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REVIEW

Assessment of lymph node involvement in colorectal cancer

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Abstract

Lymph node metastasis informs prognosis and is a key factor in deciding further management, particularly adjuvant chemotherapy. It is core to all contemporary staging systems, including the widely used tumor node metastasis staging system. Patients with node-negative disease have 5-year survival rates of 70%-80%, implying a significant minority of patients with occult lymph node metastases will succumb to disease recurrence. Enhanced staging techniques may help to identify this subset of patients, who might benefit from further treatment. Obtaining adequate numbers of lymph nodes is essential for accurate staging. Lymph node yields are affected by numerous factors, many inherent to the patient and the tumour, but others related to surgical and histopathological practice. Good lymph node recovery relies on close collaboration between surgeon and pathologist. The optimal extent of surgical resection remains a subject of debate. Extended lymphadenectomy, extra-mesenteric lymph node dissection, high arterial ligation and complete mesocolic excision are amongst the surgical techniques with plausible oncological bases, but which are not supported by the highest levels of evidence. With further development and refinement, intra-operative lymphatic mapping and sentinel lymph node biopsy may provide a guide to the optimum extent of lymphadenectomy, but in its present form, it is beset by false negatives, skip lesions and failures to identify a sentinel node. Once resected, histopathological assessment of the surgical specimen can be improved by thorough dissection techniques, step-sectioning of tissue blocks and immunohistochemistry. More recently, molecular methods have been employed. In this review, we consider the numerous factors that affect lymph node yields, including the impact of the surgical and histopathological techniques. Potential future strategies, including the use of evolving technologies, are also discussed.

Key words: Colorectal cancer; Lymphatic metastases; Lymph node metastasis; Neoplasm staging; Tumor node metastasis classification; Sentinel lymph node biopsy; Lymph node excision; Histopathological assessment; Surgery

Core tip: The number of lymph nodes in surgical resection specimens is influenced by numerous factors. Good practice by surgeons and pathologists is essential to maximize lymph node yields, but there are non-modifiable factors related to patient and tumour. Extended lymphadenectomy, extra-mesenteric lymph node dissection, high arterial ligation and complete mesocolic excision, all increase lymph node yields, but a definite benefit in prognosis is not proven and the optimal extent of surgical resection remains contentious. Conversely, further development in sentinel lymph node biopsy techniques could allow selective lymphadenectomy, whilst providing appropriate information to guide adjuvant therapy.

Ong MLH, Schofield JB. Assessment of lymph node involvement in colorectal cancer. *World J Gastrointest Surg* 2016; 8(3): 179-192 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i3/179.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i3.179

INTRODUCTION

Lymph node metastasis (LNM) informs prognosis and is a key factor in deciding further management, particularly adjuvant chemotherapy. As such, lymph node metastasis has had a role in colorectal cancer staging from the earliest classification systems. Its importance in prognosis has been borne out by successive classification systems and is reflected in all contemporary staging systems, in particular the widely used tumor node metastasis (TNM) staging system, developed and maintained by the Union for International Cancer Control and American Joint Committee on Cancer (AJCC).

Patients with node-negative disease have 5-year survival rates of 70%-80% in contrast to 30%-60% in those with node-positive disease. Survival is improved in the latter group by adjuvant chemotherapy. The 20%-30% disease recurrence in apparently completely excised tumours without lymph node metastases is thought to be due to occult lymph node disease. If this subset could be identified by better lymph node staging, they might also benefit from adjuvant chemotherapy.

There are several prognostic factors other than lymph node disease status that also identify patients who might benefit from adjuvant treatment. These include venous invasion, peri-neural invasion, tumour perforation, serosal involvement and incomplete resection[1,2]. However, lymph node assessment remains a mainstay of deciding adjuvant chemotherapy. To achieve accurate staging, surgeons and pathologists must exercise due diligence in their respective practices. Most authorities recommend examination of a minimum of 12 lymph nodes, although the evidence base for this is weak. Behind this apparently simple number are numerous complex issues, many without clear solutions. In this review, we consider the factors that affect lymph node yields including the influence of surgical and histopathological techniques. Evolving concepts and technologies that are not in widespread use, such as sentinel lymph node evaluation, are also discussed.

FACTORS INFLUENCING LYMPH NODE ASSESSMENT

In order to identify and maximise the diagnostic information from lymph nodes within a specimen, it is important to understand the factors that influence the lymph node harvest (LNH). This relates to a range of different factors: The pathologist, the surgeon and factors inherent to the patient and tumour. While tumour and patient characteristics cannot be changed, the pathologist can employ various techniques to maximise both the LNH and gain additional diagnostic information from enhanced study of the lymph node. The surgeon can modify the surgical procedure to excise more tissue or use ancillary techniques to aid selection and examination of lymph nodes by the pathologist.

ROLE OF THE HISTOPATHOLOGIST

Contemporary lymph node staging

There are several tumour staging systems, of which the TNM staging system is the most widely used internationally. It seems self-evident that lymph node metastasis indicates the presence of tumour cells within a lymph node. However, precise definition of different types of burden is crucial. Metastatic disease is often sub-classified into isolated tumour cells (ITCs, < 0.2 mm), micrometastases (defined as > 0.2 mm but < 2 mm) and macrometastases (⩾ 2 mm). More recently, the concept of molecular positivity has been introduced. The classification of nodal disease (N-stage) under the current 7th edition of the TNM staging system (TNM7) is summarised in Table 1.

A universally agreed definition of what constitutes lymph node metastasis is important for communication between all parties involved in treating, diagnosing and researching colorectal cancer. It facilitates uniformity for the purposes of entry to clinical trials, subsequent applicability of the ensuing results and interpretation of historical trends. Any criteria should be objective, reproducible, evidence-based and met with broad agreement. However, significant changes to the criteria in successive editions of TNM have been criticised for lacking some of the above qualities.

Detailed analysis of the changes wrought by the two most recent TNM editions is presented elsewhere[3-5]. The main changes are summarised diagrammatically in Figure 1, but a few points warrant discussion. In the 6th edition (TNM6)[6] of the TNM staging system, isolated tumour cells became classed as N0 for the purposes of grouping tumours into AJCC stage Ⅰ to Ⅳ, in contrast to N1 in the 5th edition (TNM5)[7]. Secondly, extra-mural

Table 1 Nodal staging in the 7th edition of the tumor node metastasis staging system

N Stage	Description
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N0 (i-)	No regional lymph node metastases histologically, negative IHC
N0 (i+)	Isolated tumour cells, identified by H&E and/or IHC
N0 (mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
N0 (mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
N1mi	Micrometastases
N1	Metastasis in 1-3 regionl lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2b	N2b Metastasis in seven or more regional lymph nodes
N2a	N2a Metastasis in 4-6 regional lymph nodes

IHC: Immunohistochemistry. RT-PCR: Reverse transcription-polymerase chain reaction.

deposits are difficult to classify. In a study of 69 tumour deposits, step sections were performed on what were initially diagnosed as tumour deposits. A significant proportion were found to represent other patterns of tumour spread[8]. The "3 mm rule" stipulated in TNM5 was not based on published data, but had the advantage of being objective and reproducible[9], in contrast to the assessment of "contour" introduced in the 6th edition (TNM6)[10]. The "contour rule" was dropped in the 7th edition (TNM7), but explicit criteria were not provided to replace it. Left to the discretion of the pathologist, classification of extra-mural tumour is fraught with inter-observer variability[11]. Unsurprisingly, there has been stage migration as a result of these changes, making it difficult to compare historical data. Data from the Surveillance, Epidemiology and End Results population-based registries showed that 10% of colorectal cancer cases had "tumour deposits", of which 30%-40% occurred without concomitant lymph node metastases. Compared to TNM6, this represented up-staging of 2.5% of colon and 3.3% of rectal cases to N1c, a significant stage migration from stage Ⅰ to stage Ⅲ[12]. There have also been misgivings over the use of TNM7 following neoadjuvant treatment, where patchy tumour regression may give the false appearance of lymph node metastasis or discontinuous tumour deposit. Finally, the changes in definition tend to reduce lymph node counts[13], a concern where LNH is being used as a marker of "quality". It is hoped than the 8th of edition, due to published this year, will resolve some of these issues.

Dissection

In many pathology laboratories, macroscopic examination and dissection of colorectal cancer specimens is delegated to trainee pathologists, sometimes with limited experience and expertise. These large resection specimens tend to be left to the end of the "cut-up" session when time may be limited. Even in experienced hands, the detection of minute lymph nodes in mesenteric fat by palpation and dissection is painstaking and time-consuming. Marked variation in the assessment of colorectal cancer in the pathology laboratory, particularly in lymph node yields, is not a new issue[14,15], but there is now more awareness of the crucial role of dissection. Results from staff pathologists[16] and non-pathologist dissectors[17-19] may be superior, but it is likely that a major factor is not the expertise of the operator, but rather the time devoted to searching for lymph nodes. de Burlet *et al*[20] studied LNH in gastrointestinal tumour resection specimens. Twenty minutes was allocated to an initial lymph node search, followed by an extra 5 and 10 min, which increased yields by 12% and 20% respectively. Twenty additional minutes added a mean of 6 lymph nodes, albeit with a diminishing rate of lymph node discovery. The United Kingdom Royal College of Pathologists' Guidelines on Staffing and Workload allocates 8 points for cutting-up a colorectal resection, corresponding to an anticipated time spent of 31-50 min[21]. This would appear to underestimate the time required for a thorough job if de Burlet *et al*[20] findings are correct. Often little thought is given to the ergonomics around cut-up. To optimise lymph node yields, we recommend that large specimens should be dealt with first when the operator is still fresh.

Handling

Current practice in handling of lymph nodes is not uniform. The United Kingdom Royal College of Pathologist guidance recommends embedding each lymph node whole, if < 4 mm, and a central block through longest axis for larger nodes[22]. It is common practice to bisect or serially slice larger lymph nodes.

Typically, a single haematoxylin and eosin stained section is cut from each lymph node block, representing only a tiny volume of the lymph node in a single axis. Cutting more sections increases detection of lymph node metastases, including up-staging of several cases[23], but the workload implications for the laboratory and histopathologist makes routine application of this unfeasible. Similarly, identification of small deposits of tumour by immunohistochemistry increases detection, but once again, has significant cost and workload implications.

Lymphatic mapping, the process of injecting tracer at the tumour site and following lymphatic flow to identify lymph nodes, has been used to identify sentinel lymph nodes (SLN). These SLNs are then subject to more intensive histopathological scrutiny, so-called ultrastaging[24], typically consisting of additional levels and/or immunohistochemistry and in some cases molecular techniques[25]. The utility of SLN ultrastaging is hampered by the limitations of current

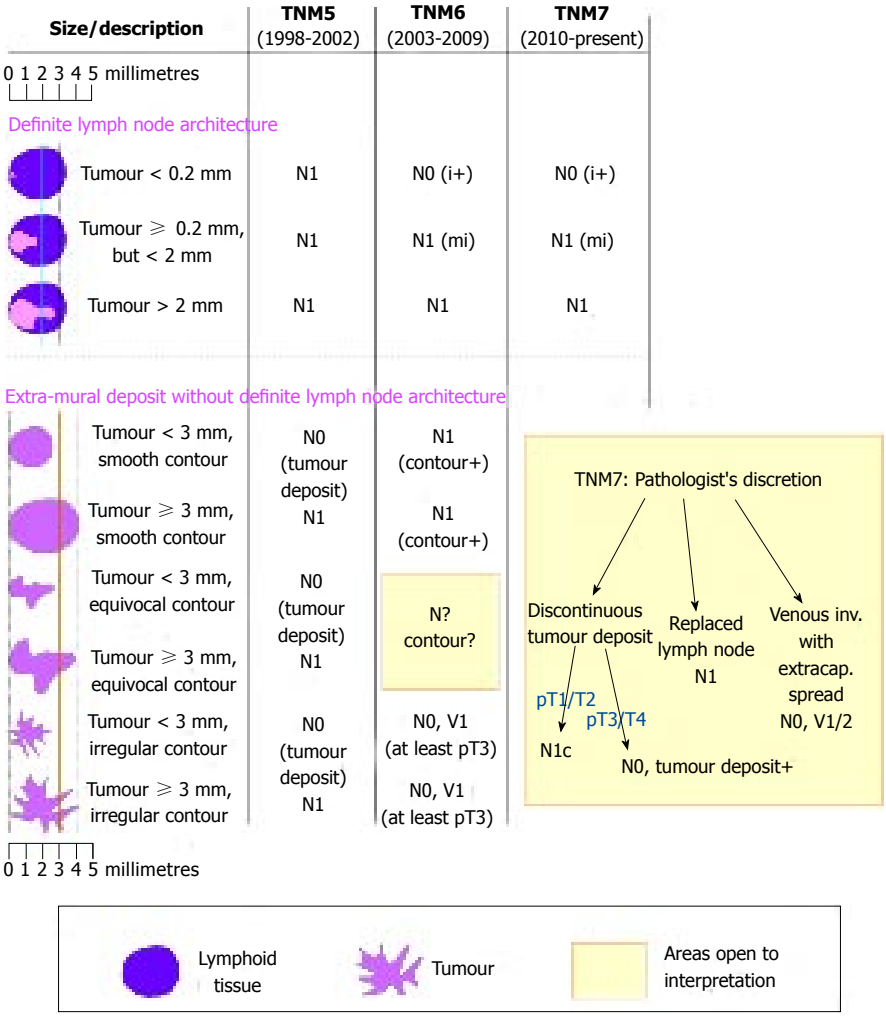

Figure 1 Changes in successive editions of the tumor node metastasis staging system. Top 3 rows: Size of deposit within definite lymph node. Under the 5th edition of the TNM staging system (TNM5)[7], the volume of tumour cells is immaterial, but from the 6th edition (TNM6) onwards[6], tumour burden is sub-classified by size; bottom 6 rows: Extra-mural deposits. TNM5 uses a 3 mm threshold; above this, the deposit is regarded as a lymph node metastases, below this, the deposit is regarded as a discontinuous extension of the main tumour. TNM6 relies on assessment of contour; smooth deposits are counted as nodes, whereas irregular contours are considered vascular invasion and upstaged in the T category. TNM7 leaves the decision to the judgement of pathologist with a wide range of outcomes.

SLN procedures, namely false negatives, skip lesions and failure to identify a SLN (see later section on SLN). The significance on prognosis of isolated tumour cells identified in this way is also contentious[25] and is discussed in the later section on the size of tumour deposits.

Several other ancillary techniques have been employed to aid the LNH. Modified lymphatic mapping can be achieved by injection of India ink at the time of surgery[26,27] and, similarly, *ex vivo* intra-arterial injection of methylene blue can accentuate lymph nodes[28,29]. Chemical fat clearance can be performed with a variety of chemical regimens, typically a mixture of fixatives and organic solvents, such as glacial acetic acid, xylene, acetone, and alcohol. With the fat partially removed, nodes are accentuated, facilitating manual dissection and increasing yields. The clearance techniques are not in universal usage due to the slight delay introduced in finalizing a report and safety issues related to the disposal of the volumes of hazardous chemicals generated. The entire mesentery can be embedded without fat clearance, so-called entire residual mesenteric tissue examination, which also increases yields[30]. There is no doubt that many of these techniques increase LNH, but there are not currently enough data to show that they result in significant up-staging[31].

Molecular techniques

The disadvantage of conventional ultrastaging is that it still relies on examination of a tiny volume of the lymph node. Lymph nodes harvested fresh can be processed to extract nucleic acids that can be analysed using reverse transcriptase and polymerase-based technologies. Some studies have used conventional polymerase chain reaction, but loop-mediated isothermal amplification, also known as one-step nucleic acid amplification (OSNA) can be performed in less than an hour and can be used intra-operatively. The results are quantitative and should reflect mRNA copy number. Thresholds are set to give grades of molecular lymph node involvement equivalent to conventional nodal staging, typically

⩾ 250 copies for micrometastases and ⩾ 5000 for macrometastases, although these figures are based on work done with breast cancer cases. Typical markers including carcinoembryonic antigen, cytokeratins 19/20 and guanylyl cyclase C. OSNA can be performed on the entire node[32-34] or half of the node in combination with conventional sections[35]. While up-staging was described in most series, there have been discrepancies not entirely explained by tissue allocation, suggesting conventional methods, albeit with ultrastaging-type protocols may have superior sensitivity and specificity. The data on how OSNA results correlates with the performance of single section histopathological analysis is sparse, particularly when isolated tumour cells are not included as a molecular category. Application of the OSNA technique to all lymph nodes harvested is not currently feasible outside of the research setting and practically-speaking, its main role is likely to be for the purposes of analysing sentinel lymph nodes.

Sentinel lymph node biopsy

The principle of sentinel lymph node biopsy (SLNB) is well established in melanoma and breast cancer, where the aim is to avoid unnecessary and potentially morbid lymphadenectomy. Unlike these two malignancies, where lymphadenectomy is a separate procedure, lymphadenectomy in elective colorectal cancer surgery is typically performed as part of a single surgical procedure. The lymphadenectomy component carries a low, but not entirely negligible morbidity. In a review of SLNB, Cahill questions the assumption that additional surgery carries no or minimal risk, particularly if radical lymphadenectomy is performed[36]. The effects of excising unnecessary tissue are difficult to quantify. However, if SLNB can readily and reliably determine lymph node status, permitting more conservative surgery, then reduced tissue dissection, shortened operative time and better bowel function are all desirable outcomes.

Another scenario where SLNB may be informative is in early T-stage colorectal cancers, particularly pT1 polyp cancers identified by bowel cancer screening programmes. Adequate local excision of these polyp cancers is often achieved by endoscopic resection, but there is uncertainty about whether segmental resection for lymphadenectomy is indicated, a particular dilemma in patients with significant co-morbidities. While certain tumour characteristics predict lymph node metastases[37-40], a SLNB should provide a definitive answer. SLNB can be performed laparoscopically[41,42] and potentially *via* other minimally invasive techniques, *e.g.,* a transcolonic approach using with natural orifice transluminal endoscopic surgery[43].

In this context, SLNB data specific to pT1/T2 tumours is of particular relevance, but many studies are small, typically include all T-stages or, in some studies, omit T-stage data. SLNB may have less of a role in pT3/T4 tumours as they are more likely to harbour lymph node metastases and therefore less likely to benefit from initial SLNB[44]. Additionally, an increased rate of false negatives has also been described in pT3/pT4 tumours[36].

Broader adoption of SLNB, however, is limited by the guarded results from existing studies. SLNB is beset by a number of problems: Failure to identify a SLN, false negatives and skip lesions[45-47]. Skip lesions have been hypothesised to be due to blocked lymphatic flow into involved lymph nodes, but this is not entirely explained by some data. It is unclear if the poor results are explained by technical problems, sub-optimal implementation of the technique or whether the concept is fundamentally flawed because of the inherently unpredictable pattern of lymph node involvement[36,48]. Further evaluation of these techniques is required to determine whether they should be generally adopted.

ADDITIONAL HISTOPATHOLOGICAL ASPECTS IN LYMPH NODE ASSESSMENT

The most obvious measurable parameter relating to lymph nodes is the total LNH. Sampling as many lymph nodes as possible is ideal, but the focus on absolute counts alone ignores the complex and sometimes interacting factors that influence LNH. A detailed analysis of lymph node counts is presented later in this review, but other characteristics related to lymph nodes are discussed here.

Size of tumour deposit and/or lymph node

There are two separate aspects to consider. Firstly, does lymph node size, irrespective of tumour involvement, have implications on LNH or prognosis? Secondly, if a lymph node is involved, is the size of the deposit within the lymph node significant?

Chirieac *et al*[49] showed that nodal size significantly predicted overall survival in patients with node-negative colorectal cancer. They also speculated that high numbers of bulky negative lymph nodes were a product of an active host immune response, which ultimately contributed to improved patient prognosis and survival.

In some studies, LNM were more likely to be found in larger lymph nodes[50,51], perhaps because they are easily palpable and therefore preferentially sampled. In node-positive disease, the size of the lymph node (as opposed to the tumour deposit) appears to have no significance on outcome[52,53]. These studies and several others have demonstrated that many, if not the majority, of LNM occur in lymph nodes < 5 mm[51,54]. The relevance of this is that small LNs are harder or impossible to palpate and are therefore less likely to be sampled during pathological dissection. Secondly, it is hard to completely separate the size of the tumour deposit from the size of the lymph node as the deposit obviously cannot exceed the size of the node. According to TNM7 rules, a positive 1.9 mm lymph node will either be involved by isolated tumour cells or micrometastases, but never a macrometastases (Figure 1).

This leads to the next question: Is the size of LN tumour deposit significant? The size of the largest lymph node tumour deposit appears to be prognostic[55], but the overall volume of lymph node tumour burden appears to be less important than the number of involved lymph nodes[56].

There is also considerable debate about the significance of isolated tumour cells. The data shows a wide variation in the incidence of isolated tumour cells and micrometastases, ranging from 11% to 59%. Some demonstrate an adverse effect on survival[57-60], but others show no significance[61-64]. The discrepancy reflects the differences in study design such as method of detection, length of follow-up and whether other confounding factors were considered. As previously discussed, more thorough scrutiny of lymph nodes with ultrastaging and/or molecular methods may increase detection of tumour, but it is unclear what significance this has on prognosis as direct comparison of data difficult. A 2014 meta-analysis suggests micrometastases have an adverse prognosis whilst isolated tumour cells do not[65], but this distinction is not always straight-forward: The size cut-off of 0.2 mm is arbitrary and other definitions in terms of total cell numbers are hard to apply consistently.

Oncological practice in the United Kingdom continues to use the TNM5 definitions of lymph node metastasis, which defines the presence of any metastatic disease as N-positive, warranting adjuvant chemotherapy. Practice in other parts of the world differs, particularly in countries that have already adopted TNM7, which classifies isolated tumour cells as N0.

Extracapsular spread

Extracapsular extension is typically associated with more aggressive and infiltrative tumours. Heide *et al*[66] noted that extracapsular extension in rectal resections was connected with adverse local control and a higher rate of distant metastases. In another study, the survival rates and disease-free survival rates for patients with metastatic lymph nodes showing an extracapsular invasion pattern were significantly worse than cases showing no evidence of extracapsular extension[67].

Lymphoid hyperplasia/sinus histiocytosis

LNs negative for tumour may show reactive patterns such as follicular, parafollicular hyperplasia, as well as sinus histiocytosis. These have been regarded as indicators of active host immune response and are associated with an improved prognosis and 5-year survival rate[68]. A survival advantage has also been established in metastatic lymph nodes that also demonstrate a background of benign reactive inflammatory changes[69]. The host-response hypothesis may also explain why patients with lower lymph node yields are generally found to have a poorer prognosis, although reactive lymph nodes are more easily identified and may result in higher LNH and more accurate staging.

Ratio of involved lymph nodes

The use of the ratio of positive nodes to total LNH was first proposed by Berger *et al*[70] in 2005 as an additional prognostic factor. Several subsequent studies have corroborated the original findings[71-77], although what threshold to use is not clear. The results are not entirely consistent and there may also be differences between colonic and rectal tumour[78]. A minimum LNH is required to make the ratio valid. Conversely, large numbers of lymph nodes obtained through techniques such as fat clearing may increase the overall denominator, disproportionately reducing the ratio.

Mucin pools

LNM from tumours showing prominent mucinous differentiation may manifest as pauci-cellular mucin pools. Following neoadjuvant treatment, these may be rendered acellular. Further step levels are helpful to exclude viable tumour cells, but if no cells are found, these are regarded by most pathologists as lymph node negative[79,80].

ROLE OF THE SURGEON

The role of the surgeon is to excise the primary tumour and an appropriate amount of mesenteric tissue with clear margins, to allow adequate staging, whilst minimising potential complications. This raises the question of how much tissue should be removed to achieve optimal oncological outcomes.

Lymphadenectomy - therapeutic or prognostic?

How much tissue to remove is guided by the interpretation of the fundamental purpose of lymphadenectomy. There are divergent views on whether it is directly therapeutic or whether it provides mainly staging and prognostication[81]. The model espoused by Halsted at the end of the 19th century assumes sequential and step-wise spread of tumour outwards from the primary site. Radical surgery to remove all tumour not only provides staging information, but also potentially cures the tumour. In contrast, the Cady *et al*[82] paradigm assumes systemic spread may occur early in tumour growth and that improved outcomes derive from delivery of the optimum adjuvant treatment as determined by accurate staging. The Halsted radical mastectomy has been consigned to surgical history, but it is unclear if principles gleaned from breast cancer can be extrapolated to colorectal cancer.

Indirect evidence for a therapeutic effect has been inferred from studies looking at lymph node counts. The Intergroup Trial INT-0089 showed 5-year overall survival increased from 51% to 71% for N2 disease if > 35 lymph nodes were harvested compared to < 35[83]. Given this was N2 disease, better staging and stage migration cannot entirely explain the results which showed superior survival to that of published trials using optimal adjuvant chemotherapy, implying a curative component. Other explanations are possi-

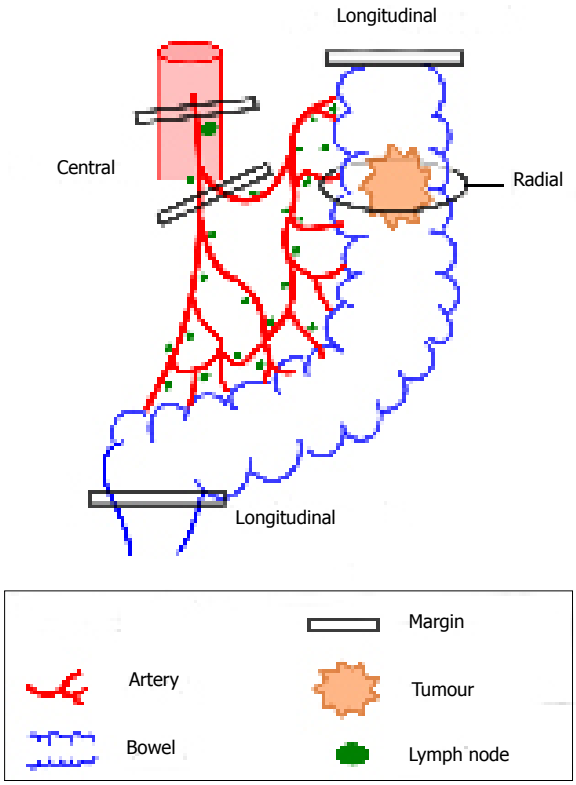

Figure 2 Anatomical extent of surgery. Schematic representation of the 3 anatomical boundaries of colorectal surgery.

ble, *e.g.,* high lymph node counts representing good host inflammatory response, but it is likely that lymphadenectomy is both prognostic and therapeutic, particularly in the rectum where total mesorectal excision (TME) achieves simultaneous local control and lymphadenectomy, with both components inherently inseparable. It is no surprise that when more mesenteric tissue is removed, LNH also increases. In theory, this leads to more accurate staging and potential therapeutic removal of involved lymph nodes. However, for many of the surgical techniques described below, the highest levels of evidence are lacking. It is therefore unclear whether the benefits of removing more tissue outweigh the increased operating time and potential morbidity associated with these procedures. A detailed review of surgical practice is beyond the scope of this review, but salient issues are considered below and readers are directed to other surgical guidelines[84-87].

What is adequate surgery?

Margins can be thought of as extending to 3 anatomical boundaries (Figure 2). Firstly, the longitudinal margin as determined by the axial extent of the bowel excised. Secondly, the extent of mesenteric tissue excised, in a centripetal direction towards the root of the supplying artery. Thirdly, radial margins, in the broadest sense, which may include *en bloc* excision of advanced local spread, *e.g.,* the abdominal wall or adjacent organs, but also encompasses the circumferential margin, or more accurately, the non-peritonealised margin. Frequently, these three margins cannot be manipulated independently of each other, but as a general rule, increasing the first two margins also increases lymph node yields.

Longitudinal margins

Typically, the segment of bowel containing the tumour is excised along with the mesentery delineated by its arterial supply. For colonic tumours, at least 5 cm of longitudinal clearance is advised to minimise anastomotic recurrence[88,89]. In the rectum, 5 cm proximal and 2 cm distal appears sufficient[90]. The Japanese Society for Cancer of the Colon and Rectum guidelines recommend at least 5 cm in the direction of lymph flow and 10 cm in opposite direction[91]. In practice, it is the vascular supply that dictates the extent of surgery. If the tumour straddles two arterial branches, both segments should be excised. Anatomical and functional considerations may also extend resection beyond oncological requirements. For instance, in left-sided tumours, many surgeons avoid anastomoses with the sigmoid colon as it is regarded as a "high pressure" segment and also receives no contribution from the marginal artery.

The length of bowel resected may be extended in several scenarios on the basis that spread of tumour beyond normal segmental boundaries has been described, a finding partially borne out by intra-operative lymphatic mapping. Extended lymphadenectomy can be achieved by performing an extended right hemicolectomy for proximal right-sided tumours[92,93]. Extended right hemicolectomy is also common performed for transverse colon and splenic flexure tumours, although there are no randomised, controlled trials to support this. Similarly, for left-sided tumours, one of the few randomised controlled trials in this area showed no benefit of left hemicolectomy over segmental resection[94]. The type of surgery employed, particularly the length of specimen, has a clear influence on LNH, but without lymphatic mapping, is not clear when extended surgery should be performed.

Central margins and extra-mesenteric lymphadenectomy

Classically, colonic tumour spreads along lymphatics in the distribution of the arterial supply[92,95,96]. Depending on their anatomical distribution, lymph nodes in the colon are described as pericolic, intermediate and apical/central/main, broadly corresponding to D1, D2 and D3 in the Japanese notation[87]. Lymphadenectomy can be performed up to and flush with the level of the origin of the artery[97], so-called complete vascular ligation, one of the key components of complete mesocolic excision (see below). This manoeuvre takes the apical node which is involved in about 3%-11% of tumours[93,97,98]. In tumours of the sigmoid colon and upper rectum, high ligation of the inferior mesenteric artery has been advocated as oncologically superior. This was first promulgated by Moynihan in 1908[99] and the debate on its value has continued for more than a

century. Despite good results in several, mainly cohort studies, other studies have shown no benefit (see systematic reviews in[100-103]). No benefit was seen in sigmoid tumours in a multicentre randomised controlled trial[94]. The issue, however, has not entirely been laid to rest and a randomised controlled trial of high ligation in the context of laparoscopic surgery is on-going[104].

Routine excision or sampling of lymph nodes outside the typical lymph node basin has also been advocated. Tumours around the hepatic flexure may spread to infra-pyloric nodes[97]. In the rectosigmoid region, the arterial supply is variable and spread to lateral (extra-mesorectal) pelvic lymph nodes may occur[96]. One paper describes lateral pelvic node involvement in up to 18%, rising to 36% in the sub-group of Dukes' C tumours[105]. Proponents of radical lymphadenectomy argue it is oncologically superior, both in achieving better staging but also therapeutically by removing all diseased lymph nodes. However, all of the above additions and modifications to "standard" lymphadenectomy may result in additional morbidity, particularly damage to neighbouring structures.

Depending on the anatomical site, this includes the duodenum, ureters and nerve plexuses[106]. Vascular compromise may occur from direct vascular damage or *via* reduction in collateral flow[107]. As extra-mesenteric and apical lymph node involvement is present only in a minority of cases, routine extended dissection represents unnecessary surgery for most patients. A selective approach has been advocated[98], but patients with the highest rates of aberrant lymph node involvement are those with high T-stage, the same group where lymphadenectomy is least likely to be curative due to the increased risk of systemic disease. The benefit of these procedures is unproven and potential morbidity may outweigh the benefits[108,109].

Radial margins

TME has been established as the optimal surgical technique for rectal tumours. Pioneered by Heald, introduction of the technique reduces local recurrence[110,111]. The same anatomical and oncological principles have been extrapolated to colonic tumours, so-called complete mesocolic excision (CME)[112]. Although a relatively new concept in the West, CME shares many features with D3 excisions that have been performed routinely in East Asia[113,114]. It is associated with better LNHs[115]. However, while it is supported by some compelling oncological and anatomical concepts, it encompasses many of the unproven surgical elements discussed above. The technique may prove itself in the fullness of time, but there is presently insufficient evidence to support it[116,117]. Furthermore, the unsuccessful attempts by European surgeons to adopt D3 lymphadenectomy for gastric cancer is a salutary reminder of how challenging it is to "import" purportedly superior surgical techniques from established centres[118].

Type of surgery

Laparoscopic and laparoscopic-assisted surgery is increasingly the default surgical approach to colorectal cancer resection. Superior peri-operative recovery and oncological equivalence has been demonstrated by several randomised controlled trials, including no significant difference in lymph node counts[119]. Many of techniques described above can be achieved laparoscopically, *e.g.,* CME[120-126], although randomised controlled trials are difficult to undertake. Laparoscopic CME therefore still lacks a convincing body of supportive evidence. The data on robotic surgery are promising[127], but at present only includes a single randomised-controlled trial.

INTRA-OPERATIVE PROCEDURES

A number of procedures can be performed intra-operatively to assist in lymph node staging. As previously discussed, lymphatic mapping entails injecting a tracer at the tumour site, which travels along lymphatics and facilitates identification of lymph nodes[24], including the sentinel lymph node. SLNs can be excised intra-operatively and for immediate results, can be subject to frozen section histological examination or OSNA[128]. Other technologies that provide immediate intra-operative results are the subject of on-going research, *e.g.,* optical coherence tomography and real time elastography[129].

Outside these techniques, the default histological analysis is performed on sections cut after formalin-fixation and paraffin embedding of the SLN. The results are therefore not available to influence immediate operative management. The exception is where the lymphatic mapping process identifies tracer in "aberrant" lymph node territory. The surgeon can choose to sample the abnormal lymph nodes or perform more radical lymphadenectomy. In 2 studies, *in vivo* lymphatic mapping changed the procedure in 9% and 22% of cases respectively[129,130]. In the latter study, nodal positivity was higher in patients undergoing a change of procedure.

THE INFLUENCE OF PATIENT AND TUMOUR CHARACTERSTICS

Patient

Several patient characteristics have been identified that influence LNHs[131]. However, factors identified in some studies are not corroborated by others. Fewer lymph nodes are generally obtained from specimens from older patients[132-134]. Gender seems to have no effect, while low counts have an inconsistent association with obesity, as measured by body mass index[135,136].

Tumour characteristics

Several histological characteristics of the primary

tumour have been shown to be associated with an increased risk of LNM. One meta-analysis identified 42 different factors. Only 15 were reported in 2 or more studies and not all are routinely analysed during standard reporting procedures[137]. Factors that are easily assessed during routine histological reporting include tumour site[133,134,138], stage[133] and differentiation. Higher counts are seen in tumours with microsatellite instability[139]. While not an exhaustive list, many of these features lack reproducibility, sensitivity and/or specificity. It is therefore uncertain whether any single feature in isolation is reliable enough to influence decisions on adjuvant treatment. Neoadjuvant chemotherapy and/or radiotherapy typically reduces the numbers of nodes sampled[133,140].

Predictive factors in submucosal (pT1) tumours are of particular interest as these are typically resected endoscopically and may require segmental resection for lymphadenectomy. Adverse factors in this group include poor tumour differentiation, depth of invasion and lymphovascular invasion[37-40]. If sentinel lymph node biopsy techniques can be refined, this would greatly aid decision-making in this group on whether additional surgery is appropriate.

LYMPH NODE YIELDS AS A MEASURE OF QUALITY

Many of the surgical and histopathological techniques discussed are based on the presumption that increased lymph node yields invariably leads to more accurate stage. This assumption warrants critical appraisal. Many organizations such as the American Society of Clinical Oncology, the National Comprehensive Cancer Network and the United Kingdom Royal College of Pathologists have guidance stipulating a minimum lymph node yield of 12 lymph nodes per case. The choice of 12 was proposed in 1990 by the Working Party Report to the World Congress of Gastroenterology in Sydney[141], partly supported by subsequent studies, but has a poor evidence base.

Others have suggested alternative minimum numbers depending on the T-stage of tumour[142], with more numbers required for low T-stage disease. While it has been clearly demonstrated in numerous studies that prognosis improves with the number of lymph nodes sampled[143-146], this association does not prove causation. Furthermore, the association of lymph node counts and survival applies even in node-negative disease[147] which lends support to the alternative explanation that high lymph node yields are a surrogate marker of a vigorous host immune response to tumour. Conversely, low lymph node counts are associated with a worse survival and may, in itself, be an indication for adjuvant treatment. Much of the existing evidence is based on studies where LNs were harvested without recourse to special techniques and it is unclear if the same survival associations apply when additional or special techniques "inflate" the number of lymph nodes sampled. Not all studies have demonstrated a beneficial effect of higher lymph node yields[148]. Yet others have observed a trend of increased lymph node yields over several years, most likely reflecting better surgical and histopathological practice, but without a corresponding increase in the detection rate of LNM[149,150]. Similarly, the use of special techniques fares no better[151]. At the risk of repetition, we need to clearly distinguish the principle of association from causality. Increased lymph node yields show an association with survival, but do not cause it. Various techniques may increase the lymph node count, but may not change the underlying nature of the disease. It is established that lymph node yields are multifactorial, influenced by a combination of patient, tumour, surgical and pathological factors[131,152].

Clearly, there must be minimum standards in both surgical and histopathological practice. Surgery that fails to remove enough mesentery for staging and a cursory, hurried dissection by a pathologist, sampling only a handful of lymph nodes are likely, in combination, to lead to under-staging. However, for the majority of practitioners, the message about the importance of achieving accurate lymph node staging has been heard and implemented. Audit of LNHs is good practice, but the unthinking pursuit of ever higher lymph node yields should be resisted. In particular, it is unreasonable to link lymph node yields with quality payments, particularly when it is established that many factors influencing lymph node yields are outside the control of both surgeon and pathologist.

CONCLUSION

The importance of colorectal cancer lymph node staging cannot be over-emphasised. We have discussed many of the controversies associated with this challenging area and provided guidance about the rational application of additional techniques. TNM7 has not been universally adopted internationally[22], but publication of TNM8 is anticipated in this year. The authors anticipate that this will address some of the issues and lead to a consensus approach. The variable contribution of surgical, pathological, patient and tumour related factors means that this remains a contentious subject. This complex area continues to evolve with new developments, surgically and pathologically, providing novel methods to evaluate nodal disease.

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REVIEW

Relevance of fecal calprotectin and lactoferrin in the post-operative management of inflammatory bowel diseases

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Abstract

The role of fecal lactoferrin and calprotectin has been extensively studied in many areas of inflammatory bowel disease (IBD) patients' management. The post-operative setting in both Crohn's disease (CD) and ulcerative colitis (UC) patients has been less investigated although few promising results come from small, cross-sectional studies. Therefore, the current post-operative management still requires endoscopy 6-12 mo after intestinal resection for CD in order to exclude endoscopic recurrence and plan the therapeutic strategy. In patients who underwent restorative proctocolectomy, endoscopy is required whenever symptoms includes the possibility of pouchitis. There is emerging evidence that fecal calprotectin and lactoferrin are useful surrogate markers of inflammation in the post-operative setting, they correlate with the presence and severity of endoscopic recurrence according to Rutgeerts' score and possibly predict the subsequent clinical recurrence and response to therapy in CD patients. Similarly, fecal markers show a good correlation with the presence of pouchitis, as confirmed by endoscopy in operated UC patients. Fecal calprotectin seems to be able to predict the short-term development of pouchitis in asymptomatic patients and to vary according to response to medical treatment. The possibility of both fecal markers to used in the routine clinical practice for monitoring IBD patients in the post-operative setting should be confirmed in multicentric clinical trial with large sample set. An algorithm that can predict the optimal use and timing of fecal markers testing, the effective need and timing of endoscopy and the cost-effectiveness of these as a strategy of care would be of great interest.

Key words: Calprotectin; Lactoferrin; Fecal markers; Inflammatory bowel disease; Post-operative; Surgery; Crohn's disease; Ulcerative colitis

Core tip: Inflammatory bowel diseases (IBDs) are chronic conditions, requiring life-long therapy and monitoring. Surgery is not curative and the disease

might recur after operation as post-operative recurrence in Crohn's disease patients and pouchitis in ulcerative colitis patients. In both cases, endoscopy with histology is the gold standard procedure to assess disease activity. Non-invasive markers of intestinal inflammation, such as fecal calprotectin and lactoferrin, might be useful in the post-operative management of IBD patients, in order to identify individuals requiring endoscopy, so that they can avoid unnecessary invasive investigations. This paper reviews the current knowledge on the use of fecal markers in this specific setting.

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INTRODUCTION

Inflammatory bowel disease (IBD) is chronic, relapsing-remitting inflammatory conditions of the gastrointestinal tract. Both Crohn's disease (CD) and ulcerative colitis (UC) might require surgical intervention for different indications. Operated patients, both CD and UC patients, need to be followed-up regularly, because the risk of post-operative recurrence (CD patients) and of pouchitis (UC patients) is very common. However, the post-operative management is not clearly defined, in terms of needs of medications and timing of clinical, biochemical and endoscopic follow-up. Therefore, patients often undergo several invasive procedures to re-assess disease activity and exclude complications.

The role of non-invasive markers has been extensively studied in the diagnosis, management and monitoring of IBD patients. In particular, fecal markers, calprotectin (FC) and lactoferrin (FL), represent intestinal infiltration by leukocytes and correlate with the severity of endoscopic and histological intestinal inflammation[1,2].

Calprotectin is a calcium- and zinc-binding protein of neutrophils, that is released in case of activation or apoptosis/necrosis[3]. It displays several physiological roles in inflammatory and infectious processes and has anti-proliferative capability. The long stability of FC at room temperature (up to 7 d) is an advantage for its use in clinical practice. Lactoferrin is an iron-binding glycoprotein of neutrophils that, after degranulation, regulates their margination and diapedesis through the intestinal wall in case of inflammation[4]. Unlike calprotectin, its stability at room temperature is guaranteed only for 2 d.

More recently, a meta-analysis confirmed the usefulness of C-reactive protein (CRP) and FC in excluding IBD in patients with symptoms of irritable bowel syndrome[5]. Another meta-analysis showed that CRP, FC, and FL might aid in the triage of IBD patients for endoscopic evaluation when they are symptomatic[6]. Currently, FC and FL do not replace endoscopy with histology, however this might become the future approach.

Still now, due to limited studies on the efficacies of FC and FL as non-invasive biomarkers, no consistent conclusion was made about their use in post-operative management of IBD patients. In this context, we aimed to review the efficacy of FC and FL from the available studies for use of FC and FL as non-invasive diagnostic markers of inflammation in post-operative CD and UC.

