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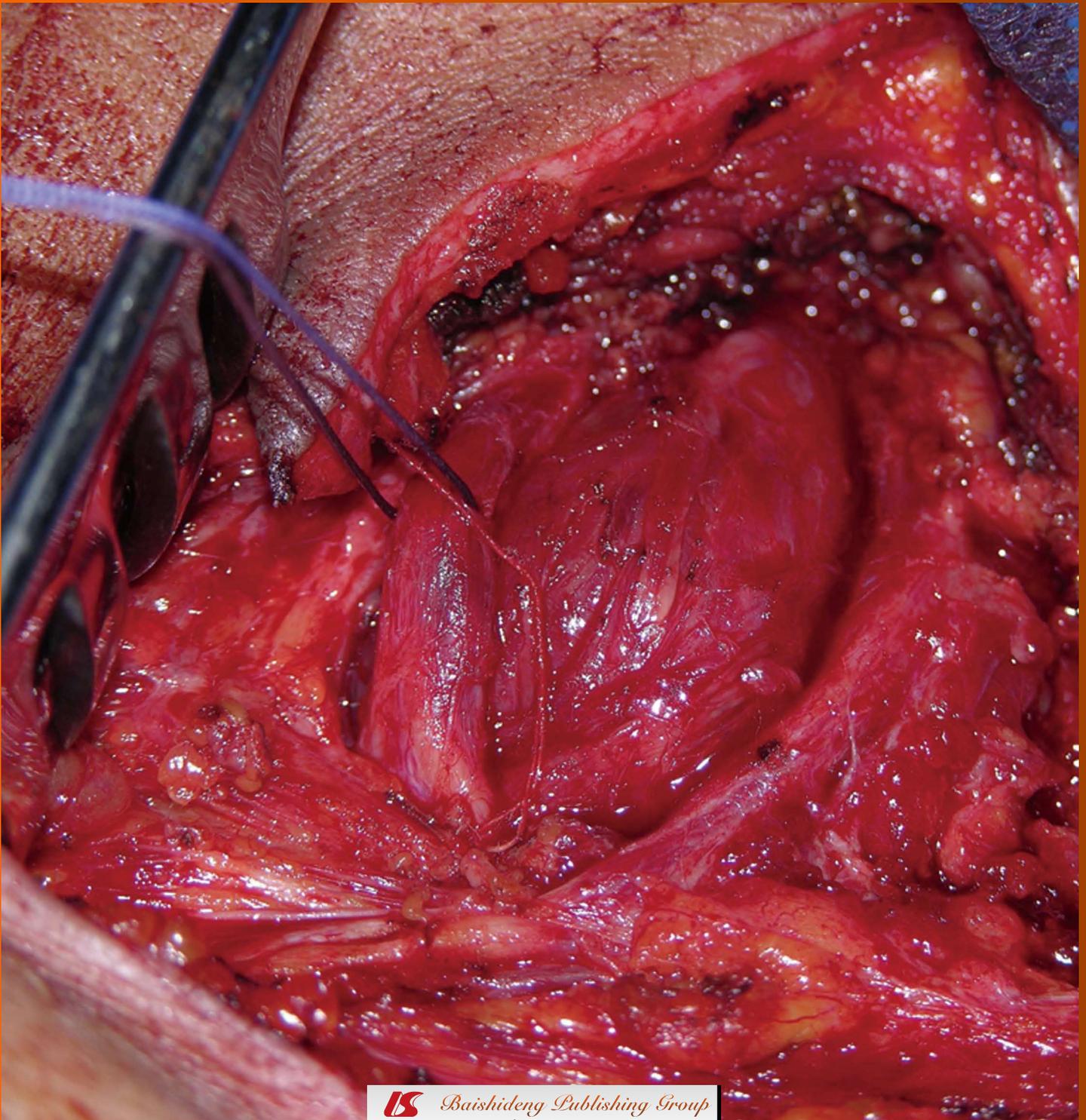
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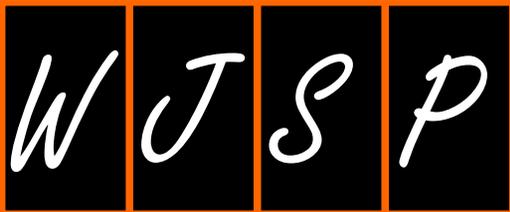
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## A rare case of malignant schwannoma of the brachial plexus

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### INTRODUCTION

Peripheral nerve sheath tumors (PNST) include the schwannoma, the most common tumor arising from peripheral nerves, and neurofibromas. Malignant PNST (MPNST), also known as neurogenic sarcomas, include schwannomas and neurofibrosarcomas which are indistinguishable when viewed with histological techniques. MPNST account for 5% to 10%<sup>[1]</sup> of soft tissue sarcomas, and have an incidence of 0.001% in the general population<sup>[2]</sup>. MPNST develop 4% to 10% in neurofibromatosis type 1 (NF1), an autosomal dominant neurocutaneous disorder with an estimated incidence of 1 in 2500 births.

Peripheral nerve tumors of the upper limb are very rare; they represent less than 5% of all tumors in this region<sup>[2]</sup>. Solitary benign peripheral nerve schwannomas are the most common. These can cause nerves to exhibit different clinical features depending on type, site of lesion and their histopathologic pattern. Benign schwannomas are generally solitary, oval, capsulated and elastic. Malignant tumors are very rare with rapid growth, invasion of the nerve and neurological deficit<sup>[3]</sup>.

Magnetic resonance imaging and ultrasound can localize the tumor but definitive diagnosis is possible only with a histopathological exam.

Although rare, MPNST is one of the most aggressive tumors of the head and neck area. Complete surgical removal is the main treatment and most important prognostic factor. Adjuvant radiotherapy should be used

### Abstract

We report a rare case of malignant schwannoma of the brachial plexus treated during a surgical campaign aimed at the poorest communities in the Cuzco region of Peru. A Peruvian 40-year-old-female from a mountain community presented with a mass on the lateral side of her left supraclavicular space. No imaging tools were available during this surgical campaign and so a biopsy of the tumor was carried out. Histopathological examination revealed it to be a low grade malignant schwannoma. A nerve enucleation of the tumor was chosen as neither chemotherapy nor radiotherapy was available. The tumour was a firm mass 4 cm x 3 cm x 2 cm in size. After excision of the lesion the patient presented neurological sequelae (deltoid, bicep, and tricep weakness) but her condition improved over the next 3 years. We report this case of malignant schwannoma of the brachial plexus as its incidence is very rare (the reported incidence is 0.001%) and because of its challenging treatment in poor healthcare conditions.

to assist surgical excision in local control<sup>[4]</sup>. The role of adjuvant chemotherapy remains controversial<sup>[4]</sup>.

Schwannomas originating from the brachial plexus are extremely rare and to our knowledge those manifesting preoperatively as a large lesion have rarely been reported. We report a case of malignant schwannoma of brachial plexus manifesting as an enlarging mass in the supraclavicular space, treated during a surgical campaign in difficult healthcare conditions.

## CASE REPORT

A 40-year-old woman presenting a mass of the left supraclavicular fossa, was referred to us during a surgical campaign in October 2008 aimed at the poorest communities in the Cuzco region of Peru. She showed no signs of any neurological disturbances to the left upper limb. In her past history there was no significant disease and physical examination showed no abnormalities. Radiology was unavailable in our hospital so we performed a surgical biopsy. The excised section was gray-white to gray-yellow, soft and fleshy in appearance. Pathologically it was diagnosed as a low-grade malignant schwannoma composed of two types of regions known as Antoni A and B regions; we decided to remove the mass completely.

An anterior supraclavicular approach was used. After the small skin incision, we displaced the sternocleidomastoideus muscle and proceeded with the complete dissection of this solid vascularised mass arising from the medial cord (Figure 1). The nerves were enlarged by the tumour. Finally, while trying to preserve the nervous structures, the mass was removed (Figure 2).

The histopathology of the tumour was consistent with a low grade malignant schwannoma.

After surgery the patient had motor disturbances on the left upper limb, particularly on the biceps muscle, she kept deltoid and distal finger movements and she retained sensation. Radiotherapy and chemotherapy weren't available in this clinical centre and we couldn't follow the patient for a possible period of rehabilitation. When she returned to the medical centre, 3 years later, she was improved, without any further symptoms and, at physical examination, showed no sign of relapse.

## DISCUSSION

The aetiology of PNST is usually unknown. However, several hereditary disorders are known to predispose to benign and MPNSTs, notably NF1 and NF2<sup>[5]</sup>, both of which are inherited in an autosomal dominant fashion.

All ages and both sexes may be affected by PNSTs. Sporadic MPNSTs are most common between 40 and 50 years of age, while those occurring in the setting of NF1 are diagnosed some 10 years earlier. In total, MPNSTs account for 5%-10% of all soft tissue sarcomas.

Schwannomas are encapsulated spindle cell tumors with distinct Antoni A and B components, hyaline vessel walls, and nuclear palisading<sup>[6]</sup>.

Neurofibromas are unencapsulated tumors composed

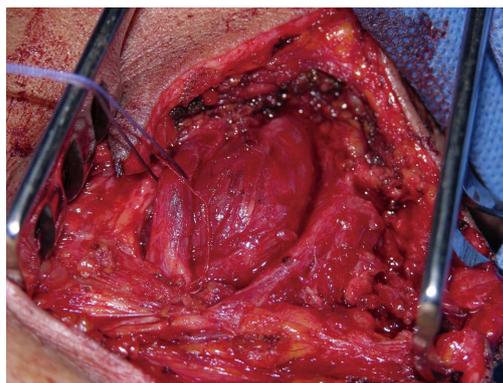


Figure 1 Tumor's dissection and exposure of the surrounded nerves.

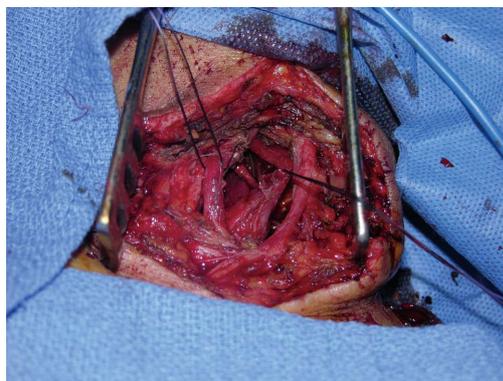


Figure 2 Nerve preservation after tumor excision.

of spindle cells dispersed in fibromyxoid stroma.

Perineuriomas may arise in soft tissues or within nerves, and are composed of cells with elongated bipolar cytoplasmic processes frequently arranged in whorls or a storiform pattern.

MPNSTs typically are characterized by the presence of pale spindle cells often arranged in fascicles with alternating cellular and more myxoid areas. Most MPNSTs arise from Schwann cells, but the possibility remains that some arise from nerve sheath cells other than the Schwann cells. Approximately two-thirds of all MPNSTs are associated with neurofibromas<sup>[3]</sup>.

In the literature survival rate is estimated to be 48% at 5 years and prognostic factors are: tumour localization, size, grade of malignancy and radical surgical treatment<sup>[7]</sup>.

Benign PNSTs rarely recur after surgery. MPNST, on the other hand, are often highly aggressive tumors, and more than 60% of patients die of the disease<sup>[8]</sup>.

In the treatment of malignant schwannoma, surgical removal is the first choice<sup>[9]</sup>; however the resecting margin of the tumor is always difficult and controversial<sup>[10]</sup>. Sometimes, in the case of malignant lesions, only the sacrifice of involved nerves allows complete resection. Aggressive surgical intervention and radiotherapy can result in good survival<sup>[11]</sup>. In our case the pathology result reported a low grade malignant lesion and for this reason we decided to resect the tumor, even if we couldn't perform any additional necessary treatment, principally radiotherapy. Our

patient showed signs of neurological disorder postoperatively as she presented deltoid, bicep, and tricep weakness. Unfortunately we couldn't follow her with further therapy, but she came back to the medical centre after 3 years and was improved.

In conclusion we experienced an unusual case of malignant schwannoma involving nervous structures of the brachial plexus. We report its difficult treatment in a poor social and cultural context during a surgical campaign and the particular importance of its complete surgical removal in these complicated conditions, even though no adjuvant treatment was available.

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**APPENDIX** I-V Instructions to authors

**ABOUT COVER** Mori S, Baba K, Yanagita S, Kita Y, Maemura K, Matakai Y, Uchikado Y, Okumura H, Nakajyo T, Natsugoe S, Takao S, Aridome K. Reduced port surgery for appendectomy: early experience and surgical technique. *World J Surg Proced* 2013; 3(2): 8-12  
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## A simple alternative technique for harvesting split thickness skin grafts

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### Abstract

**AIM:** To assess the use of a simple split skin graft harvesting technique, requiring only a scalpel and a swab.

**METHODS:** During the last 8 mo, we operated on a consecutive series of 52 patients (30 males, 22 females) with a mean age of 60 years (33-80). We used the technique we present in order to cover small skin defects. All procedures were performed under local anesthesia. Thirty-seven patients underwent bedside surgery, 8 patients were operated on in the outpatient department and the remaining 7 had their graft harvested in the operating room. After antiseptic preparation of the donor site, the margins of the graft were drawn by the use of a surgical marker. A No 15 scalpel was used for the graft elevation, under constant traction with a moist swab.

**RESULTS:** All procedures were completed successfully without immediate complications. The patients toler-

ated the procedure well. The mean operative time was 15 min. Twenty-four donor sites were left to heal by secondary intention, whereas 28 were sutured with interrupted 3/0 silk sutures in order to heal by primary intention. All 24 sites that were left to heal by secondary intention healed completely in approximately 14 d. For the sites that were sutured, the sutures were removed on the 10<sup>th</sup> postoperative day. Out of the 52 operated cases, 6 patients (11%) developed complications. In 4 patients, the split thickness skin grafts were partially lost, whereas in 2 patients the grafts were completely lost. Wound dehiscence was observed in 2 patients, which were treated with local antiseptic and antibiotic therapy.

**CONCLUSION:** The skin graft technique described is simple, costless and effective and can be performed even on an outpatient basis, without the need for special equipment.

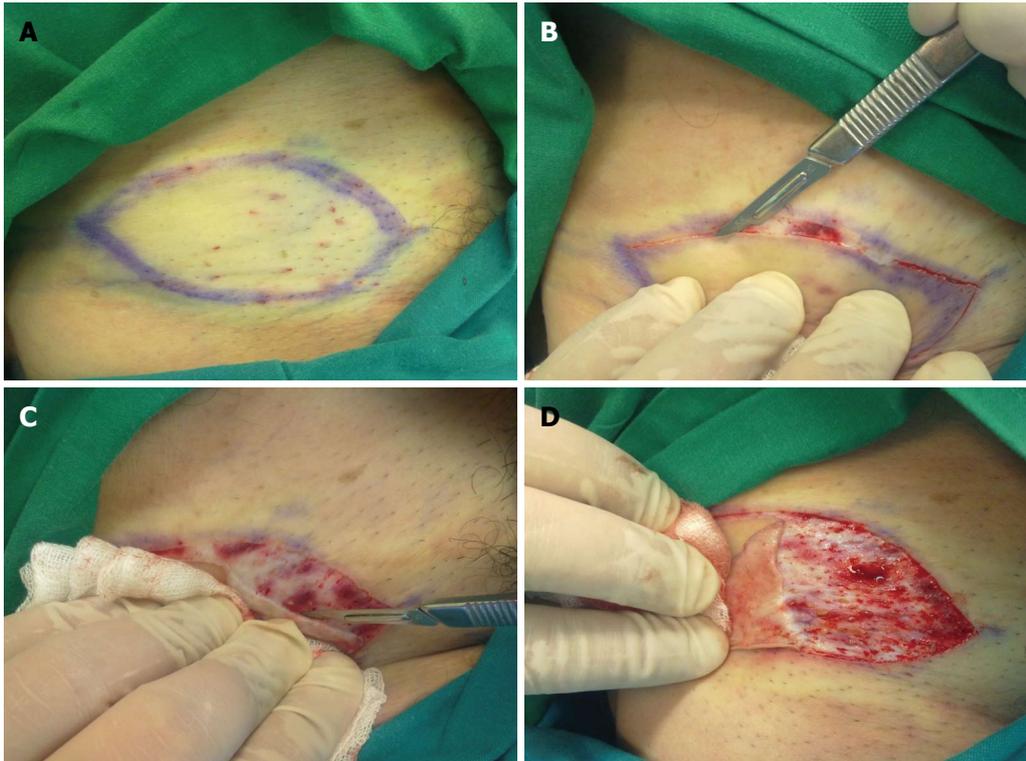
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**Key words:** Skin graft; Skin defect; Split thickness; Skin reconstruction; Dermatome; Tissue harvesting

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### INTRODUCTION

The reconstruction of skin defects with the use of split thickness skin grafts (STSG) is a mainstay technique in dermatological plastic surgery<sup>[1]</sup>. We present a new simple method of harvesting split thickness skin grafts using only a surgical blade and a swab/gauze. In contrast to



**Figure 1** Our technique procedures. A: Donor area (right groin) with the graft designed on it; B: Split thickness skin grafts edges elevated (shave excision); C: Skin graft separation from the underlying dermis; D: Moist swab repositioning exerts a gentle pull in a horizontal plane.

other techniques, the advantages of this technique include no requirement for special surgical equipment (such as a dermatome) and the simplicity of the procedure<sup>[2]</sup>. Moreover, cost is minimized as there is no need for sterilization of the dermatome or its blades.

## MATERIALS AND METHODS

In the last 8 mo (from February 2012 to October 2012), we used our technique in a consecutive series of 52 patients (30 males, 22 females) who required split thickness skin grafts for the covering of small defects. All procedures were performed under local anesthesia. Thirty-seven patients underwent bedside surgery, 8 patients were operated on in the outpatient department and the remaining 7 had their graft harvested in the operating room.

According to our technique, we first mark and inject local anesthetic at the donor area. Following that, the skin graft edges are elevated with a No 15 scalpel. The elevation is performed in a “shave excision” manner (Figure 1A, B). A moist swab/gauze exerts gentle traction on the raw area produced by the graft’s elevation, while the scalpel is being moved on a horizontal plane, in an oscillating fashion, in order to separate the skin from the underlying soft tissue at the level of the dermis (Figure 1C). Frequent repositioning of the moist swab is mandatory following the harvest of the skin graft (Figure 1D). The donor site can be sutured directly, as is the case following the traditional method of full thickness graft harvesting,

or it can be left to heal by secondary intention. The graft is placed on the recipient site immediately after harvesting. Meshing of the graft is possible if necessary.

## RESULTS

All procedures were completed successfully without immediate complications. The patients tolerated the procedure well. The mean operative time was 15 min. Twenty four donor sites were left to heal by secondary intention, whereas 28 were sutured to heal by primary intention. Forty-eight (96%) skin grafts were successfully taken on the acceptor site, whereas 4 were partially lost. The patients (4) whose grafts were partially lost were re-operated on 14 d after the initial operation following the same technique successfully. The donor sites that were left to heal by secondary intention healed in approximately two weeks. The remaining patients whose donor sites were sutured directly after the graft was harvested (primary intention donor sites) had their sutures removed on the 10<sup>th</sup> postoperative day.

Out of the 52 operated cases, 6 patients (11%) developed complications. In 4 patients, the split thickness skin grafts were partially lost, whereas in 2 patients the grafts were completely lost. Two partial wound dehiscences were treated with local antiseptic and antibiotic therapy.

All patients were followed up at the outpatient clinics of our department on the 1<sup>st</sup>, 3<sup>rd</sup> and 6<sup>th</sup> month postoperatively. All grafts were already integrated in the donor site successfully after the 1<sup>st</sup> month.

## DISCUSSION

Skin grafting has always been a valuable option in covering skin defects and soft tissue defects that cannot be closed primarily<sup>[3]</sup>. Split-thickness skin grafts contain varying thickness of dermis, whereas full thickness skin grafts contain the entire dermis. Freshly harvested skin grafts react primarily with contraction, mostly due to the elastin in the dermis<sup>[4]</sup>. The more dermis contained in a graft, the earlier that the contraction appears<sup>[5,6]</sup>.

The take of a skin graft depends on the graft nutrition, which is achieved through a process of revascularization<sup>[7-10]</sup>. Two time periods of skin graft or skin substitute adherence on the recipient area have been described<sup>[11,12]</sup>. The first starts immediately after the placement of the skin graft on the skin defect and is based on serum imbibitions<sup>[13-15]</sup>. Graft adhesion is based on fibrin formation. The second period starts 24 to 48 h after the graft placement and is based on vessel formation into the graft<sup>[16,17]</sup>.

During the last two decades, many different skin flap and graft transfer techniques have been developed<sup>[18,19]</sup>. Modern skin grafting research incorporates the cost parameter, as the latter represents an important factor influencing surgical planning<sup>[20,21]</sup>. The cost of surgical equipment used for split skin grafting can be minimized, especially when small defects can be treated on an outpatient basis or when the grafts can be harvested at a bedside<sup>[22,23]</sup>. Treatment of skin defects can become very expensive, especially in patients suffering with multiple burns<sup>[24-27]</sup>.

We believe that the technique of split skin harvesting we describe is inexpensive, easy to perform and suitable for small skin defects. It can certainly be performed on an outpatient basis. The possible disadvantages of this technique are the fact that the skin graft thickness cannot be estimated accurately and that it is operator dependent. Moreover, we would not recommend this method for larger skin defects because the operative time would be significantly prolonged.

## COMMENTS

### Background

Skin defects are a very common phenomenon in plastic surgery. The high frequency of this condition requires significant theater time and specific surgical equipment.

### Research frontiers

Split thickness skin grafts can be successfully harvested using the scalpel – gauge technique described. However, the exact thickness of the skin graft cannot be predicted, as is the case when an electrical dermatome is used. Moreover, this technique can be quite time consuming when used to cover larger skin defects which need to be operated on in an operating theater compared to the standard dermatome technique. In this study, the authors demonstrate a method which can be used to treat small and moderate defects.

### Innovations and breakthroughs

Recent reports have highlighted the importance of the cost factor when planning the covering of skin defects. This study suggests a new surgical technique based on simplicity and low cost parameters with proven good results on small and moderate skin defects.

### Applications

Given the fact that this new surgical technique presupposes a short learning curve, it may represent a useful and reliable tool which can be incorporated in everyday practice.

### Terminology

Split thickness skin grafts (STSG) include only a part of the dermis, whereas full thickness skin grafts contain the entire dermis. STSG are usually harvested by the use of specific surgical equipment, the dermatome. Donor sites are skin areas where skin grafts are harvested from and acceptor sites or skin defects are to be covered by skin grafts.

### Peer review

In this study, the authors presented a new surgical technique for covering skin defects, based on ease and simplicity. Theater operation time was significantly reduced since the patient can be operated on as an outpatient or "bedside" basis. The results are interesting and this technique may take its position among standard skin harvesting techniques.

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## Reduced port surgery for appendectomy: Early experience and surgical technique

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### Abstract

**AIM:** To evaluate our experience and surgical technique of laparoscopic appendectomy *via* reduced port surgery (LARPS).

**METHODS:** Sixteen patients (8 men and 8 women; median age: 31.0 years) who underwent LARPS between November 2009 and May 2012 were included in the present study. We performed LARPS, in which access devices were inserted through an umbilical skin incision with 1 additional skin incision in the left lower abdomen. After setting access devices, pneumoperitoneum was maintained at 10 mmHg using CO<sub>2</sub> and a 3 mm trocar was positioned (or direct puncture was performed by the Endo Relief system) under laparoscopic

guidance. The mesoappendix was dissected using an ultrasonically activated device. After mesoappendix dissection, ligation was performed near the appendix base and the appendix was dissected using an ultrasonically activated device. The appendix was then removed. At the end of surgery, we administered local anesthesia with ropivacaine 1% (10 mL) for the skin incisions. The outcomes were evaluated in terms of operation time, intraoperative blood loss, length of postoperative hospital stay and surgical complications.

**RESULTS:** Our surgical procedure allowed operators to use instruments as in conventional laparoscopic appendectomy. The basic principle of triangulation of instrumentation was maintained to some degree. LARPS was performed in 9 patients with catarrhal appendicitis, 5 with phlegmonous appendicitis, and 2 with gangrenous appendicitis. The median surgery time was 60 min and the median intraoperative blood loss was 1.2 mL. The median length of postoperative hospitalization was 4 d. There were no conversions to open surgery, no operation-related complications or mortality.

**CONCLUSION:** Our experience and surgical technique suggest that LARPS is a safe and feasible procedure for patients with appendicitis.

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**Key words:** Reduced port surgery; Appendectomy; Laparoscopy; Cosmesis; Single incision

**Core tip:** Our experience and surgical technique suggest that laparoscopic appendectomy *via* reduced port surgery is a safe and feasible procedure for patients with appendicitis. Although the present study showed that this procedure offers cosmetic advantages and technical simplicity, the effectiveness and feasibility of this method should be assessed in randomized trials.

Mori S, Baba K, Yanagita S, Kita Y, Maemura K, Mataka Y, Uchikado Y, Okumura H, Nakajyo T, Natsugoe S, Takao S, Aridome K. Reduced port surgery for appendectomy: Early experience and surgical technique. *World J Surg Proced* 2013; 3(2): 8-12 Available from: URL: <http://www.wjgnet.com/2219-2832/full/v3/i2/8.htm> DOI: <http://dx.doi.org/10.5412/wjssp.v3.i2.8>

## INTRODUCTION

Laparoscopic appendectomy has become a commonly performed surgical procedure worldwide. It is safe, effective and minimally invasive. Compared with open appendectomy, laparoscopic appendectomy is associated with less overall morbidity, an acceptable operation time, a lower incidence of superficial surgical site infection, and a shorter hospital stay<sup>[1-5]</sup>. Single-incision laparoscopic surgery is a novel technique that may be performed when considering minimally invasive surgery and desiring a cosmetic benefit. Recently, single-incision laparoscopic appendectomy (SILA) has become a major focus of study<sup>[6-12]</sup> and prospective randomized studies were performed to compare the outcome of SILA and conventional laparoscopic appendectomy (CLA)<sup>[13-16]</sup>. The results showed the SILA approach to be similar in terms of perioperative outcomes. In the SILA group, wound cosmesis and satisfaction scores were better; however, the operative time was longer and worse pain scores were demonstrated upon exertion.

