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MINIREVIEWS

"Acute postoperative open abdominal wall": Nosological concept and treatment implications

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Abstract

The so-called "burst abdomen" has been described for many years and is a well-known clinical condition, whereas the concept of the "open abdomen" is relatively new. In clinical practice, both nosological entities are characterized by a complex spectrum of symptoms apparently disconnected, which in many cases poses a great challenge for surgical repair. In order to assess the management of these disorders in a more comprehensive and integral fashion, the concept of "acute postoperative open abdominal wall" (acute POAW) is presented, which in turn can be divided into "intentional" or planned acute POAW and "unintentional" or unplanned POAW. The understanding of the acute POAW as a single clinical process not only allows a better optimization of the therapeutic approach in the surgical repair of abdominal wall-related disorders, but also the stratification and collection of data in different patient subsets, favoring a better knowledge of the wide spectrum of conditions involved in the surgical reconstruction of the abdominal wall.

Key words: Burst abdomen; Open abdomen; Evisceration; Abdominal wall; Mesh; Negative pressure wound therapy; Incisional hernia; Enteroatmospheric fistula

Core tip: Burst abdomen and open abdomen are clinical conditions apparently disconnected. In order to assess the management of these disorders in a more comprehensive and integral fashion, the concept of "acute postoperative open abdominal wall" (acute POAW) is presented. The understanding of the acute POAW as a single clinical process allows stratification and collection of data in different patient subsets, favoring a better knowledge of conditions involved in the surgical reconstruction of the abdominal wall.

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INTRODUCTION

Excluding the defects of the abdominal wall secondary to trauma, tumors or necrotizing infections, the "acute postoperative open abdominal wall" (acute POAW) embracing evisceration and the open abdomen, appears to include a number of heterogeneous and unrelated processes[1]. Different descriptors found in the PubMed data-

base[2] may be applicable to the concept of acute POAW, such as "burst abdomen", "postoperative burst abdomen", "abdominal evisceration", "bowel evisceration", "abdominal wall dehiscence", "abdominal fascial dehiscence", "acute abdominal wound failure", "open abdomen", "abdominal wound dehiscence", "abdominal wall rupture" and "disruption of abdominal wall wounds". In this previous context, definition of what constitutes an acute POAW becomes a maze.

We here propose that acute POAW is a single nosological entity formed by patients with different interrelated categories of treatment approaches. Therefore, the purpose of this article is to present the conceptual frame for an analysis of the acute POAW and their subgroup categories of treatment. For clarity purposes, the information is divided into definition of acute POAW, description and treatment of intentional (planned) and unintentional (unplanned) acute POAW, followed by some concluding remarks.

DEFINITION OF ACUTE POAW

Acute POAW consists of the separation of the cutaneous, muscular and aponeurotic layers of the abdominal wall that occurs immediately or within the first hours or days after laparotomy. It may be considered a unique nosological clinical entity resulting from intentional or unintentional surgical-related actions and composed by different interrelated clinico-therapeutical scenarios.

INTENTIONAL (PLANNED) ACUTE POAW

Intentional acute POAW is the result of a deliberate therapeutic procedure, the so-called "open abdomen"[3,4]. This entity was described for the first time in the context of patients with intra-abdominal infection due to pancreatitis or peritonitis[5,6], but the indications for the use of the open abdomen technique have expanded to patients without intra-abdominal infection[7]. Nowadays the main indications are (1) damage control for life-threatening intra-abdominal bleeding; (2) management of severe intra-abdominal sepsis; and (3) prevention or treatment of intra-abdominal hypertension.

Once the therapeutic objective has been achieved, closure of the musculofascial layers should be performed[3,4,8-10]. However, closure of the open abdomen depends on the method used for temporary abdominal wall closure[3,8,9], the capacity of tissues for healing without tension, and whether or not enteroatmospheric fistulas are present.

The ideal temporary abdominal wall closure should protect the abdominal contents, prevent evisceration, allow removal of infected or toxic fluid from the peritoneal cavity, avoid damage to the musculofascial tissue, preserve the abdominal wall domain, facilitate reoperation for definitive closure and, very importantly, prevent the formation of enterocutaneous fistulas[11]. Different methods for temporary abdominal closure have been used, including among others: skin approximation with towel clips or running suture, application of a plastic silo (the Bogota bag), absorbable synthetic meshes [Safil®Mesh (BBraun, Rubí, Barcelona, Spain); BIO-A Tissue Reinforcement® mesh (Gore and Associates, Flagstaff, AZ)], non-absorbable synthetic meshes (polypropylene, e-PTFE), dynamic methods [ABRA® (Canica Design Inc, Almonte, Ontario, Canada); Wittmann Patch® (Starsurgical, Burlington, WI)], biological implants or negative pressure dressing systems [RENASYS AB® Abdominal Kit (Smith and Nephew, Hull, United Kingdom); ABThera® (KCI International, San Antonio, TX)][12]. The capacity of tissues for healing without tension depends on wound-related factors and the patient's general condition[11]. Independently of the technique used for temporary abdominal wall closure, there is a limited window of 2-3 wk to assess early *vs* delayed closure[8-11,13,14]. Early definitive closure (final closure of the abdominal defect within the window of 2-3 wk) is based on the resolution of interstitial edema and the evidence of non-adherence between the bowel loops and the abdominal wall. In contrast, when the abdominal content adheres to the undersurface of the anterior abdominal wall ("frozen abdomen" generally beyond 2-3 wk), delayed closure ("planned" incisional hernia repair) is the only realistic alternative in the operative management of the open abdomen. There are mixed situations between non-adherent loops and abdominal wall and the "frozen abdomen".

The development of enteroatmospheric fistulas is the most serious and challenging local complication[15], with an overall incidence still reported between 5% and 75%. Mortality of patients with fistula can be still high, up to 42% according to a review of different studies[15].

Treatment options

According to the aforementioned features, we have four different subgroup categories of treatment options: (1) Patients within the 2-3 wk time window with non-adherent bowel loops/abdominal wall and without intestinal fistula are candidates for definitive fascia-to-fascia closure using a continuous slowly absorbable monofilament suture and following the 4:1 suture length (SL): wound length (WL) ratio[16,17]. Also, autologous tissue reconstruction procedures (component separation technique, anterior rectus sheath flaps, oblique muscles) to improve closure or to further reduce tension have been reported[13,18-20]. There are no data in the literature on the usefulness of synthetic (absorbable or non-absorbable) meshes or biological implants to reinforce the repair, which mostly relies on the surgeon's experience and decision and the risk factors present in each individual patient; (2) Patients within the 2-3 wk time window with partially non-adherent bowel loops/abdominal wall and without enteroatmospheric fistula are candidates for a definitive early progressive abdominal wall closure, which will depend on the progressive improvement of the patient's general condition and the interstitial edema. In these cases, combinations of non-absorbable synthet-

ic meshes and negative pressure wound therapy (NPWT) are generally indicated. NPWT and non-absorbable synthetic mesh traction (pleating or serial excision of the mesh as the fascial edges are re-approximated) have been reported to be a practical wound closure system for the treatment of the open abdomen[21-25]. In addition, several types of extracellular matrix-derived biological implants have been used[26,27], although they are not recommended to bridge a fascial defect, and the long-term durability and functional outcome of biological implants is still unknown[28]. Other techniques for progressive closure of the abdominal wall, in combination or not with NPWT, include dynamic wound closure systems based on continuous dynamic tension to achieve re-approximation of the fascial edges of the abdominal wall[29,30] or the use of patches of synthetic material as a temporary, gradual means for abdominal closure[31]; (3) Patients beyond the 2-3 wk window without progress towards closure or improvement of general condition and interstitial edema ("frozen abdomen") and without bowel fistulization. In these cases, the treatment options include skin cover over the defect or allow wound granulation (absorbable synthetic mesh implant, NPWT) and thereafter cover with skin grafts and subsequent definitive delayed closure (after 6-12 mo) in the context of a "planned" incisional hernia repair[32-37]; and (4) Patients with enteroatmospheric fistula. In these cases, the constant leak of enteric contents on the open abdomen aggravates the inflammation and encourages the formation of new fistulas. The control is extremely difficult[3]. Management includes systemic treatment (nutritional support) and temporary local control to prevent spillage of the enteric contents and excoriation of the surrounding skin while planning for definitive closure of the fistula. Due to the large variability of enterocutaneous fistulas, treatment should be individualized[15,38-40].

UNINTENTIONAL (UNPLANNED) ACUTE POAW

Unintentional acute POAW or acute wound failure (also known as burst abdomen, evisceration, wound dehiscence, wound disruption and fascial dehiscence) is a postoperative complication after primary closure of an abdominal laparotomy incision[41]. The incidence of fascial dehiscence ranges between 0.5% and 3% of all laparotomies[42,43]. The morbidity is high, with prolonged hospital stay and an increase in direct costs[44-48]. The dehiscence-associated mortality rate (range 34%-44%) does not appear to be declining[49,50]. Moreover, unintentional acute POAW is associated with a high incidence of subsequent incisional hernia (40%-60%)[49,50]. Wound breakdown may be complete, affecting all layers of the abdominal wall including the skin[51,43] or incomplete when the skin remains intact. Drainage of serosanguinous fluid from the incision precedes dehiscence in up to 84% of cases[41].

Predisposing factors to the development of wound disruption include the technique of wound closure, type of incision, indication for operation (emergency operations, malignant tumors, infectious diseases), raised intra-abdominal pressure (coughing, vomiting, abdominal distension from ileus or vigorous postoperative ventilation), age > 65 years, chronic obstructive pulmonary disease (COPD), hemodynamic instability, malnutrition, diabetes, obesity, ascites, jaundice and steroid use[43]. However, wound infection due to intra-abdominal infection (20%-40% of cases)[52,53] or wound contamination (up to 52% of cases)[52] is the single most important risk factor for abdominal wound disruption[43].

Unintentional acute POAW may occur during the first 24 h after surgery[43], although it may range from 1 to more than 23 d[41,47], with an average of 7 d postoperatively[41]. The preferred treatment of unplanned acute POAW regarding definitive early or delayed closure[43-45,47,48,51-53] should be established according to the possibility of early reclosure without tension during the window period of 2-3 wk (as in planned acute POAW), the identification and proper treatment of intra-abdominal infection including intra-abdominal abscesses (appropriate antibiotic treatment and drainage preferably by the percutaneous route) and the presence or absence of enterocutaneous fistulas.

