.65%
56-65	165	352	517	3.13%
66-75	135	205	340	2.06%
76-85	89	79	168	1.02%
> 85	23	17	40	0.24%
Total	7494	9050	16544	100.00%
	45.30%	54.70%		

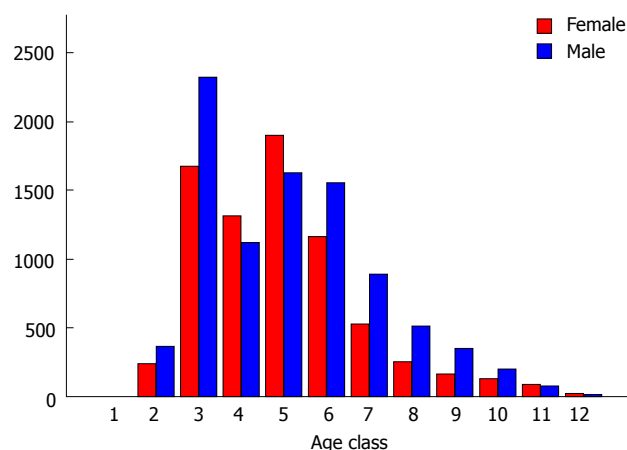
recorded.

For each patient further data on hospitalization related to acute appendicitis (same code) and bowel occlusion (ICD9-CM code 560.X) were collected, as well as the number of further hospitalizations, interventions, length of stay of each hospitalization and cumulative length of stay during the study period.

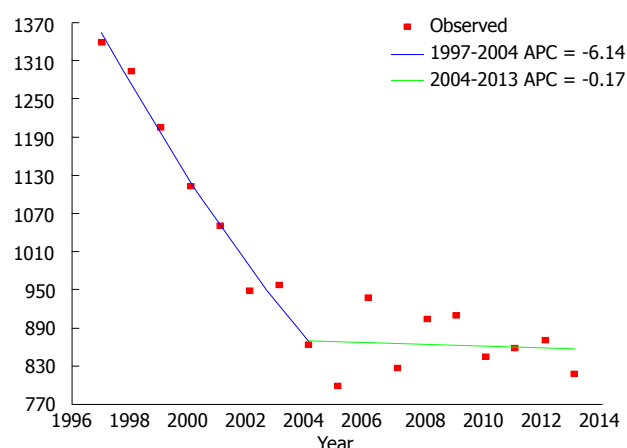
Continuous variables were expressed as mean  $\pm$  SD and were compared with the Mann-Whitney *U* test; association was tested with the Pearson's  $\chi^2$  test. Correlations were calculated with the Pearson's correlation test. Multivariate analyses were performed with the logistic regression method. Survivals were calculated with the Kaplan Meier method. Statistical analysis was performed with SPSS software (SPSS version 20, IBM, United States). Trends were studied with the Joinpoint model: Joinpoint regression analysis was performed using the Joinpoint software from the Surveillance Research Program of the United States National Cancer Institute (Joinpoint Regression Program, Version 4.1.1 - August 2014; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute). Trends were summarized with Average Annual Percent Change (AAPC). Calendar years started from 1997, until 2013. Crude rates are per 100000 inhabitants.

## RESULTS

From 1997 to 2013 in the Bergamo district we collected 16544 cases of AA, with a crude incidence rate of



**Figure 1** Age class and sex distribution. 1: 0-1; 2: 1-6; 3: 7-13; 4: 14-17; 5: 18-25; 6: 26-35; 7: 36-45; 8: 46-55; 9: 56-65; 10: 66-75; 11: 76-85; 12: > 85.



**Figure 2** Number of patients discharged with acute appendicitis diagnosis during the years.

89/100000 per year; mean age was  $24.51 \pm 16.17$ , 54.7% were male and mean Charlson comorbidity index was  $0.32 \pm 0.92$ . Mortality was recorded for 7 patients ( $< 0.0001\%$ ). Table 1 and Figure 1 show the distribution of age categories and sex: differences among sex in the different age categories were statistically significant ( $P < 0.001$ ). The incidence of AA decreased during the years starting from 120/105 in 1997 to 73/105 in 2013 with a statistically significant negative value (AAPC =  $-2.8$ ,  $P < 0.001$ ) (Figure 2).

### Operative treatment

An appendectomy was performed in 94.7% of the patients: Mean age was  $24.39 \pm 15.98$ , mean Charlson's comorbidity index was  $0.31 \pm 0.90$  and 53.1% were male. Patients were operated after a mean of  $0.85 \pm 1.46$  d and the mean length of stay was  $5.08 \pm 2.88$  d with a negative trend over the considered period, starting from  $6.09 \pm 2.94$  in 1997 to  $4.58 \pm 2.33$  in 2013 (AAPC  $-1.5$ ,  $P < 0.001$ ). Mortality was  $< 0.0001\%$ .

Data about laparoscopic procedures was available only after the year 2000: 48% of the patients were operated with the laparoscopic technique with a positive

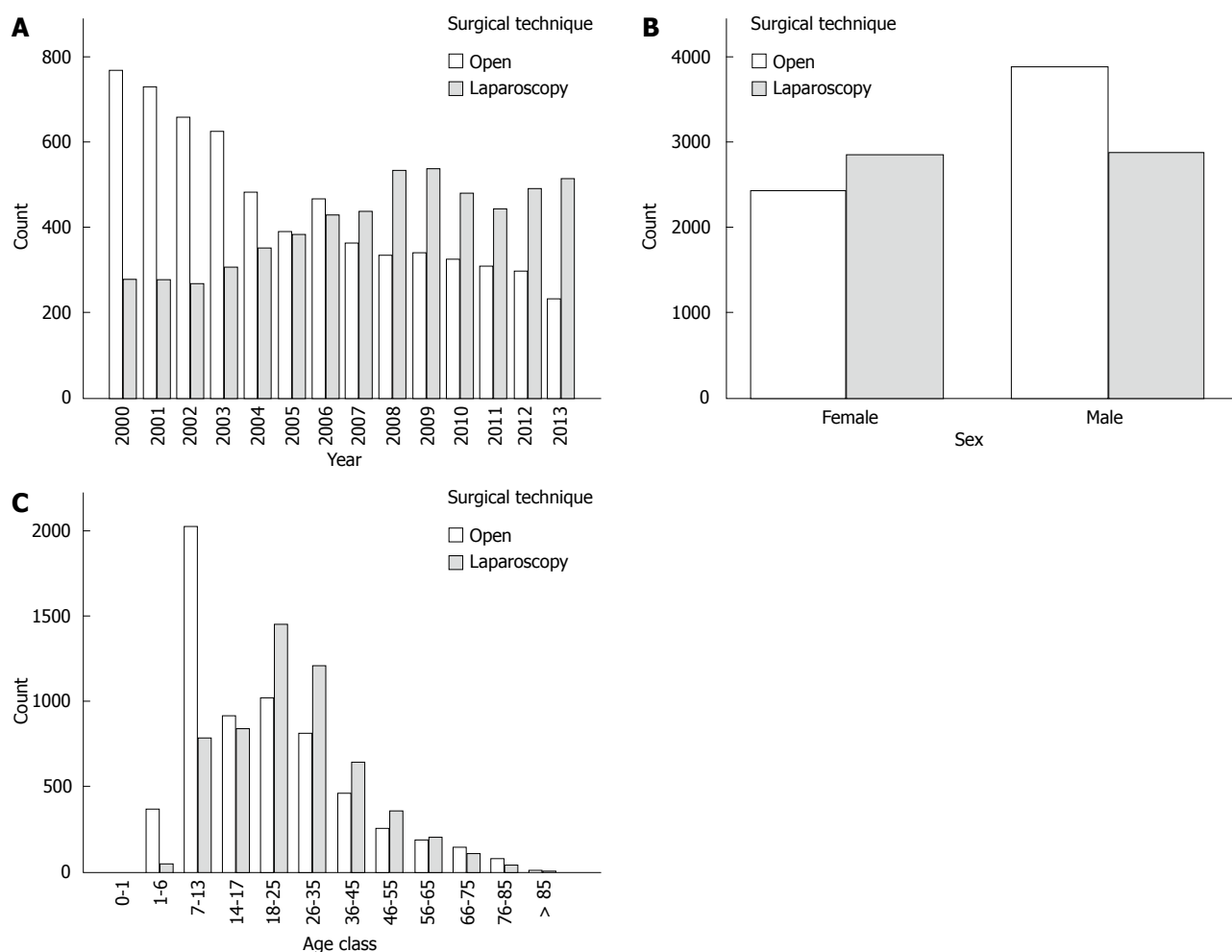


Figure 3 Surgical technique during the years (A), between sex (B) and among age classes (C).

trend during the years, starting from 26% in 2000 to 68.8% in 2013 (AAPC 5.2,  $P < 0.001$ ) (Figure 3A) and with a mean length of stay of  $4.47 \pm 2.66$  d (compared to  $5.43 \pm 2.94$  with the open technique,  $P < 0.001$ ). Laparoscopy was associated with a higher age, female sex and year in both univariate and multivariate analysis ( $P < 0.0001$ ) (Table 2, Figure 3B and C).

The cumulative hospital stay during study period was  $5.19 \pm 3.36$  d with a mean of  $1.01 \pm 0.13$  hospital admissions. One hundred and ninety-two patients (1.2%) had at least one further hospitalization due intestinal occlusion after a mean of  $30.53 \pm 41.23$  mo (median 11 mo) and 59.9% of them were operated on (Figures 4 and 5).

### Conservative treatment

In general, 5.34% of the patients were treated conservatively: Mean age was  $26.68 \pm 19.04$ ; 56.1% were male and mean Charlson's comorbidity index was  $0.51 \pm 1.26$ ; mean length of stay was  $3.98 \pm 3.96$  d; mortality was 0.1%. The proportion of patients treated conservatively increased during the years, from 6.1% in 1997 to 8.7% in 2013, although the trend was not significant ( $P = 0.6$ ) (Figure 6).

Overall, relapse rate was 23.1% and a new episode of acute appendicitis occurred after a mean of  $6.5 \pm 15$  mo (median 32 d); 89% of patients were operated on at relapse. The mean number of hospital admissions was  $1.26 \pm 0.47$  with a cumulative hospital stay during the study period of  $5.46 \pm 6.05$  d (Figures 4 and 5).