CD

CD is a chronic progressive destructive, disabling disease, clinically characterized by relapsing-remitting behavior. Even during periods of clinical remission the disease progresses, leading to structural and irreversible bowel damage in the majority of patients[7]. In the natural history of CD, intestinal resection is often required to treat strictures, fistula, or abscesses. Historical population-based studies reported that, overall, the cumulative risk for surgery 10 years after diagnosis is around 40%-55%[8]. There are emerging data suggesting that the early use of immune-modulators and biologics might delay disease progression and thus the timing of first surgical intervention. In an Australian population-based registry, authors observed indeed a fall in surgery rates (the one and 5 year resection rates were 13% and 23%, respectively)[9]. Similarly, a Hungarian population based study showed that reduction of surgery rates was independently associated with early introduction of immune-modulators[10].

Although, surgery is not curative and the disease often recurs in many cases (in the neoterminal ileum or in the ileo-colonic anastomosis), that leads to progressive loss of intestinal function and disability. Post-operative recurrence can be clinical, endoscopic, radiological or surgical. The reported incidence rates of post-operative recurrence depend on the definition used, the time of observation and the study design. Unfortunately, the available epidemiological data are heterogeneous and difficult to interpret. Buisson *et al*[11] summarized the data coming from randomized controlled trials; referral centers studies and population-based studies. Clinical recurrence was higher in population-based studies and referral center studies, reaching 61% at 10 years. Data about endoscopic recurrence at one year derived mainly from referral center studies (rates ranging from 48% to 93%) and randomized controlled trials (rates ranging from 35% to 85%). However, the definition of endoscopic post-operative recurrence was heterogeneous.

The established risk factors for post-operative recurrence are smoking, prior intestinal resection, fistulizing behavior, perianal disease and extensive disease (> 50 cm)[11]. It is fundamental to identify high-risk patients and offer efficient treatment in order to maintain remission. However, the most appropriate therapeutic approach has still to be established. At present, the only universally accepted preventive measure for post-

operative recurrence is to quit smoking[12,13].

Landmark studies by Rutgeerts *et al*[14,15] demonstrated that the post-operative clinical course of CD is predicted by the severity of endoscopic lesions during the first year after surgery. The presence of severe endoscopic lesions (Rutgeerts' score ⩾ i2) gives a high risk of early clinical relapse and complications[14], but this can be observed already 6 mo after curative resection[16].

As mentioned, detection of post-operative recurrence is mainly based on endoscopic appearance. Therefore, patients soon after surgery are expected to undergo endoscopy and repeat several evaluations, which timing is still need to be determined.

Fecal markers might be the most realistic alternative to ileocolonoscopy; their reliability as markers of intestinal inflammation has been proved in different settings and they are entering routine management. However, data about their use in the post-operative setting are poor.

Clinical and biochemical recurrence

The correlation between fecal markers and clinical and serological activity is controversial also in the post-operative setting.

We observed in 63 operated CD patients that levels of both FL and FC remained high after a median follow-up of 40.5 mo even in case of clinical remission, suggesting the persistence of subclinical inflammation[17]. However, episodes of clinical flares predicted higher levels of FL. Only FL significantly correlated with CRP, showing a potential also as a maker of systemic inflammation. We investigated the correlation between FL levels and systemic inflammation in other 36 CD patients in clinical remission after ileo-colonic resection[18], and demonstrated a significant correlation with IL-6 and CRP and an inverse correlation with albumin and serum iron. A major limitation of both studies was the absence of endoscopic evaluation to confirm endoscopic recurrence and its correlation with fecal markers.

Lamb *et al*[19] followed-up a small cohort of 13 CD patients for one year after surgery with regular FC and FL measurements. In case of early normalization of these biomarkers (within two months), a subsequent two-fold increase in the upper limit of FC and FL correlated with a relapse. Both markers demonstrated better performance than CRP. The authors studied also a second post-operative cohort of 104 patients in a cross-sectional study. In this study, both FC and FL correlated significantly with the Harvey Bradshaw Index (HBI) of clinical activity; in particular, severely active patients (HBI ⩾ 6) had higher levels of fecal markers (more than twice the upper normal limit). However, surprisingly there was no significant difference between the FC and FL values in those with endoscopic post-operative recurrence (25 patients out of 43 patients who underwent endoscopic assessment) and those without.

Yamamoto *et al*[20] prospectively investigated the relationship between the severity of endoscopic inflammation and fecal markers in 20 CD patients in remission during 6-12 mo after ileocolic resection. All patients underwent ileocolonoscopy at study entry and were then followed for 12 mo. Both fecal markers were significantly higher in patients (30%) who developed clinical recurrence. A cutoff value of 170 μg/g for FC had 83% sensitivity and 93% specificity to predict a risk of clinical recurrence within 12 mo from the baseline endoscopy, while a cutoff value of 140 μg/g for FL had a sensitivity of 67% and a specificity of 71%.

Endoscopic recurrence

The correlation of fecal markers with the presence of endoscopic recurrence should be the major endpoint in studies evaluating their role in post-operative recurrence. Orlando *et al*[21] observed that amongst 50 CD patients who underwent intestinal resection a FC level > 200 mg/L had 63% sensitivity and 75% specificity to diagnose endoscopic post-operative recurrence one year after the operation.

In the study performed by Yamamoto *et al*[20] both FC and FL correlated with the presence of endoscopic post-operative recurrence according to Rutgeerts' score. On the contrary, laboratory measurements (white blood cell count, platelet count and CRP level) did not significantly correlate with the endoscopic score.

A recent study performed in Sweden did not confirm the promising results of fecal markers in the post-operative setting proposed by the earlier studies[22]. Authors evaluated the correlation between FC and the endoscopic findings one year after ileo-caecal resection in 30 CD patients; they observed that the median FC values did not significantly differ between patients in endoscopic remission or recurrence. However, most patients with low values were in remission and all patients with FC > 600 μg/g had recurrence. The collection of the stool sample for FC measurement after colonoscopy might influence FC levels. This happened for only six patients, who collected the sample 1-4 wk after the endoscopy, and might not be sufficient to explain the absence of statistically significant difference between the groups of patients. Furthermore, the longitudinal part of the study, in which stool samples were delivered monthly until ileocolonoscopy, showed an important variability in FC concentrations. According to these findings, a single measurement of calprotectin might not be significant in the decision making process, and this was already demonstrated in the follow-up of patients undergoing anti-TNF treatment[23].

Recently, results from the Post-Operative Crohn's Endoscopic Recurrence (POCER) Trial became available[24] and data about the role of FC in monitoring and detecting post-operative recurrence were extracted[25]. It is a prospective, randomized, controlled, multicenter trial, which evaluated a therapeutic strategy based on risk stratification of patients, with treatment step-up in case of recurrence detected at ileocolonoscopy, performed at

6 and 18 mo after surgery[26]. This trial clarified that an active strategy based on the postoperative endoscopic monitoring, together with treatment intensification for early recurrence, is more effective (at least in the short term) than standard drug therapy alone and waiting for clinical recurrence. The surgically induced and verified remission (after resection of the macroscopically involved intestine) is an ideal starting point for the use of a noninvasive marker to monitor for recurrent inflammation. In the POCER trial FC concentration was increased markedly before surgery and decreased substantially after resection of all macroscopic diseased segments at 6 mo. Combined 6- and 18-mo FC levels correlated significantly with endoscopic recurrence, whereas CRP and CDAI did not. A cutoff of FC > 100 mg/g detected patients with endoscopic recurrence with 89% sensitivity and 58% specificity; the negative predictive value (NPV) was 91%. In this cohort, colonoscopy could be avoided in 47% of cases without endoscopic recurrence, but at the cost of missing 11% of patients with endoscopic recurrence. FC could be useful also in treatment monitoring, since it decreased in patients who underwent treatment intensification. A FC level of < 51 μg/g in patients in remission at 6 mo after surgery predicted maintenance of remission at 18 mo, with NPV 79%; sensitivity, specificity and PPV in this particular situation were less satisfying (50%, 68% and 36%, respectively), therefore the FC measurement remains of modest value in predicting long term future endoscopic recurrences.

Rapid test

Usually fecal markers are determined through the conventional ELISA method, that is effective, but time-consuming. A new rapid test for FC (FC-QPOCT) has been evaluated for the prediction of endoscopic remission in 115 CD patients[27]. Twenty nine out of these patients were previously resected and endoscopic activity was scored according to the Rutgeerts' score. Median FC-QPOCT levels were able to discriminate between patients with and without endoscopic post-operative recurrence (98 μg/g *vs* 234.5 μg/g, respectively; $P = 0.012$). There was no significant difference in FC levels between the different degrees of the Rutgeerts' score. The accuracy of FC-QPOCT in predicting post-operative recurrence presented an AUC of 71.53. A 283 μg/g cut-off value had 67% sensitivity and 72% specificity (similar results were obtained with the ELISA method). However, accuracy was lower than that obtained in non-resected patients (AUC 0.933). Neither clinical activity nor serological biomarkers had a significant correlation with post-operative recurrence.

The validation of rapid fecal tests could be of further utility in the out-patient management of operated patients, avoiding the waiting time of laboratory reports.

Taken these results together, serial measurement of FC at regular intervals in the postoperative period might be the best way to predict future endoscopic behavior[25,28].

It has been proposed that an algorithm combining FC and colonoscopy, based on the stratification of patients according to the risk of permanent bowel dysfunction, could be a cost-effective strategy to detect asymptomatic recurrence[28]. This approach need further validation in larger, prospective trials, but might be a cost-effective strategy for the management of operated CD patients.

Results of the major studies in CD patients are reported in Table 1.

UC

The clinical course of UC may range from prolonged periods of remission to acute severe colitis requiring intensive medical treatment. Emergency colectomies are required in case of life-threatening complications of colitis in hospitalized patients unresponsive to medical treatment. Elective colectomy is indicated for refractory disease, intolerance to medical treatment and colonic neoplasia.

Surgery rates at 10 years from diagnosis are approximately 10%[29,30], showing a decline over the years for elective colectomies (probably due to immunemodulators)[31]; in contrast, emergent colectomy rates remain stable. Extensive colitis at diagnosis is proposed as a risk factor for colectomy in several studies across different cohorts of patients[29,30].

Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the procedure of choice for most patients with UC requiring colectomy. Pouchitis is a nonspecific inflammation of the ileal reservoir and the most common complication of IPAA in patients with UC[32,33]. The incidence of a first episode of pouchitis depends on the duration of follow up, occurring in up to 45% of patients 10 years after surgery[34,35]. Pouchitis recurs in more than 50% patients and up to 10% of patients develop chronic pouchitis; refractory pouchitis is rare[33]. Increased bowel movements, urgency, and abdominal pain in patients with IPAA may be caused by different inflammatory conditions (pouchitis, cuffitis, or CD) or non-inflammatory conditions (irritable pouch syndrome). The diagnosis of pouchitis requires therefore endoscopic confirmation with mucosal biopsies[36,37]. The Pouchitis Disease Activity Index (PDAI) was developed to standardize diagnostic criteria and assess the severity of pouchitis, combining symptoms, endoscopy and histology[36]; a total PDAI score $\geqslant 7$ is diagnostic for pouchitis. Patients with suspected pouchitis need endoscopy for a proper diagnosis. The use of fecal markers for the detection of pouch inflammation might avoid the repetition of such invasive investigation[38].

The literature on fecal markers in the post-operative setting in UC patients is quite scarce. Furthermore, the majority of studies was conducted on small samples of patients and have a cross-sectional design, which do not permit to clarify the evolution over time of the disease and the consensual behavior of the fecal markers. However, these studies form the basis of evidence that FC and FL are useful as inflammatory markers also in

Table 1 Studies evaluating fecal calprotectin and lactoferrin in operated Crohn's disease patients

Ref.	FC/FL	Method	No. of patients	Aim	Best cut-off	Sens %	Spec %	Main findings
Scarpa *et al*[17]	FC and FL	ELISA	63 (22 endoscopy)	Role as marker of intestinal inflammation after ileocolonic resection	/	/	/	High FC and FL levels at long-term follow-up after resection even in case of clinical remission Correlation between FL and CRP Higher levels of FL in case of clinical recurrence
Ruffolo *et al*[18]	FL	ELISA (IBD-scan)	36	Correlation with systemic inflammation and prognostic value in terms of need of surgery for recurrence	/	/	/	FL as expression of subclinical intestinal inflammation (through IL6-CRP cascade)
Lamb *et al*[19]	FC and FL	ELISA (PhiCal) ELISA (IBD-Scan)	13 (prospective cohort) 104 (cross-sectional cohort; 43 endoscopy)	Evaluation of the course of FL and FC after ileocaecal resection. Identification of postoperative recurrence; Correlation between FC and FL	/	/	/	Prospective cohort: Normalization of fecal markers by 2 mo after surgery in uncomplicated patients Cross-sectional cohort: Significant correlation between FC and FL Significant correlation of fecal markers with HBI No significant difference between the FC and FL values in those with endoscopic recurrence and those without
Yamamoto *et al*[20]	FC and FL	ELISA (Cell Science) and Colloidal Gold Agglutination reagent (Auto Lf-Plus, respectively)	20	Evaluation of the relationship between endoscopic activity and FC/FL Assessment of Fc and FL predictive value for future clinical recurrence	FC 170 mg/g FL 140 mg/g (for prediction of clinical relapse)	83 67	93 71	Significant correlation between FC and FL Correlation with endoscopic activity Ability to predict clinical post-operative recurrence
Orlando *et al*[21]	FC	ELISA	50 (39 endoscopy)	Evaluation of the one year postsurgical endoscopic recurrence	200 mg/L	63	75	FC > 200 mg can be an indication to colonoscopy in patients with negative ultrasound in order to detect early recurrence
Lasson *et al*[22]	FC	ELISA (Buhlmann)	30	Correlation of FC with the endoscopic findings one year after ileocaecal resection Evaluation of the variation of FC in individual patients during 6 mo prior to the ileocolonoscopy	/	/	/	No difference in the concentrations of FC between patients in endoscopic remission and patients with recurrence one year after ileocaecal resection Significant variability of FC concentrations over time
Wright *et al*[25]	FC	ELISA (fCAL, Buhlmann)	135 (319 fecal samples)	To assess whether monitoring FC can substitute endoscopy and be used as surrogate marker of recurrent post-operative disease	100 μg/g	89	58	FC correlated with the presence of recurrent disease at endoscopy and with endoscopic severity FC has sufficient sensitivity and negative predictive values to monitor for recurrence FC can be used to monitor response to treatment after detection of recurrence FC has better diagnostic performance than CRP and clinical index of activity
Lobaton *et al*[27]	FC	ELISA (Buhlmann) FC-QPOCT (Quantum Blue)	115 (29 resected)	To evaluate the performance of a new rapid test for FC in predicting endoscopic remission (in both operated and non-operated CD patients)	283 μg/g	67	72	Significant correlation between ELISA and rapid test FC was able to discriminate between the presence or absence of endoscopic recurrence, but not distinguish different levels of severity

CD: Crohn's disease; CRP: C-reactive protein; ELISA: Enzyme-linked immunoassay; FC: Fecal calprotectin; FL: Fecal lactoferrin; HBI: Harvey Bradshaw Index; Sens: Sensitivity; Spec: Specificity.

the post-operative setting.

In 24 patients with ileo-anal pouch (both UC patients and with familial adenomatous polyposis) FC showed a strong association with pouchitis (P = 0.0002), and correlated with the severity of inflammation detected at endoscopy and histology in the 9 patients having pouchitis[39]. A cut-off of 92.5 μg/g feces in 54 patients who underwent restorative proctocolectomy (46 UC patients and 8 with familial adenomatous polyposis coli) reached 90% sensitivity and 76.5% specificity in diagnosing pouchitis[40]. No difference was found in symptom scores of patients with FC concentrations above or below 50 μg/g (P = 0.155), confirming that the clinical presentation is aspecific.

Thirty-two patients with pediatric-onset of UC who underwent proctocolectomy with IPAA were enrolled in a cross-sectional study to assess whether FC was related to pouchitis[41]. Patients with recurrent pouchitis had significantly higher FC levels (832 ± 422 μg/g) followed by those with a single episode (290 ± 131 μg/g) and those with no history of pouchitis (71 ± 50 μg/g) (P = 0.019). FC levels correlated also with the amount of neutrophilic infiltration of the distal ileum at histology. The cross-sectional design of the study and the small sample size are of course important limits of the study.

Also FL showed satisfactory results in detecting pouch inflammation (due to either pouchitis, cuffitis or CD). In 60 patients with IPAA, a cut-off of 13 μg/mL could distinguish irritable pouch syndrome from pouchitis, cuffitis, or CD, with 97% sensitivity and 92% specificity[42]. FL levels correlated with the PDAI score (correlation coefficient 0.73; P < 0.001), especially with the endoscopic subscore. Although the cut-off level of 13 μg/mL showed the best combination of specificity and sensitivity, authors recommended a cutoff level of 7 μg/mL to decrease the possibility of false negative results. In case of higher levels, pouch endoscopy with biopsy is necessary to distinguish among different causes of inflammation. Lim *et al*[43] achieved similar results in 2008, evaluating the levels of FL in 32 patients with IPAA, showing 100% sensitivity and 86% specificity in diagnosing pouchitis, according to PDAI.

We evaluated the interplay between the ileal-pouch microbiota and several inflammatory parameters in the pathogenesis of pouchitis in 32 consecutive patients[44]. Although it was not the primary aim of the study, we observed that FL correlated with the presence of mucosal ulcers, neutrophils and monocytes infiltration and the histologic diagnosis of pouchitis, confirming the ability of the fecal marker in detecting mucosal inflammation.

Recently, Yamamoto *et al*[45] conducted a longitudinal study to assess the utility of sequential dosage of FC and FL for the early diagnosis and prediction of pouchitis after restorative proctocolectomy for UC. Sixty patients were followed up (with clinical and biochemical assessments) every 2 mo for one year after the ileostomy closure. In case of symptoms suggestive of pouchitis, endoscopic examination was immediately undertaken; otherwise, asymptomatic patients performed endoscopy at one year. Between 4 and 10 mo before the diagnosis of pouchitis (10 patients, 17%), the median FC and FL levels remained low and stable. However, these levels significantly increased 2 mo before the diagnosis of pouchitis, although patients were asymptomatic. In contrast, in 50 patients without pouchitis fecal levels did not change. In particular, a cut-off value of 56 μg/g for FC had a NPV of 100% and a diagnostic accuracy of 87% to predict pouchitis; a cut-off value of 50 μg/g for FL had a NPV of 98% and a diagnostic accuracy of 88% to predict pouchitis. Again, there was no significant correlation between the clinical subscore of PDAI and fecal biomarkers (FC: r = 0.230, P = 0.08 and FL: r = 0.163, P = 0.21); on the contrary, both fecal markers correlated with the endoscopic and histological subscores. In patients with pouchitis who responded to antibiotics (8/10) median FC levels dropped from 106 to 34 μg/g and FL levels from 89 to 31 μg/g; in non-responders the levels of these fecal biomarkers increased, suggesting their usefulness for evaluating the efficacy of medical treatment and possibly for the early detection of pouch inflammation without repeating endoscopy.

In summary, fecal proteins demonstrated the potential to monitor intestinal inflammation in UC patients after proctocolectomy with IPAA. The early detection of subclinical inflammation with serial measurements of fecal markers might facilitate pre-emptive treatments in asymptomatic patients. Prospective studies need to confirm the cost-effectiveness of such strategy, especially evaluating the reduction of rates of chronic pouchitis and pouch failures[46].

Results of the major studies in UC patients are reported in Table 2.

CONCLUSION

The role of fecal markers in the post-operative management of IBD patients seems promising. Preliminary data in CD patients came from small studies, sometimes relying only on clinical activity, without endoscopic confirmation of recurrence, and produced inconsistent data. More recently, studies have revealed the potential use of fecal markers, especially FC, in the post-operative management of CD, for the diagnosis of post-operative recurrence and possibly for monitoring the response to therapy. In UC patients, studies, although heterogeneous, have more consistently showed the correlation between fecal markers and the presence of inflammation of the pouch. Furthermore, there are no data showing that the early diagnosis of post-operative recurrence in CD patients and of pouchitis in UC patients might alter the long term outcome. The evidence of the reliability of FC and FL as markers of inflammation in the post-operative setting in both CD and UC should be strengthened in larger, longitudinal, multicentric studies, addressing the aim to refine an algorithm that stratifies the use and the optimal timing of fecal markers testing

Table 2 Studies evaluating fecal calprotectin and lactoferrin in operated ulcerative colitis patients

Ref.	FC/FL	Method	No. of patients (No. of patients with inflammation of the pouch) and type of disease	Aim	Best cut-off	Sens %	Spec %	Main findings
Thomas *et al*[39]	FC	ELISA	24 (9) UC and familial polyposis coli	Comparison between single and 24-h stool collections in patients with and without pouchitis (endoscopic, histologic and immunohistochemical indeces)	/	/	/	Mean first morning stool concentration correlated with 24-h collection Levels of FC were significantly higher in patients with pouchitis Correlation with % of mature granulocytes and activated macrophages
Johnson *et al*[40]	FC	ELISA (PhiCal)	54 (20) UC and familial polyposis coli	Differentiation between inflamed and noninflamed pouches Correlation with inflammation severity	92.5 μg/g	90%	76.50%	FC levels significantly higher in pouchitis (> 50 μg/g had higher endoscopic and histological scores) Correlation with endoscopic score (r = 0.605) and histological score (r = 0.708)
Pakarinen *et al*[41]	FC	ELISA (PhiCal)	32 (22) UC	Cross-sectional assessment of FC after proctocolectomy for pediatric onset UC	300 μg/g (for detection of recurrent pouchitis)	57%	92%	Higher levels of FC in patients with recurrent pouchitis, followed by those with a single episode and those without (832, 290, 71 μg/g respectively, P = 0.019) Correlation with neutrophilic infiltration and overall inflammatory activity in the distal ileum
Parsi *et al*[42]	FL	In-house test	60 (30) UC	Evaluate the usefulness of FL in symptomatic patients with IPAA	13 μg/mL	97%	92%	Higher levels in patients with inflammation of the pouch Not able to distinguish between pouchitis, cuffitis and CD Not able to distinguish between asymptomatic patients and those with irritable pouch syndrome Correlation with PDAI (better for endoscopic subscore)
Lim *et al*[43]	FL	Rapid immuno-chromatographic test	32 (11) Healthy controls and pouchitis patients	Diagnostic yield for pouchitis	/	100%	86%	Sensitive method for the non-invasive diagnosis of pouchitis
Scarpa *et al*[44]	FL	ELISA (IBD-scan)	32 UC	Evaluate the relationship between ileal-pouch microbiota and inflammatory parameters	/	/	/	Correlation with histological inflammation Correlation with mucosal ulcers, mucosal immune infiltration Inverse correlation with *Eubacteriaceae spp.*, *Burkholderiaceae spp* and *Moraxellaceae spp.* counts
Yamamoto *et al*[45]	FC FL	ELISA (Cell Science) and Colloidal Gold Agglutinantion reagent (Auto Lf-Plus, respectively)	60 (10) UC	Evaluate the significance of consecutive monitoring of fecal markers for early diagnosis and prediction of pouchitis	56 μg/g 50 μg/g	100% 90%	84% 86%	Elevation of FC and FL already 2 mo before the diagnosis of pouchitis Correlation with PDAI score (correlation with endoscopic and histological subscores, but not with the clinical subscore) Correlation with response to therapy

CD: Crohn's disease; CRP: C-reactive protein; ELISA: Enzyme-linked immunoassay; FC: Fecal calprotectin; FL: Fecal lactoferrin; PDAI: Pouch disease activity index; Sens: Sensitivity; Spec: Specificity; UC: Ulcerative colitis.

and the effective need of colonoscopy. This should be based on patients-tailored approach, in order to

improve the cost-effectiveness of several postoperative fecal testing and examine the ability of such a strategy to prevent both clinical relapse and subsequent surgical resections in CD patients and the early identification with prompt treatment of pouchitis in UC patients.

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REVIEW

Current perspectives on pancreatic serous cystic neoplasms: Diagnosis, management and beyond

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Abstract

Pancreatic cystic neoplasms have been increasingly recognized recently. Comprising about 16% of all resected pancreatic cystic neoplasms, serous cystic neoplasms are uncommon benign lesions that are usually asymptomatic and found incidentally. Despite overall low risk of malignancy, these pancreatic cysts still generate anxiety, leading to intensive medical investigations with considerable financial cost to health care systems. This review discusses the general background of serous cystic neoplasms, including epidemiology and clinical characteristics, and provides an updated overview of diagnostic approaches based on clinical features, relevant imaging studies and new findings that are being discovered pertaining to diagnostic evaluation. We also concisely discuss and propose management strategies for better quality of life.

Key words: Pancreatic cystic neoplasm; Serous cystic neoplasm; Diagnosis; Management strategy; Surgery

Core tip: Pancreatic cystic neoplasms (PCNs) have been more frequently recognized clinically in recent years and serous cystic neoplasms (SCNs) account for a large proportion of all PCN cases. Recent reviews have paid much attention to general aspects of PCNs and have discussed various subtypes of PCNs, but there is still a lack of comprehensive review exclusively focused on SCNs. This review attempts to provide a concise overview and outlook of pancreatic SCN and propose management strategies.

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INTRODUCTION

Pancreatic cystic neoplasms (PCNs) are increasingly being recognized incidentally with widespread use of advanced imaging techniques, including computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS). According to the most recent WHO classification[1], PCNs comprise serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs) and solid pseudopapillary neoplasms (SPENs). SCNs account for nearly 16% of surgically resected PCNs and > 30% of all clinically diagnosed PCNs[2-4], hence, they have become of concern and have posed a challenge to primary care clinicians and general practitioners. Not surprisingly, SCNs harbor some already known epidemiological characteristics. SCNs largely affect women (approximately 75% of all cases), and the mean age of patients who underwent pancreatic surgery for SCNs was 56 years in Europe, 58 years in Asia and 62 years in the United States[5,6]. SCNs tend to be larger if they occur in male patients[4]. In contrast with other premalignant or malignant PCNs (MCNs, IPMNs and SPENs), SCNs are usually benign, and the malignant variant serous cystadenocarcinoma is rare. To date, only approximately 30 cases of serous cystadenocarcinoma are reported in the literature[7]. Therefore, correct diagnosis is needed to avoid unnecessary surgical interventions and exclude other malignancies.

Morphologically, SCNs can be divided into four subtypes: Microcystic, macrocystic or oligocystic (< 10% of cases), mixed form (micro-macrocystic) and a solid variant form[8]. SCNs may arise in any part of the pancreas and occasionally can spread throughout the organ. The majority of SCNs are the microcystic lesions, which occur predominantly in the body and tail of the pancreas, whereas the oligocystic lesions normally arise from the head of the pancreas[9,10]. When multiple lesions are identified, Von Hippel-Lindau (VHL)-disease-associated pancreatic cysts should be taken into consideration[11]. VHL disease is a genetic disease, driven by mutation of the VHL tumor suppressor gene located on chromosome 3, which leads to development of several tumors, primarily hemangioblastoma of the central nervous system, retinal hemangioblastoma, renal cell carcinoma, adrenal pheochromocytoma and pancreatic tumors, mainly represented by pancreatic endocrine tumors and cystic tumors[12]. It is reported that SCNs are involved in 2.7%-9.5% of patients with VHL disease[13].

Histologically, SCN cystic walls are lined with cubic flat epithelia consisting of glycogen-rich, watery-fluid-producing cells[14] (Figure 1). The cytoplasm is either clear or eosinophilic and the nuclei are normally centrally located, small and hyperchromatic; mitoses are not commonly found[15]. Although some controversy still exists, it is widely accepted that SCNs originate from the centroanicar cells[16]. They normally express cytokeratins AE1/AE3, CAM 5.2, CK7, CK8, CK18 and CK19, epithelial membrane antigen, α-inhibin, and mucin 6[16,17].

CLINICAL PRESENTATION AND DIAGNOSIS OF SCN

According to a study led by Tseng *et al*[4], approximately 47% of patients with SCN were asymptomatic and diagnosed incidentally. As for symptoms, they are not specific and often attributed to mass effects or to infiltration of adjacent structures. Abdominal pain (25%), palpable mass (10%) and jaundice (7%) are the main clinical manifestations. It also has been shown that when lesions are > 4 cm, symptoms do occur more frequently if compared to lesions < 4 cm (72% *vs* 22%, $P < 0.001$)[4], which is in line with several studies reported elsewhere[18,19]. A more recent multinational study of 2622 cases of SCN revealed that patients could present with nonspecific abdominal pain (27%), pancreaticobiliary symptoms (9%), diabetes mellitus (5%), or other symptoms (4%), with the remaining patients being asymptomatic (61%)[20].

Given that SCNs are usually benign and asymptomatic, better surveillance and management strategies for these cysts call for accurate preoperative diagnosis. CT, MRI and EUS are three most commonly used imaging techniques for revealing SCNs. A recent study stated that the accuracy of preoperative diagnosis of PCN remains low, reaching approximately 60%, and in light of the exact diagnosis by pathology, surgical resection, most of which were Whipple resections, should not have been performed in approximately 8% of patients[21]. In another study cohort, 9% of PCN patients underwent pancreatic resection for a non-neoplastic condition[22], which further demonstrated the difficulty in differentiation between benign and premalignant lesions and that better preoperative diagnosis is urgently needed. Pancreatic cysts are readily identified in up to 20% of MRI studies, and 3% of CT scans[23,24]. Both CT and MRI predict the presence of malignancy in pancreatic cysts with 73%-79% accuracy[25]. In addition to routine radiological studies, EUS has emerged as a useful tool because it provides high-resolution imaging of the pancreas through the lumen of the stomach or duodenum and helps obtain detailed information of the cystic lesions, such as wall, margins, internal structures and parenchyma[26,27]. In a recent prospective cross-sectional study of the prevalence of incidental pancreatic cysts during routine outpatient EUS, the prevalence of incidental pancreatic cyst was 9.4% and most were < 1 cm[28]. The accuracy of EUS to differentiate benign from malignant neoplastic tumors and from non-neoplastic

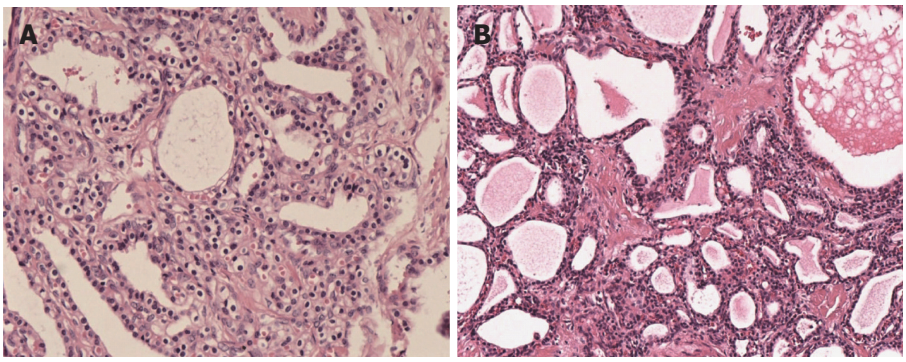

Figure 1 Pathological examinations revealing that serous cystic neoplasm cystic walls are lined with cubic flat epithelia consisting of glycogen-rich, watery-fluid-producing cells (hematoxylin and eosin × 100). A: Pathology of a microcystic SCN of the pancreas; B: Pathology of a macrocystic SCN of the pancreas. SCN: Serous cystic neoplasm.

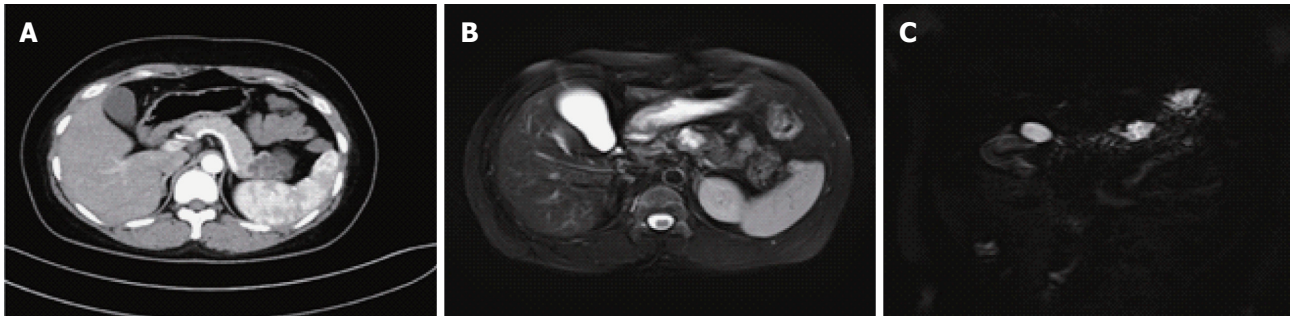

Figure 2 Microcystic pancreatic serous cystic neoplasm presentation on computed tomography/magnetic resonance imaging. A: A microcystic pancreatic SCN lesion was revealed in the tail of the pancreas; B: MRI showed a microcystic lesion in the body of pancreas; C: A microcystic SCN lesion was revealed by magnetic resonance cholangiopancreatography. Images B and C came from the same patient. SCN: Serous cystic neoplasm; MRI: Magnetic resonance imaging.

cysts remains debatable. Some studies have stated an accuracy of > 90%, while others have expressed doubt, especially when there is a lack of evidence of a solid mass or invasive tumor[29-31]. Despite this debate, another major advantage of EUS is its ability to collect fluid from cystic lesions *via* fine-needle aspiration (FNA) for cytological and biochemical analysis, such as carcinoembryonic antigen (CEA), amylase, and *KRAS* mutations[32].

Compared to other cystic neoplasms, accurate preoperative diagnosis of SCNs seems more feasible. As mentioned before, SCNs can be divided into four subtypes: Microcystic, macrocystic or oligocystic (< 10% of cases), mixed form (micro-macrocystic) and solid variant form[8]. VHL-disease-associated pancreatic cysts should be considered when other cystic lesions exist. A Japanese multicenter study of 172 SCNs diagnosed by resection and typical imaging findings noted highest diagnostic accuracy for microcystic SCN (85%), with lower diagnostic rates (17%-50%) for macrocystic and mixed types. CT alone is approximately 23% accurate at diagnosing SCN[33]. Diffusion-weighted MRI has proved to be a powerful tool with 100% sensitivity and 97% specificity for differentiating mucinous cysts from SCNs[34]. The pathognomonic central scar, which is formed by central coalescence of the septa and commonly contains foci of calcification on imaging, is present in only approximately 30% of these cysts[35].

On CT/MRI, microcystic SCN typically appears as an isolated, lobulated, well-marginated, multilocular lesion, comprising a cluster of multiple (usually > 6) small cysts separated by a thin septum[26,36] (Figure 2). Each of the small cysts is usually < 2 cm[37]. Occasionally, the "honeycomb" pattern, characterized by numerous, subcentimeter cysts appears as a solid mass on CT (Figure 3), but has high signal intensity when T2-weighted MRI is applied[37]. Macrocystic SCN is characterized by a limited number of cysts, usually < 6, showing a diameter > 2 cm, or even one single cyst[38] (Figure 4). This subtype can be seen in approximately 10% of all cases of SCN but poses difficulty for differentiating it from MCN and branch-duct (BD)-IPMN, based on the findings of CT or MRI[39]. In addition, if a patient has a reported history of pancreatitis, pseudocyst should be considered[40]. The mixed micro-macrocystic type is depicted as a combination of the above two types of lesions. As for the solid variant, it consists of small cysts separated by multiple, thick fibrous septa[41]. VHL-disease-associated pancreatic cysts, which can occur in 50%-80% of the patients with VHL disease, and are occasionally misdiagnosed as macrocystic SCNs, tend to form multiple lesions and are even diffuse throughout the pancreas[42,43].

Generally, microcystic SCNs on EUS are imaged as numerous (> 6) small (< 1-2 cm) fluid-filled cysts with

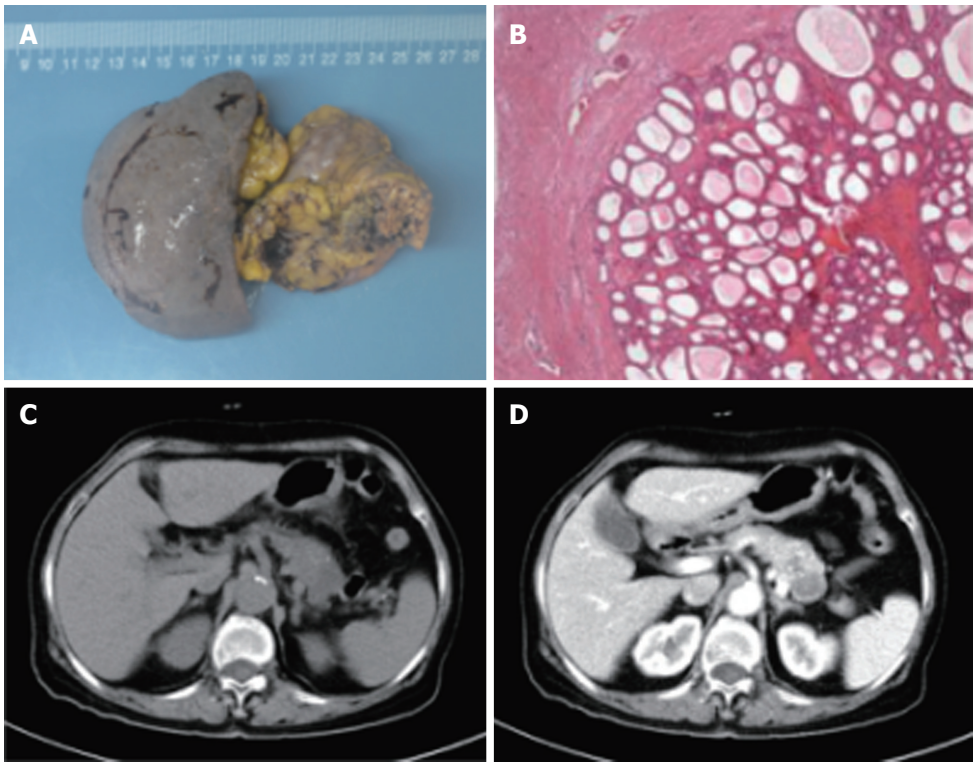

Figure 3 Solid variant microcystic serous cystic neoplasm with honeycomb characteristics. A: Gross pathology of a solid variant microcystic SCN; B: Histology of solid variant microcystic SCN; C: Solid variant lesion was detected by CT; D: Solid variant lesion was detected by contrast-enhanced CT. These four images were acquired from the same patient. SCN: Serous cystic neoplasm; CT: Computed tomography.

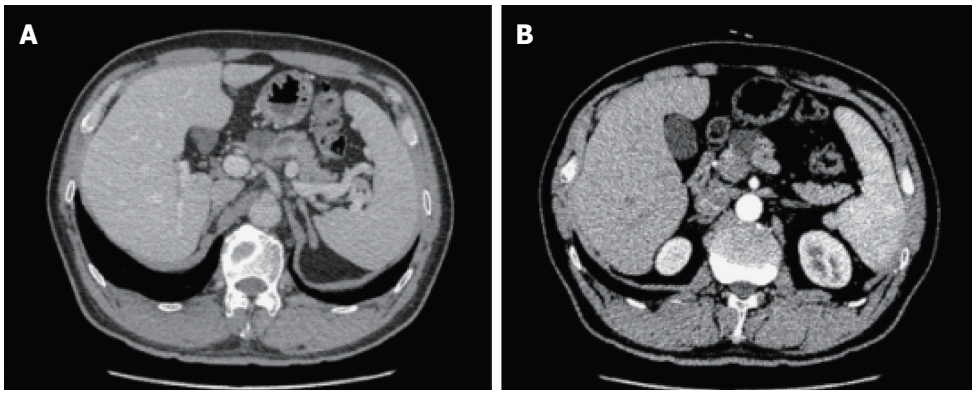

Figure 4 A macrocystic pancreatic serous cystic neoplasm was detected on computed tomography with (B) and without enhancement (A).

thin-walled septa and possibly calcification of the central septum[44,45] (Figure 5). The honeycomb variants are interspersed within dense fibrous septa, with or without central fibrosis or calcification[46,47]. The less common oligocystic SCNs usually contain larger (> 2 cm) cysts[48]. However, the solid variant, which is defined when lesions are predominantly solid (< 10% cystic portion) and might resemble a ductal carcinoma on CT, contains numerous tiny cysts (1-2 mm) and appears as a hypoechoic mass on EUS[49].

Management and surveillance of SCNs depend on correct preoperative diagnosis. One major concern is potential misdiagnosis of a malignancy or premalignancy as a benign SCN, which was more frequent in the past; it was reported in seven of 28 patients in one study and in two of 49 patients in another[50,51]. Among SCNs, macrocystic SCNs are frequently undistinguishable from MCNs and BD-IPMNs. BD-IPMNs may also present in a polycystic pattern, similar to microcystic SCNs[52]. Typically, unlike IPMNs, SCNs are characterized by lack of communication with the main pancreatic duct. However, the absence of communication does not allow for the exclusion of IPMN, although this absence may favor the diagnosis of MCN over SCN[53,54]. In contrast to MCNs, which usually exhibit a smooth oval shape and varied signal intensity (depending on the fluid viscosity of each lobule), macrocystic SCNs typically present with a thin wall and lobulated contours and can be

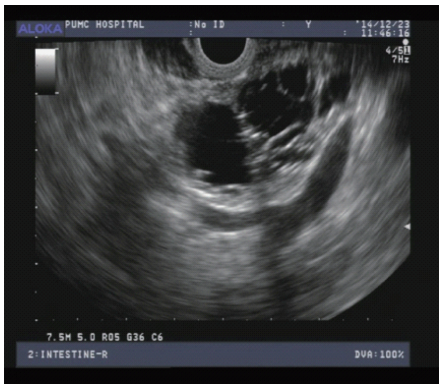

Figure 5 A microcystic pancreatic serous cystic neoplasm was discovered by endoscopic ultrasonography.

found in the head of the pancreas[55]. A central calcified scar is virtually pathognomonic for SCNs (Figure 6), whereas peripheral calcifications are frequently observed in MCNs[56]. Many solid variant SCNs show arterial hypervascularity on imaging studies and are frequently misdiagnosed as pancreatic neuroendocrine tumors (pNETs)[57-59]. A recent study found that the frequency of hypervascular solid-appearing SCNs was 7.3% among surgically confirmed SCNs and unenhanced CT and MR features can help to differentiate solid variant SCNs from pNETs[60].

Despite various potential complications of EUS-FNA, such as bleeding caused by injury of the subepithelial vascular plexus of SCNs, pancreatitis, infection, and even the seeding of malignant cells along the tract of the needle have been suggested[61-63], EUS-FNA-related morbidity and mortality rates have remained low[64] and the widespread use of EUS-FNA has yielded a wealth of information for cytological, chemical and molecular analysis of SCNs.