In the present study, we describe our experience and surgical technique in patients who underwent laparoscopic appendectomy *via* reduced port surgery (LARPS).

## MATERIALS AND METHODS

### Patients

Sixteen patients (male,  $n = 8$ ; female,  $n = 8$ ; mean age: 31.0 years; range, 16-49 years) who were admitted to our hospital from November 2009 to May 2012 were included in this study. Patients were excluded if they had high dense adhesions, perforated appendicitis, acute appendicitis with abscess, or American Society Anesthesiologist scores (ASA) of 4 or 5. All patients had appendicitis and underwent LARPS. Nine patients had catarrhal appendicitis, 5 had phlegmonous appendicitis, and 2 had gangrenous appendicitis.

### Surgical procedures

All patients underwent general anesthesia and were placed in the supine position. The operator and assistant stood on the left side of the patient. The skin was cut along a Z-line marked in the umbilical region (Figure 1A). We used an EZ-access with a Lap-Protector (Hakko Medical Inc., Chikuma, Japan) for the umbilical access device and an Endo Relief (Hope Denshi Co., Kamagaya, Japan) which has a 2.4 mm shaft with a 5 mm diameter head. Two 5 mm trocars were placed through the EZ-access for a 5 mm laparoscope and 5 mm instrument (Figure

1B). After setting the EZ-access with the Lap-Protector, pneumoperitoneum was maintained at 10 mmHg using CO<sub>2</sub> and a 3 mm trocar was positioned (or direct puncture was performed by the Endo Relief system) under laparoscopic guidance into the left lower abdomen (Figure 1B). Laparoscopic instruments were inserted and the mesoappendix was dissected using an ultrasonically activated device (Figure 2). After mesoappendix dissection, ligation was performed near the appendix base using 1 endoloop (Figure 3A) (Ethicon, PDS 0)<sup>[17]</sup> and the appendix was dissected using an ultrasonically activated device (Figure 3B). The appendix was then removed through the Lap-Protector without contacting the abdominal wall. We administered local anesthesia with ropivacaine 1% (10 mL) for the skin incisions at the end of surgery.

### Intraoperative and postoperative observations

Intraoperative information about the surgical duration, complications and blood loss was collected. Postoperative data comprised of complications, length of postoperative hospital stay, and pathological findings. We also conducted the interview post operatively about whether the operative scars were excellent, not bad or bad.

## RESULTS

Our surgical procedure allowed operators to use instruments as in conventional laparoscopic appendectomy and the basic principle of triangulation of instrumentation was maintained to some degree. The umbilical and another skin incision positioned on the left lower abdomen shrunk in the wrinkle (Figure 4). The mean surgical duration was 60 min (range, 35-150 min) and the mean amount of blood loss was 1 mL (range, 0-20 mL). The median hospital stay after surgery was 4 d (range, 3-7 d). No intraoperative complications developed in this series. One patient received 1 additional port because of dense adhesions; however, there were no conversions to open surgery. All patients were free of complications such as leakage of the appendix stump, bleeding, intra-abdominal abscesses and small bowel obstruction. There was no intraoperative or postoperative mortality. Additionally, 9, 5 and 2 patients had catarrhal, phlegmonous and gangrenous appendicitis, respectively. For our interview about the operative scars, all patients answered that the scars were excellent.

## DISCUSSION

Recently, SILA has been reported to demonstrate perioperative outcomes and safety similar to that shown by CLA<sup>[15,16]</sup> as a result of innovation and technological advances. It has been suggested that SILA results in better cosmetic outcomes than CLA<sup>[9-11]</sup>. However, SILA resulted in worse pain scores upon exertion, required a higher dosage of intravenous analgesics, and involved a longer operative time compared with CLA<sup>[15,16]</sup>. We performed LARPS to treat appendicitis by cutting the skin over the

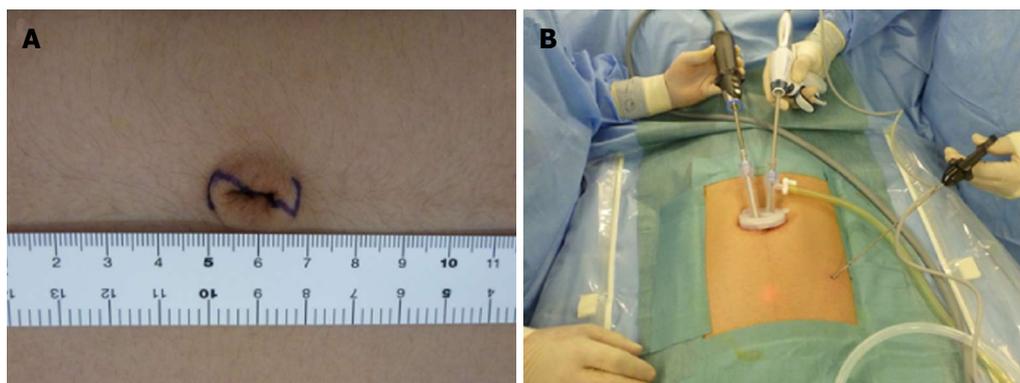


Figure 1 Design for umbilical Z-incision (A) and positioning of the EZ-access and Endo Relief (B).

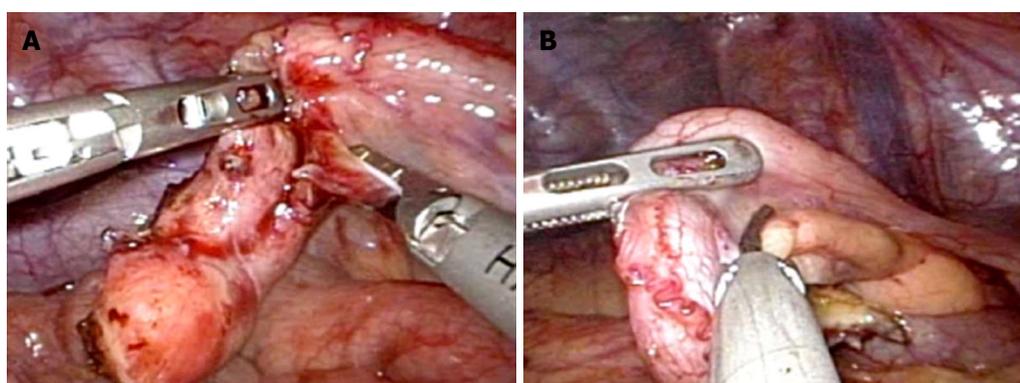


Figure 2 Dissection of the mesoappendix using an ultrasonically activated device.

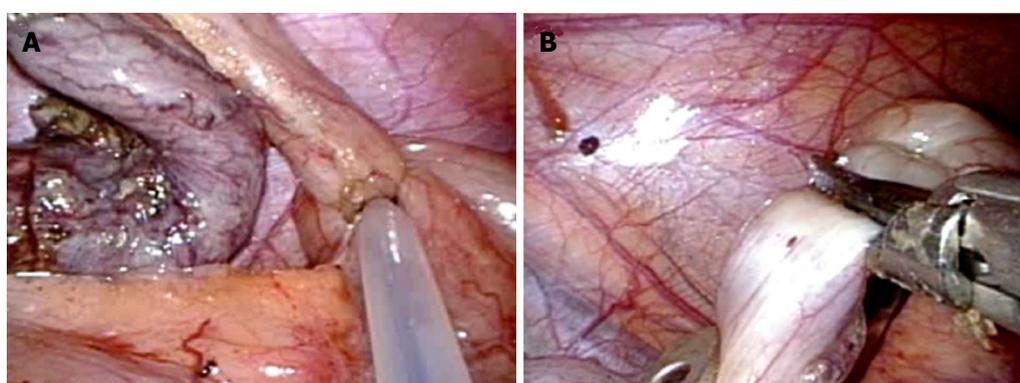
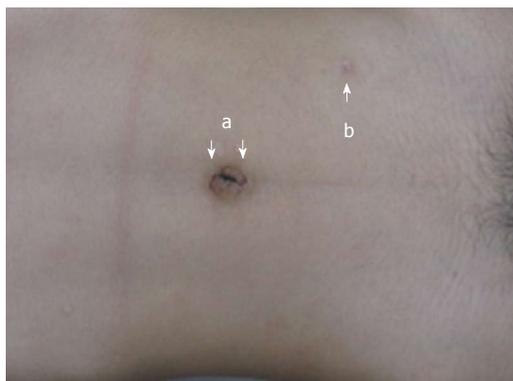


Figure 3 Placement of an endoloop near the appendix base (A) and dissection of the appendix using an ultrasonically activated device (B).

umbilicus with a 2 cm long Z-incision, inserting 2 trocars into the incision and placing another 3 mm trocar (or performing direct puncture by the Endo Relief system) into the left lower abdomen to assist the surgeon. The assisting surgeon usually operates the camera on left side of the patients. Because the appendix was adherent near the lower peritoneal midline, the assisting surgeon stood opposite the operator at the beginning of operation (Figure 1B). The skin incisions were almost hidden after surgery and most patients expressed satisfaction with the virtually scarless outcome. The potential advantages of our procedure are a well-balanced cosmetic outcome and technical

simplicity for laparoscopic appendectomy.

We performed LARPS, a novel surgical procedure, to treat appendicitis. This method yielded good short-term outcomes, including good cosmetic results and a technically simplified SILA. Generally speaking, single-incision laparoscopic surgery is somewhat ergonomically challenging to the operator because the basic principle of triangulation of instrumentation, which is applicable to conventional laparoscopic surgery, is lost to some degree and instruments often interfere with one another. Our surgical procedure allows operators to use instruments as in CLA. Both the triangulation of instrumentation and



**Figure 4 Operative scar 2 wk after surgery.** The arrows show operative scars of umbilical Z-skin incision (a) and Endo Relief (b).

eye-hand and hand-hand coordination are improved, resulting in less interference among instruments compared with SILA. We needed to insert an additional trocar into 1 patient with gangrenous acute appendicitis because of dense adhesions. The duration of surgery and volume of blood lost were 150 min and 20 mL, respectively. This patient did not develop any intraoperative or postoperative complications.

In our procedure, another 3 mm skin incision to assist the surgeon was positioned on the left lower abdomen. The skin incision shrunk in the wrinkle, resulting in a virtually scarless outcome. Positioning one instrument upon the left lower abdomen allowed the operator to maintain eye-hand and hand-hand coordination, maintain the basic principle of triangulation of instrumentation, and avoid interference of instruments. If drain placement was required, the drain could be inserted into the skin incision on the left lower abdomen. In this series, 2 patients required drain placement in the pouch of Douglas because of gangrenous acute appendicitis.

The specimens could be removed through the umbilical skin incision protected by the Lap-Protector. After removing the specimens, pneumoperitoneum was easily maintained using the EZ-access. After washing the intraperitoneal cavity, we removed the Endo Relief or trocar under laparoscopic guidance, closed the peritoneum and fascia at the umbilicus, and administered local anesthesia with ropivacaine 1% (10 mL) for the skin incisions. No patients required a higher dosage of intravenous analgesics postoperatively; the only additional analgesia comprised of oral non-steroidal anti-inflammatory drugs (NSAIDs).

Although our experience was limited to 16 patients, none experienced any intraoperative or postoperative complications, the operative time and length of postoperative hospital stay were acceptable, and the postoperative pain upon exertion was controlled with occasional NSAIDs.

In conclusion, our experience and surgical technique suggest that LARPS is a safe and feasible procedure for patients with appendicitis. Although the present study showed that this procedure offers cosmetic advantages

and technical simplicity, the effectiveness and feasibility of this method should be assessed in randomized trials.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

Laparoscopic appendectomy has become a commonly performed surgical procedure worldwide. It is safe, effective and minimally invasive. Compared with open appendectomy, laparoscopic appendectomy is associated with less overall morbidity, an acceptable operation time, a lower incidence of superficial surgical site infection, and a shorter hospital stay.

### Research frontiers

It has been suggested that SILA results in better cosmetic outcomes than conventional laparoscopic appendectomy (CLA). However, SILA resulted in worse pain scores upon exertion, required a higher dosage of intravenous analgesics, and involved a longer operative time compared with CLA.

### Innovations and breakthroughs

The authors' experience and surgical technique suggest that laparoscopic appendectomy *via* reduced port surgery (LARPS) is a safe and feasible procedure for patients with appendicitis.

### Applications

The authors performed LARPS, a novel surgical procedure, to treat appendicitis. This method yielded good short-term outcomes, including good cosmetic results and a technically simplified SILA.

### Peer review

The paper flows straight through and the authors present their experience well. Although the number of subjects is very small, they present the data as safe and feasible, recommending randomized trials to show any benefit. This is appropriate.

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## Screening for colorectal neoplastic lesions following acute diverticulitis: Would a sigmoidoscopy suffice?

Leong Ung Tiong, Ryan Jalleh, Edward J Travers, Thomas Paxton, Cecilia Innes-Wong, Savio G Barreto, Randall Williams

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**Author contributions:** Tiong LU contributed to design of study, acquisition of data, data analysis and interpretation, drafting of the manuscript; Jalleh R, Travers EJ, Paxton T and Innes-Wong C contributed to acquisition of data, drafting of the article; Barreto SG and Williams R contributed to conception and design of study, data interpretation, critical revision for important intellectual content; all authors read and approved the final manuscript.

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### Abstract

**AIM:** To investigate the yield of colorectal malignant or premalignant lesions during colonoscopy performed following an episode of acute diverticulitis.

**METHODS:** A prospectively maintained electronic database of a public teaching hospital (Modbury Hospital, South Australia) was searched for international classification of diseases codes for acute diverticulitis from July 2007 to June 2011. The electronic database and each patient's medical records were reviewed for demographic data, clinical presentation, investigation results, colonoscopy details and surgical intervention.

**RESULTS:** Two hundred and nineteen patients were diagnosed with acute diverticulitis with a median age of 60 years (range 24-93). One hundred and thirty-nine patients (63.5%) had follow-up screening colonoscopy, with the

median interval between the episode of acute diverticulitis and colonoscopy being 8 wk (range: 1-66). Colonoscopy revealed polyps in 21 patients (15%) and no cases of colorectal cancer. Of the 21 patients with polyps, there were 14 patients (10%) with tubular/villous adenomas (13 in rectosigmoid region and 1 in descending colon).

**CONCLUSION:** Detection of colorectal cancer in patients undergoing routine colonoscopy following acute diverticulitis is rare. However, colonic polyps in the left colon are noted. A flexible sigmoidoscopy is an adequate screening tool in such patients. A complete colonoscopy reserved for patients with family history of colorectal cancer or with polyps detected on flexible sigmoidoscopy to evaluate the rest of the colon.

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**Key words:** Polyps; Surgery; Diverticulitis; Colonoscopy; Colorectal cancer

**Core tip:** This paper shows that of the 139 patients who underwent routine colonoscopy after an episode of acute diverticulitis, the incidence of adenomatous and malignant colonic polyps discovered were 10% and 0% respectively. These figures are similar to that in the general population. In addition all the polyps were discovered in the left colon, therefore a flexible sigmoidoscopy may be adequate for the purpose of excluding the presence of neoplastic lesions.

Tiong LU, Jalleh R, Travers EJ, Paxton T, Innes-Wong C, Barreto SG, Williams R. Screening for colorectal neoplastic lesions following acute diverticulitis: Would a sigmoidoscopy suffice? *World J Surg Proced* 2013; 3(2): 13-17 Available from: URL: <http://www.wjgnet.com/2219-2832/full/v3/i2/13.htm> DOI: <http://dx.doi.org/10.5412/wjssp.v3.i2.13>

## INTRODUCTION

Diverticulosis and colorectal cancer are 2 common diseases affecting the Western population which share many similar characteristics. For instance, both clinical entities have an increasing prevalence with advancing age<sup>[1,2]</sup>, they tend to affect the left side of the colon more often than the right side<sup>[3,4]</sup>, and have been associated with inadequate dietary fibre intake<sup>[5,6]</sup>. It has been advocated that a screening colonoscopy be performed for all patients following an episode of acute diverticulitis to exclude colorectal cancer<sup>[7]</sup>. However, the evidence in literature for such a practice is unclear. Some authors reported positive correlation between diverticulitis and colon cancer and therefore support routine screening colonoscopy<sup>[8,9]</sup>. Others, however, have found no increased risk of colon cancer in patients who were diagnosed with diverticulitis and thought that a screening colonoscopy was unnecessary<sup>[10-12]</sup>.

The aim of the current study was, thus, to retrospectively determine the yield of colonoscopy performed routinely following an episode of acute diverticulitis in detecting colorectal malignant or premalignant lesions in a consecutive cohort of patients diagnosed with diverticulitis.

## MATERIALS AND METHODS

A retrospective search of a prospectively maintained electronic database of a public teaching hospital was undertaken. International classification of diseases codes for acute diverticulitis over a 54-mo period, from January 2007 to October 2011 were analysed with the aim of identifying all patients treated for the disease at the hospital. The overall cohort included patients who were diagnosed and treated for acute diverticulitis. Each admission was reviewed within the electronic database. The case records of patients within the stated study period were manually reviewed.

It is a standard practice at the institute to advise all patients diagnosed with acute diverticulitis to undergo a colonoscopy within 8 wk of discharge so as to exclude a co-existent colorectal neoplastic/pre-neoplastic lesion.

### Variables collected for each patient

The main presenting symptoms, demographic data, blood investigations [white cell count (WCC), neutrophil count and C-reactive protein (CRP) levels], computed tomography (CT) scan, and length of hospital stay were recorded.

The basis for diagnosis of the episode as acute diverticulitis, viz., clinical impression, radiological features or a combination of both, was noted. The management of each patient was also assessed as to whether they required only conservative treatment with antibiotics, or whether more invasive procedures (*e.g.*, percutaneous drainage of diverticular abscess or surgery) were needed. In case of patients with recurrent diverticulitis, only the first episode was included in this analysis. The CT scan images of the abdomen were assessed with regards to the following features; presence and location of the diverticulae, signs of acute inflamma-

tion, and the presence of intra-abdominal complications, *e.g.*, perforation or abscess formation. The severity of diverticulitis was graded according to the European Association for Endoscopic Surgery classification<sup>[13]</sup>.

Additionally, complete data of the colonoscopic procedures were recorded. The colonoscopy reports were assessed with regards to: the time interval between the episode of acute diverticulitis and the colonoscopy, as well as the presence and location of any diverticulae, colitis, polyps, or cancer. The histological results were reviewed for polypectomies or biopsies performed. In patients in whom a colonoscopy was not performed, the reason for this was determined.

The operative notes, in patients who underwent surgery, were assessed for the details of the operation (elective or emergency; and the intra-operative findings). If bowel resections were performed, the histologic results were reviewed for the presence of diverticulitis and/or cancer.

### Patient excluded from the study

Patients who had episodes of per rectal bleeding since the investigation for this group of patients would normally include colonoscopy to exclude bowel cancer.

## RESULTS

A total of 219 patients were diagnosed with acute diverticulitis from July 2007 until June 2011. There were 114 males and 105 females respectively, with a median age of 60 (range 24-93) years. The median length of hospital stay was 3.5 d (range 1-58 d). The inflammatory markers were raised with median WCC of  $11.4 \times 10^9/L$  and CRP of 72.5 mg/L respectively. There were 129 (58.9%), 30 (13.7%) and 40 (18.3%) patients respectively with grade I, II and III diverticulitis according to the European Association for Endoscopic Surgery diverticulitis severity classification. Details of severity of diverticulitis were not available for 20 (9.1%) patients. 196 (89%) patients were managed conservatively, whilst 23 (11%) patients required emergency surgery for complicated diverticulitis; Hartman's procedure ( $n = 5$ ), anterior resection with loop stoma ( $n = 5$ ), right hemi-colectomy for right sided diverticulitis ( $n = 1$ ), open/laparoscopic washout of abscesses ( $n = 4$ ), and no data available ( $n = 8$ ).

### Patients who had colonoscopy

A total of 139 (63.5%) patients had follow-up screening colonoscopy. The median time lapse between the episode of acute diverticulitis and the colonoscopy was 8 wk (range 1-66). During colonoscopy, diverticulosis was confirmed in 120 (86%) of the patients. Of the 19 (14%) patients whose colonoscopy did not show diverticular disease, 8 had been diagnosed with diverticulitis on CT scan while the other 11 had been labelled to have acute diverticulitis based on clinical presentation and laboratory parameters. Five (4%) patients had inflammatory strictures secondary to the diverticulitis found during colonoscopy.

**Table 1** Colorectal polyps and cancer detection in 139 patients who had screening colonoscopy

Polyps	n (%)
Yes	21 (15)
No	116 (84)
N/A	2 (1)
Histology	
Tubular adenoma	4 (2.9)
Tubular adenoma with low grade dysplasia	7 (5)
Tubulovillous adenoma	2 (1.4)
Sessile serrated adenoma	1 (0.7)
Others including benign polyps	3 (2.2)
N/A	4 (2.9)

N/A: Not available.

Table 1 provides a complete depiction of the findings of 139 patients who underwent colonoscopy. No colorectal cancer was found during the screening colonoscopy in all 139 patients. Polyps were discovered in 21 (15%) patients, of which 14 (10%) had tubular/villous adenomas and 3 (2.2%) had benign hyperplastic polyps. The polyps could not be retrieved in 4 (2.9%) patients and so no histological information was available. Of the 14 patients with adenomatous polyps, 13 (93%) had polyps excised from the recto-sigmoid area while 1 patient had a polyp excised from the descending colon.

#### Patients who did not have screening colonoscopy

There were 43 (19.3%) patients who did not have screening colonoscopy for various reasons as shown in Table 2.

#### Miscellaneous

Eighteen (8.2%) patients elected to be treated and followed-up by their private doctor, and therefore no further reports were available. Nineteen (8.7%) patients did not return for their colonoscopy or outpatient appointment, and therefore were lost to follow-up.

## DISCUSSION

The data from our study indicate that 14 (10%) of the 139 patients with acute diverticulitis who subsequently had a screening colonoscopy had colorectal polyps removed, all of which originated from the left colon. No colorectal cancer was found in this cohort of patients. Other studies have reported an incidence of 6%-10% and 1%-2% for colorectal polyps and cancer, respectively<sup>[8,10,12]</sup>.

Several clinical practice guidelines have been published in recent years on the indications for colonoscopy, some of which include lower gastro-intestinal bleeding, unexplained iron-deficiency anaemia, patients with significant family history of colorectal cancer, and inherited colorectal cancer syndromes, *e.g.*, familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC)<sup>[14-16]</sup>. However acute diverticulitis is not listed as an indication for screening colonoscopy to exclude colorectal cancer.

**Table 2** Patient whose colonoscopy did not occur

Reasons no colonoscopy was arranged	n (%)
Advanced age and severe co-morbidities	7 (16)
Had diverticulosis confirmed on colonoscopy previously	7 (16)
Emergency surgery	3 (7)
Deceased	3 (7)
Discharged directly from the emergency department	5 (12)
Transferred to another hospital	1 (2)
Unknown	17 (40)

There is evidence of a significant association between diverticular disease and colorectal polyps<sup>[17-19]</sup>, and research has shown that removal of adenomatous polyps significantly reduces the incidence of colorectal cancer<sup>[20-22]</sup>. Therefore routine colonoscopy after diverticulitis may facilitate early detection of these polyps, the removal of which may reduce the risk of developing a future cancer. On the other hand the association between diverticulitis and colorectal cancer is unclear; some authors reported a positive correlation and supported routine screening colonoscopy<sup>[8,9]</sup>, whilst the others have not<sup>[10-12]</sup>.

Colonoscopy in patients after an episode of acute diverticulitis is not without risks. The risk of perforation during colonoscopy in the general population has been reported to be about 0.1%<sup>[23]</sup>. Patients with diverticulitis have higher risk of complications as the nature of their disease makes the colonoscopy more difficult with strictures, spasms, muscular hypertrophy and colonic fixation<sup>[24]</sup>.

It would be more useful to identify risk factors that could better categorize the patients with diverticulitis who have an increased risk of having colorectal adenomas or cancer, and therefore warrant a colonoscopy. A recently published article reported that the risks of cancer was higher in patients with CT diagnosed left sided diverticulitis complicated by abscess [odds ratio (OR) = 6.7, 95%CI: 2.4-18.7], local perforation (OR = 4, 95%CI: 1.1-14.9) or fistula (OR = 18, 95%CI: 5.1-63.7)<sup>[8]</sup>. There are at least 2 other reports in the literature showing evidence of a higher incidence of left sided colon cancer in patients with diverticulitis<sup>[10,11]</sup>. Data from our own study showed that almost all of the adenomatous polyps (13 out of 14 patients) originated from the recto-sigmoid area, while the last one originated from the descending colon.

An alternative option worth considering is performing a flexible sigmoidoscopy instead of a full colonoscopy. A flexible sigmoidoscopy has the advantage of having less risks as it is easier to perform and can be done without sedation. In addition patients do not need to take a full bowel preparation; instead 1-2 rectal enemas can usually clear the left colon enough to provide satisfactory views. It can also be more cost-effective as the cost according to the current Australian Medicare Benefit Schedule<sup>[25]</sup> for a flexible sigmoidoscopy is \$109.25, which is less than half that of a colonoscopy (\$328.10). CT colonography is another option as it does not carry the risk of bowel perforation as colonoscopy does. Although CT colonography is a relatively new radio-imaging modality, there is

increasing evidence that it is useful for the screening of colorectal cancer. A recently published meta-analysis of CT colonography for the detection of colorectal cancer showed a sensitivity of 96%<sup>[26]</sup>. There is no data currently available on the usefulness of CT colonography as a screening tool for colorectal cancer in patients with acute diverticulitis, and therefore there is a need for further investigation in this area. The cost for a CT colonography (\$600) according to the Australian Medicare Benefit Schedules is much higher than those of a colonoscopy or a flexible sigmoidoscopy. Therefore, further studies are required to investigate the cost-effectiveness of CT colonography in comparison to colonoscopy or flexible sigmoidoscopy as a screening tool for colorectal cancer in patient with diverticulitis.