After univariate analysis, conservative treatment was associated with higher age, higher comorbidity index, and year of treatment ( $P < 0.0001$ ); after multivariate analysis only Carlson's comorbidity index ( $P = 0.004$ ) and year of treatment ( $P < 0.0001$ ) remained significant (Table 3).

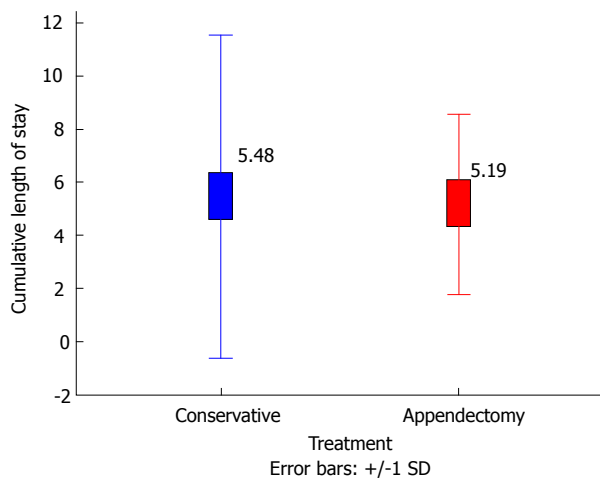
## DISCUSSION

Acute appendicitis in Northern Italy has a crude rate of 89 cases per 100000 inhabitants per year, and this data is comparable to similar studies in other country worldwide<sup>[18-21]</sup>. Surprisingly, during the study period the incidence decreased significantly, from 120 to 73 cases per 100000 inhabitants. This data contrasts with the data reported by Buckius *et al.*<sup>[20]</sup> in the United States over a similar period of time. Acute appendicitis is already a poorly understood disease and its diagnosis is still

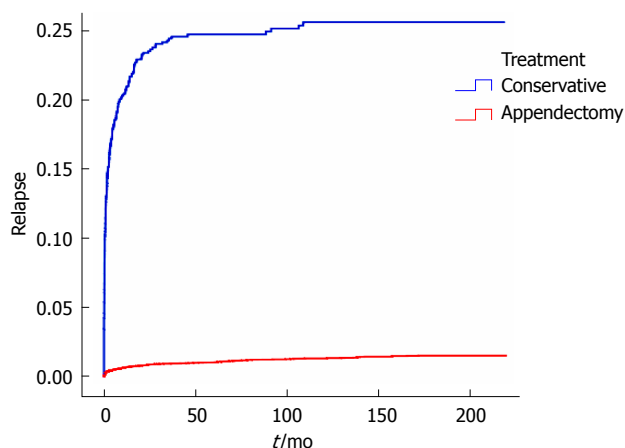
**Table 2 Surgical technique: Data about surgical techniques were available only after year 2000**

	Open appendectomy	Laparoscopic appendectomy	Total	Univariate analysis P value	Multivariate analysis	
					OR	P value
n (%)	6321 (52)	5734 (48)	12055			
Age	22.79 (17.01)	27.57 (15.19)	25.06 (13.55)	< 0.0001	1.018 (1.018-1.0121)	< 0.0001
Sex	M: 61.5%	M: 50.2%	M: 54.6%	< 0.0001	1.80 (1.66-1.94)	< 0.0001
Charlson's	0.33 (0.97)	0.35 (0.87)	0.34 (0.92)	0.385		
Year	0.277 (Pearson Correlation)			< 0.0001	1.15 (1.14-1.16)	< 0.0001
Time to surgery (d)	0.66 (1.35)	0.97 (1.53)	0.81 (1.45)	< 0.0001		
Length of stay (d)	5.28 (3.00)	4.47 (2.66)	4.89 (2.85)	< 0.0001		
Mortality	5 (0.1%)	1 (0.001%)	6 (< 0.0001)	0.13		

Data are expressed as mean  $\pm$  SD or number and proportion. Multivariate analysis was calculated for the correlation with laparoscopic approach.

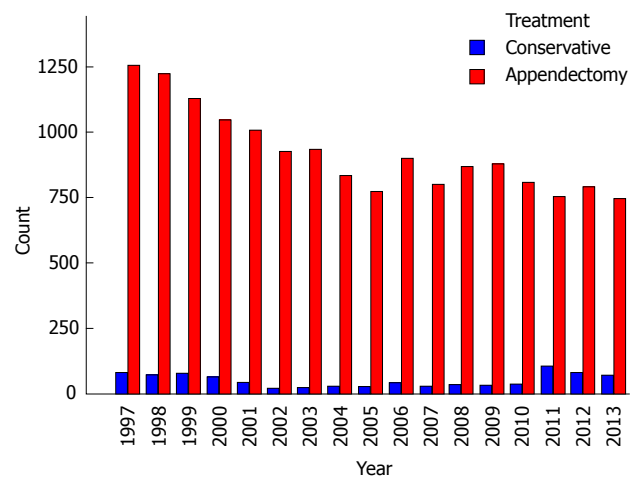


**Figure 4** Cumulative length of stay between treatment options. Data are expressed in days (SD).



**Figure 5** Kaplan-Meier curve of failure of conservative treatment (blue line) and incidence of intestinal obstruction in operated patients (red line).

based on clinical judgment, with great variability among surgeons. Clinical scores have been developed and proposed in the last years to help surgeons reaching a diagnosis of acute appendicitis, such as the Alvarado and the Andersson score<sup>[22,23]</sup>. The decrease in the incidence rate could be explained by the diffusion of these scores and a consequent increased attention in the diagnosis of



**Figure 6** Treatment option during the years.

acute appendicitis, in order to reduce the rate of negative appendectomies. As expected, acute appendicitis is more frequent in young and male patients (Figure 1), as reported by the literature<sup>[18-20]</sup>, with augmented incidence among patients in the 7-25 years categories. In the years categories 14-25, acute appendicitis is more frequent in females: A possible reason is the starting of childbearing ages and the sexual transmitted disorders that could mime acute appendicitis - with lower quadrant abdominal pain - and a consequent higher rate of negative appendectomies, as reported by Seetahal *et al*<sup>[3]</sup>. Unfortunately there are no data available on the rate of negative appendectomies to confirm this hypothesis. The possibility of a diagnosis other than appendicitis in women justifies the higher frequency in this subgroup of the laparoscopic technique, which give the possibility to thoroughly explore the peritoneal cavity, as shown in Figure 3B. Laparoscopic appendectomy was performed in 48% of the cases, with an enormous increase across the years, from 26% to 69% (Figure 3). This data demonstrates the gradual diffusion of the laparoscopic technique, as shown by a similar study in the same contest for acute cholecystitis<sup>[24]</sup>. After multivariate analysis, the laparoscopic approach was correlated to the year of treatment, female sex and older age: Figure 3C demonstrates that open appendectomy is still the

**Table 3** Different treatments

	Total	Treatment		Univariate analysis <i>P</i> value	Multivariate analysis	
		Appendectomy	Conservative		OR (95%CI)	<i>P</i> value
<i>n</i> (%)	16544	15661 (94.7)	883 (5.3)			
Age	24.51 (16.17)	24.39 (15.98)	26.68 (19.04)	< 0.0001	1.006 (0.999-1.013)	0.095
Sex	M: 54.7%	M: 54.6%	M: 56.1%	0.424		
Charlson's	0.32 (0.92)	0.31 (0.90)	0.51 (1.26)	< 0.0001	0.826 (0.703-0.868)	< 0.0001
Year	-0.33 (Pearson Correlation)			< 0.0001	0.973 (0.959-0.986)	< 0.0001
Time to surgery (d)		0.85 (1.46)				
Length of stay (d)	5.02 (2.92)	5.08 (2.88)	3.98 (3.46)	< 0.0001		
Mortality	7 (< 0.0001%)	6 (< 0.0001%)	1 (0.1%)	0.292		
Relapse		1.20%	23.10%	< 0.0001		
Time to relapse (mo)	Mean	30 (45)	6.5 (15)	< 0.0001		
Time to relapse (mo)	Median	11 (1.17-49)	1 (0.16-6.63)			
number of hospitalization	1.03 (0.18)	1.01 (0.13)	1.26 (0.47)	< 0.0001		
Cumulative LOS	5.20 (3.56)	5.19 (3.36)	5.47 (6.05)	0.02		

Data are expressed as mean  $\pm$  SD or number and proportion. Multivariate analysis was calculated for the conservative treatment.

preferred technique for children.

Conservative treatment for acute appendicitis in Northern Italy is still a neglected option, with only 5% of patients treated not operatively; however, over the period of study there was a small increase in the proportion of patients treated conservatively. Despite the small number, conservative treatment seems to be an effective treatment option, showing a reduced length of stay and, notwithstanding an overall relapse rate of 23%, a similar cumulated length of stay and number of hospital admissions during the study period, with a clinically not significant difference (Figure 4). Conservative treatment, as shown in Figure 5, fails after a median of 32 d and leads to an operative treatment in the majority of cases. Factors involved in the choice of this approach are represented by the comorbidities of the patient and the year of treatment, showing that this option is slowly spreading, but still depends on the surgeon's preference. Conservative treatment resulted in 77% reduction of surgical procedures for appendicitis during the study period, maintaining a similar length of stay; moreover, appendectomy exposes patients to the risk of intestinal obstruction due to adhesions in 0.7%-10.7%<sup>[25-27]</sup>. In our group of patients, 1.3% of the patients needed a further hospitalization due to bowel obstruction after a median of 11 mo and required a further surgical operation in 60% of cases. Laparoscopic appendectomy has been shown to reduce the risk of intestinal obstruction<sup>[28]</sup> and our results confirm this evidence, although the clinical effect is not significant (Table 2). A cost-effectiveness study demonstrated that conservative treatment, with a failure rate of less than 40% is more cost effective than operative management: Our results on a large population study during a long period show that treating a patient with acute appendicitis conservatively could be considered the better treatment option.

The study was performed retrieving data from an administrative register that allows for a long-term follow up for each patient included; unfortunately,

administrative registries do not include data about histopathological diagnosis. Moreover, figures about failure of conservative treatment could be slightly underestimated, considering the lack of data about the immediate failure during the first hospital admission.

In conclusion the treatment of acute appendicitis in Northern Italy is slowly changing, with the large diffusion of laparoscopic approach; conservative treatment of non-complicated appendicitis is still a neglected option, but full of promising results.

## COMMENTS

### Background

Acute appendicitis is the commonest surgical emergency. Despite appendectomy is considered the definitive treatment there is great interest in the conservative management.

