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THERAPEUTIC ADVANCES

Roux-en-Y augmented gastric advancement: An alternative technique for concurrent esophageal and pyloric stenosis secondary to corrosive intake

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Abstract

Select group of patients with concurrent esophageal and gastric stricturing secondary to corrosive intake requires colonic or free jejunal transfer. These technically demanding reconstructions are associated with significant complications and have up to 18% ischemic conduit necrosis. Following corrosive intake, up to 30% of such patients have stricturing at the pyloro-duodenal canal area only and rest of the stomach is available for rather less complex and better perfused gastrointestinal reconstruction. Here we describe an alternative technique where we utilize stomach following distal gastric resection along with Roux-en-Y reconstruction instead of colonic or jejunal interposition. This neo-conduit is potentially superior in terms of perfusion, lower risk of gastro-esophageal anastomotic leakage and technical ease as opposed to colonic and jejunal counterparts. We have utilized the said technique in three patients with acceptable postoperative outcome. In addition this technique offers a feasible reconstruction plan in patients where colon is not available for reconstruction due to concomitant pathology. Utility of this technique may also merit consideration for gastroesophageal junction tumors.

Key words: Corrosive strictures; Roux-en-Y augmented gastric advancement; Colonic interposition

Core tip: Selected patients with concurrent esophageal and gastric stricturing secondary to corrosive intake require colonic or free jejunal transfer. These technically demanding reconstructions are associated with significant conduit necrosis. An alternative technique we utilize stomach with Roux-en-Y reconstruction instead of colonic or jejunal interposition has been presented.

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INTRODUCTION

Corrosive upper gastrointestinal (GI) strictures still remain challenging in surgical practice[1]. Fortunately in majority of cases these either preferentially involve esophagus or stomach making surgical decision easier in favor of either esophagectomy or a form of gastric bypass[1,2]. However in approximately 6%-50% of the cases it involves both esophagus and stomach making reconstruction a technically demanding task with inherent potential of multiple complications[1-3].

Various surgical techniques with pros and cons have been advocated previously[4-6]. Colonic and free jejunal conduits remain a standard for such difficult cases with favorable outcomes however with significant graft necrosis rates of 2.4%-18% and 14.1% respectively[6-8]. Although proponents of colonic conduit have significant reasons in favor of its use however majority of the surgeons doing transhiatal resections of esophagus would agree that stomach is the most favorable conduit in terms of quality of blood supply and hence anastomotic leak rate[9]. In a study by Mansour *et al*[10], bowel interposition was associated with significant complications including 14.8% anastomosis leakage rate and 3% ischemic colitis rate. Similarly, Davis *et al*[6] and Moorehead *et al*[11] have previously shown that stomach is better in terms of postoperative ischemia than the colon. Stomach had lowest conduit ischemia rate of 0.5%-1% while jejunum had colon had ischemia up to 11.3% and 13.3% respectively[6-11]. Patients having colonic interposition however, have low rates of GERD postoperatively[12,13].

In a group of selected patients where the stomach has mere concentric pyloric stenosis along with esophageal involvement, many practicing surgeons would have questioned themselves per-operatively: "Can we employ this dilated well vascularized stomach instead of less vascular and technically more demanding colon or free jejunal transfer?" Here we describe alternative reconstruction plan which we have successfully employed in three of our patients with reasonable outcome.

OPERATIVE TECHNIQUE

A 33-year-old male patient presented with development of progressive dysphagia following history of caustic intake 3 years back. Endoscopy showed two significant strictures in upper GI tract, one 30 cm distal to cricopharyngeus and the second one in pyloric sphincter region. During last three years patient was managed by repeated dilatations of esophageal and pyloric strictures. Now he presented with strictures which were not dilatable due to extensive fibrosis in the said areas of the upper GI tract. A barium study showed esophageal stricture in the region of upper esophagus and the stomach was full of the contrast material without any distal evacuation (Figure 1). Another dilatation of the upper esophageal stricture was possible in up to 5 mm at best. Considering the above surgical reconstruction was planned. Peroperatively the stomach was massively dilated with only distal stricturing at the pyloric region. Stomach was mobilized with preservation of right gastroepiploic vessels. Distal gastrectomy was done and distal end of stomach was closed along with closure of the duodenal stump. Transhiatal esophagectomy was done and jejunum was fashioned as a Roux-en-Y loop which was anastomosed to the distal end of the mobilized stomach. The stomach was delivered into the chest the way that the gastrojejunal anastomosis of Roux-en-Y loop lays in hiatus. Neck dissection was done with predictable safety of recurrent laryngeal nerve. End to side triangulated gastroesophageal anastomosis was done with interrupted Prolene stitches (Figure 2). Postoperatively patient did well and was discharged on 18th postoperative day. We have employed the same technique in three of our patients, tow males and one female. All three patients had technically viable reconstruction. We lost one of the three patients on 12nd postoperative day due to Acinobacter positive hospital acquired pneumonia. We did not find any evidence to suggest a procedural failure or anastomotic leakage in this particular case. We have followed up the cases over a period of 19 mo in one case and 5 mo in other case with only one with mild dumping symptoms.

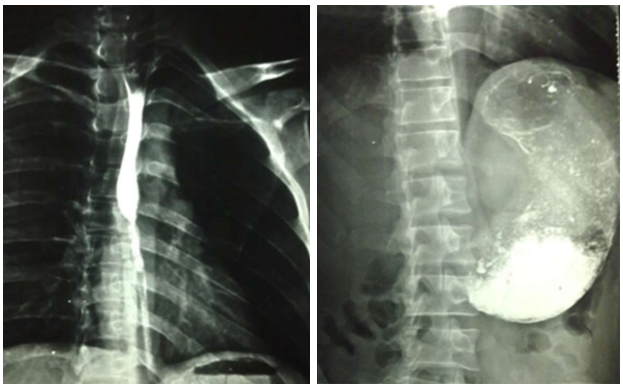

Figure 1 Barium study showing concurrent esophageal and gastric stenosis at pyloric canal level. Please note the distended stomach.

CONCLUSION

Corrosive intake depending upon the chemical composition of ingested liquid, area and time of contact can cause mild to severe stricturing of the upper GI tract[1-3]. Caustic soda preferentially affects the esophagus and the toilet cleaners in majority of cases affect the pyloric canal area[3]. Endoscopic dilatation or surgical replacement is quite effective treatment in majority of the cases[3]. In up to 50% percent of the cases there is concurrent involvement of esophagus and stomach leading to difficulty in reconstruction. In such cases, colonic interposition and free jejunal transfer still remain the gold standard conduits. Clearly such reconstructions are complex and

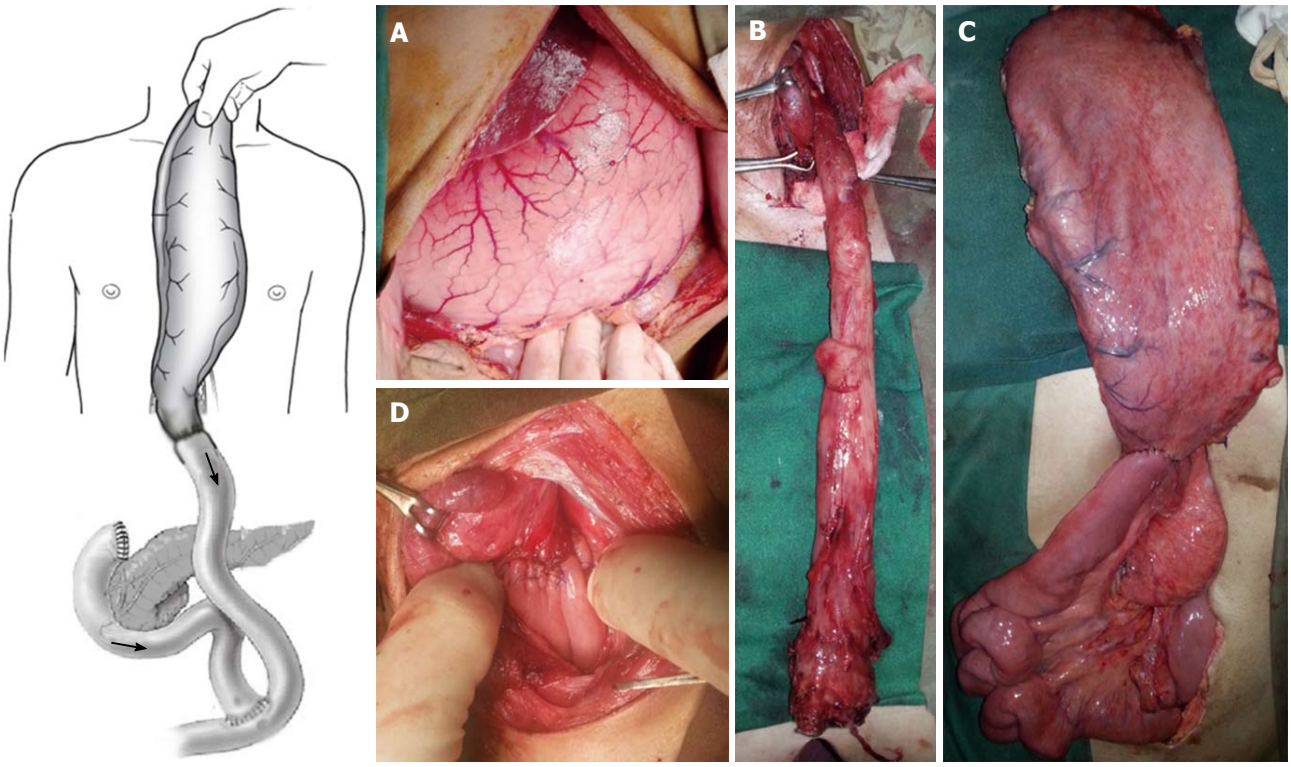

Figure 2 Roux-en-Y augmented gastric advancement with schematic reconstruction plan. A: Distended stomach; B: Esophageal specimen following standard transhiatal esophagectomy; C: Standard augmented gastric advancement reconstruction before esophageal anastomosis lying on the chest; D: Gastro-esophageal anastomosis in the neck.

are associated with higher morbidity and mortality[4]. In words of T. DeMeester, these reconstructions should be flawless because the impact of complications is not additive but logarithmic[14]. In experienced hands these reconstructions have favorable results however one of the frequently encountered problem is higher conduit necrosis rate in case of colon (2.8%-18%) and jejunum (14.1%) as opposed to stomach which has lower conduit necrosis rate (2.6%) and hence potentially lower leak rate[6-8].

In select group of the patients with concurrent involvement of esophagus and stomach where stomach is merely affected at the pyloric sphincter area, surgeons have previously avoided using stomach in favor of colonic replacement. Here we have demonstrated that stomach tube along with Roux-en-Y reconstruction can be a feasible alternative to the colonic or jejunal interposition in this select group of patients.

The interposition of stomach tube potentially adds specific superiority of excellent vascular supply and potentially reduced conduit necrosis rate and low anastomotic leakage rate, which are subject of our upcoming randomized trial. The Roux-en-Y reconstruction adds to the complexity of the reconstruction however it has three distinct advantages: Firstly, it gives significant length to the conduit (about 30-40 cm), which normally would be attained by liberal kockerization of the duodenum in a standard case of the transhiatal esophagectomy; secondly, it would function as a pyloromyotomy which is frequently done by the surgeons during transhiatal esophagectomy to prevent postoperative gastric stasis and thirdly, it potentially would reduce postoperative biliary reflux; and finally, this reconstruction plan can be of enormous value if the colon is not available for interposition due to some other concomitant reason like ulcerative colitis or Crohn's disease. Theoretically such reconstruction can also be beneficial in GE junction tumors, where we can achieve negative resection margins with limited resection of stomach.