In conclusion, based on the findings of our study, the detection of colorectal cancer in patients undergoing routine colonoscopy following an acute episode of diverticulitis is rare. However, colonic polyps in the left colon are noted. Thus, a flexible sigmoidoscopy in patients without a family history of bowel cancer (sporadic or as part of a familial syndrome) could be a viable and possibly a time- and cost-effective option. In patients with a family history of colorectal cancer or those in whom pre-malignant polyps (serrated adenomas, tubulo-villous adenomas with moderate or high grade dysplasia) or many polyps are encountered in the recto-sigmoid region, a full colonoscopy would be justified.

## COMMENTS

### Background

Diverticulosis and colorectal cancer are two common diseases, which share similar characteristics, affecting the Western population. There is evidence of a significant association between diverticular disease and colorectal polyps.

### Research frontiers

The aim of the current study was, thus, to retrospectively determine the yield of colonoscopy performed routinely following an episode of acute diverticulitis in detecting colorectal malignant or premalignant lesions in a consecutive cohort of patients diagnosed with diverticulitis.

### Innovations and breakthroughs

This paper shows that of the 139 patients who underwent routine colonoscopy after an episode of acute diverticulitis, the incidence of adenomatous and malignant colonic polyps discovered were 10% and 0% respectively. These figures are similar to that in the general population. In addition all the polyps were discovered in the left colon, therefore a flexible sigmoidoscopy may be adequate for the purpose of excluding the presence of neoplastic lesions.

### Applications

The results from this study suggest that a flexible sigmoidoscopy may be adequate to exclude colorectal neoplasms in patients after an episode of acute diverticulitis.

### Terminology

Diverticulosis is the presence of outpouchings in the colon, most commonly affecting the sigmoid colon. Diverticulitis is acute inflammation of these outpouchings. Colonoscopy is the process of inspecting the lumen and mucosa of the colon using a flexible fibre-optic camera.

### Peer review

The authors reported the result of colonoscopy after acute diverticulitis. This paper may have consequences on each National health system policy. The conclusions are based on good data.

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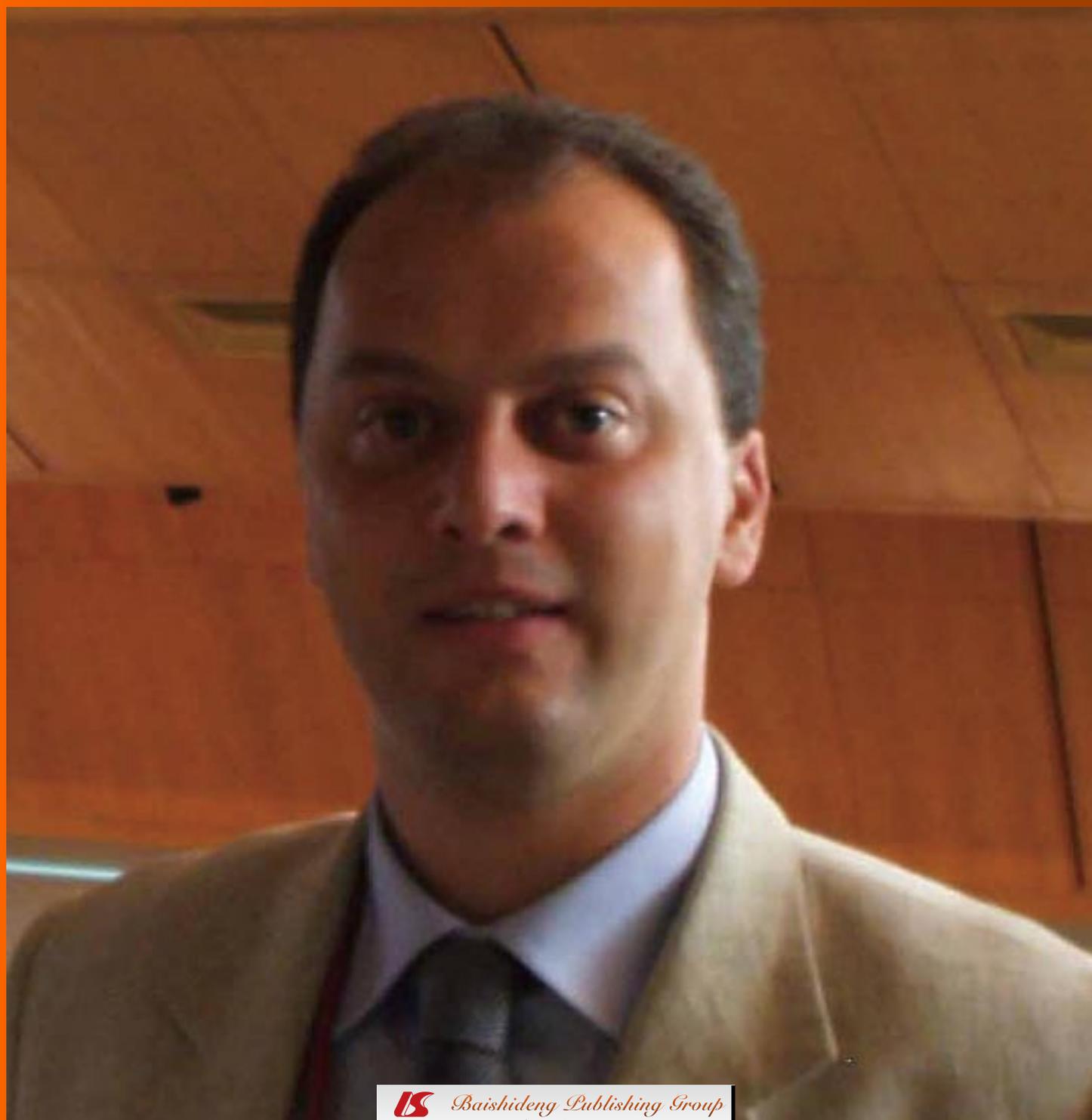
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## Intraperitoneal drains during open appendicectomy for gangrenous and perforated appendicitis

Gianpiero Gravante, John Overton, Mohamed Elshaer, Roberto Sorge, Ashish Kelkar

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### Abstract

Intra-abdominal drains are still routinely used in the surgical management of gangrenous and perforated appendicitis. A systematic review was performed with the aim of establishing their influence on postoperative complications in such cases. A literature search was conducted using the search engines PubMed and Cochrane Central Register of Controlled Trials. Included were retrospective case-controlled and prospective randomized controlled trials on the use of drain for open appendicectomy in gangrenous and perforated appendicitis. Twelve articles were found that met the inclusion criteria. Intrabdominal abscesses, postoperative ileus, surgical site infections, fecal fistulas and burst abdomen had significant higher incidences in the drain vs non drain group (10.3%, 20.3%, 32.5%, 3.4% and 5.7% vs 4.7%, 8.5%, 16.2%, 0% and 0%, respectively). In most cases the risk was more than doubled in the drain group compared to the non-drain one. There were no significant differences among groups in terms

of mortality while the results were underpowered to effectively evaluate wound dehiscence and adhesions. The use of intra-abdominal drains in the management of gangrenous and perforated appendicitis by open appendicectomy is associated with an increased rate of common postoperative complications.

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**Key words:** Appendix; Appendicectomy; Complications; Infections; Drains

**Core tip:** The prophylactic use of intraperitoneal drains for the prevention of postoperative abdominal abscesses in cases of gangrenous or perforated appendicitis remains a contentious issue, particularly considering that recent enhanced recovery programs have frequently excluded their usage in colorectal operations. With regards to open appendicectomy, most studies demonstrate an increase in the incidence of postoperative abscesses, ileus and surgical site infections in patients in whom a drain was used and currently question their routine in cases of gangrenous and perforated appendicitis.

Gravante G, Overton J, Elshaer M, Sorge R, Kelkar A. Intraperitoneal drains during open appendicectomy for gangrenous and perforated appendicitis. *World J Surg Proced* 2013; 3(3): 18-24 Available from: URL: <http://www.wjgnet.com/2219-2832/full/v3/i3/18.htm> DOI: <http://dx.doi.org/10.5412/wjsp.v3.i3.18>

### INTRODUCTION

The use of intraperitoneal drains in abdominal surgery is a long-standing and still highly controversial practice<sup>[1]</sup>. It was thought that they removed contaminated material

from the abdominal cavity and reduced the risk of forming intra-abdominal abscesses (IAAs)<sup>[2,3]</sup>. Indications for the insertion of drains were mostly based on personal experiences and preferences rather than on scientific grounds (“When in doubt, drain” - Tait 1905, cited by Yates<sup>[2]</sup> and Johnson *et al*<sup>[3]</sup>). Numerous trials and meta-analysis have challenged their routine use, for example in colorectal surgery where they do not decrease mortality, anastomotic dehiscences, surgical site infections (SSIs), re-interventions or extra-abdominal complications<sup>[4-6]</sup>. Conversely, intra-abdominal drains have been shown to contribute to postoperative ileus and increase the length of stay. Based on these findings intraperitoneal drains have been abandoned by most enhanced recovery programs for elective colorectal surgery<sup>[6-8]</sup> and their role has been limited to therapeutic purposes in cases of postoperative pelvic collections.

The use of intra-abdominal drains as part of the management of gangrenous and perforated appendicitis by open appendicectomy remains an unresolved issue<sup>[9]</sup>. The indications for the use of drains in this context are not clear and the clinical practice is operator-dependent and not evidence based. Some advocate Penrose drains in which the internal lumen allows the fluid to drain by capillary action (open drain), as opposed to single lumen silicone drains connected to a suction chamber (Hemovac or Redivac) or double lumen drains connected to suction device (Jackson-Pratt drains), both closed suction devices.

The aim of this systematic review was to establish through an analysis of the reported rates of postoperative complications whether or not there is an indication for the use of intra-abdominal drains during the open surgical management of gangrenous and perforated appendicitis.

## SEARCH STRATEGY, OUTCOMES AND STATISTICS

Articles were systematically reviewed from the results of the following searches conducted using the PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) search engines: “appendicitis AND drain” ( $n = 664$ ), “open AND appendicectomy AND drain” ( $n = 63$ ), “appendicectomy AND drain” ( $n = 140$ ). Included were retrospective case-controlled studies and prospective randomized controlled trials reporting the postoperative complication rates for patients with gangrenous and perforated appendicitis managed by open appendicectomy who either did or did not receive an intra-abdominal drain during surgery. An acute appendicitis with an already concomitant periappendicitis abscess was considered in the group of perforated appendicitis. Excluded were all studies including cases of endoappendicitis, phlegmonous or catarrhal appendicitis, those that did not report a comparison between the use of drain *vs* non drain, case reports, studies on laparoscopic appendicectomy or those comparing open *vs* laparoscopic appendicectomy, reviews, those regarding the management of appendicular mass, those in which drains were used to

treat an abscess *via* a percutaneous drainage, cost analysis studies.

Primary end-point of the study was to examine the influence of intraperitoneal drains in preventing postoperative IAAs following open appendicectomy for gangrenous and perforated appendicitis. Secondary end-points were the relationships between drains and the occurrence of other postoperative complications such as SSIs, wound dehiscence, adhesions, fecal fistula, burst abdomen and mortality. All studies reporting data on IAAs only, secondary outcomes only, or both were included in the review and data were analysed in the specific chapters. A specifically designed data form was generated in order to capture the demographics and reported rates of postoperative complications considered. Data analysis was performed by two researchers (Gravante G and Sorge R).

## Statistical analysis

All data were inserted into an Excel database (Microsoft, Redmond, Washington - United States). Parameters evaluated were categorized either as “present” or “absent” (categorical variables) and descriptive statistics used were frequencies. Analysis of comparison between groups was conducted with the  $\chi^2$  test or Fisher’s exact test if counts were less than five. The power calculation was verified for each complication and reported. The odds ratio for the use of drains on the occurrence of postoperative complications was also calculated. *P* values less than 0.05 were considered statistically significant.

## LITERATURE AVAILABLE

A total of 871 articles were identified, which were assessed by 2 authors (Gravante G and Overton J) using the PRISMA flow diagram for systematic reviews (Figure 1)<sup>[10]</sup>. Following the removal of duplicated articles the number of articles screened was 719. Two hundred and forty seven articles were directly excluded from the analysis because their title and abstract made it immediately apparent that they were not relevant to the study question. The titles and abstract of the remaining 472 articles were assessed in more detail and a further 451 articles were excluded for the following reasons: unrelated to the study question of the systematic review ( $n = 113$ ), case reports ( $n = 97$ ), laparoscopic appendicectomy ( $n = 2$ ), open *vs* laparoscopic study ( $n = 47$ ), review article ( $n = 43$ ), management of appendicular mass ( $n = 57$ ), percutaneous appendicular abscess drainage ( $n = 23$ ), report of experience ( $n = 20$ ), phlegmonous or catarrhal appendicitis ( $n = 19$ ), single port surgery ( $n = 12$ ), technical note ( $n = 7$ ), pain study ( $n = 4$ ), survey ( $n = 3$ ), natural orifice transluminal endoscopic surgery appendicectomy ( $n = 2$ ), pilot study ( $n = 1$ ), cost analysis study ( $n = 1$ ).

The full texts for the remaining 23 articles were assessed by the authors (Gravante G and Overton J) and nine articles were excluded from the qualitative and quantitative analysis for the following reasons: the study included cases of gangrenous and perforated appendicitis managed with all drain types and did not focus on

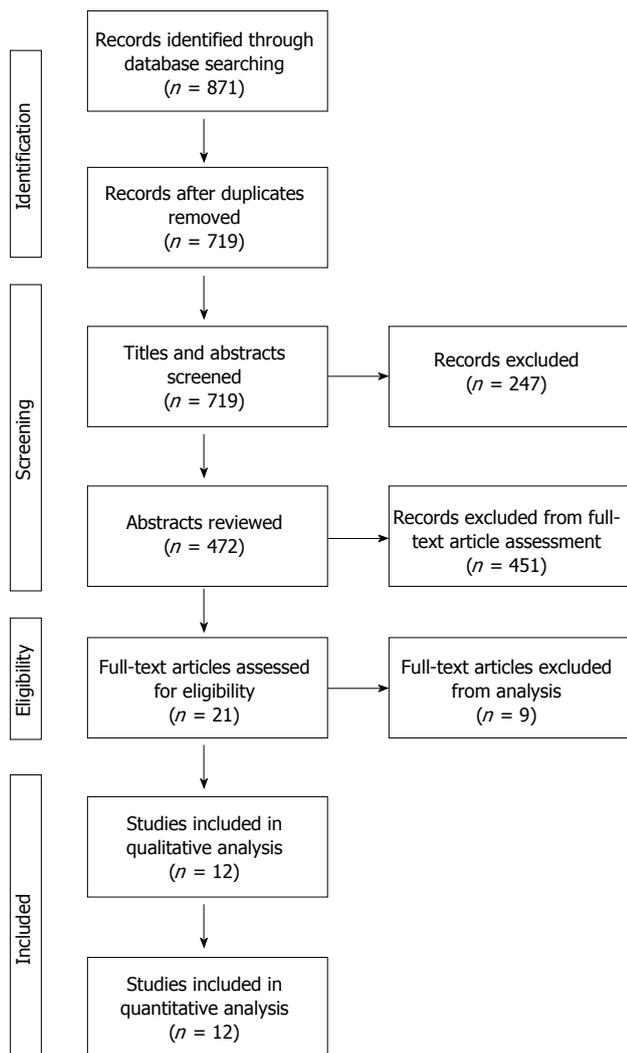


Figure 1 PRISMA figure showing the results of the search strategy.

the use of intra-abdominal drains placed at the time of surgery ( $n = 3$ ); the outcomes of the respective groups were not presented separately ( $n = 2$ ); the study included patients with phlegmonous or catarrhal appendicitis ( $n = 1$ ), did not specify the numbers of patients allocated to the respective groups ( $n = 1$ ), included patients managed by transperitoneal drainage ( $n = 1$ ), or presented outcome data relating to groups according to the type of antibiotic used ( $n = 1$ ).

Twelve articles presented the outcomes for the usage of intra-abdominal drains in the management of gangrenous and perforated appendicitis by open appendicectomy. These were the studies eligible for inclusion in the systematic review and therefore were included in the quantitative analysis: 6/12 were randomized controlled trials, 6/12 were retrospective case-controlled studies (Figure 1).

### RATE OF POSTOPERATIVE INTRA-ABDOMINAL ABSCESS FORMATION

Rates of postoperative intra-abdominal abscess formation

in open appendicectomy with drainage *vs* non-drainage were presented in 9/12 studies (5/12 were retrospective case-controlled studies and 4/12 were randomised controlled trials) (Table 1)<sup>[3,11-18]</sup>. The overall rate of intra-abdominal abscess was more than two times higher in the drainage group (10.3%; 39/378) than in the non-drainage group (4.7%; 37/779,  $\chi^2 P < 0.0001$ ; Table 1)<sup>[3,11-18]</sup>. Unfortunately, 2/12 articles span over a long period of time (1978 to 2012)<sup>[11,18]</sup> and 5/12 of them were retrospective case-controlled studies<sup>[3,12,13,16,18]</sup>. Studies published before the year 2000 reported an average rate of postoperative intra-abdominal abscess formation of 11.7% in the drainage group (19/163) was compared with a rate of 6.8% in the non-drainage group (30/444;  $\chi^2$  test,  $P < 0.05$ )<sup>[3,11-14]</sup>, Studies published after the year 2000 have an average rate of postoperative intra-abdominal abscess formation of 9.3% in the drainage group (20/215) when compared with 2.1% in the non-drainage group (7/335;  $\chi^2$  test,  $P < 0.0001$ )<sup>[16-18]</sup>.

### RATE OF POSTOPERATIVE ILEUS

Only six studies compared the occurrence of postoperative ileus among the drain *vs* non-drain group and all of them showed higher occurrences of postoperative ileus in the drain one<sup>[3,11,14,17-19]</sup>. Overall, the incidence of postoperative ileus was significant higher (more than 2 times) in patients receiving drains: 20.3% (50/246) for the drain group *vs* 8.5% (33/389) for the non-drain group ( $P < 0.0001$ ; Table 1). Similar to what evidenced for the IAAs, early studies had occurrences significant higher than late studies in both groups: 33.3% (40/120 - before 2000) *vs* 7.9% (10/126 - after 2000;  $\chi^2$  test,  $P < 0.001$ ) for the drain group, 20.7% (28/135 - before 2000) *vs* 2.0% (5/254 - after 2000;  $\chi^2$  test,  $P < 0.001$ ) for the non-drain group.

### RATE OF SSI

Eleven (6/11 randomised controlled trials and 5/11 retrospective case-controlled studies) reported the rates of SSIs in the drain (149/458; 32.5%) *vs* non-drains group (112/692; 16.2%)<sup>[3,11,12,14-21]</sup>. The risk was two times greater in the drain group compared to the non-drain one ( $P < 0.0001$ ; Table 1). Early studies had occurrences significant higher than late studies in both groups: 39.0% (69/177 - before 2000) *vs* 28.5% (80/281- after 2000;  $\chi^2$  test,  $P = 0.02$ ) for the drain group, 22.9% (73/319 - before 2000) *vs* 11.2% (46/409 - after 2000;  $\chi^2$  test,  $P < 0.001$ ) for the non-drain group.

### RATE OF OTHER POSTOPERATIVE COMPLICATIONS

A higher incidence of fecal fistulas<sup>[11,14,17,21]</sup> and burst abdomen<sup>[11,14]</sup> was also present in the drain *vs* non drain group, however a formal odds ratio could not be calculated due to the absence of events in the non-drain group (Table 1). No significant differences were found among

Table 1 Comparative studies analyzing the effects of drainage vs non drainage in open appendectomies conducted for perforated and gangrenous appendix

Ref.	Year	Country	Type of study	Type of appendix	Treatment	Patients (n)	Antibiotic regimen	Abdominal abscess	Postoperative ileus	Surgical site infections	Wound dehiscence	Adhesions	Fecal fistula	Burst abdomen	Mortality
Everson <i>et al</i> <sup>[20]</sup>	1977	United Kingdom	RCT	PR/GA	D	14	Cephaloridine 1gr QDS - 3 d coverage	-	-	3 (21)	-	-	-	-	-
Greenall <i>et al</i> <sup>[11]</sup>	1978	United Kingdom	RCT	PR	ND	16	Cephaloridine 1gr QDS - 3 d coverage	-	-	6 (38)	-	-	-	-	-
Mackellar <i>et al</i> <sup>[12]</sup>	1986	Australia	Retros.	PR/GA	ND	48	(various antibiotics)	7 (15)	18 (38)	34 (71)	-	-	2 (4)	3 (6)	3 (6)
					ND	55	(various antibiotics)	12 (22)	12 (22)	38 (69)	-	-	0 (0)	0 (0)	1 (2)
					D	19	Metronidazole ± Gentamycin and Ampicillin (if suspected peritonitis)	1 (5)	-	3 (16)	-	-	-	-	-
					ND	139	Metronidazole ± Gentamycin and Ampicillin (if suspected peritonitis)	2 (1)	-	2 (1)	-	-	-	-	-
Samelson <i>et al</i> <sup>[13]</sup>	1987	United States	Retros.	PR	D	24	Ampicillin, Gentamycin and Clindamycin if suspected perforation for 7-10 d	3 (13)	-	-	-	-	-	-	-
					ND	170	Ampicillin, Gentamycin and Clindamycin if suspected perforation for 7-10 d	3 (2)	-	-	-	-	-	-	-
Dandapat <i>et al</i> <sup>[14]</sup>	1992	India	RCT	PR	D	40	-	8 (20)	17 (43)	22 (55)	-	-	2 (5)	2 (5)	4 (10)
					ND	46	-	10 (22)	13 (28)	23 (50)	-	-	0 (0)	0 (0)	1 (2)
Johnson <i>et al</i> <sup>[15]</sup>	1993	United States	Retros.	PR	D	32	-	0 (0)	5 (16)	1 (3)	-	-	-	-	-
					ND	34	-	3 (9)	3 (9)	2 (5.9)	-	-	-	-	-
Toki <i>et al</i> <sup>[15]</sup>	1995	Japan	RCT	PR	D	24	Aminoglycoside and Cephem	2 (8)	-	6 (25)	-	0 (0)	-	-	-
Perović <i>et al</i> <sup>[16]</sup>	2000	Croatia	Retros.	PR	D	29	Aminoglycoside and Cephem	0 (0)	-	2 (7)	-	0 (0)	-	-	-
					ND	20	-	-	4 (20)	13 (65)	2 (10)	-	-	-	-
Narci <i>et al</i> <sup>[16]</sup>	2007	Turkey	Retros.	PR	ND	36	-	-	1 (3)	7 (19)	2 (6)	-	-	-	-
					D	109	-	14 (13)	-	31 (28)	-	3 (3)	-	-	-
					ND	117	-	4 (3)	-	19 (16)	-	4 (3)	-	-	-
Jani <i>et al</i> <sup>[17]</sup>	2011	Kenya	RCT	PR	D	45	Cefuroxime and Metronidazole or Penicillin, Gentamicin and Metronidazole or Amoxicillin-Clavulanate and Metronidazole	3 (7)	1 (2)	15 (33)	-	-	2 (4)	-	-
					ND	45	Clavulanate and Metronidazole	0 (0)	0 (0)	3 (7)	-	-	0 (0)	-	-
					ND	45	Cefuroxime and Metronidazole or Penicillin, Gentamicin and Metronidazole or Amoxicillin-Clavulanate and Metronidazole	0 (0)	0 (0)	3 (7)	-	-	0 (0)	-	-
Akoyun <i>et al</i> <sup>[18]</sup>	2012	Turkey	Retros.	PR	D	61	-	3 (5)	5 (8)	3 (5)	1 (2)	1 (2)	-	-	-
					ND	173	-	3 (2)	4 (2)	3 (2)	0 (0)	1 (1)	-	-	-
Al-Shahwany <i>et al</i> <sup>[21]</sup>	2012	Iraq	RCT	PR	D	46	Ceftriaxone and Metronidazole	-	-	18 (39)	-	-	0 (0)	-	0 (0)
					ND	38	Ceftriaxone and Metronidazole	-	-	14 (37)	-	-	0 (0)	-	0 (0)
Total					D	482		39/378 (10.3)	50/246 (20.3)	149/458 (32.5)	3/81 (3.7)	4/194 (2)	6/179 (3.4)	5/88 (5.7)	7/134 (5.2)
					ND	862		37/779 (4.7)	33/389 (8.5)	112/692 (16.2)	2/209 (0.95)	5/319 (1.6)	0/184 (0)	0/101 (0)	2/139 (1.4)
Power calculation odds ratio							80%	95%	95%	99%	1%	0.02%	99%	99%	99%
P value (D vs ND)							<0.0001	<0.0001	<0.0001	<0.0001	0.11 (NS)	0.68 (NS)	0.01	0.01	0.08 (NS)

<sup>1</sup> Although the incidence was higher in the drain vs non drain group, the odds ratio could not be formally calculated for this complication because of the lack of occurrences in the latter. PR: Perforated appendix; GA: Gangrenous appendix; D: Drainage; ND: Non drainage; RCT: Retrospective randomised trial; Retros.: Retrospective; UTI: Urinary tract infections; QDS: Every 6 h.

groups for the mortality rate (7/134, 5.2% *vs* 2/139, 1.4%;  $P = 0.08$ )<sup>[11,14,21]</sup> (Table 1). With regards to the incidence of wound dehiscences<sup>[18,19]</sup> and bowel obstruction due to adhesions<sup>[15,16,18]</sup> the data were underpowered to produce reliable result in terms of significant differences among groups (Table 1).