Treatment options

According to the aforementioned features, we have different subgroup categories of treatment which are also closely interrelated with the subgroup categories of intentional acute POAW. (1) Patients with unintentional acute POAW with complete wound dehiscence shared the same characteristics and should be managed as patients with intentional acute POAW; (2) Patients with incomplete unintentional acute POAW with non-adherent bowel loops/abdominal wall and without fistula are candidates for fascia-to-fascia closure using a continuous slowly absorbable monofilament suture and following the 4:1 SL: WL ratio[16,17,41-48,51-53]. Placement of retention sutures is controversial and negative side-effects of the retention closure technique have been reported[41,54-58]. Development of recurrence of unintentional acute POAW has been described with a 5% incidence and development in long term follow-up of incisional hernia in 40%-60% of the cases[49,50]. For this reason, reinforcement with a synthetic mesh may be useful, especially in the absence of intra-abdominal infection, although mesh closure has also been recommended in clean-contaminated/contaminated wounds[59-63]. Use of absorbable mesh is discouraged by the high incidence of incisional hernias in the long-term[64]. In contaminated/dirty fields, other methods such as NPWT or dynamic wound closure systems are more appropriate[65]. The usefulness and long-term results of biological implants is uncertain and are not recommended in cases of large bacterial inocula[28]; (3) Patients within the 2-3 wk time window with incomplete unintentional acute POAW and partially non-adherent bowel loops/abdominal wall and without enteroatmospheric fistula are candidates for a definitive early progressive abdominal wall closure in the same way as planned acute POAW; (4)

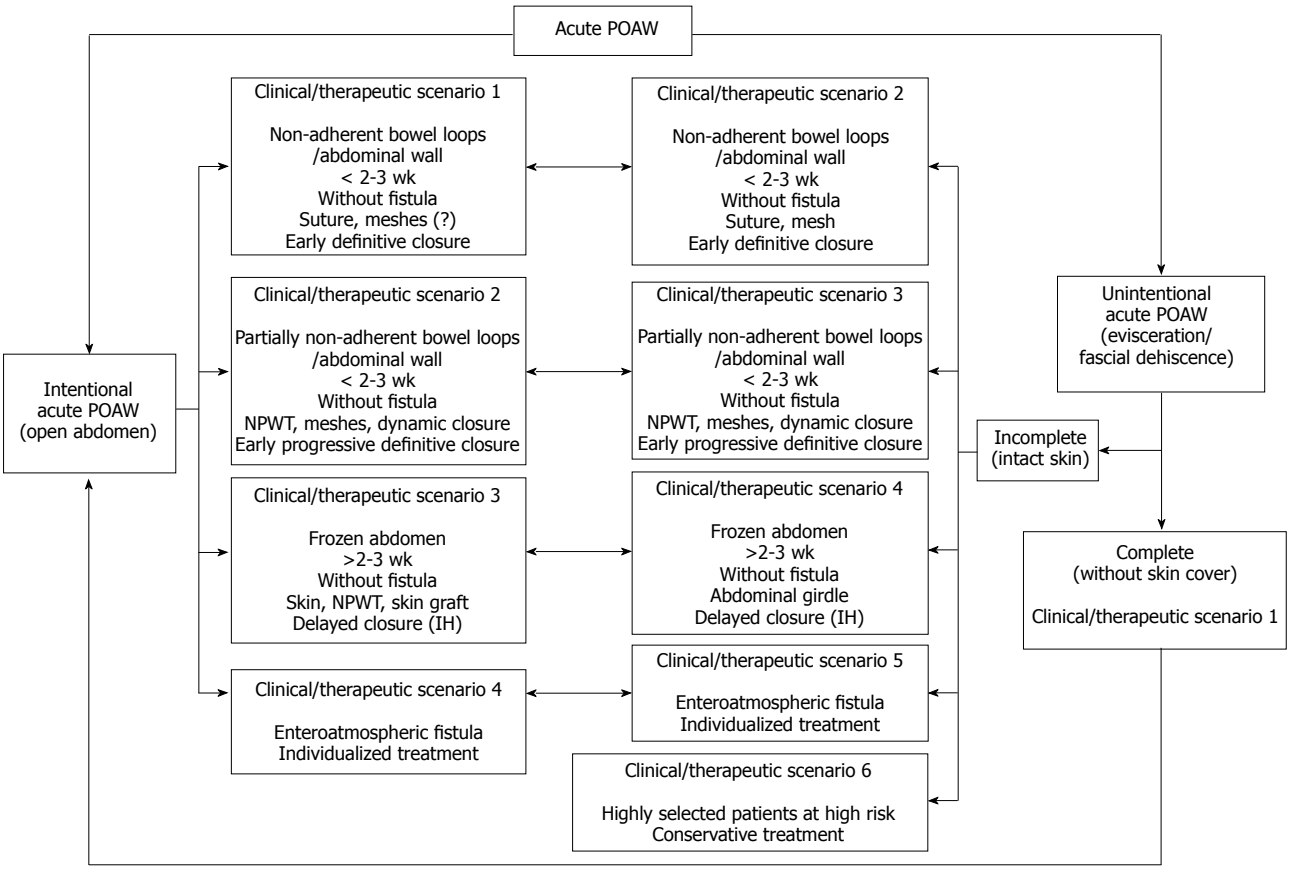

Figure 1 Treatment strategies of acute postoperative open abdominal wall (intentional and unintentional) for the different clinical/therapeutic scenarios. POAW: Postoperative open abdominal wall; NPWT: Negative pressure wound therapy; IH: Incisional hernia.

In patients with incomplete wound dehiscence and bowel loops adherent to the abdominal wall beyond 2-3 wk (frozen abdomen), abdominal girdles may be used before planning a delayed closure method (after 6-12 mo) in the context of an incisional hernia repair[49,50]; (5) Patients with incomplete wound failure and enterocutaneous fistula should be managed individually and the technique of closure of the wound depends on the surgeon's discretion (as in planned acute POAW); and (6) In highly selected patients at high risk for surgery, the use of some type of compression garment (such as a girdle) is recommended and attempts of closure of the musculofascial layers are contraindicated.

Treatment strategies and relationships of acute POAW (intentional and unintentional) for the different clinical/therapeutic scenarios are summarized in Figure 1 and Tables 1 and 2. However, the description of different options do not lead to the definitive concept of "how I do it" in each scenario because of a lack of a systematic approach (low level of evidence) in the management of this serious and heterogeneous surgical problem. In addition, the use of different techniques is still dependent on the individual surgeon's decision and experience.

CONCLUSION

We believe that in daily surgical practice, burst abdomen/evisceration/fascial dehiscence and the open abdomen are viewed as different and unrelated processes, possibly because the first is considered a complication of surgery[41,43] and the second as a procedure of surgery[1,3]. On the other hand, the abdominal wall is a complex and unique biological "organ"/mechanism contributing to the correct maintenance of the organism homeostatic balance through contention of the abdominal viscera in the right position, dynamics of respiratory activity[66], movement of the trunk[67], statics of the spine[68,69] and generation of intra-abdominal pressure for physiological functions such as cough, micturition and defecation. In this context, acute postoperative open abdominal wall as a result of unintended complications of surgery (*i.e.,* burst abdomen/evisceration/fascial dehiscence) or intended surgical options (*i.e.,* the open abdomen) originates from different and interrelated groups of patients with a common characteristic: impaired abdominal wall, which in turn may be grouped together under the term of acute POAW. Conceptual understanding of acute POAW as a nosological entity would allow stratification and collection of data in different patient subsets, favoring a better knowledge and optimization of the therapeutic approach of patients with this kind of abdominal wall-related disorders. In addition, it allows considering the abdominal wall system as an independent "organ" involved in other pathological and/or therapeutic conditions with a final

Table 1 Groups and therapeutic options in complete intentional and unintentional acute postoperative open abdominal wall

Clinical/therapeutic scenario	Intestinal fistula	Non-adherent bowel loops	Free inner abdominal wall	Window ⩽ 2-3 wk	Window > 2-3 wk	Therapeutic option
1	No	Yes	Yes	Yes Early definitive closure	-	Fascia to fascia closure. Continuous slowly absorbable monofilament suture, 4:1 rule
2	No	Partially	Partially	Yes Definitive early progressive closure	-	Vacuum-assisted wound closure and mesh traction or dynamic wound closure systems
3	No	No "Frozen abdomen"	No "Frozen abdomen"	-	Yes Delayed closure	Skin cover or after granulation skin graft "Planned" incisional hernia repair
4	Yes	-	-	-	-	Individualized

Table 2 Groups and therapeutic options in incomplete (intact skin) unintentional acute postoperative open abdominal wall

Clinical/therapeutic scenario	Intestinal fistula	Non-adherent bowel loops	Free inner abdominal wall	Window ⩽ 2-3 wk	Window > 2-3 wk	Therapeutic option
2	No	Yes	Yes	Yes Early definitive closure	-	Fascia to fascia closure, 4:1 No retention sutures Mesh depending contamination Biologics doubtful
3	No	Partially	Partially	Yes definitive early progressive closure	-	Vacuum-assisted wound closure and mesh traction Or dynamic wound closure systems
4	No	No "Frozen abdomen"	No "Frozen abdomen"		Yes Delayed closure	Abdominal girdles Planned incisional hernia repair
5	Yes	-	-	-	-	Individualized
6 High surgical risk	-	-	-	-	-	Abdominal girdle

common challenge: closure of the abdominal wall.

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BRIEF ARTICLE

Timing of chemotherapy and survival in patients with resectable gastric adenocarcinoma

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Abstract

AIM: To evaluate the timing of chemotherapy in gastric cancer by comparing survival outcomes in treatment groups.

METHODS: Patients with surgically resected gastric adenocarcinoma from 1988 to 2006 were identified from the Los Angeles County Cancer Surveillance Program. To evaluate the population most likely to receive and/or benefit from adjunct chemotherapy, inclusion criteria consisted of Stage Ⅱ or Ⅲ gastric cancer patients > 18 years of age who underwent curative-intent surgical resection. Patients were categorized into three groups according to the receipt of chemotherapy: (1) no chemotherapy; (2) preoperative chemotherapy; or (3) postoperative chemotherapy. Clinical and pathologic characteristics were compared across the different treatment arms.

RESULTS: Of 1518 patients with surgically resected gastric cancer, 327 (21.5%) received perioperative chemotherapy. The majority of these 327 patients were male (68%) with a mean age of 61.5 years; and they were significantly younger than non-chemotherapy patients (mean age, 70.7; $P < 0.001$). Most patients had tumors frequently located in the distal stomach (34.5%). Preoperative chemotherapy was administered to 11.3% of patients ($n = 37$) and postoperative therapy to 88.7% of patients ($n = 290$). An overall survival benefit according to timing of chemotherapy was not observed on univariate or multivariate analysis. Similar results were observed with stage-specific survival analyses (5-year overall survival: Stage Ⅱ, 25% *vs* 30%, respectively; Stage Ⅲ, 14% *vs* 11%, respectively). Therefore, our results do not identify a survival advantage for specific timing of chemotherapy in locally advanced gastric cancer.

CONCLUSION: This study supports the implementation of a randomized trial comparing the timing of perioperative therapy in patients with locally advanced gastric cancer.

Key words: Chemotherapy; Gastric cancer; Adjunct therapy; Postoperative therapy; Preoperative therapy; Timing

Core tip: Curative intent surgical resection offers the

best survival potential in conjunction with chemotherapy for patients with gastric cancer. Few studies have evaluated the optimal timing of chemotherapy. This study shows that in the setting of resectable gastric cancer, there is no survival advantage based on the timing of chemotherapy.