RAGA like other constructions plans can be associated with potential complications. The preparation of the conduit requires special attention and preservation of blood supply as the conduit would be solely based on right gastroepiploic artery and its corresponding venous system as opposed to right gastroepiploic and right gastric arteries which are usually preserved during a standard transhiatal esophagectomy. This can potentially add to the probability of gastric erosions due to mucosal ischemia. Secondly the retention gastritis leading to postoperative gastric erosions are likely to be higher and hence patients may require use of proton pump inhibitors to prevent gastric erosions due to gastritis. One of our patient developed postoperative gastric erosions on 6th postoperative day owing to retention gastritis which was successfully treated with proton pump inhibitor infusion. A predicted comparison of the two said techniques has been tabulated in Table 1.

In select group of the patients of corrosive intake with concomitant involvement of esophagus and stomach where stomach is partially available for reconstruction, it

Table 1 Predicted potential comparison of the two techniques for esophageal replacement

	Colonic interposition	Roux-en-Y augmented gastric advancement
Vascular supply and conduit necrosis rates	Good; conduit necrosis rate 2.4%-18%	Potentially excellent; conduit necrosis rate 2%-5%
Mild mucosal ischemia	Ischemic colitis (3%)	Gastric erosions
Gastroesophageal and colo-esophageal reflux rates	Low (4%-5%)	Low
Conduit reservoir capacity	Acceptable	Better
Postprandial conduit fullness	Less	More
Probability of cervical esophageal anastomotic leakage rate	Low	Low
Probability of postoperative esophageal anastomotic stricture formation	Low	Higher
Potential complications	Higher probability of anastomotic leakage in colonic anastomosis	Higher probability of gastric erosions postoperatively due to retention gastritis

is feasible to utilize stomach for reconstruction in place of more complex colonic or jejunal transfer with favorable results. A randomized trial is warranted to compare this alternative reconstruction plan with gold standard colonic and jejunal transfer.

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ORIGINAL ARTICLE

Observational Study

Abdominosacral resection for locally recurring rectal cancer

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Abstract

AIM

To investigate feasibility and outcome of abdominal-sacral resection for treatment of locally recurrent rectal adenocarcinoma.

METHODS

A population of patients who underwent an abdominal-sacral resection for posterior recurrent adenocarcinoma of the rectum at the National Cancer Institute of Milano, between 2005 and 2013, is considered. Retrospectively collected data includes patient characteristics, treatment and pathology details regarding the primary and the recurrent rectal tumor surgical resection. A clinical and instrumental follow-up was performed. Surgical and oncological outcome were investigated. Furthermore an analytical review of literature was conducted in order to compare our case series with other reported experiences.

RESULTS

At the time of abdomino-sacral resection, the mean age of patients was 55 (range, 38-64). The median operating time was 380 min (range, 270-480). Sacral resection was performed at S2/S3 level in 3 patients, S3/S4 in 3 patients and S4/S5 in 4 patients. The median operating time was 380 ± 58 min. Mean intraoperative blood loss was 1750 mL (range, 200-680). The median hospital stay was 22 d. Overall morbidity was 80%, mainly type Ⅱ complication according to the Clavien-Dindo classification. Microscopically negative margins (R0) is obtained in all patients. Overall 5-year survival after first surgical procedure is 60%, with a median

survival from the first surgery of 88 ± 56 mo. The most common site of re-recurrence was intrapelvic.

CONCLUSION

Sacral resection represents a feasible approach to posterior rectal cancer recurrence without evidence of distant spreading. An accurate staging is essential for planning the best therapy.

Key words: Rectal cancer recurrence; Local recurrence; Sacral resection; Abdominosacral resection; Recurrent rectal cancer

Core tip: During the last years, great efforts have been invested by many authors to contribute in treatment of rectal cancer recurrence without evidence of distant spreading. The most difficult surgical problem is to perform an affective radical R0 salvage resection. However, with the introduction of sacral resection, consistent improvements have been achieved in recent years, particularly when local tumor relapse occurs in the posterior part of the pelvis, from the presacral to the retrovescical spaces. However, abdominosacral resection is a complex surgical procedure affected by several postoperative complications. For this reason, these patients should be treated into dedicated and specialized institutions.

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INTRODUCTION

Local relapse of rectal cancer is still one of the most complex and challenging issue concerning surgical oncology of the last years. Indeed, nowadays, rectal cancer relapses during the first two years in the 7%-30% of patients after receiving surgical resection[1-3]. In about half of these cases of relapse, the cancer remains confined in the pelvis without extraregional diffusion and most of the deceases associated to the disease are only due to local progression of it in the following periods.

The infiltration of the pelvic walls had represented up to recent years the main limitation to achieve a radical resection in the majority of relapsed rectal cancer cases. Nevertheless, the recent advancements in surgical techniques especially regarding posterior and anterior relapse resection, have widen up the spectrum of possibilities for effective curative treatment[4-6].

With the aim of contribute in the field, we present the review of the literature and report the implications from the experience obtained at our hospital, the National Cancer Institute of Milan, on abdomino-sacral resection (ASR) for pelvic posterior recurrences of rectal cancers expanding toward the sacral plane.

MATERIALS AND METHODS

Between 2005 and 2013 in our Unit 1324 patients affected with rectal cancer were treated with different surgical procedures. One hundred and sixty-two (12.2%) recurred in the pelvis in a period ranging from 10 to 38 mo after surgery. One hundred and fifty-four of these were considered candidates to a second surgical salvage approach. Different surgical procedures were applied accordingly with the extension, the site and the characteristic of the relapsing lesion.

In the same period, a population of ten patients underwent an ASR for recurrent adenocarcinoma of the rectum at the National Cancer Institute of Milano. These patients are included in the present study.

All the patients underwent, in the first place, a radical resection for the rectal cancer followed by at our Institution in combination with a total mesorectal excision (TME) and a local, nerve sparing, node dissection extended to the origin of low mesenteric vessels. Local recurrence is defined as the relapse of the tumour at the primary site confirmed by radiologically and/or histologically. In all cases the recurrence was mainly posterior and invading the presacral space or directly the sacral plane.

Indications for ASR exist when there is evidence of involvement of the sacrum detected by preoperative exams (Figure 1) or when there is a highly probability of it according with the pelvic local extension of local relapse.

Patients were staged preoperatively by a thoraco-abdominal computed tomography (CT)-scan, a pelvic magnetic resonance imaging (MRI), a positron emission tomography and, when possible, a colonoscopy. The study excluded patients whose recurrent rectal cancer was developed after a simple local excision or patients receiving a simple and limited coccyx resection.

Patients who had undergone resection of liver metastasis at initial surgery or before the diagnosis of local relapse were also considered suitable for ASR, given an adequately long distant metastasis-free survival period. All data are retrospectively collected and registered prospectively into an electronic database. Collected data includes patient characteristics, treatment and pathology of the primary rectal cancer, neoadjuvant therapy and operative details for recurrent tumor, pathology of recurrent tumor, length of hospital stay, peri-operative complications, blood transfusion needed and oncological outcome.

The macroscopic and microscopic assessments of the pathology specimens were done by a single pathologist at our Hospital. Pathological examination included histological type, number of lymph nodes harvested, number of metastatic lymph nodes, analysis of specimen resection margins and evaluation of sacral involvement. An R0

Figure 1 Radiological aspect of a local relapse infiltrating the coccix and lower sacral bone.

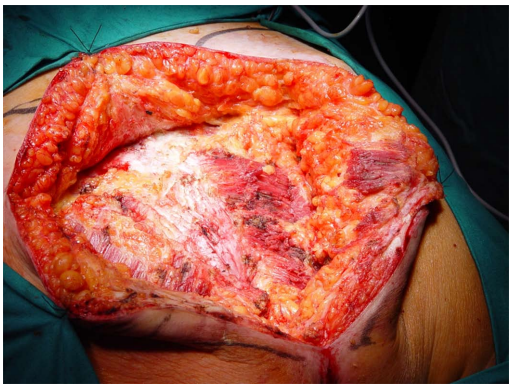

Figure 2 Preparation of skin flaps allows a complete exposure of maximus gluteus muscles.

resection is defined when no tumour cells are shown in the surgical resection margin. Pathologic stage information was assessed using the 7th edition of the American Joint Committee on Cancer TNM system.

Surgical complications and overall morbidity complications are defined as adverse events that occurred within a 30 d period after surgery. Surgical complications are staged according to the Claviene Dindo Classification.

After ASR, clinical and instrumental evaluations were performed every 6 mo for the first three years and one a year for the following years. Computed axial CT-scan and MRI surveillance, as well as carcinoembryonic antigen levels, were the exams performed to assess patient outcome.

Surgical procedure

The surgical procedure is divided in three following steps: Abdominal, perineal and sacral.

Under general anesthesia the patient was placed in Lloyd-Davies position (lithotomic position with flexed and abducted thighs). After placement of ureteral stents (4 cases) in order to identify the ureters, a midline laparotomy was performed. The dissection of common and external iliac vessels is started from the promontorium. The anterior area from the aortic bifurcation to the sacral promontory is exposed to have access to the anterior surface of the sacrum. The dissection is made down to the distal sacrum paying the upmost attention to avoid bleeding from the prescral space that in some case could be really important. The area from the common iliac artery to the bifurcation between the internal and external iliac arteries is exposed. The dissection is then made toward the presacral space along the parietal pelvic fascia, outside the original plane of dissection. During this phase the endopelvic fascia and pubo-prostatic ligaments can be identified bilaterally and divided using electric cautery to expose the levator ani muscle. Some Authors propose preventive ligation of internal iliac vessels along the sacral plane, in order to control the risk of bleeding during surgical dissection. However, this procedure was not routinely performed in our series because we believe that this approach is needed only in upper sacral resection due to a higher risk of local bleeding. The perineal phase corresponds to the typical procedure adopted in an abdomino-perineal resection performed for a primary rectal or anal carcinoma but avoiding to remove the surgical specimen through the perineal wound because the rectum and the other tissues will be removed "en block" with the sacrum during the following surgical steps. After formation of a terminal colostomy and closure of abdominal wound, the patient is placed in a prone position, with flexed and abducted thighs. Then, a posterior midline incision including the perineal lesion is made. The gluteus maximus muscles are dissected and detached from the sacrum in order to obtain a full exposure (Figure 2). The next step of this phase involves detaching the gluteal muscles, the sacrotuberous and sacrospinous ligaments and the piriform muscle from the sacrum to, subsequently, access the pelvic cavity. The surgeon inserts an index finger into the pelvic cavity from the lower edge of the sacroiliac joint and checks the dissected level of the anterior surface of the sacrum to determine the level of sacral amputation. The posterior wall of the sacrum is then osteotomized using a proper chisel and hammer at a stretch (Figure 3) scalpel and en-bloc resection of the tumor with the sacrum and the surrounding organs is accomplished (Figure 4). The canal is sealed with bone wax and fibrin sealant. A prolene mesh is placed anterior to the sacrum in order to close the perineal defect. A primary wound closure is usually performed. In some cases (two patients of the present series), perineal reconstruction is achieved with a pedicled musculocutaneous flap (Figure 5).

RESULTS

All ten patients included in this study (4 males and 6 females) underwent an anterior rectal resection as first operation at our hospital. Patients characteristics are reported in Table 1.

