

RESEARCH ARTICLE

Acidic Pelvic Drainage as a Predictive Factor For Anastomotic Leakage after Surgery for Patients with Rectal Cancer**Liu Yang^{1&}, Xin-En Huang^{2*}, Lin Xu^{3*}, Xin Zhou^{1&}, Jian-Nong Zhou¹, Dong-Sheng Yu¹, Dong-zheng Li¹, Xin Guan¹****Abstract**

Purpose: To demonstrate the value of sequential determinations of pelvic drainage in the identification of increased risk of anastomotic leakage (AL) after anterior resection for rectal cancer with a double stapling technique. **Patients and Methods:** Between January 2004 and December 2011, data for the daily postoperative pH of pelvic drainage fluid in 753 consecutive patients with rectal cancer who initially underwent anterior resection with a double stapling technique were reviewed. All patients experienced a total mesorectal excision. Patients with anastomotic leakage (Group AL, n=57) were compared to patients without leakage (Group nAL, n=696). Patients with perioperatively abdominopelvic implants that were likely to affect pH value (determined at 25 °C) other than leakage were excluded. Mean postoperative values were compared. **Results:** Anastomotic leakage was noted in 57 (7.6%) of 753 patients with rectal cancer. The diagnosis of AL was made between the 6th and 12th postoperative day (POD; mean 8th POD). There was no significance of the daily average values of pH on POD1 & 2 in group AL while a significantly sharp decline mean pH value reached its diagnostic point of AL ($p<0.001$) on POD3. A cut-off value of 6.978 on the 3rd POD maximized the sensitivity (98.7%) and specificity (94.7%) in assessing the risk of leakage. **Conclusion:** According to these results, an early and persistent decline of pH value of pelvic drainage fluid after rectal surgery with anastomosis, is a marker of AL. A cut-off value of 6.978 determined at 25°C on POD3 maximizes sensitivity and specificity.

Keywords: Rectal cancer - anastomotic leakage - pH value - pelvic drainage - anterior resection

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Introduction

It has been found that colorectal cancer (CRC) is the third commonest cancer in males and the second in females. In 2008, more over 1.2 million new CRC cases and 608.700 deaths were reckoned to be occurred (Ahmedin et al., 2011). With the advent of stapling devices, surgical operation combining with preoperative chemo-radiation therapy (PCRT) and by means of total preventive ileostomy rate of anal sphincter preservation in present days (Tjandra et al., 2005). Nevertheless, patients with rectal cancer undergoing anterior resection can develop various postoperative complications. It is quite obvious that AL is the severest and most morbid complication.

Anastomotic leak after rectal cancer surgery has been reported to range between 5% and 25% of patients (Mileski et al., 1988; Fazio et al., 2007; Veenhof et al., 2007). Not only, the instant clinical consequences, but also AL carries long-term outcome, such as intra pelvic infection, peritonitis, sepsis, longer hospital stay,

considerable extra cost, increased in-hospital morbidity and mortality, impaired pelvic organ function (Eriksen et al., 2005; Law et al., 2007; Lee et al., 2008; Riss et al., 2011).

Although there are multiple risk factors, such as being male, advanced age, severe obesity, lower tumor site (less than 4cm from the anal verge) and the reduction of TSGF in POD5, which are associated with anastomotic leakage have been reported in our previous study (Yang et al., 2013), it is difficult to predict this complication in individual patients on account of the absence of a diagnostic test and the difficulty with identifying AL at a early stage.

The diagnosis of AL should be as early as possible for the sake of reducing its associated morbidity and mortality (Doeksen et al., 2007). Many studies on anterior resections regarding AL come from multi-center and different surgeons. A variety of factors predisposing to AL have been reported in the previous investigations. However, lack of data about the risk factors and incidence associated with AL from a single-institute of one team of doctors.