### Research frontiers

Epidemiology and treatment of acute appendicitis.

### Innovations and breakthroughs

The study outlines the current epidemiology of acute appendicitis giving an overview on the state of the art of the treatment's choice in the daily clinical practice.

### Applications

The study gives the state of the art of the treatment of acute appendicitis and its changes during the last years.

### Terminology

Conservative treatment: Medical therapy based on antibiotics administration.

### Peer-review

This is a well-written article with good statistical analysis.

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## Retrospective Study

# Peptide-based enteral formula improves tolerance and clinical outcomes in abdominal surgery patients relative to a whole protein enteral formula

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**Author contributions:** Liu MY and Hu SH carried out the studies and data analyses; Liu MY drafted the manuscript; Chang SJ supervised the procedure, provided significant advice and revised the manuscript; Tang HC developed the protocol, cared the patients, provided advice and revised the manuscript; Hu SH collected the data and provided nutrition care; all of the authors have read and approved the final manuscript; Liu MY and Hu SH contributed equally to this work.

**Institutional review board statement:** The study was eligible for a determination of "exempt review" status by the ethics committee of the Tainan Sin-Lau Hospital (Grant No. SLH919-02).

**Informed consent statement:** A retrospective study was deployed to investigate the effects of a dipeptide- and tripeptide-based enteral formula. Patients were screened from the ICU database, therefore we did not seek informed consent. Acquisition of patient data and its subsequent use were approved by the ethics committee of the Tainan Sin-Lau Hospital (Grant No. SLH919-02). Patient information was anonymized and de-identified prior to analysis.

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## Abstract

### AIM

To compare a dipeptide- and tripeptide-based enteral formula with a standard enteral formula for tolerance and nutritional outcomes in abdominal surgery patients.

### METHODS

A retrospective study was performed to assess the differences between a whole-protein formula (WPF) and a dipeptide- and tripeptide-based formula (PEF) in clinical outcomes. Seventy-two adult intensive care unit (ICU) patients with serum albumin concentrations less

than 3.0 g/dL were enrolled in this study. Patients were divided into two groups (WPF group = 40 patients, PEF group = 32 patients). The study patients were fed for at least 7 d, with  $\geq 1000$  mL of enteral formula infused on at least 3 of the days.

### RESULTS

The mean serum albumin level on postoperative day (POD) 10, prealbumin levels on POD-5 and POD-10, and total lymphocyte count on POD-5 were significantly higher in the PEF group compared to those in the WPF group ( $P < 0.05$ ). The average maximum gastric residual volume of the PEF patients during their ICU stays was significantly lower than that for WPF patients.

### CONCLUSION

Dipeptide- and tripeptide-based enteral formulas are more efficacious and better tolerated than whole-protein formulas.

**Key words:** Dipeptides and tripeptides; Enteral nutrition; Abdominal surgery; Gastric residual volume; Absorption

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**Core tip:** Few trials thus far have investigated the benefits of dipeptide- and tripeptide-based enteral formulas for abdominal surgery patients. The results of the present study suggest that dipeptide- and tripeptide-based enteral formulas are more efficacious and better tolerated than whole-protein formulas and could shorten the intensive care unit stays of malnourished abdominal surgery patients.

Liu MY, Tang HC, Hu SH, Chang SJ. Peptide-based enteral formula improves tolerance and clinical outcomes in abdominal surgery patients relative to a whole protein enteral formula. *World J Gastrointest Surg* 2016; 8(10): 700-705 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i10/700.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i10.700>

## INTRODUCTION

Malnutrition is a common finding in critically ill patients. Enteral nutrition is a preferred means of support for stimulating gut hormones, modulating immunity, and maintaining the barrier function of the intestinal mucosa. However, malabsorption, poor emptying, and hypoalbuminemia often occur in patients given enteral nutrition.

Proteins are hydrolyzed to small peptides in the intestines, which are then efficiently absorbed through a variety of specific transport mechanisms, as has been previously described<sup>[1]</sup>. Some investigators have reported that peptide-based enteral diets are associated with better protein responses and less diarrhea compared to

intact-protein diets<sup>[2,3]</sup>. On the other hand, others have reported that peptide-based formulas seem to offer no benefits over intact-protein diets in acutely injured, hypoalbuminemic patients<sup>[4]</sup>. However, while previous studies have described the small peptide formulas, no particular dipeptide- or tripeptide-based formulas have been investigated.

Studies have demonstrated that dipeptides and tripeptides are the major products of proteins that are absorbed. Proteins are hydrolyzed in the intestines to small peptides, which are then efficiently absorbed through specific transport mechanisms. The major mechanism for absorption of the dipeptides and tripeptides of protein digestion products across the brush border is absorption through proton-coupled oligopeptide transporters (POTs)<sup>[5-11]</sup>. Dietary proteins are converted into large peptides by gastric and pancreatic proteases in the gastrointestinal lumen and then undergo further hydrolysis into small peptides (80%) and free amino acids (20%) by various peptidases in the brush border membrane of the intestinal epithelium<sup>[12]</sup>. Previously, Yoshihara *et al.*<sup>[13]</sup> studied the absorption of a 100% free amino acids formula, a 60% dipeptides and tripeptides with 40% free amino acids mixture, a 100% dipeptides and tripeptides mixture, and a lactalbumin mixture. Absorption was evaluated by calculating the area under the curve of amino acid concentration in portal vein plasma of rats for 120 min after administration of each nitrogen source<sup>[13]</sup>. The results indicated that the absorption was maximal upon administration of the nitrogen source when the 60% dipeptides and tripeptides with 40% free amino acids mixture was used.

Few clinical trials thus far have investigated the benefits of dipeptide- and tripeptide-based enteral formulas. In our hospital, however, critically ill patients in the intensive care unit (ICU) began receiving such a formula from July 2015. The aim of this study, then, was to compare this dipeptide- and tripeptide-based enteral formula with a standard enteral formula in terms of tolerance and nutritional outcomes in abdominal surgery patients.

## MATERIALS AND METHODS

### Patients

A retrospective study was deployed to investigate the effects of a dipeptide- and tripeptide-based enteral formula. Patients screened from the ICU database for abdominal surgery with serum albumin concentrations less than 3.0 g/dL were included in the study. The patients who received dipeptide- and tripeptide-based enteral formula from July 2015 to December 2015 were classified as the dipeptide- and tripeptide-based formula (PEF) group. Other patients who were fed a whole-protein formula were classified as the WPF group. These patients were generally included the study, although any patients with renal failure, hepatic

failure, or who required parenteral nutrition intervention were excluded. This study was approved by the ethics committee of Tainan Sin-Lau Hospital (Grant No. SLH 919-02). Patient information was anonymized and de-identified prior to analysis.

### Enteral nutrition care

Patients in both groups received the same feeding protocol, when they were transferred to the ICU. Each patient received 18 kcal per kilogram of body weight on postoperative day (POD-) 1, 23 kcal on POD-3, and 28 kcal on POD-7. The patients were fed for at least 7 d, with  $\geq 1000$  mL of enteral formula infused on at least 3 of the days. The composition of the WPF (Osmolite HN, Abbott Laboratories) was 16.7% of protein, 54.3% of carbohydrate, and 29.0% of lipid. The composition of the PEF (Twinline, Otsuka Pharmaceutical Co, Ltd) was 16.0% of protein, 59.0% of carbohydrate, and 25.0% of lipid. The WPF contained only whole proteins (*e.g.*, calcium-potassium caseinate), whereas the protein source of the PEF (from enzymatically hydrolyzed milk protein) consisted of amino acids and peptides with molecular weights  $< 500$  Da (approximately 78%), peptides with molecular weights between 500 and 1000 Da (approximately 15%), and peptides with molecular weights between 1000 and 3000 Da (approximately 7%).

On POD-1 with stable hemodynamic status, the full-strength diet was administered at 30 mL/h through a naso-gastric (NG) tube or *via* percutaneous endoscopic gastrostomy (PEG) feeding tubes, with the rate increasing as tolerated to a goal of 75–100 mL/h. A gastric residual volume (GRV) of over 150 mL was the threshold for suspension of feeding<sup>[14]</sup>, which was followed by re-evaluation to reduce the feeding rate 2 h later. The GRV was calculated every 4 h by refractometry (Model N.O.W. 507-1; Nippon Optical Works, Tokyo, Japan) during each patient's stay in the ICU. A refractometer measures the "total soluble solids in solution" and a Brix value (BV) is assigned to the liquid. We examined the BV in order to measure the actual GRV<sup>[15,16]</sup>. The GRV was recorded when volumes exceeded 150 mL. At such times, feeding of the patient was suspended for re-evaluation and reduction of the feeding rate 2 h later. No prokinetic drugs were used within 10 d in both groups.

### Data collection

Demographic data obtained at the start of the study included gender, age, body mass index (BMI), APACHE II score, and major diagnoses. Additional data including the length of stay in the ICU, total enteral volume, GRV, and the prevalence of diarrhea were also collected for this study. The occurrence of diarrhea was defined as greater than three loose stools per day or greater than 300 mL/d. Serum albumin, prealbumin, C-reactive protein (CRP) and total lymphocyte count (TLC) were measured at baseline, day 5, and day 10.

**Table 1 Comparison of demographic and clinical characteristics between the whole-protein formula group and the dipeptide- and tripeptide-based formula group**

	WPF group	PEF group	P-value
<i>n</i>	40	32	
Gender (Male/Female)	23/17	19/13	0.873
Feeding route (PEG <sup>1</sup> /NG <sup>2</sup> )	2/38	3-29	0.468
Major diagnoses			
Esophageal cancer	4	5	0.473
Colon cancer	22	16	0.673
Gastric cancer (subtotal gastrectomy)	2	3	0.468
Bile duct cancer	4	2	0.567
Ischemic bowel	8	6	0.894
Age	67.5 $\pm$ 10.5	64.7 $\pm$ 10.1	0.263
APACHE II score	11.6 $\pm$ 2.3	12.4 $\pm$ 2.6	0.201
Ventilator dependence, <i>n</i> (%)	15 (37.5)	13 (40.6)	0.787
Body mass index	22.3 $\pm$ 2.1	21.9 $\pm$ 2.2	0.398

<sup>1</sup>Percutaneous endoscopic gastrostomy; <sup>2</sup>Naso-gastric tube. Values are presented as number of patients or mean  $\pm$  SD. WPF: Whole-protein formula; PEF: Dipeptide- and tripeptide-based enteral formula.