All the tumors were adenocarcinomas. Median distance from anal verge was 6 cm (range, 3-11). No patient received a pre-surgical neo-adjuvant therapy. In the pT3 cases this was mainly due to the bad clinical

Table 1 Patient characteristics and final outcome

Case	Age	Sex	First surgery	Pathological stage	DFS (mo)	OS[1] (mo)	OS[2] (mo)	Status
1	63	F	ARR	pT3 pN0 M0	103	216	111	DOD (local and lung recurrences)
2	60	F	ARR	pT2 pN0 M0	89	135	41	NED
3	62	F	ARR	pT2 pN0 M0	114	154	34	NED
4	53	F	ARR	pT2 pN1 M0	76	93	22	DOD (local recurrence)
5	46	M	ARR	pT3 pN1 M0 (R1)	12	54	41	DOD (local and lung recurrences)
6	64	F	ARR	pT2 pN0 M0	22	83	57	NED
7	57	F	ARR	pT3 pN2 M0	16	38	13	DOD (liver recurrence)
8	47	M	ARR and liver metastasectomy	pT3 pN1 M1 (liver)	29	47	14	DOD (local recurrence)
9	38	M	ARR	pT2 pN0 M0	49	110	57	NED
10	57	M	ARR	pT2 pN0 M0	17	56	29	NED

[1]OS from first surgery to last follow-up or death; [2]OS from ASR to last follow-up or death. NED: Non evidence disease; DOD: Dead of disease; DFS: Disease free survival; F: Female; M: Male; ARR: Anterior rectal resection; OS: Overall survival.

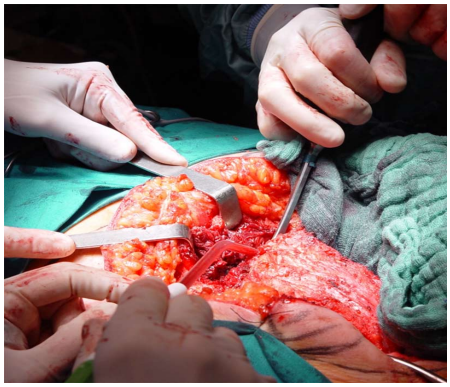

Figure 3 After the level of sacral transaction is identified the sacrum is osteotomized using normally a proper hammer and scalpel.

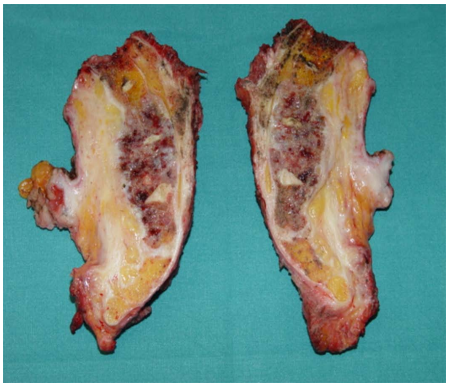

Figure 4 The figure shows a section of sacral specimen after S2 osteotomy.

status of the patients at the moment of diagnosis (occluding or bleeding lesions). All patients with histological nodal involvement or diffusion of disease into the perirectal fat received a post-operative CT-RT treatment in accordance to standardized schedules. The results of the pathological staging according to TNM are as follows: Stage Ⅰ (5 cases), stage Ⅱa (1 case), stage Ⅲa (1 case), stage Ⅲb (2 case) and stage Ⅳa (1 case). In our case series, all stage Ⅰ reported were high grade tumors with associated vascular and perineural invasion. Radicality was achieved during first surgery in all cases excepting one (R1, case 5).

Figure 5 Example of a complex plastic reconstruction of the sacral area by a pedicled musculocutaneous flap and a thigh thin graft.

At the time of ASR, the mean age of patients was 55 ± 9 years old, ranging from 38 to 64 years old. One out of ten patients was asymptomatic at presentation while 9 patients had increasing lower sacrococcygeal region pain. All patients were free of distant metastases at ASR and were considered eligible for a radical resection. In 6 patients surgery was performed 4 to 6 wk after the completion of a new chemo-radiation therapy. All patients underwent ASR according to the technique reported in the previous section. The median operating time was 380 ± 58 min (range, 270-480 min). In one case, a posterior colpectomy was needed due to a direct infiltration of posterior vaginal wall (Table 2). Sacral resection was performed at S2/S3 level in 3 patients, S3/S4 in 3 patients and S4/S5 in 4 patients.

In our case series, overall morbidity was 80%, *i.e.*, 5 presented postoperative type Ⅱ complications, 2 had type Ⅲb and one 1 a type Ⅲa complication according to the Clavien-Dindo classification, whereas the most frequent complication (7 patients) was sacral wound skin infection and dehiscence. List of main complications are reported in Table 2. No differences in complication rates between higher and lower sacral resection are detected. Mean intraoperative blood loss was 1750 mL (range, 200-6800 mL). Blood transfusion was administered to 5 patients (median 1 unit; range, 0-8 units) during the surgical procedure and to 5 patients (median 2 units,

Table 2 Treatments for recurrence and complications

	Pre-ASR CT-RT	Surgical procedure	Level of sacrectomy	Procedure lenght (min)	In-hospital stay (d)	Sacral involvement	Early complications (within 30 d)	Late complications (after 30 d)
1	Yes	ASR	S2-S3	380	11	Yes	Neurologic bladder dysfunction	Perineal wound infection and leakage
2	Yes	ASR	S4-S5	400	10	Yes	Pelvic abscess	Uterus/bladder prolapsus
3	Yes	ASR	S2-S3	420	24	Yes	Perineal wound leakage and Neurologic bladder	No
4	No	ASR	S4-S5	370	10	Yes	Perineal wound leakage	No
5	No	ASR	S3-S4	430	93	No	Uretral fistula, perineal flap necrosis and wound leakage	No
6	Yes	ASR	S3-S4	360	25	No	Perineal wound leakage	No
7	CT only	ASR and posterior colpectomy	S3-S4	360	8	No	Perineal wound leakage	Pelvic abscess and ileal fistula
8	No	ASR	S4-S5	480	11	Yes	No	No
9	Yes	ASR	S2-S3	270	9	No	No	No
10	Yes	ASR	S4-S5	330	15	No	Perineal wound infection	No

ASR: Abdomino-sacral resection; CT: Computed tomography.

range, 0-8 units) during the postoperative period. No in-hospital mortality was observed. The median hospital stay was 22 d (range, 8-93 d). Adjuvant chemotherapy was performed in 2 patients under suggestion of medical oncologists due to local extension of disease. Microscopically negative margins (R0) is obtained in all patients. Previous diagnosis was confirmed by histopathological examination. Sacral bone invasion was detected in 50% of the cases. Postoperative lymph node harvested are 4 ± 3 (range, 0-10). No node localizations are identified.

Survival

Five of 10 patient (50%) died at a median time from ASR of 38 ± 29 mo.

Overall 5-year survival after first surgical procedure is 60%, with a median survival from the first surgery of 88 ± 56 mo. Median disease free interval from first surgery to local recurrence is 39 ± 39 mo (range 12-114 mo). The most common site of re-recurrence was intrapelvic in 4 patients and two of these presented also lung metastases. One patient had liver metastasis alone.

DISCUSSION

The adoption of TME, described by MacFarlane *et al*[7] associated with preoperative radiation has improved surgical management of primary rectal cancer leading to a significant decrease of locoregional recurrence from 33% to less than 10%[8,9].

Despite these recent advancements, the occurrence of local relapse of rectal cancer is still quite frequent and produces a particular cancer situation characterized by the persistence of the disease in the pelvis without extraregional diffusion to distant sites. The specific behavior of this recurring tumor calls for the need of an advanced surgical or combined therapy in order to obtain a R0 resection in the pelvis.

Regretfully, these locoregional recurrences are often spread through the whole pelvis and a salvage surgery cannot be attempted. As a result many of them die in very bad conditions only for progression of the local relapse.

Several risk factors for the recurrence of rectal tumors have been studied. Some of them are related to tumor features, including tumor localization and pathological stage[10]. However, the main risk factors are linked to which and how surgical technique is performed, *e.g.*, incomplete resection of mesorectal fatty tissue and R1/R2 resection[11]. This explains why up to 90% of these relapses occur in an extra-bowel site and justify the difficulties of diagnosis and complexity of surgical resection for the adhesion-infiltration of these recurrences to the pelvic structures.

An accurate locoregional staging of a rectal relapsing tumor is essential for planning the best therapy[12-14]. A careful radiological examination provides information about the local extension of the disease, which is critical for the treatment decision-making process. A attentive evaluation of both tumor extent and anatomic planes is needed to determine a correct line during resection that is usually altered by the previous surgery and radiotherapy. Pelvic MRI and CT-scanning of the thorax and abdomen are the most used imaging modalities technique in pre-operative staging to evaluate whether or not curative surgery is feasible, although some authors underline a low sensitivity in accurate assessment of side wall involvement[15,16].

The definition of the site distribution of the relapse is crucial because, from a practical point of view, the factor that seems to play the upmost relevant role in evaluating the surgical resectability of these peculiar lesions is the anatomical sites of recurrences in the pelvis, irrespective in many cases, of the dimension and time of occurrence.

The relevance of the sites of recurrences is confirmed by the effort that has been dedicated to this issue in all the schemes of classifications proposed in the past recent

years[17-21]. Guillem *et al*[19] in 1998 classified relapses into four groups: Axial, anterior, posterior and lateral. Furthemore, Guillem's classification was adopted by Moore *et al*[21] to show that the likelihood of achieving a R0 resection is strongly correlated to the type of recurrence, reporting an higher R0 resection rate in axial and anterior lesions than in lateral and posterior ones. Others studies confirm that central or anterior localization of a relapse produced less complex difficulties due to the possibility of removing pelvic organs such as uterus, vagina or bladder by means of well defined procedures[22-24]. With respect to lateral and posterior relapses, a crucial role is played by the presence/absence of infiltration of structures such as iliac vessels, ureters, bony pelvis and great sciatic notch. Extensive infiltration of the pelvic sidewall is also a poor prognostic factor for the oncological outcome[25,26].

There are, anyway, bone sections that can be removed through complex surgical procedures with relatively limited functional consequences. This concerns, specifically, the middle and distal portion of the sacrum. Facing this technical problem there are many points that should be considered.

The first one is defining the level of bone transection to be done that must be at least 1-2 cm above the upper edge of the visible tumor, when possible. As a matter of fact, the level of resection in almost all published series remains as the key factor, influencing the neurological and intraoperative complications rate[27-29]. In all generality, there are not absolute limitation even to the resection of the whole sacrum from S1 to the coccyx, but this massive resection has been considered an alternative in rare situations, mainly due to the complexity of the procedure and to the functional consequences that may affect the patient against the expected limited benefit for the extension of the disease[30,31]. Regularly, the section of neural roots at S3 level has no main sequelae and it is well accepted. Moving to S2 the cutting of the second root could produce important modification of bladder function up to a complete loss of bladder motility. Upper sections produce remarkable lower limb motor disability and plantar flexion weakness and the need of a walking aid. Commonly, the level considered as acceptable limit for this type of surgery is the space between S2 and S3; this allows classifying as "high sacrectomy" all resections extended from the space between S2 and S3 and, as "low sacretomy", the procedures performed below this level[18,26,32]. Other authors suggest a different classification indicating as "high sacrectomy" resection from the intervertebral disk between S1 and S2, "middle sacrectomy" resections between S2 and S3, and "low sacrectomy" all the others below[33]. High sacrectomy are indeed followed by significant complications and morbidity. Bhangu *et al*[23] reports a 60% incidence of major complications for S1-S2 resection in comparison to a 27%-29% rate for S3 and S4-S5 sacrectomy. These data have been strongly confirmed in the recent years by many others studies[1,6,34-38].