## OTHER OUTCOMES

Two retrospective case-controlled studies reported that overall operative times were 8 min longer in the drainage group as compared with the non-drainage group<sup>[16,18]</sup>. Four articles (2 retrospective case-controlled studies and 2 randomised controlled studies) reported longer length of hospital stay in the drainage group as compared with the non-drainage group<sup>[3,15,18,21]</sup>.

## CRITICAL EVALUATION

Appendicectomy is the most common emergency operation performed in abdominal surgery. Generally considered a technically simple procedure, the variability of the intraoperative findings (normal appendix, perforated appendix, presence of IAA or widespread peritonitis, appendicular mass, retrocecal appendix, involvement of the terminal ileum mesentery)<sup>[22-24]</sup> coupled with the patient's characteristics (*i.e.*, extremes of age, pregnancy, obesity, comorbidities)<sup>[25-27]</sup> and the approach used (open, laparoscopic, single incision, natural orifice surgery)<sup>[28]</sup>, may increase the technical difficulties and therefore challenge even experienced surgeons. The incidence of postoperative complications differs significantly according to the stage of the disease. Simple appendicitis is when the appendix presents macroscopically normal and the inflammatory infiltrate, if present, is confined mainly to the mucosa (35% of total cases), or when the appendix is macroscopically indurated or purulent and the histological analysis shows mucosal necrosis and transmural inflammation (36% of cases)<sup>[29]</sup>. In these cases the incidence of postoperative complications is relatively low: SSIs are present in 8.5% of patients (272/3196)<sup>[30-40]</sup>, IAAs in 0.4% (13/3196)<sup>[30-40]</sup>, and bowel obstruction due to adhesions in 0.5% (10/1853)<sup>[31,32,34,38,39,41]</sup>. Differently, gangrenous and perforated appendicitis is when the appendix presents macroscopically gangrenous with part or whole of the appendix necrotic (9% of cases) or perforated with peritonitis (20% of cases)<sup>[29]</sup>. In these cases the incidence of complications is higher: SSIs are present in 22.6% of patients (268/1186)<sup>[3,11,12,14-21]</sup>, IAAs in 6.4% (78/1210)<sup>[3,11-18]</sup>, and bowel obstruction due to adhesions in 1.8% (9/513)<sup>[15,16,18]</sup>.

The insertion of intraperitoneal drains during appendicectomies in cases of perforated appendicitis is meant to prevent the formation of IAAs in the early postoperative period. The idea is based on the significant amount of bacterial contamination usually found during the operation that originated from the perforation of the hollow viscus. Following the appendix removal

(source of the contamination) and an adequate wash-out of the abdominal cavity (mechanically removal of the contaminated fluid), the insertion of an intraperitoneal drain is meant to continuously aspirate any contaminated pollution leftover that could eventually re-start a local infection. At the same time the patient usually receives an appropriate perioperative course of antibiotic therapy to definitely sterilize the abdominal cavity. If the assumption that drains remove infected fluids and allow the antibiotics a more efficacious action is true, the incidence of postoperative IAAs should be inferior in patients receiving drains *vs* those that do not. Studies available have a significant degree of data heterogeneity with regards to age, co-morbidities, time of presentation to the hospital, type of antibiotic used when considering studies conducted before the year 2000 and those conducted after (including some which are rarely used, *i.e.*, tetracycline, colomycin, streptomycin)<sup>[11]</sup>, the amount of wash-out of the abdominal cavity performed, and the experience of the surgeon. Bearing in mind these limitations some important points can still be made. With the exception of for Greenall *et al*<sup>[11]</sup> in which the occurrence of abscesses was less in the drainage group than compared to the non-drainage group, 6/12 studies reported higher rates of intra-abdominal abscesses<sup>[12,13,15-18]</sup> and 2/12 reported comparable rates of intra-abdominal abscesses between the respective groups<sup>[3,14]</sup>. These reported outcomes demonstrate that the rates of postoperative intra-abdominal abscess formation are lower in the non-drainage group as compared with the drainage group irrespective of the time period during which the study was conducted. Therefore, when considering the rate of intra-abdominal abscess formation reported in early studies (*i.e.*, those published before the year 2000) as compared with those from late studies (*i.e.*, those published after the year 2000) the rate has remained similar in the drainage group among early *vs* late studies (19/163 *vs* 20/215,  $\chi^2$  test,  $P = \text{NS}$ ), while it significantly decreased in the non-drainage group (30/444 *vs* 7/335,  $\chi^2$  test,  $P < 0.001$ ).

Simple guidelines for the use of drains according to the intraoperative findings cannot be easily drawn and a large role in these cases is actually played by the personal experience and practice. When IAAs are still not formed and the intraoperative findings are those of free pus, a prolonged and abundant irrigation with large amounts of normal saline solution accompanied by a thorough aspiration until the washing liquid is completely clear are frequently sufficient manoeuvres to remove most of the infected material. The abundant wash-out of the abdominal cavity removes the "bulk" of the contamination and facilitates the task for perioperative antibiotics to sterilise the remaining pollution. A careful irrigation is also necessary to remove fecaliths located in remote regions which are not easily accessible by direct exploration (*i.e.*, subphrenic, Douglas, interloop) and in which IAAs are more likely to form<sup>[42]</sup>. Such areas may require positional changes (*i.e.*, Trendelenburg, anti-Trendelenburg,

right- or left-sided positions) or using the drain shelf to introduce and aspirate the washing liquid in such remote regions. However, it is the authors opinion that when the IAA is completely formed the aspiration of pus leaves an infected cavity that may create an adequate isolated environment for a local recurrence. We believe that if the abscess wall can be adequately removed from the surfaces of the bowel, omentum, and peritoneum then a drain is likely to be superfluous and a thorough irrigation will suffice. However, in cases of incomplete removal, difficult dissection or oozing from raw surfaces a tube drain might be useful to prevent postoperative IAAs. No study has investigated this possibility so far.

The effects of drains manifest also on the occurrence of postoperative ileus and SSIs. Postoperative ileus could be associated to the presence of intraoperative drain for a direct irritant effect of the drain on the bowel serosa and consequently the recovery of peristalsis, or for an indirect effect of reduced mobilisation of the patient due to the drain<sup>[6]</sup>. With regards to SSI, the same considerations of heterogeneity that were observed for the analysis of IAAs can also be applied here. This heterogeneity is reflected in the wide range of reported rates of SSIs (1% to 71%). Rates were 3%-71% in the drainage group and 1%-69% in the non-drainage group (Table 1) but were reportedly lower in the non-drainage group for 9 out of 12 studies presented, suggesting that intra-abdominal drains may represent an independent risk factor for the development of SSIs. A simple explanation to this phenomenon is found in the rare eventuality that drain are exteriorised directly through the main surgical wound, a manoeuvre used to avoid additional wounds in the abdominal wall. In such cases wounds tend to contaminate quickly due to the direct link between the septic intrabdominal focus and the abdominal wall operated by the drain itself. The purulent exudates travel by capillarity not only within the lumen but also on the outer surface of the drain where they easily come into contact with the main wound and start a new infection. For these reasons it is common surgical practice not to drain the infected abdominal cavities through the main wound but to perform a new different one where the drain is exteriorised. When reported, the drainage was operated through a separated wound in most studies<sup>[12,15,17]</sup>, through the same wound in others<sup>[20]</sup>, or the decision was left to the operating surgeon<sup>[11]</sup>. Therefore, it is still possible that SSIs originate from the direct communication between the intra-abdominal cavity and the external skin surface operated by the outer surface of the drain even when this is exteriorised through separate wounds close to the main one.

## CONCLUSION

The prophylactic use of intraoperative drains for gangrenous or perforated appendicitis remains a contentious issue, particularly in the context of enhanced recovery programs that frequently exclude their usage. Considering the management of gangrenous or perforated appendi-

citis by open appendectomy, all but one study failed to demonstrate any reduction in the rate of postoperative complications and the majority of them found higher incidences associated with the use of drains.

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## Retroileal trans-mesenteric colorectal anastomosis

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### Abstract

Colorectal anastomosis after extended left colectomies may result difficult, and, sometimes, impossible due to the shortness of the vascular pedicles and the distance between the two ends. Total colectomy with ileo-rectal or ileo-anal anastomosis with sacrifice of healthy colon and ileocaecal valve is usually preferred to overcome this problem. In this manuscript we describe the step-by-step surgical technique of retroileal transmesenteric colorectal anastomosis which can be used as a salvage technique for both open and laparoscopic surgeries. We also discuss the advantages and disadvantages of this approach compared to other techniques. We believe that the widespread of laparoscopic colorectal surgery as well as the raising volume of metachronous colorectal resections will revive this vintage overlooked approach.

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**Key words:** Colorectal anastomosis; Retroileal anasto-

mosis; Extended left colectomy

**Core tip:** Several approaches have been proposed as salvage techniques to avoid total colectomy with ileo-rectal or ileo-anal anastomosis after an extensive mobilization and left colon resection. However, as these techniques, which we are going to discuss hereafter, involve various technical difficulties, we present a valid alternative to ileo-rectal or ileo-anal anastomosis: a retro-ileal, trans-mesenteric colorectal anastomosis, first described by R. Turnbull in 1972, which allows a safe and tension free anastomosis after both open and laparoscopic extended left colon resections with inadequate residual length for standard colo-rectal anastomosis.

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### INTRODUCTION

After extensive mobilization and left colon resection, the colorectal anastomosis may result impossible due to the distance between the two ends and the shortness of the middle and right colic pedicles. Several approaches have been proposed as salvage techniques to avoid total colectomy with ileo-rectal or ileo-anal anastomosis in these cases. It is well known that low colo-rectal anastomosis may have septic complications as high as 15%, while ileo-rectal anastomosis may have a risk of anastomotic leak between 3%-17%<sup>[1,2]</sup>. It is obvious that the aim of surgery should be to preserve the function (*i.e.*, ileo-caecal valve and a portion of the colon) as well as reduce complications (*i.e.*, anastomotic leak or septic complications). In particular, when an ileo-rectal anastomosis is avoided, the terminal ileum and the ileo-caecal valve preservation reduces malabsorption, bacterial overgrowth, while improv-

ing diarrhoea, urgency or incontinence, usually occurring after extended colonic resection. Over the last decades few approaches have been described mainly in the open surgery era.

The Deloyers<sup>[3]</sup> procedure, consisting in an anastomosis between the right or the transverse colon and the rectum or anus after mobilizing and rotating into a counter clockwise direction the right colon (including the caecum and the ascending colon, up to the hepatic flexure) with preservation of the ileo-colic junction and the ileocolic artery. After the initial Deloyers' report only 5 studies, including less than 100 patients have shown good functional results mainly after surgery for chronic constipation or Hirschprung disease<sup>[4-6]</sup>. Among these, only one paper considered this approach after Hartmann reversal, failed previous colorectal anastomosis, diverticular disease, left colon cancer and ischemic colitis. This retrospective study observed the largest population (48 patients), reporting early complications up to 23% (mainly intra-abdominal haemorrhage, wound infection, persistent ileus) and 23% of late complications (incisional hernias, colo-anal anastomosis stenosis)<sup>[7]</sup>.

Subtotal colectomy with caeco-rectal end-to-end anastomosis, when the right colon can not be preserved. This technique seems, however, to be comparable to the total colectomy with ileo-rectal anastomosis technique in terms of therapeutic effectiveness, postoperative morbidity and mortality and impact on the quality of life<sup>[8]</sup>.

Moreover, these two approaches may present several technical difficulties when a laparoscopic approach is needed. Obviously, the widespread of laparoscopic colorectal surgery demands for faster and easier techniques.

In 1972, Turnbull proposed a retro-ileal tunnel to anastomose the proximal transverse colon to the rectum. This technique consists in performing a passage through an avascular plan at the terminal ileum mesentery and the proximal transverse colon, anastomosed to the rectum. However, this old technique has been largely overlooked for decades, although it represents a valid alternative to ileo-rectal or ileo-anal anastomosis, allowing a safe and tension free anastomosis. Since it is very easy to perform, we believe that this is the technical solution for both open and laparoscopic extended left colon resections with inadequate residual length for standard colo-rectal anastomosis.

In the manuscript we present the surgical technique with a series of figures suitable either for open or laparoscopic approach.

## SURGICAL TECHNIQUE DESCRIPTION

### *Ileal mesentery window creation*

After extended left colectomy, the remnant colon is vascularized only by the tributaries of the superior mesenteric artery. The entire small intestine is retracted on the left side of the patient and cranially, in order to expose the root of the mesentery. At this point, the terminal

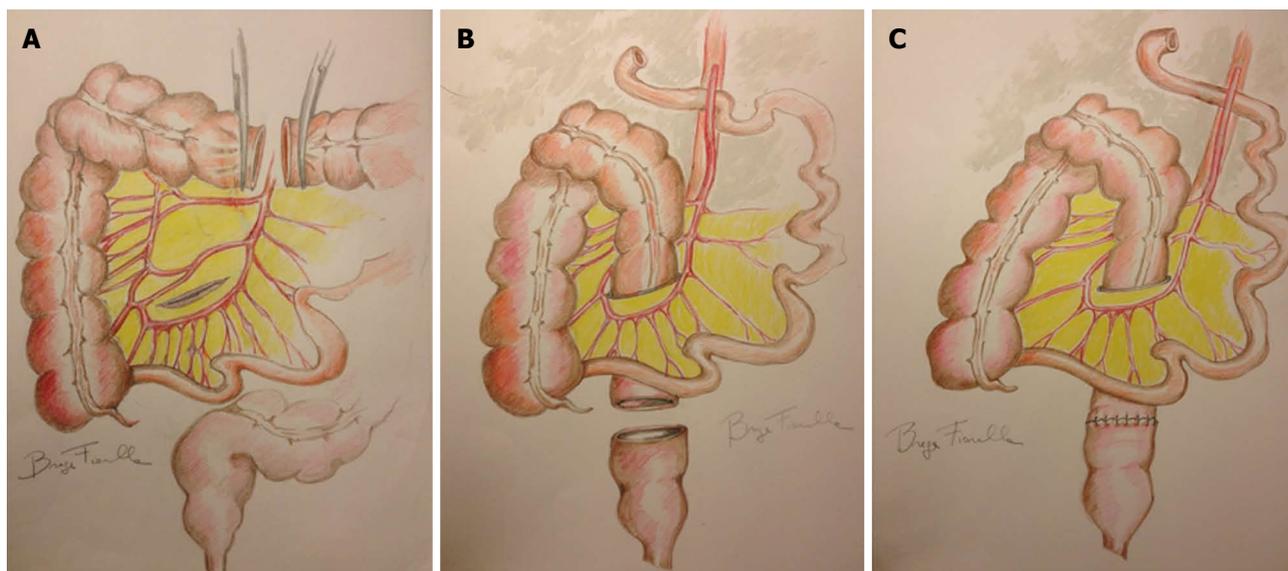
ileum is identified for a segment of 30-50 cm and the mesentery is inspected for the vascular arcades. This allows the respect of the terminal ileum and caecum vascularization when the window is created and tailored for the transverse colon passage. Usually, a 3 cm opening is necessary (Figure 1A). While in open surgery a trans-mesenteric lighting, in order to individualize the avascular plane, is possible, during laparoscopic surgery this is not doable, since the light is in the same direction of the scope. However, the window can be created immediately proximal to the take-off of the ileo-colic vessel, where an avascular plane is usually present.

### *Freeing the transverse colon*

It is necessary to free the transverse colon from its attachments, particularly from the gastro-colic ligament as well as all the folds that may create tension thus creating tension through the mesenteric passage. The distance that needs to be covered can be measured above the mesentery. If a laparoscopic approach is used and a mechanical anastomosis is planned, the anvil is inserted after a standard purse-string is performed. After the colon has been passed through the avascular mesenteric window (Figure 1B), the anastomosis is performed. If an open technique is chosen an end-to-end or side-to-end anastomosis is performed. At this point the anvil is gently passed through the mesentery and the anastomosis performed to the rectal stump. Once these two elements have been connected, an anastomosis is performed and checked, to ensure that there is no tension or twisting (Figure 1C). Finally, the colon is fixed to the border of the mesenteric passage using interrupted absorbable 2-0 stitches and the posterior mesenteric window (or residual gap) is closed with interrupted stitches to avoid internal hernias.

### *Our experience*

Since 2007 we have performed this procedure in 10 patients. All patients were male with a mean age of 65.1 years (range: 41-82 years). Indications for surgery were: left colon cancer ( $n = 2$ ), left colon cancer associated with diverticular disease ( $n = 2$ ), metachronous left colorectal cancer in previously resected patients ( $n = 2$ ), synchronous cancer of the recto-sigmoid colon and the splenic flexure ( $n = 2$ ), extensive diverticular disease ( $n = 2$ ). Of these surgeries, 8 were open while 2 were laparoscopic. Median follow up was 40 mo. One patient had superficial Surgical Site Infection. One patient developed an incisional hernia on the site of 15 mm trocar insertion, repaired 6 mo after surgery. Three patients experienced longer term diarrhoea, and 2 of them required occasional Loperamide treatment. One patient died 2 mo after surgery due to sequelae of his Chronic Renal Failure. He had a previous failed renal transplant, secondary to acute rejection. Two patients died due to cancer recurrence, 2 and 4 years after surgery, respectively. No complications related to the surgical procedures were encountered, including anastomotic leaks, stenosis or small bowel obstruction secondary to internal hernia or adhesions.



**Figure 1** Ileal mesentery surgical technique description. A: After the proximal resection, an avascular mesenteric window is created; B: After an extended left colectomy has been performed, the remnant colon is passed through the avascular mesenteric window, behind the ileum; C: An end-to-end, trans-mesenteric, retro-ileal colo-rectal anastomosis is performed.

## DISCUSSION

We believe that this “vintage” technique has been overlooked for decades and it may turn to be fashion again after the widespread of colorectal laparoscopy. Major drawbacks such as the need of proximal transverse colon taking down and risk of internal hernia through the mesenteric window or jejunum loop obstruction favoured the Deloyers procedure. However, literature on trans-mesenteric lowering is scant<sup>[9-11]</sup>. The first Turnbull’s report presented 11 retroileal colo-rectal anastomosis with a total of 3 minor postoperative complications, including partial small bowel obstructions resolved medically, 1 small incisional hernia and minor wound infection. For more than 20 years the technique was not presented and reappeared in the literature in 1994 when Nafe *et al.*<sup>[10]</sup> reported a series of 28 cases with a single case of anastomotic leak (about 3%) comparable to conventional anastomosis. Overall, including sporadic case reports, a handful of reports are present in literature with a lack of surgical indications, specific surgical technique description as well as outcomes.

Supporters of the Deloyers procedure aimed that the retro-ileal anastomosis requires the preservation of the entire transverse colon. Obviously, the ligation of the left branch of the middle colic pedicle is often sufficient, but, if a more extended resection is required with a proximal transverse colon anastomosis, the middle colic pedicle ligation is possible at the origin but, in this case, the sole Drummond’s arcade will supply the right transverse colon. Regarding the risk of jejunum loop obstruction or the risk of internal hernia through the mesenteric window, it should be minimized by narrowing the mesenteric window and performing mesenteric-to-bowel sutures<sup>[9]</sup>. Moreover, according to our experience, since the peritoneal window is performed 20-30 cm from the ileo-cecal

valve, proximal to the marginal arcade, this does not represent a limit, when a loop diverting ileostomy is needed.

On the other hand, the Deloyers procedure has the main disadvantage of creating torsion of the vascular pedicle increasing the risk of venous ischemia, despite few modifications have been proposed<sup>[12-14]</sup>.

Moreover, when a laparoscopic approach is chosen, the retroileal passage seems to be a valid option to overcome the distance between the two ends and to perform a safe, tension-free anastomosis. It is intuitive that a distance between the proximal transverse colon and the rectal stump is less when the intestine crosses the mesenteric route on the right side, through the peritoneal window. In fact, anatomically, the small bowel mesentery from its origin goes mainly from the middle to the left side, leaving the right part to the right colon mesentery. The passage of the colon above the small bowel may result impossible and may jeopardize the vascularization, creating tension. However, the retroileal window may result more difficult in laparoscopic surgery, especially in obese patients, thus a more careful identification of the ileo-colic vessels should be performed. In conclusion, we do believe that this technique can be always used, when an extended left colon resection is required.

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## Platelet therapy: A novel strategy for liver regeneration, anti-fibrosis, and anti-apoptosis

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### Abstract

Platelets contain bio-physiological substances, including insulin-like growth factor-1, vascular endothelial growth factor, platelet-derived growth factor, hepatocyte growth factor, serotonin, transforming growth factor- $\beta$ , adenosine diphosphate, adenosine tri-phosphate, and epidermal growth factor. Platelets have conventionally been considered to exacerbate the inflammatory response and liver injury. Recently, platelets were discovered to have a positive impact on the liver. In this review, we present experimental and clinical evidence indicating that platelets accelerate liver regeneration and have anti-fibrosis and anti-apoptosis activity, and we detail the mechanisms of action. Platelets accelerate liver regeneration by three different mechanisms: (1) a direct effect on hepatocytes, (2) a cooperative effect with liver sinusoidal endothelial cells, and (3) a collaborative effect with Kupffer cells. Platelets exert anti-fibrotic activity by deactivating hepatic stellate cells *via* the adenosine-cyclic adenosine 5'-monophosphate signaling pathway. Platelets prevent hepatocyte apoptosis by activating the Akt pathway and up-regulating Bcl-xL, which sup-

presses caspase-3 activation. Platelet therapy with thrombopoietin, thrombopoietin receptor agonists, and platelet transfusion has the advantages of convenience and cost-efficiency over other treatments. We propose that in the future, platelet therapy will play a promising role in the treatment of the various liver disorders that currently challenge the surgical field, such as liver failure after a massive hepatectomy, hepatectomy of a cirrhotic liver, and small grafts in liver transplantation.

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**Key words:** Platelet therapy; Liver regeneration; Liver fibrosis; Hepatocyte apoptosis; Growth factor

**Core tip:** Platelets have conventionally been considered to exacerbate the inflammatory response and liver injury. Recently, some studies have demonstrated a role for platelets in promoting liver regeneration, improving liver fibrosis, and attenuating hepatitis. In this review, the experimental and clinical evidence that platelets accelerate liver regeneration and attenuate fibrosis and apoptosis are described, as are the mechanisms of action. Platelet therapies, such as thrombopoietin, thrombopoietin receptor agonists, and platelet transfusion, will play a promising role in the treatment of the various liver disorders that currently challenge the surgical field.

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### INTRODUCTION

Platelets contain bio-physiological substances, such as

growth factors and cytokines<sup>[1,2]</sup>. Platelets are activated by various types of stimulation, and they release these physiologically active substances in a context-dependent manner<sup>[5]</sup>. The predominant function of platelets is in hemostasis and thrombosis, where they play a complex role with other cellular participants<sup>[2,4]</sup>. Recently, platelets have been determined to have various roles in the body in addition to these primary functions<sup>[5-7]</sup>. Platelet-rich plasma is a source of platelet growth factors and cytokines<sup>[8]</sup> and has increased in popularity since the late 1990s<sup>[9]</sup>. Currently, platelet-rich plasma is widely accepted as the best treatment to promote wound healing and tissue regeneration in many fields, including orthopedics<sup>[10,11]</sup>, plastic surgery<sup>[12,13]</sup>, and maxillofacial surgery<sup>[14]</sup>.

Thrombocytopenia is frequently observed in patients with chronic liver disease<sup>[15]</sup>. This condition results from hypersplenism secondary to portal hypertension and decreased thrombopoietin production by hepatocytes<sup>[16]</sup>. Liver regeneration after hepatectomy in this patient population is severely impaired, and preventing postoperative liver failure has long been considered a critical issue in the surgical fields<sup>[17,18]</sup>. Recently, several attempts have been made to overcome this problem, including gene therapy<sup>[19]</sup>, bone marrow cell infusion therapy<sup>[20]</sup>, macrophage therapy<sup>[21]</sup>, and platelet therapy. In platelet therapy, thrombopoietin treatment and platelet transfusions have positive effects on the liver and are innovative treatments for various pathological liver conditions<sup>[22,23]</sup>. Eltrombopag, an oral thrombopoietin agonist, has recently been developed<sup>[24]</sup> and is beginning to be utilized to treat various health conditions, including liver disease<sup>[25,26]</sup>.

In this review, we present the experimental and clinical evidence that platelets accelerate liver regeneration and inhibit fibrosis and apoptosis; we also present the mechanisms of action for these functions. We propose that platelet therapy, including thrombopoietin and eltrombopag treatment and platelet transfusion, has a promising role in the treatment of the various liver problems, such as liver failure after a massive hepatectomy<sup>[27]</sup>, hepatectomy of a cirrhotic liver<sup>[18]</sup>, and small grafts in liver transplantation<sup>[28]</sup>, that currently challenge the surgical field.

## PLATELETS AND LIVER REGENERATION

Liver regeneration after a hepatectomy is accomplished *via* the proliferation of hepatocytes, biliary epithelial cells, liver sinusoidal endothelial cells, Kupffer cells, and hepatic stellate cells<sup>[29-31]</sup>. Intercellular interactions between numerous growth factors and cytokines, including hepatocyte growth factor (HGF), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), transforming growth factor- $\alpha$ , and endothelial growth factor, play important roles during this process<sup>[29,30]</sup>. Each mediator activates downstream cascades by releasing hepatocytes from a quiescent state and allowing them to enter the cell cycle<sup>[29,30]</sup>. The TNF- $\alpha$ /nuclear factor-kappa B (NF- $\kappa$ B)<sup>[32,33]</sup>, IL-6/signal transducer and activator of tran-

scription 3 (STAT3)<sup>[34]</sup>, and phosphatidylinositol-3-kinase (PI3K)/Akt<sup>[35]</sup> pathways are the three major signaling cascades that are engaged during liver regeneration.