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In addition, a great deal previous studies are repetitive works and duplicated efforts because of the limited power of innovative thinking. The pathophysiological character of AL is acute inflammation. In view of the essential role that neutrophils play in acute inflammatory processes and considering that interstitial acidic pH characterizes most inflammatory microenvironments, the notion that extracellular acidosis may intensify the acute inflammatory responses by enhancing neutrophil activity and extending its functional lifespan (Trevani et al., 1999; Martínez et al., 2006). The acidic microenvironments and acute inflammatory promote mutually so that AL is developing and the pelvic draining is becoming acidic, which is the main theoretical foundation for the present research. This study aimed to evaluate the utility of sequential postoperative pelvic drainage determinations of pH value in the identification of the increased likelihood of AL after anterior resection of rectal cancer, which has not been reported ever before.

Materials and Methods

Between January 2004 and December 2011, 753 consecutive patients with rectal cancer underwent anterior resection with double stapling anastomosis for primary rectal cancer at Colorectal Cancer Center, the Affiliated Jiangsu Cancer Hospital of Nanjing Medical University & Jiangsu Institute of Cancer Research, Nanjing, China. The medical notes of all patients were reviewed in detail. Eligibility criteria included rectal cancer, phase I to III of TNM stage, histologically proven adenocarcinoma, open and laparoscopic surgery with pelvic drainage, all patients with 12 postoperative determinations of pH value, and antibiotics using for 7 PODs. Exclusion criteria were as follows: Hartmann's and Miles' procedure, phase IV of TNM stage, colon cancer, hand-sewn anastomosis and perioperatively abdominopelvic implants that might be affect pH value, ongoing infection before surgery or an acquired infection in the postoperative period other than leakage. Rectal cancer was classified according to the distance from the anal verge, as determined by rigid sigmoidoscopy. Total mesorectal excision was adopted as the standard surgical technique according to tumor location. The Ethics Committee of Science approved data collection in the register.

All the patients were assigned to one of two groups according to the presence or absence of AL: with AL (Group AL, n=57), without AL (Group nAL, n=696). The two groups were compared according to the following characteristics: median age, gender, physical status (ASA score), the alcohol and tobacco abuse, tumor site, TNM stage, preoperative BMI, preventive ileostomy, surgical approach (laparotomy vs. laparoscopy), diabetes mellitus (DM), neoadjuvant chemoradiotherapy that was defined as a regimen of oral chemotherapy (carmofur or capecitabine) combined with radiotherapy (45 Gy), sequential postoperative pelvic drainage determinations of pH value that was determined by the pH meter, pp-15 (Sartorius Ltd., Germany) (determined at 25°C). In this study, the considered normal pH values of the pelvic draining were consulted by the mean pH values in Group

nAL, which ranged from 7.200 to 7.700.

The patient was placed in a modified lithotomy, right side down, Trendelenburg position. For patients undergoing laparoscopic surgery, an initial 12-mm port placement was carried out using the open technique, and pneumoperitoneum was accomplished using carbon dioxide. A standard 10-mm laparoscope was inserted through the 12-mm trocar, and then two 5-mm ports were inserted in the upper right and left abdominal quadrants and two more 12-mm ports were placed in the lower right and left abdominal quadrants under laparoscopic guidance. For patients undergoing open surgery, a median incision in lower abdomen was made to expose surgical field.

Clinical AL was defined as the presence of leakage signs and confirmed by diagnostic work-up; consequently, additional surgical treatment was mandatory. All patients diagnosed with AL in present study were defined as the presence of leakage signs (pelvic abscess, fecal or purulent discharge from a drainage tube or wound, peritonitis) and confirmed by radiographic work-up or by operative findings between the 6th and 12th POD (mean 8th POD). The AL in this study was determined by ICD-9 codes 997.4, 567.22 (abdominopelvic abscess), and 569.81 (fistula of the intestine).