### Statistical analysis

Data were analyzed using SPSS version 12.0 (SPSS, Inc). The differences between the two groups were analyzed by Student's *t*-test. Data are presented as mean  $\pm$  SD.  $\chi^2$  analysis was used for comparisons of the proportions of subjects in the two groups. A *P*-value  $< 0.05$  was considered significant.

## RESULTS

### Study population

A total of 86 abdominal surgery patients with serum albumin concentrations less than 3.0 g/dL were identified who were admitted to the ICU during the study period. Seven of these 86 patients developed renal failure, one patient developed hepatic failure, and 6 patients required parenteral support; these 14 patients (WPF group = 6 patients, PEF group = 8 patients) were excluded from the study. The remaining 72 patients were divided into two groups (WPF group = 40 patients, PEF group = 32 patients), and the patient characteristics of the two groups are provided in Table 1. Colon cancer was the most common major diagnosis in both groups. Most colonic surgery patients can resume oral intake on POD-1. Some colon cancer patients were elderly, confused and had comorbid diseases such as diabetes, heart disease, and chronic obstructive pulmonary disease; thus they could not resume oral intake on POD-1. Therefore, we used an NG tube for intervention. There were no significant differences between the two groups in terms of age, APACHE II score, ventilator dependence, and BMI (Table 1).

### Serum albumin, prealbumin, TLC and CRP

The patients were fed for at least 7 d, with  $\geq 1000$  mL of enteral formula infused on at least 3 of the days. On



**Table 2** Differences in nutritional status between the whole-protein formula group and the dipeptide- and tripeptide-based formula group

	WPF group	PEF group	P-value
Albumin (g/dL)			
POD <sup>1</sup> -1	2.59 ± 0.21	2.57 ± 0.19	0.652
POD-5	2.60 ± 0.26	2.68 ± 0.28	0.198
POD-10	2.70 ± 0.30	2.89 ± 0.27	0.010
Prealbumin (mg/dL)			
POD-1	11.1 ± 1.4	10.6 ± 1.3	0.201
POD-5	11.6 ± 1.2	12.8 ± 2.1	0.006
POD-10	12.9 ± 1.7	15.1 ± 1.5	< 0.001
TLC <sup>2</sup> (cell/mm <sup>3</sup> )			
POD-1	1069 ± 135	1077 ± 148	0.801
POD-5	1082 ± 149	1192 ± 168	0.012
POD-10	1231 ± 162	1311 ± 182	0.052
CRP <sup>3</sup> (mg/L)			
POD-1	43.7 ± 7.8	43.0 ± 9.4	0.742
POD-5	32.7 ± 4.9	33.4 ± 5.2	0.824
POD-10	19.7 ± 5.0	18.5 ± 5.4	0.416

<sup>1</sup>Postoperative day; <sup>2</sup>Total lymphocyte count; <sup>3</sup>C-reactive protein. Values are presented as mean ± SD. WPF: Whole-protein formula.

POD-1 with stable hemodynamic status, a full-strength enteral formula (1.0 kcal/mL) was administered through NG or PEG. The prealbumin levels and TLCs were similar between the two groups on POD-1. There was also no significant difference between the serum albumin levels on POD-1 and POD-5 for the two groups, but the level for the PEF group was significantly higher than that of the WPF group on POD-10 ( $2.89 \pm 0.27$  vs  $2.70 \pm 0.30$ ,  $P = 0.01$ ; Table 2). Prealbumin levels on POD-5 and POD-10 were significantly higher in the PEF group than in the WPF group ( $P < 0.01$ ). The TLC of the PEF group was higher than that of the WPF group on POD-5, but there was no significant difference on POD-10. In critical patients protein parameters depend on inflammation. We checked the CRP levels, and there was no significant difference between the two groups.

### Clinical outcomes

The prevalence of suspended feeding due to high gastric residuals and maximum caloric intake during ICU stay was similar between the two groups (Table 3). The average maximum GRV for the PEF group patients during their ICU stays was significantly lower than that for the WPF group (Table 3). There was no significant difference between the groups in terms of the caloric intake on POD-5, but the average intake for the PEF group on POD-10 was higher than that of the WPF group. There was no significant difference between the two groups in terms of the prevalence of diarrhea and pneumonia. The average length of stay in the ICU for the PEF group was  $6.2 \pm 0.8$  d, which was significantly shorter than that for the WPF group ( $6.8 \pm 1.5$  d).

## DISCUSSION

Providing enteral nutrition care for critically ill patients is challenging in general, but it is even more difficult to

**Table 3** Clinical outcomes for the whole-protein formula group and the dipeptide- and tripeptide-based formula group

	WPF group	PEF group	P-value
Length of stay in the ICU <sup>1</sup> (d)	6.8 ± 1.5	6.2 ± 0.8	0.047
Maximum caloric intake during ICU stay (kcal/kg)	22.5 ± 1.9	23.2 ± 2.4	0.063
Caloric intake (kcal/kg body weight/d)			
POD <sup>2</sup> -5	20.7 ± 2.3	21.5 ± 1.7	0.116
POD-10	23.5 ± 2.4	25.1 ± 2.9	0.010
Maximum GRV <sup>3</sup> during ICU stay (mL)	183.6 ± 88.0	138.0 ± 63.9	0.016
Prevalence of suspended feeding due to high GRV (%)	21.8	15.2	0.071
Prevalence of diarrhea (%)	19.9	13.2	0.056
Prevalence of pneumonia (%)	5	3.1	0.692

<sup>1</sup>Intensive care unit; <sup>2</sup>Postoperative day; <sup>3</sup>Gastric residual volume. Values are presented as mean ± SD. WPF: Whole-protein formula.

provide such care for abdominal surgery patients. In this study, except the enteral formulas used, the care received by the two groups of patients was the same. Both groups of patients would be unable to achieve their caloric intake goals under normal circumstances. As noted above, there were no significant differences between the two groups in terms of their average caloric intakes and rates of diarrhea and pneumonia complications. The average maximum GRV recorded for each patient during ICU stay among the WPF group patients was higher than that among the PEF group patients, but there was no significant difference between the two groups in terms of the prevalence of suspended feeding due to high GRV ( $P = 0.071$ ). It was easy and effective to calculate GRV values by refractometry. More specifically, BV measurements and the following equation were used:  $(\text{GRV} \times \text{pre-dilution BV}) = (\text{GRV} + 30 \text{ mL water}) \times \text{post-dilution BV}$ . We accurately grasped the GRV values to avoid the risk of aspiration pneumonia and to assess the digestion conditions. The dipeptide- and tripeptide-based enteral formula seemed to have been efficiently absorbed and resulted in better prealbumin, albumin (POD-10), and TLC (POD-5) levels in the PEF group, in addition to shortening the ICU stay. Prealbumin is a rapid-turnover protein (half-life < 48 h), which is a more sensitive indicator to assess the nutritional status than albumin (half-life 21 d). When patients' nutrition is improved, the serum prealbumin will increase rapidly (POD-5 and 10).

Four members of the POT superfamily have previously been identified, namely, PepT1 (SLC15A1), PepT2 (SLC15A2), PHT1 (SLC A4), and PHT2 (SLC A3). In humans, PepT1 expressed in the small intestine epithelium is involved in the absorption of nutritional peptides<sup>[17,18]</sup>. Previously, the effects of PepT1 activity on a variety of pathological conditions have been studied. Ziegler *et al.*<sup>[19]</sup> found that patients with short-bowel syndrome may experience up-regulation of the expression of colonic PepT1 adapted to malabsorption of dipeptides and

tripeptides, independent of changes in the mucosal surface area. In other studies, intestinal villous atrophy due to prolonged fasting was investigated in fasting animals, and it was observed that PepT1 expression increased during metabolic fasting phases<sup>[20,21]</sup>. Ogiwara *et al.*<sup>[22]</sup> showed that 4 d of starvation markedly increased the PepT1 in the jejunum, while a study by Ihara *et al.*<sup>[23]</sup> demonstrated that starvation for 4 d and semistarvation for 10 d increased PepT1 mRNA and protein in the rat jejunum. That the cell population of PepT1 is increased in starvation may explain these results of earlier studies. In a study by Vazquez *et al.*<sup>[24]</sup> this increase was expected to reduce the absorption of amino acids in human volunteers' jejunum after 14 d of hunger. In fact, while the absorption of amino acids was decreased, surprisingly, no significant change in the absorption of peptides was observed. In the present study of malnourished abdominal surgery patients, we conjectured that the patients' PepT1 levels would result in an increase in the absorption of dipeptides and tripeptides.

A randomized trial by Heimbürger *et al.* demonstrated that 10 d of feeding with a small-peptide diet produced slightly greater increases in serum rapid-synthesis proteins than did a whole-protein diet, especially between days 5 and 10<sup>[25]</sup>. Our study found a similar result. The PEF group patients received the dipeptide- and tripeptide-based enteral feeding formula, and this formula was more efficacious and better tolerated than the whole-protein formula received by the patients in the other group. The present study suggests that 7 d of feeding of the dipeptide- and tripeptide-based enteral feeding formula may benefit a patient's nutritional status. Peptide formulas, however, are more expensive than whole-protein formulas, costing approximately five times more. More specifically, feeding a patient for 7 d with a peptide formula rather than whole-protein formula will cost roughly \$140 more. The mean cost of ICU is \$350 per day in Taiwan. However, peptide formulas seem to shorten the average ICU stay by about one day, and this should be factored into overall consideration of the cost and quality of care.

There were no significant differences in the prevalence of GRV, diarrhea, and pneumonia complications between the two groups, but the PEF group did exhibit a lower tendency for GRV and diarrhea than the WPF group. Two limitations of this study were its retrospective study design and low number of admitted patients. Well-designed clinical trials are needed to survey the efficacy, tolerance, and cost effectiveness of using dipeptide- and tripeptide-based enteral formulas for abdominal surgery patients.

In conclusion, the results of the present study suggest that dipeptide- and tripeptide-based enteral formulas are more efficacious and better tolerated than whole-protein formulas and could shorten the ICU stays of malnourished abdominal surgery patients.

intolerance often occurs in these patients. Few trials thus far have investigated the benefits of dipeptide- and tripeptide-based enteral formulas for abdominal surgery patients. The aim of this study, then, was to compare this dipeptide- and tripeptide-based enteral formula with a standard enteral formula in terms of tolerance and nutritional outcomes in abdominal surgery patients.

## Research frontiers

The previous studies have described the small peptide formulas, but no particular dipeptide- or tripeptide-based formulas have been investigated.