A 22- or 25-gauge needle is often used when aspirating cyst fluid during EUS-FNA. SCNs usually contain little fluid and the fluid usually contains few cellular components, and FNA cytological analysis has an unreliable sensitivity of only 30%-40%[65]. For chemical analysis, assessment of tumor markers such as CEA, carbohydrate antigen (CA)19-9, CA15-3, CA72-4, and enzymes like amylase and lipase is often carried out, although it has proved of limited diagnostic value[66]. Fluid from SCNs universally has low CEA levels. A level < 5 ng/mL is 95% specific for SCN, pseudocyst or pNET[67]. However, an elevated CEA level favors a mucinous lesion, although the exact cut-off level is still in debate. It is also important to mention that the CEA threshold varies in different centers, ranging from 5 ng/mL to > 100 ng/mL[68]. When a classic CEA cut-off level of 192 ng/mL is applied, it yields 73% sensitivity and 84% specificity for mucinous cysts[69]. An amylase level < 250 U/L favors diagnosis of SCN over pseudocyst, with a sensitivity of 44%, specificity of 98% and overall accuracy of 65%[68]. Other than CEA and amylase, recent studies have revealed that levels of cystic fluid metabolites glucose and kynurenine are markedly elevated in SCNs compared to MCNs, which aids the diagnosis of SCNs[70,71]. Although large prospective studies are warranted to validate these promising results, they shed light on a new path to seek better biomarkers. Molecular analysis of cystic fluid has gained in interest in recent years, in parallel with the advent of new techniques on sequencing. DNA analysis of KRAS mutations may help identify mucinous cysts with 54% sensitivity and 100% specificity, as demonstrated in a study containing 142 surgically resected cysts. When CEA and KRAS analysis were collectively applied, the sensitivity climbed to 83% while the specificity dropped to 85%[72]. More interestingly, data from whole-exome sequencing of PCNs revealed that the application of a panel of five genes (*VHL*, *RNF43*, *KRAS*, *GNAS* and *CTNNB1*) allowed correct distinction of mucinous from nonmucinous cysts. All eight SCNs had intragenic mutations of VHL or loss of heterozygosity in or adjacent to VHL and did not contain mutations of the other four genes. Furthermore, point mutations of *VHL* gene were detected in cystic fluid analysis in half of the SCNs. Nevertheless, IPMNs had alterations of RNF43, GNAS or KRAS and never had *VHL* or *CTNNB1* mutations. MCNs always harbored KRAS or RNF43 mutations but never contained *GNAS*, *CTNNB1* or *VHL* mutations[73]. Another study stated that GNAS mutations were present in 10% of their cases of SCN, which was still significantly lower than in IPMNs[74]. Thereafter, the identification of GNAS mutation may help discrimination of SCN from IPMN. Another mainstay of research of cystic molecular analysis gives insights into miRNAs. A panel of four miRNAs comprised miR-31-5p, miR-483-5p, miR-99a-5p and miR-375 has been developed to differentiate SCNs accurately from mucinous lesions, with 90% sensitivity and 100% specificity[75]. While promising, these results were based on surgically archived specimens but not on cystic fluid, therefore, validation in cystic fluid samples should be addressed in future studies to fit these findings better in preoperative scenarios.

MANAGEMENT AND INTERVENTION STRATEGY FOR SCNs

As mentioned before, most SCNs follow a benign course and malignant SCNs (serous cystadenocarcinoma) are rare (< 1% of all cases). According to an investigation of 193 SCNs, along with a literature review, the clinicopathological characteristics of solid and macrocystic SCN variants are similar to those of their microcystic counterpart, and there are no deaths that are directly attributable to dissemination/malignant behavior of SCNs[76]. It is also recommended to consider and manage SCNs as benign neoplasms initially[77]. For this reason, correct preoperative diagnosis of SCNs could spare many unnecessary interventions and guide optimal management strategies. Currently, there

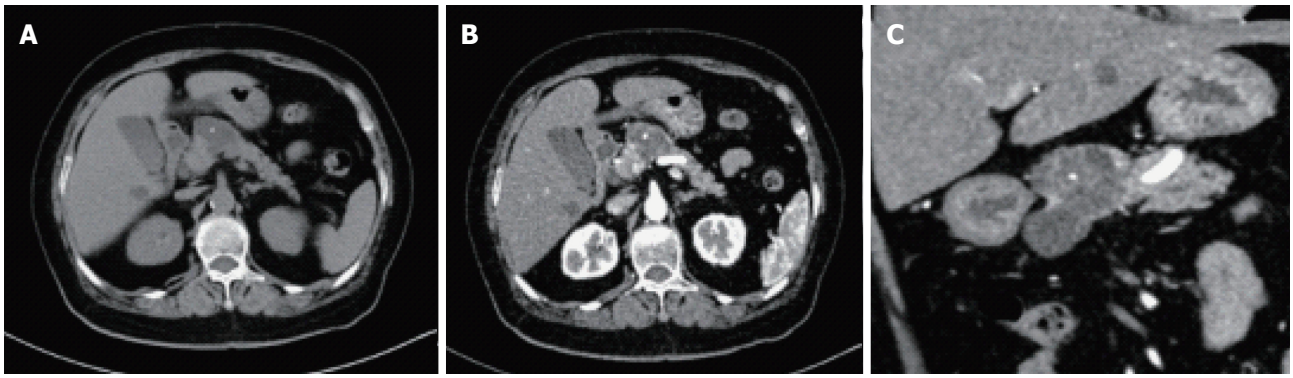

Figure 6 Central calcifications were found by computed tomography with and without enhancement (A and B), and also shown after three dimensional reconstruction (C).

is no universal consensus on the best management strategy, but it is widely accepted that not every single case should be surgically resected, regardless of how advanced surgical technology has been developed, and symptomatic, local invasive or potential malignant SCNs should be resected[37,54,78]. It is also advised that resection should be considered for large (> 4 cm), rapidly growing SCNs, given that such SCNs are more likely to cause symptoms[4,33]. However, it is difficult for a clinician to predict whether and when an incidentally found asymptomatic SCN will grow to cause symptoms. One older study claimed that a more rapid growth rate of approximately 1.98 cm/year was observed in cysts > 4 cm, whereas the growth rate was approximately 0.12 cm/year in cysts < 4 cm[4]. A more recent multicenter study failed to confirm those results. In that same study, a rate of growth of 6.2% per year or a doubling time of 12 years was calculated for the nonresected SCNs, while resected SCNs grew faster (17% per year for a doubling time of 4.5 years)[18]. In addition, there is also a paucity of knowledge about the relationship between growth rate and potential malignancy[7]. Obviously, symptoms do occur when fast-growing SCNs are left unresected[79]. It is tempting to conclude that initial size is neither associated with malignant transformation, nor proportionally related to developing symptoms. However, growth rate is more powerful to predict if and when the symptoms occur. Thus, the growth rate should be weighed when considering if an SCN should be subjected to surgical intervention. One multinational study stated that, in patients followed beyond 1 year (*n* = 1271), size increased in 37% (growth rate: 4 mm/year), was stable in 57%, and decreased in 6%, hence, surgical treatment should be proposed only in cases in which diagnosis remains uncertain after complete work-up[20].

Surgery is considered curative. Despite increasing experience and advanced surgical techniques, pancreatic surgery holds a perioperative morbidity of 15%-30% and a mortality rate of 1%-2%, even in high-volume centers[3]. The indications for surgical intervention are as follows: (1) presence of symptoms; (2) Uncertain diagnosis. MCNs and IPMNs can mimic SCNs on radiology scans, especially macrocytic SCNs. When premalignant MCNs and IPMNs cannot be excluded, the lesions can be managed as IPMNs when the cysts are < 4 cm[80] and are advised to be surgically removed accordingly following the International consensus in 2012 and the European consensus in 2013[81,82]; and (3) growth rate of the neoplasm. As discussed above, large SCNs are not correlated with an increased risk of malignancy. Also, growth rate is not linked with initial size. The notion that any cyst > 4 cm or even > 5 cm be resected should be abandoned. In this regard, clinicians need to remain cautious when neoplasms grow rapidly, and make decisions on a case-by-case basis, including patient's age, comorbidity and tumor location. Large SCNs can always be closely observed first and then sent for surgery once they grow faster and cause unrelieved symptoms.

From an anatomical point of view, surgical resection of an SCN largely depends on the location of the lesion. As a result of the benign nature of SCN, as a general rule, it is recommended that pancreatic functions are protected and preserved as much as possible for better outcome and quality of life. If SCNs are localized in the pancreatic head, pylorus-preserving pancreatoduodenectomy or Begar procedure is often carried out. If SCNs are located in the body or tail of the pancreas, spleen-preserving distal pancreatectomy should be the first choice. For patients whose SCNs are located in the neck of the pancreas, central segmental pancreatectomy is an alternative procedure, preserving islet cell mass and reducing the risk of iatrogenic insulin-dependent diabetes. Enucleation is not recommended because greater morbidity (up to 35%) and associated complications such as pancreatic fistula[83] have been reported.

As mentioned above, clinicians are encouraged to manage SCNs in a conservative manner, which means that, initially, these lesions do not require surgery but serial follow-up when radiological diagnosis is certain and symptoms are absent. However, to date, the best follow-up strategy has not been standardized. Some advocate follow-up imaging every 12 mo, while others suggest biennial surveillance[84,85]. The European con-

sensus in 2013 suggests that asymptomatic nonresected patients should enter a follow-up program, initially repeated after 3-6 mo, and then individualized depending on growth rate[81]. Once SCNs are resected, no further surveillance imaging is needed.

CONCLUSION AND FUTURE DIRECTIONS

Comprising about 16% of all resected PCNs, SCNs are uncommon benign lesions that are asymptomatic and found incidentally. Despite overall low risk of malignancy, the presence of these pancreatic cysts still generates anxiety, leading to extensive medical investigation with considerable financial cost to health care systems. CT and MRI alone are not powerful enough to characterize cystic pancreatic lesions fully, and more specifically, to differentiate macrocystic SCNs from MCNs. However, EUS, with or without addition of FNA, adds more diagnostic value to conventional imaging techniques. CEA, although not perfect, plays a role in differentiating pancreatic cystic lesions. New cystic fluid markers from chemical and molecular analyses are just beginning to emerge, paving a new way to future research. As for treatment and management strategy, surgery should be limited only to symptomatic SCNs and lesions that show aggressive behavior, while the majority of patients should be strictly monitored and followed up by serial imaging. Further investigations on best follow-up strategy are warranted. Patients would benefit from multidisciplinary management and receive precise medical advice once gastroenterology, surgery, pathology and radiology are all involved in individual patient care as a team. As such, patient care based on a multidisciplinary team is encouraged if applicable.

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MINIREVIEWS

Duodenal adenocarcinoma: Advances in diagnosis and surgical management

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Abstract

Duodenal adenocarcinoma is a rare but aggressive malignancy. Given its rarity, previous studies have traditionally combined duodenal adenocarcinoma (DA) with either other periampullary cancers or small bowel adenocarcinomas, limiting the available data to guide treatment decisions. Nevertheless, management primarily involves complete surgical resection when technically feasible. Surgery may require pancreaticoduodenectomy or segmental duodenal resection; either are acceptable options as long as negative margins are achievable and an adequate lymphadenectomy can be performed. Adjuvant chemotherapy and radiation are important components of multi-modality treatment for patients at high risk of recurrence. Further research would benefit from multi-institutional trials that do not combine DA with other periampullary or small bowel malignancies. The purpose of this article is to perform a comprehensive review of DA with special focus on the surgical management and principles.

Key words: Duodenal cancer; Duodenal adenocarcinoma; Periampullary; Whipple; Pancreaticoduodenectomy; Segmental resection; Small bowel

Core tip: Duodenal adenocarcinoma is a rare but aggressive malignancy. Complete surgical resection is recommended when technically feasible. Pancreaticoduodenectomy or segmental duodenal resection may be employed, depending on the tumor location, and either are acceptable options as long as negative margins and adequate lymphadenectomy can be achieved. Although specific data are limited, adjuvant chemotherapy and radiation should be considered for patients at high risk of recurrence.

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INTRODUCTION

Although the majority of small bowel adenocarcinomas arise in the duodenum, duodenal adenocarcinoma (DA) still represents less than 1% of all gastrointestinal cancers[1,2]. Not surprisingly, given the rarity of the disease, there is limited data to guide treatment decisions. Early studies grouped DA with other periampullary tumors (pancreatic, ampullary, distal bile duct) when discussing their management options. However, in general, DA has a more favorable outcome. For example, compared to some other periampullary malignancies, DA is more likely to be amenable to curative resection and has more favorable long term outcomes[3]. As a result, treatment strategies have tended to favor aggressive surgical resection. The purpose of this article is to provide a comprehensive review of the epidemiology, presentation, diagnosis, management and prognosis of DA with a special emphasis on surgical principles.

Epidemiology

Small bowel malignancies are relatively rare, accounting for only 2% of all gastrointestinal cancers in the United States[4]. Among small bowel tumors, most malignancies arise from the ileum, followed by the duodenum and lastly the jejunum. While most tumors of the ileum are neuroendocrine in origin, adenocarcinoma is the most common duodenal cancer[4-6]. One large population-based analysis found the duodenum to be the location of 55.7% of adenocarcinomas of the small bowel[5]. The majority of DA arise in the second portion of the duodenum, followed by D3/D4, with cancers of the first portion of the duodenum, especially the duodenal bulb, extremely rare[7,8].

The causative factors for DA have not been clearly identified. Dietary factors, such as increased intake of bread, pasta, sugar and red meat or reduced intake of fruits and vegetables, are risk factors for small bowel adenocarcinoma (SBA) as they are for colorectal cancer[9]. Ingestion of alcohol, coffee and use of tobacco also seem to be risk factors[10]. Nevertheless, the strength of these associations are small and the majority of cases of DA are not associated with any known causative agents. However, duodenal adenomas, such as those that occur in familial adenomatous polyposis (FAP) and Gardner syndrome, are associated with elevated risk of DA[11,12]. Similarly, patients with duodenal polyps are also at increased risk[13]. Although less investigated than in colon cancer, the adenoma-carcinoma sequence is still largely accepted in SBA as well[14,15].

CLINICAL PRESENTATION

Since patients do not typically present until tumors have grown to sufficient size to cause symptoms, the diagnosis of DA is difficult and often delayed. When symptoms do appear they are nonspecific and include abdominal pain, nausea, vomiting, fatigue, weakness, and weight loss. Anemia, gastrointestinal obstruction and jaundice are symptoms associated with advanced disease. Abdominal pain is the most common presenting symptom, associated with 56% of cases[16]. As a result of these delays in diagnosis, many cases of DA are not resectable at presentation due to local and distant invasion. Less often, patients undergoing screening programs may be found to have early DA or even adenoma with dysplasia before symptoms begin[17].

DIAGNOSIS

Imaging

Since early symptoms are typically vague, most patients initially undergo either esophagogastroduodenoscopy or cross sectional imaging. Endoscopy is the preferred diagnostic modality as it allows simultaneous visualization and biopsy. Evaluation by an experienced endoscopist is critical as examination of the entire duodenum is required. While lesions in the third or fourth portion of the duodenum can be technically challenging to view endoscopically, the use of extra-long fiber optic scopes may be helpful[18]. Lesions in the distal duodenum may be missed on initial endoscopic evaluation, resulting in further diagnostic delays. Careful attention to proximity of pertinent structures such as the ampulla of Vater should be given. Endoscopic ultrasound may be performed simultaneously to evaluate local extension or lymphadenopathy. In addition, it may facilitate tissue diagnosis when attempts at luminal biopsy are not successful. Upper gastrointestinal series with oral contrast may facilitate precise localization, evaluate for obstruction and rule out other causes of patients' symptoms. Contrast-enhanced computed tomography is important for assessing involvement of nearby structures, determining resectability and planning surgery. In cases without a confirmed diagnosis, sensitive but non-specific radiographic features suggestive of malignancy include an exophytic or intramural mass, central necrosis and ulceration[19]. While the role of conventional abdominal ultrasound is limited, especially for tumors < 2 cm in size, lesions appear as irregularly marginated hypoechoic masses[20].

Pathology

Diagnosis of DA requires a thorough histopathologic examination of tissue specimens. Adenocarcinoma of gastric, pancreas, distal bile duct and ampullary origin must be ruled out. The degree of associated dysplasia should be assessed. Among extra-ampullary DA, several distinct subtypes have been described: intestinal, gastric, pancreaticobiliary and indeterminate (Table 1)[21,22]. Interestingly, intestinal type DA has been associated with more favorable prognosis compared to other histological subtype[22-24]. Variable expression of the classic cytokeratin markers CK7 and CK20 have made them largely unhelpful in diagnosing DA[25,26]. However, CDX2, a sensitive marker for colorectal

Table 1 Histopathologic subtypes of duodenal adenocarcinoma

Phenotype	Histological characteristics	Histologically similar	Immunophenotype markers	Prognosis
Intestinal	Tubular/cribiforming glands lined by columnar neoplastic cells	Colonic adenocarcinoma	MUC2, CD10, CDX2	+
Gastric	Tubular/papillary proliferation with foveolar or pyloric-type differentiation	Gastric adenocarcinoma	MUC5AC, MUC6	-
Pancreaticobiliary	Simple glands of cuboidal/columnar cells with rounded pleomorphic nuclei; prominent desmoplastic stroma	Pancreatic and Extrahepatic bile duct adenocarcinoma	MUC1	-
Indeterminate	Poor differentiation	None	MUC1	-

Adapted from Ushiku *et al*[22].

Table 2 7th edition of the American Joint Committee on Cancer's staging system for small bowel adenocarcinoma

Primary tumor (T)	Regional lymph nodes (N)			Distant metastases (M)
Tx - Primary tumor cannot be assessed	Nx - Regional lymph nodes cannot be assessed			Mx - Distant metastases not assessed
Tis - Carcinoma *in situ*	N0 - No regional node metastasis			M0 - Distant metastases not present
T1a - Tumor invades lamina propria	N1 - Metastasis in 1-3 regional nodes			M1 - Distant metastases present
T1b - Tumor invades submucosa	N2 - Metastasis in 4 or more regional nodes			
T2 - Tumor invades muscularis propria			Stage grouping	
T3 - Tumor invades into the subserosa	Stage 0	Tis	N0	M0
	Stage I	T1-T2	N0	M0
T4 - Tumor perforates visceral peritoneum; or invades pancreas/bile duct	Stage IIA	T3	N0	M0
	Stage IIB	T4	N0	M0
	Stage IIIA	Any T	N1	M0
	Stage IIIB	Any T	N2	M0
	Stage IV	Any T	Any N	M1

carcinoma, is more often expressed in DA and SBA[25,27]. Expression of Her2 in DA has been inconsistently reported in the literature[25,28], perhaps because expression may be limited to gastric subtypes of DA[22]. Conversely, Overman *et al*[25] found EGFR and VEGF expression rates of 71% and 91%, respectively, in a large series of SBA which was primarily comprised of DA.

Staging

Staging of DA is based on the 7th edition of the American Joint Committee on Cancer's TNM staging system that was published in 2010 (Table 2)[29]. Accurate nodal staging depends on adequate lymphadenectomy at the time of surgery[30,31].

SURGICAL MANAGEMENT

Relevant anatomy

The duodenum is the first of portion of the small intestine and functions as a conduit between the stomach and the jejunum while regulating the emptying of gastric contents and enzymatically breaking down the chyme received from the stomach. The surgical management of duodenal cancers varies by the portion of the duodenum involved, and hence the basic anatomic divisions merit review. The first segment of the duodenum is suspended by the hepatoduodenal ligament, lies intraperitoneally, begins caudal to the pylorus and extends 5 cm to the duodenal flexure. Moving retroperitoneally, the second segment spans approximately 7.5 cm and is fixed to and curves around the head of the pancreas to travel medially at the level of L3. The transverse, or third, portion of the duodenum is 10 cm in length and lies anterior to the aorta and inferior vena cava but posterior to the superior mesenteric vein and artery. The ascending, or fourth, segment of the duodenum is approximately 2.5 cm in length and heads superior and laterally to become intraperitoneal again as it reaches the ligament of Treitz at the anatomical boundary of the duodenojejunal junction.

Surgical approach

Tumors located in the second portion of the duodenum typically require pancreaticoduodenectomy (PD) because of proximity to head of the pancreas, distal bile duct and ampulla of Vater. Conversely, tumors occurring in the first, third or fourth portion of the duodenum may be managed by either PD or segmental resection (SR). Some will argue that PD should be used for all DAs, regardless of location, to ensure wide margins and adequate regional lymphadenectomy. This opinion is based on the results of early series reporting few long-term survivors of SR[32-39]. Still others will argue for SR of tumors in either the very proximal or very distal duodenum provided that wide margins can be achieved[40-42] in order to avoid the morbidity of PD. Most studies that compared outcomes of two approaches found no statistically significant difference

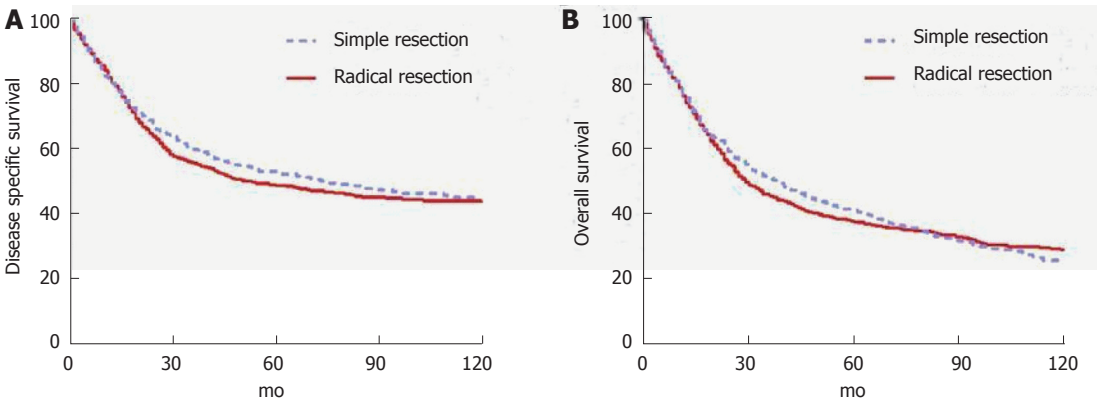

Figure 1 Outcomes of surgery for duodenal adenocarcinoma based on type of surgery. Used with permission: Cloyd *et al*[49].

in outcomes, but were limited by small sample sizes and retrospective design[13,42-48]. Cloyd *et al*[49] recently utilized the surveilance, epidemiology and end results database to retrospectively compare the outcomes of radical resection (defined as a resection of the primary duodenal tumor *en bloc* with an adjacent organ, as is performed in PD) *vs* SR across a population-based cohort of patients with DA. In this study of 1611 patients from 1988 to 2010, radical resection was associated with a greater number of LNs excised but not improved survival (Figure 1). Although PD may be required for technical reasons in some situations, the study suggests that SR is an appropriate strategy as long as negative margins can be obtained[49].

Regardless of the approach, an R0 resection remains the most important goal for surgery with curative attempt. Margin status directly impacts outcomes. Sohn *et al*[35] reported the Johns Hopkins experience and showed a 5 year OS of 58% in margin negative patients *vs* 0% in margin positive patients. Similarly, Poultsides *et al*[50] reviewed the Memorial Sloan Kettering Cancer Center (MSKCC) experience and found 5 year OS rates of 55% and 0% among R0 and R1 patients, respectively.

Lymphadenectomy

The importance of an adequate lymphadenectomy cannot be underscored. Sarela *et al*[51] were among the first to report improved prognostic abilities of the N staging system with higher number of lymph nodes retrieved. In fact, a greater lymph node retrieval has independently been associated with improved survival for patients with DA[2,31,49]. Although the American Joint Committee on Cancer has recommended a minimum pathologic evaluation of 6 lymph nodes, several authors have questioned whether this minimum number should be raised[50,52]. Intuitively, one might expect operations that enable a better lymphadenectomy, such as a classic PD *vs* a pylorus-preserving PD or PD *vs* SR, would therefore be associated with improved survival. However, this has not been found to be the case, either in randomized controlled trials[53] or population-based analyses[49]. Although the reasons behind why greater lymph node retrieval is associated with improved survival may be complex and multifactorial, it is likely primarily secondary to improved stage stratification and prognostication.

Palliative surgery

Among patients with localized DA, approximately 43%-87% will have resectable disease[54]. Of the remainder, some will require palliation. The goals of palliative surgery for DA may include relief of gastric outlet obstruction, relief of biliary obstruction and/or pain relief. Operative interventions for gastroduodenal obstruction may include gastrojejunostomy or duodeno-jejunostomy; either may be constructed in a roux-en-y or loop fashion. Minimally invasive approaches are possible in the correct context. Surgery for biliary obstruction typically involves a roux-en-y hepatico-jejunostomy. A 13-year prospective study from the United Kingdom examining surgery for DA found that of the 178 patients included in the study, 150 underwent surgery with curative intention and 28 underwent surgery for palliation. Of those who received palliation, 15 had a gastrojejunostomy, 9 had a double bypass and 4 underwent an exploratory laparotomy without further intervention. Median survival in the palliative surgery group was 8 mo. Not surprisingly, those who undergo palliative surgery are more likely to have a larger tumor, greater degree of invasiveness, as well as regional and distant metastases[55]. For patients who are not already undergoing surgical exploration and require palliation for enteral or biliary obstruction, endoscopically placed duodenal and biliary stents, when technically feasible, are preferable to avoid laparotomy given the limited prognosis.

Pancreas-preserving total duodenectomy

Although a comprehensive discussion is outside the scope of this review article, pancreas-preserving total duodenectomy (PPTD) has emerged as an alternative to PD or SR for patients with benign or pre-malignant conditions of the duodenum, most commonly in the setting of FAP. After total proctocolectomy, upper gastrointestinal cancers are the most common cause

Table 3 Series reporting factors associated with worse survival in duodenal adenocarcinoma

Ref.	Study period	Total No. of patients	No. of patients resected (%)	PD	5-year overall survival after resection (%)	Negative predictors of survival		
						Non-predictor	Univariate	Multivariate
Solaini *et al*[48]	2000-2013	178	150 (84.2)	132	43	T stage, grade, AJCC stage, perineural invasion, size, age	-	Lymphovascular invasion, nodal metastasis
Poultsides *et al*[50]	1984-2006	122	122 (100)	122	48	T stage, tumor grade	Tumor grade, positive margins, perineural invasion, nodal metastasis, vascular invasion	Nodal metastasis
Onkendi *et al*[79]	1994-2009	124	99 (79.8)	70	37	Tumor size, positive nodes, surgical approach, adjuvant therapy	-	T stage and pathologic grade
Cecchini *et al*[80]	1982-2010	169	103 (60.9)	87	42	T stage, nodal metastasis, grade, AJCC stage, lymphovascular invasion, size, age	-	Perineural invasion
Liang *et al*[77]	1993-2010	36	36 (100)	31	NA	T stage, grade, AJCC stage, lymphovascular invasion, perineural invasion, size	Age > 75, body weight loss, nodal metastasis	Nodal metastasis
Malleo *et al*[73]	2000-2009	37	25 (67)	25	71[1]	T stage, nodal metastasis, AJCC stage, lymphovascular invasion, perineural invasion, size, age	-	Tumor grade, lack of post-operative complications
Zhang *et al*[16]	1995-2008	91	59 (65)	NA	49[1]	T stage, grade, AJCC stage, lymphovascular invasion, perineural invasion, size, age	-	Nodal metastasis, positive margins
Han *et al*[81]	1990-2006	32	28 (88)	18	30	-	Positive margins	-
Struck *et al*[78]	1989-2006	30	30 (100)	25	33[2]	Positive margins, T stage, adjuvant therapy		Nodal metastasis, stage
Lee *et al*[74]	1995-2007	53	28 (53)	26	44	Age, gender, weight loss, CA19-9, grade, tumor size	T stage, nodal metastasis, AJCC stage	Nodal metastasis
Hurtuk *et al*[82]	1984-2005	52	35 (67)	24	NA	Grade, positive margins, nodal metastasis, venous or perineural invasion	Stage T4, tumor size < 3.5 cm	-
Hu *et al*[47]	NA	43	28 (65)	11	27	-	Positive margins	-
Sarela *et al*[51]	1983-2000	137	72 (52.5)	56	71[1]	Gender, grade, T stage	Age, nodal metastasis	Age, nodal metastasis
Tocchi *et al*[13]	1980-2000	47	25 (53)	9	23	T stage, grade, AJCC stage, lymphovascular invasion, perineural invasion, positive margins, size, age	-	Nodal metastasis
Ryder *et al*[83]	1957-1998	49	31 (63)	27	43	Nodal metastases, location in duodenum, type of resection, adjuvant chemoradiation	-	Tumor size, histologic grade, transmural invasion
Kaklamanos *et al*[43]	1978-1998	63	37 (59)	26	30	Age, gender, grade, T stage	Nodal metastasis	Nodal metastasis
Bakaeen *et al*[44]	1976-1996	101	68 (67)	50	54	Histologic grade, tumor size, location in duodenum, adjuvant chemoradiation	Age, weight loss, T stage, nodal metastasis, AJCC stage	Weight loss, positive margins, nodal metastasis, AJCC stage
Sohn *et al*[35]	1984-1996	55	48 (87)	35	53	Nodal metastasis, adjuvant chemoradiation, tumor size, histologic grade	Positive margins, segmental resection, tumor in third/fourth portion of duodenum	-
Sexe *et al*[76]	1987-1991	85	34 (40)	31	23	AJCC Stage	-	-
Rotman *et al*[84]	1978-1988	66	46 (70)	38	45	Gender, age, weight loss, jaundice, T stage, tumor size, pancreatic invasion nodal metastasis, location of metastatic nodes	-	-
Delcore *et al*[85]	1960-1990	35	28 (80)	21	60	-	GI bleeding, symptomatic > 4 mo, nodal metastasis	-
Barnes *et al*[40]	1967-1991	67	36 (54)	27	54	Nodal metastasis	Stage	

Lowell *et al*[42]	1970-1991	17	17 (100)	8	45	-	First/second portion of the duodeum	-
Ouriel *et al*[33]	1950-1981	65	19 (29)	1	30	-	Histologic grade, nodal metastasis	-

Values in parentheses are percentages. [1]R0 resection only; [2]Three-year survival. PD: Pancreaticoduodenectomy; AJCC: American Joint Committee on Cancer; NA: Not available.

of death in patients with FAP[56]. Intense screening programs utilizing duodenoscopy with endoscopic polypectomy have proven effective in reducing the incidence of DA in this high risk population[57]. In patients with diffuse polyposis or Spigelman stage Ⅳ disease, however, prophylactic duodenectomy may be indicated[56,58,59]. Several techniques of PPTD have been described[60-63] including minimally invasive options[64]. Despite the advantages of organ preservation, short term morbidity and mortality rates remain high[65]. It is important to note that invasive carcinoma in FAP patients should be treated similarly to sporadic DA with either PD or SR (as described above) in order to ensure adequate margins and lymphadenectomy. Pylorus-preserving PD should be avoided in patients with FAP as the residual duodenal bulb remains at risk for new polyp and carcinoma formation[66].

ADJUVANT THERAPY

Chemotherapy

Unfortunately, little data is currently available to inform the choice of adjuvant chemotherapy following complete surgical resection. The ESPAC-3 trial was a phase 3, multi-institutional, randomized controlled trial comparing observation *vs* adjuvant fluorouracil *vs* adjuvant gemcitabine in patients with periampullary cancers (ampullary, bile duct, duodenal or other) who underwent PD with R0 or R1 resection status. Although median survival was not significantly different between the observation and adjuvant therapy groups in the primary analysis (35 mo *vs* 43 mo), adjuvant chemotherapy was associated with improved OS after multivariable regression (HR = 0.75, 95%CI: 0.57-0.98)[67]. Importantly, periampullary DA comprised a small subset of this study's population and extra-ampullary DA was not included.

Given its rarity, most therapeutic studies have traditionally combined DA with either other periampullary cancers or small bowel adenocarcinomas. For this reason, chemotherapeutic regimens are not standardized, but increasingly DA is being treated similar to colorectal adenocarcinoma with oxaliplatin-based chemotherapy. Given the tendency of this disease to recur systemically, the role of adjuvant chemotherapy warrants further investigation. Current practice at many centers is to treat patients with high risk features (*e.g.,* nodal metastasis) with oxaliplatin-based chemotherapy[50].

Definitive, or palliative, chemotherapy should be offered to all eligible patients with metastatic or unresectable disease. A phase Ⅱ prospective trial studied 30 patients with metastatic or unresectable small bowel or ampullary adenocarcinoma who received capecitabine and oxaliplatin and noted a 50% overall response rate, 10% complete response. Median time to progression was 11 mo with median overall survival 20 mo[68,69]. Patients should also be considered for clinical trials as appropriate.

Chemoradiation

The role of adjuvant radiotherapy in the treatment of DA is not well defined. No studies have demonstrated an effect on OS with the use of chemoradiotherapy (CRT). One small study of 14 patients from Johns Hopkins with node-positive DA treated with PD and adjuvant CRT (median dose of 50 Gy, concurrent 5-FU) resulted in improved local control compared with surgery alone (93% *vs* 67%)[70]. Similarly, a retrospective study of 32 patients from Duke University Medical Center was able to show modest improvement in local control (70% *vs* 49%) with adjuvant CRT[71]. Unfortunately, neither study showed that adjuvant chemoradiation contributed to improved overall survival: 5-year survival 44% *vs* 43%[70] and 44% *vs* 57%[71], respectively. Other retrospective series have shown similar results with improvements in locoregional control but not OS[72]. Nevertheless, this approach targeting improved locoregional control may make CRT particularly useful in patients with lymph node metastases. In a study of 122 patients at a single institution who underwent curative resection for DA, adjuvant CRT in patients with a higher prevalence of regional lymph node metastases was associated with a similar overall survival to that of a group of patients with limited or no nodal metastases who did not receive adjuvant therapy[50].

OUTCOMES

Short term

Surgery for DA can be associated with significant morbidity and mortality. Poultsides *et al*[50] in their contemporary series of PD at MSKCC, reported a postoperative morbidity rate of 35% and 30-d mortality rate of 2.4%. Solaini *et al*[48] published a postoperative complication rate of 40% and in-hospital mortality rate of 3.3% for all patients undergoing surgery for DA. In these studies, postoperative pancreatic fistulae (POPF) developed following PD in 14.0% and 10.6% of patients, respectively[48,50]. The impact of the type of resection on postoperative outcomes is controversial. Some have suggested that SR is associated with

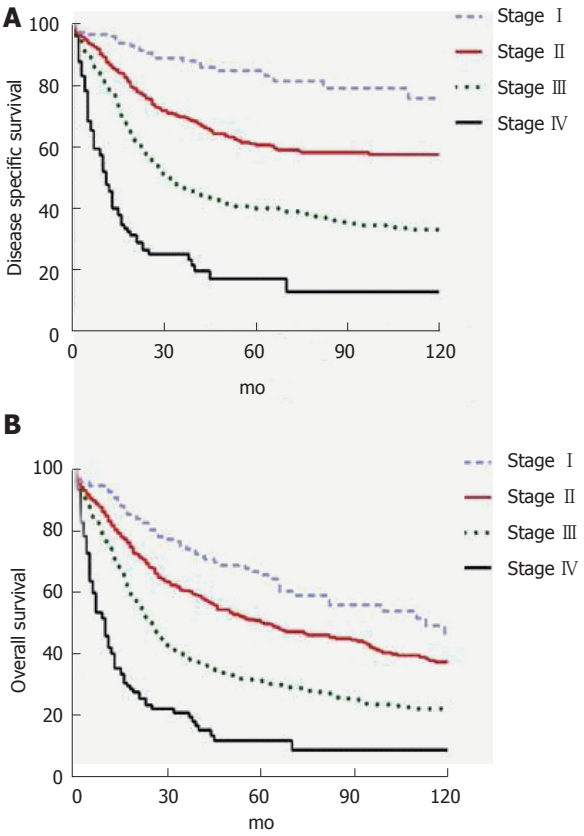

Figure 2 Stage-based disease free (A) and overall (B) survival for patients undergoing surgery for duodenal cancer based on seer data. Used with permission: Cloyd *et al*[49].

improved outcomes as it avoids the opportunity for POPF. Tocchi *et al*[13] reviewed their series of 47 patients undergoing surgery for DA and found SR to be associated with less postoperative morbidity, mortality and length of hospital stay. Bakaeen *et al*[44] found similar complication rates but shorter LOS in the patients undergoing SR. Other studies have failed to find an effect of surgery type on complication rates[43,48]. The occurrence of a postoperative complication may be associated with worse long term survival[73].

Long term

DA represents an aggressive cancer but in patients with resectable disease, long term outcomes are better than with other periampullary malignancies. In a retrospective study of 122 patients who underwent PD for DA over a 22 year period at MSKCC, ten-year OS was 41%[50]. A prospective cohort study of 150 patients from six United Kingdom hepatopancreaticobiliary centers undergoing curative intent surgery for DA from 2000-2013 found 1-, 3- and 5-year OS rates of 83.9%, 66.7% and 51.2%, respectively. Median disease-free survival was 53 mo[48]. A recent population-based study suggested worse outcomes with 5-year OS rates of 65.9%, 50.4%, 31.4%, and 11.9% for Stage Ⅰ, Ⅱ, Ⅲ and Ⅳ, respectively (Figure 2)[49]. Patients with metastatic or unresectable disease have median survival that ranges from 2-8 mo[68,69,74,75].

Prognostic factors

Factors associated with worse outcome in DA include patient age, distant metastasis, lymph node metastasis, lymph node ratio, number of lymph nodes harvested, high tumor grade, tumor (T) stage, margin status, lymphovascular or perineural invasion, and overall cancer stage (Table 3). Lymph node metastasis remains one of the most important prognostic determinants[41,43,44,49-51,74,76-78]. In the largest single institution series of 122 patients who underwent PD for DA, the presence of lymph node metastases was the only independent predictor of decreased survival in multivariate analysis. Five-year survival for node negative (N0) patients was 68% compared to 17% in patients with N2 disease[50]. Another study calculated 3-year survival for node negative patients to be 87.5% compared to only 21% in patients with nodal disease[74]. LNR, the ratio of positive LNs to number of LNs excised, may be even a more accurate predictor of prognosis[2,31,49].

CONCLUSION

Duodenal adenocarcinoma is a rare but aggressive malignancy. Because of the nonspecific symptoms it presents with and the difficulty in confirming a diagnosis, patients may often present with advanced disease. Nonetheless, aggressive surgical resection, when possible, affords the best chance at survival. The decision of whether to perform pancreaticoduodenectomy *vs* segmental resection depends on the location of the primary tumor as both are acceptable options as long as negative margins can be safely obtained. Lymph node positivity is one of the most important prognostic indicators and a wide lymphadenectomy should be routinely performed. Although data are limited guiding adjuvant therapy options, oxaliplatin-based chemotherapy is typically offered to high risk patients, such as those with positive lymph nodes. In some series, adjuvant radiation is associated with improved local control but no difference in overall survival. Previous research on DA has been limited by small sample sizes and single institutional design. Further research would benefit from multi-institutional trials that do not combined DA with other periampullary or small bowel malignancies.

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MINIREVIEWS

Adhesive small bowel adhesions obstruction: Evolutions in diagnosis, management and prevention

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Abstract

Intra-abdominal adhesions following abdominal surgery represent a major unsolved problem. They are the first cause of small bowel obstruction. Diagnosis is based on clinical evaluation, water-soluble contrast follow-through and computed tomography scan. For patients presenting no signs of strangulation, peritonitis or severe intestinal impairment there is good evidence to support non-operative management. Open surgery is the preferred method for the surgical treatment of adhesive small bowel obstruction, in case of suspected strangulation or after failed conservative management, but laparoscopy is gaining widespread acceptance especially in selected group of patients. "Good" surgical technique and anti-adhesive barriers are the main current concepts of adhesion prevention. We discuss current knowledge in modern diagnosis and evolving strategies for management and prevention that are leading to stratified care for patients.

Key words: Adhesive disease; Intestinal obstruction; Diagnosis of adhesive small bowel obstruction; Non-operative management of adhesive disease; Emergency surgical treatment

Core tip: Adhesive disease is a consequence of all intra-peritoneal surgeries. We decided to carry out a systematic review about the adhesive small bowel

obstruction because it is still difficult to make differential diagnosis and to understand the right time to operate and which surgical technique to perform. Besides there is a way to prevent major adhesive disease: "Good" surgical technique and anti-adhesive barriers are the main current concepts of adhesion prevention. We discuss all current knowledge in this field.

Catena F, Di Saverio S, Coccolini F, Ansaloni L, De Simone B, Sartelli M, Van Goor H. Adhesive small bowel adhesions obstruction: Evolutions in diagnosis, management and prevention. *World J Gastrointest Surg* 2016; 8(3): 222-231 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i3/222.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i3.222

INTRODUCTION

Adhesive disease is the most frequently encountered disorder of the small intestine; in one review of 87 studies including 110076 patients, the incidence of adhesive small bowel obstruction (ASBO) following all types of abdominal operations was 2.4%[1].

In North America, there are more than 300000 annual hospital admissions for ASBO accounting for 850000 d of inpatient care, costing more than $1.3 billion in medical expenditures and contributing to more than 2000 deaths annually[2].

Dembrowski published the first data on induction of adhesions in an animal model in 1889 and in the following 120 years there have been extensive studies both *in vitro* and *in vivo*[3].

In the past decade, limited clinical research has produced uncertainty about best practice with subsequent international variation in delivery and in outcome.

There is a diagnostic dilemma on how to distinguish between adhesive SBO and other causes, and how to distinguish between ASBO that needs emergency surgery and ASBO that can be successfully treated conservatively.

ASBO after peritoneal cavity surgery is a well-known disease entity that still harbors challenges regarding prevention, diagnosis and treatment despite general improvements in care. Good surgical technique, *e.g.*, laparoscopy, and anti-adhesive barriers at initial surgery seem to reduce ASBO but reports have conflicting results and only provide general conclusions which do not apply for each individual patient. Contrast enhanced computed tomography (CT) has improved diagnosis of ASBO in general but cannot be performed in each patient (severe vomiting, kidney failure) and fails to accurately identify adhesions as the cause. Also, predicting which treatment should be installed and success of treatment by CT is under debate. Regarding surgical treatment laparoscopy has gained popularity but also is associated with increased risk of iatrogenic complications. Particularly, identifying patients who might benefit from laparoscopic adhesiolysis and who should not and should be treated by open surgery is a challenge.

Therefore, ASBO diagnosis, treatment and prevention are important for reducing mortality, morbidity and for socioeconomic reasons.

The aim of this review is to provide an update of the current controversies over diagnosis, non-operative/operative management and prevention of ASBO.