Differences between groups were evaluated based on the chi-square or Fisher's exact test for the dichotomic variables and on the ManneWhitney test for the continuous variables. Significance was calculated at the 95% CI and *p* value < 0.05. The ROC (receiver operator characteristic) curves of pH value were used to determine the best cut-off values for AL. The ROC curves are a plot of the sensitivity (true positives) of the test against 1-specificity (false positives), for each threshold of the test (each pH value level). Each point on the ROC curve represents a particular pair of sensitivity and (1-) specificity for each determined threshold. Statistical analyses were performed using IBM SPSS statistics 19.0 for Windows (SPSS Inc; IBM, Chicago, IL).

Research experience

We have published medical researches that were conducted in Jiangsu Cancer Center elsewhere (Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Liu et al., 2012; Gu et al., 2013; Li et al., 2012; Shu et al., 2012; Zhan et al., 2012; Zhan et al., 2012; Xu et al., 2012; Xu et al., 2012; Yu et al., 2012; Zhang, et al., 2012; Zhang et al., 2012; Chen et al., 2013; Dai et al., 2013; Deng et al., 2013; Huang et al., 2013; Liu et al., 2013; Liu et al., 2013; Liu et al., 2013; Lu et al., 2013; Sun et al., 2013; Wei et al., 2013; Wu et al., 2013; Yang et al., 2013; Yin et al., 2013; Yin et al., 2013)

Results

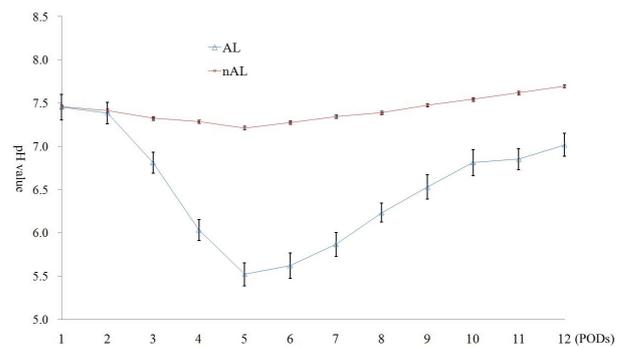
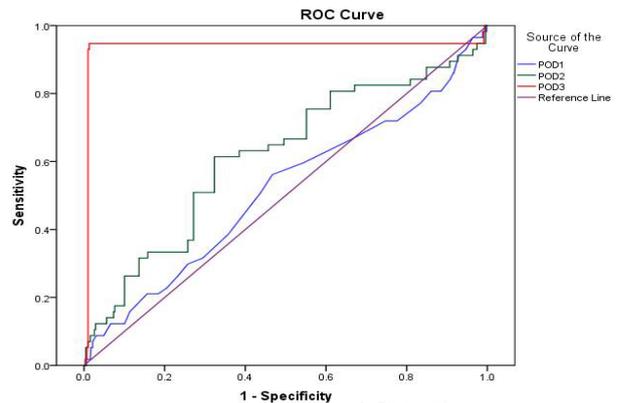
The clinical characteristics of the selected sample stratified by group are detailed in Table 1. The overall AL rate was 7.6% (57/753 patients). A total of 753 patients [452 male patients (60.0%)] with a median age of 65 (50-74) years at the time of surgery were included. The physical