## Innovations and breakthroughs

The dipeptide- and tripeptide-based enteral formulas are more efficacious and better tolerated than whole-protein formulas, which shortened intensive care unit stay by about one day.

## Applications

Early initiation of feeding with a dipeptide- and tripeptide-based enteral formulas for 7 d is a feasible approach in malnourished abdominal surgery patients.

## Peer-review

This study is acceptable and very useful.

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## COMMENTS

### Background

Early enteral nutrition in critically ill patients is important, however, gut

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## Clinical Trials Study

# Phase II study of docetaxel, cisplatin and capecitabine as preoperative chemotherapy in resectable gastric cancer

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## Abstract

### AIM

To investigate the feasibility of preoperative docetaxel, cisplatin and capecitabine (DCC) in patients with resectable gastric cancer.

### METHODS

Patients with resectable gastric cancer fulfilling the inclusion criteria, were treated with 4 cycles of docetaxel (60 mg/m<sup>2</sup>, cisplatin (60 mg/m<sup>2</sup>) and capecitabine (1.875 mg/m<sup>2</sup> orally on day 1-14, two daily doses) repeated every three weeks, followed by surgery. Primary end point was the feasibility and toxicity/safety profile of DCC, secondary endpoints were pathological complete resection



rate and pathological complete response (pCR) rate.

## RESULTS

All of the patients (51) were assessable for the feasibility and safety of the regimen. The entire preoperative regimen was completed by 68.6% of the patients. Grade III/IV febrile neutropenia occurred in 10% of all courses. Three patients died due to treatment related toxicity (5.9%), one of them (also) because of refusing further treatment for toxicity. Of the 45 patients who were evaluable for secondary endpoints, four developed metastatic disease and 76.5% received a curative resection. In 3 patients a pCR was seen (5.9%), two patients underwent a R1 resection (3.9%).

## CONCLUSION

Four courses of DCC as a preoperative regimen for patients with primarily resectable gastric cancer is highly demanding. The high occurrence of febrile neutropenia is of concern. To decrease the occurrence of febrile neutropenia the prophylactic use of granulocyte colony-stimulating factor (G-CSF) should be explored. A curative resection rate of 76.5% is acceptable. The use of DCC without G-CSF support as preoperative regimen in resectable gastric cancer is debatable.

**Key words:** Gastric cancer; Preoperative chemotherapy; Docetaxel; Capecitabine

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**Core tip:** The use of the combination of docetaxel, cisplatin and capecitabine in resectable gastric cancer has resulted in a high curative resection rate of 77%, although it also resulted in a high rate of febrile neutropenia, and in treatment related mortality.

Dassen AE, Bernards N, Lemmens VEPP, van de Wouw YAJ, Bosscha K, Creemers GJ, Puijt HJFM. Phase II study of docetaxel, cisplatin and capecitabine as preoperative chemotherapy in resectable gastric cancer. *World J Gastrointest Surg* 2016; 8(10): 706-712 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i10/706.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i10.706>

## INTRODUCTION

Although declining, gastric cancer is still ranking in the top 5 of incidence and mortality rates of malignancies in Europe<sup>[1]</sup>. Loco-regional and metastatic recurrence rates are high and prognosis remains poor, with a 5-year survival rate of 20%-31% for stage I - III disease<sup>[2]</sup>. Surgery is still the cornerstone of treatment for gastric cancer, although survival can be improved by adding perioperative treatment. In 2006, the results of the MAGIC trial were published showing that perioperative chemotherapy with epirubicin-cisplatin-5-fluorouracil

(FU) (ECF) improved survival compared to surgery alone (5-year survival 36% vs 23%, respectively). Although most patients assigned to the perioperative chemotherapy tolerated the preoperative chemotherapy well, only 55% of them started the postoperative chemotherapy due to postoperative complications with only 42% of the patients completing the entire regimen<sup>[3]</sup>. These results demonstrate the problems encountered with the perioperative approach, *i.e.*, many patients do not complete the full number of post-operative chemotherapy cycles.

In an attempt to increase efficacy and tolerability of chemotherapy regimen in gastric cancer other cytotoxic agents have been explored. The combination of docetaxel, cisplatin and fluorouracil has shown to be effective in advanced gastric cancer with reported overall response rates of 37%-43% and an acceptable safety profile<sup>[4-6]</sup>. Capecitabine, an orally substitute of 5-FU, offers a clear advantage in terms of convenience and safety without compromising efficacy<sup>[7]</sup>. The combination of cisplatin and capecitabine showed an overall response rate of 46%-54.8% in advanced gastric cancer<sup>[8,9]</sup>. In addition, in a phase II study using preoperative docetaxel, capecitabine and cisplatin in initially locally advanced unresectable gastric cancer a R0 resection could still be achieved in 63% of the patients with an acceptable toxicity (febrile neutropenia 4%, no treatment related mortality)<sup>[10]</sup>.

Taking these promising results into consideration we decided to conduct a one arm phase II trial investigating the feasibility of 4 cycles of preoperative chemotherapy with docetaxel, cisplatin and capecitabine in patients with resectable gastric cancer, followed by a standardized gastric resection and lymphadenectomy.

## MATERIALS AND METHODS

### Patient selection

Inclusion criteria were histologically proven gastric cancer [including gastro-oesophageal junction/cardia carcinoma (Siewert 2 and 3<sup>[11]</sup>)], stage I b-IVa (6<sup>th</sup> TNM classification), WHO performance state 0-1, age  $\geq$  18 years and adequate hematologic, renal and hepatic function. All patients signed an informed consent and were expected to comply with treatment, management of toxicity and scheduled follow-up. Exclusion criteria were non-resectability, previous or current malignancies, other serious illness or medical conditions, known hypersensitivity to any of the chemotherapies used, contraindication for the use of corticosteroids, use of immunosuppressive or antiviral medication, and pregnant or lactating women. A certified ethics committee (METOPP) and the institutional review board at each centre approved the protocol. Screening included a history and physical examination, structural assessment of malnutrition, oesophagoduodenoscopy, blood sampling and CT scan of the chest and abdomen. Evaluation CT-

**Table 1 Patient characteristics at baseline**

Characteristics	No. of patients	%
Age, yr		
Median	64	
Range	34-84	
Age, category		
< 50 yr	5	9.8
50-59 yr	8	15.7
60-69 yr	22	43.1
70-79 yr	15	29.4
> 80 yr	1	2
Sex		
Male	36	70.6
Female	15	29.4
WHO performance status <sup>1</sup>		
0	37	72.5
1	13	25.5
2	1	2
Clinical T stage <sup>2</sup>		
T1	5	9.8
T2	12	23.5
T3	21	41.2
T4	2	3.9
Unknown	11	21.6
Clinical N stage <sup>2</sup>		
N0	16	31.4
N1	19	37.3
N2	4	7.8
N3	2	3.9
Unknown	10	19.6

<sup>1</sup>WHO: World Health Organization; <sup>2</sup>TNM classification.

scans were performed after the second and fourth cycle of chemotherapy.

### Treatment

**Chemotherapy:** Preoperative chemotherapy was administered for four cycles. Based on the described by Sym *et al*<sup>[10]</sup>, each 3-wk cycle consisted of docetaxel 60 mg/m<sup>2</sup> IV infusion and cisplatin 60 mg/m<sup>2</sup> IV infusion on day 1, and capecitabine 1.875 mg/m<sup>2</sup> orally on days 1-14 divided into two daily doses (DCC). Prior to each cycle a full physical examination was performed, and a full blood count and chemistry was obtained. The neutrophil count had to be  $\geq 1.5 \times 10^9/L$  and the platelet count  $\geq 100 \times 10^9/L$ . Dose reductions and delays were predefined for granulocytopenia, thrombocytopenia, and non-hematological toxicity. Secondary use of growth factors was not part of the protocol. Any adverse event was collected and registered according to Common Toxicity Criteria (CTC, version 3). A serious adverse event (SAE), defined as an event that is either fatal, life-threatening, requiring or prolonging hospitalization or resulting in persistent or significant disability or incapacity, was reported to the study coordination centre, and evaluated by the principle investigators. Furthermore, these SAE's were reported to the central medical ethics committee.

**Surgery and pathology:** Patients were scheduled for surgery approximately four to six weeks after the

last cycle of chemotherapy. A (partial) gastric resection and a standardized lymphadenectomy, the so-called D1extra lymphadenectomy specified to tumour location was performed by a local surgeon specialized in gastrointestinal surgery, assisted by a surgeon of the study team. The D1extra lymphadenectomy is a newly defined dissection in which lymph node stations 1-10 and/or 12 (according to the Japanese Classification<sup>[12]</sup>) prone to metastases<sup>[13]</sup> are removed.

### Evaluation and outcome

The primary endpoint of this feasibility study was the toxicity and safety profile of 4 courses of DCC in patients diagnosed with primary resectable gastric cancer. The secondary endpoint of this study was the determination of pathological complete response (pCR) and pathological resection rate (R0). The results, *e.g.*, numbers and proportions of patients reaching the primary and secondary endpoints, will be evaluated using describing statistical analyses.

## RESULTS

### Patient characteristics

Between November 2008 and November 2012, 53 patients from five participating hospitals were included in the study. Two patients were classified by the monitoring committee as having distal oesophageal cancer instead of gastric cancer and were therefore excluded from the study. In Table 1 the patient characteristics are outlined. The median age was 64 years (range 34-84), and 75% of the patients exhibited an WHO performance state of 0. One patient having a WHO performance state of 2, as re-assessed later on, was not excluded because of an intention-to-treat protocol.

### Feasibility

All 51 patient started preoperative chemotherapy. In total, 35 patients completed 4 cycles of chemotherapy (68.6%). In Table 2 the feasibility results are outlined. A total of 169 cycles of chemotherapy were administered. The percentage of intended dose delivered in the intention-to-treat group was 78%-79% for each drug, calculated as the percentage of dose delivered in patients eligible for chemotherapy (deceased patients were excluded). Reasons for dose reduction and discontinuation were treatment related toxicity, including two deaths and a tumour related bleeding in two patients (Figure 1).