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INTRODUCTION

Despite an overall decrease in the incidence and mortality in gastric cancer patients in the United States, nearly 22000 patients will be diagnosed with gastric cancer in the United States each year[1]. More alarmingly, gastric cancer remains the 2nd leading cause of cancer-related deaths worldwide accounting for an estimated 436930 deaths in 2013[2,3]. In Western societies, where screening is not routine (compared to Asian countries[4,5]), the majority of patients present with regional or distant disease[6,7], and the 5-year overall survival is 30%-40%[8-10]. In these cases, the only hope for long term survival remains surgical resection with curative intent[11]. Despite aggressive surgical measures, rates of disease recurrence remain high following surgery[12,13]. In fact, approximately 50% to 90% of patients die as a result of disease relapse[14]. As a result, much attention has been placed on the identification of optimal adjunct therapies for gastric cancer.

Adjunct therapies for gastric cancer may be administered in the pre-operative (*i.e.*, neoadjuvant) or post-operative (*i.e.*, adjuvant) settings. Multiple trials have assessed these treatment strategies; and potential benefits have been drawn from both options[14-19]. In a landmark study, the investigators of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial reported an overall survival benefit with a regimen that incorporated neoadjuvant and adjuvant (*i.e.*, perioperative) timing of chemotherapy consisting of epirubicin, cisplatin, and fluorouracil (ECF) when compared to surgery alone[18]. From the Intergroup 0116 trial, investigators reported a 9 mo improvement in survival (27 mo *vs* 36 mo) when adjuvant chemoradiation was administered compared to surgery alone[17]. More recently, the CLASSIC trial investigators reported an overall survival benefit from adjuvant chemotherapy (capecitabine and oxaliplatin) compared to surgery alone[20]. However, there has been no trial that has directly compared neoadjuvant versus adjuvant chemotherapy administration. Using a large, population-based cohort, the objective of this study was to assess whether the timing of chemotherapy affects the survival of patients following surgical resection for gastric cancer.

MATERIALS AND METHODS

Los Angeles County Cancer Surveillance Program

The Los Angeles County (LAC) Cancer Surveillance Program (CSP) is the cancer registry that collects information for all cancer diagnoses in LAC since 1972. As part of the National Cancer Institute's Surveillance, Epidemiology, and End Results program, CSP routinely collects data on patient demographics, primary tumor site, tumor morphology, disease stage at diagnosis, treatment received, and follow-up. CSP monitors the quality of data by performing annual reviews and training of staff. Approval to conduct this study was obtained from the Institutional Review Boards of the City of Hope and the State of California.

CSP tumor coding and study criteria

Using the CSP registry, we identified patients diagnosed with gastric adenocarcinoma from 1988 to 2006. Inclusion criteria consisted of Stage Ⅱ or Ⅲ gastric cancer patients above 18 years of age who underwent curative-intent surgical resection. As Stage Ⅰ disease is more likely to be treated by surgery alone and patients with Stage Ⅳ disease are more likely not to undergo surgery given metastatic/unresectable disease, these patients were excluded from the current study. Therefore, this study was designed to evaluate the population most likely to receive and/or benefit from adjunct chemotherapy (Stage Ⅱ or Ⅲ).

Specifically, we included only gastric cancer patients with International Classification of Diseases for Oncology histology codes for adenocarcinoma: 8140-8145, 8210-8211, 8480-8481, and 8490. In CSP, the location of tumor was categorized as proximal, distal, middle, or whole stomach. For each patient, stage was categorized according to the American Joint Commission on Cancer (AJCC) 7th Edition classification system. Furthermore, size and depth of tumor invasion were categorized by AJCC T-stage as: T1A, T1B, T2, T3, or T4. The presence or absence of nodal involvement was designated by AJCC N-stage as: N0, N1, N2, or N3. Our survival analysis included only patients with AJCC Stage Ⅱ and Ⅲ gastric cancer. Finally, we obtained data regarding the timing of chemotherapy administration (none, preoperative, or postoperative). As the CSP database only codes the date of the first chemotherapy treatment, patients who did receive preoperative (neoadjuvant) chemotherapy may or may not have received subsequent postoperative chemotherapy. Therefore, we could not distinguish between neoadjuvant and perioperative chemotherapy in this database. Thus, this study compares neoadjuvant chemotherapy, adjuvant chemotherapy, and no chemotherapy.

Statistical analysis

Patients were categorized into three groups according to the receipt of chemotherapy: (1) no chemotherapy; (2) neoadjuvant chemotherapy (± postoperative chemother-

Table 1 Comparison of the characteristics of the surgical groups *n* (%)

Characteristic		No chemo *n* = 1191	Received chemotherapy *n* = 327	*P* value
Age, yr	Mean ± SD	71 ± 12	61 ± 14	< 0.0001
Sex	Men	741 (62)	221 (68)	0.0743
	Women	450 (38)	106 (32)	
Race/ ethnicity	Non-hispanic white	438 (37)	118 (36)	0.9833
	Black	112 (9)	33 (10)	
	Hispanic white	322 (27)	88 (27)	
	Asian/pacific islanders	319 (27)	88 (27)	
Tumor location	Proximal	296 (25)	98 (30)	0.0290
	Distal	423 (36)	100 (31)	
	Whole	167 (14)	59 (18)	
	Middle	305 (26)	70 (21)	
Grade	Well differentiated	26 (2)	1 (0)	0.0178
	Moderately differentiated	312 (26)	70 (21)	
	Poorly differentiated	792 (66)	234 (72)	
	Undifferentiated	40 (3)	18 (6)	
	Unknown	21 (2)	4 (1)	
Tumor size	≤ 5 cm	462 (39)	117 (36)	0.6048
	>5 cm	507 (43)	145 (44)	
	Unknown	222 (19)	65 (20)	
T stage[1]	T2	108 (9)	24 (7)	0.1556
	T3	620 (52)	163 (50)	
	T4a	319 (27)	96 (29)	
	T4b	144 (12)	44 (13)	
N stage[1]	N0	334 (28)	38 (12)	< 0.0001
	N1	786 (66)	261 (80)	
	N2	31 (3)	15 (5)	
	N3	40 (3)	13 (4)	
Node status	N-	334 (28)	38 (12)	< 0.0001
	N+	857 (72)	289 (88)	
AJCC7 group	Ⅱ	767 (64)	187 (57)	0.0168
	Ⅲ	424 (36)	140 (43)	

[1]*P* values shown are based on the Jonckheere-Terpstra test for ordinal data. AJCC: American joint commission on cancer.

apy); or (3) adjuvant chemotherapy.

Clinical and pathologic characteristics were compared across the different treatment arms by χ^2 analyses for categorical variables and student's *t* test for continuous variables. Cox-proportional hazards modeling was used to evaluate the role of chemotherapy and other variables on overall survival as represented by hazard ratios (HR) with 95%CI. Variables included in the univariate analyses were age, sex, race/ethnicity, tumor location, AJCC stage, T-stage, N-stage, tumor grade, tumor size, lymph node number, and timing of chemotherapy regimen (neoadjuvant ± adjuvant *vs* adjuvant alone). Variables included in the multivariate analyses were age, AJCC stage, and timing of chemotherapy regimen (preoperative *vs* postoperative). Because tumor size, T stage and lymph node status are multi-collinear with AJCC stage, the multivariate model included AJCC stage alone to represent the staging variable.

Survival was defined as survival throughout the study period (1988-2006). Mortality was defined through the database used as all-cause mortality since date of diagnosis of gastric cancer. Overall survival (OS) for the treatment arms was calculated by the Kaplan-Meier method, and differences in survival were compared by the log-rank test. Proportional hazard assumptions for the Cox models were tested by calculating scaled Schoenfeld residuals with results indicating model fit. Two-sided *P* values < 0.05 were considered to be statistically significant. All statistical analyses were completed using SAS software, (SAS institute Inc. Cary, NC).

RESULTS

Patient and tumor demographics

Of 1518 patients with AJCC Stage Ⅱ or Ⅲ surgically resected gastric cancer between 1988 and 2006, 22% of patients (*n* = 327) received chemotherapy as part of their cancer treatment. The demographics of the study cohort are presented in Table 1. Most tumors were observed in the proximal (26%) or distal stomach (35%) and were poorly differentiated (68%) by histology. The majority (76%) of the study cohort had lymph node positive disease; and most patients had Stage Ⅱ disease (63%) rather than Stage Ⅲ disease (37%). Patients who did not receive chemotherapy were more likely to have lymph node negative disease than those who did receive chemotherapy (28% *vs* 12%, *P* < 0.001).

Comparison of patients by treatment group

As shown in Table 1, patients who did not receive chemotherapy were older than those who did (71 *vs* 61, respectively, *P* < 0.001). Within the chemotherapy groups (Table 2), more patients received adjuvant chemotherapy (*n* = 290, 89%) than neoadjuvant chemotherapy (*n* = 37, 11%, *P* < 0.001). The mean ages of patients receiving chemotherapy were similar (65 and 61 years, neoadjuvant and adjuvant, respectively). The majority of patients were male in both chemotherapy groups. There was no difference in race/ethnicity, tumor location, tumor grade, T stage, N stage, node status or AJCC stage group.

Survival by treatment group and univariate and multivariate analysis

Patients who received chemotherapy were compared according to the timing of administration of chemotherapy (neoadjuvant *vs* adjuvant). By Kaplan-Meier method, a difference in overall survival was not observed between the neoadjuvant *vs* adjuvant chemotherapy groups (Figure 1A). This was consistent when the groups were evaluated by stage of disease as well (Figure 1B and C). Next, univariate and multivariate analyses were performed to identify factors associated with improved survival (Table 3). In univariate analysis, younger age, lower T stage, node negative status and Stage Ⅱ disease were associated with improved survival. On multivariate analysis, older age and Stage Ⅲ disease were independently associated with shorter survival. All other factors fell out of multivariate analysis and were not significant. When grouped by stage, age continued to be an independent predictor of survival in both the Stage Ⅱ and Ⅲ gastric cancer patients (data

Table 2 Comparison of characteristics by chemotherapy groups *n* (%)

Characteristic		Neoadjuvant *n* = 37	Adjuvant *n* = 290	*P* value
Age, yr	Mean (± SD)	65 (± 10)	61 (± 14)	0.0583
Sex	Men	23 (62)	198 (68)	0.4543
	Women	14 (38)	92 (32)	
Race/ ethnicity	Non-hispanic white	18 (49)	100 (34)	0.2885
	Black	3 (8)	30 (10)	
	Hispanic white	6 (16)	82 (28)	
	Asian/pacific islanders	10 (27)	78 (27)	
Tumor location	Proximal	12 (32)	86 (30)	0.9189
	Distal	10 (27)	90 (31)	
	Whole	6 (16)	53 (18)	
	Middle	9 (24)	61 (21)	
Grade	Well differentiated	0 (0)	1 (0)	0.9087
	Moderately differentiated	7 (19)	63 (22)	
	Poorly differentiated	27 (73)	207 (71)	
	Undifferentiated	2 (5)	16 (6)	
	Unknown	1 (3)	3 (1)	
Tumor size	≤ 5 cm	10 (27)	107 (37)	0.2297
	> 5 cm	16 (43)	129 (44)	
	Unknown	11 (30)	54 (19)	
T stage[1]	T2	0 (0)	24 (8)	0.4283
	T3	19 (51)	144 (50)	
	T4a	15 (41)	81 (28)	
	T4b	3 (8)	41 (14)	
N stage[1]	N0	7 (19)	31 (11)	0.2684
	N1	27 (73)	234 (81)	
	N2	1 (3)	14 (5)	
	N3	2 (5)	11 (4)	
Node status	N-	7 (19)	31 (11)	0.1413
	N+	30 (81)	259 (89)	
AJCC7 group	Ⅱ	23 (62)	164 (57)	0.5160
	Ⅲ	14 (38)	126 (43)	

[1]*P* values shown are based on the Jonckheere-Terpstra test for ordinal data. AJCC: American joint commission on cancer.

not shown).