Table 1. Clinical Characteristics of the Selected Sample Stratified by Group

Variable	Group nAL(n=696)	Group AL(n=57)	p value
Age mean (IQR) y	61(50-69)	68 (55-74)	
<65	518	15	<i>p</i> <0.001
≥65	178	42	
Gender			
Male	406	46	<i>p</i> <0.001
Female	290	11	
Physical status (ASA score)			
ASA≤2	607	47	<i>p</i> =0.307
ASA≥3	89	10	
Tobacco abuse			
≤4 cigarettes per day	395	16	<i>p</i> <0.001
≥5 cigarettes per day	301	41	
Alcohol abuse			
≤2 glasses per day	476	42	<i>p</i> =0.407
≥3 glasses per day	220	15	
Tumor site (from the anal verge)			
<4 cm	112	46	<i>p</i> <0.001
≥4 cm	584	11	
TNM stage			
I-II	366	33	<i>p</i> =0.44
III	330	24	
Preoperative BMI			
<35	669	32	<i>p</i> <0.001
≥35	27	25	
Surgical approach			
Laparotomy	616	49	<i>p</i> =0.566
Laparoscopy	80	8	
Preventive ileostomy			
No	647	56	<i>p</i> =0.123
Yes	49	1	
Neoadjuvant chemoradiotherapy			
No	680	54	<i>p</i> =0.170
Yes	16	3	
Diabetes mellitus			
Absence	664	55	<i>p</i> <0.001
Presence	32	9	

status of patients at large were ASA 1 or 2 (86.9%). One hundred and fifty eight (21.0%) patients presented rectal cancer within 4 cm from the anal verge. Among all the patients, 45.4% (342) & 32.2% (235) of whom abused tobacco and alcohol, respectively. Three hundred and fifty four (47.0%) sufferers were diagnosed with phrase III rectal cancer pathologically and postoperatively. The preoperative BMI was equal or greater than 35 (severe obesity) in 52 (6.9%) patients. Nineteen (2.5%) patients received neoadjuvant chemoradiotherapy. A preventive ileostomy was proceeded in 50 (6.6%) sick, and a laparoscopic surgery was performed in 88 (11.7%) patients. Forty one (5.4%) patients presented diabetes mellitus preoperatively.

The correlations between clinical characteristics and AL are summarized in Table 1. Univariate analysis

**Figure 1. Evolution of PH Values in the Postoperative Period in Patients with and Without AL****Figure 2. Receiver Operator Characteristic (ROC) Curve for Cut-off Analysis of Pelvic Drainage PH Value on POD1, 2 and 3 in Patients with AL**

demonstrated that AL was more common in patients with elder age (*p*<0.001), male gender (*p*<0.001), tobacco abuse (*p*<0.001), lower tumor site (*p*<0.001), high preoperative BMI (*p*<0.001), diabetes mellitus (*p*<0.001). Preventive ileostomy and neoadjuvant therapy tended to be associated with the development of anastomotic leakage, with *p* values less than 0.20. Surgical approach, Alcohol abuse, ASA score and TNM stage were not significant risk factors in univariate analysis.

The diagnosis of AL was performed between the 6th and 12th POD (mean 8th POD). There was no statistically significant difference of pH value of pelvic drainage on POD1&2 between the two groups. In the postoperative period, however, it was clearly observed that from POD3 onwards, the values of pelvic pH were significantly lower in group AL (Table 2). The alterations of mean pH values in group nAL were different from group AL. The mean pelvic pH values of both group nAL and AL reached their bottom on POD6, followed by a rapid rise in Group AL while a slight rise in Group nAL, thereafter (Figure 1).

On POD2, mean pH value was 7.384 in group AL and 7.412 in group nAL (*p*=0.821). On POD3, those values were 6.811 in group AL and 7.325 in group nAL (*p*<0.001)

Table 2. Mean Values of pH in the Postoperative Periods (Group AL; Group nAL)

	pH value											
	POD1	POD2	POD3	POD4	POD5	POD6	POD7	POD8	POD9	POD10	POD11	POD12
Group AL	7.453	7.384	6.811	6.034	5.522	5.621	5.867	6.234	6.529	6.812	6.852	7.017
Group nAL	7.459	7.412	7.325	7.285	7.211	7.277	7.346	7.387	7.476	7.543	7.618	7.697
<i>p</i>	0.968	0.821	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table 3. Sensitivity and Specificity of pH Value of Pelvic Drainage Used as a Cut-off in the Identification of AL, Calculated on POD 2 and 3 (ROC analysis)

pH value	POD2		POD3	
	sensitivity(%)	specificity(%)	sensitivity(%)	specificity(%)
6.691	99.4	5.3	99	10.5
6.875	99.4	5.3	99	84.2
6.911	99.4	5.3	99	93
6.978	99.4	5.3	98.7	94.7
7.058	99.3	5.3	98	94.7
7.108	99	5.3	95.5	94.7

(Table 2). Based on the evaluation of the ROC curves (Figure 2), a cut-off value of 6.978 on POD3 maximized the sensitivity (98.7%) and specificity (94.7%) of pH value in predicting the risk of leakage (Table 3).