In 2004, Murata *et al.*<sup>[36]</sup> were the first to demonstrate that platelets promoted liver regeneration during the early phases after a partial hepatectomy. Using mouse models, Lesurtel *et al.*<sup>[37]</sup> reported that platelet-derived serotonin mediated liver regeneration. In this section, the clinical and experimental evidence that platelets promote liver regeneration and the three different mechanisms involved in this process are described.

### Clinical evidence

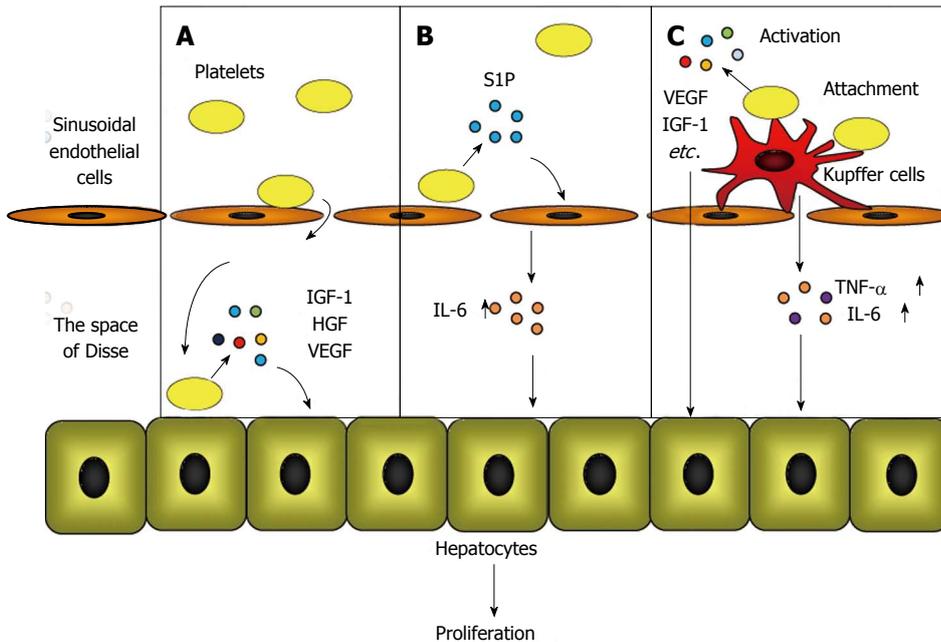
In a retrospective analysis of 216 consecutive patients who underwent a partial hepatectomy for colorectal metastasis, Alkozai *et al.*<sup>[38]</sup> reported that an immediate post-operative platelet count below 100000/ $\mu$ L was an independent risk factor for the delayed recovery of postoperative liver function and was associated with an increased risk of postoperative mortality. Kim *et al.*<sup>[39]</sup> analyzed 87 patients who received adult-to-adult living donor liver transplants and determined that the total number of units of transfused platelet concentrate was significantly associated with graft regeneration, which was assessed by CT scan. Furthermore, the stepwise regression analysis revealed that the total amount of the platelets was independently associated with graft regeneration.

### Effect of thrombocytosis on liver regeneration

Murata *et al.*<sup>[22]</sup> determined that a 2- to 3-fold elevation in platelet count induced by thrombopoietin increased the liver/body weight ratio, the hepatocyte Ki-67 labeling index, and the mitotic index after a 70% partial hepatectomy. Myronovych *et al.*<sup>[40]</sup> reported that the incremental increase in platelet count after thrombopoietin treatment accelerated liver regeneration within 24 h after a 90% hepatectomy and improved the postoperative survival rate. They determined that under thrombocytotic conditions, there was a significant increase in HGF expression in liver tissue and the early phosphorylation of Akt and STAT3. These results implied that the thrombocytotic state induced by thrombopoietin promoted liver regeneration *via* an early activation of the PI3K/Akt and IL-6/STAT3 pathways, leading to hepatocyte cell cycle entry and mitosis. In both studies, thromboembolic events, organ damage, and other side effects were not observed in response to the increased platelet count.

### Effect of platelet transfusion on liver regeneration

Matsuo *et al.*<sup>[23]</sup> examined the effects of platelet transfusion on liver regeneration by transfusing platelet-rich plasma into rats after a 70% partial hepatectomy. After a hepatectomy, platelet transfusion increased the liver/body weight ratio and the hepatocyte Ki-67 labeling index at 24 h without damaging the liver. Furthermore, platelet transfusion accelerated Akt phosphorylation and prolonged the activation of the extracellular signal-reg-



**Figure 1 Platelet-mediated liver regeneration.** Platelets accumulate in the liver immediately after a hepatectomy. A: Platelets translocate into the space of Disse and release insulin-like growth factor (IGF)-1, hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) by directly contacting hepatocytes; B: Direct contact of platelets with liver sinusoidal endothelial cells induces the release of S1P from platelets and the secretion of interleukin-6 (IL-6) from liver sinusoidal endothelial cells; C: Kupffer cells activated in response to a hepatectomy induce the accumulation and activation of platelets. Growth factors released from platelets and the enhanced release of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and IL-6 from Kupffer cells promote liver regeneration.

ulated kinase 1/2 pathway. These results indicated that platelet transfusion had a positive impact by accelerating liver regeneration after a hepatectomy without damaging the liver.

#### **Mechanisms: The direct effect of platelets**

Murata *et al.*<sup>[22]</sup> observed that platelets accumulated in the liver immediately after a hepatectomy and translocated into the space of Disse to directly contact the hepatocytes. These data implied that platelets in the liver provide signals for hepatocyte proliferation through direct contact with hepatocytes. To prove this hypothesis, Matsuo *et al.*<sup>[41]</sup> utilized a co-culture chamber system that separates the platelets and hepatocytes with a permeable membrane and clarified that direct contact between platelets and hepatocytes triggered the release of HGF, insulin-like growth factor (IGF)-1, and vascular endothelial growth factor (VEGF) from platelets, resulting in hepatocyte proliferation.

The direct effect of the platelet mechanism occurs when platelets translocate to the space of Disse and directly contact the hepatocytes, which triggers the secretion of HGF, IGF-1, and VEGF from the platelets. These growth factors initiate mitosis in hepatocytes and promote liver regeneration (Figure 1A).

#### **Mechanism: The effect involving liver sinusoidal endothelial cells**

Kawasaki *et al.*<sup>[42]</sup> studied the role of platelets in liver regeneration in relation to liver sinusoidal endothelial cells using co-culture chamber systems. They demonstrated that the direct contact of platelets with liver sinusoidal endothelial cells increased the release of IL-6 from liver sinusoidal endothelial cells, which accelerated DNA synthesis through the IL-6/STAT3 pathway in hepatocytes. They also proved that platelet-derived sphingosine-1-phosphate (S1P) induced IL-6 secretion from liver

sinusoidal endothelial cells.

In the platelet mechanism of action that involves liver sinusoidal endothelial cells, the direct contact between the platelets and the liver sinusoidal endothelial cells induces S1P release from the platelets, which promotes IL-6 secretion from the liver sinusoidal endothelial cells. IL-6 subsequently accelerates hepatocyte mitosis *via* the IL-6/STAT3 pathway (Figure 1B).

#### **Mechanism: The effect of Kupffer cells**

Takahashi *et al.*<sup>[43]</sup> studied the positive impact of platelets on liver regeneration and focused on the role of Kupffer cells by transfusing platelets into mice. These authors discovered that after a 70% hepatectomy, transfused platelets accumulated and acted locally in the residual liver in the presence of activated Kupffer cells. The hepatic expression of TNF- $\alpha$  and IL-6, which are predominantly produced by Kupffer cells<sup>[30,44]</sup>, increased in response to a platelet transfusion, indicating that the function of the Kupffer cells was enhanced by a platelet transfusion. Furthermore, it was determined by electron microscopy that the transfused platelets were attached to the surface of the Kupffer cells, providing a reason why the platelets accumulated and were activated in the liver after a hepatectomy.

The mechanism involving platelets and Kupffer cells occurs when platelets accumulate and are locally activated in the liver by attaching to the surface of activated Kupffer cells. Liver regeneration is promoted by growth factors that are released from accumulated platelets and by the enhanced release of TNF- $\alpha$  and IL-6 from Kupffer cells (Figure 1C).

## **ANTI-FIBROSIS EFFECT OF PLATELETS**

Liver fibrosis is a major cause of morbidity and mortality in the world<sup>[45]</sup>. It results in liver failure, portal hy-

pertension, and an increased risk of carcinogenesis<sup>[45,46]</sup>; liver transplantation is currently the only cure<sup>[47]</sup>. Fibrosis is characterized by an excessive deposition of extracellular matrix proteins, which disrupt the liver structure and cause pathophysiological damage to this organ<sup>[45,46]</sup>. Matrix metalloproteinases (MMPs) are enzymes that are responsible for the degradation of extracellular matrix proteins<sup>[48,49]</sup>, and the production of MMPs is regulated by HGF<sup>[50,51]</sup>. Activated hepatic stellate cells are the primary cells that are responsible for the excessive synthesis of extracellular matrix proteins<sup>[47]</sup>. Transforming growth factor- $\beta$  (TGF- $\beta$ ), which is predominately released from hepatic stellate cells and Kupffer cells<sup>[52]</sup>, is the most potent cytokine that activates hepatic stellate cells. The effects of TGF- $\beta$  are mediated by intracellular signaling *via* Smad proteins<sup>[53]</sup>, and TGF- $\beta$  is suppressed by HGF<sup>[19]</sup>.

Despite improvements in the preoperative assessment of liver function and advances in surgical techniques, liver resection still carries the risk for postoperative hepatic failure, especially in patients with cirrhosis<sup>[54]</sup>. This risk occurs because a cirrhotic liver has an impaired regenerative ability, and the risk of post-operative hepatic failure correlates with the degree of fibrosis<sup>[55]</sup>. Accelerating liver regeneration and improving liver fibrosis would avoid liver failure after a hepatectomy. Although previous studies have viewed platelets as promoters of liver fibrosis<sup>[56]</sup>, recent studies have uncovered anti-fibrotic effects of platelets in the liver. This section describes the experimental and clinical evidence that platelets are anti-fibrotic as well as the mechanisms of action.

### Clinical evidence

Maruyama *et al.*<sup>[57]</sup> conducted a prospective clinical trial of the effect of platelet transfusion on liver fibrosis. Patients with chronic liver disease (Child-Pugh classes A and B) and a platelet count below 100000/ $\mu$ L were registered. Ten patients received ten units of platelet concentrate once 1 wk for 12 wk. Four patients discontinued this treatment because of the appearance of mild hives, anti-human platelet antigen, and anti-human leukocyte antigen. Six patients completed the platelet transfusions and were followed for 9 mo after the last treatment; these patients exhibited increased concentrations of serum albumin and cholinesterase. Furthermore, there was a decrease in the serum hyaluronic acid, one of the serum fibrotic markers. It was determined that platelet transfusion improved liver function and decreased liver fibrosis.

### Effect of thrombocytosis on liver fibrosis

Watanabe *et al.*<sup>[58]</sup> reported that thrombocytosis induced by thrombopoietin treatment or splenectomy reduced liver fibrosis and the hydroxyproline content of liver tissue. Thrombocytosis suppressed TGF- $\beta$  mRNA expression and increased MMP-9 expression in the liver. Furthermore, the liver volume, the hepatocyte proliferating cell nuclear antigen (PCNA) labeling index,

and the mitotic index in fibrotic liver increased under thrombocytotic conditions. These findings indicated that thrombocytosis reduced liver fibrosis and promoted liver regeneration.

Murata *et al.*<sup>[59]</sup> examined the effect of a single thrombopoietin treatment on fibrosis and liver regeneration in a cirrhotic liver after a 70% partial hepatectomy. Thrombocytosis improved fibrosis and increased the hepatocyte PCNA labeling index and the mitotic index in the cirrhotic liver. The authors also injected anti-platelet serum after administering thrombopoietin to determine whether the effects were due to the thrombopoietin or to the increased platelet number. The anti-platelet serum injection significantly increased liver fibrosis and decreased liver regeneration. According to these studies, increasing the number of platelets attenuated liver fibrosis and accelerated liver regeneration even in a cirrhotic liver.

### Mechanism: The direct effect of platelets

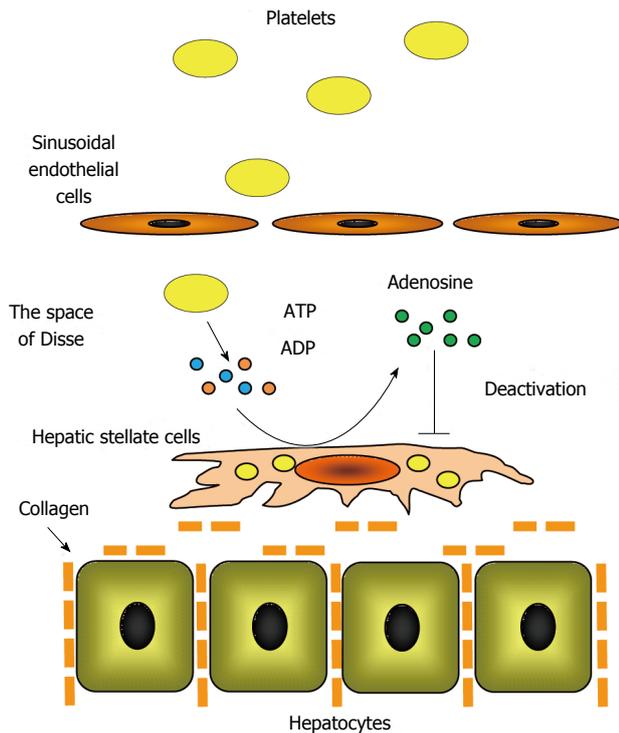
Ikeda *et al.*<sup>[60]</sup> reported that platelet extracts suppressed hepatic stellate cell activation *in vitro*. They determined that adenine nucleotides, such as adenosine triphosphate and adenosine diphosphate, were enriched in platelets and that ecto-nucleotide triphosphate diphosphodiesterase, ecto-nucleotide pyrophosphatase/phosphodiesterase, and ecto-5'-nucleotidase located on the plasma membrane of hepatic stellate cells degraded these adenine nucleotides to adenosine<sup>[61]</sup>. The authors demonstrated that adenosine increased the intracellular concentration of cyclic adenosine 5'-monophosphate (cAMP) in hepatic stellate cells, which suppressed hepatic stellate cell activation by phosphorylating cAMP-response element binding protein. These findings indicated that hepatic stellate cell activation is directly suppressed by platelets *via* the adenosine-cAMP signaling pathway (Figure 2).

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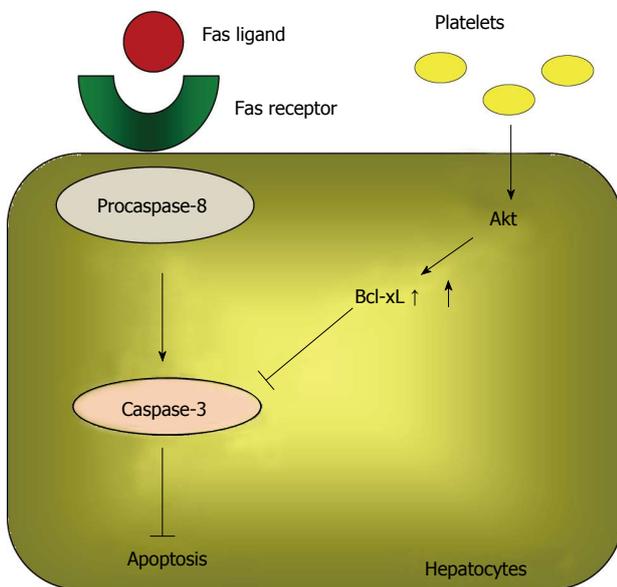
## INHIBITION OF LIVER DAMAGE AND APOPTOSIS BY PLATELETS

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Liver failure after a hepatectomy is caused by various events, including a massive hepatectomy, ischemic-reperfusion injury, and a postoperative infection<sup>[62]</sup>. Hepatocyte apoptosis and diminished liver regeneration are the most important molecular events that occur during liver failure<sup>[63]</sup>. Apoptosis is an active form of cell death, and two signaling pathways lead to apoptosis: the intrinsic and extrinsic pathways<sup>[64]</sup>. The intrinsic pathway is characterized by mitochondrial dysfunction. Various stimuli damage the mitochondrial inner membrane, resulting in a permeability transition and the mitochondrial release of cytochrome C<sup>[64]</sup>. In the cytosol, cytochrome C complexes with Apaf-1 to activate procaspase-9, which in turn activates its downstream effectors, caspases 3, 6, and 7, which are responsible for degrading several cellular substrates that are associated with the morphological changes representative of apoptosis<sup>[65]</sup>. The Fas/Fas



**Figure 2 Platelet-mediated inhibition of fibrosis.** Platelets release adenosine nucleotides, which are degraded to adenosine by enzymes located on the plasma membrane of hepatic stellate cells. The activation of hepatic stellate cells is directly suppressed by the adenosine-cAMP signaling pathway.



**Figure 3 Platelet-mediated inhibition of apoptosis.** Platelets activate the Akt pathway and up-regulate Bcl-xL, which suppresses caspase-3 activation to prevent hepatocyte apoptosis.

ligand system plays an important role in the extrinsic pathway. Upon activation by the Fas ligand, Fas complexes with procaspase-8. The aggregation of this complex initiates the cleavage of procaspase-8 into its active form, which subsequently activates caspase-3, its downstream effector<sup>[66]</sup>. Therefore, the Fas/Fas ligand system

affects both the intrinsic and extrinsic pathways. Bcl-xL, a member of the Bcl-2 family, prevents mitochondria permeability transition and Fas-mediated apoptosis by inhibiting the signaling cascades<sup>[67]</sup>.

This section describes the effect of thrombocytosis on liver damage and apoptosis. Because the Fas/Fas ligand system and apoptosis are hypothesized to be responsible for hepatitis<sup>[68,69]</sup>, we examined the anti-apoptotic effects using a hepatitis model.

**Effect of platelets on liver damage and apoptosis after a massive hepatectomy**

Hisakura *et al*<sup>[70]</sup> examined the ability of thrombopoietin-mediated thrombocytosis to protect the liver from damage after an extended hepatectomy using a pig model. The authors discovered that in thrombocytotic conditions, liver cholestasis, ballooning, and necrosis were attenuated and that serum aspartate amino transferase and alkaline phosphatase (ALT) levels were low after an extended hepatectomy. Furthermore, electron transmission microscopy revealed that the structure of the endothelial lining was well preserved in thrombocytotic conditions. These data indicated that thrombocytosis protects the sinusoidal lining and prevents acute liver damage after an extended hepatectomy.

Hisakura *et al*<sup>[71]</sup> also investigated the effects of thrombocytosis in acute hepatitis induced by an anti-Fas antibody. The authors demonstrated that serum ALT levels were significantly decreased in thrombocytotic conditions at 6, 24 and 72 h after administering an anti-Fas antibody. They also determined that the percent of TdT-mediated dUTP-biotin nick end labeling-positive hepatocytes and the expression of cleaved caspase-3 in the liver were significantly decreased by thrombocytosis. Furthermore, *in vitro* Akt phosphorylation, increased Bcl-xL, and decreased cleaved caspase-3 were observed sequentially in hepatocytes co-cultured with platelets. Because Akt is a critical suppressor of apoptosis<sup>[72,73]</sup>, the above data suggested that an increase in the platelet count prevents hepatocyte apoptosis by activating the Akt pathway and up-regulating Bcl-xL, which suppresses caspase-3 activation (Figure 3).

**CONCLUSION**

This review describes the published evidence that platelets promote liver regeneration, attenuate liver fibrosis, and prevent liver damage and hepatocyte apoptosis; it also details the mechanisms of action. In the blood, platelets are constituents that contain numerous biologically active growth factors and cytokines, and it was recently determined that platelets have various functions in addition to hemostasis and thrombosis<sup>[5-7]</sup>. Currently, thrombopoietin<sup>[22,40,58,59,70]</sup>, thrombopoietin receptor agonists<sup>[24]</sup>, artificial platelets<sup>[74,75]</sup>, and freeze-dried platelets<sup>[76]</sup> are in development and are beginning to be utilized in various clinical settings, and the importance of platelets is becoming more obvious. Despite some side

effects<sup>[57]</sup>, platelet therapy has advantages in its convenience and cost-efficiency, and it provides another therapeutic strategy to address the current surgical issues and challenges, such as liver failure after a massive hepatectomy, hepatectomy of a cirrhotic liver, and small grafts in liver transplantation, in the near future.

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## Treatment of cervico-mediastinal goiters

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### Abstract

**AIM:** To compare our ten year results for thyroidectomy for cervico-mediastinal goiters with the best surgical treatment reported in the literature.

**METHODS:** From January 2000 to December 2009, of 1530 patients who underwent thyroidectomy in our department, we selected 105 cases of cervico-mediastinal goiter. In the majority of cases, the cervical approach is the standard procedure and only occasionally sternotomy or thoracotomy is necessary. The indications for surgery are generally related to a progressive increase of the thyroid mass into the anterior mediastinum with compression and dislocation of the trachea or esophagus and the possibility of an unknown malignancy.

**RESULTS:** In 98 (93.3%) of our 105 patients, the standard surgical approach was anterior cervicotomy followed by total thyroidectomy. In three cases, total sternotomy was performed and in the remaining four patients, a partial split sternotomy was effective to remove the intrathoracic mass. Post-operative complications included transient recurrent laryngeal nerve palsy

in 6 patients (5.7%) which only became permanent in 2 patients (1.9%). The transient hypoparathyroidism rate was 22% but 2 mo after surgery permanent hypoparathyroidism was confirmed in only 2% of our selected group. No patients required temporary tracheostomy following surgery related to a possible bilateral nerve palsy. Patients received a single prophylactic antibiotic dose preoperatively and wound infections were not significant. There was no mortality in our selected group and most patients showed a significant improvement of dyspnea and other correlated symptoms postoperatively.

**CONCLUSION:** The majority of cervico mediastinal goiters can be completely removed through a cervical incision. In selected cases, generally malignancies with local infiltration of mediastinal soft tissues and adhesions to large vessels, split sternotomy may be a safer approach to not increase morbidity.

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**Key words:** Goiter; Sternotomy; Thyroidectomy; Mediastinum; Thoracotomy

**Core tip:** The majority of cervico-mediastinal goiters can be completely removed through a cervical incision. Volume reduction by a vascular peduncle ligature can facilitate the extraction of big goiters, with the result that sternotomy or thoracotomy is seldom necessary. Care must be taken to avoid recurrent laryngeal nerve injuries.

Magistrelli P, D'Ambra L, Bonfante P, Francone E, Leoncini R, Cappagli M, Falco E. Treatment of cervico-mediastinal goiters. *World J Surg Proced* 2013; 3(3): 37-40 Available from: URL: <http://www.wjgnet.com/2219-2832/full/v3/i3/37.htm> DOI: <http://dx.doi.org/10.5412/wjsp.v3.i3.37>

## INTRODUCTION

Cervico-mediastinal goiters are a common pathology and their incidence may reach 15% of patients undergoing thyroidectomy<sup>[1]</sup>. There is agreement that in the majority of cases, cervical approach is the standard procedure and only occasionally sternotomy or thoracotomy is necessary<sup>[2]</sup>. The indications for surgery are generally related to a progressive increase of the thyroid mass into the anterior mediastinum with compression and dislocation of the trachea or esophagus and the possibility of an unknown malignancy.

In the past, medical treatment based on thyroxine was considered the first option to reduce the size of the gland. Now, surgery is also considered an appropriate treatment as negative intrathoracic pressure and retrosternal space tend to facilitate the migration of the goiter into the chest<sup>[3]</sup>. We retrospectively reviewed our ten year experience to evaluate the choice of surgical approach, notes of surgical technique and range of complications with the aim to compare our results with the best surgical treatment reported in the literature.

## MATERIALS AND METHODS

Cervico-mediastinal goiter is defined as a thyroid mass extending into the mediastinum in the prevascular or retrovascular space, reaching at least the level of the aortic arch. Surgical therapy considers extrathoracic enucleation of the thyroid mass. In this study, we excluded multinodular goiters with minimal or limited substernal extension.

From January 2000 to December 2009, of 1530 cases who underwent thyroidectomy in our department, we selected 105 patients operated on for cervico-mediastinal goiter. A total of 71 patients were women and 34 men, with a mean age of 61 years (range 22-80). All patients were referred to our unit by specialists and preoperative work up included blood examination and functional thyroid tests, chest X ray and a computed tomography (CT) scan to evaluate intrathoracic extension of the goiter. Only 23 of 105 patients underwent fine needle aspiration because of suspected nodules. The most frequent clinical symptoms are indicated in Table 1. Predominantly, patients reported a history of mild or severe dyspnea, although a considerable proportion (12 patients, 11.4%) had no palpable mass in the neck. In 5 cases (4.7%), the compression and dislocation of the trachea was masked by other conditions such as obstructive chronic diseases and asthma.

## RESULTS

In 98 (93.3%) of our 105 patients, the standard surgical approach was anterior cervicotomy followed by total thyroidectomy. In three cases, total sternotomy was performed and in the remaining four patients, a partial split sternotomy was effective in removing the intrathoracic mass.