LITERATURE RESEARCH

We searched the Cochrane Library, MEDLINE, and EMBASE, limited to the final search date (31/03/2015) and not limited to English language publications.

We used the search terms "small bowel" or "obstruction" in combination with the terms "adhesions" or "adhesive" or "adherences".

We largely selected publications in the past five years, but did not exclude commonly referenced and highly regarded older publications.

We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant.

We searched ClinicalTrials.gov (01/01/2000-31/03/2015) for current trials in ASBO.

EPIDEMIOLOGY

Intra-abdominal adhesions following abdominal surgery represent a major unsolved problem; in patients with abdominal pain, ASBO is a common cause that accounts for 4% of all emergency department admissions and 20% of emergency surgical procedures[4].

These fibrous bands are thought to occur in up to 93% of patients undergoing abdominal surgery and can complicate future surgery considerably[5].

Adhesion formation can result in significant morbidity, mortality and infertility in women, and adhesion-related complications are also responsible for up to 74% cases of ASBO in adults and 30% of re-admissions at 4 years after an incident intra-abdominal surgery[6].

It is unknown whether the increase in laparoscopic intra-abdominal surgery has translated into fewer postoperative complications due to adhesions; a recent review of 11 experimental studies involving seven animal models and four human studies reported mixed results. Some reported decreased rates of adhesion formation after laparoscopy. However, there was significant heterogeneity among the human studies[7,8].

Furthermore, some evidence suggests that this decrease in adhesion formation has not necessarily translated to a decrease in adhesion-related obstruction; in a recent randomized, multi-center trial comparing outcomes in laparoscopic *vs* conventional approaches in colorectal surgery for malignancy, there was no difference between the two groups in obstruction-related complications at 3-year follow-up consultations[9].

However, in a long-term follow-up study examining the rate of hospitalization due to ASBO for patients

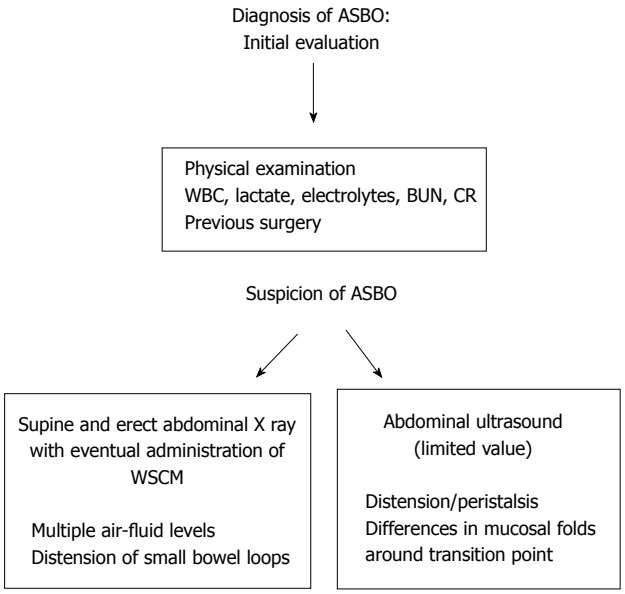

Figure 1 Adhesive small bowel obstruction diagnosis: Initial evaluation. ASBO: Adhesive small bowel obstruction; WBC: White blood cell count; BUN: Blood urea nitrogen; CR: Creatinine; WSCM: Water soluble contrast medium.

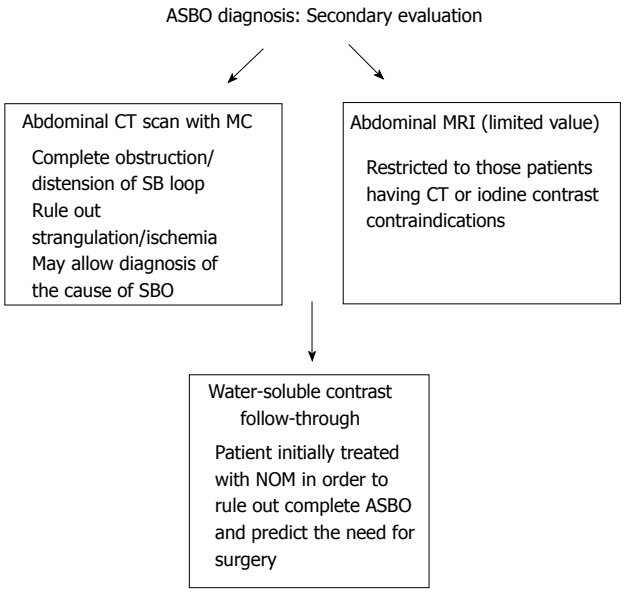

Figure 2 Adhesive small bowel obstruction diagnosis: Secondary evaluation. ASBO: Adhesive small bowel obstruction; NOM: Non operative management; CT: Computed tomography; MC: Medium contrast.

operated on due to suspected appendicitis, the laparoscopic approach resulted in significantly lower rates compared to open surgery. However, frequency of ASBO after the index surgery was low in both groups[10].

In a recent meta-analysis the incidence of adhesive small bowel obstruction was highest in pediatric surgery (4.2%, 2.8% to 5.5%; I^2 = 86%) and in lower gastrointestinal tract surgery (3.2%, 2.6% to 3.8%; I^2 = 84%); the incidence was lowest after abdominal wall surgery (0.5%, 0.0% to 0.9%; I^2 = 0%), upper gastrointestinal tract surgery (1.2%, 0.8% to 1.6%; I^2 = 80%), and urological surgery (1.5%, 0.1% to 3.0%; I^2 = 67%)[1].

DIAGNOSIS

Preliminary assessment

The first step in the diagnostic work flow for ASBO is a detailed anamnesis and physical examination, followed by the evaluation of a complete blood count with differential especially white blood cell (WBC) count, electrolytes including blood urea nitrogen and creatinine, C-reactive protein, serum lactate, lactate dehydrogenase (LDH) and creatine kinase (CK). In patients who present with systemic signs (*e.g.*, fever, tachycardia, hypotension, altered mental status), additional laboratory investigation should include arterial blood gas and serum lactate. Although patients with ASBO generally may complain a varied assortment of symptoms, such as discontinuous abdominal pain, nausea and vomiting, associated, in the vast majority of cases, with a history of previous abdominal surgery[11], these clinical symptoms contribute only to some extent to the diagnosis of ASBO[12]. Unfortunately, the clinical symptoms of ASBO are even less consistent predictors in differentiating patients with bowel strangulation who need emergency surgical intervention[13]. Laboratory tests may be more useful to estimate the grade of systemic illness, than to confirm clinical suspicions. Actually the typical inflammatory markers, like WBC count and CPR levels, cannot discriminate between the inflammation due to ASBO and that caused by other inflammatory conditions[14,15]. In the case of bowel ischemia due to strangulation, these markers cannot discriminate the patients who benefit from conservative treatment and those who need surgery[16,17]. Nevertheless, when evolution to ischemia follows, serum lactate, LDH and CK may increase due to bowel hypoperfusion[16]. However, since LDH and CK increase in any ischemic state, they are consequently quite unspecific. Instead, because serum lactate rises only at a stage when widespread bowel infarction is already well established, lactate increase is highly sensitive, but not specific, for ischemia in patients with ASBO (sensitivity 90%-100%, specificity 42%-87%), being thus a robust sign to proceed to urgent surgery[18,19]. Recent reports indicate that, although there is no reliable clinical or laboratory marker for intestinal ischemia, an intestinal fatty acid binding protein, which is released by necrotic enterocytes, may become a useful marker for the detection of bowel ischemia[20]. In conclusion, laboratory tests can simply indicate general disease severity and can be used to support or rule out an emergency surgical choice only in the context of agreement of a number of other clinical findings. Moreover, serum tests are clearly worthwhile in the evaluation of any patient with acute obstruction, because they may indicate needed adjustment of electrolyte abnormalities and fluid resuscitation (Figure 1).

Secondary evaluation

While ASBO may be suspected based only upon

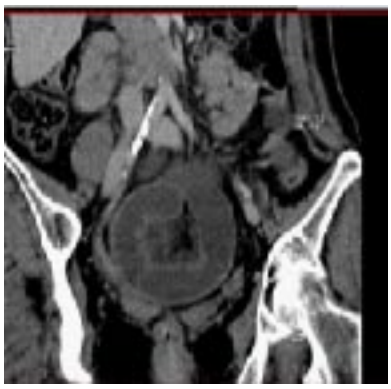

Figure 3 Adhesive small bowel obstruction caused by single band adhesion: Computed tomography scan.

risk factors, symptoms, and physical examination, abdominal imaging is usually required to confirm the diagnosis, eventually detecting the location of obstruction and identifying complications, like ischemia, necrosis, and perforation[21,22]. Although multiple imaging modalities are available to confirm a suspected diagnosis of ASBO, plain radiography and abdominal CT are those most suitable and useful. Thus, the preliminary assessment for all patients suspected for ASBO should include supine and erect plain abdominal radiography that can display multiple air-fluid levels with distension of small bowel together with the absence of gas in the colon[23]. However, it must be said that the reason or site of obstruction is usually not clear on plain radiography, since a specific site between the enlarged proximal and undilated distal bowel frequently cannot be recognized with certainty. For the diagnosis of ASBO, the sensitivity, specificity, and accuracy of plain X-ray are from 79% to 83%, from 67% to 83%, and from 64% to 82%, respectively (Figure 2).

Abdominal CT scans (Figure 3), especially with administration of oral or intravenous contrast medium, perform better than plain X-ray in finding the transition point, evaluating the severity of obstruction, identifying the cause of obstruction, and recognizing complications (ischemia, necrosis, and perforation)[24]. The sensitivity, specificity, and accuracy of CT scans for ASBO diagnosis are, respectively, from 90% to 94%, 96%, and 95%[25]. CT has been demonstrated to be highly diagnostic in ASBO, especially in all patients with inconclusive plain X-ray[26]. However, it should not be routinely implemented in the diagnosis-making process except when clinical history, physical examination, and plain film were not convincing for ASBO diagnosis[27], since these are readily available, less expensive, expose the patient to less radiation, and may highlight the need for abdominal CT in some patients.

Abdominal ultrasound and magnetic resonance enterography may be useful for the diagnosis of ASBO only in selected patients and their use should be restricted to those patients having CT or iodine contrast contraindications[28].

Although small bowel contrast studies, in general, have a limited role in the initial diagnosis of ASBO and in some circumstances, like in the presence of perforation, some of them, as those with the use of barium, are contraindicated[24], instead those using water-soluble contrast agents (WSCA), being safer than barium in cases of perforation and peritoneal spread, are extremely valuable in patients undergoing initial non-operative conservative management in order to rule out complete ASBO and predict the need for surgery[29]. In this sense, small bowel WSCA studies in the presence of ASBO have not only diagnostic, but especially therapeutic value[26].

TREATMENT - NON-OPERATIVE MANAGEMENT

Patient selection

For patients presenting with ASBO without signs of strangulation, peritonitis or severe intestinal impairment there is good evidence to support NOM.

Free intraperitoneal fluid, mesenteric edema, lack of the "small bowel feces sign" at CT-scan, history of vomiting, severe abdominal pain (VAS > 4), abdominal guarding, raised white cell count and devascularized bowel at CT-scan predict the need for emergent laparotomy[30].

Moreover, patients with repeated ASBO episodes, many prior laparotomies for adhesions and prolonged conservative treatment should be cautiously selected to find out only those who may benefit from early surgical interventions[30].

At present, there is no consensus about when conservative treatment should be considered unsuccessful and the patient should undergo surgery; in fact, the use of surgery to solve ASBO is controversial, as surgery induces the formation of new adhesions[30].

Level I data have shown that NOM can be successful in up to 90% of patients without peritonitis[31].

As a counterpart, a delay in operation for ASBO places patients at higher risk for bowel resection. A retrospective analysis showed that in patients with a $\leqslant$ 24 h wait time until surgery, only 12% experienced bowel resection and in patients with a $\geqslant$ 24 h wait time until surgery, 29% required bowel resection[32].

Schraufnagel *et al*[33] showed that in their huge patient cohort, the rates of complications, resection, prolonged length of stay and death were higher in patients admitted for ASBO and operated on after a time period of $\geqslant$ 4 d.

The World Society of Emergency Surgery 2013 guidelines stated that NOM in the absence of signs of strangulation or peritonitis can be prolonged up to 72 h. After 72 h of NOM without resolution, surgery is recommended[30].

There are no objective criteria that identify those patients who are likely to respond to conservative treatment. Less clear, in fact, is the way to predict

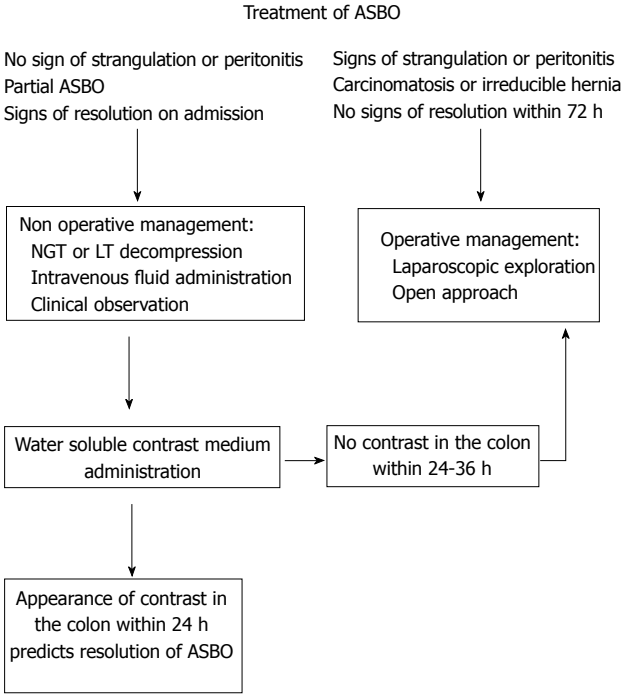

Figure 4 Adhesive small bowel obstruction treatment. ASBO: Adhesive small bowel obstruction; NGT: Naso-gastric tube; LT: Long tube.

between progression to strangulation or resolution of ASBO. Some authors suggested the following as strong predictors of NOM failure: The presence of ascites, complete ASBO (no evidence of air within the large bowel), increased serum creatine phosphokinase and ⩾ 500 mL from nasogastric tube on the third NOM day[30].

However, at any time, if there is an onset of signs of strangulation, peritonitis or severe intestinal impairment, NOM should be discontinued and surgery is recommended.

It is really difficult to predict the risk of operation among those patients with ASBO who initially underwent NOM[30].

Tube decompression, WSCA and other treatments

Randomized clinical trials showed that there are no differences between the use of nasogastric tubes compared to the use of long tube decompression[34].

In any case, early tube decompression is beneficial in the initial management, in addition to required attempts of fluid resuscitation and electrolyte imbalance correction. For challenging cases of ASBO, the long tube should be placed as soon as possible, more advisable by endoscopy, rather than by fluoroscopic guide[35].

Several studies investigated the diagnostic-therapeutical role of WSCA[36]. Gastrografin is the most commonly utilised contrast medium. It is a mixture of sodium diatrizoate and megluminediatrizoate. Its osmolarity is 2150 mOsm/L. It activates movement of water into the small bowel lumen. Gastrografin also decreases oedema of the small bowel wall and it may also enhance smooth muscle contractile activity that can generate effective peristalsis and overcome the obstruction[37].

The administration of WSCA proved to be effective in several randomized studies and meta-analysis. Three recent meta-analyses showed no advantages in waiting longer than 8 h after the administration of WSCA[26] and demonstrated that the presence of contrast in the colon within 4-24 h is predictive of ASBO resolution. Moreover, for patients undergoing NOM, WSCA decreased the need for surgery and reduced the length of hospital stay[38,39].

Oral therapy with magnesium oxide, *L. acidophilus* and simethicone may be considered to help the resolution of NOM in partial ASBO with positive results in shortening the hospital stay[40].

Lastly hyperbaric oxygen therapy may be an option in the management of high anesthesiologic risk patients for whom surgery should be avoided[41].

No agreement exists about the possibility to predict the recurrence risk. Factors associated with a higher risk of recurrence are age < 40 years, matted adhesion and postoperative surgical complications[42]. Compared to traditionally conservatively treated patients, Gastrografin use does not affect either the ASBO recurrence rates or recurrences needing surgery (Figure 4)[29].

SURGERY

Open surgery

Until recently open surgery has been the preferred method for the surgical treatment of ASBO (in case of suspected strangulation or after failed conservative management), and laparoscopy has been suggested only in highly selected group of patients (preferably in case of first episode of ASBO/or anticipated single band adhesion) using an open access technique and the left upper quadrant for entry[30] (Figure 5).

More recently, the use of laparoscopy is gaining widespread acceptance and is becoming the preferred choice in centers with specific expertise.

A meta-analysis by Li *et al*[43] found that there was no statistically significant difference between open *vs* laparoscopic adhesiolysis in the number of intraoperative bowel injuries, wound infections, or overall mortality. Conversely there was a statistically significant difference in the incidence of overall and pulmonary complications and a considerable reduction of prolonged ileus in the laparoscopic group compared with the open group. The authors concluded that laparoscopic approach is safer than the open procedure, but only in the hands of experienced laparoscopic surgeons and in selected patients[43].

However, no randomized controlled trial comparing open to laparoscopic adhesiolysis exists to date, and both the precise indications and specific outcomes of laparoscopic adhesiolysis for adhesive SBO remain poorly understood. The only randomized controlled trial aiming to provide level Ib evidence to assess the use of laparoscopy in the treatment of adhesive small bowel

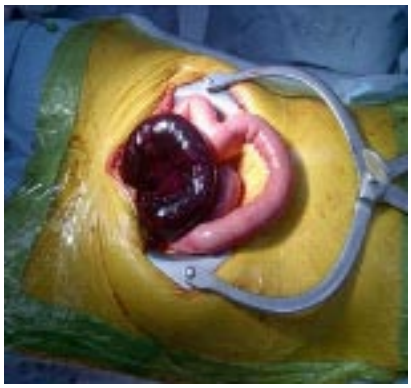

Figure 5 Adhesive small bowel obstruction caused by single band adhesion: Open surgery.

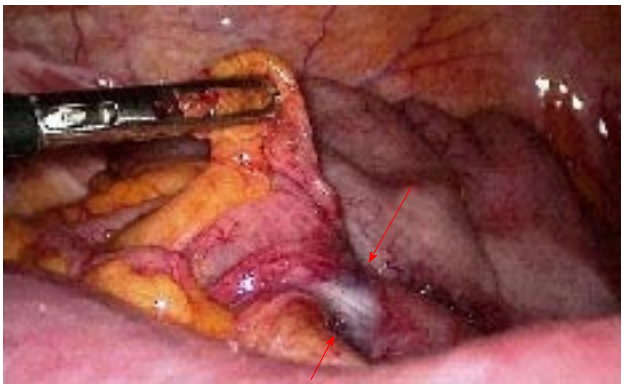

Figure 6 Adhesive small bowel obstruction caused by single band adhesion: Laparoscopic surgery.

obstruction is currently ongoing, having the length of postoperative hospital stay as the primary endpoint and the passage of stools, commencement of enteral nutrition, 30-d mortality, complications, postoperative pain, length of sick leave, rate of ventral hernia and the recurrence of small bowel obstruction during long-term follow-up as secondary and tertiary endpoints[44].

Laparoscopy

Laparoscopic adhesiolysis (Figure 6) for small bowel obstruction has a number of potential advantages including less postoperative pain, faster return of intestinal function, shorter hospital stay, reduced recovery time, allowing an earlier return to full activity, fewer wound complications, and decreased postoperative adhesion formation[45].

In a recent large population-based propensity score-matched analysis involving 6762 patients[46], laparoscopic treatment of ASBO was associated with lower rates of postoperative morbidity, including SSI, intraoperative transfusion, and overall lower resource use compared with laparotomy as well as shorter hospital stay. Laparoscopic treatment of surgical ASBO is not associated with a significant difference in operative time, rates of re-operation within 30 d, or mortality.

Further recent reports confirmed that laparoscopic surgical management of adhesive SBO is associated with quicker gastrointestinal recovery, shorter length of stay (LOS), and reduced overall complications compared to open surgery, without significant differences in operative times[47]. Furthermore, following exclusion of bowel resections, secondary outcomes continued to favor laparoscopy.

Although laparoscopic adhesiolysis requires a specific skill set and may not be appropriate in all patients, the laparoscopic approach demonstrates a clear benefit in 30-d morbidity and mortality even after controlling for preoperative patient characteristics (lower major complications and incisional complications rate) as well as shorter postoperative LOS and shorter mean operative times. Given these findings in more than 9000 patients and consistent rates of SBO requiring surgical intervention in the United States, increasing the use of laparoscopy could be a feasible way of to decrease costs and improving outcomes in this population[48].

Patient selection is still a controversial issue. From a recent consensus conference[49], a panel of experts recommended that the only absolute exclusion criteria for laparoscopic adhesiolysis in SBO are those related to pneumoperitoneum (*e.g.*, hemodynamic instability or cardiopulmonary impairment); all other contraindications are relative and should be judged on a case-to-case basis, depending on the laparoscopic skills of the surgeon.

Nonetheless it is now well known that the immune response correlates with inflammatory markers associated with injury severity and, as a consequence, the magnitude of surgical interventions may influence the clinical outcomes through the production of molecular factors, ultimately inducing systemic inflammatory response and the beneficial effect of minimally invasive surgeries and of avoiding laparotomy is even more relevant in the frail patients[50].

Laparoscopic adhesiolysis is technically challenging, given the bowel distension and the risk of iatrogenic injuries if the small bowel is not appropriately handled. Key technical steps are to avoid grasping the distended loops and handling only the mesentery or the distal collapsed bowel. It is also mandatory to fully explore the small bowel starting from the cecum and running the small bowel distal to proximal until the transition point is found and the band/transition point identified. After release of the band, the passage into distal bowel is restored and the strangulation mark on the bowel wall is visible and should be carefully inspected.

As a precaution in the absence of advanced laparoscopic skills, a low threshold for open conversion should be maintained when extensive and matted adhesions are found[51].

Reported predictive factors for a successful laparoscopic adhesiolysis are: Number of previous laparotomies $\leqslant$ 2, non-median previous laparotomy, appendectomy as previous surgical treatment causing adherences,

unique band adhesion as pathogenetic mechanism of small bowel obstruction, early laparoscopic management within 24 h from the onset of symptoms, no signs of peritonitis on physical examination, and experience of the surgeon[52].

Because of the consistent risks of inadvertent enterotomies and the subsequent significant morbidity, particularly in elderly patients and those with multiple (three or more) previous laparotomies, the lysis should be limited to the adhesions causing the mechanical obstruction or strangulation or those located at the transition point area; some authors have attempted to design a preoperative nomogram and a score to predict risk of bowel injury during adhesiolysis, and they found that the number of previous laparotomies, anatomical site of the operation, presence of bowel fistula and laparotomy *via* a pre-existing median scar were independent predictors of bowel injury[53,54].

PREVENTION

Surgical technique

Small bowel obstruction has been the driver of research in adhesion prevention measures, barriers and agents. Recent data from cohort studies and systematic reviews point at major morbidity and socioeconomic burden from adhesiolysis at reoperation, which have broadened the focus of adhesion prevention[55]. Applying adhesion barriers in two-stage liver surgery and cesarean section, to reduce the incidence of adhesions and adhesiolysis related complications, are examples of the change in paradigm that reducing the incidence of adhesions is clinically more meaningful than only aiming at preventing adhesive small bowel obstruction[56]. Increasing the number of patients without any peritoneal adhesion should be the general aim of adhesion prevention.

"Good" surgical technique and anti-adhesive barriers are the main current concepts of adhesion prevention. From a recent systematic review and meta-analysis on the impact of different surgical techniques on adhesion formation it was concluded that laparoscopy and not closing the peritoneum lower the incidence of adhesions[1].

However, the burden of adhesions in laparoscopy is still significant most likely due to the necessity to make specimen extraction incisions in addition to trocar incisions and the unavoidable peritoneal trauma by surgical dissection and the use of CO_2 pneumoperitoneum (intraperitoneal pressure and desiccation). Reduced port laparoscopy and specimen extraction *via* natural orifices may theoretically further reduce peritoneal incision related adhesion formation[57].

Anti-adhesive barriers

Since all abdominal surgeries involve peritoneal trauma and potential healing with adhesion formation, additional measures are needed to reduce the incidence of adhesions and related clinical manifestations. These measures consist of systemic pharmacological agents, intraperitoneal pharmaceuticals or adhesion barriers[58]. Most clinical experience is with intraperitoneal adhesion barriers, applied at the end of surgery with the aim to separate injured peritoneal and serosal surfaces until complete adhesion free healing has occurred. Efficacy of anti-adhesion barriers in open surgery has been well established for reducing the incidence of adhesion formation[59]. For one type of barrier (Hyaluronate-carboxymethylcellulose, HA-CMC, Seprafilm, Sanofi, Paris, France) the reduction of incidence of adhesive small bowel obstruction after colorectal surgery has also been established (RR = 0.49, 95%CI: 0.28-0.88) without patient harm[59,60]. Oxidized regenerated cellulose (Interceed, Ethicon, West Somerville, NJ, United States) reduces the incidence of adhesion formation following fertility surgery (RR = 0.51, 95%CI: 0.31-0.86), but the impact on small bowel obstruction after gynecological surgery has not been studied[59,61]. Drawback of both products is the difficulty to use in laparoscopic surgery, underlining the need to develop gel, spray or fluid barriers that are easy to apply *via* a trocar.

In the Prevention of Postoperative Abdominal Adhesions (P.O.P.A) study, authors randomized 91 patients to have 2000 cc of icodextrin 4% and 90% to have the traditional treatment. The authors noted no significant difference in the incidence of small bowel leakage or anastomotic breakdown; operative times, blood losses, incidence of small bowel resections, return of bowel function, LOS, early and late morbidity and mortality were comparable. After a mean follow-up of 41.4 mo, there have been 2 cases of ASBO recurrence in the icodextrin group and 10 cases in the control group ($P < 0.05$)[61].

Consistent safety and efficacy evidence has not led to routine application of barriers in open or laparoscopic surgery. Reasons might be the lack of awareness, the question if the "effect size" is large enough for routine application or the belief that adhesion formation even may benefit the patients, *e.g.*, reinforcing intestinal anastomosis or walling off peritoneal infection. However, the most used argument against routine use is the doubt regarding cost-effectiveness of adhesion barriers. The direct hospital costs in the United States in 2005 for adhesive small bowel obstruction alone was estimated at $3.45 billion. Costs associated with the treatment of an adhesive SBO are estimated to be $3000 per episode with conservative treatment and $9000 with operative treatment. The additional costs incurred by operative treatment are partially due to complications of adhesiolysis. The incidence of bowel injuries during adhesiolysis for SBO is estimated to be between 6% and 20%. Inadvertent enterotomy due to adhesiolysis in elective surgery is associated with a mean increase in costs of $38000[58,61,62].

In a model, counted for in-hospital costs and savings resulting from adhesive SBO based on United Kingdom price data from 2007, Wilson showed that a low priced barrier at about $160 with 25% efficacy in preventing SBO would result in healthcare savings. Another

concept with a $360 priced barrier, would result in a net investment on the long-term unless a higher efficacy of 60% could be achieved. In this model treatment costs for small bowel obstruction were substantially lower than more recent cost calculations. Recent direct healthcare costs associated with treatment of major types of adhesion related complications (small bowel obstruction, adhesiolysis complications and secondary female infertility) within the first 5 years after surgery are $2350 following open surgery and $970 after laparoscopy. Application of an anti-adhesion barrier could save between $678-1030 following open surgery and between $268-413 following laparoscopic surgery on the direct healthcare costs related to treatment of adhesion related complications (data not published). Benefits from reduction in SBO were $103 in open surgery and $32 in laparoscopic surgery, using a high ($360) priced product and only taken into account reoperations for adhesive small bowel obstruction. From these cost modeling it seems that even routine use of anti-adhesion barriers is cost-effective in both open and laparoscopic surgery[62-64].

CONCLUSION

Unfortunately, there are not yet devices able to totally prevent the intraperitoneal adhesion formation after abdominal surgery; only the use of correct surgical technique and the avoidance of traumatic intraperitoneal organ maneuvers may help to reduce postoperative adhesion incidence.

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MINIREVIEWS

Doppler-guided hemorrhoidal dearterialization/transanal hemorrhoidal dearterialization: Technical evolution and outcomes after 20 years

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Abstract

In the setting of Hemorrhoidal Disease treatment, the option of conventional hemorrhoidectomy is highly effective, but it is still associated with postoperative pain and discomfort. For this reason, technical alternatives have been developed in order to reduce complications and to provide better postoperative recovery. To accomplish this aim, non-excisional techniques such as stapled hemorrhoidectomy and Doppler-guided hemorrhoidal ligation have been introduced into clinical practice with high expectations. The aim of this article is to revise the literature about transanal hemorrhoidal dearterialization technique in the treatment of hemorrhoidal disease, looking into its evolution, results and possible benefits over other modalities of surgical treatment. The literature review showed that Doppler-guided hemorrhoidal dearterialization is a safe and effective method to treat grades II to IV hemorrhoidal disease. Outcomes in patients presenting prolapse are satisfactory and the association of anopexy is an important aspect of this operation. Anal physiology disturbances are rarely observed and mainly transitory. This technique is an excellent option for every patient, especially in those with previous anal surgeries and in patients with previous alterations of fecal continence, when an additional procedure might represent a risk of definitive incontinence.

Key words: Doppler-guided hemorrhoidal dearterialization; Hemorrhoids; Transanal hemorrhoidal dearterialization

Core tip: Management of hemorrhoidal disease is a tough task. First of all, because there are some technical alternatives that should be adequately indicated to different patients; secondly, because patients desire a good alternative associated with low morbidity, good long-term results and less postoperative pain. In this setting, the transanal hemorrhoidal dearterialization

(THD) technique is considered a safe and effective choice for internal hemorrhoids of grades II to IV. The present paper reviews technical aspects and literature results of THD in comparison to other operative techniques.

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INTRODUCTION

For over 60 years, since the description of hemorrhoidectomy by Milligan and Morgan *et al*[1] and Ferguson *et al*[2], conventional hemorrhoidectomy (CH) has been the standard treatment for grades III and IV hemorrhoids. It is also indicated for grade II hemorrhoids refractory to conservative methods (such as rubber band ligation or infrared coagulation) or to those that have recurred. However, CH is still associated with postoperative pain and discomfort. Thus, technical alternatives to manage hemorrhoidal disease have been sought, in order to reduce complications and to provide better postoperative recovery, especially less pain.

In this scenario, stapled hemorrhoidectomy (SH) and Doppler-guided hemorrhoidal ligation have been introduced in our practice since the 90's[3,4]. Whether called Doppler-guided hemorrhoidal artery ligation (DG-HAL) or transanal hemorrhoidal dearterialization (THD), it is a technique for the treatment of internal hemorrhoids and it was first described by Morinaga *et al*[3] in 1995. Few studies have addressed the technique until after the year 2000, with a lot of papers since then.

The aim of this article was to revise the literature about this technique in the treatment of hemorrhoidal disease, looking into its evolution, results and possible benefits over other modalities of surgical treatment.

A literature search was performed in PubMed, looking for "THD", "transanal hemorrhoidal dearterialization", "DG-HAL" and "Doppler guided hemorrhoidal artery ligation". References from the selected articles were also reviewed in order to find additional studies in the subject.

TECHNICAL ASPECTS

Before Morinaga's work for the surgical treatment of hemorrhoids with Doppler-guided ligation, Jaspersen *et al*[5] described the successful use of Doppler-guided location of hemorrhoidal vessels for phenol injection for treatment of 1st grade hemorrhoids.

Hemorrhoidal vessels are usually found in the mucosa within 2 cm up from the anorectal junction[6] and this is the place where the sutures should be made in this technique (the Dearterialization itself). In the case anopexy is also to be made, this is the position where the first ligation should be made, before the running suture for the anopexy is continued distally.

Different devices were developed to accomplish the location of vessels by Doppler signal as well as to permit the ligation at the same time. Morinaga *et al*[3] used a device called the Moricorn to find Doppler signal 2 cm above the dentate line and then ligate arterioles at this point. Afterwards, other proctoscopes were developed and nowadays most studies use THD (THD S.p.A. Correggio, Italy), DG-HAL/DG-RAR (Agency for Medical Innovations GmbH (AMI), Feldkirch, Osterreich, Austria) or HAL-Doppler (AMI Dufour MedicalTM, Maurepas, France).

There does not seem to exist any difference in results according to the type of device used, since they operate in the same way despite the different appearance of each one.

Table 1 refers to difference in rates of success and recurrence for each technique used for the treatment of hemorrhoidal disease: conventional, stapled and dearterialization.

INITIAL RESULTS WITH THD/HAL

When we look at the studies published in the first 12 years following Morinaga's publication, only ligation was performed (without anopexy). It was only in 2007 when a modification of the technique was made, with additional anopexy for patients with prolapse[7]. Morinaga *et al*[3] reported this first series with 112 patients, obtaining satisfactory results in 78% of patients with prolapse, as well as resolution of pain in 96% of patients and of bleeding in 95%.

After 6 years, Sohn *et al*[8] published another series of patients treated with hemorrhoidal ligation in 2001. Sixty patients were submitted to a procedure (THD) based on the principles described by Morinaga, and the authors achieved complete success in 92% of patients with prolapse, 88% of those with bleeding and 71% of those with pain. Early postoperative pain, precluding normal activities, was reported in only 8% of patients.

Giordano *et al*[9] published the first systematic review concerning THD/DG-HAL in 2009, analyzing 17 papers from 1995 to 2008. In all articles revised no anopexy was performed. The rate of recurrent prolapse varied between 0% and 37%. In the study where this recurrence rate of 37% was found, most patients were lost to follow up, which might have interfered in the results[10]. The overall rate of prolapse, according to the review, was 9%. Regarding recurrent anal bleeding, the rates ranged between 0% and 21% in those 17 studies, with most papers reporting rates around 4% to 10%. The overall rate of recurrent bleeding, also according with this systematic review, is 7.8%. Early post-operative pain was reported in 18% of patients in

Table 1 Rates of success, post-operative pain and long-term recurrence after different techniques for treatment of hemorrhoidal disease

Technique	Symptom control	Post-operative pain	Recurrence
Conventional hemorrhoidectomy	95%	70%-75%	5%
Stapled hemorrhoidectomy	85%-90%	5%-20%	2%-24%
THD/DG-HAL	80%-95%	2%-20%	8%-10%
THD/DG-HAL + Anopexy	85%-95%	6%-50%	8%

THD: Transanal hemorrhoidal dearterialization; DG-HAL: Doppler-guided hemorrhoidal artery ligation.

the review.

ADDITIONAL ANOPEXY

In 2007, Dal Monte *et al*[7] were the first to describe a modification of THD/HAL, adding anopexy of the cushions where prolapse was found. They included patients with hemorrhoidal disease grades Ⅱ to Ⅳ, and anopexy was performed in a group of patients with disease grades Ⅲ and Ⅳ. They compared the latter with patients not submitted to anopexy and there was a tendency of worse prolapse relapse without anopexy, although not statistically significant.

Technical aspects of anopexy consist of extending the suture in a continuous manner after the first figure-of-eight stitch, involving mucosa more superficially than the first stitch, until above the pectinate line. The exact point where the suture is to be ended is identified with an audible Doppler signal before the sutures are done. The rationale of this modification was to treat prolapse at the same procedure.

Infantino *et al*[11] published a multicentric study showing results of the modified technique, treating grades Ⅱ and Ⅲ hemorrhoids. Their recurrence rate was 14.3% and patient satisfaction after 15 mo was 87%. Other 4 papers in 2009 and 2010 showed prolapse recurrence in 5%-17%[12-15].

Several articles on THD/DGHAL with anopexy were published, and the reported prolapse recurrence rates ranged between 3% and 21% and satisfaction rates of 84% to 96%, with follow ups of until 3 to 37 mo[12-14,16-24]. Scheyer *et al*[25] reported good results with Dearterialization and anopexy, but in their conclusion results were not good when prolapse was not the main complaint. In one of the most recent papers on the matter, Ratto *et al*[26] reported a recurrence of prolapse in only 6.3% and a satisfaction rate of 90% after a 11 mo follow up. In this series, 13% of patients suffered pain or tenesmus after surgery.

THD/HAL IN THE TREATMENT OF GRADE IV HEMORRHOIDAL DISEASE

Results of this treatment in patients with high-grade disease (grade Ⅳ) seem to be satisfactory in terms of prolapse resolution.

Two series were published involving only patients with grade Ⅳ disease. In both studies anopexy was performed in addition of hemorrhoidal ligation. Giordano *et al*[19] found an incidence of pain in 70% of patients in the first postoperative day, tenesmus in 10%, but a recurrence of prolapse of only 3% after a follow up of almost 3 years. Faucheron *et al*[22] reported postoperative pain in only 6% of patients, tenesmus in 1% and recurrence of prolapse in 9% after 34-mo follow up.

COMPARATIVE STUDIES WITH SH

Ramírez *et al*[27] were the first to publish a randomized trial comparing THD and PPH in 2005. Several other studies compared both techniques from 2009 until 2014. Festen *et al*[28] published a series comparing 18 patients submitted to stapled hemorroidopexy and 23 patients submitted to THD. After a very short follow up of only 3 wk, THD patients had less pain in the first week, with similar results after 3 wk. Symptoms resolution was also similar between groups[28].

Three studies found that THD patients had an earlier return to normal activities[29-31]. Tsang *et al*[31] found similar complication rates and similar satisfaction rates but follow up after procedures was very different (8 mo after THD and 36 mo after SH). Verre *et al*[32] published a prospective randomized trial in 2013, with 7.9% bleeding rate after SH and none after THD. Postoperative pain was lower in THD group although not statistically significant.

Lucarelli *et al*[33] reported a randomized trial with long-term follow up, where recurrent prolapse was the primary outcome, after a follow up of 40-43 mo. The technique performed in their study was THD with anopexy *vs* stapled hemorrhoidopexy. The last follow up was done through a telephone interview, with reports of prolapse recurrence in 25% of patients in the THD group *vs* 8.2% (P = 0.021) in the SH group. In spite of that, patient satisfaction was 73% in THD group *vs* 86.9% in the SH group. One might argue about detecting recurrence of prolapse by phone interviews, when one study by Ratto *et al*[13] showed that patients misreported skin tags for prolapse, after a physical examination took place.

As in the study by Infantino *et al*[34], Lucarelli *et al*[33] did not find significant difference in levels of post-operative pain. Other studies have found lower pain levels after THD when compared to stapled hemorrhoidopexy[30,31,35] while in some it was a trend in the group submitted to THD but did not reach statistical significance[28,29,32].

Giordano *et al*[29] compared THD *vs* SH for grades Ⅱ and Ⅲ, and reported a recurrence of symptoms recurrence of 14% *vs* 13%, while satisfaction was also similar between groups (89% *vs* 87%), respectively. THD technique comprised also anopexy in this study. There were no reports of fecal incontinence in both

groups.

A systematic review included 3 trials comparing these techniques, with a total of 150 patients concluded that both techniques were effective, but THD patients had less immediate postoperative pain[36].

COMPARISON WITH CH

In our literature search, three studies were found comparing Dearterialization and CH.

In a non-blind randomized study, Elmér *et al*[37] compared 20 patients in each group. Although patients presented less postoperative pain after THD, symptoms were effectively controlled in both groups after long-term follow-up.

Bursics *et al*[38] randomized 60 patients in 2 groups and also showed similar results after 12 mo of follow up. THD group had an earlier return to normal activities ($P < 0.0005$) and less post-operative pain ($P < 0.005$). Another randomized trial was published recently, with a follow up of 24 mo, showing no difference between groups in terms of postoperative pain in the first month after surgery or regarding resumption of normal activities. Patient satisfaction in the end of follow up was also similar between THD and CH ($P > 0.05$)[39].

Denoya *et al*[40] published the article with the longest follow up, 3 years. Forty patients were randomized in each group, and they also found similar results regarding resolution of symptoms and patient satisfaction.

RESULTS REGARDING ANAL PHYSIOLOGY

According to Walega *et al*[41], resting and squeeze pressures following DG-RAR were lower 3 mo after surgery comparing to pre-operative measures ($P < 0.05$) and this result was maintained after 12 mo after surgery.

In their comparative article, Giordano *et al*[29], found no complaint of incontinence after THD or SH. Only 2 patients in the SH group ($n = 24$) complained of transient urgency. Tsang *et al*[31] described 1 case of incontinence in SH group ($n = 37$) and none in THD group ($P = 0.111$).

In the systematic review by Giordano *et al*[9] the overall incontinence rate after THD was 0.4%.

IMPORTANT CONSIDERATIONS

Morinaga *et al*[3] described Doppler arterial hemorrhoidal ligation in 1995 as a novel treatment for hemorrhoids. This technique has become more popular and, nowadays, it is used worldwide. It is based on the premise that arterial ligation would lead to a lesser pressure on the vessels on the anal canal, thus relieving the symptoms as bleeding and prolapse. Initial articles reporting this technique showed satisfactory results. On 2007 Dal Monte *et al*[7] were the first to publish a modification on the described technique, including anopexy in order to better treat prolapse for 3rd and 4th grade hemorrhoids. With this, treatment of prolapse associated with 3rd and 4th grade hemorrhoids was guaranteed and recurrence rates were better.

One of the main advantages of the THD/DG-HAL is the low morbidity rate. After CH pain can be an important distress for the patient, influencing return to normal activities. Postoperative pain seems to be lower after THD when compared to CH, as seem in comparative studies[37,38,40]. In a systematic review concerning THD, 18.5% of patients suffered from pain in the first operative day[9]. Although this review points out that published data on THD was low quality, thus low significance/power, many studies evaluating this technique showed good results in short-term follow-up, with immediate postoperative bleeding occurring in 0%-8% and recurrence of 3%-20%.

Some works show a high recurrence rate related to grade Ⅲ or Ⅳ hemorrhoids[10,42,43], but those studies were done before the anopexy was associated with the arterial ligation. The study with the longest follow up showed a trend to higher recurrence rate for grade Ⅲ hemorrhoids compared to grade Ⅱ after 5 years, but the difference was not statistically significant[42]. Two studies involving patients only with grade Ⅳ hemorrhoidal disease showed a recurrence of 3%-9% after a follow up of almost 3 years.

SH was first described by Longo[4] in 1998 and is also a non-excisional technique for the treatment of hemorrhoidal disease. As THD, the goal is to treat hemorrhoids without the risk of sphincter impairment and to reduce postoperative pain. However, serious complications after SH, such as major bleeding, rectovaginal fistulas and perianal sepsis, have been described[44]. One study prospectively comparing SH and THD for grades Ⅱ and Ⅲ hemorrhoidal disease showed no difference regarding recurrent symptoms or patients' satisfaction with their results[29].