Discussion

The AL rate after colorectal surgery varies between 1% and 40%, rest with the definition of AL and on the type of resection performed, being higher in extraperitoneal anastomosis (Bellows et al., 2009). The rate of 7.6% in this study falls within the range of previously published series. This rate is, however, lower than the average leakage rate of 10% reported in a systematic review (Paun et al., 2010). It is also lower than the leakage rate reported in a similar study from Denmark looking at this complication using a population database (Bertelsen et al., 2009).

It is not different from comparable reports that the low leakage rate in the present study could be explained by the fact that may be a reflection of technically skilled surgery. Success to mobilize the splenic flexure, success to perform high ligation of the inferior mesenteric artery to ensure the collateral blood supply, and success to test the integrity of the anastomosis can contribute to the low leakage rate.

In previous study, this complication is associated with high mortality (4%-15%), result in more than a third of hospital deaths after colorectal surgery (Bokey et al. 1995). Hence, the need for an early diagnosis of AL turns into clear. However, this diagnosis is always difficult in the early postoperative days because of lack of clinical manifestations present at that time, which contributes to increased morbidity and mortality. The develop a fever, presence of infectious or abdominal symptoms, such as pain and tympany do not allow an early diagnosis of leakage, as these symptoms usually occur after POD5. Nevertheless, in accordance with some studies, these may be perceived as complications that precede by several days the diagnosis of AL. Not only the presence of fever and abdominal symptoms, but also the time it takes to recover bowel function, are lacking in specificity in identifying patients with AL (Bellows et al., 2009; Ortega-Deballon et al., 2010).

In the light of the viewpoint that the delayed diagnosis (after POD5) of AL is related to a mortality of 18%, but bottommost morbidity if diagnosed and treated before POD5. Early detection of the complication is imperative for prompt establishment of treatment, making early

characteristic markers utile (Alves et al., 2002).

The abbreviation pH can be viewed as power of the concentration of the Hydrogen ion. In technical terms, pH is the negative logarithm of the activity of the solvated hydronium ion, more often expressed as the measure of the hydronium ion concentration. In chemical field, pH is a measure of the acidity or basicity of an aqueous solution. The pH value is stemmed from a set of standard solutions whose pH is established by international agreement (Covington et al., 1985). Measurements of pH are important in medicine, biology and many other scientific applications. In present study, sequential postoperative pelvic drainage determinations of pH value that was determined by the pH meter, pp-15 (Sartorius Ltd., Germany), which was accurate and convincing. Its advantage and convenient, makes pH a valuable marker for detecting disease activity, inflammatory response and the appearance of postoperative complications. Based on the academic and technical applications above, the pH values of both groups in the postoperative periods were determined in this series.

The anastomosis after a low anterior resection, however, usually leads to local acute inflammation at the anastomotic site in pelvic cavity. It has been reported that the decreased pH at the site of an inflammatory reactions is attributed to the local increase in the concentration of lactic acid produced by the glycolytic activity of the polymorphonuclear leukocytes of the exudates, furthermore, although the blood pH remained unchanged, the pH of the inflammatory exudate decreased with time showing a definite fall at 24 hour and reaching the lowest value at 72 hour (Donald et al., 1971).