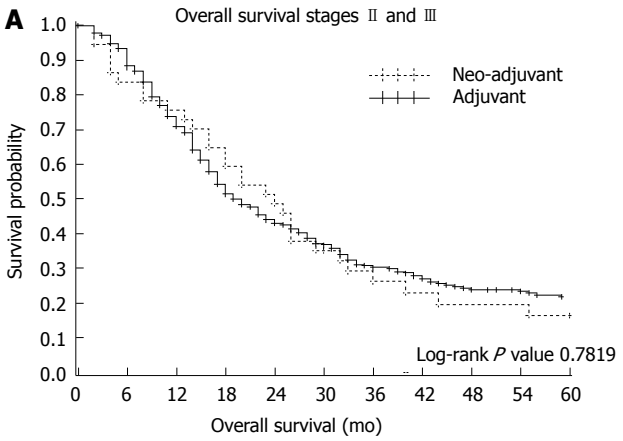
DISCUSSION

Despite advances in medical and surgical therapies, the prognosis of advanced gastric cancers remains poor, with a dismal 5-year relative survival rate of 28%[1]. With locoregional and distant recurrence rates approaching > 70%, an emphasis has been placed on identifying effective adjunct therapeutic regimens[18,17,20-23]. Systemic chemotherapy has been a logical choice, but the optimal timing of its administration remains unclear. In this study we compared the outcomes of Stage Ⅱ-Ⅲ surgically resected gastric cancer patients who received neoadjuvant (± postoperative chemotherapy) versus adjuvant chemotherapy and observed no difference in overall survival between the two treatment groups.

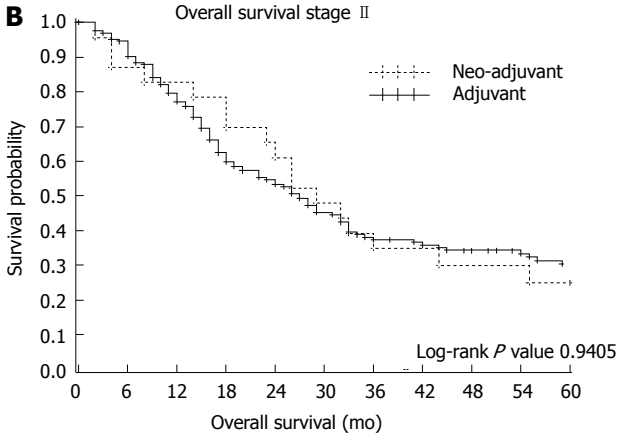
Several trials have examined the use of chemotherapy in the management of gastric cancer. One landmark study, the MAGIC trial by Cunningham *et al*[18], showed that perioperative chemotherapy with ECF decreased tumor size and stage while improving both progression-free and overall survival when compared to surgery alone. In this randomized controlled prospective study, 503 patients were randomly assigned to either perioperative ECF chemotherapy (three cycles preoperative and three cycles postoperative) or surgery alone. Of the perioperative group, only 41.6% completed all six cycles of chemotherapy due to disease progression, toxic effects, or complications[18]. The use of neoadjuvant chemotherapy decreased tumor size (3 cm *vs* 5 cm, $P < 0.001$) and stage of the pathologic surgical specimens. Therefore, by administering chemotherapy neoadjuvantly, the chance of curative resection by downstaging the tumor is increased. Other benefits of neoadjuvant chemotherapy include the elimination of micrometastasis, the improvement of tumor-related symptoms, and the determination of whether the tumor is chemotherapy-sensitive[18]. The MAGIC trial concluded perioperative chemotherapy should be considered in patients with resectable gastric cancers. Although we observed no difference between neoadjuvant and adjuvant timing of chemotherapy, nevertheless our findings suggest that patients with Stage Ⅱ or Stage Ⅲ gastric cancer indeed benefit from chemotherapy in conjunction with surgery. The 3-year OS was 16.6% in the MAGIC trial compared to 35% and 37% in the neoadjuvant and adjuvant arms, respectively, in our study. Given the inherent limitations of our database, we could not assess the effect of neoadjuvant chemotherapy on downstaging the gastric cancer, an outcome also not reported in the MAGIC trial.

The use of adjuvant chemotherapy has also been a treatment choice in the setting of chemotherapy. Adjuvant chemotherapy provides the benefit of removing disease burden upfront with a surgical resection, followed by chemotherapy. The potential downfall of adjuvant chemotherapy is the delay in beginning systemic treatment in the postoperative period for recovery from surgery. Further, downstaging tumor is not possible with adjuvant chemotherapy. Bang *et al*[20] evaluated the use of adjuvant chemotherapy after gastrectomy with D2 lymph node dissection in patients with Stage Ⅱ-ⅢB gastric cancer in the recent CLASSIC (Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer) trial. In this phase Ⅲ randomized controlled, multi-institutional study, 1035 patients were randomized to surgery alone or surgery followed by chemotherapy (capecitabine plus oxaliplatin). The CLASSIC trial found a 34% reduction in the risk of death in the chemotherapy arm (HR = 0.66, 95%CI: 0.51-0.85; $P = 0.0015$) and a 5-year overall survival that was significantly increased in the chemotherapy arm (78% chemotherapy arm *vs* 69% surgery alone arm, $P < 0.0029$)[20,24]. However, the CLASSIC trial was reported in an eastern hemisphere patient population and has not been readily accepted in the United States[20,24]. Further, the CLASSIC trial had a 56% rate of grade 3 or 4 adverse effects (neutropenia, nausea, and vomiting) requiring dose modifications in a significant portion of patients, thereby limiting completion of adjuvant therapy[20].

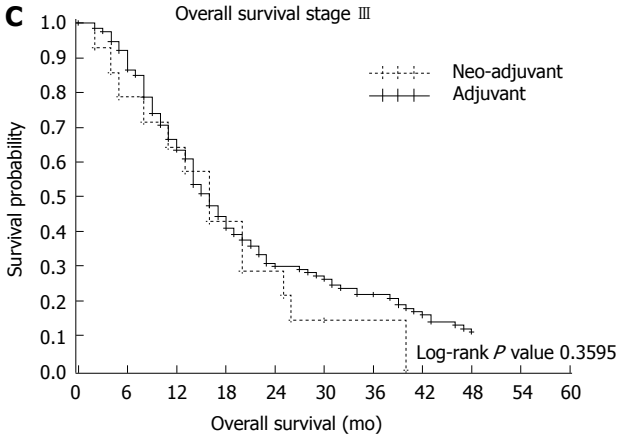
The MAGIC and CLASSIC trials, however, did not



	Neo-adjuvant	Adjuvant
No. of patients	37	290
Death	31 (84%)	219 (76%)
Censored	6 (16%)	71 (24%)
Median OS	24 mo	20 mo
1-yr OS	76%	71%
3-yr OS	26%	30%
5-yr OS	16%	22%



	Neo-adjuvant	Adjuvant
No. of patients	23	164
Death	18 (78%)	111 (68%)
Censored	5 (22%)	53 (32%)
Median OS	29 mo	27 mo
1-yr OS	83%	77%
3-yr OS	35%	37%
5-yr OS	25%	30%



	Neo-adjuvant	Adjuvant
No. of patients	14	126
Death	13 (93%)	108 (86%)
Censored	1 (7%)	18 (14%)
Median OS	16 mo	16 mo
1-yr OS	64%	63%
3-yr OS	14%	22%
5-yr OS	14%	11%

Figure 1 Comparison of Kaplan-Meier survival curves. A: For Stage Ⅱ and Ⅲ gastric cancer patients who underwent preoperative chemotherapy compared to those who had postoperative chemotherapy (MS 24 mo *vs* 20 mo, respectively; $P = 0.7819$); B: Stage Ⅱ gastric cancer patients who underwent neoadjuvant chemotherapy (with or without adjuvant therapy) compared to those who had adjuvant chemotherapy alone (MS 29 mo *vs* 27 mo, respectively; 5-yr operating system (OS) 25% *vs* 30%; $P = 0.9405$); C: Stage Ⅲ gastric cancer patients who underwent neoadjuvant chemotherapy (with or without adjuvant therapy) compared to those who had adjuvant chemotherapy alone (MS 16 mo *vs* 16 mo, respectively; 5-yr OS 14% *vs* 11%; $P = 0.3595$).

examine the role and timing of radiation for gastric cancer. Adjuvant chemoradiation has been shown to improve overall survival in patients with locally advanced gastric cancer. Macdonald *et al*[16,17,25-27] reported in the INT0116 Phase Ⅲ randomized multi-institutional trial of adjuvant chemoradiation compared to surgery alone that adjuvant chemoradiation improved overall survival and disease-free survival. Though Macdonald *et al*[16,17,25-27] evaluated adjuvant chemoradiation to surgery alone, there are no phase Ⅲ trials that directly compare neoadjuvant with adjuvant chemoradiation. With the database used for this study, only receipt of radiation could be determined. Therefore, we could not assess the timing of radiation in relation to surgery and to exclude bias of radiation in our analysis, patients who received radiation were excluded from this current study.