Regarding anal physiology, it seems reasonable to believe that hemorrhoidal dearterialization may contribute with only minor disruption of continence, since there is no risk of anal sphincter damage. On the other hand, the technique affects hemorrhoidal cushions in the anal canal, which play a role in anal continence as well. At the same time, all techniques interfere with the cushions, since it is the goal of the treatment. Maybe due to the fact that THD is a non-excisional technique, the impact after surgery might be reduced compared to excisional techniques.

Incontinence is rarely described, and when it happens it is transitory. More important is the complaint of tenesmus after THD surgery, which is rather common, in about 10% of patients, but also transitory. In a study by Ratto *et al*[13], tenesmus was reported by 24% of patients but symptoms disappeared 10 d following surgery. Even though alterations in resting

and squeeze anal pressures might be seen in anorectal manometry after THD, there is no evidence of risk of incontinence with this procedure[41].

In conclusion, Doppler-guided hemorrhoidal dearterialization is a safe and effective method to treat grades II to IV hemorrhoidal disease. Outcomes in patients presenting prolapse are satisfactory and the association of anopexy has become an important aspect of this operation, contributing to a higher success rate. Anal physiology disturbances are rarely observed and are transitory. This technique is an excellent option for every patient, especially in those with previous anal surgeries and in patients with previous alterations of fecal continence, when an additional procedure might represent a risk of definitive incontinence.

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ORIGINAL ARTICLE

Retrospective Study

Long-term results after revisions of failed primary vertical banded gastroplasty

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at (email address or URL). Participants gave informed consent for data sharing and data was anonymized.

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Abstract

AIM: To compare the results after revision of primary vertical banded gastroplasty (Re-VBG) and conversion to sleeve gastrectomy (cSG) or gastric bypass (cRYGB).

METHODS: In this retrospective single-center study, all patients with a failed VBG who underwent revisional surgery were included. Medical charts were reviewed and additional postal questionnaires were sent to update follow-up. Weight loss, postoperative complications and long-term outcome were assessed.

RESULTS: A total 152 patients were included in this study, of which 21 underwent Re-VBG, 16 underwent cSG and 115 patients underwent cRYGB. Sixteen patients necessitated a second revisional procedure. No patients were lost-to-follow-up. Two patients deceased during the follow-up period, 23 patients did not return the questionnaire. Main reasons for revision were dysphagia/vomiting, weight regain and insufficient weight loss. Excess weight loss (%EWL) after Re-VBG, cSG and cRYGB was, respectively, 45%, 57% and 72%. Eighteen patients (11.8%) reported postoperative complications and 27% reported long-term complaints.

CONCLUSION: In terms of additional weight loss, postoperative complaints and reintervention rate, Roux-en-Y gastric bypass seems feasible as a revision for a failed VBG.

Key words: Vertical banded gastroplasty; Conversion; Revision; Gastric bypass; Sleeve gastrectomy; Additional weight loss

Core tip: This study assesses the long-term outcome after revision of a failed vertical banded gastroplasty (VBG). This manuscript compares three types of revision: revision of the primary VBG, conversion to sleeve gastrectomy and conversion to Roux-en-Y gastric bypass. The main finding in this study is that in terms of additional weight loss, postoperative complaints and reintervention rate, Roux-en-Y gastric bypass seems feasible as a revision for a failed VBG.

van Wezenbeek MR, Smulders FJF, de Zoete JPJGM, Luyer MD, van Montfort G, Nienhuijs SW. Long-term results after revisions of failed primary vertical banded gastroplasty. *World J Gastrointest Surg* 2016; 8(3): 238-245 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i3/238.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i3.238

INTRODUCTION

Obesity is a growing global problem, associated with morbidity, health care costs and even an increased mortality rate[1]. For the treatment of obesity, bariatric surgery is very effective in achieving significantly more long-term weight loss and an improved lifestyle compared with conventional therapy[2,3]. In 2011, over 340000 bariatric procedures were performed worldwide. Among those procedures, around 2300 procedures were a vertical banded gastroplasty (VBG), first described by Mason *et al*[4] and later altered by MacLean *et al*[5] and Buchwald *et al*[6]. Aim of this procedure was to establish a restriction on food intake with a small stomach pouch, without compromising passage of food through the entire gastro-intestinal tract and thereby avoiding malabsorption of nutrients and medication[7]. This procedure has shown in earlier reports to have good short-term results in terms of weight loss and reduction in comorbidities[8-11]. However, there are many studies reporting on the poor long-term results after VBG, showing a tendency for weight regain and other complications resulting in a high revision rate[12-14]. Various options are available for revisional surgery after VBG, such as revision of the VBG (Re-VBG), conversion to sleeve gastrectomy (cSG) and conversion to Roux-en-Y gastric bypass (cRYGB), in which Re-VBG appears to have the poorest outcome and cRYGB has the best short- and long-term results[15-19]. However, data on the comparison between the revisional options remains scarce.

Although VBG had been abandoned some years ago in the Netherlands, still a number of patients can be expected to return with complaints after VBG. In the current series, all three mentioned options for revision have been performed. The aim of this study is to compare the outcome after these revisional procedures.

MATERIALS AND METHODS

Methods

This is a single-center retrospective study. A total of 392 patients underwent primary VBG, between January 1998 and December 2008. Since 2009, VBG was not performed anymore. Only patients undergoing primary VBG at the current center were included to reduce heterogeneity. Medical charts as well as additional postal questionnaires were reviewed. Included parameters were patient's characteristics, operative details of primary and secondary procedures, evolution of weight and comorbidities following both operations, findings at additional imaging, reason for revision, short-term complications and long-term complaints after revisional surgery. The postal questionnaire contained questions on weight and comorbidities, on complaints dysphagia, vitamin deficiencies and incisional hernia. In case of insufficient weight loss, weight regain or complaints and without participation the follow-up program, the patient was invited to the outpatients department. In case of non-response, patients received a phone call and when there was no response at all, the data of the latest visit at the outpatient clinic were used as final outcome.

Excess weight was defined as the difference between the weight before surgery and the highest healthy weight, which is at a body mass index (BMI) of 25 kg/m^2. Total excess weight loss (%EWL) was defined as a percentage of the amount of excess weight lost after surgery, as described by Deitel *et al*[20] The weight before the primary VBG was used as baseline value to calculate %EWL.

Weight loss was categorized according to the criteria described by Reinhold *et al*[21] These criteria consider a bariatric procedure successful when an %EWL of at least 50% is achieved. Furthermore, change in BMI and % total body weight loss (TBWL) was calculated. The evolution of any present comorbidities was categorized in stable, improved (reduced amount of medication used and/or a lower setting of a Continuous Positive Airway Pressure-device), resolved (no treatment), worse and *de novo*.

Treatment

Before primary VBG, all patients underwent assessment at our outpatient clinic by a surgeon, a psychologist and a dietitian to consider whether or not they were qualified for a bariatric procedure according to the standard IFSO guidelines for bariatric surgery. There was no specific algorithm for choosing the operative technique if they were approved for a bariatric procedure. There was a tendency for the option of a gastric bypass in case of more comorbidities, otherwise a VBG was chosen at

Table 1 Baseline characteristics (n = 152)

	Re-VBG n = 21 (13.8%) Mean ± SD	cSG n = 16 (10.5%) Mean ± SD	cRYGB n = 115 (75.7%) Mean ± SD	P value
Age (yr)	42.3 ± 8.6	41.6 ± 11.4	43.0 ± 8.9	0.828
Male:female	5:16	3:13	19:96	0.674
Body mass index before VBG (kg/m^2)	42.6 ± 5.4	43.6 ± 5.0	44.1 ± 4.9	0.445
Preoperative comorbidities				
Type 2 diabetes mellitus (n)	4	2	13	0.538
Hypertension (n)	4	2	25	0.79
Dyslipidemia (n)	0	3	11	0.111
Sleep apnea (n)	1	1	2	0.249
Osteo-articular disease (n)	5	0	9	0.038
Patients with 1 or more comorbidity	10	5	41	0.512
Operative time (min)	77.0 ± 39.2	100.6 ± 19.6	130.7 ± 47.3	< 0.001
Length of hospital stay (d)	3.1 ± 2.9	3.8 ± 2.2	4.1 ± 5.8	0.761
Interval between VBG and revision (mo)	12.3 ± 10.7	30.7 ± 26.5	47.8 ± 34.8	< 0.001
Average %EWL after VBG (%)	61.7 ± 27.0	38.7 ± 22.9	43.5 ± 25.0	0.007

Re-VBG: Revision of the vertical banded gastroplasty; cSG: Conversion to sleeve gastrectomy; cRYGB: Conversion to Roux-en-Y gastric bypass; VBG: Vertical banded gastroplasty; %EWL: Percentage of excess weight loss.

the time. All patients underwent Mason-MacLean VBG, a standard VBG first described by Mason *et al*[4] with transection of the vertical staple line as described by MacLean *et al*[5].

Follow-up for these patients consisted of one year guidance by a psychologist, dietician and surgeon. Thereafter, a GP continued care unless weight loss problems or complaints were an issue. In such case patients underwent an analysis by all three disciplines and/or by means of a stomach X-ray and/or a gastroscopy. If considered eligible for revision the options were a re-VBG, cSG or cRYGB.

The Re-VBG technique meant in essence one of the 2 following adjustments. If the pouch was too large, a reshaping of the pouch was performed. The other option was an adjustment of the primarily placed band at the end of the gastric pouch.

A cSG meant a division of the lower part of the stomach 6cm from the pylorus up to the transgastric window to remove the gastric fundus and part of the corpus and antrum[22]. All sleeve gastrectomies were performed using a 34-Fr intraluminal boogie and stapled by use of the Endo GIA™ (Covidien, New Haven, CT, United States).

A cRYGB started with identification of the polytetrafluoroethylene (PTFE) band. Then the stomach was transected horizontally at the proximal side of the band. The band was removed in most cases. The pouch was resized with use of the endoscopic stapler up to the angle of His. Then, an end-to-side gastro-jejunostomy was constructed by a linear stapler and closed using Polysorb™ sutures before 2009 and V-Loc™ sutures after 2009 (Covidien, Mansfield, MA, United States). The alimentary limb, measuring 150-180 cm, was pulled up in an antecolic position. Finally, a side-to-side jejuno-jejunostomy was constructed, also using a linear stapler and closing the defect again with either Polysorb™ or V-loc™ sutures. Mostly, the procedure was finished by closing the mesenteric defects.

Statistical analysis

All data were collected retrospectively. Management and analysis as performed by using SPSS version 22, for Windows (SPSS Inc, Chicago, IL). Quantitative data are denoted as mean ± SD, whereas rates of complications and evolution on comorbidities are presented as a percentage. The student t test, linear regression analysis and logistic regression analysis were used to determine any significance of the observed differences among subgroups. Statistical significance was identified when the P value was less than 0.05. An odds ratio (OR) was provided when applicable and considered significant when OR (95%CI) ≠ 1. Summative figures and tables were used when necessary.

No ethical approval was required for this study.

RESULTS

Three hundred and ninety-two patients who underwent primary VBG were identified. According to the medical charts and questionnaires a total of 152 revisional procedures (38.7%) were performed between April 1999 and June 2014, of which six patients underwent revision in another hospital. Necessary data of these patients was retrieved. Furthermore, these six patients did complete the postal questionnaire, so they were included in the analysis, together with the rest of the study population. Baseline characteristics are shown in Table 1.

The initial 392 patients showed an average %EWL of 51.2% ± 27.4% and 54% of all known comorbidities were either improved or resolved. The resolved comorbidities were not taken into account in the current study. The patients necessitating revision showed a lower %EWL of 45.4% ± 25.8%, compared to those not necessitating revision (54.9% ± 27.7%, P = 0.001). At last follow-up, 58.4% (n = 229) of the total of 392 patients reported long-term complaints, which in 152 patients led to a revisional procedure.

Eighty-two point two percent of the current study population was female. Follow-up of patients necessitating second revision was taken into account until second revision. A total of 127 patients (83.6%) successfully completed last follow-up by either returning the postal questionnaire or answering the questions on the phone. This resulted in a mean follow-up after

Table 2 Complaints before revision (*n* = 152)

	Re-VBG *n* = 21 (*n*)	cSG *n* = 16 (*n*)	cRYGB *n* = 115 (*n*)	Total (%)	*P* value
Vomiting/ dysphagia/food intolerance	17	8	36	40.2	< 0.001
Weight regain	1	4	42	30.8	0.007
Insufficient weight loss	3	4	25	21.1	0.665
Unknown	0	0	6	3.9	0.792
Severe GERD	0	0	4	2.6	1.000
Decline comorbidities	0	0	1	0.7	1.000
Excessive weight loss	0	0	1	0.7	1.000

Re-VBG: Revision of the vertical banded gastroplasty; cSG: Conversion to sleeve gastrectomy; cRYGB: Conversion to Roux-en-Y gastric bypass; GERD: Gastro esophageal reflux disease.

revisional surgery of 56.5 ± 37.9 mo. In total, 25 patients did not return the postal questionnaire and could not be reached despite repeated attempts. Of these 25 patients, two patients deceased during follow-up due to a cause unrelated to bariatric surgery. Of these patients, the unreturned questionnaires were considered as missing data and the data of last known follow-up was used as final outcome so patients could be included in the analysis.

Reasons for revision

Complaints leading to revisional surgery are shown in Table 2. Six patients have had their revisional procedure in another center and therefore the complaints remained unknown. A possible surgically technical cause for failure of the VBG was found in 54.2% of all patients in this study.

Additional tests, in this study a stomach X-ray and/or a gastroscopy, were performed for additional analysis when necessary. The three main technical problems in this study population were a wide outlet, allowing faster passage of food through the pouch (17.1%), pouch dilatation (15.8%) and outlet stenosis (9.9%). Other technical reasons for failure were band erosion (5.3%), band luxation (displacement of the PTFE-band from its original position) (2.0%), staple line dehiscence resulting in a fistula (2.7%), pouch rotation (0.7%) and band dehiscence (0.7%).

Intra- and post-operative complications

126 procedures (82.9%) were performed laparoscopically, 15 procedures (9.9%) had a primary open approach and 11 (7.2%) procedures were converted from a laparoscopic to an open approach. One conversion was due to an intra-operative gastrointestinal perforation which could not be managed laparoscopically, the other procedures were converted because of an unacceptable laparoscopic overview due to extensive intra-abdominal adhesions. Only 2 intra-operative complications (1.4%) occurred during surgery, both being an iatrogenic gastro-intestinal perforation.

Complications in the 30-d postoperative period were seen in a combined total of 18 patients (11.8%). No complications were seen after revision of the primary VBG (0/21). After cSG, three complications were objectified (3/16 = 18.8%): One pneumonia, one patient suffering from persistent vomiting after surgery causing dehydration. No evident cause was found for the persistent vomiting. The third patient had an ileus. In the group of patients who underwent cRYGB, 15 complications were registered (15/115 = 13.0%). Reoperation was necessary in two out of three patients with bleeding and in all patients with anastomotic leakage (*n* = 3). All leakages were found at the gastro-jejunostomy. Other complications included intra-abdominal abscesses (*n* = 3), wound infection (*n* = 2), pneumonia (*n* = 1), urinary tract infection (*n* = 1), ileus (*n* = 1) and deep venous thrombosis (*n* = 1). The intra-abdominal abscesses all necessitated re-admission to the hospital for intravenous antibiotic treatment combined with either CT- or ultrasound-guided drainage. In total, eight patients were admitted for appropriate treatment of the complication, three patients did not necessitate readmission and seven complications occurred during primary admission. No significant difference was found in the total number of complications between the groups.

Weight loss and evolution of comorbidities

When not including the follow-up after any secondary revisional procedure, the mean total %EWL at last follow-up after primary revisional surgery was 66.4% ± 25.8%. In terms of change in BMI, this meant an average reduction of 12.5 ± 5.6 kg/m^2. Mean TBWL was 28.1% ± 11.2%. When including the 16 patients that underwent a second revisional procedure, %EWL was 68.2% ± 26.4%. Change in BMI was 12.7 ± 5.4 kg/m^2 and TBWL was 28.7% ± 11.1%.

At baseline, a total of 82 comorbidities were found amongst 56 patients. The separate improvement/resolution percentages for the three different procedures were 71.4%, 77.8% and 67.8% for respectively Re-VBG, cSG and cRYGB when considering each comorbidity as a separate entity. Figure 1 shows the improvement/resolution rates divided between the three groups. Table 3 shows the results after primary revisional surgery, stratified for each procedure.

Long-term complaints

At last follow-up after revisional surgery, 41 patients (27.0%) reported complaints, which in 16 cases necessitated a second revisional procedure. All long-term complaints are displayed in Table 4. In one patient after Re-VBG, complaints were caused by band erosion.

Subgroups based on reason for revision

Since the reason for revision may affect the outcome

Table 3 Results after primary revision at last follow-up (*n* = 152)

	Re-VBG *n* = 21 Mean ± SD	cSG *n* = 16 Mean ± SD	cRYGB *n* = 115 Mean ± SD	Corrected *P* value		
				Re-VBG *vs* cSG	cRYGB *vs* Re-VBG	cRYGB *vs* cSG
Follow-up (mo)	39.1 ± 48.7	49.3 ± 17.6	50.0 ± 33.3			
Average %EWL after VBG (%)	61.7 ± 27.0	38.7 ± 22.9	43.5 ± 25.0			
Additional %EWL	-14.6 ± 19.9	17.9 ± 32.7				
Total %EWL (%)	45.4 ± 25.5	56.6 ± 24.4	71.7 ± 23.8	0.614	0.006	0.025
Total body weight loss (%)	18.4 ± 11.1	24.1 ± 11.6	30.4 ± 10.1	0.049	< 0.001	0.016
Change body mass index (kg/m^2)	8.1 ± 5.8	10.8 ± 5.8	13.5 ± 5.1	0.119	< 0.001	0.042
Reinhold (%EWL > 50%) (%)	47.6	56.3	82.6	0.791[1] (0.211; 2.972)	0.342[1] (0.125; 0.934)	0.271[1] (0.090; 0.812)
Long-term complications (%)	61.9	62.5	15.7	0.833[1] (0.214; 3.244)	10.105[1] (3.600; 28.367)	8.421[1] (2.733; 25.950)
2nd revisional procedure (*n*, %)	10 (47.6%)	5 (31.3%)	1 (0.9%)	NA	NA	NA
Improvement/ resolution in patients with 1 or more comorbidities (%)	80 (8/10)	60 (3/5)	92.7 (38/41)	0.375[1] (0.081; 1.738)	1.247[1] (0.476; 3.265)	0.468[1] (0.126; 1.740)

[1]Odds ratio (95%CI). Re-VBG: Revision of the vertical banded gastroplasty; cSG: Conversion to sleeve gastrectomy; cRYGB: Conversion to Roux-en-Y gastric bypass; %EWL: Excess weight loss; NA: Not available. *P* value is corrected for operative time, time between VBG and revision, osteo-articular disease and mean %EWL after VBG. No correction possible in logistic regression analysis due to limited events and group sizes. In case of a second revisional procedure, follow-up until second was taken into account.

of the total weight loss, the evolution of comorbidities and potentially also the early postoperative course, additional analysis was performed. Patients undergoing revision for either weight regain or insufficient weight loss (WR/IWL) were compared to the other reasons given earlier in this manuscript. Results are shown in Table 5.

Second revisional procedures

A total number of 16 patients underwent a second revisional procedure. 10 patients underwent conversion from a revised VBG to RYGB, five patients had their sleeve converted to RYGB. One patient necessitated revision due to persistent vomiting after RYGB. Additional analysis showed a stenosis of the gastrojejunostomy. The most common reasons for second revision were weight regain (43.7%) and DVFI (31.3%). Other reasons were insufficient weight loss (18.7%) and band erosion (6.3%).

Table 4 Long-term complaints after revision (*n* = 152)

	Re-VBG *n* = 21 (*n*)	cSG *n* = 16 (*n*)	cRYGB *n* = 115 (*n*)	Total (%)
Vomiting/dysphagia/ food intolerance	4	4	6	9.2
Weight regain	6	4	4	9.2
Insufficient weight loss	2	1	0	2.0
Petersen's hernia	NA	NA	4	2.6
Incisional hernia	0	0	3	2.0
Recurrent abdominal pain	1	1	1	2.0
None	8	6	97	73.0

Re-VBG: Revision of the vertical banded gastroplasty; cSG: Conversion to sleeve gastrectomy; cRYGB: Conversion to Roux-en-Y gastric bypass; NA: Not available.

Table 5 Subgroup analysis (*n* = 152) (weight regain/ insufficient weight loss *vs* other complaints)

	WR/IWL *n* = 79 Mean ± SD	Other *n* = 73 Mean ± SD	*P* value
Age (yr)	41.6 ± 7.4	43.9 ± 10.7	0.121
Male:female (*n*)	13:66	14:59	0.661
Body mass index before VBG (kg/m^2)	44.7 ± 5.0	42.8 ± 4.8	0.016
Operative time (min)	128.2 ± 46.3	109.7 ± 48.6	0.02
Length of hospital stay (d)	4.3 ± 6.8	3.4 ± 2.0	0.858
Type of revision			
Re-VBG	4	17	0.004
cSG	8	8	
cRYGB	67	48	
Average %EWL after VBG (%)	31.3 ± 19.0	61.2 ± 23.1	< 0.001
Postoperative complications < 30 d (*n*, %)	12 (15.2%)	6 (8.2%)	0.184
Total %EWL (%)	67.5 ± 23.7	65.2 ± 28.1	0.583
Reinhold (%EWL > 50%) (%)	79.7	74	0.398
Long-term complications (%)	22.8	28.8	0.399
2nd revisional procedure (*n*)	5	11	0.079
Improvement/resolution rate (%, *n*)			
Type 2 diabetes mellitus	90 (9/10)	55.6 (5/9)	NA
Hypertension	76.9 (10/13)	44.4 (8/18)	NA
Dyslipidemia	100 (9/9)	100 (5/5)	NA
Sleep apnea	0 (0/1)	66.7 (2/3)	NA
Osteo-articular disease	57.1 (4/7)	57.1 (4/7)	NA

WR: Weight regain; IWL: Insufficient weight loss; Re-VBG: Revision of the vertical banded gastroplasty; cSG: Conversion to sleeve gastrectomy; cRYGB: Conversion to Roux-en-Y gastric bypass; %EWL: Excess weight loss; NA: Not available.

DISCUSSION

The absolute number of performed bariatric procedures is still increasing and therefore the number of revisional procedures can be expected to rise as well. Combined with the known poor long-term outcome after VBG, this fact strengthens the belief that more revisional procedures of failed VBG can be expected in the future. This study is the first to report on the comparison

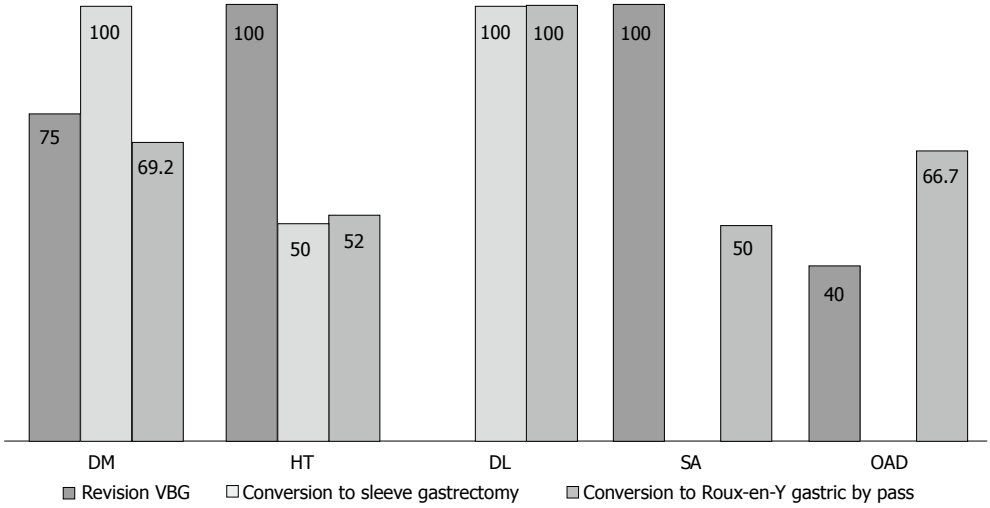

Figure 1 Improvement/resolution rates comorbidities. DM: Type 2 diabetes mellitus; HT: Hypertension; DL: Dyslipidemia; SA: Sleep apnea; OAD: Osteo-articular disease; VBG: Vertical banded gastroplasty.

between Re-VBG, cSG and cRYGB after failed primary VBG.

The revision rate of VBG was almost 39% (152 patients out of a total of 392 primary VBGs). The average %EWL after failed VBG was 45.4% ± 25.8% at last follow-up before revision. Patients who underwent Re-VBG had a noticeable better %EWL after VBG at baseline. This can be explained by the much shorter average interval of only 12 mo between the VBG and the revision, making follow-up too short to start noticing weight regain, a common reason for revision[17].

The main reasons for revision overall were similar to many other studies assessing either the long-term follow-up after VBG or the results after revision of the failed VBG[12,15,17,19,23]. However, there is a difference in the type of complaints leading to the different revisional procedures in this study. Furthermore, the number of procedures differed between the groups in this study. These facts can be explained by various reasons. First of all, the indication for Re-VBG was limited (mainly band-related problems). In the early years, when a patient had complaints of DVFI, a Re-VBG was performed, especially when the DVFI was caused by band erosion. As more reports became available over the years, showing that cRYGB is a better revisional option than Re-VBG, that latter procedure was abandoned at an early stage and cRYGB has proven to be a better option and has been for quite some years, explaining the low number of VBGs[15,16,18]. The last Re-VBG was performed in 2006. The second group, representing the cSGs, appears to have a more similar pattern of reasons for revision as seen in the cRYGB group, compared to the Re-VBG group. The size of the cSG group however is small, mainly due to early abandonment of this procedure, because there are very limited reports on the outcome of cSG over the last years and the larger experience with cRYGB, which had already proven to be a reliable procedure[16,17,22]. The last cSG after VBG was performed in January 2010. Since then, all revisional procedures after failed VBG were cRYGB.

The results in this study show that, although no early postoperative complications were seen in this group and the improvement/resolution rate of comorbidities is comparable with the other groups, Re-VBG is not the preferred revisional procedure after failed primary VBG. The reasons are a low total %EWL, high long-term complication rate and a high revision rate at long-term follow-up. Considering %EWL, this study actually showed an average decrease after Re-VBG, resulting in patients regaining nearly 15% of their initial excess weight. This result may be biased by the already available experience that cRYGB appeared superior to Re-VBG and the limited indication for Re-VBG[18].

The second group in this study was the cSGs. The long-term results after cSG are acceptable, with a significant better additional excess weight loss compared to Re-VBG and an improvement/resolution rate of comorbidities comparable with cRYGB. Although cSG appears to give a lower chance on postoperative complications compared to cRYGB, a significant higher long-term complication rate compared to cRYGB and a high second revision rate are showing the limits of this revisional procedure after failed primary VBG.

Although cSG appears to be superior compared to Re-VBG, this study confirms that cRYGB seems to be the best option of these three procedures. At last follow-up, patients showed an average %EWL of almost 72%, improvement or even resolution of comorbidities in 92.8% patients familiar with one or more obesity-related comorbidities. Furthermore, the chance of developing long-term complications after cRYGB is lower compared to the other two revisional procedures. In contrast of these good results, we noticed a high postoperative complication rate of 13.0% after cRYGB. However, this rate is comparable with many previously published results showing postoperative complication rates of 6.5%-25%[15,23-25]. In terms of %EWL, these results are comparable with previously reported data

after both revisional RYGB for failed VBG as well as after primary RYGB[24-27]. The current good results may be affected by the used alimentary limb length of 150-180 cm, on the other hand, this seems unlikely, since previous studies have shown that a limb length of 150 cm did not produce a better %EWL compared to a limb length of 75-100 cm[28,29].

Considering the subgroup analysis performed to differentiate between weight loss related complaints and other complaints, an expected significant difference was found in terms of %EWL. Furthermore, a difference was found in the number of different revisional procedures between the two groups, which can be explained by the earlier reported difference in reason for revision between procedures. This may also explain the difference in operative time, since a Re-VBG takes a significant shorter time than a cRYGB. After revisional surgery, no significant differences were found in terms of %EWL, postoperative complications and number of long-term complications and number of performed 2nd revisional procedures.

The reported high revision rate and previously published unfavorable results underline the limits of this old restrictive procedure[12,13]. These rates also strengthen the expectation that a number of patients will necessitate revision in the future, since VBG is currently still performed as a primary procedure[6]. Although revisional surgery seems feasible, the high number of complications after revision should be taken into account.

These results should be interpreted with caution due to a number of limitations in this study. First of all, the unequal distribution of groups, mainly due to a bias caused by the center's greater experience with cRYGB, thereby explaining the small number of Re-VBGs and cSGs. Furthermore, the retrospective design limits the reliability of the reported outcome. Since not all patients responded to our question to update the last known follow-up, a number of long-term complaints might have been missed, as well as potential revisional procedures performed in other hospitals. Not only the distribution between groups is unequal, also total time of follow-up is unequal, since Re-VBGs were performed only in the early and cRYGBs are still performed nowadays. The mean follow-up appears to be similar, but it should be kept in mind that Re-VBG showed a higher second revision rate as opposed to cSG and cRYGB and follow-up of the primary revision was taken into account until second revision. Keeping these limitations in mind, this study still suggests that Roux-en-Y gastric bypass is the superior choice for revisional surgery after failed primary VBG due to a good long-term %EWL, a high improvement rate of comorbidities, a low long-term complication rate and a low percentage of necessitated second revisional procedures.

In conclusion, in terms of additional weight loss, number of postoperative complaints and necessitation of a second revision, the Roux-en-Y gastric bypass seems feasible as a revision for a failed. Furthermore, the high number of complications after VBG and complications due to revisional procedures underline that VBG should be excluded as a primary option in bariatric surgery and other restrictive should be considered instead.

COMMENTS

Background

Vertical banded gastroplasty (VBG) was a popular restrictive bariatric procedure however, has been abandoned due to a high long-term complications rate in many cases leading to the necessitation of revisional surgery. As a number of these revisions can be expected, this study reports and compares the results after revision of the primary VBG (Re-VBG), conversion to sleeve gastrectomy (cSG) and conversion to Roux-en-Y gastric bypass (cRYGB). As the number of patients with a bariatric procedure rises annually, the number of failed procedures will rise as well, some necessitating surgical treatment (by either revision or conversion). It is good to know what can be expected in both the short term and the long term when it comes to complications, weight loss and other complaints.

Research frontiers

Research on the conversion or revision of failed VBG is limited to mainly results after conversion to Roux-en-Y gastric bypass. These articles show decent results, suggesting that Roux-en-Y gastric is a feasible option as revision of a failed VBG. Results on the comparison of different conversions after failed VBG are limited.

Innovations and breakthroughs

The current article is, by the authors' knowledge, the first to compare different surgical options as treatment of failed VBG.

Applications

When confronted with failed VBG, either due to insufficient weight loss, weight regain or (other) physical complaints, conversion to Roux-en-Y gastric bypass appears to be more feasible compared to revision of the VBG or cSG.

Terminology

Re-VBG: Revision of a primary VBG; cSG: Conversion to sleeve gastrectomy; cRYGB: Conversion to Roux-en-Y gastric bypass.

Peer-review

The paper is acceptable and very interesting.

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ORIGINAL ARTICLE

Retrospective Study

Changes over time in milk test results following pancreatectomy

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Author contributions: Aoki H, Utsumi M, Sui K, Kanaya N and Kunitomo T performed operations; Takeuchi H supervised the research; Aoki H, Takakura N, Shiozaki S and Matsukawa H established milk test; Aoki H wrote this paper.

Institutional review board statement: This study was reviewed and approved by the Iwakuni Clinical Center Institutional Review Board.

Informed consent statement: Patients were not required to give informed consent to this study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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Data sharing statement: Participants gave informed consent for data sharing.

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Abstract

AIM: To investigate changes over time in, and effects of sealing technology on, milk test results following pancreatectomy.

METHODS: From April 2008 to October 2013, 66 pancreatic resections were performed at the Iwakuni Clinical Center. The milk test has been routinely conducted at the institute whenever possible during pancreatectomy. The milk test comprises the following procedure: A nasogastric tube is inserted until the third portion of the duodenum, followed by injection of 100 mL of milk through the tube. If a chyle leak is present, the patient tests positive in this milk test based on the observation of a white milky discharge. Positive milk test rates, leakage sites, and chylous ascites incidence were examined. LigaSure™ (LS; Covidien, Dublin, Ireland), a vessel-sealing device, is routinely used in pancreatectomy. Positive milk test rates before and after use of LS, as well as drain discharge volume at the 2nd and 3rd postoperative days, were compared retrospectively. Finally, positive milk test rates and chylous ascites incidence were compared with the results of a previous report.

RESULTS: Fifty-nine milk tests were conducted during pancreatectomy. The positive milk test rate for all pancreatectomy cases was 13.6% (8 of 59 cases). One case developed postoperative chylous ascites (2.1% among the pancreatoduedenectomy cases and 1.7% among all pancreatectomies). Positive rates by procedure were 12.8% for pancreatoduodenectomy and 22.2% for distal pancreatectomy. Positive rates by disease were 17.9% for pancreatic and 5.9% for biliary diseases. When comparing results from before and after use of LS, positive milk test rates in pancreatoduodenectomy were 13.0% before and 12.5% after, while those in distal pancreatectomy were 33.3% and 0%. Drainage volume tended to decrease when LS was used on the 3rd postoperative day (volumes were 424 ± 303 mL before LS and 285 ± 185 mL after, P = 0.056). Both chylous ascites incidence and positive milk test rates decreased slightly compared with those rates from the previous study.

CONCLUSION: Positive milk test rates and chylous ascites incidence decreased over time. Sealing technology may thus play an important role in preventing postoperative chylous ascites.

Key words: Chylous ascites; Milk test; Pancreatectomy; Surgical energy device; Drain discharge

Core tip: Chylous ascites is sometimes a severe complication of pancreatectomy. We previously reported that the milk test could serve to prevent chylous ascites following surgery. In this study, changes over time in milk test results, and effects of new energy devices on the test results, were investigated. Compared with the first report results, positive milk test rates and chylous ascites incidence were found to have decreased slightly. Use of the new energy devices also tended to result in decreased drainage volume. These findings suggest that the vessel-sealing technology could play an important role in preventing postoperative chylous ascites.

Aoki H, Utsumi M, Sui K, Kanaya N, Kunitomo T, Takeuchi H, Takakura N, Shiozaki S, Matsukawa H. Changes over time in milk test results following pancreatectomy. *World J Gastrointest Surg* 2016; 8(3): 246-251 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i3/246.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i3.246

INTRODUCTION

Chylous ascites is a condition defined by the secretion of milky white fluid with high triglyceride content. Generally, it occurs due to traumatic injury or obstruction of the lymphatic system. Although it is a rare condition, there are multiple causes, such as neoplasm, inflammation, infection, surgery, trauma, and so on[1]. As for postoperative causes, pancreatic surgery is a major cause of chylous ascites[2-6]. According to reports, rates of chylous ascites incidence after pancreatoduodenectomy ranged from 1.8% to 13%. The cisterna chili lies anteriorally of the first and second lumbar vertebrae, on the same plane as the pancreas. Injury to the cisterna chili or its tributaries can occur during pancreatic resection. We experienced several cases of chylous ascites after pancreatectomy, and the condition is often associated with prolonged hospitalization. These are the reasons why we started studying the milk test in 2004 for its potential as a treatment to prevent the development of chylous ascites following pancreatic resection[5].

On the other hand, remarkable advances have been witnessed in surgical energy technology. Such surgical energy devices as the vessel-sealing system represent a new hemostatic technology based on the combination of pressure and bipolar electrical energy that leads to the denaturation of collagen and elastin in the vessel walls and fusion of these into a hemostatic seal. Besides hemostatic ability, the new surgical energy devices might be used to block lymphatic flow. In terms of technical issues, we cannot ignore the effects of such new surgical energy technologies.

The aim of this study is to investigate changes over time in milk test results following pancreatectomy and the effects of vessel-sealing devices on milk test results.

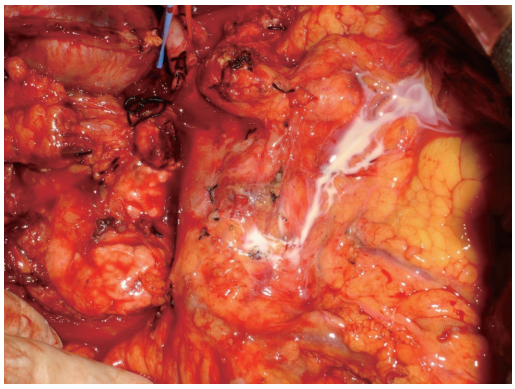

Figure 1 Milk test positive case.

MATERIALS AND METHODS

From April 2008 to October 2013, 66 pancreatic resections were performed at the Iwakuni Clinical Center, Iwakuni, Japan. Starting in 2004, the milk test has been routinely conducted whenever possible during pancreatectomy. Briefly, the milk test is conducted in the following way: A nasogastric tube is inserted until the third portion of the duodenum, followed by injection of 100 mL of milk through the tube. If a chyle leak is present, the patient tests positive in this milk test based on the observation of a white milky discharge (Figure 1). Seven cases were excluded: 2 laparoscopic surgeries,

Table 1 Positive rate of milk test

Negative	Positive[1]
51	8 (13.6%)
	leakage site[2]
	SMA 4
	SMV 2
	LRV 1
	Paraaorta 1
	Mesentery 1

[1]Includes one case of postoperative chylous ascites; [2]One case showed two leakage sites. SMV: Superior mesenteric vein; LRV: Left renal vein.

Table 2 Positive rate of milk test by operative procedure

Procedure	Positive	Negative
PD (n = 47)	6 (12.8%)	41
DP (n = 9)	2 (22.2%)	7

PD: Pancreatoduodenectomy; DP: Distal pancreatectomy.

as well as 2 emergency and 3 unexpected pancreatic resections. The milk test was used in 59 of these 66 cases [47 pancreatoduodenectomy (PD); 2 total pancreatectomy (TP); 9 distal pancreatectomy (DP); 1 middle pancreatectomy]. Final diagnoses were 21 cases of pancreatic cancer, 12 intraductal papillary mucinous neoplasm, 9 bile duct cancer, 7 ampulla of Vater cancer, 2 each of chronic pancreatitis, gallbladder cancer, and duodenal cancer, and 1 each of metastatic pancreatic cancer and endocrine tumor.

Positive milk test rates, leakage sites, and chylous ascites incidence were examined. Since May 2011 in the Iwakuni Clinical Center, a vessel-sealing system (LigaSure small jaw instrument) is routinely used in pancreatectomy. Positive milk test rates before and after introduction of LigaSure (LS) as well as drain discharge volume were compared retrospectively. Finally, positive milk test rates and chylous ascites incidence were compared with the results of our previous report (conducted from 2004 to 2008)[5].

Variables were compared using χ^2 test or Student's t test. JMP 9 statistical software (SAS Institute, Cary, NC, United States) was used for all analyses. $P < 0.05$ was considered statistically significant. This study was reviewed and approved by the Iwakuni Clinical Center Institutional Review Board.

RESULTS

Positive milk test rate among all pancreatectomy cases was 13.6% (8 of 59 cases). Leakage sites were as follows: Superior mesenteric artery: 4 cases; superior mesenteric vein: 2; left renal vein: 1; paraaorta: 1; and mesentery: 1. One case had two leakage sites. Six of 8 cases presented with leakage sites around superior mesenteric vessels (Table 1). One case demonstrated postoperative chylous ascites. Incidence of chylous ascites was 2.1% among the PD cases and 1.7% among all pancreatectomies. This case was milk test positive and treated with a conservative method using octreotide.

Table 3 Positive rate of milk test by diseases

Disease	Positive	Negative
Biliary disease (n = 17)	1 (5.9%)	16
Panceatic disease (n = 39)	7 (17.9%)	32
Panceatic disease with PD (n = 30)	4 (13.3%)	26

PD: Pancreatoduodenectomy.

Positive rates by procedure were 12.8% for PD and 22.2% for DP (Table 2). No significant differences in positive rates were observed between the different procedures. Positive rates by diseases were 17.9% in pancreatic diseases and 5.9% in biliary diseases. When limited to PD patients in pancreatic diseases, the positive rate reached 13.3%. The positive rates were higher in pancreatic diseases, but this difference did not reach the level of statistical significance (Table 3).

When comparing figures before and after the introduction of LS, positive milk test rates for PD and TP were 13.0% before and 12.5% after, and for DP 33.3% and 0%. There was no statistical significance (Figure 2). As for drain discharge volume, the two groups were compared on the 2nd and 3rd postoperative days (POD) on average. Drain discharge volumes for the 2nd POD cases were 454 ± 237 mL (mean ± SD) before introduction of LS and 383 ± 279 mL after; for the 3rd POD cases, the volumes were 424 ± 303 mL and 285 ± 185 mL, respectively (Figure 3). Although no statistical differences were evident, a tendency for decreased drainage volume was observed when using LS on the 3rd POD cases (P = 0.056).

Incidences of chylous ascites were 2.9% in the previous study's period (2004-2008) among all pancreatectomy[5] cases and 1.7% in this study. Positive milk test rates were 22.1% in the previous study[5] and 13.6% in this study (Figure 4). Both rates represented a slight decrease compared with the first report, but this difference did not reach the level of statistical significance.

DISCUSSION

Postoperative chylous ascites is a relatively rare condition, but once it occurs the disorder can cause hyponutrition and prolonged hospitalization.

Positive milk test rates by procedure were higher for DP than for PD, but this difference was not significant. In our previous report, the incidences were nearly the same. Some authors report lower rates of chylous ascites in DP[3], but others do not[6]. This result might be due to the difference in disease incidence itself, but this aspect is not yet fully understood. According to the positive milk test rates, chylous ascites might

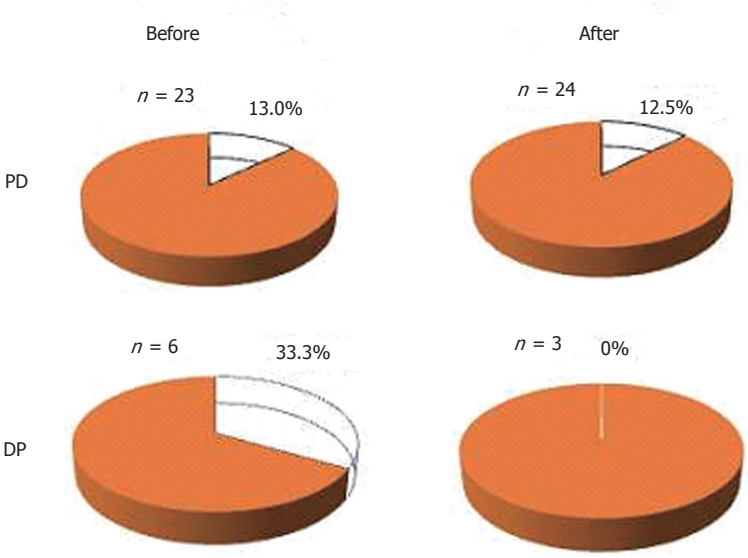

Figure 2 Comparison of milk test positivity: Before and after induction of sealing devise. PD: Pancreatoduodenectomy; DP: Distal pancreatectomy.