Numerous studies of the cellular and molecular mechanism about pH and acute inflammation indicated that large numbers of cells, cytokines, ions and inflammatory mediators migrate from the blood into the exudate during acute inflammatory reactions. It has been proven that the inflammatory cells, with the ability to produce free radicals, are working in a surrounding environment of low pH so that the free radical can mediate tissue injury. Moreover, it is showed that production of superoxide and nitric oxide was also pH-dependent. Impaired pH, regulation of exudative cells mediate cellular dysfunction and impaired resolution of infection at inflammatory sites (Dahlén et al., 1981; Hackam et al., 1996; Benz et al., 1997). In recent years, it was reported that the acute inflammatory responses via inducing neutrophil activation as well as delaying spontaneous apoptosis and extending neutrophil functional lifespan, based on a mechanism dependent on activation of phosphatidylinositol 3-Kinase/Akt and ERK pathways, which were intensified by pH-Dependent regulation of leukocyte 5-lipoxygenase activity in inflammatory exudates. In addition, low pH can also increase stabilin-1 expression and stabilin-1 phagocytosis in macrophages. Extracellular acidification (pH 5.5-7.0) up-regulates stabilin-1 expression in macrophages, thereby modulating the phagocytic capacity of macrophages. Furthermore, extracellular acidosis in peripheral tissues contribute to the initiation of adaptive immune responses by DCs, favoring the development of Th1 immunity (Trevani et al., 1999; Carbonell et al., 2002; Martínez et

al., 2006; Martínez et al., 2007; Park et al., 2012).

To sum up, the acidic microenvironments during inflammatory reactions against pathogens are the outcome of local acid production by anaerobic, glycolytic infiltrating neutrophils and macrophages, and low oxygen tensions in inflammatory regions. As is mentioned above, together with clinical signs and other inflammatory markers, pH level can be evaluated as an indicator of an unfavorable postoperative course. Given the potential complications associated with AL in rectal surgery, particular emphasis has also been given to this marker in this area.

For the reason that tissue ischemia at the anastomotic loop by a double stapling technic of a leaking anastomosis, it seems to be responsible for the appearance of an intense and early inflammatory response, with subsequent decreased pelvic pH value. The theory stating that poor tissue perfusion increases the risk of anastomotic complications. In a series of animal and human models, the decrease in anastomotic tissue oxygen tension that causes changes in the healing process could be demonstrated (Shandall et al., 1985; Sheridan et al., 1987; Attard et al., 2005). The decrease in anastomotic intramucosal pH level in the postoperative period is significantly associated with increased risk of dehiscence and supports the theory that poor tissue perfusion of an anastomosis starts early and increases the risk of complications (Millan et al., 2006).

In the present study, we have, for the first time, demonstrated that a rapid decrease (6.811) of the pelvic drainage determinations of pH value is on 3rd POD (72 hours after surgical trauma) and the lowest one (5.522) is on POD5 (120 hours after surgical trauma). Thus, somehow, the results are consistent with the reports above for a acute inflammation of surgical injury combining with the acidic stubborn stool leaked from the fistula of the anastomosis, which brings about a secondary infection so that bottom of the pelvic pH value in patients with AL shifts to POD5. On the other side, the pH level of patients without AL goes slowly down to its bottom of 7.211, then smoothly goes up to its top of 7.697, caused by operative trauma only. The changes observed in postoperative pH value of pelvic drainage in patients who developed leakage demonstrate the presence of an inflammatory process after the surgical procedure (and before the occurrence of clinical manifestations).

In this series, we observed that from the third POD onwards, mean pH value was significantly lower in the group who developed leakage, and the diagnosis of the complication was made on the very day, then this marker remained declining until POD5. These results have never been reported before and seem to suggest that the early and sustained decrease of postoperative pelvic pH value may be used as a predictor of AL in patients underwent rectal surgery. Thus, the pretty marker is superior to the others, such as C-creative protein (CRP), which is a hot marker that has been studied repeatedly in present day (Welsch et al., 2007; Matthiessen et al., 2008; Ortega-Deballon et al., 2010; Woeste et al., 2010). The high level CRP in patients with AL may be caused by other infections including respiratory, urinary tract and surgical wound infections, which should be excluded; however the low pH value of pelvic draining in patients with AL is not necessary to

exclude those infectious complications.