A other relevant technical aspect concerns the intraoperative complications related to this difficult surgical procedure with special regards to the occurrence of sacral bleeding. Furthermore, in this case, the level of transaction is directly correlated to the incidence and severity of venous blood loss that, in some cases, could be not easily controlled, even become life threatening. Intraoperative bleeding during this surgery can be sudden and severe, and more often in patients who underwent preoperative radiotherapy, as frequently observed in these cases[39-42].

The postoperative period could also be compromized by different and complex problems. As indicated in several studies, perioperative complication rate is high, especially in upper sacral resections. Morbidity and mortality rate at three months after radical ASR for recurrence are reported to be 30% and 8%, respectively[1,6,34-36]. The most common complications occurring after sacropelvic resection are wound infections and dehiscences, pelvic abscesses and clinical complication, like as pneumonia, urinary tract infections and sepsis[6]. Between the 15%-58% local complication rate (wound dehiscence, pelvic sepsis, flap necrosis, *etc*.) are justified by a modified and affected wound healing processes of the perineal and sacral zone. This event is often due to a heavy and prolonged radiotherapy treatment applied to the perineum and to the sacral area following rectal resection[6,23,29,36]. All these occurrences explain as well the need to perform, in many of these cases, different and elaborated plastic reconstructions (mio-cutaneos or fascial-cutaneous flaps, rotation flaps or others) or more specific procedures when the site of the disease request further and more extended demolitions, *e.g.*, the vaginal or bladder areas[37].

Up to few years ago, the diagnosis of a local recurrence was strongly correlated to a poor prognosis with a mean 5 years overall survival not greater than 10%[26]. However, despite all these technical difficulties, the application of correct, enlarged and radical procedures have achieved positive and consistent clinical results in terms of local control of disease and improvements in the final outcome of these patients.

Recently, many authors have contributed to this topic, most of them confirming the safety of these surgical approaches when performed by dedicate and experienced groups of physicians. Several studies have demonstrated a 5-year global survival rates in local relapses surgery ranging between 25% and 60%[1,6,30-36], rate confirmed by our study in which out of 10 operated patients, all submitted a middle-distal resection of sacral body, 50% are currently alive with a 38 mo mean follow-up from ASR.

In order to increase radicality rate and have a better local control, neoadjuvant treatment may be useful, excepting patients who had previously received high dose radiotherapy for primary cancer or other diseases[43-45]. The role of intraoperative radiotherapy in the treatment of patients with pelvic relapses is still under discussion, notwithstanding several studies have shown the benefits in survival, especially in recurrent unresectable rectal tumors due to bone involvement. Some authors have

reported an increase survival rate of 15% when this modality of radiotherapy is performed[43].

Despite all these particular aspects, the key issue to be addressed when managing this kind of disease is the appropriate selection of treatment by the patient in order to achieve symptom control and even a curative treatment with acceptable morbidity. When presenting a surgical alternative to the patient, the specialist should take into account several prognostic factors including: The age and comorbities of the patient, disease free interval and features of the recurrence of tumor presented earlier.

The most recent studies, as well as the one presented here, are highlighting that partial sacrectomy can be considered a safe and feasible approach for recurrent rectal cancer but also that such a complex surgical resection must only be considered if a radical resection is technically possible[37,46-53] on the basis of a multidisciplinary team evaluation only into dedicated and specialized institutions.

The results obtained in our series are consistent with what reported in other studies and suggest that, currently, a 5 years survival up to 60% is achieved with an acceptable morbidity and minor functional failure, when partial sacrectomy, below S2 level, is performed.

COMMENTS

Background

Local relapses of rectal cancer remain one of the most complex and challenging aspects of surgical oncology of the last years.

Research frontiers

Recently, a consistent improvement has been achieved with the introduction of sacral resection for the patients with posterior pelvic extension of the recurrent tumor. Although abdominosacral resection could improve outcome in patients affected by rectal cancer recurrence, it is been reported to be a complex surgical procedure affected by several postoperative complications.

Innovations and breakthroughs

Reporting their experience, the authors would like to give a better comprehension of a challenging disease with some suggestions about its surgical management.

Applications

The results of this study support the previously published evidences, underling the indication to performed a carefully selection of patient to treat. Further researches are needed to improve surgical technique and patient selection.

Peer-review

This is an interesting article on a limited series of a surgical procedure which is not often performed for treatment of local recurrent rectal cancer. Authors report data from their own experience and also make a review of the literature on this subject.

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ORIGINAL ARTICLE

Prospective Study

Complete rectal prolapse in young Egyptian males: Is schistosomiasis really condemned?

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Abstract

AIM

To investigate the assumption that schistosomiasis is the main cause of rectal prolapse in young Egyptian males.

METHODS

Twenty-one male patients between ages of 18 and 50 years with complete rectal prolapse were included in the study out of a total 29 patients with rectal prolapse admitted for surgery at Colorectal Surgery Unit, Ain Shams University hospitals between the period of January 2011 and April 2014. Patients were asked to fill out a specifically designed questionnaire about duration of the prolapse, different bowel symptoms and any past or present history of schistosomiasis. Patients also underwent flexible sigmoidoscopy and four quadrant mid-rectal biopsies documenting any gross or microscopic rectal pathology. Data from questionnaire and pathology results were analyzed and patients were categorized according to their socioeconomic class.

RESULTS

Twelve patients (57%) never contracted schistosomiasis and were never susceptible to the disease, nine patients (43%) had history of the disease but were properly treated. None of the patients had gross rectal polyps

and none of the patients had active schistosomiasis on histopathological examination. Fifteen patients (71%) had early onset prolapse that started in childhood, majority before the age of 5 years. Thirteen patients (62%) were habitual strainers, and four of them (19%) had straining dating since early childhood. Four patients (19%) stated that prolapse followed a period of straining that ranged between 8 mo and 2 years. Nine patients (43%) in the present study came from the low social class, 10 patients (48%) came from the working class and 2 patients (9%) came from the low middle social class.

CONCLUSION

Schistosomiasis should not be considered the main cause of rectal prolapse among young Egyptian males. Childhood prolapse that continues through adult life is likely involved. Childhood prolapse probably results from malnutrition, recurrent parasitic infections and diarrhea that induce straining and prolapse, all are common in lower socioeconomic classes.

Key words: Rectal prolapse; Schistosomiasis; Young Egyptian males; Low socioeconomic status; Chronic straining

Core tip: Rectal prolapse in Western countries is mainly a disease of old women but in Egypt, the incidence of complete rectal prolapse was found to be highest among young males. Previous studies have attributed this to proctosigmoiditis caused by schistosomiasis, which is endemic in many rural areas of Egypt, and to which young males are more susceptible. In this study we disprove this assumption and shed light on other factors related to socioeconomic status that are more likely to be the cause of this disease distribution in the population.

Abou-Zeid AA, ElAbbassy IH, Kamal AM, Somaie DA. Complete rectal prolapse in young Egyptian males: Is schistosomiasis really condemned? *World J Gastrointest Surg* 2016; 8(12): 779-783 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i12/779.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i12.779

INTRODUCTION

Complete rectal prolapse is not uncommon. Unlike Western countries, the disease in Egypt predominantly affects young males. This has been attributed to intestinal schistosomiasis[1-3], a parasitic endemic disease in Egypt that predominantly affects young males causing periportal hepatic fibrosis, portal hypertension, and proctosigmoiditis. The latter is associated with thickening, edema and inflammation of the bowel wall as well as rectal inflammatory polyps, fibrosis and strictures. It has been postulated that the heavy weight of the rectum caused by rectal wall edema and polyps, the chronic dysentery and straining during defecation caused by rectal wall inflammation, and the pelvic floor myopathy caused by the general malnutrition that is frequently seen in schistosomiasis patients are the cause of complete rectal prolapse in this young Egyptian age group[1-3]. Despite those plausible explanations, it is not clear why complete rectal prolapse in Egypt is so infrequent when compared to other diseases associated with schistosomiasis such as liver cell failure, ascites, splenomegaly and hematemesis[4]. It is also not clear why other inflammatory and polypoidal diseases such as ulcerative colitis, Crohn's colitis and familial adenomatous polyposis are not known to be associated with complete rectal prolapse. Finally, it is not clear why the significant reduction in the incidence of schistosomiasis in Egypt that resulted from the aggressive national program for eradication of the disease was not reflected in a similar decrease in the incidence or change in the pattern of rectal prolapse in this country[5,6]. The present study is trying to answer the question: Is schistosomiasis really condemned as a cause of complete rectal prolapse in young Egyptian males.

MATERIALS AND METHODS

Patient recruitment

This prospective study included all male patients with complete rectal prolapse in the age group 18-50 years (n = 21, median age 23 years, range 18-45 years) who were admitted for surgery for their disease to the Unit of Colorectal Surgery, Ain Shams University Hospitals, Cairo, Egypt in the period between January 2011 and April 2014. Female patients in the same age group (n = 3), patients younger than 18 years (n = 2) or older than 50 years (n = 4) were excluded from the study.

Assessment methods

All patients were requested to fill out a questionnaire about duration of the prolapse, different bowel symptoms and any past or present history of schistosomiasis. All patients had flexible sigmoidoscopy and four quadrant mid-rectal biopsies documenting any gross or microscopic rectal pathology. Patients were categorized according to their socioeconomic class (Table 1)[7].

Ethical considerations

The nature and importance of the study were explained to all patients who were consented to participate in the study. The study was reviewed and approved by the IRB.

RESULTS

Twelve patients (57%) never contracted schistosomiasis and neither lived in a rural area nor worked in a job where they can come in contact with infested Nile water to contract the disease. Nine patients (43%) contracted the disease in the past and received timely proper treatment. None of the patients had gross polyps on sigmoidoscopy and none of the patients had evidence of

Table 1 Description of different socioeconomic classes

Class	Description
The lower class	Typified by poverty, homelessness, and unemployment
	Few individuals in this class finish their high school education
	They suffer from lack of medical care, adequate housing and food, decent clothing, safety, and vocational training
The working class	Minimally educated people who engage in "manual labor" with little or no prestige
	Unskilled workers in the class-dishwashers, cashiers, maids, and waitresses-usually are underpaid and have no opportunity for career advancement
	Skilled workers in this class-carpenters, plumbers, and electricians-may make more money than workers in the middle class, however, their jobs are usually more physically taxing, and in some cases quite dangerous
The middle class	Have more money than those below them on the "social ladder," but less than those above them
	The lower middle class is often made up of less educated people with lower incomes, such as managers, small business owners, teachers, and secretaries
	The upper middle class is often made up of highly educated business and professional people with high incomes, such as doctors, lawyers, stockbrokers, and CEOs
The upper class	The lower-upper class includes those with "new money," or money made from investments, business ventures, and so forth
	The upper-upper class includes those aristocratic and "high-society" families with "old money" who have been rich for generations. The upper-upper class is more prestigious than the lower-upper class
	Both segments of the upper class are exceptionally rich. They live in exclusive neighborhoods, gather at expensive social clubs, and send their children to the finest schools. As might be expected, they also exercise a great deal of influence and power both nationally and globally

CEOs: Chief executives.

Table 2 Distribution of gross appearance by sigmoidoscopy

Gross pathology	*n* (%)
Normal mucosa	10 (48)
Mucosal edema	8 (38)
Fine mucosal granularity + small superficial ulcers	3 (14)

Data are number of patients (and percentage of total).