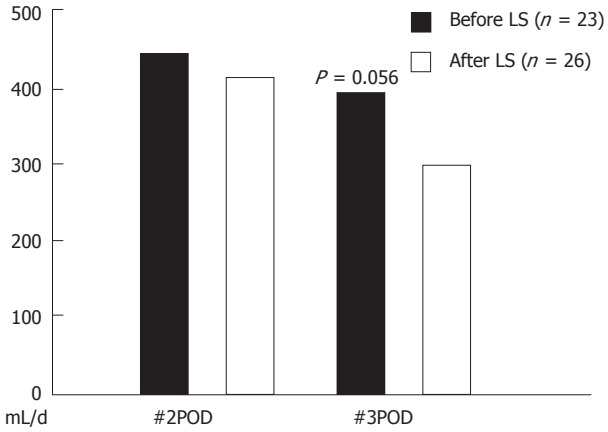

Figure 3 Drain discharge of pancreatoduodenectomy and total pancreatectomy.

occur at least equally in DP. Positive milk test rates by disease were higher in pancreatic than in biliary disease. The existence of concomitant pancreatitis with pancreatic disease might have played a role in this result. In one study, van der Gaag *et al*[4] reported that chronic pancreatitis is one of the risk factors for the development of postoperative chylous ascites. Kuboki *et al*[6] reported manipulation of the paraaortic area, retroperitoneal invasion, and early enteral feeding to be independent risk factors associated with chylous ascites. The first two of these three factors may have had something to do with the operative procedure itself. As for early enteral feeding, Malik *et al*[2] also alerted the medical community about the risk for chyle leak in this treatment. Careful observation of drain discharge is thus necessary before allowing such patients to begin meal intake after pancreatectomy.

The management algorithm used to treat chylous ascites integrates repeat palliative paracentesis, dietary measures, total parenteral nutrition therapy, peritoneovenous shunting, and surgical closure of the lymphoperitoneal fistula. Somatostatin therapy should be attempted with or without total parenteral nutrition early in the course of treatment of chylous ascites before any invasive steps are taken[7]. In addition, Kawasaki *et al*[8] reported effectiveness of lymphangiography not only for diagnosis but also for treatment of postoperative chylothrax and chylous ascites. In our experience, albeit somewhat limited, none of the cases required surgical treatment for postoperative chylous ascites. Chylous ascites should thus be treated by surgical procedure at the time of the initial operation. We emphasized the importance of steady ligation in our previous report. But now, new surgical energy technologies are gradually replacing that technique.

New surgical energy devices-such as the harmonic scalpel or vessel-sealing system-are reported to be useful in reducing drain discharge in colonic surgery[9] and in axillary lymphadenectomy[10], respectively. Nakayama *et al*[11] reported the utility of an ultrasonic scalpel in sealing the thoracic duct based on use of a pig model. The burst pressure after sealing by this ultrasonic scalpel was 188-203 mmHg, which is far above the pressure at which lymph vessels are occluded.

The question is what type of surgical energy device should we use to prevent chylous ascites? Seehofer *et al*[12] performed a comparison among a new surgical tissue management system that combines ultrasonic vibration and tissue dissection with bipolar coagulation [thunderbeat (TB)], a conventional ultrasonic scissor [Harmonic Ace (HA)], and a bipolar vessel clamp (LS), in terms of safety and efficacy. The burst pressure of the TB technique in the larger-artery category (5-7 mm) was superior to that of the HA technology. The dissection speed of the TB was significantly faster than that of the LS. Although seal width was influenced by the width of the jaw, LS had the widest seal width and the fewest gas pockets. This means that histologically LS is superior in terms of seal reliability and prevention

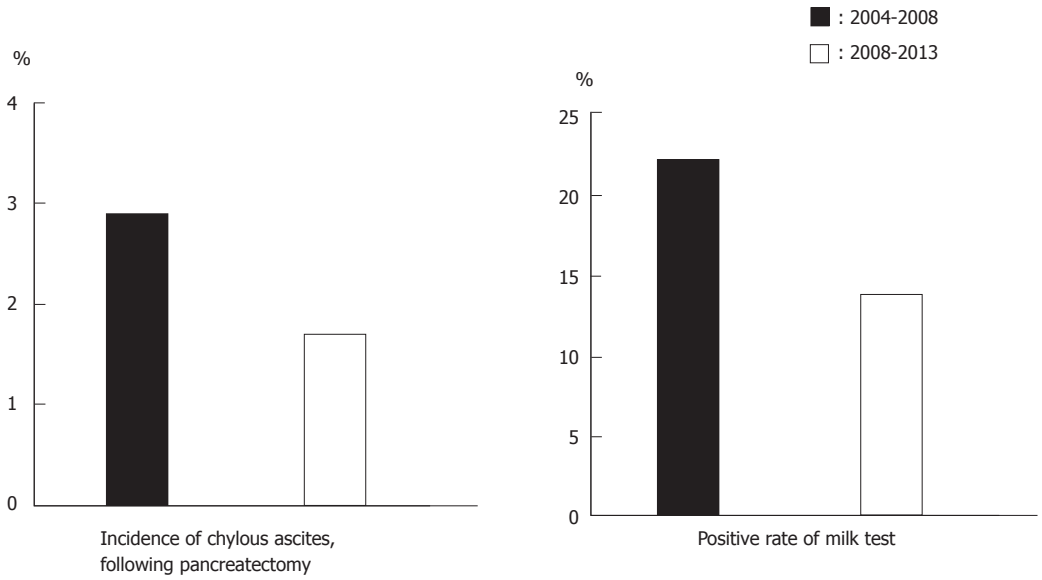

Figure 4 Changes over time in incidence of chylous ascites and milk test positivity.

of thermal injury. Janssen[13] conducted a systematic search for randomized controlled trials that compared the effectiveness and costs of vessel-sealing devices with those of other electrothermal or ultrasonic devices in abdominal surgical procedures. The researchers involved in the study concluded that vessel-sealing devices may be considered safe and that their use may reduce costs due to reduced blood loss and shorter operating time in some abdominal surgical procedures compared to mono- or bipolar electrothermal devices. Though thermal injury is an issue that needs to be resolved, surgical energy devices can be used as another contributing factor for prevention of chylous ascites.

In our study, although there was no significant difference, both chylous ascites incidence and positive milk test rates decreased over time. The reasons for that are partly because we are more knowledgeable about chylous ascites and because of the technical advances made especially in surgical energy devices. Although we could not prove our results definitively, we think it is a matter of more numbers of cases. We therefore started planning in November 2013 a randomized prospective milk test study. In this study, we will investigate the utility of the milk test and chyle leak sites more comprehensively. We plan for the next study to include comparisons of different surgical energy devices.

In conclusion, positive milk test rates were higher in DP and pancreatic disease. Both chylous ascites incidence and positive milk test rates decreased over time. Based on the study results, surgical energy devices should be used as another contributing factor for the prevention of chylous ascites. Further investigation is needed to confirm the utility of the milk test.

COMMENTS

Background

Postoperative chylous ascites is a rare condition, but once it occurs the disorder can cause hyponutrition and prolonged hospitalization. Although chylous ascites after pancreatectomy has recently become an issue in the field of abdominal surgery, methods for prevention of chylous ascites are not well established. The authors therefore investigated the milk test as a method to resolve this condition starting in 2004. In their previous study, use of the milk test contributed to a decrease in incidence of chylous ascites. In this study, they looked at changes over time in milk test results. In addition, they assessed the effects of energy devices, which first appeared during the study period and now cannot be ignored in cases of abdominal surgery.

Research frontiers

The authors believe that the milk test is a useful method for detecting lymphorrhea during surgery. But to truly prove its utility, a prospective study is necessary. The authors therefore initiated a prospective randomized study in 2013.

Innovations and breakthroughs

To date, many papers have been published about chylous ascites, but most of them are focused on its pathogenesis or treatment. There is no study about prevention, especially in the case of pancreatectomy. The authors emphasize that postoperative chylous ascites should and can be prevented during surgery. The results of this study also suggest that new energy devices may play an important role in decreasing drain discharge.

Applications

A benefit to the milk test is that milk is easy to obtain and inexpensive. When the milk test is used, there is no need for special drugs or instruments. In addition, no complications accompany use of the milk test.

Peer-review

Reviewers mentioned that our paper provided interesting methodology and results. They stated that they are looking forward to the new study results.

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Primary squamous cell carcinoma of the rectum: An update and implications for treatment

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Abstract

AIM: To provide an update on the aetiology, pathogenesis, diagnosis, staging and management of rectal squamous cell carcinoma (SCC).

METHODS: A systematic review was conducted according to the preferred reporting items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive search of Ovid MEDLINE was performed with the reference list of selected articles reviewed to ensure all relevant publications were captured. The search strategy was limited to the English language, spanning from 1946 to 2015. A qualitative analysis was undertaken examining patient demographics, clinical presentation, diagnosis, staging, treatment and outcome. The quantitaive analysis was limited to data extracted on treatment and outcomes including radiological, clinical and pathological complete response where available. The narrative and quantitative review were synthesised in concert.

RESULTS: The search identified 487 articles in total with 79 included in the qualitative review. The quantitative analysis involved 63 articles, consisting of 43 case reports and 20 case series with a total of 142 individual cases. The underlying pathogenesis of rectal SCC while unclear, continues to be defined, with increasing evidence of a metaplasia-dysplasia-carcinoma sequence and a possible role for human papilloma virus in this progression. The presentation is similar to rectal adenocarcinoma, with a diagnosis confirmed by endoscopic biopsy. Many presumed rectal SCC's are in fact an extension of an anal SCC, and cytokeratin markers are a useful adjunct in this distinction. Staging is most accurately reflected by the tumour-node-metastasis classification for rectal adenocarcinoma. It involves examining locoregional disease by way of magnetic resonance imaging and/or endorectal ultrasound, with systemic spread excluded by way of computed tomography. Positron emission tomography is integral in the workup to exclude an external site

of primary SCC with metastasis to the rectum. While the optimal treatment remains as yet undefined, recent studies have demonstrated a global shift away from surgery towards definitive chemoradiotherapy as primary treatment. Pooled overall survival was calculated to be 86% in patients managed with chemoradiation compared with 48% for those treated traditionally with surgery. Furthermore, local recurrence and metastatic rates were 25% *vs* 10% and 30% *vs* 13% for the chemoradiation *vs* conventional treatment cohorts.

CONCLUSION: The changing paradigm in the treatment of rectal SCC holds great promise for improved outcomes in this rare disease.

Key words: Squamous cell carcinoma; Rectal cancer; Chemoradiotherapy; Surgery; Complete response

Core tip: Primary squamous cell carcinoma (SCC) of the rectum is a rare entity with a historically poor prognosis. This systematic review provides an in depth summary of the current body of knowledge surrounding the aetiology, pathogenesis, diagnosis, staging and prognosis of this disease. Given the current paradigm shift in the first line treatment of rectal SCC away from traditional surgical management towards definitive chemoradiotherapy, the evidence supporting this change is examined.

Guerra GR, Kong CH, Warrier SK, Lynch AC, Heriot AG, Ngan SY. Primary squamous cell carcinoma of the rectum: An update and implications for treatment. *World J Gastrointest Surg* 2016; 8(3): 252-265 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i3/252.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i3.252

INTRODUCTION

Rectal squamous cell carcinoma (SCC) is a rare malignancy of the gastrointestinal (GI) tract. Due to the low incidence of this cancer and subsequent lack of literature, the underlying pathogenesis and risk factors are yet to be clearly defined. Furthermore, there is significant heterogeneity in the treatment regimens utilised, with the optimal management yet to be clarified. Nonetheless, certain patterns do emerge on reviewing all published cases by way of a systematic review, to determine where our future research should be directed in order to improve upon treatment and facilitate best patient outcomes.

MATERIALS AND METHODS

A systematic literature review was conducted according to the preferred reporting items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive search of Ovid Medline was performed with the abstracts screened to determine relevant articles, following which the full texts were obtained. A directed manual review of all embedded references was undertaken of the selected articles to ensure all studies published on primary SCC of the rectum were identified.

The search strategy was based on a combination of medical subject heading terms (carcinoma, squamous cell; rectum) and text words (SCC and rectum), spanning from 1946 to May 2015. The search was limited to English language with the most recent search performed on 8th May 2015.

Inclusion and exclusion criteria

The definition of rectal SCC as stipulated by Williams *et al*[1] which requires three exclusion criteria to be met (detailed in "diagnosis" below) was used to identify relevant studies. Consequently, studies reporting rectal SCC arising in the presence of a fistula, from an anal or gynaecological origin, a distant site *via* metastasis, or where the pathology was mixed (*e.g.*, adenosquamous) were excluded. Additionally, studies where the lesion was premalignant (*e.g.*, metaplasia or SCC *in situ*), of colonic rather than rectal origin or where the data was inadequate were excluded from the quantitative analysis.

Data extraction

Data extracted included the names of the authors, date of publication, demographic information and clinical presentation. Location of the lesion and treatment detailing the primary modality, the use of pre- and/or post-operative modalities and the type of operation where present was also noted. Other collated information included patient outcomes in the form of local recurrence, metastasis, and survival, as well as the length of follow up. Radiological, clinical and pathological complete response (CR) was also recorded where available.

RESULTS

The database and bibliography search identified 487 articles in total. After screening the articles for inclusion and exclusion criteria, 79 were included in the qualitative review and 63 in the quantitative analysis as detailed in Figure 1. This included 43 case reports and 20 case series with a total of 142 individual cases reported. Given the inherent bias in case reports and the inconsistency with reporting important prognostic variables including stage and pathological grade, an in depth individual patient data meta-analysis was not performed.

DISCUSSION

Background

Epidemiology: Rectal SCC is a rare disease with the current literature consisting primarily of case reports, case series and one large population based study.

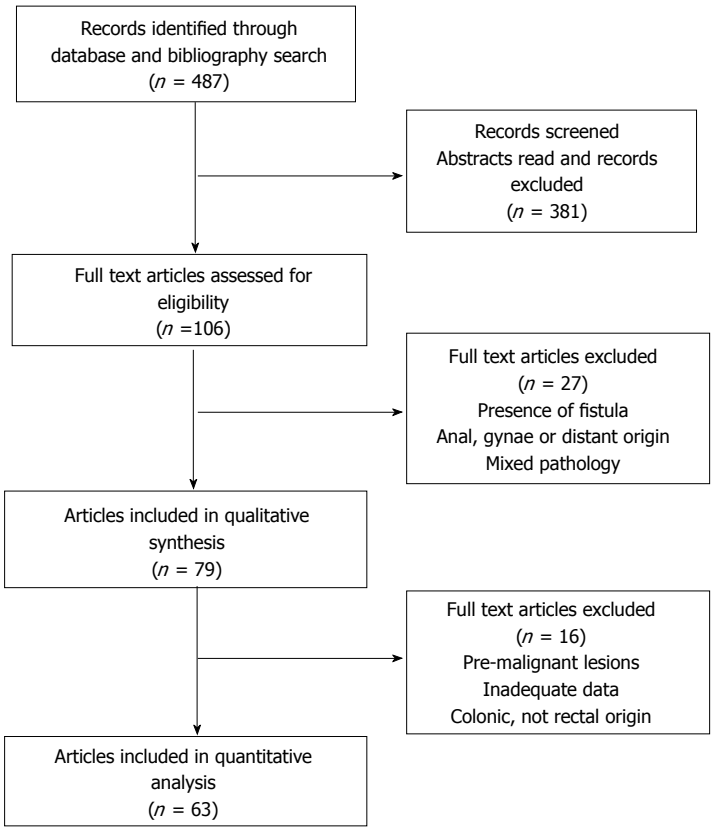

Figure 1 Preferred reporting items for Systematic Reviews and Meta-Analyses flow diagram.

While SCC can occur throughout the GI tract, it most commonly affects the upper aerodigestive tract down to the oesophagogastric junction, and the anal canal. SCC of the rectum however is much less common accounting for 0.3% of all histological subtypes[2]. While pure SCC is the most frequent histology, cases with a mixed histologic pattern, generally adenosquamous, have been described[3]. While other rectal cancer subtypes including neuroendocrine, lymphoma and gastrointestinal stromal tumours occur infrequently, rectal SCC remains the most rare with the exception of sarcoma[2].

Schmidtmann[4] reported the first case of SCC of the colon in 1919, with Raiford[5] publishing on the first case of rectal SCC in 1933. While SCC can be diagnosed throughout the colorectum, the most common site of predilection is the rectum (93.4%), followed by the right colon (3.4%)[2]. The true incidence of rectal SCC can be most accurately drawn from the large population based study from the National Cancer Institute (NCI), which estimated it at 1.9 per million population in the year 2000, or 3 per 1000 colorectal cancers. This study also identified a significant rise in the incidence of rectal SCC between 1992 and 2000, estimating it at 5.9% per year. Extrapolating from this figure, the current incidence may be as high as 3.5 per million population[2].

While strong epidemiological evidence on rectal SCC is absent, patient demographics and risk factors can be gauged from the published retrospective reviews and population study. Patients diagnosed with SCC of the rectum have ranged in age from 39 to 93 years old, with an average age of 63 years. Female gender predominates, accounting for 57.4% *vs* 42.6% of cases in the NCI study. Patients most frequently present with early stage localised (stage Ⅰ/Ⅱ, 52.8%) or regional (stage Ⅲ, 29.3%) disease and there is no apparent ethnic or geographic predisposition[2].

Despite a lack of firm risk factors with a causal link to the development of rectal SCC, loose associations have been identified. The strongest association evident in the literature is that of proctitis, generally secondary to ulcerative colitis. There have been multiple case reports of rectal SCC in this setting, one of which compared the incidence with that of the general population to demonstrate a markedly increased risk in ulcerative colitis patients[6-15]. Of significance, there has also been a report of rectal SCC in the setting of active Crohn's disease of the rectum[16], and in the setting of chronic prolapse[17]. Drawing upon this association with inflammation, the literature also contains three reports of parasitic infections with colorectal SCC, in the form of Schistosomiasis in two cases, and Amoebiasis in one, however, their significance is unclear[1,18,19].

Other postulated risk factors have included a past history of radiotherapy for other pelvic malignancies, which has been noted in several case reports[20-23]. Additionally, colorectal adenocarcinoma, both synchronous and metachronous has been identified in patients with SCC of the rectum[3,24-27]. For colonic SCC, asbestos exposure and colonic duplication have also been associated, but this has not been the case for SCC of rectal origin.

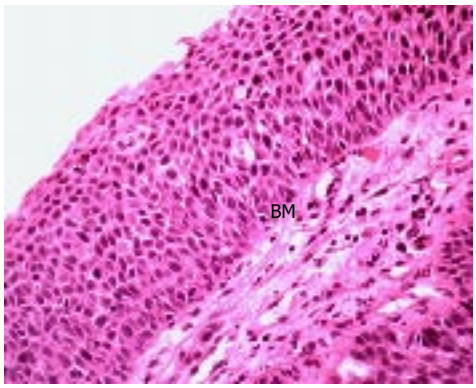

Figure 2 Haematoxylin and eosin stain of rectal squamous cell carcinoma *in situ*. This demonstrates architectural distortion, marked nuclear hyperchromatism and pleomorphism, along with full thickness basal layer expansion and no surface maturation. There is no evidence of invasion through the basement membrane (BM) (Image courtesy of Associate Professor Ken Opeskin, Department of Pathology, St Vincent's Hospital, Melbourne).

Given the strong association of human papilloma virus (HPV) with anal SCC, several studies have investigated its role in rectal SCC. This has produced variable results, with as many studies identifying HPV 16 in colorectal SCC specimens[12,17,28,29], as those that have failed[3,16,18]. Given this limited evidence, HPV infection as a risk factor for rectal SCC remains to be proven.

Pathogenesis: Despite reports of rectal SCC since the early 20th century, it's underlying aetiology remains unclear. While multiple theories have been postulated over this time period, its pathogenesis continues to be unravelled by assimilating the current body of evidence.

The theory of chronic inflammation leading to squamous metaplasia and subsequent carcinoma is one of the most prominent. This idea draws upon the fact that irritation and inflammation can lead to a change in the epithelial lining. This is termed metaplasia and is known to occur in the GI tract in response to exposure to various stressors[30]. Metaplasia is the reversible change of one adult cell type into another and represents an adaptive substitution of stress-sensitive cells by a cell type better able to withstand that particular insult[31]. The postulated inciting cause for the chronic inflammation leading to metaplasia has included the risk factors mentioned above of ulcerative colitis[6,32], radiotherapy[14,20-23] and infection[18].

Adding support to this theory is firstly the description of squamous metaplasia in the colorectum in numerous instances. This has included sporadically[33-36], in the regenerating epithelium of chronic ulcerative colitis[15,32], in a rat by instillation of a chronic irritant (H_2O_2) and in a mouse secondary to chronic rectal prolapse[37,38]. Secondly and of most significance, is the demonstration of an adjacent histological sequence in the rectum, from squamous metaplasia through dysplasia to carcinoma *in situ* (Figure 2) and invasive squamous carcinoma (Figure 3)[6,7,12,15,24,35].

Drawing further upon this theory is the idea of pluripotent mucosal stem cells capable of multidirectional differentiation, first postulated in the 1950's[17,39-41]. Further work by Nahas *et al*[16] in 2007 was based on the fact that keratin profiles vary amongst epithelia but remain constant in neoplastic transformation. They demonstrated that rectal SCC and adenocarcinoma stain for cytokeratin CAM5.2, unlike SCC of the anal margin, suggesting a common cell of origin for both rectal cancer subtypes. This lends support to an idea that the mucosal lining of the rectum contains a common pluripotent endodermal stem cell, which under certain conditions (inflammation and epithelial damage) can undergo squamous differentiation to better protect the rectum from the inciting cause. This is visualised as an area of metaplasia, which can subsequently undergo dysplasia and carcinomatous change if the inciting cause is not removed.

HPV has been postulated as a possible factor in inciting the dysplastic change of the squamous metaplasia. However, while there is a strong association between HPV and SCC of multiple sites including the anus, head/neck and cervix, the role in SCC of the rectum has not currently been established. There are more than 100 subtypes of HPV, with the most frequently encountered oncogenic forms being HPV 16 and 18. There are only a limited number of studies that have examined for HPV in rectal SCC, and they have utilised varying techniques for detection with discordant results. Audeau *et al*[18] used immunohistochemistry to examine 20 squamous lesions (squamous metaplasia, SCC, adenosquamous carcinoma), without evidence of HPV 6, 11, 16 or 18. Frizelle *et al*[3] and Nahas *et al*[16] used an *in situ* hybridisation technique on 6 and 5 rectal SCC specimens respectively, again without evidence of HPV deoxyribonucleic acid (DNA). However, studies by Sotlar *et al*[28] (1 rectal SCC), Kong *et al*[12] (2 rectal SCC, 1 rectal SCC *in situ*), Matsuda *et al*[29] (1 rectal SCC) and Jaworski *et al*[17] (2 rectal SCC *in situ*), all identified HPV 16 in 7 rectal squamous lesions when utilising the PCR method, which is regarded as the gold standard. This may indicate that the sensitivity of the test employed in the detection of HPV has previously masked its presence.

The case presented by Sotlar *et al*[28] is also of particular interest, given that it reported the findings of adjacent squamous metaplasia, dysplasia, and carcinoma in sequence, with HPV 16 identified in all three components and the surrounding non-tumour affected rectal mucosa. This mirrors the pre-neoplastic to neoplastic progression well documented in HPV driven anogenital cancers. Furthermore, they identified transcriptional activity of the HPV E6/7 oncogenes critical to HPV's role in carcinogenesis. This may suggest that there are two possible pathways to the pathogenesis of colorectal SCC, HPV driven and non-HPV driven. However, while there is currently limited evidence surrounding HPV in rectal SCC, a clear association and a role in causation remains to be

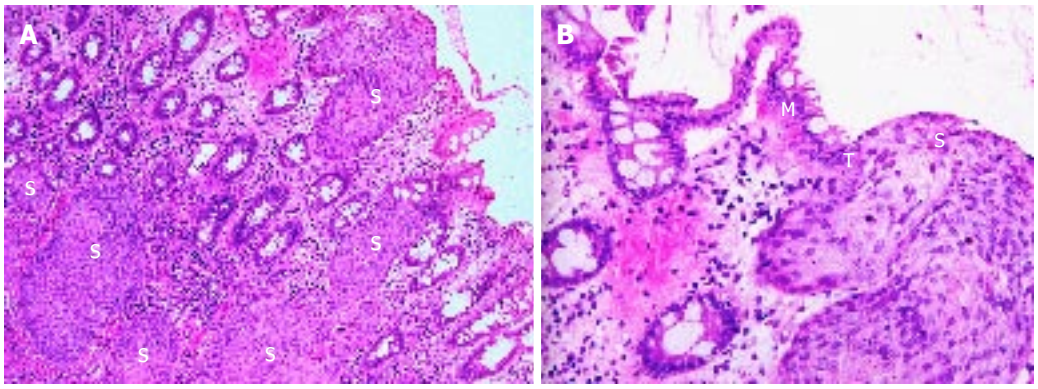

Figure 3 Haematoxylin and eosin stain of rectal squamous cell carcinoma. A: Widespread invasive squamous cell carcinoma (S) throughout the mucosa and submucosa of the rectal wall; B: Demonstration of the clear transition (T) between normal rectal mucosa (M) and invasive squamous cell carcinoma (S).

proven.

Patients with HIV have a higher incidence of HPV infection than the general population and additionally, HIV infection increases susceptibility to virally promoted cancers including Burkitt's lymphoma (Epstein barr virus), Kaposi's sarcoma (human herpes virus 8) and anogenital carcinoma (HPV). Consequently, it could be inferred that the cell mediated immune deficiency associated with HIV would predispose to rectal SCC. However, this is not borne out on review of the literature, with only two case reports of rectal SCC in the setting of HIV infection[29,42].

Another postulated aetiology, has arisen from the finding of squamous differentiation within colorectal adenomas. Williams *et al*[1] found this to be present in 3 of 750 adenomas, with a separate villous adenoma containing both invasive squamous and adenocarcinoma. Others have reported squamous metaplasia in adenomatous polyps[43-46] in addition to a further case of SCC in a villous adenoma[47]. These findings may again represent the squamous differentiation of a basal colonic cell, with changes inciting development of the adenoma also possibly leading to the metaplastic change.

Diagnosis and staging

Clinical presentation and diagnosis: The pattern of presentation for patients with rectal SCC is similar to those with adenocarcinoma of the rectum. The most frequently reported symptom is per rectal bleeding, followed less commonly by altered bowel habit (constipation, diarrhoea, tenesmus), pain and weight loss[48]. The duration of symptoms can be variable, but most patients report a symptom history of weeks to months[49,50].

Many presumed rectal SCCs are in fact an extension of an anal or gynaecological carcinoma, and consequently vigilance in diagnosis is important. Certain exclusion criteria stipulated by Williams *et al*[1] in 1979, remain relevant for a diagnosis of primary rectal SCC to be established: (1) metastasis to the rectum from SCC of another organ; (2) squamous-lined fistula tract involving the affected region of rectum; and (3) SCC of anal or gynaecological origin extending into the rectum.

With the above in mind, a detailed history and physical examination should be undertaken, with particular attention to the gynaecological system and anal canal. This often necessitates an examination under anaesthesia of both systems in addition to endoscopy.

The definitive diagnosis of rectal SCC is confirmed by performing a complete colonoscopy with biopsies of any abnormalities. Demonstration of the discontinuity of a lesion from the anal squamous mucosa is of great importance. Rectal SCC has been reported to have a varied endoscopic appearance dependent on the stage of disease. This can range from a small mucosal polyp (Figure 4), plaque or ulceration through to a large obstructing mass (Figure 5)[51]. Pre-malignant lesions in the form of squamous metaplasia have also been identified by way of narrow band imaging (NBI) in addition to rectal SCC[32,52]. One report identified an appearance of dark brown dots similar to the intraepithelial papillary capillary loops (IPCL) which herald squamous epithelium in the oesophagus using NBI[32]. There are classification systems utilising the appearance of IPCL in the oesophagus in order to identify and differentiate squamous lesions along the spectrum towards invasive carcinoma[53]. Given the possible aetiological sequence of metaplasia through to invasive carcinoma, NBI may find a role in the detection and treatment of pre-malignant lesions for those at high risk, in particular ulcerative colitis patients.

Histologically, if the diagnosis remains unclear, immunohistochemistry can aid in the characterisation of the lesion. This is particularly useful in cases of poorly differentiated tumours where the morphology and architecture provide little clue to the origin. Cytokeratins AE1/AE3, CK 5/6 (34BE12 stains CK5) and p63 stain for cells of squamous origin, assisting in the differentiation from a rectal adenocarcinoma. Cytokeratin CAM5.2 aids in the differentiation of rectal from anal, characteristically staining for rectal squamous cell or adenocarcinoma but not anal SCC. This is particularly useful for squamous carcinomas of the lower rectum[16].

Squamous cell carcinoma associated antigen is

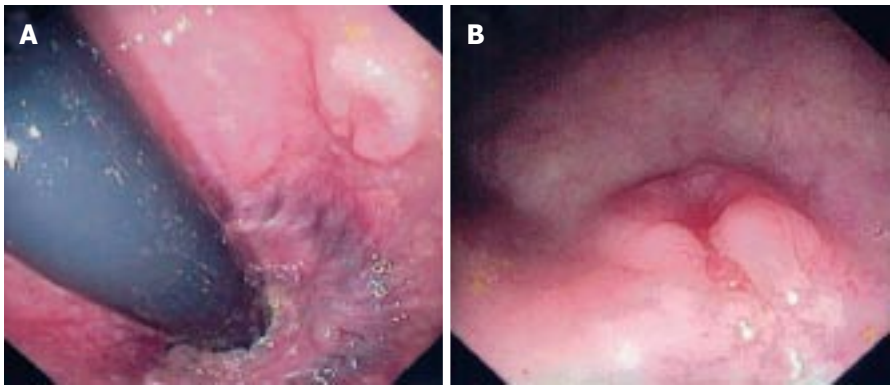

Figure 4 Endoscopic appearance of an early rectal squamous cell carcinoma. Rectal SCC presenting as a flat polypoid lesion with a central ulcerated depression in the distal rectum, 6 cm from the anal verge. A: Endoscopic retroflexed view; B: Endoscopic end-on view. SCC: Squamous cell carcinoma.

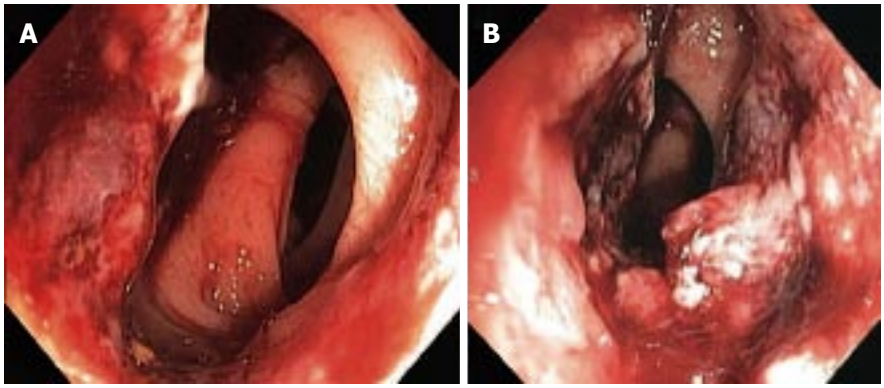

Figure 5 Endoscopic appearance of an advanced rectal squamous cell carcinoma. Large near circumferential rectal SCC with areas of necrosis and friability lying 3 cm above the anorectal ring. A and B: Endoscopic end-on view. SCC: Squamous cell carcinoma.

a serum tumour marker expressed by epidermoid tumours, including squamous carcinomas of the anal canal. Despite studies demonstrating weak evidence it may relate to nodal or relapsed disease in anal SCC, its use in diagnosis and follow-up remains controversial[54-56]. With very limited data in the setting of rectal SCC, there is currently no clear utility for SCCAg in the diagnosis or management of these patients[57].

Staging: Accurate staging of rectal SCC is of critical importance, in the same way that it dictates prognosis and management in anal SCC and rectal adenocarcinoma. In the literature, various staging systems have been translated into use for rectal SCC, most commonly the tumour-node-metastasis (TNM) system for rectal adenocarcinoma[18,49,58-62] or the TNM system for anal SCC[16,63,64]. While arguments can be made for the use of either staging system, the AJCC staging for rectal carcinoma is likely to have the greatest relevance. Firstly, the tumour stage focuses on the importance of the level of invasion through the rectal wall rather than the maximal dimension of the carcinoma. Secondly, nodal involvement is likely to follow the lymphatic drainage to the mesorectum and higher echelons, in preference to the alternative routes often involved in anal carcinoma such as the inguinal basins.

Staging involves evaluation of the primary tumour, and assessment for regional and metastatic disease. For loco-regional evaluation, as with rectal adenocarcinoma, magnetic resonance imaging (MRI) pelvis and endorectal ultrasound (ERUS) both have a role[65]. A preference for either modality is often dependent on the experience with each technique at individual institutions. In terms of utility, ERUS has advantage in determining the depth of tumour invasion, particularly with differentiating T1/2 lesions. For delineation of more advanced T3/4 tumours and to determine local nodal involvement, pelvic MRI provides improved definition[65,66]. Recently, there has been growing interest in the use of MRI diffusion weighted imaging (DWI) as a functional modality to assess treatment response in the staging of rectal adenocarcinoma[67]. With the current shift towards definitive chemoradiotherapy in the treatment of rectal SCC, MRI is likely to find an increasingly useful role, not only for structural pre-treatment staging, but more importantly to determine the functional response of the tumour post-treatment in order to guide the need for operative intervention (Figure 6).

Computed tomography (CT) chest, abdomen and pelvis should be undertaken routinely in order to exclude metastatic disease. Increasingly, Fluorodeoxyglucose -

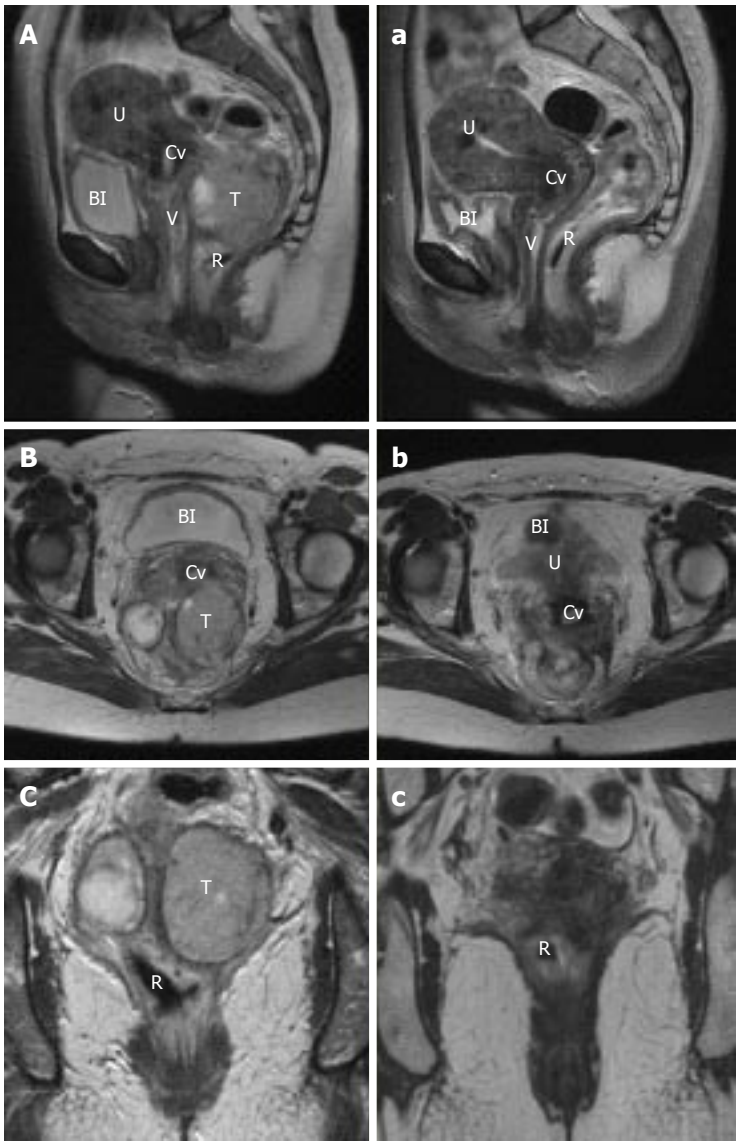

Figure 6 Magnetic resonance imaging appearance of rectal squamous cell carcinoma. Pre (A, B, C) and post (a, b, c) treatment T2 magnetic resonance imaging in sagittal (A, a), axial (B, b) and coronal (C, c) planes of a large rectal SCC, demonstrating an excellent response. T: Tumour; U: Uterus; V: Vagina; Cv: Cervix; Bl: Bladder; R: Rectum; SCC: Squamous cell carcinoma.

positron emission tomography fused with simultaneous CT and more recently MRI imaging, is also finding a role in the staging of rectal SCC. Firstly, it allows exclusion of a non-rectal primary SCC that has metastasised to the rectum. Secondly it defines the extent of the primary and nodal disease. Thirdly, it has utility similar to MRI DWI imaging, in assessing the functional response of the tumour by comparing pre and post-treatment scans (Figure 7)[65,68].

Treatment

The treatment of rectal SCC has traditionally involved surgery, in some cases preceded or followed by adjuvant radiotherapy or chemotherapy (Table 1)[16,69]. However, in the last decade, there has been increasing interest in the response of rectal SCC to definitive chemoradiotherapy, with very encouraging results (Table 2).

Surgery: Surgery has historically been adopted from the treatment of rectal adenocarcinoma with the operative technique, dependent upon the stage and location of the tumour. Local excision either trans-anal or endoscopic, has been advocated for selected cases, with several publications reporting short-term survival without recurrence in the setting of trans-anal excision followed by chemoradiotherapy[12,16,48,70,71]. This included a T3 lesion and another with positive distal and radial margins, suggesting the chemoradiation may have played an important role in reducing local recurrence[16,70]. With the evolution of endoscopic techniques, in particular endoscopic mucosal resection and submucosal dissection in the treatment of early rectal cancers[72], these procedures may have a role in managing rectal SCC. Generally, the option of local excision would be limited to low risk T1 lesions, characterised as being well differentiated, without lymphovascular involvement, nodal or metastatic disease.

For most rectal SCC's, anterior resection (AR) or abdominoperineal resection (APR) has classically been performed. The choice and extent of the operation is dependent upon the tumour location and depth of invasion, occasionally requiring exenteration, with

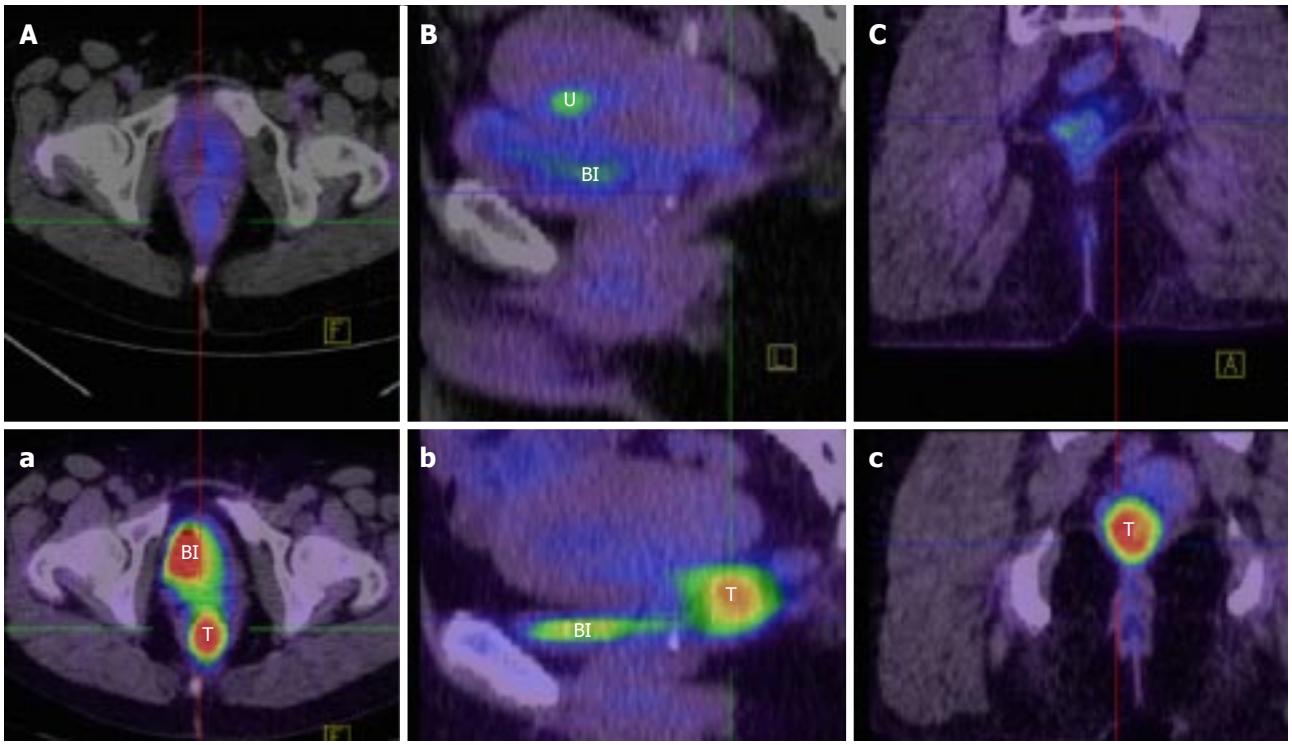

Figure 7 Positron emission tomography/computed tomography appearance of rectal squamous cell carcinoma. Pre (a, b, c) and post (A, B, C) treatment fused FDG-PET/CT imaging in axial (A, a), sagittal (B, b) and coronal (C, c) planes of a rectal SCC (T), demonstrating a complete metabolic response. [FDG is also visibly concentrated anteriorly in the bladder (BI) in images a, B, b, and in the endometrium (U) in image B (menstruation)]. FDG: Fluorodeoxyglucose; CT: Computed tomography; PET: Positron emission tomography; SCC: Squamous cell carcinoma.

removal of involved pelvic structures. On review of the literature, APR was performed much more frequently than AR prior to the year 2000, with an equal split in the frequency of both procedures following the turn of the century (Table 1). This is likely to reflect both the change towards sphincter preservation and avoidance of a permanent stoma in operations for rectal cancer over previous decades, in addition to a down-staging effect of chemoradiation, which is now commonplace. While the incidence of APR and a definitive stoma has been falling, in a similar manner to rectal adenocarcinoma, most patients with a low rectal SCC will require a temporary covering ileostomy given the greater risk of anastomotic leak. Furthermore, for those patients presenting with an obstructing tumour, the use of a defunctioning stoma is an attractive option, providing time to appropriately stage the patient and consider the optimal treatment, including definitive chemoradiotherapy.