Currently procalcitonin has been studied as another earlier marker of inflammatory changes, but squint towards reflect the magnitude of the systemic inflammatory response only on the first half POD, especially after major operation and has to be interpreted with caution (Lagoutte et al., 2012; Garcia-Granero et al., 2013; Ortega-Deballon et al., 2013).

It is possible that some patients in group nAL might have had a subclinical anastomotic leakage. However, these patients usually do not require therapeutic intervention and our primary goal was to achieve an early identification of clinically significant complications, associated with increased morbidity and mortality, and that might benefit from earlier treatment.

Present study is a retrospective analysis of a large sing-center database with limitations. Coding for comorbidities and postoperative complications may result in skewed results due to the vague nature of ICD-9 definitions for these variables. This retrospective review, however, is one of the largest and most comprehensive studies investigating the risk factors for AL after anterior resection.

In summary, according to the results of present study, an early and persistent decline of pH value of pelvic drainage after rectal surgery with anastomosis, is a marker for predicting and diagnosing AL. A cut-off value 6.978 determined at 25°C on POD3 maximizes sensitivity and specificity. Daily postoperative pelvic pH value measurements may therefore be useful in identifying those patients requiring careful clinical reassessment and possibly imaging to confirm or exclude AL.

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References

- Alves A, Panis Y, Trancart D, et al (2002). Factors associated with clinically significant anastomotic leakage after large bowel resection: multivariate analysis of 707 patients. *World J Surg*, **26**, 499-502.
- Attard JA, Raval MJ, Martin GR, et al (2005). The effects of systemic hypoxia on colon anastomotic healing: an animal model. *Dis Colon Rectum*, **48**, 1460-70.
- Bellows CF, Webber LS, Albo D, et al (2009). Early predictors of anastomotic leaks after colectomy. *Tech Coloproctol*, **13**, 41-47.
- Benz M, Werz O, Jacob R, et al (1997). pH-dependent regulation of leukocyte 5-lipoxygenase activity in inflammatory exudates by albumin. *Inflamm Res*, **46**, 366-72.
- Bertelsen CA, Andreasen AH, Jørgensen T, et al (2010). Anastomotic leakage after anterior resection for rectal cancer: risk factors. *Colorectal Dis*, **12**, 37-43.