The combined approach was performed in the five

**Table 1 Clinical symptoms n (%)**

Symptoms	No. of patients
Dyspnea	75 (71)
Dysphagia	17 (16)
Neck mass	86 (82)
Hoarseness	14 (13)

**Table 2 Definitive histology**

Histology	n (%)
Benign multinodular disease	86 (8.2)
Papillary carcinoma	12 (11.5)
Follicular carcinoma	5 (4.8)
Medullary carcinoma	2 (1.9)

cases of malignancy (3 papillary and 2 medullary carcinoma) and in two patients in which the inveterate multinodular goiters had established important adhesions with the mediastinal surrounding soft tissues.

Over the last five years, consolidation of our experience has avoided performing sternotomy even in cases of cervico-mediastinal goiters with development in the retrovascular space. The vast majority of patients were discharged in the second post-operative day. Two patients needed a re-exploration for wound hematoma and another three required further checks of blood calcium level.

Post-operative complications included transient recurrent laryngeal nerve palsy in 6 patients (5.7%) which only became permanent in 2 patients (1.9%). The transient hypoparathyroidism rate was 22% but 2 mo after surgery permanent hypoparathyroidism was confirmed in only 2% of our selected group. No patients required temporary tracheostomy following surgery related to a possible bilateral nerve palsy. Patients received a single prophylactic antibiotic dose preoperatively and wound infections were not significant. Definitive histology of the specimens is indicated in Table 2.

There was no mortality in our selected group and most patients showed a significant improvement of dyspnea and other correlated symptoms postoperatively.

## DISCUSSION

Our selected group of patients was composed of cases with a prevalent anterior development of the cervical mass (Figure 1) and cases with dominant extension into the anterior mediastinum (Figure 2A). Development in the retrosternal space is favored by negative intrathoracic pressure and by gravity mechanisms. At first examination, the chest X-ray indicates the right or left dislocation of the trachea and this radiological evidence requires a CT scan for further definition of intrathoracic goiter (Figure 2).

In case of difficult oral intubation, evaluated preoperatively by the anesthesiologist, a fiber optic bronchoscopy guide was considered to facilitate the procedure.

The standard surgical approach to perform total

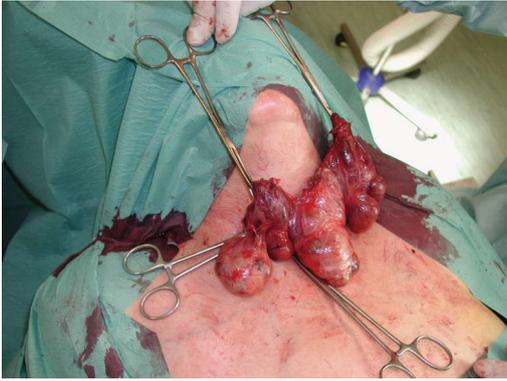


Figure 1 Giant multinodular goiter.



Figure 3 Post operative field showing inferior laryngeal nerve sparing.

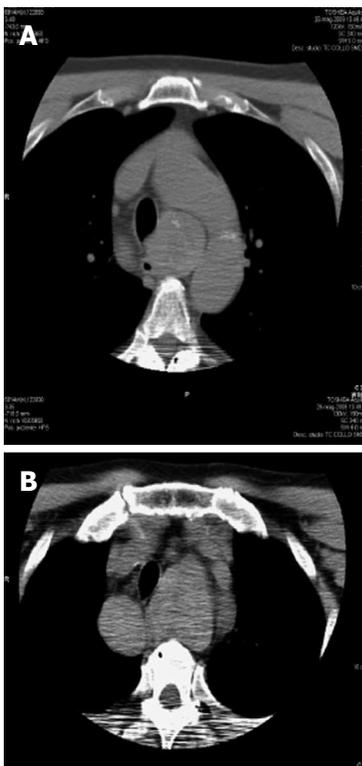


Figure 2 Computed tomography scan showing a mediastinal goiter descending between trachea and aortic arch (A) and surrounding trachea (B).

thyroidectomy was cervicotomy. Sternotomy has to be considered a selective option in cases of malignancy with soft tissue infiltration and/or gross mediastinal masses and lymphadenopathies which require a more aggressive surgery<sup>[4,5]</sup>. We needed to execute total sternotomy only in the past decade. Nowadays, we perform split sternotomy in cases of invasive malignancy to avoid hemorrhage originating from mediastinal vessel laceration and malignant tumor relapses. Other factors that can influence the likelihood of sternotomy are posterior mediastinal and ectopic goiters. In these cases, gentle handle maneuvers do not permit a sufficient traction for enucleation<sup>[6]</sup>. A mediastinal CT scan may be an important predictive factor. The presence of a clear plane around the intrathoracic nodule may be an indicator for a successful cervical

approach<sup>[1]</sup>.

Our surgical strategy is based on two principles: (1) the section of superior thyroid peduncles and (2) clear evidence of recurrent laryngeal nerve course.

As a priority, we section superior vascular pedicles to reduce thyroid vascularization and consequently volume and tension of the gland. The further step is cervical enucleation of the mediastinal mass by using careful hand maneuvers.

Once the goiter is reduced, it is necessary to identify recurrent laryngeal nerves and following their course up to the larynx to avoid possible damage to a dislocated or compressive nerve caused by the thyroid mass (Figure 3). We do not section any structure until there is clear identification of the nerves and we emphasize this procedure because the recurrent laryngeal branches may reach the larynx with extreme variability through the tracheoesophageal groove.

Recently, a new technique based on nerve monitoring during surgery has been considered a good option that reduces but does not eliminate the risk of laryngeal nerve palsy. This electromyography, which is becoming a standard procedure in the United States, is becoming accepted in Europe, especially for legal medical reasons<sup>[7]</sup>.

At the moment, we are only considering nerve monitoring technique in cases of large relapsing goiters and this is because we systematically identify the nerves before any tissue section. However, the reported risk of nerve palsy using the monitoring technique is still around 1%<sup>[7]</sup>. It must be emphasized that the complications of thyroid surgery need to be avoided for the important functional impact on the life quality of patients. There is agreement that this type of surgery needs to be performed by dedicated specialist surgeons. The majority of cervico-mediastinal goiters can be completely removed through a cervical incision.

In very selected cases, generally for malignancies with local infiltration of mediastinal soft tissues and adhesions to large vessels, split sternotomy may be a safer approach without increasing morbidity. Regular and systematic bilateral identification of recurrent laryngeal nerves and their variations is a priority to avoid complications. Our results are similar to the experiences reported by several

specialized center series.

## COMMENTS

### Background

The cervico-mediastinal goiter rate is about 15% of patients who undergoing thyroidectomy. Common agreement exists that in the majority of cases, the surgical cervical approach is the standard procedure and only occasionally sternotomy or thoracotomy is necessary. The indications for surgery are generally related to a progressive increase of the thyroid mass into the anterior mediastinum with compression and dislocation of the trachea or esophagus and the possibility of an unknown malignancy. In very selected cases, generally malignancies with local infiltration of mediastinal soft tissues and adhesions to large vessels, split sternotomy may be a safer approach without increasing morbidity.

### Research frontiers

The standard surgical approach to perform total thyroidectomy is cervicotomy. Sternotomy has to be considered a selective option in case of cervico-mediastinal goiters and malignancy with soft tissue infiltration and/or gross mediastinal masses and lymphadenopathies which require a more aggressive surgery. The majority of cervico-mediastinal goiters can be completely removed through a cervical incision.

### Innovations and breakthroughs

During thyroidectomy, identification of recurrent laryngeal nerves is mandatory to avoid possible injuries. Lately, a new technique based on nerve monitoring during surgery has been considered a valid option. In the authors' experience, a nerve monitoring technique is used only in cases of large relapsing goiters because the nerves are usually identified before any tissue section. However, the reported risk of nerve palsy using a monitoring technique is still around 1%.

### Applications

The authors compare their ten year results in a surgical approach for thyroidectomy for cervico-mediastinal goiters with the best surgical treatment reported in the literature.

### Peer review

The authors describe their experience of a cervicotomy approach for cervico-mediastinal goiters, focusing on a nerve preserving technique and also highlighting the feasibility of the above-mentioned surgical procedure in a giant thyroid.

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## Operative indications of follicular type tumors, based on Japanese clinical guidelines

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### Abstract

**AIM:** To investigate the accuracy of preoperative examinations in follicular type tumors, we re-evaluate results of our operative cases.

**METHODS:** Cases are follicular neoplasms in 36 patients, which are more than 30 mm in diameter and underwent surgery in our hospital in 2005-2006. These cases had been suspected of malignancy on one or more of the preoperative examinations, including ultrasound (US), thallium-technecium (TI-Tc) scintigram, computed tomography (CT), or fine needle aspiration biopsy (FNA) examinations. Concern about operative procedure, lobectomy plus sentinel lymph node biopsy (SNB) was performed in all 36 follicular tumors at the first surgery. Because we can diagnose a suspected follicular tumor as carcinoma and can change the operative procedure intra-operatively, when the metastasis of lymph nodes, outside of the thyroid, is found. The operative procedure was changed from lobectomy to total thyroidectomy plus lymph nodes dissection (central

component), when the SNB has metastasis. All thirty six cases were obtained to track the prognosis until 2012, for 6-7 years follow up periods.

**RESULTS:** The final pathological results are 3 cases of follicular carcinoma, 6 cases of papillary carcinoma, 1 case of papillary carcinoma follicular type, 1 case of malignant lymphoma, 16 cases of follicular adenoma, and 9 cases of adenomatous goiter. The malignant tumor were observed in 11/36 (30.6%) cases. All six papillary carcinomas were less than 20 mm, and present with follicular adenoma and adenomatous goiter, which have more than 40 mm diameter. In physical examination, tumor size of 36 cases of follicular neoplasm is more than 30 mm all at the time of surgery. The tumors were palpable somewhat stiff, such as no cystic component in 34 cases. Occasional dyspnea, dysphagia, and cough was accompanied in all 36 cases. The true ratio of correct diagnosis of preoperative US, TI-Tc scintigram, CT, and FNA were 17/36 (47.2%), 16/36 (44.4%), 24/36 (66.7%), 21/36 (58.3%), respectively. In 11 malignant cases, there was one SNB positive case (one lymph node metastasis in 3 SNB: 1/3). This case was changed the operative procedure from lobectomy to total thyroidectomy plus lymph node dissection (central component). There is other lymph nodes metastasis in dissected lymph nodes (4/15). For the remaining malignant 10 cases, the observations were selected without additional resection, because surgical margins and SN were negative in postoperative pathology results at the first operation. No recurrence and metastasis are allowed in 11 malignant cases, up to 7 years after post-operation. Over all, the more than 30 mm in diameter follicular neoplasms, which were suspected the malignancy in the one and more preoperative examinations, are present the malignancy by pathological diagnosis in 11/36 (30.6%) cases after surgery. The non SNB metastasis cases had no symptoms of lymph nodes metastasis up to 7 years after post-operation.

**CONCLUSION:** We think that more than 30 mm in diameter follicular neoplasms are considered as candidates of surgery from our results.

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**Key words:** Follicular type tumor; Preoperative diagnosis; Operative indication; Guideline of thyroid tumor; Prognosis

**Core tip:** To know the accuracy of preoperative examinations, we investigated the operated 36 follicular type tumors, according to the postoperative final pathological diagnosis. We also re-evaluate the operative indication and operative procedure. The true ratio of correct diagnosis of preoperative ultrasound, thallium-technecium scintigram, computed tomography, or fine needle aspiration biopsy were 17/36 (47.2%), 16/36 (44.4%), 24/36 (66.7%), 21/36 (58.3%), respectively, and there were no statically differences between the accuracy of these preoperative diagnoses. The more than 30 mm in diameter tumors, which were suspected the malignancy in the one and more preoperative examinations, are present the malignancy in 11/36 (30.6%) cases by final pathological diagnosis.

Takeyama H, Tabei I, Kato K, Kamio M, Nogi H, Toriumi Y, Kinoshita S, Akiba T, Uchida K, Morikawa T. Operative indications of follicular type tumors, based on Japanese clinical guidelines. *World J Surg Proced* 2013; 3(3): 41-46 Available from: URL: <http://www.wjgnet.com/2219-2832/full/v3/i3/41.htm> DOI: <http://dx.doi.org/10.5412/wjssp.v3.i3.41>

## INTRODUCTION

The diagnostic accuracy of papillary carcinoma is over 90% by preoperative examinations. On the other hand, the diagnostic accuracy of follicular type tumors is only 20%-40%.

For example, the accuracy of fine needle aspiration biopsy (FNA) is more than 90% in papillary carcinoma, because the morphology of papillary cell has some distinctive features, such as intra-nuclear inclusion or notching of nuclei. In contrast, there are no differences between follicular malignant tumors and benign follicular tumors morphologically by FNA. For the preoperative diagnosis of thyroid tumor, ultrasound (US) examination, thallium-technecium (Tl-Tc) scintigram, computed tomography (CT), and fine needle aspiration biopsy (FNA) are usually recommended. We decided the operative indication and resected area with these results.

Recently, some physical signs and radiological imagings are indicated as the detection tools of malignant follicular type tumor by the new Japanese guide line of thyroid tumor, published in 2010<sup>[1]</sup>.

In this study, we re-evaluate the results of preoperative examinations of follicular type tumors according to the guide line, using the pathologically final diagnosed cases, and re-consider the operative indications.

## MATERIALS AND METHODS

### Case and examinations

Cases are follicular neoplasms in 36 patients, which are more than 30 mm in diameter and underwent surgery in our hospital in 2005-2006. These cases had been suspected of malignancy by the one or more of preoperative examinations, including US, Tl-Tc scintigram, CT, or FNA examinations.

### Operative procedure

Usually, the operation of follicular type tumor performs tumor-side lobectomy, as the differential diagnosis is difficult in preoperative examinations.

In the Japanese thyroid cancer treatment protocol in 2005 Edition<sup>[2]</sup>, follicular carcinoma diagnostic criteria are determined as follows: (1) membrane invasion of the tumor cells; (2) lymphatic or vessel duct invasion of the tumor cell; and (3) metastasis outside of the thyroid gland being able to confirm one of either of these histological examinations.

In this study, we tried the lobectomy plus sentinel nodes biopsy (SNB) as a first operation. Because we can diagnose a follicular tumor as carcinoma and can change the operative procedure intra-operatively, when the metastasis of lymph nodes, outside of the thyroid, is found.

### Pathological diagnosis

The final diagnosis of tumor was determined by formalin-fixed, Hematoxylin-Eosin (HE) stained specimen after surgery. SNB was evaluated by HE stained frozen section intra-operatively, and reevaluated by formalin-fixed specimen after surgery.

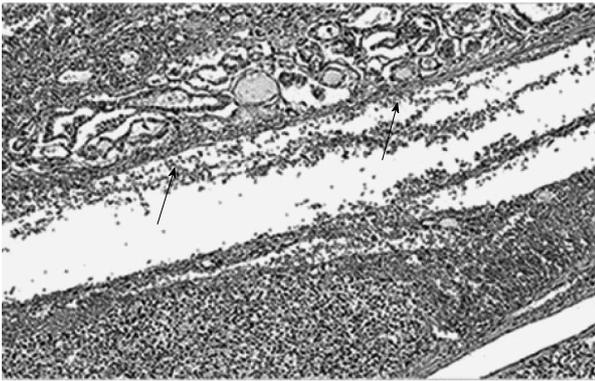
## RESULTS

### The final pathological diagnosis

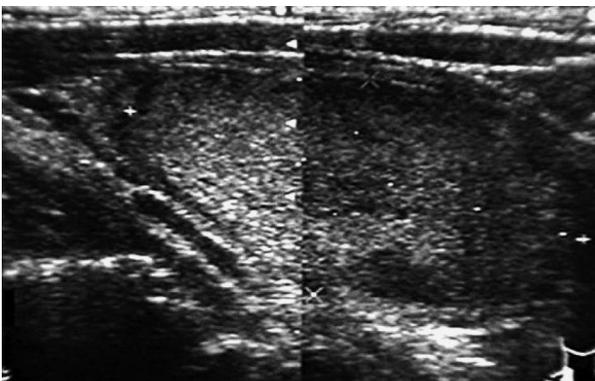
The final pathological diagnosis and the results of preoperative examinations were summarized in Tables 1 and 2. The pathological diagnoses are 3 cases of follicular carcinoma (diameter 40-54 mm), 6 cases of papillary carcinoma (5-14 mm), 1 case of papillary carcinoma follicular variant type (30 mm), 1 case of malignant lymphoma (45 mm), 16 cases of follicular adenoma (30-80 mm), 9 cases of adenomatous goiter (43-170 mm). The malignant tumors were observed in 11/36 (30.6%) cases.

About seven papillary carcinomas including follicular variant type, 6 papillary carcinomas were present with adenoma and adenomatous goiter that have more than 40 mm diameter (Figure 1).

In 36 patients performed SNB intraoperative, there was one positive metastasis case of papillary carcinoma follicular variant type (1/36, 2.7%).



**Figure 1** Hematoxylin-Eosin staining shows micropapillary carcinoma (diameter 10 mm, arrow, upper part) with follicular adenoma (diameter 50 mm, lower part).



**Figure 2** A tumor diameter of approximately 60 mm, solid and accounts for most of the left lobe were suggested by ultrasound. Although capsular invasion was unclear, Doppler examination were revealed abundant blood flow and high blood flow resistance value inside the tumor. The result of ultrasound suspected the malignancy.

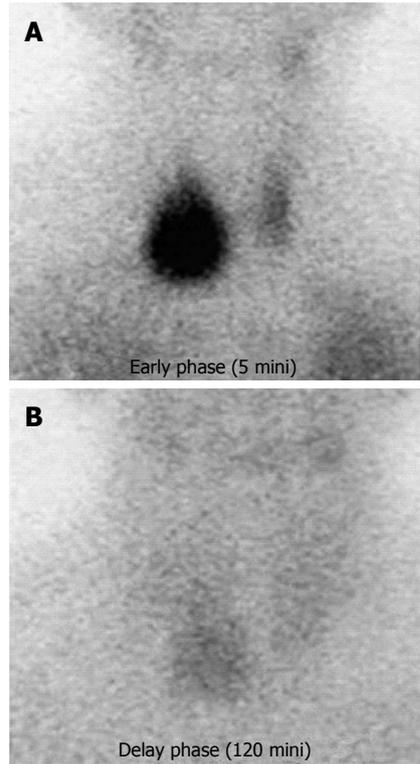
**Table 1** Final pathological diagnosis of follicular type tumor that was suspected malignancy by preoperative examinations

Pathological diagnosis	Cases	Tumor size (mm)
Malignant lesion		
Papillary carcinoma	7	5-30
Follicular carcinoma	3	40-54
Malignant lymphoma	1	45
Benign lesion		
Follicular adenoma	16	33-80
Adenomatous goiter	9	43-170

**Examinations**

**Physical examination:** Tumor size of 36 cases is more than 30 mm all at the time of surgery. The tumors were palpable somewhat stiff, such as no cystic component in 34 cases. Occasional dyspnea, dysphagia, and cough was accompanied in all 36 cases, but was not accompanied lymph node swelling, paralysis of the vocal cords.

**US:** US examination diagnosed 24 cases as benign tumors including adenoma, adenomatous goiter, and 12 cases as suspicion of malignant or malignant tumor. The



**Figure 3** In the Tl early phase of 5 min after injection, a prominent accumulation of isotope to the tumor was observed. In the delay phase of 120 min after injection, a remaining of isotope in tumor was also found. These accumulations of isotope and delay of wash out suggest the suspicion of malignancy findings.

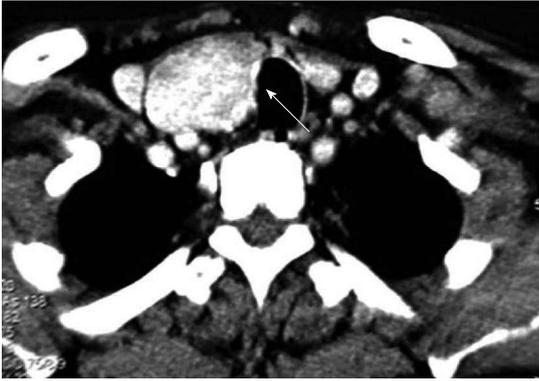
true positive ratio (TP) was 2/11 (18.2%), the true negative ratio (TN) 15/25 (60.0%), the false-positive ratio (FP) 10/25 (40.0%), the false negative (FN) 9/11 (81.8%), respectively. The true ratio (TR) of correct diagnosis (TP + TN/Total cases) by US was 17/36 (47.2%). The malignant tumor suspected by US, were indicated in Figure 2.

**Scintigraphy (Tl-Tc scintigram):** Tl-Tc scintigram examination diagnosed 9 cases as benign tumor, and 27 cases as suspicion of malignant or malignant tumor. TP was 9/11 (81.8%), TN7/25 (28.0%), FP18/25 (72.0%), FN 9/11 (81.8%), respectively. TR by Tl-Tc scintigram was 16/36 (44.4%). The malignant tumor suspected by scintigraphy was suggested in Figure 3.

**CT:** CT examination diagnosed 31 cases as benign tumor, and 5 cases as suspicion of malignant or malignant tumor (Figure 4).

TP was 2/11 (18.2%), TN 22/25 (88.0%), FP 3/25 (12.0%), FN 9/11 (81.8%), respectively. TR by CT was 24/36 (66.7%).

**FNA:** Twenty cases were benign, and 16 cases were suspicion of malignancy by FNA examination. TP was 6/11 (54.5%), TN 15/25 (60.0%), FP 10/25 (40.0%), and FN 5/11 (45.5%), respectively. TR by FNA was also 21/36 (58.3%).



**Figure 4** Computed tomography image of follicular neoplasm of 45 mm diameter in the right lobe. It showed some irregular border and extension of the right wall of the trachea. There is a suspicion of tracheal invasion of tumor.

**Table 2** True positive, true negative, and accuracy rates of preoperative examinations, based on the final pathological diagnosis of follicular tumors

	US	Tl-Tc scintigram	CT	FNA
True positive: TP (malignant)	2 (18.2)	9 (81.8)	2 (18.2)	6 (54.5)
True negative: TN (benign)	15 (40.0)	7 (28.0)	22 (88.0)	15 (60.0)
TP + TN (accuracy)	17 (47.2)	16 (44.2)	24 (66.7)	21 (58.3)

US: Ultrasound; Tl-Tc: Thallium-technecium, scintigram; CT: Computed tomography; FNA: Fine needle aspiration biopsy; TN: True negative ratio; TP: True positive ratio.

**Operation:** Lobectomy plus SNB was performed in all 36 follicular tumors at the first surgery.

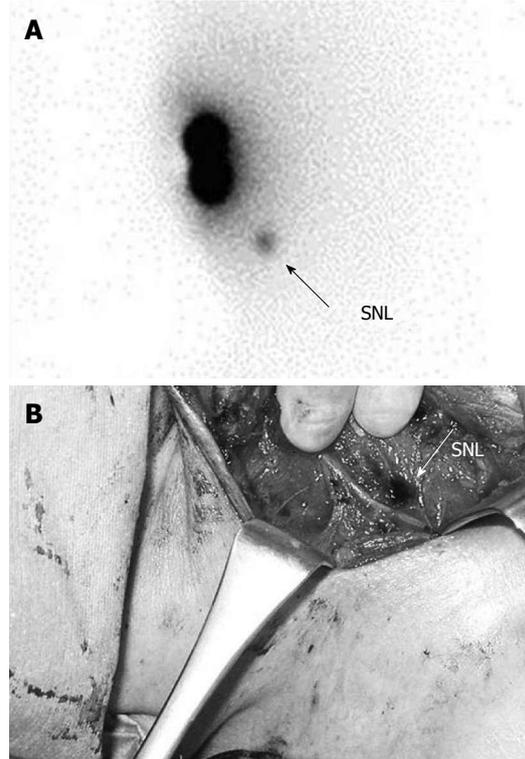
Figure 5A is a statue of SN identification using Tc-physic acid for the 40 mm diameter follicular neoplasm of the right lobe.

Figure 5B is the photo of SN stained by the dye at the time of surgery of the same case. The stained SN was acknowledged in the central component lymph nodes near the right recurrent nerve. The SN was counted the accumulation of isotope, excised, and submitted to the intraoperative pathologic examination to confirm the presence or absence of lymph node metastasis. In 36 patients, there was one positive lymph nodes metastasis case (SNB: 1/3). The surgical procedure was changed to total thyroidectomy plus lymph node dissection (central component) during surgery in this case. There is other lymph nodes metastasis in dissected lymph nodes (4/15).

For the remaining malignant 10 cases, the observations were selected without additional resection, because surgical margins and SN were negative in postoperative pathological diagnosis.

**Prognosis**

The recurrence or metastasis has not been recognized in these 11 cases of malignant tumor from 2005 to 2012, more than five years after surgeries.



**Figure 5** Sentinel nodes. A: Sentinel nodes (SNL, arrow) revealed in the central component lymph nodes using Tc-physic acid. B: SNL (arrow) is performed using 4% isosulfan blue dye during operation. The stained lymph node is seen near the right pharyngeal recurrent nerve in the central component lymph nodes.

**DISCUSSION**

In clinical question (CQ) 6 of the 2010 Thyroid Tumor Treatment Guidelines created by Japan Endocrine Surgery Society/Japan Thyroid Surgery Society, US, Tl-Tc scintigraphy, CT, and fluoro-deoxyglucose positron emission tomography are given as diagnostic imaging methods in the diagnosis of malignant tumors as grade B recommendations<sup>[1,3-5]</sup>. Among these, US is recommended as the most useful modality<sup>[1,6-8]</sup>.

In this follicular tumor study, correct diagnostic rates of FNA and CT were relative high with 50%-60% on the preoperative examinations.

When we compared these 2 examinations, true positive rate, both true negative rates were more than 50% together in FNA examination. On the other hand, the CT test identified true positive rate 18.2%, and true negative rates 88.0%.