Chemoradiotherapy: Following the validation of Nigro's protocol in multiple randomised controlled trials, it has now become the accepted standard treatment for anal SCC. Surgery, previously the preferred management, has subsequently been relegated to a salvage role[73,74]. In light of this development, a trend of treating rectal SCC in the same manner has emerged.

On review of the literature, which spans from 1933 to the present, it is difficult to compare the treatment of rectal SCC, given the lack of a standardised staging system and treatment protocol. Nonetheless, an increasing trend in the use of chemoradiation either as definitive treatment or in conjunction with surgery is emerging. There have been several prospective studies evaluating the role of chemoradiation as the primary therapy. The earlier cohorts demonstrated suboptimal outcomes, without a change in mortality or avoidance of surgery[25,75]. However, with improvements in chemotherapy, radiotherapy and the accuracy of determining stage and response, a multitude of recent studies utilising an anal SCC based treatment regimen have reported promising results (Table 2)[3,16,49,57,61,63,69].

The 3 most recent case series all published in 2015, comprise 22 patients treated with definitive chemoradiotherapy. Of this grouped cohort, a CR was identified by clinical examination and/or imaging in 14 of the 22 patients[59,63,76]. The remaining 8 patients who demonstrated either progression of disease, a partial response or discordance between clinical and radiological findings, underwent a salvage operation. Of this group, 5 were noted to have a complete pathological response, equating to 19 of the 22 patients demonstrating a CR. Median follow up was 25 mo, with three patients suffering a recurrence, two of whom underwent a salvage operation, and one who received radiotherapy given the recurrence was outside the original field of treatment. Of these three, one succumbed to their disease at 14 mo post salvage surgery. One patient with an initial partial response and subsequent salvage operation developed metastatic disease without local relapse. The remaining 20 patients

Table 1 Conventional treatment of primary rectal squamous cell carcinoma

Ref.	Pts	Initial Rx	Surgery	Adjuvant Rx	Recurrence	Survival (ANED)	Follow up (mo)
Raiford *et al*[5]	1	-	PP	-	1 - LR	0%	21
Catell *et al*[81]	1	-	APR	-	-	100% (1)	42
LeBlanc *et al*[30]	5	-	1 - APR, PR - 4	-	1 - LR	40% (2)	3-60
O'Brien *et al*[82]	2	-	APR × 2	-	-	100% (2)	12
Kron *et al*[83]	1	-	APR	-	1 - M, 1 - LR	0%	5
[2]Dixon *et al*[84]	1	-	PR	-	NR	NR	-
Burns *et al*[85]	1	-	APR	-	-	100% (1)	42
Wiener *et al*[86]	1	-	APR	-	M - 1, LR - 1	0%	12
Zirkin *et al*[6]	1	-	TPC/APR	-	-	100% (1)	16
Hohm *et al*[7]	2	-	APR × 2	-	-	100% (1)	156-252
Angelchik *et al*[87]	1	-	AR	-	-	100% (1)	18
Cabrera *et al*[34]	1	-	APR	-	-	100% (1)	10
Minkowitz *et al*[88]	1	-	TPC	-	M - 1	0%	5
[2]Higton *et al*[11]	1	-	AR	-	NR	NR	-
Comer *et al*[10]	1	-	APR	-	-	100% (1)	156
Williams *et al*[1]	1	-	APR	-	M - 1	0%	9
Vezeridis *et al*[25]	4	CTx - 1	APR - 3	CTx - 1	M - 2, LR - 1	0%	0-15
Lafreniere *et al*[48]	1	-	TAE	CRTx	-	100% (1)	24
Pigott *et al*[89]	1	-	APR	RTx	-	100% (1)	13
Woods *et al*[35]	1	-	APR	-	-	0%	3
Prener *et al*[71]	5	-	APR - 4, TAE - 1	RTx - 1	LR - 3, M - 1	20% (1)	3-36
Schneider *et al*[70]	1	-	TAE	CRTx	-	100% (1)	6
Fazzi *et al*[90]	1	-	Y	RTx	-	100% (1)	72
Copur *et al*[91]	1	-	APR	CRTx	M - 1	NR	-
[2]Frizelle *et al*[3]	9	-	NR	NR	NR	NR	-
Sotlar *et al*[28]	1	-	AR	-	LR - 1	0%	21
Gelas *et al*[69]	4	RTx - 2	APR x 3	CRTx - 1, RTx - 1	LR - 1, M - 2	25% (1)	4-192
Anagnostopoulos *et al*[92]	1	-	APR	CTx	-	100% (1)	14
Fahim *et al*[93]	1	-	APR	CTx	LR - 1, M - 1	0%	11
[2]Lam *et al*[94]	1	RTx	AR	-	-	NR	-
[2]Cheng *et al*[15]	1	-	TPC	CRTx	-	NR	-
Kong *et al*[12]	2	CTx - 1	TAE - 1	CRTx - 1	-	50% (1)	36
Nahas *et al*[16]	3	CTx - 1	APR, TAE	CRTx - 2	-	100% (3)	6-192
[1]Leung *et al*[20]	1	-	S	-	M - 1	0%	-
[2]Dzeletovic *et al*[52]	1	NR	NR	NR	NR	NR	-
Sameer *et al*[95]	1	-	AR	CTx	-	100% (1)	24
Wang *et al*[60]	2	-	H, TAE	CRTx - 2	M - 1	50% (1)	21, 120
Sanal *et al*[96]	1	CTx	AR	-	-	100% (1)	12
Yeh *et al*[49]	1	-	APR		M - 1	0%	7
Faidzal *et al*[97]	1	-	AR	CRTx	-	100% (1)	15
Wang *et al*[98]	1	-	APR	RTx	-	100% (1)	43
Scaringi *et al*[23]	1	-	AR	-	LR - 1, M - 1	0%	4
Ozuner *et al*[14]	7	-	APR - 3 AR – 1 TPC - 1 TAE 1, H – 1	CTx - 4	M - 4, LR - 3	43% (3)	12-96
Péron *et al*[59]	1	RTx	-	-	LR - 1	0%	40
Overall	63 (78[2])	CTx 4 RTx 4	Resection 53 (PP/PR 6, APR 34, TPC/AR 13) TAE 7, H 2, S 1	CRTx 11 CTx 8 RTx 5	LR 25% (16) M 30% (19)	48% (30)	0-252

[1]Not included in analysis as refused treatment; [2]Not included in analysis as no relevant information recorded. Pts: Number of patients in study; Rx: Treatment; ANED: Alive, no evidence of disease; AR: Anterior resection; APR: Abdominoperineal resection; PR: Posterior resection; PP: Perineal proctectomy; TPC: Total proctocolectomy; TAE: Trans-anal excision; H: Hartmann's; S: Diverting Stoma; NR: Not recorded; M: Metastasis; LR: Local recurrence.

are alive without evidence of disease[59,63,76].

Expanding from the above findings, when all cases reported in the literature are examined, it is obvious that patients undergoing definitive chemoradiotherapy have a far superior survival then what has been historically recorded (Table 1 compared with Table 2). The overall survival for the chemoradiation group was 86% compared with 48% for conventional treatment. Likewise, the local recurrence and metastatic rates were respectively 25% *vs* 10% and 30% *vs* 13% for the chemoradiation *vs* conventional treatment cohorts. These differences are likely due to a combination of factors, including improvements in imaging, tumour staging and perioperative workup and patient care over time. Furthermore, there are significant limitations in the analysis and interpretation of these results, related to the inherent heterogeneity of case reports and the inconsistency in recording important prognostic variables

Table 2 Chemoradiation as primary treatment of rectal squamous cell carcinoma

Ref.	Pts	Chemotherapy		RTx (Gy)	CR	Surgery	Path CR	Recurrence	Survival (ANED)	Follow up (mo)
		5FU/MMC	Other							
Vezeridis *et al*[25]	1	-	1	40	-	-	-	LR - 1	0%	15
[1]Schneider *et al*[70]	1	1	-	30	-	-	-	-	NR	-
Kulayat *et al*[13]	1	1	-	40	-	TPC	100%	-	100% (1)	48
Martinez-Gonzalez *et al*[75]	1	-	1	46	-	AR	0%	-	100% (1)	18
Gelas *et al*[69]	2	-	2	Y	-	AR - 2	0%	-	100 % (2)	6-24
Theodosopoulos *et al*[99]	1	1	-	20	-	APR	0%	M - 1	100% (1)	18
Pikarsky *et al*[9]	1	1	-	60	1	-	-	-	100% (1)	84
Nahas *et al*[16]	9	6	3	50.4	2	TAE - 2 APR - 2 AR - 3	86%	-	100% (9)	6-192
Clark *et al*[61]	7	3	4	50.4	7	AR - 1	100%	-	100% (7)	5-31
Matsuda *et al*[29]	1	-	1	59.4	-	APR	0%	LR - 1, M - 1	0%	24
Brammer *et al*[100]	1	1	-	Y	1	-	-	M - 1	100% (1)	24
Rasheed *et al*[57]	6	2	4	45-50.4	4	APR - 2	50%	LR - 1	100% (6)	2-132
Al Hallak *et al*[101]	1	1	-	Y	1	-	-	-	100% (1)	30
Tronconi *et al*[58]	6	1	5	50.4-59.4	4	AR - 1 H - 1	50%	M - 1	83% (5)	24-41
Iannacone *et al*[102]	1	1	-	59.4	1	-	-	-	100% (1)	12
Wang *et al*[60]	5	5	-	45-54	4	AR - 2 APR - 1	100%	M - 2	60% (3)	15-51
Yeh *et al*[49]	5	4	1	30-60	4	AR - 1	100%	LR + M - 1	80% (4)	24-84
Jeong *et al*[62]	4	-	4	50.4-63	4	-	-	-	75% (3)	2-99
Kassir *et al*[103]	1	-	1	Y	-	AR	0%	-	100% (1)	-
Ferreira *et al*[64]	1	1	-	52	1	-	-	-	100% (1)	40
Choi *et al*[42]	1	1	-	Y	1	APR	0%	LR - 1	100% (1)	17
Musio *et al*[63]	8	6	2	45-70.6	4	APR - 4	50%	LR - 1	88% (7)	1-164
Péron *et al*[59]	10	4	6	45-62	6	APR - 2 AR - 2	50%	LR - 1	100% (10)	6-133
Funahashi *et al*[76]	3	-	3	45-59.4	2	PE	100%	M - 1	67% (2)	14-44
Seshadri *et al*[104]	1	1	-	50.4	1	AR	0%	LR + M - 1	0%	36
Ozuner *et al*[14]	1	1	-	Y	-	-	0%	M - 1	0%	12-96
Overall	79 (80[1])	42	38	All	60% (48)	44% (35)	57% (20)	LR 10% (8) M 13% (10)	86% (68)	1-192

[1]Not included in analysis as no relevant information recorded. Pts: Number of patients in study; RTx: Radiotherapy; CR: Complete response; Path CR: Pathological complete response; ANED: Alive, no evidence of disease; Other: 5FU - 3, 5FU/Cisplatin - 26, Capecitabine/Cisplatin - 3; Capecitabine - 1; Raltitrexed/Oxaliplatin - 2; S1 - 3; Gy: Gray; AR: Anterior resection; H: Hartmann's; PE: Pelvic exenteration; TAE: Trans-anal excision; TPC: Total proctocolectomy; APR: Abdominoperineal resection; NR: Not recorded; M: Metastasis; LR: Local recurrence.

including stage and grade. Despite these limitations, the treatment itself almost certainly accounts for a significant component of the dramatically improved local control and survival.

As with rectal and anal cancer, one of the most pertinent issues with definitive chemoradiation, is determining treatment response, which currently can only be confirmed on histopathology[73,77]. In the studies to date on rectal SCC, response to chemoradiotherapy has been assessed variably, from 6-8 wk up to 6 mo after the conclusion of treatment. This generally involves a combination of a clinical assessment, by way of a repeat EUA/proctoscopy + biopsy, and an imaging assessment in the form of MRI ± PET/CT ± ERUS[49,58,60,61]. For patients with a complete clinical and radiological response, follow up and surveillance is performed at regular intervals with reducing frequency out to five years, generally 3 monthly for the first two years, and 6 monthly out to five years. While this is certainly labour and resource intensive with consequent costs, the improved overall and stoma free survival certainly justifies this approach.

For those cases with clear progression of disease through chemoradiation, salvage surgery should be undertaken as the next line of treatment to ensure optimal outcomes. However, in the setting of a partial response or stable disease, the pathway is less clear. It has been suggested that a more prolonged assessment, with regular EUAs even out to 6 mo, could be required for a better evaluation of tumour response. This is in consideration of the finding that multiple patients with an eventual pathological CR had clinical and radiological findings suggestive of persistent disease in the early post chemoradiation stage[16]. This is also in keeping with the accepted management of anal SCC, where a delayed tumour response may continue for 6 mo after the completion of chemoradiation[63]. In the grouped chemoradiation cohort (Table 2), a CR on pathology was identified in 57% of patients, suggesting that time may have played a role in assessing clinical and radiological response. As with rectal and anal cancer, this is likely to remain a contentious area until a more effective means

of determining response is available[78].

Despite the encouraging results of chemoradiotherapy, currently a set treatment protocol is yet to be established. It appears that 5FU based chemotherapy combined with high dose external beam radiotherapy may be efficacious. However, while these trends are grossly evident from the literature, there is a need for further research in order to determine the most effective regimen to optimise patient outcomes.

It is unlikely that a randomised trial comparing surgery and chemoradiotherapy will ever be conducted for this rare cancer. Given the current knowledge base, it may be reasonable to suggest that primary treatment should be chemoradiotherapy, with surgery reserved as a salvage option. The suggested regimen would be a total dose of 50.4 to 54 Gy external beam radiation in 1.8 Gy per fraction, given concurrently with 5FU and mitomycin C.

Future options: Over recent years, there has been an increasing use of molecular targeted therapies in solid and haematological malignancies[79]. Furthermore, immunotherapy in the form of tumour vaccines, adoptive T cell therapy and immune checkpoint inhibitors has become a major focus for research in the treatment of cancer, with translated clinical success in specific tumour types[80]. While there is currently no literature on these modalities in rectal SCC, the early results in other tumours holds promise for a possible role in future treatment, particularly in the cohort of patients with persistent, recurrent or metastatic rectal SCC.

Prognosis

The most important predictor of survival in all cancers is the stage of disease. This is based upon three factors; the size of the primary tumour and depth of invasion (T stage); the location and number of lymph nodes involved (N stage); and the presence or absence of metastasis (M stage). Rectal SCC follows the same route of lymphatic spread for involvement of lymph nodes as rectal adenocarcinoma. Additionally, it has a similar pattern of metastasis with the liver, lung and bones most commonly affected[66].

While the majority of patients with rectal SCC present with locoregional disease (stage I-III, 82.1%), they are associated with a poorer overall survival when compared stage for stage with adenocarcinoma. From review of the population study by the NCI, the overall 5-year survival for rectal SCC was found to be 48.9% compared with 62.1% for adenocarcinoma. When localised, the 5 years OS was 73.7% (91.8% - adenocarcinoma), with 31.3% (65.8%) for regional and 20.8% (8.8%) for metastatic[2]. While the above figures and those from older studies report a poor prognosis for patients with rectal SCC, recent studies employing a new treatment paradigm, demonstrate a significantly improved overall survival. The possibility of further advances in treatment as this disease is better defined, gives hope for improved patient outcomes.

While SCC of the rectum is a rare entity, there is an increasing body of evidence that is improving our understanding of its underlying aetiology. Despite the literature lacking uniformity in the staging and management of rectal SCC, it is hard to ignore the impressive improvements in overall survival and sphincter preservation by way of chemoradiotherapy as the primary modality of treatment. This holds much promise for the future, and certainly lays the foundation for further investigation into determining the optimal treatment regimen.

COMMENTS

Background

A summary of the current body of knowledge surrounding the pathogenesis, presentation, diagnosis, staging and management of rectal squamous cell carcinoma (SCC), with a focus on the changing treatment paradigm and consequent improved patient outcomes.

Research frontiers

While the underlying pathogenesis of rectal SCC is yet to be fully defined, a possible role for human papilloma virus presents an avenue for future investigation. Furthermore, the identification of pre-malignant lesions in the development of rectal SCC raises the possibility of surveillance in high risk patients. The use of magnetic resonance imaging (MRI) and positron emission tomography (PET) has an emerging role not only in diagnosis and staging, but also importantly as a functional modality to determine response to chemoradiotherapy. This role has arisen from the recent shift in the primary treatment of rectal SCC to chemoradiotherapy, accompanied by a dramatic improvement in overall survival.

Innovations and breakthroughs

Assimilation of the current body of evidence lends support to the presence of pre-malignant lesions and a metaplasia-dysplasia-carcinoma sequence in the development of rectal SCC. Staging for rectal SCC fits more appropriately with the tumour-node-metastasis (TNM) criteria for rectal adenocarcinoma than anal SCC. MRI and PET are finding an increasing role in diagnosis, staging and assessment of response to treatment in rectal SCC. Chemoradiotherapy offers improved patient outcomes without the associated morbidity of surgery. Improved markers of complete response will assist in determining the need for salvage treatment in this patient cohort.

Applications

Consideration should be given to screening for premalignant lesions in high risk individuals. Uniform staging utilising the current TNM criteria for rectal adenocarcinoma should be encouraged. PET and MRI should be incorporated into the evaluation of patients, pre and post treatment. Definitive chemoradiotherapy offers improved patient outcomes without the associated morbidity of surgery. While treatment must be individualised and based on patient and tumour factors, chemoradiation should form the basis of primary management.

Terminology

Complete response refers to the resolution of tumour following treatment with chemoradiotherapy. While radiological investigations and clinical examination can act as surrogate markers, a true complete response can currently only be determined post resection and pathological examination.

Peer-review

The review article described the background, diagnosis and staging, treatment,

and prognosis of primary SCC of the rectum. The whole article is well written and characterized.

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Fibrin sealant use in pilonidal sinus: Systematic review

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Abstract

AIM: To review the current data about the success rates of fibrin sealant use in pilonidal disease.

METHODS: Fibrin sealant can be used for different purposes in pilonidal sinus treatment, such as filling in the sinus tracts, covering the open wound after excision and lay-open treatment, or obliterating the subcutaneous dead space before skin closure. We searched Pubmed, Google-Scholar, Ebsco-Host, clinicaltrials, and Cochrane databases and found nine studies eligible for analysis; these studies included a total of 217 patients (84% male, mean age 24.2 ± 7.8).

RESULTS: In cases where fibrin sealant was used to obliterate the subcutaneous dead space, there was no reduction in wound complication rates (9.8% *vs* 14.6%, $P = 0.48$). In cases where sealant was used to cover the laid-open area, the wound healing time and patient comfort were reported better than in previous studies (mean 17 d, 88% satisfaction). When fibrin sealant was used to fill the sinus tracts, the recurrence rate was around 20%, despite the highly selected grouping of patients.

CONCLUSION: Consequently, using fibrin sealant to decrease the risk of seroma formation was determined to be an ineffective course of action. It was not advisable to fill the sinus tracts with fibrin sealant because it was not superior to other cost-effective and minimally invasive treatments. New comparative studies can be conducted to confirm the results of sealant use in covering the laid-open area.

Key words: Pilonidal disease; Fibrin sealant; Evidence base medicine; Systematic review

Core tip: Fibrin sealant use in pilonidal disease treatment may involve filling in the sinus tracts, covering the laid-open area after excision, or obliterating the subcutaneous dead space before skin closure. This systematic review demonstrates that when the fibrin

sealant was used to obliterate the subcutaneous dead space, there was no reduction in wound complications. It was unadvisable to fill the sinus tracts because it was not superior to the other more cost-effective treatments with a 20% recurrence rate. More studies are necessary for sealant use in covering the laid-open area, which has promising results, predicting shorter wound healing time and increased patient satisfaction.

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INTRODUCTION

Pilonidal sinus is a benign disease seen more commonly in young males and negatively alters the quality of life. Its prevalence was reported as 26 cases per 100000 people[1]. The mainstay of pilonidal sinus treatment begins with the surgical excision of the sinus tracts, which is followed by either primary closure after excision or laying open the wound for secondary healing; these are the most commonly preferred surgical methods. However, these traditional techniques prolong the recovery period, cause a delay in returning to daily life, and ultimately interrupt the educational or professional lives of these young and active patients.

Fibrin sealant may be used for different purposes in pilonidal sinus surgery. Filling the sinus tracts with the fibrin sealant instead of surgically removing the sinus tracts has been described in the literature as a minimally invasive technique. Additionally, the open surface of the surgical area may be covered with the fibrin seal in the lay-open technique. A third option requires that the potential dead space that is formed after the total excision and primary closure of the defect may be obliterated by the fibrin sealant. All these methods are used in order to accelerate the recovery period, to decrease morbidity, and to enable a quick return to work. Our aim in this review was to collect all accessible data in the literature on the treatment of pilonidal disease with fibrin sealant and to make a prediction about the promising treatments.

MATERIALS AND METHODS

The databanks of www.ncbi.nlm.nih.gov/pubmed, www.cochrane.org, scholar.google.com and web.a.ebscohost.com were last searched on the 3rd of June, 2015, using the key words [(pilonidal*) and (glue* OR sealant*)]. All varieties of researches, including congressional summaries describing the patient data about the treatment, were analyzed. Two reviewers (IE & CK) determined the selection of the searched articles on www.ncbi.nlm.nih.gov/pubmed and www.cochrane.org by the key words in all fields. Some studies were excluded due to the nature of their content (editorial letters, reviews, duplicated studies). Later, a search to scholar.google.com and web.a.ebscohost.com were done by the key words in titles of the studies. Lastly, www.clinicaltrials.gov was also searched. We performed an additional reference cross check as well.

As we were scanning the literature for the pilonidal sinus treatment modalities using fibrin glue, publications concerning the use of fibrin glue to fill the tracts without excision, publications concerning covering the defect following surgical excision and publications concerning filling the cavity with fibrin glue before primary closure were all included in this analysis. Treatments of pilonidal sinuses outside of the sacrococcygeal area (interdigital, umbilical, penile, vulvar) were excluded.

We used no limitations to the patient and journal features. All patients were were accepted for analysis if there were enough data. There was no restrain with regard to article language, country, or journal. In cases of disagreement during analysis, a consensus of the two researcher authors was necessary for the acceptance of the studies. Data for affiliation, number of patients, age, gender, history of prior pilonidal surgery, method of application, complications, recurrence, time to heal, length of follow-up period, success, clinical findings, inclusion and exclusion criteria, body mass index, intra-operative and postoperative complications, duration of surgery, postoperative pain, postoperative hospital stay, time off work, and overall satisfaction were analyzed.

Data were organized into tables, and column sums were done including percentages, means ± standard deviations, or the ranges. If the studies reported the median and range, the mean and standard deviation were estimated by Hozo *et al*[2] method. Percentages were preferred for the dichotomous parameters and means for the continuous parameters[3]. The Chi-square test or the Fisher exact test (if expected values were less than 5) and Student's *t* test were used. (SPSS 17.0). $P < 0.05$ was accepted as statistically significant.

RESULTS

A total of nine publications were found that detailed the use of fibrin sealant in pilonidal sinus treatment[4-12] (Figure 1). These publications included 217 patients that were treated between June 2001 and December 2013 (Table 1). Eighty-four percent of the patients were male, and their mean age was 24.2 ± 7.8 (ranged 12-70). One of the studies was conducted within a pediatric age group; the mean age for participants in this study was 14.5 and their mean body weight was 73 kg[12]. The inclusion criteria and the surgical techniques used in these studies constituted sufficient heterogeneity (Tables 2 and 3). The studies were gathered into three subgroups depending on the application technique of the fibrin glue (Table 3). Fibrin sealant was used to obliterate the dead space before wound closure in three studies[4,8,9]. In two other studies, it was used to cover

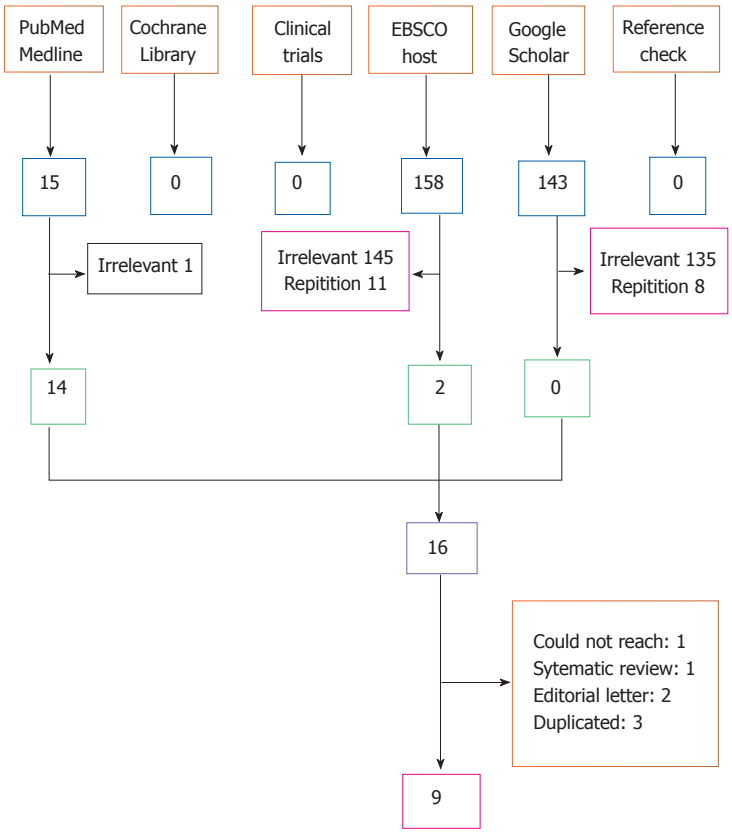

Figure 1 Flowchart of the systematic review.

Table 1 Studies of fibrin sealant at pilonidal sinus: Demographics of the patients

Ref.	Year	Country	Study period	No.	Male	Age	BMI or weight
Greenberg *et al*[4]	2004	Israel	Jun 2001 to Dec 2001	30	22	23.5 ± 2.8 (17-44)	NA
Lund *et al*[5]	2005	United Kingdom	NA	6	6	28.5 ± 5.5 (22-44)	NA
Seleem *et al*[6]	2005	Saudi Arabia	Sep 2001 to Feb 2004	25	23	26.4 ± 8.5 (17-50)	NA
Patti *et al*[7]	2006	Italy	NA	8	8	21.8 ± 6.5	NA
Altinli *et al*[8]	2007	Turkey	Jan 2003 to Jan 2004	16	16	24.5 ± 6.0	25.7 + 4.1 kg/m^2
Sözen *et al*[9]	2011	Turkey	Jan 2008 to Mar 2008	25	25	22.5 ± 4.0 (20-36)	26 kg/m^2
Elsey *et al*[10]	2013	United Kingdom	Mar 2007 to Sep 2011	57	42	26.0 ± 13.3 (17–70)	NA
Isik *et al*[11]	2014	Turkey	Dec 2007 to Dec 2011	40	32	24.0 ± 8.5 (16-50)	NA
Smith *et al*[12]	2014	United Kingdom	Aug 2006 to Dec 2013	10	NA	14.5 ± 1.0 (12–16)	73 kg
Total			Jun 2001 to Dec 2013	217	84%	24.2 ± 7.8 (12-70)	

BMI: Body mass index; NA: Not available.

Table 2 Studies of fibrin sealant at pilonidal sinus: Features of the pilonidal sinuses

Ref.	No.	Inclusion and exclusion criteria	Recurrent
Greenberg *et al*[4]	30	No exclusion criteria	8
Lund *et al*[5]	6	3-4 openings and no large cavity	3
Seleem *et al*[6]	25	1-3 openings, no prior surgery, no infection	0
Patti *et al*[7]	8	3 < openings, no prior surgery, no infection, no large cavity or distant orifice	0
Altinli *et al*[8]	16	No prior surgery	0
Sözen *et al*[9]	25	No prior surgery, no infection, no lateral extension < 3 cm	0
Elsey *et al*[10]	57	No infection, no very scarred cases due to repeated episodes or surgeries	2
Isik *et al*[11]	40	Only 1 opening, no prior surgical or medical treatment, no infection	0
Smith *et al*[12]	10	No exclusion criteria	0
Total	217		13 (6%)

the defect after the excision and lay-open technique[6,7]. In the remaining four studies, the sinus tracts were

Meta-analysis: Risk difference

Study	Intervention	Controls	Risk Difference	95%CI	Z	*P*
Altinli	0/16	2/16	-0.125	-0.287-0.0371		
Sözen	6/25	2/25	0.160	-0.0383-0.358		
Total (fixed effects)	6/41	4/41	0.0488	-0.0877-0.185	0.701	0.484
Total (random effects)	6/41	4/41	0.0125	-0.291-0.316	0.0804	0.936

Test for heterogeneity

Q	5.6258
DF	1
Significance level	$P = 0.0177$
I^2 (inconsistency)	82.22%
95%CI for I^2	25.12-95.78

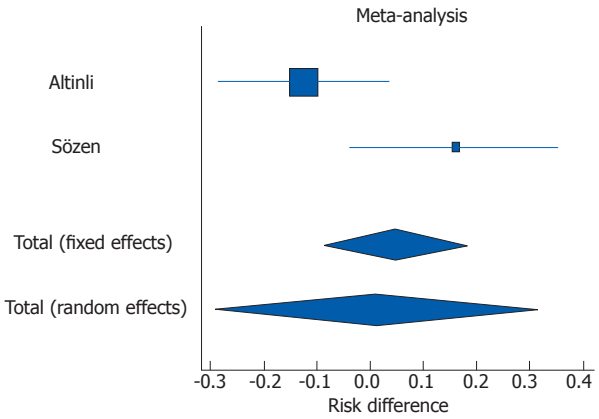

Figure 2 Obliterating the dead space under the closed wound with sealent *vs* controls: Meta-analysis of the wound complications.

Table 3 Studies of fibrin sealant at pilonidal sinus: Procedures

Ref.	No.	Surgical procedure	Aim of using fibrin sealant
Greenberg *et al*[4]	30	Excision and primary closure	Obliterate the dead space under the wound
Lund *et al*[5]	6	No sinus excision, only cleaning the tracts	Fill the tracts with sealent
Seleem *et al*[6]	25	Excision and lay open	Overlap the open wound with sealent
Patti *et al*[7]	8	Excision and lay open	Overlap the open wound with sealent
Altinli *et al*[8]	16	Excision and closure with Limberg flap	Obliterate the dead space under the wound
Sözen *et al*[9]	25	Excision and closure with Karydakis flap	Obliterate the dead space under the wound
Elsey *et al*[10]	57	No sinus excision, only cleaning the tracts	Fill the tracts with sealent
Isik *et al*[11]	40	No sinus excision, only cleaning the tracts	Fill the tracts with sealent
Smith *et al*[12]	10	No sinus excision, only cleaning the tracts	Fill the tracts with sealent

filled with the fibrin sealant without performing any surgery, which was intended to constitute a definitive treatment[5,10-12]. Thirty-nine percent of all these interventions were performed under local anesthesia. An average of 3.8 mL (ranged 1-6 mL) of fibrin glue was used; drains were used in only 7.3% of these cases (Table 4).

In three studies, fibrin sealant was applied in order to obliterate the subcutaneous dead space[4,8,9]. There were no recurrences in any of these cases after a mean follow-up period of 15.2 mo (Table 5). However, wound-related complications were observed in 16.4% of the patients. In one study, the authors declared that postoperative purulent drainage after fibrin sealant application was more frequent in cases requiring recurrent surgeries[4]. In another study, the amount of drainage decreased within the fibrin sealant group, but instances of wound complications did not decrease significantly[8]. In another study, fibrin sealant was replaced with a subcutaneous drain; there were no wound-related complications within the no-drain fibrin sealant group[9]. In the studies with control groups[8,9], it was observed that use of the fibrin sealant did not decrease wound complication rates (control groups 9.8% *vs* sealant groups 14.6%; $P = 0.48$) (Figure 2).

Fibrin sealant was used in two studies in order to shorten the wound's healing period and to mitigate the negative effects associated with an open wound following surgical excision[6,7] (Table 6). Healing periods for these patients were around 17 d and the morbidity rate was only 6%, which mainly involved early detachment of the fibrin sealant. When the fibrin sealant detached from the wound, either a new sealant was applied to the wound[7], or it was left open for secondary intention[6]. Work-off time of those patients was reported to be lower than expected (5.3 + 2.1 d)[7]. In this group of patients, there were no recurrences reported and the patient satisfaction rate was reported to be 88% (Table 6).

Simply filling the pilonidal sinus tracts with fibrin sealant after curettage was used in four studies conducted with 113 patients as a minimally invasive treatment modality. Work-off time was generally less than 7 d, and the morbidity rates were generally

Study	SD*	Proportion (%)	95%CI
Lund	6	16.667	0.421-64.123
Elsey	57	26.316	15.538-39.663
Isik	40	10.000	2.793-23.664
Smith	10	20.000	2.521-55.610
Total (fixed effects)	113	19.905	13.096-28.296
Total (random effects)	113	19.587	11.255-29.558

Test for heterogeneity

Q	4.1336
DF	3
Significance level	P = 0.2469
I^2 (inconsistency)	27.51%
95%CI for I^2	0.00-72.90

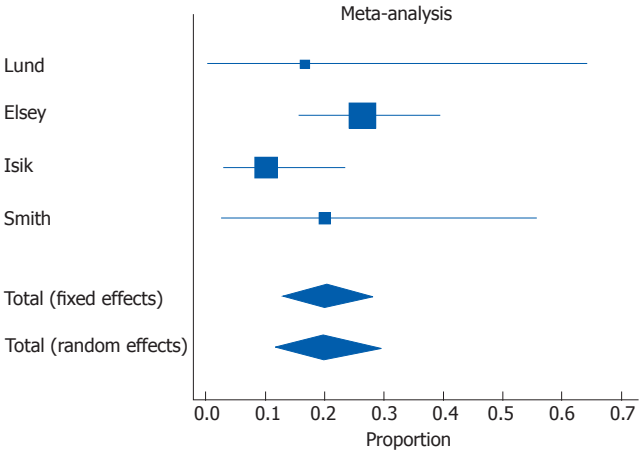

Figure 3 Filling the tracts with fibrin sealant; meta-analysis of the recurence rates.

Table 4 Surgical details

Ref.	No.	Anesthesia	Amount of glue	Drain
Greenberg *et al*[4]	30	General or spinal	2-4 mL	None
Lund *et al*[5]	6	General	1-2 mL	None
Seleem *et al*[6]	25	Local (n = 23), general (n = 2)	NA	None
Patti *et al*[7]	8	Local	1.9 ± 0.6 mL	None
Altinli *et al*[8]	16	Spinal	6 mL	Yes
Sözen *et al*[9]	25	NA	6 mL	None
Elsey *et al*[10]	57	General	NA	None
Isik *et al*[11]	40	Local	2-4 mL	None
Smith *et al*[12]	10	General	NA	None
Total	217	Local 39%	3.8 (1-6)	7.3%

NA: Not available.

reported to be less than 1% (Table 7). The success rate for this group of patients was about 80%, after a mean follow up of 21.7 mo. In other words, the recurrence rates were around 20% (Figure 3).

DISCUSSION

The fibrin sealant is composed of two ingredients; human fibrinogen and bovine thrombin. When the two of these are combined, the thrombin converts the fibrinogen into fibrin in less than a minute. This 3 dimensional fibrin plug is used as a haemostatic or a sealing agent. Fibrin was first used as a local haemostatic material in Germany about 100 years ago[13]. In the 1940s, it was used to repair the peripheral nerves[14] and to keep skin grafts in place[15]. Although it has been used commercially in Europe since 1972, it was not approved by the FDA for use in the United States[16] until around 1998. Nowadays, fibrin sealant has been approved by the FDA for the following uses; hemostasis in surgical interventions, sealing of the colon during colostomy closure, and fixation of skin grafts given to burn patients[16,17]. The other uses for fibrin sealants that fall outside of the FDA indications include prevention of seroma formation, fixation of mesh, and fistula tract closure[16].

Recently, there has been a tendency to use minimally invasive surgical techniques in the treatment of pilonidal sinus, as with other surgically-treated diseases[18]. Ideal treatment of pilonidal sinus should be conducted in outpatient settings under local anesthesia, have less postoperative pain, fast recovery, high success rates, and low costs[18]. Fibrin sealant can be used for three purposes; (1) to obliterate the dead space under a closed wound; (2) to cover an open wound; (3) for primary treatment of sinus tracts in which they are filled with the sealant.

Obliterating the dead space under the wound

Seroma formation is a commonly observed complication following primary closure or flap closure of a wound. The collection of seroma leads to dehiscence of the wound, prolongation of the healing period, necessitates increased wound dressing changes, and causes a decrease in the patient's overall comfort and satisfaction. Deep sutures or use of drains are the most common techniques for closing the dead space, which prevents seroma formation. However, deep sutures increase pain and invert the natal cleft, which is ought to be flattened. The presence of the drains detracts from patient comfort, increases the workload associated with wound care, and raises the risk of infection. It is suspected that the use of the fibrin sealant may decrease seroma formation and decrease the need for the use of drains. But this analysis did not reveal that the fibrin sealant is effective in decreasing wound complications. Similar seroma problems were reported in mastectomy and axilla dissection cases, and many studies have been conducted with the fibrin sealant as a method of seroma prevention[19]. Studies on fibrin sealant use in breast cancer surgery laid the groundwork for the use of fibrin sealant in treatment of pilonidal sinus patients. But the evidence-based medicine showed that the fibrin sealant did not influence the incidence of seromas, wound infections, overall complications, and the length of hospital stays for patients undergoing breast cancer surgery[19]. The fibrin sealant's inability to prevent

Table 5 Obliterating the dead space under the closed wound with sealent

Ref.	No.	Closure method	Return to normal activities	Complications	Mean follow-up (mo)	Recurrence
Greenberg *et al*[4]	30	Primary	11.0 + 6.0 d	Purulent discharge (n = 4)	23.0 ± 3.0	None
Altinli *et al*[8]	16	Limberg	NA	None	8.5	None
Sözen *et al*[9]	25	Karydakis	NA	Fluid collection (n = 6)	10.2	None
Total	61			10 (16.4%)	15.2	None

NA: Not available.

Table 6 Studies on covering the open wound with fibrin sealant after excision

Ref.	No.	Healing time	Morbidity	Satisfaction	Recurrence
Seleem *et al*[6]	25	2 wk	1	84%	None
Patti *et al*[7]	8	25.8 ± 13.2 d	1	100%	None
Total	33	16.9 d	2 (6%)	88%	None

Table 7 Studies on filling the tracts with fibrin sealant

Ref.	No.	Work off	Morbidity	Pain	Follow-up
Lund *et al*[5]	6	NA	None	None	18 mo
Elsey *et al*[10]	57	Median 6	None	None	23 mo
Isik *et al*[11]	40	Mean 2.0 ± 1.0	None	32	18 mo
Smith *et al*[12]	10	NA	1 (infection)	1	32 mo
Total	113	Usually < 7	0.9%	33 (29%)	21.7 mo

NA: Not available.

seroma formation can be explained by its tendency to liquefy as it dissolves, and that it causes a tissue reaction[20]. With the help of this analysis and similar studies conducted in mastectomy patients, we can conclude that the use of the fibrin sealant to obliterate the subcutaneous dead space is not very effective in preventing wound complications. Additionally, it has been observed that the use of the fibrin sealant leads to higher rates of subcutaneous fluid accumulation than treatment with drains[9].

Covering the open wound by fibrin sealant

To this aim, the fibrin sealant can be used to decrease pain, dressing changes, and healing period. Nevertheless, a control group is needed to confirm that fibrin sealant does indeed achieve these desired ends. The absence of a control group in these studies[6,7] makes it difficult to objectively evaluate the effectiveness of this technique. Without any comparative studies having been conducted, this technique cannot be proposed as an acceptable application.

Filling the sinus tracts with fibrin sealant

Fibrin sealant may be used as a sole treatment modality in pilonidal sinus treatment. Filling the sinus tracts with fibrin sealant without any other surgery has the advantages of less pain, shorter recovery period and a rapid return to daily life, and fewer dressing changes. Although it is generally recommended that this procedure be performed under local anesthesia, two thirds of all the reported cases were, surprisingly, performed under general anesthesia (Tables 3 and 4). Since even surgical excisions of the pilonidal sinus and flap procedures are performed under local anesthesia[21], the use of the general anesthesia for a mere tract debridement and fibrin sealant application may be supererogatory. According to us, general or regional anesthesia should be used under special circumstances (pediatric patients, jitters, history of adverse reactions to local anesthesia, *etc*.). In this meta-analysis, an 80% success rate for filling sinus tracts with fibrin sealant is pleasing. However, this result should be approached with caution. In one study, there was a 39% rate of non-responders[10]. Another study included sinuses only with one orifice and cases without any purulent drainage (may be asymptomatic)[11]. There was no study that was conducted with a sufficient number of symptomatic patients. Additionally, there was no information about the effect of repetitive applications of the sealant on this success rate. The results of single applications were also unknown. Conditions requiring repeated applications were not identified. Similar analyses were performed previously for phenol application in pilonidal disease; a success rate of 70% in single application and a success rate of 86.7% in repetitive applications were reported[22,23]. Even if the 80% success rate is to be accepted as accurate, it nevertheless does not constitute an advantage over phenol application. Furthermore, fibrin sealant is much more expensive than phenol. In cases where repeated sealant applications are necessary, the use of phenol may offer an advantage due to the higher cost of fibrin. We may comfortably claim that the treatment of pilonidal tracts with fibrin sealant is not definitively superior to other minimally invasive methods. Additionally, the higher cost of fibrin sealant does not justify its routine use in filling sinus tracts as a primary treatment modality.