Our study is not without its limitations. Due to the retrospective nature of this study, there may be patient

Table 3 Univariate and multivariate analysis

Factor		*n* (%)	Univariate		Multivariate	
			HR (95%CI)	*P* value	HR (95%CI)	*P* value
Chemo status[1]	Neo-Adjuvant	37 (11)	-	-	-	-
	Adjuvant	290 (89)	0.95 (0.65-1.38)	0.7854	0.97 (0.67-1.43)	0.8961
Age[1], yr	Mean ± SD	61.5 ± 14	1.02 (1.01-1.03)	0.0008	1.02 (1.01-1.03)	0.0006
Sex	Men	221 (68)	-	-		
	Women	106 (32)	1.00 (0.77-1.31)	0.9859		
Race/ethnicity	Non-hispanic white	118 (36)	-	-		
	Black	33 (10)	1.48 (0.96-2.27)	0.0765		
	Hispanic white	88 (27)	1.16 (0.84-1.59)	0.3576		
	Asian/pacific islanders	88 (27)	1.00 (0.73-1.37)	1.0000		
Tumor location	Proximal	98 (30)	-	-		
	Distal	100 (31)	0.90 (0.65-1.24)	0.5173		
	Whole	59 (18)	0.99 (0.69-1.43)	0.9621		
	Middle	70 (21)	0.94 (0.67-1.33)	0.7395		
Grade	Well differentiated	1 (0)	-	-		
	Moderately differentiated	70 (21)	0.38 (0.05-2.73)	0.3338		
	Poorly differentiated	234 (72)	0.48 (0.07-3.43)	0.4642		
	Undifferentiated	18 (6)	0.57 (0.07-4.31)	0.5843		
	Unknown	4 (1)	0.41 (0.04-4.55)	0.4687		
Tumor size	≤ 5cm	117 (36)	-	-		
	> 5cm	145 (44)	1.33 (1.02-1.75)	0.0379		
	Unknown	65 (20)	0.98 (0.66-1.46)	0.9322		
T stage	T2	24 (7)	-	-		
	T3	163 (50)	2.18 (1.17-4.05)	0.0135		
	T4a	96 (29)	2.90 (1.54-5.45)	0.0009		
	T4b	44 (13)	4.86 (2.48-9.53)	< 0.0001		
N stage	N0	38 (12)	-	-		
	N1	261 (80)	1.47 (0.99-2.20)	0.0588		
	N2	15 (5)	1.98 (0.95-4.11)	0.0666		
	N3	13 (4)	1.90 (0.94-3.84)	0.0731		
Node status	N-	38 (12)	-	-		
	N+	289 (88)	1.51 (1.01-2.25)	0.0449		
AJCC7 group[1]	Ⅱ	187 (57)	-	-	-	-
	Ⅲ	140 (43)	1.79 (1.39-2.30)	< 0.0001	1.81 (1.41-2.33)	< 0.0001

[1]Included in multivariate model. AJCC: American joint commission on cancer; Chemo: Chemotherapy.

selection bias. Surgical techniques and chemotherapy options have drastically changed over time. Therefore, resectability criteria have changed in that time period as well. Given the 18-year time period in our study, selection bias could play a role in neoadjuvant chemotherapy determination, surgical resectability criteria used, and adjuvant chemotherapy recommendations. However, we cannot determine in this retrospective study whether these biases would skew the results in any direction. To account for this, we limited our study to patients with Stage Ⅱ and Stage Ⅲ disease given that, in general, they are likely to have resectable disease. Stage I disease was omitted as Stage I patients routinely did not receive chemotherapy. The staging information in the CSP database is based on pathologic staging at the time of surgery. Therefore, we acknowledge that downstaging and decreased tumor burden could have occurred in the neoadjuvant chemotherapy group. However, to limit the potential bias of downstaging disease stage in the cohort that received neoadjuvant chemotherapy, Stage I and Ⅳ disease was omitted from our analysis. In particular, Stage I disease should be treated with surgery first, potentially followed with adjuvant chemotherapy. As such, patients who were documented to have Stage I disease and received neoadjuvant chemotherapy were more likely to have had downstaging of disease.

Another limitation is that although the CSP database provides coding for the receipt of chemotherapy and the first date of chemotherapy, we do not have data on the exact chemotherapy regimen (the type of chemotherapy, number of cycles, dose reductions, *etc.*) or on the successful completion of chemotherapy. Therefore, patients who did have preoperative chemotherapy determined by the first date of surgery could have also received postoperative chemotherapy.

Although the neoadjuvant cohort is smaller than the adjuvant group, our data does not appear underpowered. Prior to the study, a power calculation was performed. Assuming 80% power with a 2-sided log-rank alpha of 0.05 and based on the parameter estimates for neoadjuvant and adjuvant survival in stage Ⅱ patients at 1 year (83% *vs* 77%, respectively), it would take a sample size of 699 patients in each group to find these differences statistically significant. This however, assumes that the 1 year survival curves (neoadjuvant *vs* adjuvant) are parallel and do not cross. Given that the survivals do cross (Figure 1), and due to the fact that the 3 year and 5 year results showing adjuvant survival is longer than neoadjuvant sur-

vival, a larger sample size would not change our overall conclusion.

As the management of gastric cancer continues to evolve, many questions remain unanswered. The extent of surgical resection, choice of adjunct therapy, and timing of therapy remain under debate. In this study, we compared survival following postoperative and preoperative chemotherapy, with similar outcomes observed between the preoperative and postoperative chemotherapy regimens. On the basis of these observations, we propose that a randomized, controlled trial be conducted to define the optimal timing of chemotherapy administration in the management of surgically resectable gastric cancer.

ACKNOWLEDGMENTS

This study was presented at the 7th Annual Academic Surgical Congress held February 14-16, 2012.

COMMENTS

Background

Gastric adenocarcinoma is cancer of the stomach. The outcome of patients diagnosed with gastric cancer is determined by stage of disease. Though surgery remains the best curative-intent treatment, recurrence rates are unfortunately high. Multiple studies have evaluated the benefit of surgery alone or combined with chemotherapy, but there are few studies evaluating the timing of chemotherapy around surgery.

Research frontiers

Multimodality therapies are now being investigated for the treatment of gastric cancer, such as chemoradiation and intraperitoneal chemotherapy; yet these therapies are not standard of care.

Innovations and breakthroughs

The mainstay of treatment is surgical resection either with perioperative chemotherapy or postoperative chemotherapy. Most chemotherapy regimens are either 5-fluorouracil (5-FU) based or cisplatin/oxaliplatin based. Asian studies have also shown benefit with adjuvant S-1, an oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine based on a biochemical modulation of 5-FU.

Applications

This study indicates that chemotherapy and surgery provides the best survival benefits for patients with gastric cancer. There was no difference in survival when comparing neoadjuvant chemotherapy to adjuvant chemotherapy alone.

Terminology

Gastric adenocarcinoma: a cancer of the stomach; Neoadjuvant chemotherapy: chemotherapy given prior to surgical resection; Adjuvant chemotherapy: chemotherapy given after surgical resection.

Peer review

The authors investigated outcomes for patients with gastric cancer treated with surgery and chemotherapy using a population-based cancer registry (n = 327). They demonstrated that both chemotherapy and surgical resection are critically important treatment modalities, while reporting no difference in overall survival between patients given neoadjuvant chemotherapy or adjuvant chemotherapy.

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CASE REPORT

Uncommon cause of pneumoperitoneum

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Abstract

Free intraperitoneal air is thought to be pathognomonic for perforation of a hollow viscus. Here, we present a patient with pain in the upper left quadrant, a mild fever and leukocytosis. Free air was suggested under the left diaphragm but during the explorative laparotomy no signs of gastric or diverticular perforation were seen. Further exploration and revision of the computed tomography revealed a perforated splenic abscess. Splenic abscesses are a rare clinical entity. Presenting symptoms are often non-specific and include upper abdominal pain, recurrent or persistent fever, nausea and vomiting, splenomegaly, leukocytosis and left lower chest abnormalities. Predisposing conditions can be very divergent and include depressed immunosuppressed state, metastatic or contiguous infection, splenic infarction and trauma. Splenic abscess should therefore be considered in a patient with fever, left upper abdominal pain and leukocytosis. Moreover, our case shows that splenic abscess can present in an exceptional way without clear underlying aetiology and should even be considered in the presence of free abdominal air.

Key words: Spleen; Abscess; Pneumoperitoneum

Core tip: Free intraperitoneal air is thought to be pathognomonic for perforation of a hollow viscus. Here, we present a patient with pain in the upper left quadrant, a mild fever and leukocytosis. Free air was suggested under the left diaphragm but during the explorative laparotomy no signs of gastric or diverticular perforation were seen. Further exploration and revision of the computed tomography revealed a perforated splenic abscess. Splenic abscesses are a rare clinical entity. Our case shows that splenic abscess can present in an exceptional way without clear underlying aetiology and should even be considered in the presence of free abdominal air.

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INTRODUCTION

Splenic abscess is a rare condition with a reported frequency in autopsy series between 0.1% to 0.7%[1-3]. Presenting symptoms include upper abdominal pain, recurrent or persistent fever, nausea and vomiting, splenomegaly, leukocytosis and left lower chest abnormalities[4,5]. Diagnosis of a splenic abscess is confirmed on ultrasound or computed tomography (CT)-imaging of the abdomen. Splenectomy has been the gold standard treatment for splenic abscess, however more recent percutaneous drainage is also suggested to be safe and effective[1,6,7]. While gas formation in splenic abscess has been described, few have reported pneumoperitoneum as presenting symptom of a ruptured splenic abscess[8-11].

CASE REPORT

A 78-year-old man presented to our Emergency Room with acute abdominal pain located in the upper left quadrant. The pain had presented in the middle of the

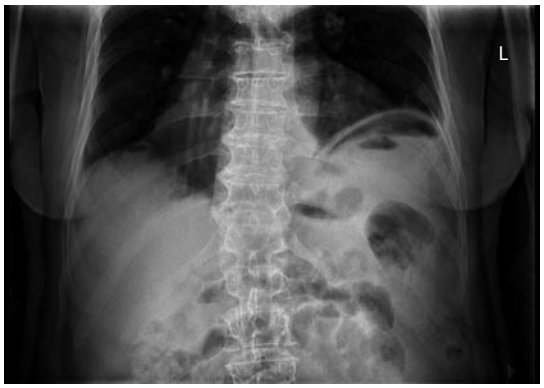

Figure 1 Pneumoperitoneum.

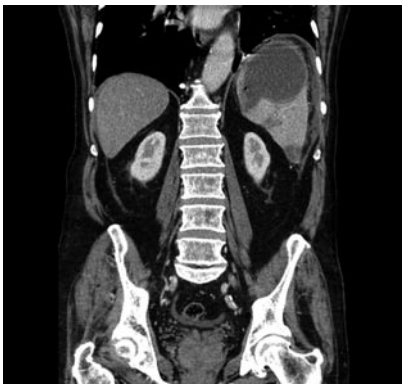

Figure 2 Splenic cyste.

night, waking the patient. No nausea nor vomiting had occurred, but he was experiencing an urge to move. His clinical record mentioned a mild mitralis valve insufficiency, atypical rheumatic complains and diverticulosis. He did not use immunosuppressive medication. Clinical examination reported a painful man with a mild fever and raised pulse. The abdomen was bloated, showed little peristaltic sounds, while percussion of the liver was normal and neither liver nor spleen were palpable. Laboratory findings showed leukocytosis and a raised CRP. On the standing X-ray of the thorax a strong suspicion of free air was suggested under the diaphragm, which was confirmed with an X-ray of the abdomen in left lateral position (Figure 1).

Additional CT showed free air in the upper abdomen with some abdominal fluid left paracolic and in the small pelvis, some left pleural effusion, thickening of the gastric wall and a cyst in the spleen (Figure 2). Therefore, a gastric perforation was suggested. There was no sign of diverticular infiltration or perforation.

After intravenous antibiotics were started on the ER, an explorative laparotomy was performed. No signs of gastric or diverticular perforation were seen. Re-evaluation of the CT in the operation room was performed and the suggestion of an abscess rather than a cyst in the spleen was introduced (Figure 2). Further exploration of the flexura lienalis was performed and pus was evacuated from the upper left quadrant. A ruptured splenic abscess was found and a splenectomy was performed. Cultures remained negative for any grow of bacteria. Pathology report of the spleen revealed an inflammation with abscess and necrosis without micro-organisms or signs of neoplasia. Post-splenectomy vaccinations were prescribed and the patient was discharged 2 wk after admission. Two months after surgery he was in a good clinical condition.