So, we think that FNA is a reliable examination for distinguish malignant and benign follicular tumor than CT study, although there is thought to be room for improvement, as many reports mentioned that diagnosis of follicular malignant neoplasm was more difficult than diagnosis of papillary carcinoma<sup>[1,5-8]</sup>.

CQ 5 of the guidelines state that “physical findings that increase the possibility of malignant neoplasm in thyroid tumors include adhesion to tissues surrounding

nodes, lymph node enlargement, vocal cord paralysis (hoarseness), dyspnea, dysphagia, coughing” and “especially in tumor size alone, nodes of  $\geq 40$  mm are a significant independent factor suggestive of malignancy”<sup>[1,9-14]</sup>. In addition, when a tumor is follicular carcinoma, tumor size  $\geq 40$  mm become stage III in the tumor node metastasis classification of Union for International Cancer Control, and the chance of remote metastasis will be increased.

Surgery is thought to be indicated in that reason for the follicular tumors  $\geq 40$  mm, which can not deny the malignancy<sup>[15,16]</sup>.

In our results, only 3 of 28 follicular tumors  $\geq 40$  mm in diameter were follicular carcinoma (10.7%), and 5 of 36 follicular tumors  $\geq 30$  mm that were suspected the malignancy by several preoperative examinations, were malignant tumors (13.9%). Concerning about papillary carcinoma, although the size of papillary carcinoma were less than 20 mm, 6 cases coexisted with follicular adenoma and adenomatous goiter  $\geq 40$  mm that were benign on postoperative pathological diagnosis.

As described above, the malignancy rate of follicular tumors  $\geq 40$  mm was not high. However, considering coexisting lesions such as papillary carcinoma with benign follicular tumors  $\geq 40$  mm, the malignant region was present in a total of 12 of 36 suspected tumor (33.3%). So, we concluded that surgery is thought to be indicated as stated in the guidelines.

For SNB, such as follicular variant of papillary carcinoma that have a fairly high frequency of lymph node metastasis, the surgical procedure can be changed depending on lymph node metastasis status during surgery. So, SNB is thought to have a high likelihood of being useful<sup>[15,17]</sup>.

It is a tiny and one facility study, we think that follicular neoplasms  $\geq 40$  mm in diameter, which had been suspected of malignancy on one or more of the preoperative examination are considered as candidates of surgery, as suggested in the Treatment of Thyroid Tumor-Japanese Clinical Guidelines<sup>[1]</sup>.

## COMMENTS

### Background

The diagnostic accuracy of papillary carcinoma is over 90% by preoperative examinations. On the other hand, the diagnostic accuracy of follicular type tumors is only 20%-40%.

### Research frontiers

Recently, some physical signs and radiological imagings are indicated as the detection tools of malignant follicular type tumor by the new Japanese guide line of thyroid tumor, published in 2010. In this study, they re-evaluate the results of preoperative examinations of follicular type tumors according to the guide line, using the pathologically final diagnosed cases, and re-consider the operative indications.

### Innovations and breakthroughs

In their results, only 3 of 28 follicular tumors  $\geq 40$  mm in diameter were follicular carcinoma (10.7%), and 5 of 36 follicular tumors  $\geq 30$  mm that were suspected the malignancy by several preoperative examinations, were malignant tumors (13.9%). Concerning about papillary carcinoma, although the size of papillary carcinoma were less than 20 mm, 6 cases coexisted with follicular

adenoma and adenomatous goiter  $\geq 40$  mm that were benign on postoperative pathological diagnosis. As described above, the malignancy rate of follicular tumors  $\geq 40$  mm was not high. However, considering coexisting lesions such as papillary carcinoma with benign follicular tumors  $\geq 40$  mm, the malignant region was present in a total of 12 of 36 suspected tumor (33.3%). So, the authors concluded that surgery is thought to be indicated as stated in the guidelines.

### Applications

Authors think that follicular neoplasms  $\geq 40$  mm in diameter, which had been suspected of malignancy on one or more of the preoperative examination are considered as candidates of surgery, as suggested in the Treatment of Thyroid Tumor-Japanese Clinical Guidelines.

### Peer review

This is a very interested topic for the readers. It shows the guidelines of the Japanese Society of Endocrine Surgery.

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## Back to basics: A meta-analysis of stump management during open appendicectomy for uncomplicated acute appendicitis

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### Abstract

**AIM:** To compare simple ligation vs stump invagination during open appendicectomy for uncomplicated acute appendicitis on the risk of postoperative complications.

**METHODS:** A meta-analysis was conducted on randomised controlled trials comparing the two stump closure methods in open appendicectomy. Databases searched were PubMed, EMBASE and Cochrane Library databases. Included were those studies focusing on inflamed and suppurative appendicitis while perforated and gangrenous appendix was excluded. We also excluded retrospective case-control studies, commentaries, historical technical articles, or trials involving laparoscopic appendicectomies. The outcome of the meta-analysis was to find eventual differences in the

incidence of postoperative ileus and wound infections between the two techniques of stump invagination.

**RESULTS:** Seven studies were included corresponding to 1468 patients. Postoperative complications consisted in wound infections (7%), ileus (4%), pyrexia (2%), vomiting (1%), obstructions from adhesions (0.1%). No cases of peritonitis, fecal fistulas (stump leaks), abdominal abscesses or wound dehiscences were reported. Postoperative ileus within the first 72 h was four times more frequent with stump invagination compared to simple ligation (OR: 4.06; 95%CI: 2.14-7.70;  $P < 0.0001$ ). No significant differences were noted for wound infections (OR: 1.24; 95%CI: 0.83-1.87;  $P = 0.30$ ) while for the remaining complications the incidence was extremely low in both groups. There was a high homogeneity on results ( $Q$  value for heterogeneity of postoperative ileus  $P = 0.17$ ;  $Q$  value for heterogeneity of wound infections  $P = 0.98$ ).

**CONCLUSION:** Stump invagination does not seem to prevent infective complications but is associated with an increased risk of postoperative ileus in uncomplicated cases. Appropriate studies on complicated appendicitis should now evaluate the influence of the two techniques in this higher-risk subgroup.

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**Key words:** Appendiceal stump; Open appendicectomy; Invagination; Appendicitis; Complications

**Core tip:** Despite the increased use of the laparoscopic approach, open appendicectomy is an operation still performed on a large scale worldwide. Two main approaches exist for the stump closure, the simple ligation and the stump invagination. Compared to the simple ligation the invagination of the stump aim to provide an extra safety measure for the prevention

of postoperative complications, but the study demonstrated that in cases of non-complicated appendicitis it increases the risks of postoperative ileus and does not decrease the wound infections rate.

Gravante G, Yahia S, Sorge R, Mathew G, Kelkar A. Back to basics: A meta-analysis of stump management during open appendicectomy for uncomplicated acute appendicitis. *World J Surg Proced* 2013; 3(3): 47-53 Available from: URL: <http://www.wjgnet.com/2219-2832/full/v3/i3/47.htm> DOI: <http://dx.doi.org/10.5412/wjsp.v3.i3.47>

## INTRODUCTION

In recent years the combined advantages of better diagnosis and reduced surgical trauma have progressively favoured the laparoscopic appendicectomy (LA) over open appendicectomy (OA) for the treatment of acute appendicitis. In numerous studies and meta-analyses LA has achieved less postoperative pain, reduced hospital stay and faster return to normal daily activities compared to OA at the cost of longer operating times<sup>[1-3]</sup>. Despite these positive results OA is still frequently performed worldwide: 34% of appendicitis patients receive OA in the United Kingdom<sup>[4]</sup>, 45% (university teaching hospitals) to 75% (district general hospitals) in Ireland<sup>[5]</sup>, and more than 50% in Italy<sup>[6,7]</sup>. Additionally, OA is still necessary when LA requires conversion to an open approach (*i.e.*, dense adhesions, diffuse peritonitis, difficulties in excision of the appendix due to perforation)<sup>[8]</sup>, or in special circumstances such as pregnancy where the avoidance of the pneumoperitoneum and CO<sub>2</sub> systemic absorption decrease the rate of fetal loss<sup>[9]</sup>.

One of the historical controversies of the open technique involves the management of the appendiceal stump following removal of the appendix. A long stump may produce recurrences (appendiceal stumpitis)<sup>[10]</sup>. While an inadequate closure contaminates the abdominal cavity with fecal material (fecal fistula). In both cases, the postoperative outcome is endangered and re-operations with bowel resections may become necessary. Two approaches have been described over the years for the management of the appendiceal stump during OA. The first and simplest approach is the simple ligation (SL), described in 1884<sup>[11,12]</sup>. The second consists in the ligation and invagination of the stump (SI) in the cecum<sup>[11,12]</sup> by a purse-string suture or a Z-stitch<sup>[13-18]</sup>. This was introduced to secure the stump in the bowel lumen so that any perforation or leakage would directly drain inside the gut and not in the abdominal cavity.

Both approaches have been compared in numerous trials for their ability to prevent postoperative infections, ileus and other complications but results from single studies have been contrasting. In the present article we decided to conduct a meta-analysis on those trials to evaluate the influence of SL and SI on the occurrence

of postoperative complications following OA.

## MATERIALS AND METHODS

The meta-analysis has been reported according to the QUORUM and MOOSE guidelines<sup>[19,20]</sup>.

### Study selection and data extraction

Included articles were (1) randomized controlled trials (RCTs) that (2) focused on the technique for stump management during OA for (3) uncomplicated acute appendicitis. We defined a randomized trial as one in which patients were assigned prospectively to SL or SI by a random allocation. We excluded those studies that (1) focused on complicated appendicitis or those that (2) involved complicated and uncomplicated cases without differentiation of the results between the two groups. Furthermore we excluded (3) retrospective case-control studies, (4) commentaries, (5) historical technical articles, and (6) trials involving LA.

English and non-English language studies were searched and selected in the PubMed, EMBASE and Cochrane Library databases. No time limits were used. Key words used were appendicectomy, ligation, invagination, stump, complications. Articles were searched by two Authors (Gravante G, Yahia S) and classified according to those based on uncomplicated appendicitis (inflamed or suppurative appendix), complicated appendicitis (gangrenous or perforated appendix) or both. Potentially relevant studies were identified by the title and the abstract and full papers were obtained and assessed in details. The analysis of the references list allowed also the retrieval of a further pool of articles that were collected and assessed.

The methodological quality of studies retrieved was assessed independently according to the Jadad Score<sup>[21]</sup>. Briefly, studies were scored according to the presence of three key methodological features of randomization, blinding and accountability of all patients, including withdrawals and the score ranged from 0 to 5: those that received a score of four or five were considered as high-quality studies while those with a score equal to or less than three were of low quality. A specifically designed data form was used to collect all relevant data, including details of the experimental design, patients' demographics, technical aspects, outcome measures and complications. The outcome of the meta-analysis was to find eventual differences in the incidence of postoperative ileus and wound infections between the two techniques of stump invagination (SL *vs* SI).

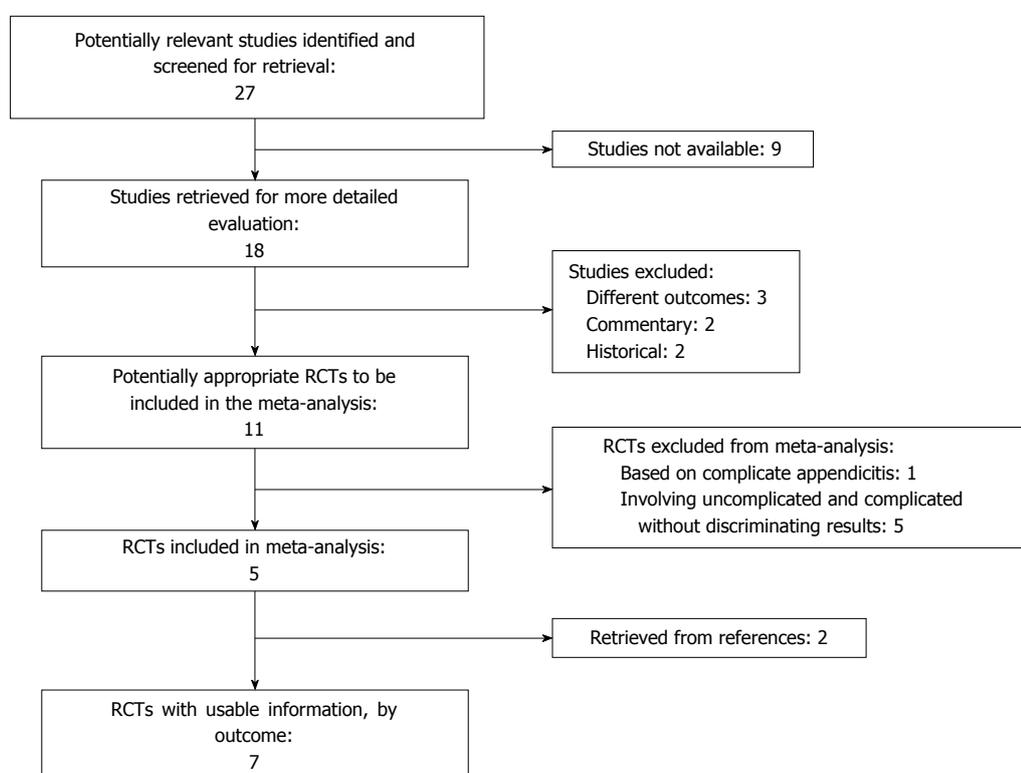
### Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences Windows version 15.0 (SPSS, Chicago, Illinois, United States) and the Meta-analysis with Interactive eXplanations (MIX-version 1.6) program. Descriptive statistics for qualitative variables was performed with occurrences and relative frequencies,

**Table 1** Characteristics of studies examined *n* (%)

Ref.	Stump closure	<i>n</i>	Age (yr)	Sex (male)	Jadad score <sup>[21]</sup>	Postoperative ileus	Wound infections	Postoperative pyrexia	Postoperative vomiting
Watter <i>et al</i> <sup>[12]</sup>	SL	44	18 (5-43)	21 (48)	1	-	8 (18.2)	-	-
	SI	59	22 (6-46)	29 (49)		-	11 (18.6)	-	-
Chaudhary <i>et al</i> <sup>[13]</sup>	SL	382	-	213 (56)	1	6 (1.6)	21 (5.5)	-	-
	SI	295	-	157 (53)		15 (5.1)	19 (6.4)	-	-
Jamal <i>et al</i> <sup>[23]</sup>	SL	40	23 ± 9	-	1	3 (7.5)	6 (15.0)	-	-
	SI	40	21 ± 6	-		11 (27.5)	9 (22.5)	-	-
Khan <i>et al</i> <sup>[24]</sup>	SL	50	24 ± 8	35 (70)	1	0	2 (4.0)	10 (20.0)	-
	SI	50	24 ± 9	32 (64)		1 (2.0)	3 (6.0)	15 (30.0)	-
Reza <i>et al</i> <sup>[25]</sup>	SL	184	27 ± 14	129 (70)	1	3 (1.6)	8 (4.2)	-	-
	SI	177	26 ± 13	124 (70)		8 (4.6)	7 (4.0)	-	-
Minhas <i>et al</i> <sup>[26]</sup>	SL	30	25 ± 2	17 (57)	0	0	2 (6.7)	-	3 (10.0)
	SI	30	25 ± 3	16 (53)		3 (10)	4 (13.3)	-	8 (26.7)
Chalya <i>et al</i> <sup>[22]</sup>	SL	43	24 ± 12	20 (47)	2	1 (2.3)	1 (2.3)	2 (4.7)	1 (2.3)
	SI	44	26 ± 15	21 (48)		5 (11.4)	2 (4.5)	3 (6.8)	2 (4.5)

SL: Simple ligation; SI: Stump invagination.



**Figure 1** Flow-chart of the study selection process. RCTs: Randomized controlled trials.

those for continuous variables with the mean and standard deviation if parametric or median and range if non-parametric. Clinical outcomes and complications of patients in the SL and SI groups were evaluated with common tests used in meta-analyses:  $\chi^2$  test or Fisher's exact test for categorical variables. The weighted odds ratio (OR) for the occurrence of complications between SL and SI was also calculated. The model used for the meta-analysis was the fixed-effect and the weighting method was the Mantel Haenszel. Heterogeneity was assessed with the funnel plots and the Bartlett's test. Results were considered significant if the probability of

chance of occurrence was less than five percent ( $P < 0.05$ ).

## RESULTS

At the end of the selection process only seven articles met the inclusion criteria<sup>[12,13,22-26]</sup> (Figure 1, Table 1) with 1468 patients presented, 773 in the SI and 695 in the SL group. One study only reported operating times, which were longer for the SI ( $45.3 \pm 36.1$  min) compared to the SL group ( $30.6 \pm 33.4$ )<sup>[22]</sup>. Postoperative complications consisted in wound infections ( $n = 103$ ; 7%)<sup>[12,13,22-26]</sup>, il-

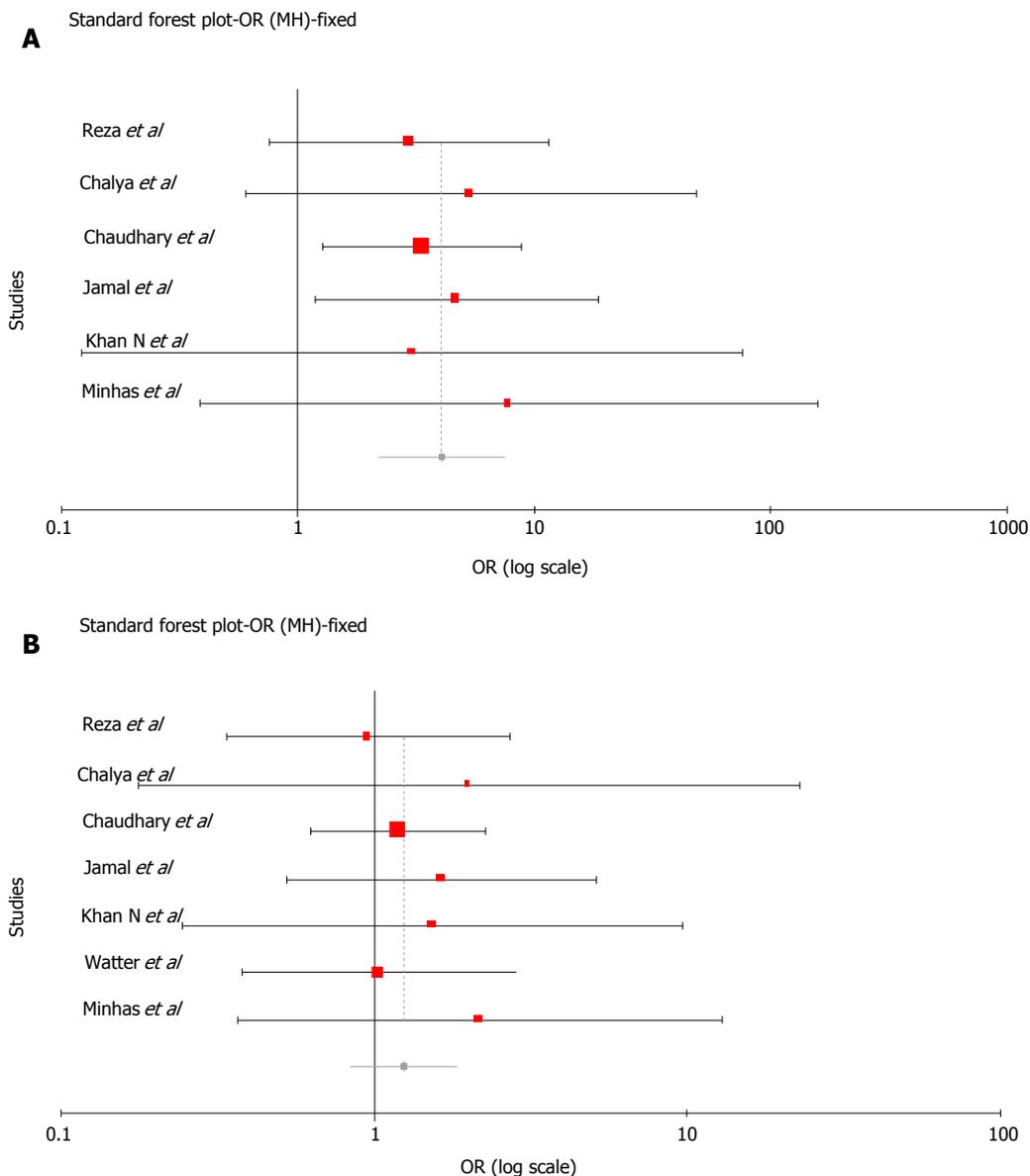


Figure 2 Forest plot graph showing results on the analysis of postoperative among simple ligation and stump invagination. A: Ileus; B: Wound infections.

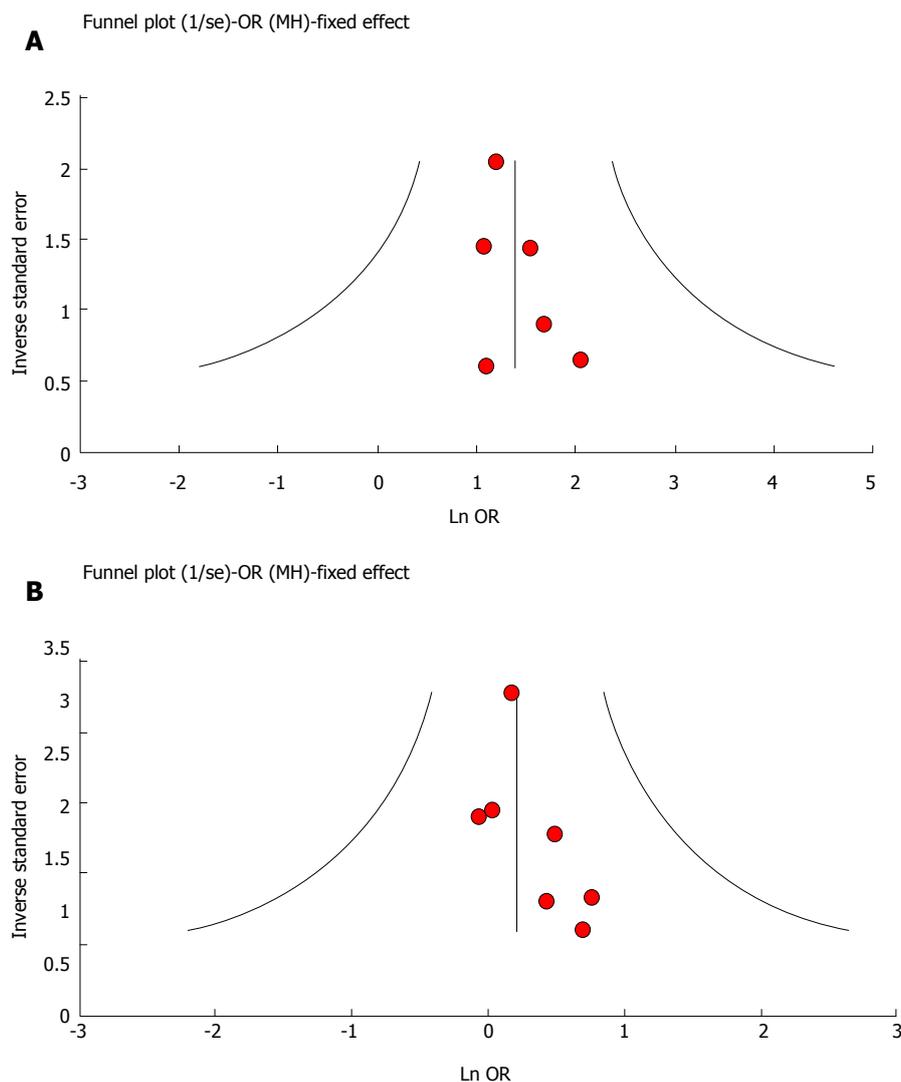
eus ( $n = 56$ ; 4%)<sup>[13,22-26]</sup>, pyrexia ( $n = 39$ ; 2%)<sup>[22,24]</sup>, vomiting ( $n = 14$ ; 1%)<sup>[22,26]</sup>, obstructions from adhesions ( $n = 1$ ; 0.1%)<sup>[12,13,22]</sup>. No cases of peritonitis<sup>[13,22-24,26]</sup>, fecal fistulas (stump leaks)<sup>[24-26]</sup>, abdominal abscesses<sup>[12,13,22-26]</sup> or wound dehiscences<sup>[25]</sup> were reported.

Six studies reported data on postoperative ileus<sup>[13,22-26]</sup>. In all cases this resolved within 72 h from the operation. The incidence was 0%-7.5% in the SL group and 2.0%-27.5% in the SI group (Table 1). The analysis of pooled data showed that SL increased the risk of postoperative ileus of four times compared to SI (OR: 4.06; 95%CI: 2.14-7.70;  $P < 0.0001$ ) (Figure 2A). Seven studies reported data on wound infections<sup>[12,13,22-26]</sup>. The incidence was 2.3%-18.2% in the SL group and 4.0%-22.5% in the SI group (Table 1). The analysis of pooled data showed no significant differences in the risk of wound infections between SL and SI (OR: 1.24, 95%CI: 0.83-1.87;  $P = 0.30$ ) (Figure 2B). The results of both complications

were homogeneous as outlined by the funnel plots that were highly symmetrical ( $Q$  value for heterogeneity of postoperative ileus  $P = 0.17$ ;  $Q$  value for heterogeneity of wound infections  $P = 0.98$  (Figure 3).