Table 3 Distribution of histopathology of sigmoidoscopic biopsies

Histopathology	*n* (%)
Normal mucosa	8 (38)
Submucosal infiltration with chronic non-specific inflammatory cells	8 (38)
Features of solitary rectal ulcer	5 (24)

Data are number of patients (and percentage of total).

active schistosomiasis on histopathology. The detailed gross and histopathology results are shown in Tables 2 and 3.

Fifteen patients (71%) had early onset prolapse that started in early childhood (age < 5 years) in 11, or in late childhood or early teen ages (age between 5 and 15 years) in 4. The duration of prolapse in those patients ranged between 3 and 40 years (median duration 15 years). The median age of presentation in this group was 21 years (range 18-42 years). Six patients had late onset prolapse that started to appear in late teen ages or adulthood. The duration of prolapse in those patients ranged between 6 mo and 10 years (median duration 2 years). The median age of presentation was 34 years (range 21-41 years) (Figure 1).

Thirteen patients (62%) were habitual strainers (9 patients with long duration prolapse and 4 patients with short duration prolapse). Four patients (19%) reported straining since early childhood and four (19%) stated that prolapse followed a period of straining that ranged between 8 mo and 2 years. Two chronic strainers had stool incontinence after long period of straining; one of them was a habitual strainer since early childhood. Seven patients had recurrent prolapse when they first presented to our institution. Five of those patients were habitual strainers and all did not stop straining after their previous non-resection surgery. Three patients stated that the prolapse followed an anal operation (haemorrhoidectomy in 2 patients and lateral sphincterotomy in one patient). Two of those patients were habitual strainers.

Nine patients (43%) in the present study came from the low social class, 10 patients (48%) came from the working class and 2 patients (9%) came from the low middle social class.

DISCUSSION

Complete rectal prolapse in Western countries occurs most commonly in elderly females, the disease being attributed to damage to the pudendal nerves during childbirth, prolonged straining at stool, and/or anatomical considerations such as a wider pelvis[8]. The majority of complete rectal prolapse in Egypt occurs in young males. Previous studies from this country attributed this young male preponderance to intestinal schistosomiasis with its associated proctosigmoiditis, the disease being prevalent in 30% to 81% of prolapse patients in those studies[1-3]. Unlike previous results, none of the patients in the present study had symptoms of active schistosomiasis at the time of presentation, none had gross polyps or dysentery and none had histologic evidence of schistosomiasis on rectal biopsies. Despite this, the majority of patients with rectal prolapse that we see in our institution are young males, implying that predisposing factors other than schistosomiasis must be

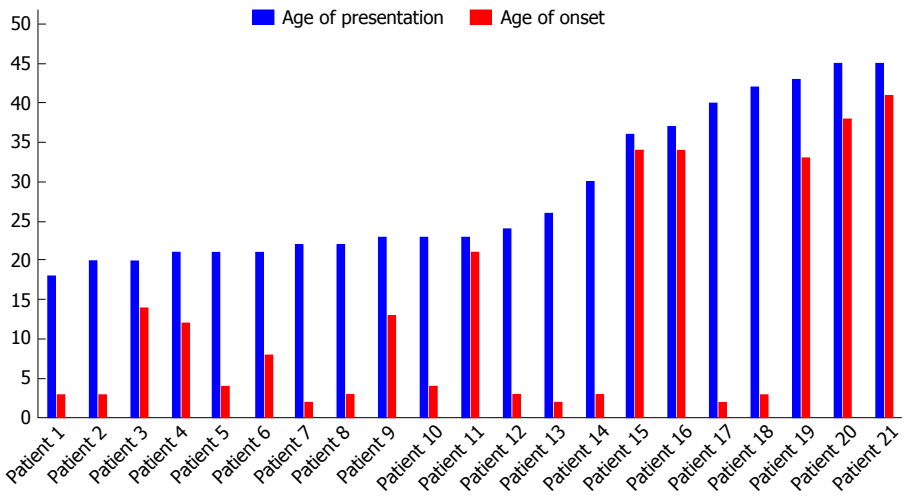

Figure 1 Age of presentation and age of onset of rectal prolapse in study subjects.

involved.

In the present study, 71% of patients had childhood or early teen age prolapse that continued through adulthood, 81% were chronic strainers at stools, and 19% started straining in their early childhood. It is therefore likely that early childhood prolapse that continues through adulthood together with chronic straining during defecation are important factors that predispose to occurrence of rectal prolapse in young Egyptian males.

Childhood rectal prolapse is uncommon in Western countries. The disease is seen more frequently in poor and developing countries where it is predisposed to by malnutrition and inadequate food hygiene[9]. Malnutrition aggravates the natural laxity of the rectal pelvic supports that is present in infants and children, and inadequate food hygiene is associated with parasitic infections of the gastrointestinal tract and chronic diarrhea that induces excessive straining during defecation and rectal prolapse[10]. Enterobiasis, Amoebiasis, Shigellosis, Giardiasis and infection with Hymenolepis nana are all common parasitic diseases that have been reported to cause diarrhea and complete rectal prolapse in children in developing countries[11-13].

Even in developing countries, a group of countries in which Egypt is categorized, malnutrition and parasitic infections are diseases that mainly affect the lower socioeconomic classes[14,15]. Population coming from lower socioeconomic classes suffer from poverty, unemployment, lack of high school education, lack of medical care and lack of adequate housing and food (Table 1). Ninety one percent of patients in the present study came from the low and working socioeconomic classes. Those patients are thus likely brought up in an environment in which they were malnourished and had recurrent infectious diarrhea that caused straining and complete rectal prolapse which continued to their adult life. Indeed, complete rectal prolapse is almost never seen in this age group in upper middle and high social classes in Egypt. The importance of malnutrition, diarrhea and straining in causing complete rectal prolapse in children was clearly demonstrated during the 1994 crisis in Rwanda when a high incidence of full-thickness rectal prolapse was noted among the refugee children in the south-west of the country, the prolapses arose as a result of acute diarrheal illness superimposed on malnutrition and worm infestation[16].

Other factors that might contribute to occurrence of complete rectal prolapse in the lower social classes are the lack of medical care for the children and the lack of high school education of the parents, the former indicates that infectious diarrhea that affects the children is unlikely to be properly treated and the latter can be reflected in bad potty training that has been shown in many studies to predispose to straining during defecation and complete rectal prolapse[11,17].

Three patients in the present study had their prolapse after different anal operations. Probably the anal complaint in those patients was a result of straining and that they also had occult prolapse when they had their surgeries, the anal procedure just unveiled the occult prolapse. Indeed, two of those patients were chronic strainers.

Finally, we believe the high incidence of schistosomiasis in prolapse patients in previous studies from Egypt was a mere coincidence because those studies came from centers which drain rural northern delta regions where schistosomiasis is prevalent. Human infection with Schistosoma requires continuous contact with fresh Nile water where cercaria, a stage of Schistosoma life cycle, live and can infect man by penetrating his skin. This scenario essentially occurs in farmers living in rural Nile delta regions where they contact Nile water all the time during irrigation of their fields. The center in which the present study was performed is located in Cairo and it drains urban regions where schistosomiasis is non-existent. This can explain the low incidence of schistosomiasis in the present study.

Schistosomiasis should no longer be considered the main culprit for the unconventional distribution of rectal prolapse among young Egyptian males. Other factors related to socioeconomic status such as malnutrition, recurrent infectious diarrhea and bad toilet training result

in habitual straining and hence increase incidence of childhood prolapse, which when combined with neglect of treatment result in continuance of the problem through adult life. We believe this to be the cause of the currently observed distribution of complete rectal prolapse in the population.

COMMENTS

Background

In Egypt, there is an abnormal distribution of rectal prolapse among young men although in Western countries the disease is usually more common in old women. Previous literature from the area has attributed this to the spread of schistosomiasis in rural areas of Egypt which causes proctosigmoiditis and hence-according to the literature - rectal prolapse.

Research frontiers

There were several findings that brought doubt to this assumption; eradication programs that caused great reduction in schistosomiasis infection, didn't similarly reduce the incidence of rectal prolapse and many of the patients with prolapse had no history of contracting schistosomiasis or even living in rural areas. This raised questions about the actual etiology for this distribution in Egypt.

Innovations and breakthroughs

Through analysis of history given by patients with rectal prolapse and assessment of possible risk factors, the authors found that socioeconomic status plays a great role in the epidemiological distribution of rectal prolapse among young males. Low socioeconomic status was associated with malnutrition, infectious diarrhea, bad toilet habits and neglect of proper treatment all of which contribute to the preponderance of rectal prolapse in this unusual subset of the population.

Applications

Identification of the actual factors causing rectal prolapse in young males is the first step in addressing the problem and directing efforts to improve conditions of lower social classes regarding sanitation, nutrition and proper treatment of various diarrheal illnesses. The authors have tried to shed some light on what the authors believe are the main causes of prolapse in young population and further studies are required in this area as proper management of etiological factors will reduce the incidence of the disease and its economic burden since young males are the main earners and source of income in many areas of Egypt.

Terminology

Authors believe there is no unusual terminology that requires further description.

Peer-review

Nice paper, well written. Very "small subject" but relevant and well analysed and discussed.

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SYSTEMATIC REVIEWS

Contemporary review of minimally invasive pancreaticoduodenectomy

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Abstract

AIM

To assess the current literature describing various minimally invasive techniques for and to review short-term outcomes after minimally invasive pancreaticoduodenectomy (PD).

METHODS

PD remains the only potentially curative treatment for periampullary malignancies, including, most commonly, pancreatic adenocarcinoma. Minimally invasive approaches to this complex operation have begun to be increasingly reported in the literature and are purported by some to reduce the historically high morbidity of PD associated with the open technique. In this systematic review, we have searched the literature for high-quality publications describing minimally invasive techniques for PD-including laparoscopic, robotic, and laparoscopic-assisted robotic approaches (hybrid approach). We have identified publications with the largest operative experiences from well-known centers of excellence for this complex procedure. We report primarily short term operative and perioperative results and some short term oncologic endpoints.

RESULTS

Minimally invasive techniques include laparoscopic, robotic and hybrid approaches and each of these techniques has strong advocates. Consistently, across all minimally invasive modalities, these techniques are associated less intraoperative blood loss than traditional open PD (OPD), but in exchange for longer operating times. These techniques are relatively equivalent in terms of perioperative morbidity and short term oncologic outcomes. Importantly, pancreatic fistula rate appears to be comparable in most minimally invasive series compared to open technique. Impact of minimally invasive technique on length of stay is mixed compared to some traditional open series. A few series have suggested

that initiation of and time to adjuvant therapy may be improved with minimally invasive techniques, however this assertion remains controversial. In terms of short-terms costs, minimally invasive PD is significantly higher than that of OPD.

CONCLUSION

Minimally invasive approaches to PD show great promise as a strategy to improve short-term outcomes in patients undergoing PD, but the best results remain isolated to high-volume centers of excellence.

Key words: Pancreatic adenocarcinoma; Periampullary malignancy; Pancreaticoduodenectomy; Minimally invasive surgery; Whipple

Core tip: In this contemporary review, we systematically review current literature regarding minimally invasive techniques and outcomes for pancreaticoduodenectomy. This review will be highly educational to providers-surgical and nonsurgical alike-who care for patients with resectable periampullary malignancies.