DISCUSSION

Diagnosis of splenic abscess is often not considered due to its rarity and the presence of predisposing conditions which obscure its clinical presentation[6]. Thereby, the aetiology of splenic abscesses is diverse. Three etiological causes of splenic abscesses have been proposed by Kuttner: trauma with secondary infection; per continuitatem; and haematogenous spread[12]. Development by continuitatem has been described in perforated gastric ulcer, perinephric abscess, septic abortion, appendicitis with perforation and in case of concomitant colon carcinoma[1,3,13,14]. Colon carcinoma are also important precursors in the small number of cases in which metastasis of the spleen were secondary infected[15]. Other haematological spread can be caused by retropharyngeal abscess, otitis media, tonsillectomy, infective endocarditis and phlebitis of the calf[3,5,16].

The most common organisms found on bacteriological examination are *Gram Negative Bacillus* (*Klebsiella Pneumoniae*, *Escherichia Coli*) and *Gram Positive Coccus* (*Staphylococcus Aureus*), although a great variety of pathogens have been described[4,17,18].

All studies on this subject stress the strong correlation between splenic abscess and predisposing factors. Direct trauma, infarction or ischemia of the spleen predispose to secondary infection. Especially immunosuppressive state seems to play a great role in the development and rising incidence of splenic abscesses[19]. Furthermore, intravenous drug abuse, human immunodeficiency virus, diabetes mellitus, tuberculosis and neoplasia seem to be contributing diseases[4,8,15,20].

Review of the literature shows only a few cases in which a splenic abscess presented with a pneumoperitoneum[8-11]. In some of these cases the aetiology is clear, but all needed an explorative laparotomy to clarify the diagnosis.

In our case, due to the free abdominal air we expected to find a gastric perforation. The splenic abscess was detected during the explorative laparotomy and only in retrospection the CT-images were interpreted accordingly. Postoperative evaluation revealed no aetiological cause of the splenic abscess. The patient did have diverticulosis, but on operative inspection no inflammation was present. Pathology report of the spleen revealed an inflammation with abscess and necrosis without micro-organisms or signs of neoplasia. Futhermore, blood cultures remained negative in our case. This appears to be the case in approximately 30% of patients with a splenic abscess[4,5]. In conclusion, splenic abscess should be considered in a patient with fever, left upper abdominal pain, and leukocytosis[7]. Moreover, our case shows that splenic abscess can

present in an exceptional way without clear underlying aetiology and should even be considered in the presence of free abdominal air.

COMMENTS

Case characteristics

The presenting symptoms include acute abdominal pain located in the upper left quadrant with and an urge to move.

Clinical diagnosis

The patient had a mild fever and raised pulse, a bloated abdomen which showed little peristaltic sounds.

Differential diagnosis

Based on these findings an extensive differential diagnosis of intra-abdominal pathology arose.

Laboratory diagnosis

Laboratory findings showed a leukocytosis and raised CRP. On the standing X-ray of the thorax free air was suggested and a strong suspicion of perforation of a hollow viscus arose.

Imaging diagnosis

Additional computed tomography showed free air in the upper abdomen with some abdominal fluid left paracolic and in the small pelvis, thickening of the gastric wall and a cyst in the spleen.

Pathological diagnosis

Review of the literature shows only a few cases in which a splenic abscess presented with a pneumoperitoneum. In some of these cases the aetiology is clear, but all needed an explorative laparotomy to clarify the diagnosis.

Treatment

After intravenous antibiotics were started, an explorative laparotomy was performed and a ruptured splenic abscess was treated by a splenectomy.

Related reports

While gas formation in splenic abscesses has been described, few have reported pneumoperitoneum as presenting symptom of a ruptured splenic abscess.

Experiences and lessons

Therefore, splenic abscess should be considered in a patient with fever, left upper abdominal pain and leukocytosis, even in the presence of free abdominal air.

Peer review

This is a very interesting case report.

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CASE REPORT

A gastrointestinal stromal tumor of the third portion of the duodenum treated by wedge resection: A case report

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Key words: Gastrointestinal stromal tumor; Duodenum; Wedge resection; Surgery

Core tip: Duodenal gastrointestinal stromal tumors (GISTs) are uncommon, with a relatively small subset of GISTs whose optimal surgical procedure has not been well defined. Because submucosal spread and local lymph node involvement is infrequent in GISTs, wide margins with routine lymph node dissection may not be required. Various techniques of limited resection for duodenal GISTs have been described, depending on the site and the size of the tumors. Herein, we present a case of GIST involving the third portion of the duodenum successfully treated by wedge resection with primary closure.

Abstract

A 65-year old woman was admitted to our hospital with abdominal pain. Computed tomography showed a tumor measuring about 3 cm in diameter with no metastatic lesion or signs of local infiltration. Gastroduodenal endoscopy revealed the presence of a submucosal tumor in the third portion of the duodenum and biopsy revealed tumor cells stained positive for c-kit. These findings were consistent with gastrointestinal stromal tumors (GISTs) and we performed a wedge resection of the duodenum, sparing the pancreas. The postoperative course was uneventful and she was discharged on day 6. Surgical margins were negative. Histology revealed a GIST with a diameter of 3.2 cm and < 5 mitoses/50 high power fields, indicating a low risk of malignancy. Therefore, adjuvant therapy with imatinib was not initiated. Wedge resection with primary closure is a surgical procedure that can be used to treat low malignant potential neoplasms of the duodenum and avoid extensive surgery, with significant morbidity and possible mortality, such as pancreatoduodenectomy.

Acar F, Sahin M, Ugras S, Calisir A. A gastrointestinal stromal tumor of the third portion of the duodenum treated by wedge resection: A case report. *World J Gastrointest Surg* 2013; 5(12): 332-336 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i12/332.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i12.332

INTRODUCTION

Gastrointestinal tumors are the most common mesenchymal tumors arising within the gastrointestinal tract[1] and the treatment of choice of these tumors is surgical resection[2,3]. The small intestine is the second most common site of gastrointestinal stromal tumor (GIST), of which approximately 20% are found in the duodenum[2]. The optimal surgical procedure for duodenal GIST, however, remains undefined[4] because, while surgical resection clearly confers survival advantage, there is little submucosal spread in GIST and lymphatic involvement is rare. The few reports in the literature addressing the surgical procedures for duodenal GIST include pancreatoduodenectomy, pancreas-sparing duodenectomy, segmental duodenectomy or local resection[4-6]. In this study, we

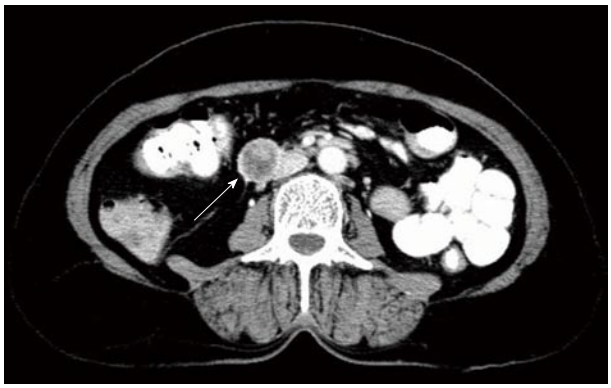

Figure 1 Computed tomography showed a well-demarcated enhancing tumor 4.0 cm in diameter in the third portion of the duodenum (white arrow).

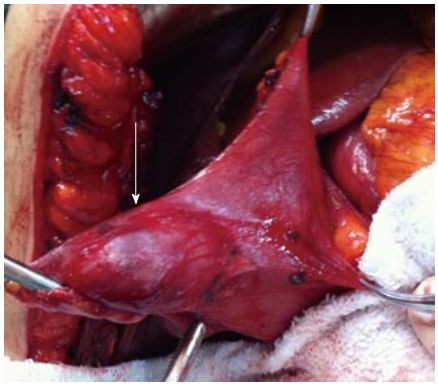

Figure 2 An endophytic gastrointestinal stromal tumor of the third portion of the duodenum (white arrow).

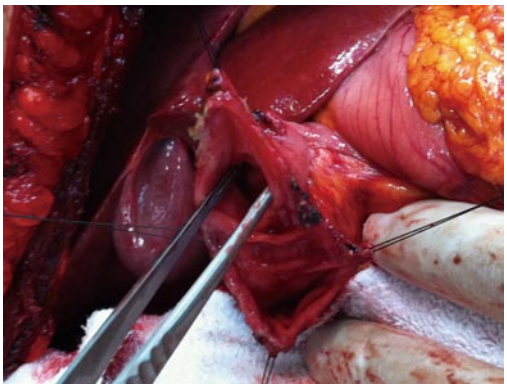

Figure 3 Local limited wedge resection was subsequently performed with clear margins. Surrounding bowel can be seen to be healthy, allowing for a primary anastomosis.

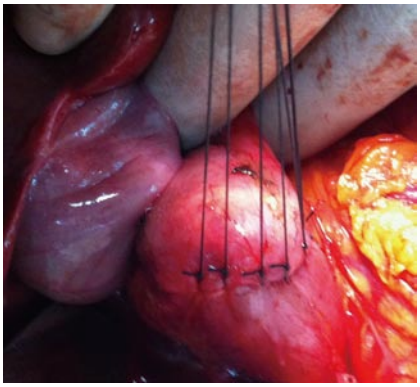

Figure 4 Wedge resection with primary closure.

report a case of GIST involving the third portion of the duodenum successfully treated by wedge resection. This surgical technique is ideal when GIST does not involve the ampulla and has not been previously described for the management of this malignancy.

CASE REPORT

A 65-year old woman presenting with abdominal pain was referred to our hospital. Her medical and family history was unremarkable. She had no history of previous abdominal surgery. On physical examination, mild tenderness was complained of in the right upper quadrant area. Abdominal computed tomography (CT) showed a well-demarcated and enhanced tumor in the third portion of the duodenum, measuring approximately 3.0 cm in diameter. The mass appeared to compress the uncinate portion of the pancreas (Figure 1). From these radiographic findings, we diagnosed a submucosal tumor of the duodenum. She underwent an esophagogastroduodenoscopy, which revealed a submucosal tumor at the second and third portion of the duodenum. A biopsy obtained was reported as GIST. There was no evidence of metastases to her liver or lung. At laparotomy, a 3.0 cm sized solid mass was identified arising from the pancreatic border of the third portion of the duodenum (Figure 2). No evidence of local invasion of the pancreas or of distant metastases was found and the duodenal wall was carefully dissected from the inferior border of the pancreas. Considering that the pancreas and major papilla were not involved, a partial resection was performed, with a 1 cm disease-free margin (Figures 3 and 4). Operative time was 125 minutes and estimated blood loss was 50 mL. Histological examination revealed that the tumor was composed of spindle cells with a mitotic count < 5 mitoses/50 high power fields (Figure 5A and B). Immunohistochemical study revealed positive staining for CD 117 (c-kit) and S-100 (Figure 5C-E). Based on the above findings, the tumor was finally diagnosed as a GIST with low-grade malignancy originating from the duodenum. A molecular genetic analysis for KIT protein mutation was not performed because of its unavailability at our institute. The patient was doing very well with no evidence of disease recurrence when she was last seen, 4 mo after her operation.