### Safety

All patients were evaluable for safety. Grade III/IV toxicity is summarized in Table 3. The most common grade III/IV toxicity was febrile neutropenia and diarrhea occurring in 10.1% and 9.5% of the cycles, in respectively 31% and 25% of patients. There were 3 chemotherapy related deaths, resulting in a mortality rate of 5.9%. In two patients, treatment-related death

**Table 2 Feasibility: Treatment cycles delivered**

	No. of patients	%
Cycles received		
1	51	100
2	44	86.3
3	39	76.5
4	35	68.6
Percentage of intended dose delivered (per evaluable patient, ITT) <sup>1</sup>		
Docetaxel		78.90
Cisplatin		78.70
Capecitabine		78.30
Percentage of intended dose delivered in patients receiving 4 courses ( <i>n</i> = 34)		
Docetaxel		92.90
Cisplatin		92.90
Capecitabine		91.60

<sup>1</sup>ITT: Percentage of dose delivered of all four courses divided by the amount of patients who could have received the full course.

was infection concomitant with grade III/IV neutropenia. One patient died after refusing further therapy of an initially successful treatment of febrile neutropenia.

### Efficacy

Of the remaining 48 patients, 3 patients were considered non-evaluable for the secondary endpoints because of major protocol violation (one patient was operated one year after completion of the preoperative regimen due to myocardial infarction, one patient switched to another chemotherapy regimen, and one patient was operated in a non-participating hospital). Of the remaining 45 patients 39 patients underwent a R0 resection. Two patients developed distant metastases assessed prior to surgery, two patients had peritoneal carcinomatosis diagnosed during explorative surgery and two patients had a R1 resection. Thus, 76.5% of the intention to treat population and 86.7% of the evaluable patients had a R0 resection with curative intend. The surgical results are described elsewhere. A pCR was reported in 3 patients (5.9%).

## DISCUSSION

Overall survival of gastric cancer after a curative resection can be improved with perioperative chemotherapy as shown in the MAGIC trial. The additional benefit of perioperative ECF on survival is probably for the larger part attributed to the preoperative part of the treatment<sup>[3]</sup>. Postoperative chemotherapy in this patient category is challenging since a high percentage of the patients is not fit enough or willing to start and complete the full postoperative part of the regimen<sup>[3]</sup>. To improve the adherence and increase the benefit of preoperative chemotherapy in resectable gastric cancer we designed this phase II study investigating the feasibility of a preoperative regimen of four cycles of docetaxel, cisplatin and capecitabine. To increase

**Table 3 Grade 3-4 adverse events related to chemotherapy**

Toxicity	No of patients	%	No of cycles	%
Hematologic				
Anemia	3	5.9	3	1.8
Neutropenia	25	49	32	18.9
Febrile neutropenia	16	31.4	17	10.1
Non-Hematologic				
Gastro-intestinal				
Anorexia	8	15.7	10	5.9
Constipation	1	2	1	0.6
Diarrhea	13	25.5	16	9.5
Dysphagia	1	2	1	0.6
Mucositis	6	11.8	6	3.6
Nausea	5	9.8	5	2.9
Vomiting	5	9.8	8	4.7
Constitutional				
Fatigue	4	7.8	4	2.4
Hand-foot syndrome	4	7.8	6	3.6
Neurosensory				
Hearing impairment	1	2	1	0.6
Neuropathy	2	3.6	2	1.2
Renal impairment	3	5.9	3	1.8

the efficacy of the preoperative regimen, we replaced epirubicin by docetaxel, since docetaxel containing combination regimens have shown to be feasible and have good response rates in locally-advanced and metastatic gastric cancer<sup>[4-6]</sup>. In our trial however, four courses of DCC as a preoperative regimen showed to be highly demanding for patients with primarily resectable gastric cancer. Only sixty-eight percent of the patients completed all 4 cycles of DCC, the other patients discontinued mainly due to treatment related toxicity. In comparison with results from other trials this percentage is rather low. In a German phase II trial investigating the same regimen as perioperative chemotherapy, with a higher dosage of docetaxel of 75 mg/m<sup>2</sup>, 94% completed all three preoperative cycles<sup>[14]</sup>. In the MAGIC trial, 86% completed the intended three preoperative cycles of ECF<sup>[3]</sup>. In a French trial the rate of patients completing two cycles of preoperative chemotherapy was 87%<sup>[15]</sup>, while in an Italian study the rate of completing 4 preoperative docetaxel based cycles was 74%<sup>[16]</sup>. Four cycles of preoperative DCC chemotherapy, therefore, might be too demanding whereas 86% and 76% of the patients in our study completed 2 and 3 cycles respectively which is comparable to the results described above. On the other hand, completing postoperative chemotherapy is even more difficult. In the aforementioned Italian study feasibility of preoperative chemotherapy was compared to the feasibility of the same regimen as postoperative chemotherapy. The rate of completing 4 postoperative cycles was 34% in this arm<sup>[16]</sup>. In the previous mentioned German and MAGIC trials only 53% and 42% respectively completed the postoperative scheme<sup>[3,14]</sup>. Although the rate of completing all 4 cycles was relatively low in our study, the intended delivered dose was reasonable with percentages of 78 for all drugs individually<sup>[7,14]</sup>. Accurate

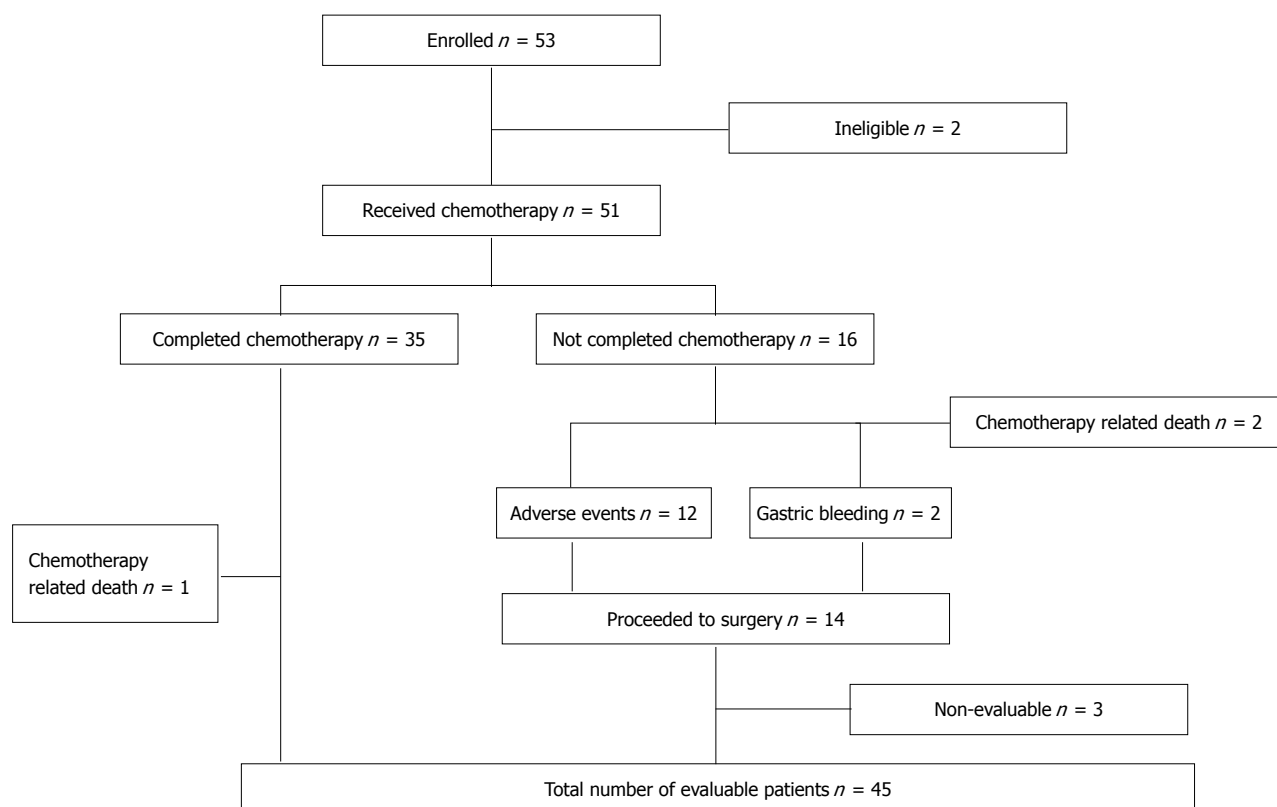


Figure 1 Flow diagram of enrolled patients.

monitoring and early intervention in case of deterioration is imperative to prevent a high amount of patients failing to complete a full chemotherapy regimen.

Treatment related mortality was 5.9% being comparable to mortality rates reported in literature (0%-6%)<sup>[4,5,7,17]</sup>. Febrile neutropenia occurred in 10% of all cycles (vs 2%-15% found in other trials<sup>[4,5]</sup>), being the cause of death of at least two of three patients. The prophylactic or secondary use of G-CSF was not part of the protocol as no data were available at the time of the study design about the interaction between G-CSF and capecitabine in case of simultaneous administration. In theory, the proliferative activity of bone marrow after the administration of G-CSF might increase the myelotoxicity of capecitabine. In literature, only scarce data are known about the simultaneous use of G-CSF and capecitabine. In a phase II trial in breast cancer, the use of pelfilgastrim was evaluated in a small subset of patients receiving docetaxel and capecitabine based chemotherapy regimen. Minimal grade III/IV neutropenia and no febrile neutropenia was observed<sup>[18]</sup>. In one phase II trial in metastatic gastric cancer with a comparable DCC regimen as in our study, patients were treated successfully with G-CSF in case of febrile neutropenia and no toxicity related deaths were reported<sup>[19]</sup>. The use of G-CSF as primary or secondary prophylaxis for (febrile) neutropenia in a docetaxel and capecitabine based chemotherapy scheme is therefore promising, and should be further investigated.

Other main toxicities we encountered were grade

III/IV hand-foot syndrome, diarrhea and anorexia. The rate of hand-foot syndrome of 7.8% in this study is acceptable compared to other studies<sup>[7-10,17]</sup>. Many patients with gastric cancer experience difficulties with eating. With addition of the toxicity of chemotherapy gastric cancer patients are prone to anorexia and weight loss. It is therefore imperative to monitor their intake and weight to be able to act in time when this is deteriorating. A dietician should be consulted and enteral feeding should be started in an early phase<sup>[20]</sup>.