Dai R, Turley RS, Blazer DG. Contemporary review of minimally invasive pancreaticoduodenectomy. *World J Gastrointest Surg* 2016; 8(12): 784-791 Available from: URL: http://www.wjgnet.com/1948-9366/full/v8/i12/784.htm DOI: http://dx.doi.org/10.4240/wjgs.v8.i12.784

INTRODUCTION

Pancreaticoduodenectomy (PD) remains the only potentially curative therapy for periampullary malignancies, including, most commonly, pancreatic adenocarcinoma. Despite advances in minimally invasive techniques over the last 2 decades, the vast majority of PDs are still performed with the standard open technique that has evolved from the original Whipple procedure described in 1935[1]. Even with modern improvements in perioperative care, contemporary complication rates after open PD (OPD) range from 25% to 65%, and thus highlight the need for surgical innovation aimed at reducing perioperative morbidity[2-9].

In general, minimally invasive techniques have been shown to provide shorter postoperative length of stay, decreased postoperative pain, fewer wound complications, and quicker return to daily activities. Despite this evidence for the benefit of minimally invasive surgery across a broad array of surgical procedures, minimally invasive approaches to PD have not been widely adopted and remain confined to large tertiary referral centers with highly experienced surgeons[10,11]. PD is a highly complex operation with a steep learning curve. This complexity has led some to question whether the advantages of minimally invasive approaches, seen in other general surgical procedures, translate to PD. In this review, we evaluate the published literature to date on contemporary approaches to minimally invasive PD-including laparoscopic, robotic, and hybrid approaches-in regards to perioperative morbidity and short-term outcomes.

MATERIALS AND METHODS

Appropriate articles were identified by manually searching through PubMed and Google Scholar databases between January 1st, 2005 to January 1st, 2015, using "laparoscopic" or "robotic" or "minimally invasive" AND "pancreaticoduodenectomy" or "Whipple". Subsequent full-text papers were screened, and only the most recent publications from individual groups were used. We only included manuscripts that distinguished among or singularly published data from laparoscopic, robotic or hybrid PDs. Similarly, we only focused on studies which included greater than 5 patients, in order to assure the surgeon's experience with the technique. We only included studies which distinguished among laparoscopic, robotic or robotic assisted laparoscopic PDs (RALPDs).

Study variables included: (1) minimally invasive technique (laparoscopic, robotic, or hybrid approach); (2) number of patients; (3) age range; (4) body mass index (BMI) range; (5) American Society of Anesthesiologist physical status classification[12]; (6) estimated blood loss; (7) operative time; (8) length of stay; (9) pancreatic fistula rate; and (10) postoperative mortality. The data are represented as average ± SD, unless otherwise indicated in the text or table.

Average American Society of Anesthesiologist physical status classification (ASA) is used as a surrogate for an independent evaluation of how well the patient presents prior to the procedure[13]. The higher the score, the more complicated the patient, where ASA Ⅰ is defined as a normal healthy patient, and ASA Ⅲ is someone with severe systemic disease. Overall complication is defined, if available, as the number of patients with post-operative complications with a graded Clavien-Dindo classification (≥ grade Ⅰ)[14]. Postoperative mortality is defined as surgical-related deaths within 30 d of procedure.

Surgical techniques

This manuscript focuses on primarily three minimally invasive surgical techniques for PD. The first is laparoscopic PD (LPD), which uses laparoscopic instrumentation to dissect, extract, and reconstruct intestinal continuity[15]. Robotic PD (RPD) uses a robotic system (da Vinci Surgical System) in lieu of handheld laparoscopic instruments (Intuitive Surgical, Inc., Sunnyvale, CA)[16]. Finally, hybrid RALPDs uses both laparoscopic and robotic techniques for various steps in the PD, most commonly laparoscopic dissection and specimen extraction followed by robotic reconstruction[17].

RESULTS

LPD

Since its introduction by Gagner *et al*[18] in 1994, widespread adoption of LPD has been limited by a steep

Table 1 Laparoscopic procedures

Ref.	Year	Robotic, open, Lap, or RAL	No. of patients	Age of patients	BMI of patients	ASA classification	EBL (mL)	Transfusion (#)	Op time (min)	Conversion (#)	Overall complications (# of patients)	Panc fistula	Length of stay	Postop death
Asbun *et al*[19]	2012	Lap	53	62.9 ± 14.14	27.64 ± 7.16	2.73	195[1] ± 136	9[1]	541[1] ± 88	Counted as open	13	7	8[1] ± 3.2	3
Dulucq *et al*[21]	2006	Lap	25	62 ± 14	NR	1.39 ± 0.5	107 ± 48	3	287[1] ± 44	3	7	1	16.2 ± 2.7	1
Kendrick *et al*[22]	2010	Lap	62	66 ± 12	26	3	240	NR	368	3	11	NR	7	1
Palanivelu *et al*[23]	2007	Lap	42	61	NR	Only I and II	65	NR	370	0	8	3	10.2	1
Pugliese *et al*[20]	2008	Lap	19	64 ± 12	< 35	2.3	180 ± 55	0	461 ± 90	6	6	3	18 ± 7	0
Zureikat *et al*[16]	2011	Lap	14	69.8 ± 10.2	28.5	2.64	300	4	456[1]	2	9	5	8	1

[1]Indicates statistically significant compared to open procedures. RAL: Robotic assisted laparoscopy; BMI: Body mass index; ASA: American Society of Anaesthesiologists physical status classification; EBL: Estimated blood loss; NR: Not reported.

learning curve confounded by modest case volumes seen in most centers. Despite these challenges, LPD has clearly been shown to be technically feasible and is purported to have tremendous potential in improving patient outcomes. Six LPD studies without robotic components were analyzed, two of which directly compare laparoscopic with open techniques[16,19-23]. There were no distinct differences in the patient populations (Table 1).

In the two studies which compared LPD outcomes to matched open cases at the same institution, the authors reported advantages of LPD over OPD[16,19]. Asbun *et al*[19] noted that LPD had significantly less intraoperative blood loss ($P < 0.001$), reduced rate of transfusion ($P < 0.001$), length of hospital stay ($P < 0.001$), and length of intensive care unit stay ($P < 0.001$). Both Asbun *et al*[19] and Zureikat *et al*[16] noted that operative time was significantly higher for LPD, but there were no differences in overall complications, pancreatic fistula rate, or delayed gastric emptying.

There were no significant differences in oncologic outcomes in these two studies. Asbun *et al*[19] found that LPD had higher number of lymph nodes retrieved ($P = 0.007$), more favorable lymph node ratio ($P < 0.001$), less estimated blood loss, transfusions, and length of stay for laparoscopic procedures, while Zureikat *et al*[24] found no significant difference in R0 resection rate, lymph node harvest, and estimated blood loss, transfusions, and length of stay.

Of the four studies that examined only LPD, all found that LPD was safe and feasible[18,21-23]. Kendrick *et al*[22] reported that only 3 of the 65 patients enrolled in the study converted to OPD, and of the 62 patients who underwent LPD, 26 experienced post-operative morbidity, including pancreatic fistula ($n = 11$), delayed gastric emptying ($n = 9$), bleeding ($n = 5$), and deep vein thrombosis ($n = 2$). There was one postoperative mortality within 30-d of operation. Median operating time reported was 368 min (range 258-608) and median length of hospital stay was 7 d (range 4-69 d)[22].

Dulucq *et al*[21] reported three of the 25 patients enrolled in the study converted to OPD, and of the 22 patients who underwent unconverted LPD, seven patients experienced postoperative complications and one patient died of a cardiac event three days after an uncomplicated surgery. A mean of 18 ± 5 lymph nodes were retrieved for malignant lesions, and all resected margins were free. Only two patients with metastatic disease received adjuvant therapy. The mean hospital stay was 16.2 ± 2.7 d. Mean operating time was 287 ± 39 min[21].

Palanivelu *et al*[23] also reported 5-year survival rates for the 42 patients enrolled in the study. They found that after 5-years, 32% survival over all malignancies, 30.7% with ampullary adenocarcinoma, 33.3% for pancreatic cystadenocarcinoma, 19.1% for pancreatic head adenocarcinoma, and 50% for common bile duct adenocarcinoma. The study presented with similar perioperative statistics with 8 patients with comorbidities, including gastrojejunostomy obstruction, postoperative pancreatic fistula, postoperative bile leak, pulmonary complications, intraabdominal abscess, and deep vein thrombosis. Mean operating time was 370 min, with 13 mean lymph nodes harvested, and 65 mL mean of estimated blood loss[23].

Pugliese *et al*[20] found that of the 19 patients undergoing LPD, 6 patients required conversion to laparotomy, 3 for bleeding and 3 for difficulties in dissection. The study recorded no mortality, but noted that 3 of the converted PDs resulted in complications including bile leakage, hemorrhage, and pulmonary embolism. The mean operating time was 461 ± 90 min, and hospital stay of 18 ± 7 d. An average of 13 ± 4 (range 4-22) lymph nodes were harvested[18].

RPD

Robotic technology has many of the advantages ascribed to laparoscopic surgery by virtue of using laparoscopic ports and minimal incision size and was first reported by Giulianotti *et al*[25] in 2003. Robotic instrumentation

Table 2 Robotic procedures

Ref.	Year	Robotic, open, Lap, or RAL	No. of patients	Age of Patients	BMI of patients	ASA classification	EBL (mL)	Transfusion (#)	Op time (min)	Conversion (#)	Overall complications (# of patients)	Panc fistula	Length of stay	Postop death
Boggi *et al*[28]	2013	Robotic	34	60	24.4	2.29	220	4	597	0	19	13	23	0
Buchs *et al*[29]	2011	Robotic	44	63 ± 14.5	27.7 ± 5.4	2.5 ± 0.5	387[1] ± 334	10[1]	444[1] ± 93.5	2	16[1]	8	13[1] ± 7.5	2
Chan *et al*[31]	2011	Robotic	8	71.5	NR	NR	200	NR	478	1	5	3	12	0
Zhou *et al*[30]	2011	Robotic	8	64.4 ± 9.1	NR	NR	153.8[1] ± 43.4	NR	718.8[1] ± 186.7	0	2[1]	NR	16.38[1] ± 4.1	0

[1]Indicates statistically significant compared to open procedures. RAL: Robotic assisted laparoscopy; BMI: Body mass index; ASA: American Society of Anaesthesiologists physical status classification; EBL: Estimated blood loss; NR: Not reported.

provides 3-dimensional visibility, increased degrees of freedom, and improved ergonomics though possibly less haptic advantage[26,27]. Advocates of robotic surgery suggest that the advantages in robotics provide obvious benefits for complex procedures such as PD surgeries[28]. However there is little comparative data available to support the routine use of robotics over laparoscopy for pancreatic resections (Table 2).

This review describes four robotics experiences, of which two incorporated comparison studies with OPD[29-31]. Buchs *et al*[29] found that despite the RPD group having statistically significant older (63 years old RPD *vs* 56 years old OPD; $P = 0.04$) and heavier patients (BMI 27.7 RPD *vs* 24.8 OPD; $P = 0.01$), with a higher American Society of Anesthesiologist score (RPD 2.5 *vs* OPD 2.15; $P = 0.01$), when compared to OPD group, there were no significant differences in complications, mortality rates, and length of hospital stays between the two groups[29]. The study found that RPD surprisingly had shorter operative time (444 min *vs* 559 min; $P = 0.0001$), reduced blood loss (387 mL *vs* 827 mL; $P = 0.0001$), and higher number of lymph nodes harvested (16.8 *vs* 11; $P = 0.02$).