DISCUSSION

GISTs are believed to originate from the interstitial cells of Cajal, which are intestinal pacemaker cells or mesenchymal stem cells[7]. A typical feature of virtually all GISTs is a positivity at immunohistochemistry for

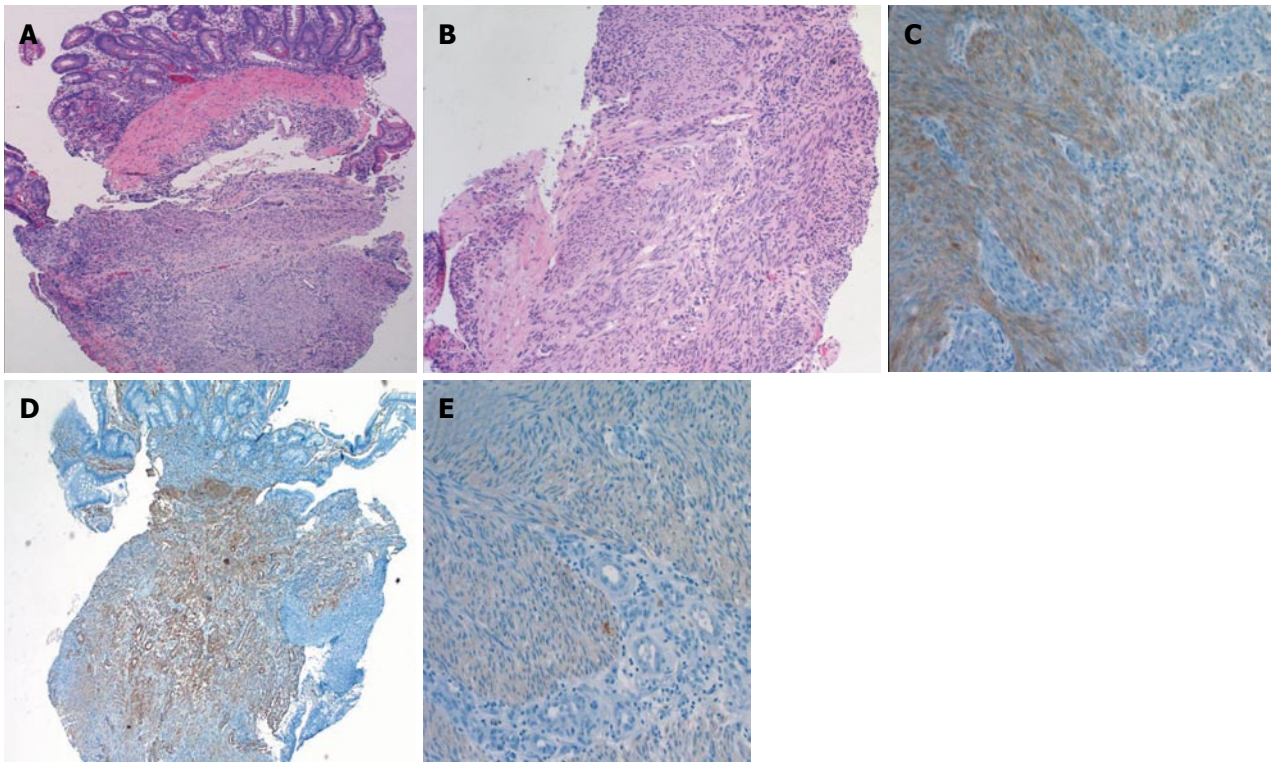

Figure 5 Histology. A: Submucosal tumor tissue is located (hematoxylin-eosin stain, original magnification, × 5); B: Spindle tumor tissue is composed of cells (hematoxylin-eosin stain, original magnification, × 10); C: Tumor tissue widely seen moderately strong staining of CD117 (CD117, original magnification, × 20); D: Tumor tissue widely seen SMA staining (SMA, original magnification, × 5); E: Tumor tissue, common, poor, S-100 staining is observed (S-100, original magnification, × 20).

the KIT protein (CD117), a transmembrane receptor linked to an intracytoplasmic tyrosine kinase[8]. Duodenal GISTs are mainly located in the second portion of the duodenum[9]. The tumors are frequently located in close relationship to the ampulla of Vater, this determining surgical treatment strategy. In the case presented here, the tumor was located 3 cm distal of the papilla. Most duodenal GISTs present with GI bleeding, usually associated with melena and occasionally with massive acute bleeding[9]. Other symptoms like abdominal pain, early satiety, bloating or obstructive jaundice due to involvement of the papilla of Vater were present in our patient. Diagnosis can be made with upper gastrointestinal endoscopy[10]. The tumor is usually exophytic and appears as a submucosal swelling. Sometimes it presents only as an endophytic tumor, as in our case. The biopsy should be deep but may not always be diagnostic. Endoscopic ultrasound can help in delineating the submucosal tumor. Alternative diagnostic means include CT, magnetic resonance imaging (MRI), barium study or ultrasonography[11]. However, CT and MRI seem to be the best imaging modalities for assessment of the primary lesion and detection of metastases[12], although CT scans are not always helpful in specifying the origin of the mass. In several cases reported in the literature, the mass was misdiagnosed as arising from the head of the pancreas[13].

There is currently uniform agreement that the surgical treatment of choice for GISTs is resection of the tumor with clear surgical margins, including adjacent organs as necessary[12]. As local and regional lymph node involvement is infrequent in GIST, routine lymph node dissection is not advocated[11,14,15] and limited resection is frequently performed. The surgical choice depends not only on the size of the tumor, but also on the location in the duodenal wall and the relationship to the ampulla of Vater[12,16,17]. Patients with duodenal GISTs close to the papilla of Vater should be treated by pancreatoduodenectomy. Various techniques of limited resection for duodenal GISTs have been advocated, depending on the site and the size of the tumors. Wedge resection with primary closure can be performed for small lesions if the resulting lumen is adequate and the ampulla can be preserved[9,18]. Segmental duodenectomy with side-to-end or end-to-end duodenojejunostomy can be performed for larger tumors located at the third and fourth portion of the duodenum[18]. Partial duodenectomy with Roux-en-Y duodenojejunostomy can be performed for larger tumors involving the antimesenteric border of the second and third portion of the duodenum[19]. Although a limited operation procedure, such as wedge or segmental resection, is relatively simple to perform, there is a risk of subsequent anastomotic leakage or stenosis development, as well as later tumor recurrence in patients treated by limited operation. By contrast, pancreatoduodenectomy as a treatment for duodenal GISTs can provide a wider surgical margin but may be associated with excessive morbidity, especially in patients with a tumor of low-grade malignancy[20]. It is not clear what the optimal

Table 1 Risk of aggressive behavior in gastrointestinal stromal tumors

Risk	Size (cm)	Mitotic count (mitoses per 50 high powered fields)
Very low risk	< 2	< 5
Low risk	2-5	< 5
Intermediate risk	< 5	6-10
	5-10	< 5
High risk	> 5	> 5
	> 10	Any mitotic rate
	Any size	> 10

Adapted from Fletcher *et al*[22].

surgical margin should be, but a negative one is essential to prevent local recurrence of the tumor. No lymph node dissection is required because they are very unlikely to be involved[18,21]. The outcome depends on the pathological features of the tumor and the completeness of surgical resection. Local recurrence is higher in tumors not completely removed or with a positive microscopic margin. In our patient, no suspicious peritumoral lymph nodes were present. Therefore, in order to minimize operative morbidity, we did not perform a formal lymph node dissection.

Fletcher *et al*[22] established a risk stratification based upon tumor diameter and mitotic activity (Table 1)[22]. The tumor presented in this case belongs to the category determined by size between 2-5 cm and a mitotic count < 5/50 high power fields, which is classified as "low risk". As we performed a wedge resection of the GIST, this indicates a good prognosis for our patient.

Imatinib (Gleevec, Novartis, Basel, Switzerland) is the treatment for locally advanced or metastatic GIST. Imatinib is a signal transduction inhibitor and in particular inhibits the binding of adenosine triphosphate to tyrosine kinase that includes PDGFRA and the c-Kit receptor expressed in GISTs[23]. Recently sunitinib malate, an oral receptor tyrosine kinase inhibitor, was approved for the treatment of GISTs after progression or intolerance to imatinib mesylate. Sunitinib inhibits platelet-derived growth factor receptors and vascular endothelial growth factor receptors, which play key roles in tumor angiogenesis and tumor cell proliferation[24]. As our patient was classified as "low risk", we did not initiate an adjuvant treatment with imatinib.

In summary, we report a case of a duodenal GIST located 3 cm distal of the ampulla of Vater successfully treated by a wedge resection. Wedge resection with primary closure is a surgical procedure that can be used to treat low malignant potential neoplasms of the duodenum and avoid extensive surgery, with significant morbidity and possible mortality, such as pancreatoduodenectomy.

COMMENTS

Case characteristics

A 65 year old woman was admitted to hospital with abdominal pain.

Clinical diagnosis

Gastroduodenal endoscopy revealed the presence of a submucosal tumor in the third portion of the duodenum and biopsy revealed tumor cells stained positive for c-kit.

Imaging diagnosis

Abdominal computed tomography showed a well-demarcated and enhanced tumor in the third portion of the duodenum, measuring approximately 3.0 cm in diameter.

Treatment

The patient underwent an esophagogastroduodenoscopy which revealed a submucosal tumor at the second and third portion of the duodenum.

Related reports

There is currently uniform agreement that the surgical treatment of choice for gastrointestinal stromal tumors is resection of the tumor with clear surgical margins, including adjacent organs as necessary.

Experiences and lessons

Wedge resection with primary closure is a surgical procedure that can be used to treat low malignant potential neoplasms of the duodenum and avoid extensive surgery with significant morbidity and possible mortality such as pancreatoduodenectomy.

Peer review

The manuscript is in general a nice case report but the discussion of the article needs polished.

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CASE REPORT

Fatal aortoesophageal fistula bleeding after stenting for a leak post sleeve gastrectomy

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Abstract

Bariatric surgeries have been used in an effort to curtail the obesity epidemic. The type of surgery used has changed over time, with sleeve gastrectomies being one of the preferred options. This has been associated with some complications, including staple line leaks. We report a 43-year old female who had undergone a laparoscopic sleeve gastrectomy that was complicated by a proximal gastric pouch leak at the gastroesophageal junction. We used self-expandable stents (SEMS) in the management of the leak. Seven weeks after the insertion of the initial SEMS, the patient presented with a massive gastrointestinal bleed that could not be localized due to profuse bleeding. The patient underwent a computerized tomography angiogram and then an angiogram that could not localize the site of the bleed. An emergency laparotomy was performed and identified the source of bleeding to be an aortoesophageal fistula. A graft of the diseased area was attempted but the patient unfortunately did not survive the procedure. An aortoesophageal fistula after an esophageal SEMS insertion for a benign disease has rarely been reported and only in cases where there was a thoracic neoplasm, thoracic aortic aneurism, endovascular stent repair, foreign body or esophageal surgery. To our knowledge, this is the first case that reports an aortoesophageal fistula as a result of a SEMS for the management of a gastric pouch leak after a laparoscopic sleeve gastrectomy.