In gastric cancer, clinical tumour staging faces several difficulties. The current imaging modalities have low sensitivity rates for T- and N-stage<sup>[21]</sup>. It is therefore difficult to clinically assess the efficacy of chemotherapy in these patients. In literature, many modalities have been used to determine response rate<sup>[4,7,15]</sup>, which makes it difficult to compare ORRs. In our study, we therefore only determined pathological response rate. A pCR was found in 3 patients (5.9%) which is lower than expected looking at other studies investigating DCF or DCC in gastric cancer in which pCRs of 6.1%<sup>[10]</sup>, 11.7%<sup>[16]</sup> and 13.7%<sup>[14]</sup> are reported. On the other hand, in the MAGIC trial using ECF as a treatment regimen no pCR was seen<sup>[3]</sup>.

Thirty-nine (76.5%) patients received a R0 resection. This is in line with rates found in the MAGIC trial (69.3%)<sup>[3]</sup>, although it is lower compared to other trials using a docetaxel based regimen in which a R0 resection was achieved in 84%<sup>[15]</sup>, 85%<sup>[16]</sup>, and 90.2%<sup>[14]</sup> of patients. The long-term effects of this docetaxel based



scheme and protocolized D1extra lymphadenectomy have to be awaited.

In conclusion, in our study the benefits defined as R0 resection and complete pathological response rates of four cycles of DCC are lower than expected, although the effects on long-term results have to be awaited. Moreover, this is coupled with a high percentage of grade III/IV toxicity, especially febrile neutropenia. The use of simultaneous G-CSF and capecitabine should be further investigated to decrease toxicity-related non-adherence and mortality. According to the results of this study, the use of DCC without G-CSF support as preoperative regimen in resectable gastric cancer is debatable.

## ACKNOWLEDGMENTS

We would like to acknowledge Sanofi for their support in this study.

## COMMENTS

### Background

Survival rates for resectable gastric cancer are still poor. Resection is the cornerstone of treatment, though the addition of perioperative chemotherapy has additional benefit. In 2006, the results of the MAGIC trial were published, comparing perioperative chemotherapy with surgery alone, which resulted in a survival benefit. Only 42% of patients completed the postoperative regimen consisting of epirubicin, cisplatin and capecitabine. Other regimens have been investigated for their effectiveness in gastric cancer, e.g., docetaxel combined with cisplatin and capecitabine, leading to promising results.

### Research frontiers

Improve survival of curable gastric cancer with the use of different regimens of (neo)adjuvant chemotherapy.

### Innovations and breakthroughs

At the time of study design, this was one of the first phase II studies to investigate the feasibility of a docetaxel based regimen in resectable gastric cancer. Although the R0 resection rates were high, it was accompanied by a high rate of febrile neutropenia which resulted in a mortality rate of 5.9%.

### Applications

The combination of docetaxel, cisplatin and capecitabine could be used as a (neo)adjuvant regimen in the setting of resectable gastric cancer, although the role of granulocyte colony-stimulating factor (G-CSF) to prevent febrile neutropenia should be investigated.

### Terminology

Docetaxel can cause neutropenia. In case of an infection, this can be fatal complication. G-CSF could prevent the development of neutropenia, thereby preventing this major complication.

### Peer-review

The present study is a phase II clinical trial which had the aim to evaluate the feasibility of three-drug regimen of preoperative chemotherapy of gastric cancer, composed by cisplatin, capecitabine and docetaxel. It is a well-conducted study.

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## Acute pain management in symptomatic cholelithiasis

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### Abstract

#### AIM

To review the evidence for the use of different non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of biliary colic.

#### METHODS

The strategies employed included an extensive literature review for articles and studies related to biliary colic from electronic databases including PubMed, Science Direct, Wiley Inter Science, Medline and Cochrane from last 15 years. Keywords: "Biliary colic", "management of biliary colic", "non-steroidal anti-inflammatory drugs", "cholelithiasis" and "biliary colic management". Six randomized control trials, 1 non-randomized trial and 1 meta-analysis were included in this review. The outcomes of these studies and their significance have been reviewed in this paper.

#### RESULTS

Current evidence suggests there are no set protocols for biliary colic pain management. NSAIDs are potent in the management of biliary colic, not only in terms of symptom control but in disease progression as well. Apart from the studies on diclofenac and ketorolac, there are studies which have shown that intravenous tenoxicam and injectable flurbiprofen are equally effective in managing biliary colic. The efficacy of NSAIDs is superior in terms of lower number of doses and longer duration of action in comparison to other analgesic agents.

#### CONCLUSION

This literature review has found that NSAIDs are safe and effective for pain control in biliary colic, and reduce the likelihood of further complications.

**Key words:** Biliary colic; Management of biliary colic; Non-steroidal anti-inflammatory drugs; Cholelithiasis; Biliary colic management

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**Core tip:** There are currently no set protocols for pain management in biliary colic. This literature review analyses studies from the last 15 years and shows that non-steroidal anti-inflammatory drugs (NSAIDs) provide safe

and effective pain control. It also suggests that NSAIDs play an important role in reducing the complication risk following episodes of biliary colic.

Masudi T, Capitelli-McMahon H, Anwar S. Acute pain management in symptomatic cholelithiasis. *World J Gastrointest Surg* 2016; 8(10): 713-718 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i10/713.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i10.713>

## INTRODUCTION

In developed countries, including United States, United Kingdom and other European countries, 10% of adults and 20% of people aged > 65 years have cholelithiasis. It is more than twice as common in females as in males<sup>[1]</sup>. Biliary colic is seen as a presenting symptom in 75%-80% of the patients with symptomatic cholelithiasis<sup>[2]</sup>.

This review examines the evidence for the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics in the management of pain in biliary colic as well as their role in the prevention of progression to complications.

## MATERIALS AND METHODS

The strategies employed included an extensive literature search for articles and studies related to biliary colic from electronic databases including PubMed, Science Direct, Wiley Inter Science, Medline and Cochrane. The keywords used in electronic search were "biliary colic", "management of biliary colic", "non-steroidal anti-inflammatory drugs" and "biliary colic management". The literature searches of the last fifteen years brought up approximately 50 studies and papers in a variety of journals. However, only 6 randomized control trials (RCTs), 1 non-randomized trial and 1 meta-analysis fell within the purview of this review, which was to study the effects of NSAIDs and other pharmacological therapies on symptomatic cholelithiasis.

## RESULTS

The studies were examined with the help of a questionnaire devised by the Critical Appraisal Skills Programme<sup>[3]</sup> recommended for evaluating RCTs in evidence-based medicine.

Akriviadis *et al*<sup>[4]</sup> designed a study investigating the effects of diclofenac in patients suffering from biliary colic. The study aimed to prove the benefits of diclofenac for pain alleviation, and also linked NSAIDs with preventing the development of complications related to cholelithiasis. The study involved 53 consenting patients who were

known to have cholelithiasis and who were diagnosed with biliary colic. One group ( $n = 27$ ) received 75 mg of 3 mL IM diclofenac and the other group ( $n = 26$ ) received 3 mL of saline. The patients were followed up for 3 d and the effect of each treatment was gauged by changes in pain severity and progression to complications. Satisfactory levels of analgesia were obtained in 21 patients from the diclofenac group whilst only 7 from the placebo group were relieved of pain. Nearly 50% of the patients in the placebo group progressed to the development of acute cholecystitis. It was concluded that diclofenac usage could provide cost-effective pain relief in the acute phase of biliary colic and could also prevent development of subsequent complications.

This was a randomized, double-blind and controlled study. The inclusion criteria were based on the presence of right upper quadrant and epigastric pain. These patients were further subjected to sonography to demonstrate the presence of cholelithiasis. The exclusion criteria were strictly monitored. There was a longer follow-up of 3 d in these patients, which aided the adequate monitoring of responses to treatment and the recording of any complications in a surgical ward setting, thus minimizing the chances of observer bias and maintaining uniformity of care. The study also employed the setting up of end points which were based on patient response to treatment and time taken to get relief or symptom progression. This made it a well-controlled study keeping the wellbeing of patients paramount. This is a level-II study with a sound aim and statistically significant results but the only limitation was the fallout of 28 patients from initial enrollment to the final conclusion.

Tomida *et al*<sup>[5]</sup> conducted an extensive study on the long-term use of ursodeoxycholic Acid (UDCA) therapy in patients with known cholelithiasis. The aim of this study was to evaluate the effects of this therapy on biliary pain and development of acute cholecystitis. The study included a cohort of 527 patients with uncomplicated cholelithiasis who were either given or withheld UDCA (600 mg/d). These patients were followed for 18 years and the results analysed. It was found that UDCA therapy was associated with reduced risk of developing biliary pain in symptomatic as well as in asymptomatic patients. The risk of conversion to surgery was also reduced in symptomatic patients treated with UDCA. On the basis of these findings it was concluded that UDCA therapy might be considered as a safe option in symptomatic patients and also in patients who carry a significant surgical risk.

This was a non-randomized prospective study designed to cover a large number of patients. The strengths of this study are that it had a large sample size and that the follow-up and data collection were uniform. The inclusion and exclusion criteria were strictly monitored and the allocation of an end-point meant that the patients were given a fair chance of getting an acceptable mode of management for their symptoms. However, the absence of randomization makes this a level-III study and there is



a lack of power calculations to support the representativeness of the study, therefore increasing the likelihood of type 2 error. There is also an element of bias in this type of observational study.

Dula *et al*<sup>[6]</sup> compared the efficacy of administering intramuscular ketorolac with intramuscular meperidine in the treatment of acute biliary colic. The study consisted of 30 patients who were divided into two groups and after the diagnosis of acute biliary colic was established, were given either meperidine 1.5 mg/kg (100 mg max.) or ketorolac 60 mg. The patients were asked to rate their pain at two time intervals; before administration and 30 min after the medication was given. This was rated on a visual analogue pain scale. The average pain score was compared between the two groups at time 0 and at 30 min. The average pain score at time 0 was 7.6 for the ketorolac group and 7.3 for the meperidine group. The visual analog scale (VAS) scores for the ketorolac group and the meperidine group were 3.8 and 3.9 at the 30-min time interval after the administration of the respective drugs. It was found that there was indeed improvement in pain control in both groups, but there was no markedly demonstrable difference in the pain relief achieved by either ketorolac or meperidine when administered intramuscularly.

This study had a definite aim and was well-designed but the size of the sample was too small to have any impact on the practice. It was a randomized, prospective and a double-blinded study. However there was an absence of power calculations, making the study less representative of the large number of cholelithiasis patients who present to emergency clinics routinely. Only 15 patients effectively got intramuscular ketorolac and this cannot constitute evidence of any consequence.