Similarly, Zhou *et al*[30] found that RPD group had longer operative times than OPD (718 min RPD *vs* 420 min OPD; $P = 0.011$), but less intraoperative blood loss (153 mL RPD *vs* 210 mL OPD; $P = 0.04$), fewer complications (25% RPD *vs* 75% OPD, $P = 0.05$), and decreased hospital stay (27.5 h RPD *vs* 96 h, $P = 0.000$). There was no significant difference in R0 resection rate between the two groups.

Boggi *et al*[28] reported for 34 patients undergoing RPD, the mean operating time was 597 min (range 420-960 min) and mean intraoperative blood loss was 220 mL (range 150-400 mL), with 4 patients requiring blood transfusions. Nineteen of the 34 patients in the study developed postoperative complications (utilizing the Clavien-Dindo classification), five of which had a classification of Ⅲ or higher. The mean number of lymph nodes retrieved in the study was 32 (range 15-76). Thirty-day mortality was 0%[28].

Chan *et al*[31] reported 55 patients undergoing robotic hepatobiliary and pancreatic surgeries, of which eight were pancreaticoduodenectomies. Of the patients undergoing pancreatic resections, Chan *et al*[31] found that the operating time had a median of 478 min, ranging from 270-692 min, with blood loss of 200 mL (range 30-300 mL). There were 4 complications resulting in pancreatic fistula and biliary fistula, but all were treated conservatively and healed without any significant sequelae. There was no mortality in the postoperative hospital stay of a median 12 d (range 6-21 d).

RALPD: Hybrid techniques (RALPD) include a combination of laparoscopic and robotic utilization for PD. We report five hybrid studies here, three of which are comparison studies to OPD[32-36]. In all 3 comparison studies, RALPD demonstrated significantly lower intraoperative blood loss. In the first reported RALPD study, Chalikonda *et al*[32] found that there was a significant increase in operative time (476.2 min RALPD *vs* 366.4 min OPD; $P = 0.005$), but decreased length of stay for RALPD (9.79 d RALPD *vs* 13.26 d OPD; $P = 0.043$)[24]. The study found that there was no significant difference between the two techniques in postoperative morbidity (30% RALPD *vs* 44% OPD; $P = 0.14$), or reoperation (6% RALPD *vs* 24% OPD; $P = 0.17$). The study noted that there were 3 patients (12%) undergoing RALPD that were converted to OPD due to excessive bleeding (Table 3).

Similarly, Kuroki *et al*[34] found decreased intraoperative blood loss with RALPD (376 mL RALPD *vs* 1509.5 mL OPD; $P < 0.01$), but there was also a significantly higher number of blood transfusions compared with OPD (0 blood transfusions in RALPD *vs* 13 in OPD; $P < 0.01$). The study found that there was no significant difference between the two techniques in operative time or postoperative complications.

Lai *et al*[35] reported that RALPD had a significantly longer operative time (491.5 min RALPD *vs* 264.9 min; $P = 0.01$), decreased blood loss (247 mL RALPD *vs* 774.8 mL OPD; $P = 0.03$), and shorter hospital stay (13.7 d RALPD *vs* 25.8 d OPD; $P = 0.02$). Conversion rate from RALOPD to OPD was 5%, and the study did not find a significant difference between the two groups in overall complication rates (50% RALPD *vs* 49.3%; $P = 0.95$), mortality rates (0% RALPD *vs* 3% OPD; $P = 0.43$), rate

Table 3 Robotic assisted procedures

Ref.	Year	Robotic, open, Lap, or RAL	No. of patients	Age of Patients	BMI of patients	ASA classification	EBL (mL)	Transfusion (#)	Op time (min)	Conversion (#)	Overall complications (# of patients)	Panc fistula	Length of stay	Postop death
Chalikonda *et al*[32]	2012	RAL	30	62	24.8	2.6	485	NR	476[1]	3	9	2	9.79[1]	1
Giulianotti *et al*[33]	2010	RAL	60	58	NR	NR	394	6	421	11	No PD only	19	22	2
Kuroki *et al*[34]	2012	RAL	20	71.2 ± 8.8	21.9	1.5 ± 0.6	376.6 ± 291.4[1]	0[1]	656.6 ± 191.4	NR	9	12	NR	NR
Lai *et al*[35]	2012	RAL	132	66.4 ± 11.9	NR	1.8	247[1]	NR	491.5[1] ± 94	1	10	7	13.7[1] ± 6.1	0
Zeh *et al*[36]	2012	RAL	50	68 ± 16	27 ± 5	2.6	350[1]	11	568[1]	8	28	11	10[1]	1

[1]Indicates statistically significant compared to open procedures. RAL: Robotic assisted laparoscopy; BMI: Body mass index; ASA: American Society of Anaesthesiologists physical status classification; EBL: Estimated blood loss; NR: Not reported; PD: Pancreaticoduodenectomy.

of reoperation (2% or 10% RALPD *vs* 3% or 4.5% OPD; $P = 0.04$), R0 resection rate (11% or 73.3% RALPD *vs* 34% or 64.1% OPD; $P = 0.92$), and harvested lymph node numbers (10 ± 6 RALPD *vs* 10 ± 8 OPD; $P = 0.99$).

Of the 2 noncomparison studies, Giulianotti *et al*[33] published the largest series of robotic pancreatic surgery to date with 134 patients, 60 of which were PD. This study reported similar outcomes to previous studies, including mean operative time with 331 min (range 75-660 min), mean length of hospital stay at 9.3 d (range 3-85 d), postoperative complication rate at 26%, and mortality rate of 2.23% (3 patients).

Zeh *et al*[36] examined 50 patients undergoing RALPD, 8 of which required conversion to open procedure (16%). Overall, 28 patients (56%) experienced postoperative complications, 13 of which were Clavien Ⅰ/Ⅱ. Intraoperative blood loss had a median of 350 mL (interquartile range: 150-625), with 11 patients (22%) requiring transfusions. The median length of stay reported by the study was 10 d (IQR 8-13). The median number of lymph nodes collected was 18 (IQR 5) and Zeh *et al*[36] report that 89% of the resections had negative margins.

Pancreatic fistula

Pancreatic leak at the pancreaticojejunostomy anastomosis is one of the most serious and common postoperative complications after PD, and can lead to erosion of adjacent tissues, bleeding from large vessels, severe pancreatitis, peritonitis, and sepsis. The complexity of this anastomosis has often been cited as the primary obstacle to widespread adoption of minimally invasive techniques for PD. Broadly, there did not appear to be significant differences in pancreatic fistula rates between minimally invasive and open techniques. Pancreatic leaks can be classified according to the International Study Group on Pancreatic Fistula criteria[37]. In Asbun *et al*[19], there were 29 (13.5%) pancreatic fistulas in the open group (Grade A = 14, B = 5, C =10), and 7 (13.2%) in the laparoscopic group (Grade A = 3, B = 1, C = 3), with a nonsignificant *P*-value[19]. Similarly, there is no significant difference in the pancreatic fistula rate between robotic and open groups as demonstrated in Buchs *et al*[29], where both open and robotic had 8 pancreatic fistulas at a rate 21% (Grade A = 5, B = 1, C = 2) and 18% (Grade A = 4, B = 3, C = 1) respectively, with a $P = 1$. The same could be seen between open and RAL groups, such as in Chalikonda *et al*[32], where there were 5 (16.7%) in the open group (Grade B = 2, C = 5), and 2 (6.7%) in the RAL group (Grade B = 1, C = 1)[32].

Cost analysis

In 2013, Mesleh *et al*[38] published an analysis of a single institution analysis of the cost of LPD *vs* OPD. Using a similar dataset as Asbun *et al*[19], Mesleh *et al*[38] found that of 123 patients who underwent PD, with 48 OPD (39%) and 75 LPD (61%), there was no significant difference in overall cost of LPD compared to OPD, because of increased postoperative cost of OPD.

Consistent with other studies, Mesleh *et al*[38] found that the intraoperative cost of LPD was significantly higher than that of OPD, due to increased equipment expense and mean operative time ($P < 0.0001$, OPD 355 min, range 199-681; LPD 551 min, range 390-819). Similarly, they determined that both OPD and LPD had similar rates of morbidity of 31% for both groups, with median hospital stay for OPD at 8 d (range 5-63), and 7 d (range 4-68) for LPD ($P = 0.5$). However in postoperative categories, OPD represented slightly higher cost per unit in anesthesia, critical care, pathology, pharmacy, nursing, and radiology. Because admission accounted for 65%-70% of the total cost, the increased postoperative cost of OPD balanced the excess intraoperative cost of LPD.

Similarly, Boggi *et al*[28] reported a cost analysis of RPD compared to OPD, and found that RPD's intraoperative cost significant exceeds that of OPD by approximately 6193 euros, or $5034.90 based on the currency exchange rate used in the study on 15 August 2012 (http://www.x-rates.com/calculator.html). In the United States, according to Chalikonda *et al*[32], the cost of disposables of robotic and laparoscopic equipment can be as high as $4000-5000 per case, plus the associated significant higher operative time.

Thus, in an era of limited health care dollars, cost

issues associated with minimally invasive techniques, especially robotic platforms, are important considerations as these techniques are adopted more broadly into less experienced centers.

With the emergence of newer technologies and improving minimally invasive techniques, it is important to understand the potential benefits of laparoscopic, robotic, and robotic assisted techniques. From this systematic review of the data presented, LPD, RPD, and RALPD in general appear to have less intraoperative blood loss than OPD, but in exchange for longer operating times. However, it is important to realize that all of these studies are subject to heavy selection bias, with the most difficult cases still typically being performed with open technique.

Most studies have failed to show any significant difference between the open and minimally invasive techniques in terms postoperative mortality and overall complications, though mortality may be higher with minimally invasive PD at less experienced centers[39,40]. This issue is an extraordinarily important consideration for centers with lower surgeon volume and potentially less expertise with minimally invasive techniques. Regarding pancreatic fistula, there does not appear to be a significant difference between minimally invasive and open techniques. As the learning curve improves and technology improves, differences between techniques may begin to emerge. This issue has been most consistently touted by robotics advocates. Finally, minimally invasive techniques also appear to be equivalent in terms of short-term oncologic endpoints.

In the context of broader oncologic issues, Some studies suggest that more favorable short-term outcomes including decreased pain, quicker return to daily activities, and potentially fewer wound issues may favor increased utilization of and shorter time to adjuvant therapy[41-44]. This issue too remains somewhat unproven but is an important consideration given the dismal outcomes with surgery alone for this disease[23,45-47].

In summary, there remain many hurdles before the widespread use of laparoscopic and RPD take hold, the most significant of which is the steep learning curve associated with minimally invasive PD[48,49]. Currently, minimally invasive PDs require extensive training and advanced equipment, and so are only performed by select surgeons for select patients at select tertiary centers[50]. Robotic approaches may shorten the learning curve for minimally invasive PD but this has yet to be definitely proven[51]. Even for OPD, the learning curve is steep, and a robust literature has shown tremendous variations in outcome for patients, depending on surgeon volume, hospital volume, and multidisciplinary collaboration. Thus, minimally invasive approaches to PD appear to be feasible and safe in the hands of highly experienced surgeons at centers of expertise, but widespread adoption remains a challenge given the steep learning curve, limitations of technology, and important cost considerations in an era of limited health care resources.

COMMENTS

Background

Pancreaticoduodenectomy (PD) remains the only potential curative therapy for periampullary malignancies, including, most commonly, pancreatic adenocarcinoma. Despite advances in minimally invasive techniques over the last 2 decades, the vast majority of PDs are still performed with a standard open technique (OPD) that has evolved from the original Whipple procedure described in 1935.