## DISCUSSION

Since the introduction of appendicectomy the treatment of the appendiceal stump has been a crucial step to determine the outcome of the operation. The proper management of the stump is important to prevent serious postoperative complications such as fecal contamination and peritonitis. After the initial introduction, the SL approach was considered not sure enough by some. Authors for an adequate closure of the stump, therefore, the invagination method was performed to avoid leaving open mucosa free in the peritoneal cavity and to favour the serosa-to-serosa contact that was believed neces-



**Figure 3** Funnel plot graph showing heterogeneity analysis on postoperative among simple ligation and stump invagination. A: ileus; B: Wound infections.

sary for a proper healing. SI became fashionable at the end of the last century since it was thought to prevent adhesions (by seroserosal healing) and stump blowout (especially when the base did not seem healthy enough to support the SL approach), or at least contain it, as the leak would drain into the cecum. Theoretical advantages of SI over SL included better control of stump hemorrhages, double secure closure of the cecal wall, reduced chances of peritoneal contamination from an infected stump and reduced risk of postoperative adhesions by minimizing the extent of raw surfaces<sup>[18]</sup>. However, a word of caution went out as the purse string technique was accused of increasing the risk of ischemia around the SI closure. Therefore, SL was indicated only in those patients where a severe inflammation and induration of the cecum could have rendered the SI approach too dangerous<sup>[27]</sup>. At the same time the SI approach can produce peculiar complications such as intramural abscesses and erosion of the cecal wall<sup>[28,29]</sup>, or fecal fistulas from reduced blood supply to the cecal wall and local ischemia<sup>[30]</sup>. Furthermore, in the long-term it can simulate a

cecal polyp on radiological imaging and potentially lead to unnecessary invasive tests in the screening of bowel cancers<sup>[27,31,32]</sup>.

In order to select only articles with homogeneous and comparable group of patients, we included in our meta-analysis only uncomplicated cases of appendicitis. The incidence of postoperative ileus in perforated appendicitis is between 28%-50%<sup>[33]</sup>, higher than in uncomplicated appendicitis<sup>[34]</sup>, because local inflammation and infection are major contributors. Therefore, the analysis of patients with complicated appendicitis could have biased the results achieved because the risk of ileus could have been higher in the complicated group *vs* the uncomplicated one. Results of the meta-analysis show that the addition of the invagination to the classic direct closure is associated with an increased risk of postoperative ileus by four times in patients with no other risk factors. Numerous hypotheses could explain the ileus pathogenesis following SI but none of them was adequately investigated experimentally. In the only study that reported the data SI took longer, a possible cause of

postoperative ileus. Additionally, the greater manipulation necessary for the invagination, or the cecum extraction through the incision to make the SI possible, could also be responsible for a serosal damage potentially combined with local ischemia. A larger incision might be necessary to perform the SI, another potential cause of postoperative ileus. Finally, the anatomical trauma on the bowel peristaltic waves deformed by the seromuscular purse-string suture or the Z-stitch, or the longer manipulation of the intestine to perform this additional step could also contribute to it.

The SI did not seem to produce specific advantages over SL regarding the other postoperative complications. Wound infection rates were similar among groups and no further comparative analysis was possible for the remaining complications due to the paucity of studies available that reported on them and the extremely low incidences (*i.e.*, peritonitis or fecal fistulas). Especially for these rare but important complications larger studies could be necessary to draw any definitive conclusions on the effects of SL or SI on its occurrence. Furthermore, appropriate studies involving only complicated cases (perforated or gangrenous appendix) should now evaluate the influence of the two techniques on postoperative complications in this higher-risk subgroup.

In the LA era results of our meta-analysis might seem less relevant, especially because cannot be applied to laparoscopic procedures in which the stump is usually fixed with endoscopic devices (*i.e.*, Endoloops, staples). However OA remains a milestone procedure during surgical training and is still performed frequently, in some hospitals by the majority of surgeons in at least 50% of cases<sup>16,71</sup>. For these reasons we focused our analysis on OAs and selected only those studies relevant for this purpose. However, one important limitation has to be acknowledged by the readers. All studies had a low Jadad score (less than 3) because of the inability to determine which methods of randomization were used in the original studies and the lack of double blinding of participants (the surgeons were always aware of the stump technique used)<sup>21</sup>. More specifically, the Jadad scores were 0 ( $n = 1$ ), 1 ( $n = 5$ ), and 2 ( $n = 1$ ). Despite the low quality of each RCT *per se*, studies were highly selected in order to present homogeneous and comparable groups of patients as showed by the funnel plots of the two complications. Therefore results of our meta-analysis should now form the theoretical background for future randomized studies in order to confirm the relationship found between the technique of stump closure and postoperative complications.

## COMMENTS

### Background

In numerous studies and meta-analyses laparoscopic appendectomy (LA) has achieved less postoperative pain, reduced hospital stay and faster return to normal daily activities compared to open appendectomy (OA) at the cost of longer operating times. Additionally, over OA is still necessary when LA requires conversion to an open approach.

### Research frontiers

The invagination of the stump (SI) approach can produce peculiar complications such as intramural abscesses and erosion of the cecal wall, or fecal fistulas from reduced blood supply to the cecal wall and local ischemia. Furthermore, in the long-term it can simulate a cecal polyp on radiological imaging and potentially lead to unnecessary invasive tests in the screening of bowel cancers.

### Innovations and breakthroughs

SI does not seem to prevent postoperative infective complications and is associated with an increased risk of ileus within the first 72 h in OAs for non-complicated appendicitis. Appropriate studies involving only complicated cases should now evaluate the influence of the two techniques in this higher-risk subgroup and possibly find a more specific indication for the SI technique.

### Applications

The meta-analysis should now form the theoretical background for future randomized studies in order to confirm the relationship found between the technique of stump closure and postoperative complications.

### Peer review

The authors describe a safer technique stump ligation compared to stump invagination. This is a well written paper with correct analysis.

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## Epidermoid cyst of intrapancreatic accessory spleen: A case report and literature review

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### Abstract

Epidermoid cyst of intrapancreatic accessory spleen is exceedingly rare; only 30 new cases have been reported in the English literature over the last 30 years. An accurate preoperative diagnosis was made in almost none of them because of the lack of reliable preoperative diagnostic methods. In this report, we present a case diagnosed with fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET). A 41-year-old female who had breast cancer was routinely followed up by measuring the concentration of tumor makers. An increasing level of serum carbohydrate antigen 19-9 was detected and a cystic lesion located at the tail of pancreas was found by ultrasonography. A whole body fluorine-18 FDG positron emission tomography was performed because of a high suspicion for either a malignancy of the pancreas or a recurrence of breast cancer. No increased uptake of FDG was noted and therefore the cystic lesion was considered as pancreatic benign disease. Because pancreatic malignancy could not be entirely ruled out, distal pancreatectomy and splenectomy were performed. The final pathological diagnosis

was epidermoid cyst of intrapancreatic accessory spleen (ECIAS). The FDG-PET findings matched the histopathology. A literature review reveals that the common clinical manifestations of ECIAS include asymptomatic findings on clinical examination, an occasional increase in tumor makers on laboratory results and occurrence only in the pancreatic tail. It is often misdiagnosed due to its extreme rarity and lack of a specific radiographic sign. There is no evidence of malignancy in ECIAS. Open or laparoscopic spleen preserving distal pancreatectomy is the minimally invasive procedure that would provide the best surgical management for epidermoid cyst of intrapancreatic accessory spleen.

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**Key words:** Epidermoid cyst; Accessory spleen; Epidermoid cyst of intrapancreatic accessory spleen; Fluorodeoxyglucose positron emission tomography; Epithelial cyst

**Core tip:** Epidermoid cyst of intrapancreatic accessory spleen (ECIAS) is extremely rare and an accurate preoperative diagnosis is almost never made. In this article, a case diagnosed with fluorodeoxyglucose positron emission tomography scanning is presented; it is also the first case from China. A literature review of the clinical characteristics of ECIAS is also given. We suggest that open or laparoscopic spleen preserving distal pancreatectomy is the minimally invasive procedure that would provide the best surgical management for ECIAS.

Lee CL, Di Y, Jiang YJ, Jin C, Fu DL. Epidermoid cyst of intrapancreatic accessory spleen: A case report and literature review. *World J Surg Proced* 2013; 3(3): 54-59 Available from: URL: <http://www.wjgnet.com/2219-2832/full/v3/i3/54.htm> DOI: <http://dx.doi.org/10.5412/wjsp.v3.i3.54>

## INTRODUCTION

Epidermoid cyst of intrapancreatic accessory spleen (ECIAS) is extremely rare. Since 1980 when Davidson *et al*<sup>[1]</sup> reported the first case, only 30<sup>[1-28]</sup> new cases have been reported in the English literature. Almost none of them were accurately diagnosed preoperatively because of the lack of reliable preoperative diagnostic methods. In this article, a case diagnosed with fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) scanning is presented, along with a review of the clinical characteristics of ECIAS experienced in our center and all the cases described in the English literature.

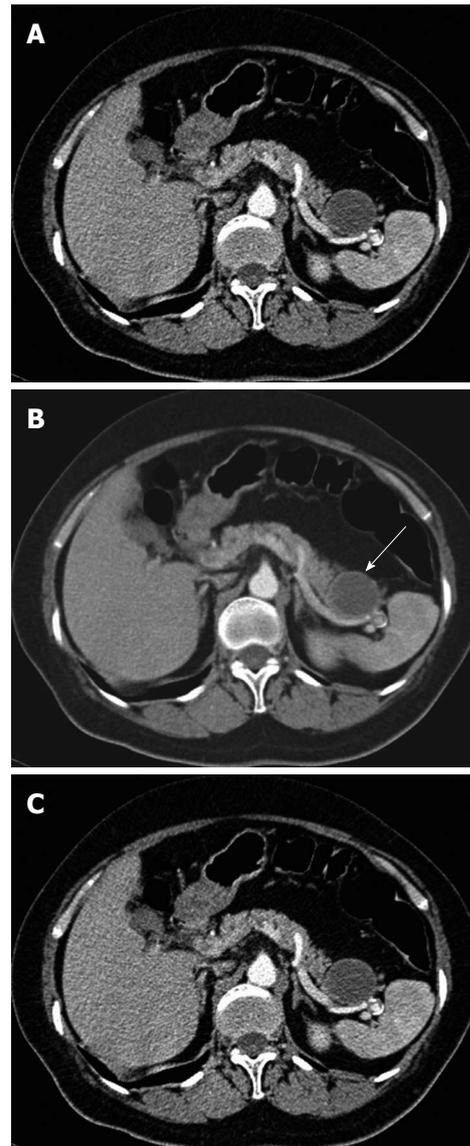
## CASE REPORT

A 41-year-old Asian female who had infiltrating ductal carcinoma of the breast was treated by modified radical mastectomy on June 9, 2008 and was then routinely followed up by measuring the concentration of tumor makers. A raised level of serum carbohydrate antigen (CA) 19-9 (68.57 U/mL, reference range, less than 37 U/mL) was detected on 7<sup>th</sup> April, 2009. Four months later, the CA 19-9 level had almost doubled to 120.49 U/mL. At the same time, abdominal ultrasonography indicated a cystic lesion located at the tail of pancreas. The patient was then referred to our department for more examinations.

The patient had no symptoms of gastrointestinal or abdominal discomfort. She had no history of abdominal trauma, pancreatic insufficiency or pancreatitis. Her family history was unremarkable. Physical examination showed no abnormalities. Except for a raised level of CA 19-9, the remaining blood tests, including carcinoembryonic antigen (CEA), CA125 and serum amylase, were within normal limits. A computed tomography (CT) scan of the abdomen revealed a 4 cm round cystic lesion anterior to the spleen near the tail of the pancreas with enhancement of the cystic wall (Figure 1). Based on the raised CA 19-9 level, pancreatic tail cyst and history of breast cancer, malignancy of the pancreas or recurrence of infiltrating ductal carcinoma of the breast was highly suspected.

A whole body fluorine-18 FDG PET (Siemens Biograph 64HD, Germany) was performed. After an overnight fast, the patient had an intravenous injection of 350 MBq FDG. The patient's blood glucose level was examined just before the administration of FDG to exclude the interference factor of hyperglycemia. After 40 min of injection, emission data was obtained and the images were analyzed. The results showed that no increased uptake of FDG was detected in the whole body, including the pancreatic tail cyst, previous operative area and axillary lymph nodes (Figure 2). Based on FDG PET images, the cystic lesion was considered as pancreatic benign disease. However, 6 mo later, the CA 19-9 level had doubled again to 259.67 U/mL. She was admitted to our hospital to undergo further treatment.

Since cystic pancreatic malignancy could not be en-



**Figure 1** Computed tomography scan of the abdomen revealed a 4 cm round cystic lesion (arrow) anterior to the spleen near the tail of the pancreas with enhancement of the cystic wall. A: Plain computed tomography (CT) scan; B, C: Enhanced CT scan.

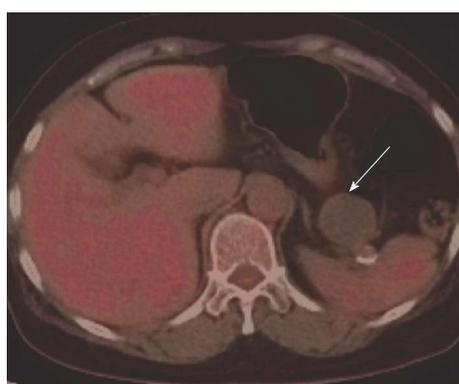
tirely ruled out, the patient underwent an exploratory laparotomy, which revealed a mass of 4 cm in diameter located in the tail of pancreas. Therefore, distal pancreatectomy and splenectomy were performed. The surgical specimen contained a 4.2 cm cyst in its greatest diameter, located near the pancreatic tail (Figure 3). On histopathological examination, the cyst was filled with reddish brown fluid. Microscopically, the cyst was covered with stratified squamous epithelium and was surrounded by normal splenic tissue (Figure 4). Moreover, immunohistochemical analysis showed a strong expression of cytokeratin but Ki67, P53, Vimentin and CD56 were not expressed. The final pathological diagnosis was ECIAS.

The patient was discharged on postoperative day 11 and her serum CA 19-9 value declined to a normal level 1 mo after surgery. During the past 2 years of follow up

**Table 1 Summary of all epidermoid cysts of intrapancreatic accessory spleen cases in the English literature from 1980 to 2011**

No	Ref.	Age/Sex	Symptoms	Preoperative diagnosis	CA 19-9 (U/mL)	Surgery	Site	Size (cm)
1	Davidson <i>et al</i> <sup>[1]</sup>	40/M	Weight loss Anorexia	Pseudocyst	NI	DPS	Tail	5.5
2	Morohoshi <i>et al</i> <sup>[2]</sup>	32/F	Left abdominal pain	Pancreatic cyst	WNL	DPS	Tail	6
3	Nakae <i>et al</i> <sup>[3]</sup>	37/F	Epigastric pain	Cystic neoplasm	NI	DPS	Tai	6.5
4	Tang <i>et al</i> <sup>[4]</sup>	38/M	Asymptomatic	Cystic neoplasm	WNL	DPS	Tail	2.3
5	Furukawa <i>et al</i> <sup>[5]</sup>	45/M	Asymptomatic	Cystic neoplasm	WNL	DP	Tail	2
6	Higaki <i>et al</i> <sup>[6]</sup>	46/F	Left back pain	Pancreatic malignancy	201	DPS	Tail	3
7	Tateyama <i>et al</i> <sup>[7]</sup>	67/F	Abdominal pain	Cystic neoplasm	WNL	DPS	Tail	3
8	Sasou <i>et al</i> <sup>[8]</sup>	49/F	Asymptomatic	Cystic neoplasm	WNL	DPS	Tail	4.3
9	Choi <i>et al</i> <sup>[9]</sup>	54/F	Epigastric discomfort	Cystic disease	NI	DPS	Tail	15
10	Tsutsumi <i>et al</i> <sup>[10]</sup>	51/M	Asymptomatic	Cystic neoplasm	WNL	DPS	Tail	2.5
11	Yokomizo <i>et al</i> <sup>[11]</sup>	38/M	Asymptomatic	Mucinous cystic neoplasm	410	DPS	Tail	2.7
12	Horibe <i>et al</i> <sup>[12]</sup>	48/M	Asymptomatic	Mucinous cystic neoplasm	53	DPS	Tail	2
13	Sonomura <i>et al</i> <sup>[13]</sup>	45/F	Epigastric pain	Cystic adenocarcinoma	159	DPS	Tail	3.5
14	Fink <i>et al</i> <sup>[14]</sup>	12/F	Fever	Infected abdominal cyst	NI	SPDP	Tail	10
15	Watanabe <i>et al</i> <sup>[15]</sup>	55/F	Postprandial epigastric pain	Mucinous cystic neoplasm	197	DPS	Tail	3
16	Kanazawa <i>et al</i> <sup>[16]</sup>	58/F	Asymptomatic	Mucinous cystic neoplasm	62	SPDP	Tail	2.5
17	Ru <i>et al</i> <sup>[17]</sup>	41/M	Asymptomatic	NI	NI	DPS	Tail	2.5
18	Itano <i>et al</i> <sup>[18]</sup>	40/M	Asymptomatic	ECIAS	WNL	DPS	Tail	4
19	Servais <i>et al</i> <sup>[19]</sup>	52/F	Asymptomatic	Pancreatic malignancy	NI	DPS	Tail	11.5
20	Gleeson <i>et al</i> <sup>[20]</sup>	32/F	Right upper quadrant pain	Cystic neoplasm	NI	DPS	Tail	1.5
21	Kadota <i>et al</i> <sup>[21]</sup>	57/F	Asymptomatic	Cystic neoplasm	WNL	DPS	Tail	6
22	Kadota <i>et al</i> <sup>[21]</sup>	70/F	Asymptomatic	Mucinous cystic neoplasm	48	DPS	Tail	1.7
23	Kadota <i>et al</i> <sup>[21]</sup>	37/M	Asymptomatic	Cystic neoplasm	647	SPDP	Tail	10
24	Itano <i>et al</i> <sup>[22]</sup>	67/M	Epigastric pain Weight loss	ECIAS	182	LA-DPS	Tail	1.5
25	Horn <i>et al</i> <sup>[23]</sup>	62/M	Left abdominal pain	NI	NI	DPS	Tail	4.8
26	Iwasaki <i>et al</i> <sup>[24]</sup>	36/F	Asymptomatic	Mucinous cystic neoplasm	79	LA-DPS	Tail	3.4
27	Yamanishi <i>et al</i> <sup>[25]</sup>	55/F	Asymptomatic	Mucinous cystic neoplasm	90	DPS	Tail	3.3
28	Khashab <i>et al</i> <sup>[26]</sup>	49/F	Abdominal pain	PNET	NI	LA-SPDP	Tail	2.3
29	Harris <i>et al</i> <sup>[27]</sup>	39/M	Asymptomatic	Cystic neoplasm	WNL	LA-DPS	Tail	2.5
30	Hong <i>et al</i> <sup>[28]</sup>	54/F	Abdominal discomfort	Pancreatic malignancy	WNL	SPDP	Tail	2
31	Present case	62/F	Asymptomatic	Mucinous cystic neoplasm	259	DPS	Tail	4.2

CA: Carbohydrate antigen; F: Female; M: Male; NI: Not informative; WNL: Within normal limit; DPS: Distal pancreatectomy with splenectomy; SPDP: Spleen preserving distal pancreatectomy; LA: Laparoscopic assisted.



**Figure 2** Fluorine-18 fluorodeoxyglucose positron emission tomography image showed no increased uptake of fluorodeoxyglucose (arrow) detected in the cyst of pancreatic tail.

she has been doing well.

## DISCUSSION

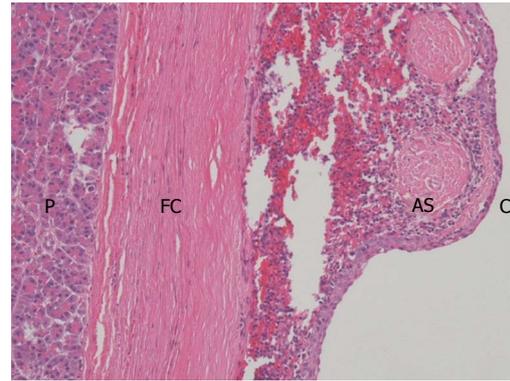
The frequency of accessory spleen is more than 10%

and nearly 20% of these are in or attached to the tail of the pancreas<sup>[5,29]</sup>. Cystic lesions are rare in the spleen and those most frequently found are parasitic<sup>[30]</sup>. Nonparasitic splenic cysts are histologically classified as either true or false cysts, according to the presence or absence of an epithelial lining on the inner surface<sup>[31]</sup>. The most common nonparasitic cysts in the spleen are epidermoid cysts<sup>[31]</sup>.

Only 30 cases of ECIAS have been reported in the English literature since the first one reported by Davidson *et al*<sup>[1]</sup> in 1980 (Table 1). ECIAS mostly occurs in middle-aged patients (average age, 47.4 years; range, 12 to 70 years). It is more common in females than males (female: male ratio, 19:12). All of the cases were found in the tail of pancreas and the size of cyst ranged from 1.5 cm to 15 cm (average, 4.35 cm). Tumor markers such as CEA and CA 19-9 (range, 48 to 647 U/mL) increase occasionally, and fall to the normal limit after excision of the lesion. It is also notable that 20 cases were from Japan, 6 from the United States, 2 from South Korea, 1 from the United Kingdom, 1 from Australia, and this is the first case from China.



**Figure 3** The cut section of surgical specimen contained a 4.2 cm cyst in its greatest diameter located near the pancreatic tail. C: Cyst; AS: Accessory spleen; P: Pancreas; S: Spleen.



**Figure 4** Microscopically, the cyst (C) was covered with stratified squamous epithelium and was surrounded by normal splenic tissue. A fibrous capsule (FC) separates the intrapancreatic accessory spleen (AS) from pancreas (P) (HE,  $\times 100$ ).

Rarity and nonspecific symptoms of ECIAS make it challenging for surgeons to accurately make a diagnosis prior to surgical treatment. More than half of the patients were asymptomatic and the others were admitted with complaints (9 with abdominal pain, 2 with abdominal discomfort, 2 with weight loss, 1 with left back pain, 1 with fever, and 1 with anorexia). Only 2 reported cases suspected the preoperative differential diagnosis of ECIAS<sup>[11,18]</sup>.

Several imaging techniques are available but the radiological features lack specificity to accurately identify the lesion. Abdominal ultrasonography and CT are usually the first tools which detect the lesion. However, images on abdominal ultrasound and CT scan look similar to pancreatic cystic neoplasm. This explains why most of the cases had the first preoperative clinical diagnosis of mucinous cystic neoplasm or pancreatic cystic neoplasm and were then followed by aggressive surgical management. Recently, Hu *et al*<sup>[32]</sup> found that the diagnosis of an ECIAS should be considered when enhancing the cystic wall of the lesion in the pancreatic tail similar to the spleen during multiphase scans in CT. The signal intensity of ECIAS is not consistent on magnetic resonance images (MRI). The cystic component occasionally shows low signal intensity on T1-weighted images and high signal intensity on T2-weighted images<sup>[9,16,24]</sup>, and sometimes it shows high signal intensity on both T1 and T2-weighted images<sup>[18,27]</sup>. Furthermore, Motosugi *et al*<sup>[33]</sup> suggested that in more than half of the cases of epidermoid cyst, heterotopic spleen surrounding the cyst can be detected and a noninvasive diagnosis is possible using super paramagnetic iron oxide enhanced MRI. Including the case we present, there are only 2 reported cases of ECIAS that have used fluorine-18 FDG PET scanning. Our findings showed no uptake of FDG and matched a maximum standard-uptake value (SUV) of 1.7 reported by Iwasaki, which means no evidence of malignancy<sup>[24]</sup>. However, scanning by FDG PET could not entirely rule out malignant cystic neoplasm because false-negative results of FDG PET have also been reported<sup>[34]</sup>.

On endoscopic retrograde pancreatography (ERP)<sup>[11,15,27]</sup>,

endoscopic retrograde cholangiopancreatography (ERCP)<sup>[26]</sup> and magnetic resonance cholangiopancreatography (MRCP)<sup>[16]</sup>, it has been shown that there are no communications between the cystic lesion and the pancreatic duct. Angiography shows a vascular mass<sup>[1]</sup> which is fed by caudal pancreatic arteries<sup>[13,16]</sup>. Endoscopic ultrasonography (EUS) suggests the existence of a cystic lesion<sup>[11,12,15]</sup> with septa surrounded by a solid area in the tail of the pancreas<sup>[16,20,26,27]</sup>. EUS elastography shows inhomogeneous hardness in an epidermoid cyst<sup>[26]</sup>. Fine needle aspiration (FNA) reveals fluid with elevated CA 19-9 and CEA and points towards a possibility of pancreatic malignancy<sup>[19,20,28]</sup>.

As listed in Table 1, 25 patients received distal pancreatectomy combined with splenectomy (DPS), 5 patients received spleen preserving distal pancreatectomy (SPDP), and only 4 of these were performed with laparoscopic assistant (LA). Based on our 3 years follow up and other reported cases (from 6 to 36 mo), there is no evidence of recurrence and metastasis<sup>[1,9,16,18,24,27,30]</sup>. ECIAS is benign and surgical treatment should be avoided when it is asymptomatic and small. However, resection should be considered for all cystic tumors of the pancreas because they are either malignant or have the potential for malignant degeneration<sup>[35]</sup>. SPDP and LA-SPDP would be the minimally invasive treatment of choice if the possibility of malignancy could be excluded. Laparoscopic pancreatic procedures are feasible and safe in patients with benign or low grade malignancies. They also minimize blood loss and morbidity, while also reducing hospital stay and promoting early recovery<sup>[36]</sup>.

In conclusion, the common clinical manifestations of ECIAS include asymptomatic findings on clinical examination, raised levels of some tumor makers on laboratory investigations and occurrence only in the pancreatic tail. It is often misdiagnosed due to its extreme rarity and non-specific radiographic findings. There is no evidence of malignancy in ECIAS. As minimally invasive procedures, SPDP and LA-SPDP would be the best surgical management. Nevertheless, it also goes without saying that ECIAS should not be forgotten as a differential di-

agnosis of pancreatic cystic lesion.

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