Henderson *et al*<sup>[7]</sup> conducted a similar study on 324 patients over a 2-year period with a view to comparing analgesic efficacy and systemic tolerability of intravenous Ketorolac and Meperidine in the treatment of acute biliary colic. The patients were between the ages of 18 and 65 years with signs and symptoms consistent with acute biliary colic. Pain scores were quantified by means of a four-point verbal rating system as well as a VAS. These are validated tools for measuring patient satisfaction and drug efficacy and thus lend validity to the findings. The results did not demonstrate any significant differences in pain or drug tolerability [mean change in the VAS at 2 h was  $6.2 \pm 3.6$  cm for the ketorolac group, compared with  $6.7 \pm 3.6$  cm for the meperidine group ( $P = 0.25$ )] but revealed higher incidences of nausea and dizziness in the Meperidine group ( $n = 149$ ). The study goes on to conclude that Ketorolac ( $n = 175$ ) is a well-tolerated and effective analgesia for biliary colic and the fact that it showed similar efficacy as Meperidine with decreased adverse effects makes it a better alternative.

This was a prospective, randomized and a double-blinded study which included a significant sample of patients. The inclusion and exclusion criteria were strictly

monitored. The limitation of this study was that out of a sizeable number of patients initially enrolled ( $n = 534$ ), more than 220 patients were lost for a variety of reasons such as loss of data and inappropriately filled forms. Also the employment of convenience sampling makes the study prone to potential bias. However, the presence of power calculations makes this a robust and acceptable study. There is certainly evidence collected in this study which could potentially change practice; more patients with biliary pathology could be treated with Ketorolac for effective analgesia.

Antevil *et al*<sup>[1]</sup> undertook a trial to determine the efficacy of intravenous glycopyrrolate for the relief of pain associated with the biliary tract. At the onset 312 patients were assessed for the study but eventually only 39 were actually included in the study. The rest either declined to participate or did not meet the inclusion criteria. The initial aim of the study was to include 54 patients but due to difficulty in patient enrollment, analysis was done on only 39 patients who completed the study protocol. The initial sample size was based on power calculations to give the study a representative character, which was later lost due to the fallouts. The results of the study failed to demonstrate any significant differences in the pain relief between patients receiving glycopyrrolate and those receiving a placebo. The statistical difference in visual analogue scale for pain between the former and the latter was 3 mm vs 8 mm respectively. It was proposed that a further, larger study would be needed to underline the supremacy (if any) of glycopyrrolate in treating patients with biliary colic.

This was a randomized, prospective and a double-blind study. The randomization was computer generated and the inclusion criteria were set up keeping in view the final size of the sample based on eligibility criteria. Factors such as the selection of patients and the methods used to sample by the enrolling physicians made the study weaker and the results less relevant. The patients enrolled for the study did not all necessarily have cholelithiasis, thus making them less suitable for treatment with an anticholinergic agent like glycopyrrolate. This was highly likely to give false negative results. This study failed to achieve its aim and left a lot to be desired in terms of patient selection and the inclusion criteria.

Kumar *et al*<sup>[2]</sup> undertook a study to compare the effects of intramuscular diclofenac with intramuscular Hyoscine-N-butyl bromide in the treatment of acute biliary colic and also to study their role in the prevention of gallstone-related complications. The study was conducted on 72 consecutive patients with biliary colic. One group ( $n = 36$ ) received 75 mg of intramuscular diclofenac and the other group ( $n = 36$ ) received 20 mg of intramuscular hyoscine. Pain severity was later measured on a visual analog scale at different time intervals of 30 min, 1 h, 2 h, and 4 h after the administration of the drug. Patients were followed for 72 h for signs of relapse or development of complications. It was found that diclofenac provided much

**Table 1** Comparison of studies with their design and outcomes

Ref.	Design of study	Sample size	Duration of treatment	Results
Akriviadis <i>et al</i> <sup>[4]</sup>	Randomized controlled trial	<i>n</i> = 53 Group I ( <i>n</i> = 26) (NSAID) Group II ( <i>n</i> = 27) (Placebo)	3 d	Superior results from Diclofenac usage
Tomida <i>et al</i> <sup>[5]</sup>	Non-randomized controlled trial	<i>n</i> = 527		Ursodeoxycholic acid a safe option in symptomatic but high surgical risk patients
Dula <i>et al</i> <sup>[6]</sup>	Randomized controlled trial	<i>n</i> = 30 Group I ( <i>n</i> = 15) (NSAID) Group II ( <i>n</i> = 15) (Meperidine)	1 d	Comparable efficacy but lesser side-effects from Ketorolac
Henderson <i>et al</i> <sup>[7]</sup>	Randomized controlled trial	<i>n</i> = 324 Group I ( <i>n</i> = 175) (NSAID) Group I ( <i>n</i> = 149) (Meperidine)		Comparable efficacy but lesser side-effects from Ketorolac
Kumar <i>et al</i> <sup>[2]</sup>	Randomized controlled trial	<i>n</i> = 72 Group I ( <i>n</i> = 36) (NSAID) Group II ( <i>n</i> = 36) (Hyoscine)	3 d	Rapid symptom relief with Diclofenac and lower rate of sequelae
Antevil <i>et al</i> <sup>[1]</sup>	Randomized controlled trial	<i>n</i> = 39 Group I (Glycopyrrolate) Group II (Placebo)		No significant difference in analgesia between glycopyrrolate and placebo
Olsen <i>et al</i> <sup>[9]</sup>	Randomized controlled trial	<i>n</i> = 46 Group I ( <i>n</i> = 23) (Ketorolac) Group II ( <i>n</i> = 23) (Butorphanol)	1 d	Both agents provided reasonable relief of symptoms
Basurto Oña <i>et al</i> <sup>[10]</sup>	Meta-analysis			NSAIDs drugs of choice for symptom control and improvement of prognosis

NSAIDs: Non-steroidal anti-inflammatory drugs.

more rapid pain relief, as shown by the fact that 91.7% of such patients recorded no symptoms at the 4-h interval. Furthermore, it was noted that progression to sequelae of cholelithiasis was significantly lower in this group of patients compared with the patients treated with hyoscine.

This was a prospective, randomized, and double-blinded study with a significant sample size. There were no dropouts in terms of follow-up and the focus of the study remained unaltered. The results of this study are precise and corroborate well with the past experiences of other researchers like Todd and Sorkin<sup>[8]</sup> in 1988. The study has, in the authors' opinion, the potential to influence practice if backed by robust statistical analysis.

Olsen *et al*<sup>[9]</sup> carried out a prospective randomized controlled trial comparing the efficacy of ketorolac vs butorphanol for patients with suspected biliary colic in the emergency department. This was a compact study with a definite aim (though limited by a small sample size) which concluded that both agents can be considered reasonable options in patients presenting with biliary colic, especially those with a need for further investigations.

Basurto Oña *et al*<sup>[10]</sup> conducted a systematic review and meta-analysis of randomized controlled trials involving the management of biliary colic with anti-inflammatory agents. A systematic and manual search was conducted in the literature. The authors selected 7 RCTs of 349 patients. The inclusion criteria were all the RCTs which compared the effects of NSAIDs with other interventions that were employed for treating uncomplicated biliary colic in an acute setting. The outcome measures were set up as rescue analgesia, rapidity of analgesic effect, adverse reactions and progression to complications.

The results were well analyzed and statistically significant. These were expressed in terms of confidence intervals and odds ratios, making the analysis more rigorous. The results showed a clear advantage in favour of NSAIDs because there was lower need for rescue analgesia (OR = 0.32; 95%CI, 0.16-0.61) and progression to complications (OR = 0.19; 95%CI: 0.08-0.44). This is a very robust study and can be assigned as level-I evidence. The results cannot, however, be extrapolated to the general population simply because 349 patients cannot be

representative of a pathology which affects such a large part of the adult population. In these types of studies there is a danger of publication bias in terms of selecting only the favourable trials for the analysis.

The findings of this study are also well supported by observations of Macintyre *et al.*<sup>[11]</sup>, who have termed NSAIDs as effective analgesics for the management of acute pain (level- I evidence).

## DISCUSSION

The review of the above studies clearly suggests that there are no set protocols for the administration of specific analgesic agents to the patients with biliary colic (Table 1). It follows that there is strong evidence demonstrating the therapeutic and preventive potency of NSAIDs in the management of biliary colic, not only in terms of symptom control but in disease progression as well<sup>[12]</sup>. Apart from studies on diclofenac<sup>[4]</sup> and ketorolac<sup>[2]</sup>, there are studies<sup>[13,14]</sup> which have shown that intravenous tenoxicam and injectable flurbiprofen (both NSAIDs) respectively are equally effective in managing biliary colic. The efficacy of NSAIDs has been proven to be superior in comparison to agents such as meperidine and hyoscine. Initial analgesic requirements may be substantial, and treatment with NSAIDs or acetaminophen (also called paracetamol) should be initiated<sup>[15]</sup>. NSAIDs also demonstrated pharmacological superiority in terms of smaller number of doses and side effects with longer duration of action in comparison to other analgesic agents<sup>[4]</sup>. Therefore enough qualitative evidence is available to influence practice.

A multi-centric study needs to be undertaken, aimed at identifying the reasons leading to variation in practice between the various centers after these patients are identified as having biliary colic. The evidence provided (level- I )<sup>[10]</sup> is significant and similar studies would go a long way toward laying down strict guidelines for prescribing analgesia to patients with biliary colic.

## COMMENTS

### Background

Cholelithiasis is a common surgical presentation in developed countries, present in 10% of the adult population and 20% of those aged over 65 years. Biliary colic is a presenting symptom in 75%-80% of those with symptomatic cholelithiasis. Despite this, there are currently no set protocols for the pain management in biliary colic.

### Research frontiers

This paper reviews extensive literature from electronic databases including PubMed, Science Direct, Wiley Inter Science, Medline and Cochrane. Six randomized control trials, 1 non-randomized trial and 1 meta-analysis were analysed from the past 15 years.

### Innovations and breakthroughs

The aim in this paper was to collate evidence for non-steroidal anti-inflammatory

drugs (NSAIDs) use in biliary colic as both pain relief and with a view to preventing further complications.

### Applications

This review shows NSAIDs to be both safe and effective for biliary colic pain management as well as reducing the incidence of complications arising from cholelithiasis. Practically this could have implications for increased use of NSAIDs for biliary colic as well as encouraging further study in this area to investigate the role of NSAIDs in improving complication rates.

### Peer-review

The article is complete and interesting.

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