Research frontiers

Even with modern improvements in perioperative care, contemporary complication rates after OPD range from 25% to 65%, and thus highlight the need for surgical innovation aimed at reducing perioperative morbidity.

Innovations and breakthroughs

Despite a growing body of evidence supporting minimally invasive techniques to expedite post-operative recovery, decrease postoperative pain and reduce wound complications, minimally invasive approaches to PD have not been widely adopted and remain confined to large tertiary referral centers with highly experienced surgeons.

Applications

In general, minimally invasive techniques have been noted to provide shorter hospitalizations, fewer post-operative complications, and less time to adjuvant therapy. However, whether the advantages of minimally invasive approaches, seen in other general surgical oncologic procedures, translate to PD remains unclear. Here, the authors review current data regarding the applicability of minimally invasive approaches to PD.

Peer-review

This is an interesting and timely study.

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CASE REPORT

Bevacizumab and gastrointestinal bleeding in hereditary hemorrhagic telangiectasia

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Author contributions: Ou G, Galorport C and Enns R designed the report and drafted the article; Ou G and Galorport C collected the data; Ou G and Enns R drafted the manuscript; all authors contributed to the critical revision and final approval of the manuscript.

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Abstract

We report a case of severe, refractory gastrointestinal (GI) bleeding in a patient with hereditary hemorrhagic telangiectasia (HHT) whose massive transfusion dependence was lifted shortly after treatment with bevacizumab, an anti-vascular endothelial growth factor. The patient's bleeding had been refractory to repeated endoscopic interventions, tranexamic acid, and tamoxifen. However, following treatment with bevacizumab at 5 mg/kg every other week, nearly 300 units of packed red blood cell transfusions were avoided in one year's time. Despite its relatively high cost, bevacizumab may have a more active role in the management of severe GI bleeding in HHT if such remarkable response can be consistently demonstrated.

Key words: Bevacizumab; Vascular endothelial growth factor; Hereditary hemorrhagic telangiectasia; Bleeding; Osler-Weber-Rendu syndrome

Core tip: Management of gastrointestinal (GI) bleeding in patients with hereditary hemorrhagic telangiectasia (HHT) can be challenging when the vascular lesions recur despite repeated endoscopic treatments. There is increasing evidence supporting the use of anti-angiogenesis agents in the management of bleeding in HHT patients. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has been shown to reduce recurrent epistaxis. This case demonstrates the therapeutic potential of bevacizumab in patients with severe GI bleeding requiring massive transfusions.

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant condition characterized by vascular malformations that occur systemically, leading to manifestations such as recurrent epistaxis, gastrointestinal (GI) bleeding, and arteriovenous malformations (AVM) of the lung, liver, and brain. Since the discovery of elevated vascular endothelial growth factor (VEGF) expression in patients with HHT[1], reports of bevacizumab, a monoclonal antibody against VEGF, in managing complications of HHT have emerged[2-16], with most of the reported experience in recurrent epistaxis. We present a case of HHT with massive, refractory transfusion requirements secondary to severe GI bleeding that did not respond to conventional therapy, but subsequently achieved transfusion-independence with anti-VEGF mono-therapy.

CASE REPORT

A 58-year-old female with HHT and positive family history, involving her mother, sister, and daughter, presents with a 30-plus-year history of increasing transfusion dependency due to a combination of daily epistaxis, gastrointestinal bleeding, and intermittent gross hematuria. She did not have hemoptysis. Relevant medical history included hepatitis C infection secondary to transfusions, pulmonary hypertension from high-output cardiac failure secondary to chronic severe anemia, pulmonary AVMs with previous embolizations, and hysterectomy at the age of 26 for menorrhagia.

Her initial transfusion requirement was approximately one unit of packed red blood cells (pRBC) per month, but as of 2003 required > 40 units per year due to persistent epistaxis and increasing upper GI bleeding in the form of melena. Capsule endoscopies and upper endoscopies demonstrated innumerable AVMs in the esophagus, stomach, duodenum, and jejunum, with the bulk of the lesions located in the proximal small bowel where active bleeding was most frequently seen. Mesenteric angiography also demonstrated diffuse vascular abnormality/telangiectasia involving proximal small bowel but no focal AVM amenable to embolization. Biochemical investigations excluding other etiologies included normal renal function, thyroid stimulating hormone, haptoglobin, bilirubin, lactate dehydrogenase, direct agglutination testing, serum protein electrophoresis, serum free light chain, urine protein electrophoresis, and von Willebrand factor studies. Her hepatitis C viral load was low and abdominal ultrasound did not demonstrate cirrhosis.

Her transfusion requirement further escalated despite successful interventions including multiple septal dermatoplasties and facial/nasal vessel angiography with embolization. At least seven upper endoscopies with argon plasma coagulation, two-month tamoxifen therapy, and tranexamic acid which led to upper extremity deep vein thrombosis, were used for ongoing bleeding from the duodenum/proximal jejunum. She received neither estrogen therapy nor thalidomide due to risk of hormone-sensitive malignancy and limited access/financial constraint, respectively. Additionally, her advanced cardiopulmonary comorbidities, which were complications of HHT, precluded surgical resection of the proximal small bowel (*i.e.,* Whipple procedure) containing the majority of the vascular lesions in order to reduce GI bleeding. Between 2008 and 2015, she received on average six units of pRBC weekly (*i.e.,* 312 unit per year) as well as monthly intravenous iron infusion.

In April 2015, she was started on bevacizumab, an anti-VEGF antibody, at 5 mg/kg every two weeks as a last resort. The patient's response to bevacizumab in terms of GI bleeding was immediate and dramatic: Her stools returned to normal color and consistency, and her transfusion requirement dropped to four units per month between May and September, and further down to only two units over the course of the following seven months with intravenous iron supplementation (Figure 1). She continued to experience minor epistaxis that was much less severe than previous, and ongoing microscopic hematuria without proteinuria or renal function impairment.

Over the past 12 mo, the administration of bevacizumab has resulted in a decrease of approximately 290 units of pRBC's and improved the patient's quality of life immensely. The patient has tolerated the infusions without any reported side-effects.

DISCUSSION

This case highlights the potential challenges in managing HHT with complicated, refractory GI bleeding. In our patient's case, she acquired hepatitis C infection due to repeated transfusions, and developed high-output cardiac failure and pulmonary hypertension due to severe chronic anemia. Her functional capacity was poor due to anemia and pulmonary hypertension, but the need for frequent transfusions three times a week (> 1400 units of pRBC in the five years prior to treatment) also posed a tremendous negative impact on her quality of life in addition to causing a significant burden on the health care system. Fortunately, the patient's response to bevacizumab exceeded our expectations. The greatest hurdle of obtaining the drug was in fact, obtaining approval from regulatory bodies for financial coverage of it. However, after one year, the overall cost to the health care system of avoiding most transfusions is staggering. Given the severity of her blood loss, which to our knowledge is one of the most severe cases reported, our initial goal had been to reduce her transfusion requirement by 40%-50%, but she essentially became transfusion-independent.

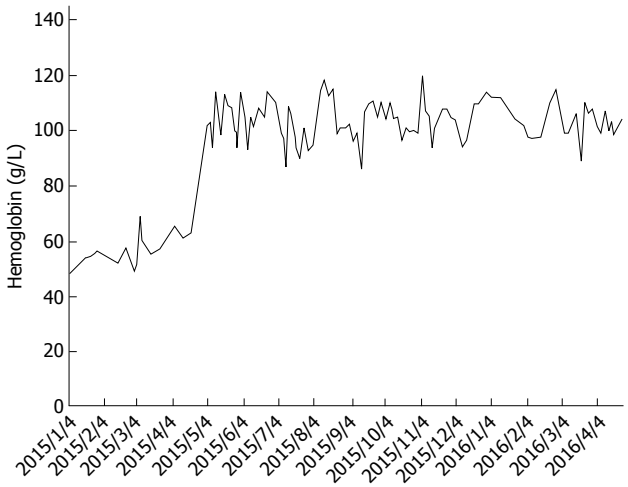

Figure 1 Hemoglobin trend. Hemoglobin trend before and after initiation of bevacizumab 5 mg/kg every other week starting in April 2015.

We opted to prescribe 5 mg/kg every other week, which is the typical dose for solid organ malignancies, since this is the regimen with the most clinical evidence to date for HHT[17]. The optimal dosage and duration of bevacizumab for GI bleeding in HHT remains to be determined, and requires balancing the clinical benefits against potential adverse events of systemic treatment such as hypertension, nephrotic syndrome, poor wound healing, bowel perforation, and thromboembolic events[18]. There have been reports successfully utilizing lower doses for GI bleeding, based on the drug's pharmacokinetics[4,5,7,15], but some patients may require higher doses to maintain optimal response[10]. Although the specific optimal dosage is not entirely clear at this time, the duration of treatment is likely indefinite as relapses upon discontinuation of therapy have been noted in previous reports, with the interval ranging from one to three months after the last dose[4,7,8,15].

This case demonstrates a remarkable response in regards to GI bleeding to bevacizumab in the setting of HHT. Although not specifically examined yet in our patient, additional benefits such as partial reversal of liver failure and high-output cardiac failure have also been reported[19-21]. Despite its high cost, earlier administration should be considered if benefit of this extent is regularly demonstrated in this group of patients as prevention of end organ complications (*i.e.,* cardiac/hepatic) theoretically might have been prevented with early administration. The issue of cost in many situations perhaps should not be paramount when aiming for ideal care in these patients with limited options.

Bevacizumab effectively controlled severe GI bleeding in this patient with complicated HHT.

COMMENTS

Case characteristics

A 58-year-old women with hereditary hemorrhagic telangiectasia (HHT) presented with severe, chronic gastrointestinal (GI) bleeding refractory to multiple treatment modalities.

Clinical diagnosis

Endoscopies demonstrated numerous arteriovenous malformations in the esophagus, stomach, duodenum, and jejunum. The majority of the lesions were located in the proximal small bowel where active bleeding was frequently seen.

Differential diagnosis

Vascular lesions of GI tract: Angiodysplasia (sporadic, end-stage renal disease, aortic stenosis, von Willebrand disease, left ventricular assist device), systemic disease (CREST, HHT).

Laboratory diagnosis

Biochemical investigations included normal renal function, thyroid stimulating hormone, haptoglobin, bilirubin, lactate dehydrogenase, direct agglutination testing, serum protein electrophoresis, serum free light chain, urine protein electrophoresis, and von Willebrand factor studies. Pre-bevacizumab mean hemoglobin was 57.2 ± 5.8 g/dL. Post-bevacizumab hemoglobin was 103.4 ± 8.3 g/dL.

Imaging diagnosis

Mesenteric angiography did not identify suitable arteriovenous malformation that was amenable to treatment *via* embolization of the gastroduodenal artery.

Treatment

Bevacizumab 5 mg/kg infusion every other week.

Related reports

There is growing evidence in the literature on bevacizumab's efficacy in treating recurrent epistaxis due to HHT, but relatively few reports exist for the management of severe, chronic, refractory GI bleeding. This case highlights the potential utility of bevacizumab for such management.

Term explanation

HHT is an autosomal dominant condition characterized by vascular malformations that can occur anywhere in the body, leading to various presentations including epistaxis, GI bleeding, high-output cardiac failure, and hypoxemia.

Experiences and lessons

Earlier administration of bevacizumab should be considered in patients with severe, refractory GI bleeding despite its relatively high cost given the potential benefit.

Peer-review

This is a pretty straightforward case report.

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