A review was published in 2012 about the fibrin sealant use in pilonidal sinus[24]. In this review, which analyzed only 5 publications with a total number of 85 patients, researchers declared that adjuvant fibrin sealant in the treatment of pilonidal sinus was a promising technique, and they justified more research about it[24]. In the last four years, new studies have been conducted; our systematic review analyzed 9 publications, which included 217 patients altogether. Analyzing more patients than the previously published review provided us to make some specific comments.

However, it is obvious that more studies are still necessary for clear comments.

The limitations of our study were (1) a low number of randomized controlled trials; (2) heterogeneity of the studies involved; and (3) a lack of subgroup analysis for special groups (pediatric cases, recurrent cases, *etc.*). Because of these constraints, we used descriptive statistics in general, and sometimes meta-analysis. Despite these limitations, some results of this analysis are able to justify certain conclusions. In our opinion, the use of fibrin sealant in preventing subcutaneous seroma formation is not advantageous. The use of the fibrin sealant in order to fill the sinus tracts is also not advised, as its success rate was not greater than that of more cost-effective minimally invasive methods. New studies must be conducted regarding fibrin sealant use in covering wounds after excision and lay-open.

COMMENTS

Background

Fibrin sealant may be used for different purposes in pilonidal sinus surgery. All the methods are used in order to accelerate the recovery period, to decrease morbidity, and to enable a quick return to work. The aim in this review was to collect all accessible data in the literature on the treatment of pilonidal disease with fibrin sealant and to make a prediction about the promising treatments.

Research frontiers

Fibrin was first used as a local haemostatic material in Germany about 100 years ago. In the 1940s, it was used to repair the peripheral nerves and to keep skin grafts in place. Although it has been used commercially in Europe since 1972, it was not approved by the Food and Drug Administration for use in the United States until around 1998.

Innovations and breakthroughs

Recently, there has been a tendency to use minimally invasive surgical techniques in the treatment of pilonidal sinus, as with other surgically-treated diseases. Ideal treatment of pilonidal sinus should be conducted in outpatient settings under local anesthesia, have less postoperative pain, fast recovery, high success rates, and low costs. Retrieved manuscripts concerning the utility of fibrin sealant in pilonidal disease were reviewed by the authors, and the data were extracted using a standardized collection tool.

Applications

This review suggests that fibrin sealant can be used for three purposes; (1) to obliterate the dead space under a closed wound; (2) to cover an open wound; (3) for primary treatment of sinus tracts in which they are filled with the sealant.

Terminology

The fibrin sealant is composed of two ingredients; human fibrinogen and bovine thrombin. When the two of these are combined, the thrombin converts the fibrinogen into fibrin in less than a minute. This 3 dimensional fibrin plug is used as a haemostatic or a sealing agent.

Peer-review

In this systematic review, the authors have presented a thorough and critical analysis of the utility of fibrin sealant for the treatment of pilonidal disease as a minimally invasive method.

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META-ANALYSIS

Post-operative abdominal complications in Crohn's disease in the biological era: Systematic review and meta-analysis

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Abstract

AIM: To perform a systematic review and meta-analysis on post-operative complications after surgery for Crohn's disease (CD) comparing biological with no therapy.

METHODS: PubMed, Medline and Embase databases were searched to identify studies comparing post-operative outcomes in CD patients receiving biological therapy and those who did not. A meta-analysis with a random-effects model was used to calculate pooled odds ratios (OR) and confidence intervals (CI) for each outcome measure of interest.

RESULTS: A total of 14 studies were included for meta-analysis, comprising a total of 5425 patients with CD 1024 (biological treatment, 4401 control group). After biological therapy there was an increased risk of total infectious complications (OR = 1.52; 95%CI: 1.14-2.03, 8 studies) and wound infection (OR = 1.73; 95%CI: 1.12-2.67; P = 0.01, 7 studies). There was no increased risk for other complications including anastomotic leak (OR = 1.19; 95%CI: 0.82-1.71; P = 0.26), abdominal sepsis (OR = 1.22; 95%CI: 0.87-1.72; P = 0.25) and re-operation (OR = 1.12; 95%CI: 0.81-1.54; P = 0.46) in patients receiving biological therapy.

CONCLUSION: Pre-operative use of anti-TNF-α therapy may increase risk of post-operative infectious complications after surgery for CD and in particular wound related infections.

Key words: Crohn's; Post-operative complications; Biological; Anti-tumor necrosis factor-α; Monoclonal antibody; Infliximab; Adulimimab

Core tip: Pre-operative use of anti-tumor necrosis

factor alpha (TNF-α) therapy increases risks of post-operative infectious complications after surgery for Crohn's disease, particularly wound sepsis. Surgery should be planned carefully and ideally performed after appropriate cessation of anti-TNF-α therapy to mitigate increased post-operative risks.

Waterland P, Athanasiou T, Patel H. Post-operative abdominal complications in Crohn's disease in the biological era: Systematic review and meta-analysis. *World J Gastrointest Surg* 2016; 8(3): 274-283 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i3/274.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i3.274

INTRODUCTION

The introduction of biological therapy for gastrointestinal Crohn's disease (CD) has been a significant landmark in non-operative management of this chronic relapsing condition. The central role of the cytokine tumor necrosis factor-α (TNFα) in persistence of mucosal inflammation underlies the marked efficacy of monoclonal antibodies such as Infliximab and Adulimimab[1,2]. Multiple randomised clinical trials including ACCENT and CHARM have shown high clinical response (35%-50%) and maintenance rates for both infliximab and adalimumab in modest to severe CD. Eight-weekly infusion regimes appear to be most effective for patients with an initial response to the induction dose of monoclonal agent. Long term use of such agents is supported up to three years and is extremely effective as a steroid-sparing therapy[1-3]. Currently monoclonal antibodies are being utilised earlier in the treatment algorithm for moderate to severe inflammatory disease, in addition to more complex intra-abdominal fistulating disease in an attempt to achieve mucosal healing and remission. However, a significant proportion of patients do not achieve mucosal healing and eventually arrive at surgical intervention after step-up therapy (10%-20% per year of use of infliximab)[4,5]. Other indications for surgery include intolerance of therapy due to complications. Thus, surgical intervention is required in up to 50% of patients with CD within 10 years of diagnosis[6]. There are concerns as to operative intervention within the context of such potent immunosuppression due to the nature of biological therapy.

Current data reveals a contradictory picture of the adverse effects of pre-operative use of anti-TNF-α agents and postoperative complications following bowel resection. Several studies indicate an increase in septic complications; whether it be abdominal sepsis or superficial wound infections[7,8]. Other studies report no adverse impact of monoclonal antibodies on post-operative outcome[9-11]. It would be beneficial to subject study findings in a comprehensive meta-analytical framework to identify any associations. Several meta-analyses have been performed previously and have examined total or major postoperative complications after abdominal surgery in treatment and control groups[12-14]. In contrast, our analysis aims to study specific septic complications in the CD patient receiving anti-TNFα therapy to investigate postoperative risk in greater detail.

MATERIALS AND METHODS

Search strategy

PRISMA statement guidelines were followed for conducting and reporting meta-analysis data. We searched Medline and Embase from inception to May 2015 using the search terms "infliximab" or "immunosuppressant" or "monoclonal antibody" or "Humira" or "Adalimumab" or "Remicade" and "Crohn's disease" or "Crohn disease" and "complications" or "outcomes" or "postoperative" or "morbidity". The identical terms were used again in PubMed. The search encompassed titles, abstracts, subject headings and registry words. Articles were limited to those published in the English language, animal studies excluded and duplicates were removed.

Study selection

Studies identified from the differing searches were amalgamated and titles and abstracts were scrutinised to include relevant material only. Full text versions were obtained of eligible articles and were reviewed by both authors (PW and HP) to ensure that appropriate data was selected for analysis. Discrepancies between the authors were resolved by discussion of the particular manuscript. Studies were only included in the analysis if patients had intestinal resection with anastomosis for CD and had been administered infliximab within 90 d preceding abdominal surgery. Postoperative complication rate (30-90 d) including anastomotic leak was a compulsory outcome measure. Studies without the aforementioned data were excluded. Studies on indeterminate colitis, ulcerative colitis (UC) or ileoanal pouch were excluded.

Data extraction

Data were interrogated by both authors (PW and HP) and salient patient, disease and surgery-related factors were noted. The number of patients in the treatment (pre-operative anti-TNF administration) and control group (no use of pre-operative anti-TNF agent) were noted and compared for the outcomes of interest. Both groups comprised of patients with CD. Studies on mixed groups of patients with CD and UC were only included if data pertinent to CD could be extracted with a separation of patients on IFX and those on other therapy. Other conditions such as neoplasia and ileoanal pouch procedures were excluded. An attempt was made to establish severity of CD by noting the presence of pre- or intra- operative abscess and use of steroids pre-operatively. The overall postoperative complication rate was analysed as well as superficial and intra-abdominal sepsis occurrence. Mortality, re-operative and stoma rates were noted if reported and duration of follow-up

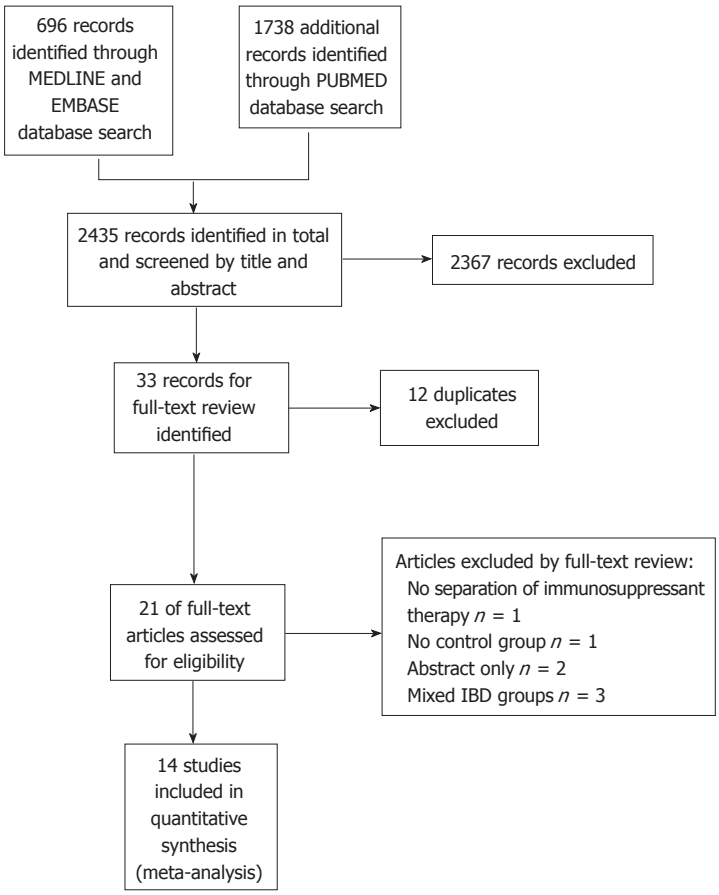

Figure 1 Preferred reporting items for systematic reviews and meta-analyses reporting diagram. IBD: Inflammatory bowel disease.

was recorded. Any intestinal resection with anastomosis and/or strictureplasty was included in analysis.

Risk of bias

The Newcastle-Ottawa score for case-control studies was used to assess the quality of included studies. A maximum of 9 stars was attainable. Publication bias was assessed by funnel plot for each outcome measure. Analysis was repeated without outlier high risk studies as required to reduce bias.

Statistical analysis

Extracted data were entered onto a Microsoft Excel spreadsheet (MS Office 2010, Microsoft, WA, United States) by the lead author (HP) with verification from the co-author (PW). All statistical analyses were performed on Rev Man 5.3 (http://tech.cochrane.org/revman; 2014) and SPSS (version 20; IBM). The groups were compared for pre-operative characteristics using χ^2 test without Yates correction and unpaired *t* test for dichotomous and continuous variables respectively. A *P* value of < 0.05 was considered significant.

Outcome measures for meta-analysis were chosen to test the null hypothesis of equivalent post-operative complications in both groups. Primary outcome measures comprised of total infectious complications, abdominal sepsis and anastomotic leak. Secondary outcome measures were wound sepsis, re-operation and mortality rate.

Dichotomous variables were analysed with the Mantel-Haenszel statistical method and random effects model. This particular model was chosen as it does not assume homogeneity between studies in terms of methodology or clinical characteristics and thus allows a more conservative analysis than the fixed effects model. Certain outcome measures were not reported by all studies and hence, the total number of patients in treatment and control groups was variable. No outcome measures were expressed as continuous variables.

Odds ratio, 95%CI, Forest and funnel plots were generated by Rev Man software. Study heterogeneity was assessed by Tau^2 and χ^2 testing with a quantitative measure of heterogeneity provided by the I^2 measure. An I^2 value of greater than 50% was considered evidence of substantial heterogeneity.

RESULTS

Search results

The search strategy identified a total of 2434 articles from Medline, Embase and Pubmed databases after application of English language and Human filters. Title and abstract screen eliminated 2367 articles with 33 remaining for analysis. Duplicates were removed at this stage as results from the 3 databases were amalgamated at this point. This left 21 articles for full text review. A total of 14 studies were relevant for meta-analysis after perusal of all 21 articles by both

Table 1 Study characteristics

Ref.	Country	Date	Type	*n*	NOS (0-9)	Pre-operative infliximab use (w)	Age[1]	Sex (m)	Steroids	Abscess
Appau *et al*[7]	United States	1998-2007	Retrospective cohort	389	7	12				
Infliximab							35.8 (11.9)	48.3%	65%	38%
No infliximab							36.8 (14.4)	45.9%	77%	44%
Canedo *et al*[10]	United States	2000-2008	Retrospective cohort	225	7	12				
Infliximab							26 (24.9-43.6)	44%	NS	37%
No infliximab							32 (29.4-41.9)	51%	NS	30%
Colombel *et al*[11]	United States	1998-2001	Retrospective cohort	270	7	8				
Infliximab							NS	NS	36%	NS
No infliximab							NS	NS	42%	NS
El Hussuna *et al*[17]	Denmark	2000-2007	Retrospective cohort	369	7	12				
Infliximab							33 (18-62)	NS	NS	34%
No infliximab							37 (8-90)	NS	NS	19%
Kasparek *et al*[15]	Munich	2001-2008	Case control match	96	7	12				
Infliximab							35 (17-66)	43%	94%	NS
No infliximab							39 (17-68)	50%	94%	NS
Kotze *et al*[23]	Brazil	2007-2010	Retrospective cohort	76	7	4				
Infliximab							NS	NS	NS	NS
No infliximab							NS	NS	NS	NS
Marchal *et al*[18]	Netherlands	1998-2002	Case control match	68	8	12				
Infliximab							36 (16-73)	NS	35%	50%
No infliximab							38.7 (17-63)	NS	35%	41%
Mascarenhas *et al*[16]	United States	2003-2010	Retrospective cohort	93	6	12				
Infliximab							35.6 (14.1)	42%	68%	NS
No infliximab							37 (14.1)	60%	44%	NS
Myrelid *et al*[21]	Europe	1989-2002	Retrospective cohort	298	6	8				
Infliximab							NS	46%	NS	20%
No infliximab							NS	36%	NS	20%
Nasir *et al*[20]	United States	2005-2008	Retrospective cohort	370	8	8				
Infliximab							38.2 (17-66)	43%	31%	NS
No infliximab							43.3 (17-77)	41%	45%	NS
Nørgård *et al*[9]	Denmark	2000-2010	Retrospective cohort	2293	6	12				
Infliximab							NS	45%	9%	NS
No infliximab							NS	41%	14%	NS
Syed *et al*[8]	United States	2004-2011	Retrospective cohort	325	7	8				
Infliximab							38.2 (13.9)	34%	40%	8%
No infliximab							40 (14.3)	45%	35%	9%
Tay *et al*[19]	United States	1998-2002	Retrospective cohort	100	7	8				
Infliximab							NS	NS	0%	NS
No infliximab							NS	NS	18%	NS
Uchino *et al*[22]	Japan	2008-2011	Retrospective cohort	405	7	12				
Infliximab							36 (14-72)	73%	37%	NS
No infliximab							37 (16-78)	69%	34%	NS
Total				5377						

[1]Given as SD or range; NS: Not stated.

authors. (Figure 1; PRISMA reporting diagram)[7-11,15-23].

Study and patient characteristics

The characteristics of the 14 included studies are summarised in Table 1. There was no overlap of study population between included studies. All studies were retrospective case control type including two that reported formal case control matching[15,18]. A total of 5425 patients with CD were included in the analysis of which 1024 received anti-TNFα agents (treatment group) and 4401 received non-biological therapy (control group). All treatment cases had received anti-TNF agents within the preceding 12 wk before surgery. Infliximab was the only biologic agent used in 8/14 studies (57%). Patients in the remaining 6 studies received either Infliximab, Adalimumab or another biological agent. Mono or combination therapy with corticosteroids and/or immunomodulators (thiopurines) was used in the majority of the control group. Unsurprisingly, there was a significant difference between steroid use in the treatment and control groups ($P = 0.0012$, χ^2 test). There was no difference between the two groups in terms of age ($P = 0.135$, unpaired t test) and gender distribution ($P = 0.456$, χ^2 test). A subset of patients was eligible for assessment of difference in age as some studies reported age as mean and others as median. Thus, the mean was used and 3 studies could be analysed with no significant difference identified ($n = 629$ in total, unpaired t test $P = 0.135$). There was no difference between the two groups in terms of pre-operative abscess ($P = 0.344$, χ^2 test) or stoma creation during the procedure ($P = 0.66$, χ^2 test).

Table 2 Studies showing primary and secondary outcome measures

Ref.	Follow-up (d)	Anastomotic leak (%)	Abdominal sepsis (%)	Wound sepsis (%)	Total infectious complications (%)	Re-operation (%)	Mortality (%)
Appau *et al*[7]							
Infliximab	30	10	10	0	40	8	1.6
No infliximab		4.2	4.3	0.3	21.5	3	0
Canedo *et al*[10]							
Infliximab	30	5.7	3.1	13.8	21.5	3	NS
No infliximab		4.9	5	8.8	18.8	6	NS
Colombel *et al*[11]							
Infliximab	30	NS	NS	NS	17.3	NS	0
No infliximab		NS	NS	NS	37	NS	0
El Hussuna *et al*[17]							
Infliximab	30	9.4	NS	NS	NS	NS	1.35
No infliximab		12.7	NS	NS	NS	NS	
Kasparek *et al*[15]							
Infliximab	30	8.3	6.2	18.8	56.2	23	2.1
No infliximab		12.5	10.4	14.6	41.6	21	0
Kotze *et al*[23]	30						
Infliximab		NS	10.5	NS	NS	NS	0
No infliximab		NS	15.8	NS	NS	NS	3
Marchal *et al*[18]							
Infliximab	90	0	12.5	5	25	0	0
No infliximab		5.8	10.3	2.5	12.8	0	0
Mascarenhas *et al*[16]							
Inflixmab	30	10.5	NS	10.5	NS	NS	0
No infliximab		4.1	NS	4.1	NS	NS	0
Myrelid *et al*[21]							
Infliximab	30	7.2	NS	NS	23.4	8	NS
No infliximab		8	NS	NS	22	7	NS
Nasir *et al*[20]							
Infliximab	30	3.4	NS	NS	NS	NS	0
No infliximab		2	NS	NS	NS	NS	0.79
Nørgård *et al*[9]							
Infliximab	30	3.7	NS	NS	NS	7	0.46
No infliximab		2.7	NS	NS	NS	8	2.59
Syed *et al*[8]							
Infliximab	NS	3.3	18.7	18.7	36	16	1.3
No infliximab		3.4	15.4	11.4	25	13	0.57
Tay *et al*[19]							
Infliximab	30	4.5	9.1	NS	13.6	NS	NS
No infliximab		5.1	5.1	NS	10.2	NS	NS
Uchino *et al*[22]							
Infliximab	30	NS	5.1	1.3	NS	NS	NS
No infliximab		NS	5.2	15.33	NS	NS	NS

NS: Not stated.

Outcome measures

Primary and secondary outcome measures from each study are summarised in Table 2.

Total infectious complications

8 out of 14 studies[7-11,15,18-21] reported total infectious complications and entered 567 treatment cases and 1291 controls for analysis. Total infectious complications were reported in 4 out of 8 and were derived in 4 studies[7,10,18,21] by summation of reported site-specific complications. A total of 165 complications were reported in the treatment group as compared to 252 in the control group. There was an increased risk of total infectious complications in the treatment group (OR = 1.52; 95%CI: 1.14-2.03) that reached statistical significance (Z = 2.87; P = 0.005) (see Figure 2. Total infectious complications: Study event rate Forest plot). There was a low risk of heterogeneity amongst analysed studies as indicated by the I^2 index (23%) and Tau^2 variable (0.04; Rev Man 5.3). The Cochran Q test revealed some heterogeneity but not to a significant extent (χ^2 = 9.06, df = 7; P = 0.25).

Postoperative abdominal sepsis

Abdominal sepsis was reported in nine out of fourteen studies[7-9,10,15,18,19,22,23] and comprised all abdominal septic complications including anastomtoic leak, abscess and/or fistula. Septic outcomes were reported in 7 studies and derived in two studies[9,15]. A total of 60 complications (60/697) were reported in the treatment group and 148 (148/3291) in the control. There was a trend towards increased postoperative abdominal sepsis

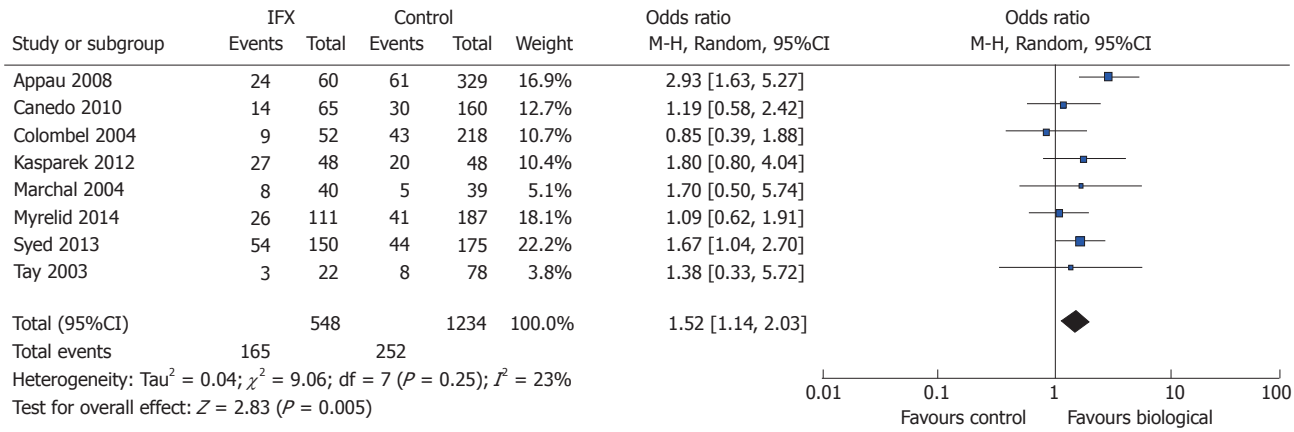

Figure 2 Total infectious complications: Study event rates and forest plot. Forest plot showing significantly higher total infective complications in patients receiving biological therapy - note confidence interval does not overlap one.

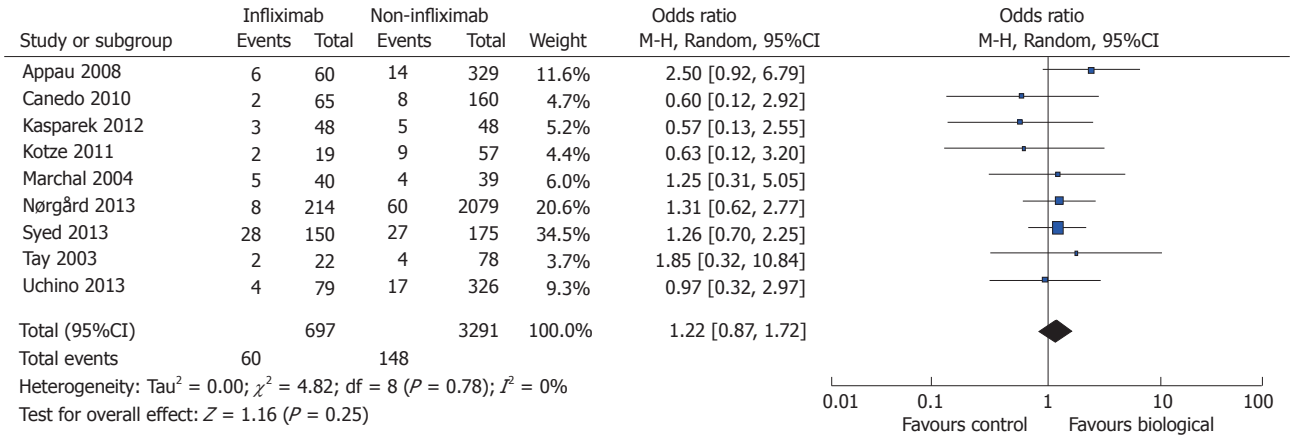

Figure 3 Postoperative abdominal sepsis: Study event rates and forest plot.

in the treatment group (OR = 1.22; 95%CI: 0.87-1.72; *P* = 0.25). (see Figure 3. Postoperative abdominal sepsis: study event rates and forest plot) Heterogeneity amongst studies was minimal with I^2 index of 0% and Tau^2 variable of zero again. Cochran *Q* test supported lack of heterogeneity with a *P* value of 0.78.

Anastomotic leak

A total of eleven studies reported on anastomotic leak rates in the two study groups which enabled 812 cases and 3356 controls to be entered for analysis[7-10,15-21]. There were 43 and 166 anastomotic complications reported in the case and control group respectively. There was a trend towards increased rate of anastomotic leak in the case/treatment group (OR = 1.19; 95%CI: 0.82-1.71; *P* = 0.26) (see Figure 4. Anastomotic leak: Study event rates and forest plot). Minimal heterogeneity was noted in the group (I^2 = 0%; Tau^2 = 0) as further confirmed by a low Cochran Q score (*Q* = 6.16; *P* = 0.72).

Wound infection

A total of seven studies reported data on postoperative wound infection in 461 cases and 1151 controls[7,8,10,15,16,18,22]. There were 51 and 96 wound complications reported in the case and control group respectively. There was a trend towards increased rate of wound sepsis in the treatment group (OR = 1.29; 95%CI: 0.62-2.68; *P* = 0.49) (see Figure 5. Wound infection: study event rates and forest plot). Substantial heterogeneity existed in the analysed studies with an I^2 value of 50% and Tau^2 value of 0.42. The Cochran *Q* test also revealed significant heterogeneity (*P* = 0.06). An outlier study[22] was identified on the funnel plot and exclusion from meta-analysis revealed an increased risk of postoperative wound infection in the treatment group (OR = 1.73; 95%CI: 1.12-2.67; *P* = 0.01) (see Figure 6. Wound infection: Funnel plot with outlier and Figure 7. Wound infection: Modified study event rates and forest plot). Heterogeneity also became minimal with the second analysis (Tau^2 = 0; I^2 = 0%).

Re-operation and mortality rates

The rate of re-operation was not reported widely and only six studies were eligible for analysis[7-10,15,21]. Thus, a total of 648 cases and 2978 controls were analysed with a predictable low re-operation rate (67 *vs* 240). There was a potential trend for increased re-operation in the treatment group (OR = 1.12; 95%CI: 0.81-1.54; *P* = 0.54) with a minimal element of heterogeneity (Tau^2

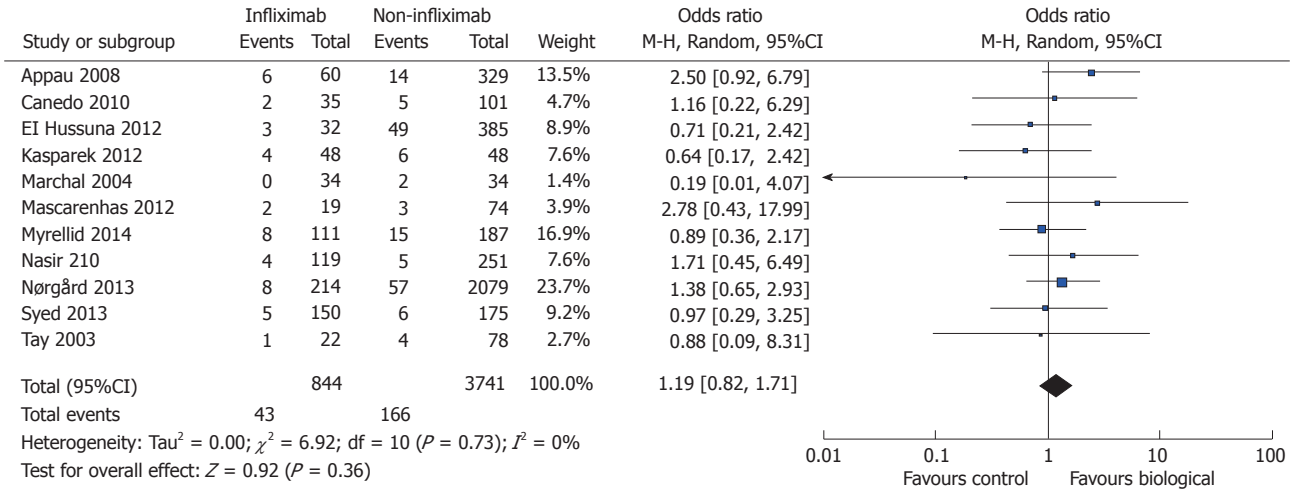

Figure 4 Anastomotic leak: Study event rates and forest plot.

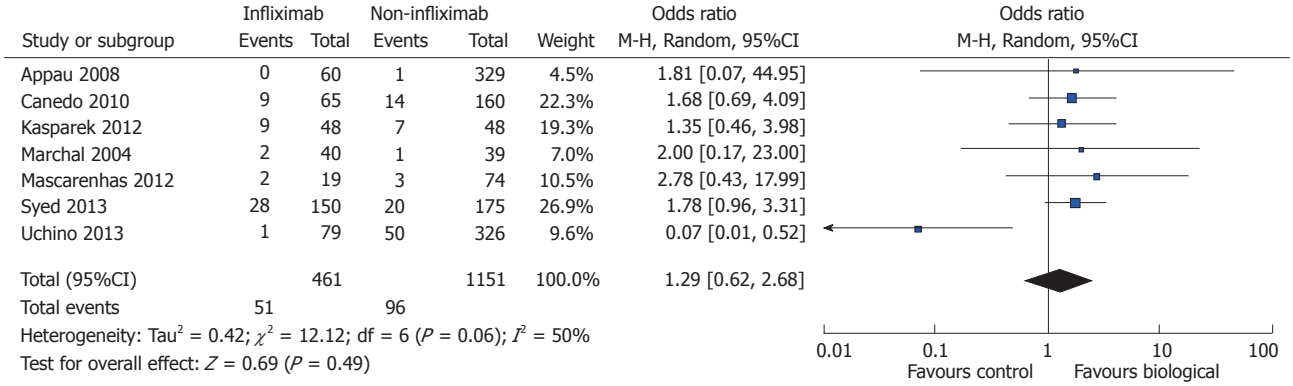

Figure 5 Wound infection: Study event rates and forest plot. Lone outlier study (Uchino 2013) visible on forest plot.

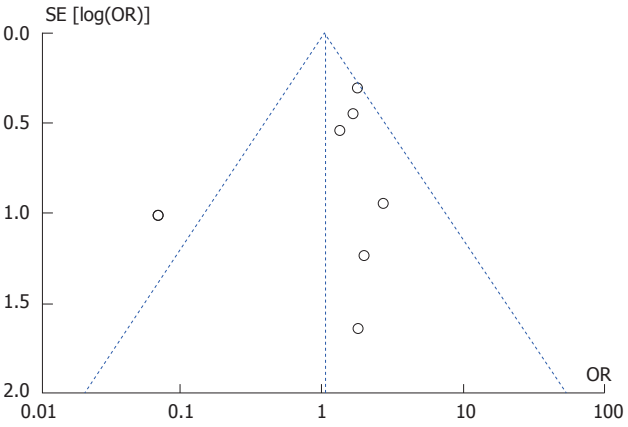

Figure 6 Wound infection: Funnel plot with outlier. A single statistical outlier visible outside the funnel plot suggestive of possible publication bias.

= 0.00; I^2 = 0%; Cochran Q = 4.65) (see Figure 8. Re-operation: Study event rates and forest plot).

Thirty-day mortality rates were reported in ten out of 14 studies and were low as expected from sample size (ranging from 0 to 3 actual events per study). There was only one large-scale study and thus further statistical analysis was not attempted[9].

DISCUSSION

Surgery for abdominal CD presents unique challenges to the surgeon and gastroenterologist. There are substantial risk factors pertaining to patient physiology, operative anatomy and co-existing medication. Anti-TNF agents have shown remarkable therapeutic efficacy in CD but concerns over increased rate of opportunistic infections and re-activation of latent TB remain[24,25]. Our meta-analysis demonstrates an increased risk of total infectious complications after abdominal surgery in patients receiving anti-TNFα therapy. Furthermore, after adjusting for publication bias a significant increase in wound sepsis was also identified. There was no increase in risk of intra-abdominal outcomes of anastomotic leak or abdominal sepsis for the same patient group. Re-operation rate was also not increased in the treatment group receiving anti-TNFα agents. Mortality rate was not compared between treatment and control groups as event numbers were too small for meaningful statistical analysis.

We defined total infectious complications to include abdominal, wound, urinary and respiratory sepsis and data was available in 8 out of 14 studies for analysis.

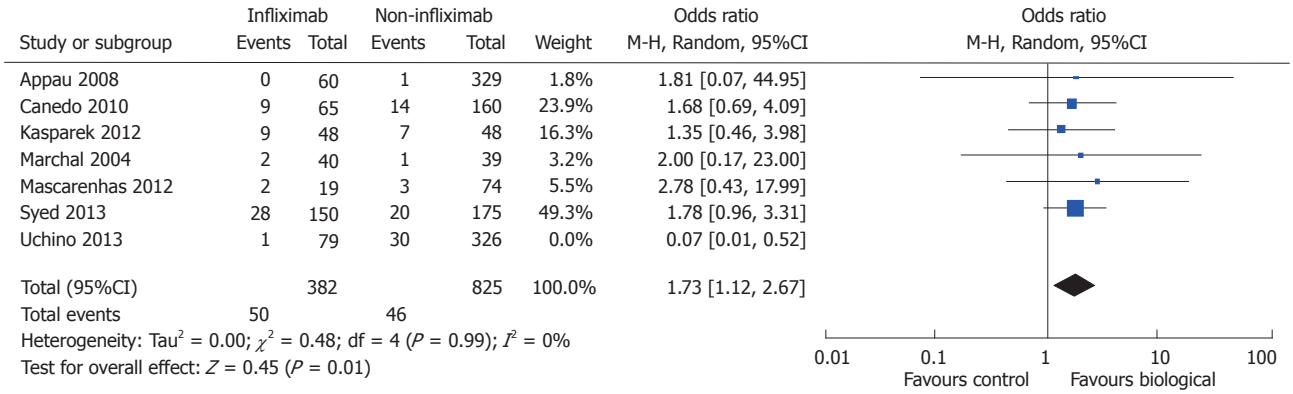

Figure 7 Wound infection: Modified study event rates and forest plot.

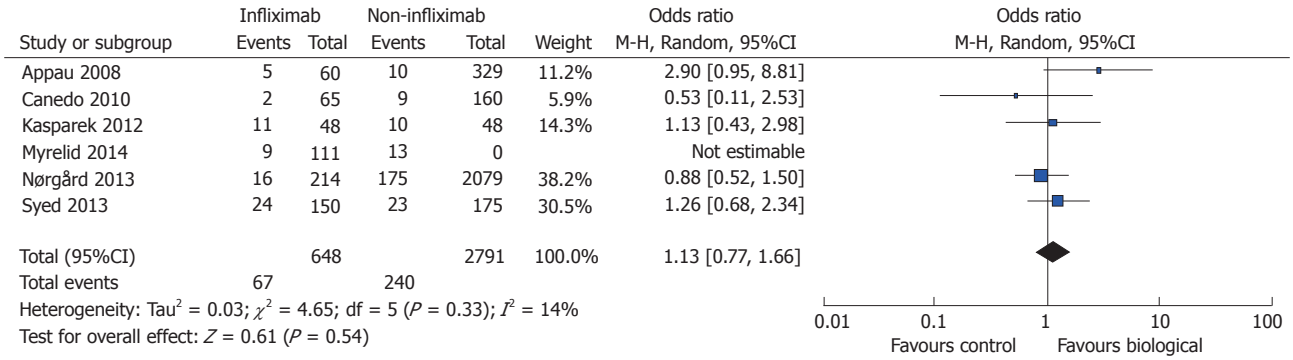

Figure 8 Re-operation: Study event rates and forest plot.

Half of the included studies reported on the full spectrum of septic complications as described previously and data was derived in the remainder. There was some minor heterogeneity noted, which may be expected with such data given variability between studies in the criteria used to define infections arising from surgical wounds, or the urinary and respiratory tracts. Use of derivative data may also lead to a degree of inaccuracy as multiple septic complications could have occurred in the same patient and as a consequence result in over or underestimation of the true absolute event rate. Reassuringly, in spite of such confounders heterogeneity was slight with no major outliers seen on funnel plot.

The outcome measures of anastomotic leak, abdominal sepsis and wound infection were analysed separately in an attempt to define the relative contribution of each outcome to the increased risk for total infectious complications. A tendency was noted towards increased complications with biological therapy for anastomotic leak and abdominal sepsis though this was not significant for either measure. In addition, heterogeneity was minimal for both analyses. The more objective nature of abdominal sepsis and anastomotic leak in terms of diagnosis and data recording may explain homogeneity in the meta-analysis. Thus, the demonstrated increase in total infectious complications in the anti-TNFα group may be inferred to be "non-abdominal" in origin. A significant increase in wound infection rates were noted in patients treated with anti-TNFα agents.

Prior meta-analyses have revealed similar findings[12,14,26,27] apart from one analysis with equivalent outcomes across both groups[13]. An increased risk was found for major postoperative infection in 4 out of 5 meta-analyses that addressed this issue[12,14,26,27]. The meta-analysis that showed no difference between treatment and control groups divided postoperative complications into major and minor categories[13]. Postoperative sepsis was allocated to either category depending on type and thus it is difficult to extrapolate the true risk of sepsis in this analysis. Our meta-analysis differs from previous efforts in that we concentrated solely on infectious postoperative complications. Analyses were also conducted separately for site specific sepsis. This was performed to assess the excess burden of each outcome in patients on anti-TNFα therapy and has not been performed previously. It is also noted that heterogeneity was markedly reduced in our analysis as compared to previous efforts and could reflect more stringent inclusion criteria.

There are several limitations to our meta-analysis. Firstly, the severity of CD is likely to be disparate between the treatment and control groups. Anti-TNFα therapy is usually prescribed for disease that is refractory to steroids and/or immunomodulators. Thus, patients would be expected to possess a greater risk for postoperative complications as operative pathology may be more complex. We attempted to analyse this by

comparing the presence of preoperative abscess or use of stoma as part of the operative procedure between the treatment and control groups. There was no significant difference identified in either of these parameters and that could indicate a degree of equivalence in disease severity between the treatment groups. However, it seems more likely that these parameters may not be sensitive enough to differentiate usefully between either group. A more objective comparison of CD severity between groups could be performed using quantitative measures such as the Crohn's Disease Activity Index (or Harvey-Bradshaw index). Unfortunately, no attempts at comparative disease severity stratification were performed within the included studies.

Patients in the control group received differing medications which again suggests that disease severity is not consistent across the control group. As previously mentioned postoperative complications are not defined or diagnosed in a standardised manner across the included studies. Thus, there may be over- or under- representation of the true extent of particular postoperative complications.

A significant limitation of this meta-analysis relates to the retrospective nature of all the included studies and the fact that only two studies attempted to match case and control groups albeit in a limited fashion[15,18]. This accurately reflects the existing literature and randomised controlled trials to address this issue are not feasible or ethical, so data is likely to be restricted to cohort studies in the future.

In conclusion, our meta-analysis may provide further support to the hypothesis of an increase in postoperative infectious complications in patients receiving anti-TNFα therapy. Our results are similar to other analyses on this subject and we have attempted to extract the specific infectious complications that are increased in this group of patients. A significant increase in both total infectious complications and wound infection rates in patients receiving anti-TNFα therapy were identified.

Our meta-analysis does not support the use of a protective stoma in patients receiving anti-TNFα therapy as a single risk factor, as there was no increase in abdominal sepsis, leak or re-operation rate. Our recommendation is to consider operative risk for patients with CD on an individual basis, incorporating recognised risk factors such as steroid use, hypoalbuminaemia, presence of fistula or abscess, in addition to preoperative anti-TNFα therapy alone. Furthermore, it seems sensible to attempt to mitigate risk of postoperative infection by planning surgery after cessation of anti-TNFα therapy where possible.

COMMENTS

Background

Current data reveals a contradictory picture of the adverse effects of pre-operative use of anti-TNFα agents and postoperative complications following bowel resection. It would be valuable to perform a comprehensive meta-analysis to identify any associations. The authors' analysis aims to study specific septic complications in the Crohn's disease patient receiving anti-tumor necrosis factor alpha (TNF-α) therapy to investigate postoperative risk in greater detail.

Research frontiers

Not applicable as this is a meta-analysis from synthesised data from previous original studies.

Innovations and breakthroughs

Their meta-analysis demonstrates an increased risk of total infectious complications after abdominal surgery in patients receiving anti-TNFα therapy. This is the first meta-analysis to show a site-specific increase in septic complications, in particular wound sepsis.

Applications

The authors recommend risk assessment on an individual basis for patients with Crohn's disease taking into account use of anti-TNFα therapy in combination with other known risk factors for post-operative septic complications. Discontinuation of anti-TNFα should be considered 6-8 wk prior to planned surgery.

Terminology

Anti-TNFα therapy: Anti-tumour necrosis factor alpha therapies are mostly monoclonal antibodies to tumour necrosis factor, a chemokine which is implicated in the abnormal inflammatory response associated with active inflammatory bowel disease. CD: Crohn's disease; UC: Ulcerative colitis; Fistulating disease: Enterocutaneous or inflammatory mass with entero-entero fistulae and/or fistula-in-ano.

Peer-review

This is a well-written review about the role of the pre-operative use of anti-TNF-alpha therapy that may increase risk of post-operative infectious complications after surgery for CD and in particular wound related infections.

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