Key words: Stents; Esophagus; Leak; Surgery; Complication; Aortoesophageal fistula; Endoscopy; Bariatric surgery; Sleeve gastrectomy

Core tip: One modality for managing staple line leaks after laparoscopic sleeve gastrectomies depends on a non-surgical approach, including elimination of oral intake, parenteral nutrition, use of broad spectrum antimicrobial therapy, drainage procedures and the use of esophageal self-expandable metal stents for sealing these leaks and the induction of tissue hyperplasia that would close these defects. Although this seems as a less invasive procedure when compared to a repeated surgical procedure and there is a body of evidence in the literature that supports such an approach, it is not void of complications. Here we report a fatal aortoesophageal fistula as a complication.

Almadi MS, Bamihriz F, Aljebreen AM. Fatal aortoesophageal fistula bleeding after stenting for a leak post sleeve gastrectomy. *World J Gastrointest Surg* 2013; 5(12): 337-340 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i12/337.htm

DOI: http://dx.doi.org/10.4240/wjgs.v5.i12.337

INTRODUCTION

Obesity has become a major public health challenge, associated with a significant morbidity, mortality as well as decreased quality of life. Bariatric surgeries have been used as a modality to treat obesity, preferably after a multidisciplinary assessment. Although such an intervention has been proven to be effective in decreasing the excess weight of patients, it is associated with some complications of which surgical leaks are one of the most unfavorable with a considerable morbidity and mortality[1]. The management of staple line leaks post sleeve gastrectomy has evolved from surgical reinterventions to a less invasive approach with elimination of oral intake, parenteral nutrition, broad spectrum antimicrobial therapy, as well as percutaneous drainage procedures[1]. More recently, the use of esophageal self-expandable metal stents (SEMS) or self-expandable plastic stents (SEPS)[1-3] as method of occluding these leaks has become a more acceptable form of management.

We present an unusual case where a SEMS resulted in a massive gastrointestinal bleed secondary to an aortoesophageal fistula.

CASE REPORT

A 43-year old female was referred to our institution after the development of a proximal gastric pouch staple line leak at the gastroesophageal junction three weeks after a laparoscopic sleeve gastrectomy, which was confirmed by a contrast swallow study. The patient was started on broad-spectrum antibiotics and a percutaneous drainage tube was inserted to treat a subdiaphragmatic fluid collection seen on computer tomography (CT). An esophagogastroduodenoscopy (EGD) showed an opening at the area of the staple line at the gastroesophageal junction (Figure 1A). As one of the preferable modalities to treat staple line leaks post sleeve gastrectomy, a 12 cm fully covered SEMS was inserted (Figure 1B). The patient presented with nausea and vomiting three weeks later. An EGD found the distal end of the SEMS to be narrowed at the antrum angulation, it was removed and a second 15 cm partially covered SEMS was inserted as the staple line leak was still present. Four weeks later, the patient presented with hematemesis, hypotension and tachycardia. She was resuscitated and an EGD showed blood in the stomach but the source of bleeding could not be identified. The patient underwent a CT angiogram (Figure 2) and then an angiogram (Figure 3), but no clear source was found apart from doubtful areas along the left gastric (Figure 4) and gastroduodenal arteries that were coiled, but the patient continued to bleed.

An emergency laparotomy was performed. During exploration, the gastric pouch was opened distally and the stent was removed but the patient continued to bleed proximally, necessitating opening the gastric pouch completely up to the level of gastroesophageal junction where the source of the fresh blood was identified. A small pinpoint hole at the base of a small ulcer in the distal esophagus was bleeding profusely. The diagnosis of an aortoesophageal fistula was made and was confirmed by a left thoracoabdominal incisional approach by a cardiovascular surgeon. A short segment of tense fibrosis between the distal esophagus and aorta with a 2-3 mm opening communicating between them was seen. A graft of the diseased area was attempted but the patient unfortunately did not survive the procedure.

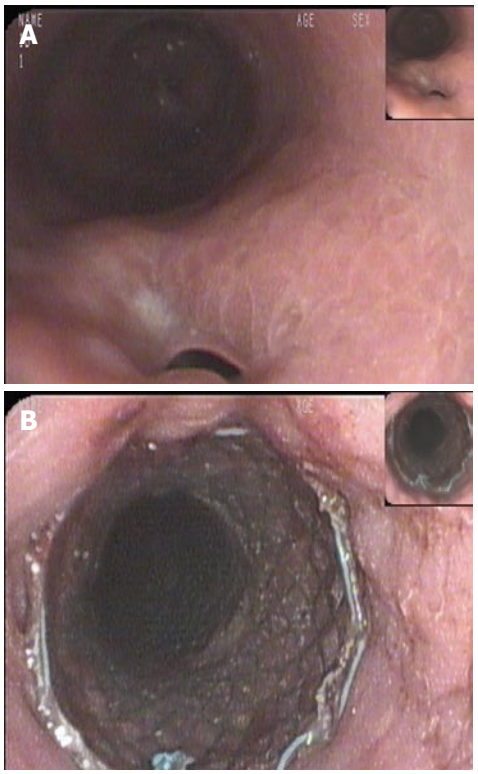

Figure 1 Endoscopic image. A: An opening at the area of the staple line near the gastroesophageal junction; B: A 12 cm fully covered self-expandable metal stent was inserted in the esophagus and overlapped the staple line leak.

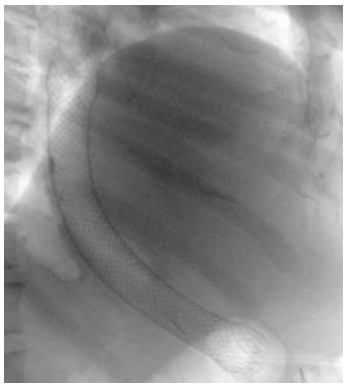

Figure 2 A fluoroscopic image demonstrating the deployed stent in the esophagus with its distal end extending into the stomach remnant.

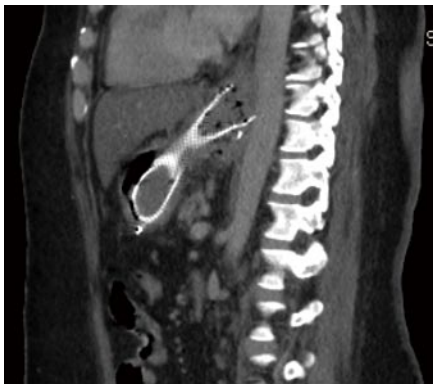

Figure 3 A reconstructed sagittal image of the computed tomography scan demonstrating the proximal aspect of the metal stent in very close proximity to the wall of the descending aorta but there was no evidence of active bleeding.

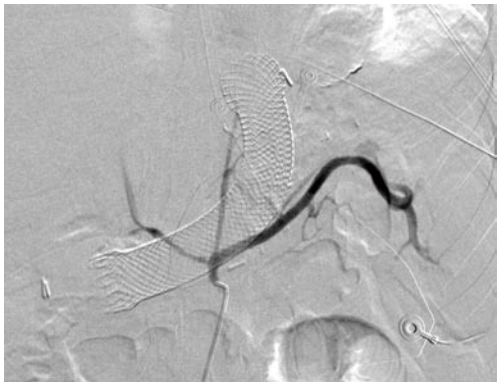

Figure 4 An angiogram of the celiac hepatic and left gastric arteries did not show active bleeding.

DISCUSSION

In two systematic reviews, the incidence of leaks after laparoscopic sleeve gastrectomy was found to be 2.2%[3] to 2.4%[4] and the leaks are usually in the proximal third of the stomach near the gastroesophageal junction in 85%-89%[1,4] of cases, with an associated mortality rate of 6%-14.7%[1]. The use of enteric SEMSs has evolved from the management of malignant diseases to benign strictures as well as leaks. A systematic review incorporating 25 studies with a total of 267 patients demonstrated a success rate of 85% with the use of SEMSs for the management of enteric leaks with no difference in the rate of clinical success between the type of SEMS used, whether partially or fully-covered SEMS or SEPS ($P = 0.97$)[5]. In these studies, the patient population included cases who had esophageal anastomotic leaks or a benign rupture of the esophagus[5]. A second meta-analysis for patients who exclusively had leaks post bariatric surgery and were managed by SEMSs found a success rate of 87.8% (95%CI: 79.4%-94.2%)[6].

An aortoesophageal fistula[7,8] is a rarely reported complication of esophageal SEMS and the majority of reported cases are secondary to thoracic aortic aneurisms, endovascular stent repairs, thoracic neoplasms, foreign bodies, radiofrequency ablation for atrial fibrillation or esophageal surgery. An aortoesophageal fistula after an esophageal SEMS insertion for an esophageal benign disease has rarely been reported and only in cases where there was an esophageal stricture[9,10]. More recently, the management of aortoenteric fistulas has been via thoracic endovascular aortic repair to control bleeding in the acute setting, either as a stand alone procedure or combined with a more definite management in an elective setting[11]. Other management strategies include endovascular aortic repair and subtotal esophageal resection followed by gastroesophageal reconstruction or open thoracic surgery[11]. The advantage of the former approach compared to the stand alone endovascular aortic repair is that, although it controls bleeding acutely, there is a higher probability of graft infection and mediastinitis given that the esophageal defect is not corrected[12]. Even when a diagnosis of an aortoesophageal fistula is reached, the morbidity and mortality is high, reaching up to 40%[13].

In a case series of 52 patients who required SEMSs for enteric leaks, there was a report of a death from severe hemorrhage after the insertion of a fully covered SEMS; the patient refused any intervention and thus the cause of the bleeding was unknown[2]. Also, there was a report of 4 deaths in a series of patients who had stents inserted for leaks after various bariatric surgeries but none were related to the stents[14].

Although the patient had adequate initial resuscitation that permitted the performance of an EGD as well as two radiological procedures, the diagnosis was not easily reached, an emergency surgery was required and even after reaching a definite diagnosis, the patient did not survive the surgery.

This case demonstrates that although the success rate with the use of SEMSs for the management of staple line leaks after laparoscopic sleeve gastrectomies is high, they still have potential complications and a high index of suspicion is required in order to pursue timely management of such complications.

To our knowledge, this is the first case that reports an aortoesophageal fistula as a result of a SEMS for the management of a gastric pouch leak after a laparoscopic sleeve gastrectomy.

COMMENTS

Case characteristics

This is a case of fatal aortoesophageal fistula bleeding after stenting for a leak post sleeve gastrectomy.

Clinical diagnosis

This is the first case that reports an aortoesophageal fistula as a result of a self-expandable stents (SEMS) for the management of a gastric pouch leak after a laparoscopic sleeve gastrectomy.

Experiences and lessons

Although the success rate with the use of SEMSs for the management of staple line leaks after laparoscopic sleeve gastrectomies is high, they still have potential complications and a high index of suspicion is required in order to pursue timely management of such complications.

Peer review

The authors have reported an interesting case of sleeve gastrectomy complication and an alarming finding on metal stent use for treatment of gastro-

esophageal leak.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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