- Bokey EL, Chapuis PH, Fung C (1995). Postoperative morbidity and mortality following resection of the colon and rectum for cancer. *Dis Colon Rectum*, **38**, 480-7.
- Carbonell T, Ródenas J, Alfaro V, et al (2002). Extracellular pH affects inflammatory cell production of superoxide and nitric oxide. *J Physiol Biochem*, **58**, 115-20.
- Chen G, Shen ZL, Wang L, et al (2013). Hsa-miR-181a-5p expression and effects on cell proliferation in gastric cancer. *Asian Pac J Cancer Prev*, **14**, 3871-5.
- Covington AK, Bates RG, Durst RA (1985). Definitions of pH scales, standard reference values, measurement of pH, and related terminology. *Pure Appl Chem*, **57**, 531-42.
- Dahlén SE, Björk J, Hedqvist P, et al (1981). Leukotrienes promote plasma leakage and leukocyte adhesion in postcapillary venules: in vivo effects with relevance to the acute inflammatory response. *Proc Natl Acad Sci U S A*, **78**, 3887-91.
- Dai XZ, Yin HT, Sun LF, et al (2013). Potential therapeutic efficacy of curcumin in liver cancer. *Asian Pac J Cancer Prev*, **14**, 3855-9.
- Deng QQ, Huang XE, Ye LH, et al (2013). Phase II trial of Loubo® (Lobaplatin) and pemetrexed for patients with metastatic breast cancer not responding to anthracycline or taxanes. *Asian Pac J Cancer Prev*, **14**, 413-7.
- Doeksen A, Tanis PJ, Vrouenraets BC, et al (2007). Factors determining delay in relaparotomy for anastomotic leakage after colorectal resection. *World J Gastroenterol*, **13**, 3721-5.
- Donald W, Edlow, Walter H, et al (1971). The pH of Inflammatory Exudates. *Exp Biol Med*, **137**, 1328-32.
- Eriksen MT, Wibe A, Norstein J, et al (2005). Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. *Colorectal Dis*, **7**, 51-7.
- Fazio VW, Zutshi M, Remzi FH, et al (2007). A randomized multicenter trial to compare long-term functional outcome, quality of life, and complications of surgical procedures for low rectal cancers. *Ann Surg*, **246**, 481-490.
- Gao LL, Huang XE, Zhang Q, et al (2011). 14.A Cisplatin and vinorelbine (NP) regimen as a postoperative adjuvant chemotherapy for completely resected breast cancers in China: final results of a phase II clinical trial. *Asian Pac J Cancer Prev*, **12**, 77-80.
- Garcia-Granero A, Frasson M, Flor-Lorente B, et al (2013). Procalcitonin and C-reactive protein as early predictors of anastomotic leak in colorectal surgery: a prospective observational study. *Dis Colon Rectum*, **56**, 475-83.
- Gong P, Huang XE, Chen CY, et al (2012). Comparison on complications of peripherally inserted central catheters by ultrasound guide or conventional method in cancer patients. *Asian Pac J Cancer Prev*, **13**, 1873-5.
- Gu M, Li SY, Huang XE, et al (2013). A phase II study on continuous infusional paclitaxel and 5-Fu as first-line chemotherapy for patients with advanced esophageal cancer. *Asian Pac J Cancer Prev*, **13**, 5587-91.
- Hackam DJ, Grinstein S, Nathens A, et al (1996). Exudative neutrophils show impaired pH regulation compared with circulating neutrophils. *Arch Surg*, **131**, 1296-301.
- Huang XE, Li CG, Li Y, et al (2011). Weekly TP regimen as a postoperative adjuvant chemotherapy for completely resected breast cancer in China: final result of a phase II trial. *Asian Pac J Cancer Prev*, **12**, 2797-2800.
- Huang XE, Wei GL, Huo JG, et al (2013). Intrapleural or intraperitoneal lobaplatin for treatment of patients with malignant pleural effusion or ascites. *Asian Pac J Cancer Prev*, **14**, 2611-4.
- Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *Ca Cancer J Clin*, **61**, 69-90.
- Lagoutte N, Facy O, Ravoire A, et al (2012). C-reactive protein and procalcitonin for the early detection of anastomotic leakage after elective colorectal surgery: pilot study in 100 patients. *J Visc Surg*, **149**, 345-9.
- Law WL, Choi HK, Lee YM, et al (2007). Anastomotic leakage is associated with poor long-term outcome in patients after curative colorectal resection for malignancy. *J Gastrointest Surg*, **11**, 8-15.
- Lee WS, Yun SH, Roh YN, et al (2008). Risk factors and clinical outcome for anastomotic leakage after total mesorectal excision for rectal cancer. *World J Surg*, **32**, 1124-9.
- Li CG, Huang XE, Li Y, et al (2011). Clinical observations on safety and efficacy of OxyContin® administered by rectal route in treating cancer related pain. *Asian Pac J Cancer Prev*, **12**, 2477-8.
- Li CG, Huang XE, Xu L, et al (2012). Clinical application of serum tumor associated material (TAM) from non-small cell lung cancer patients. *Asian Pac J Cancer Prev*, **13**, 301-4.
- Li CG, Huang XE, Li Y, et al (2011). Phase II trial of irinotecan plus nedaplatin (INP) in treating patients with extensive stage small cell lung cancer. *Asian Pac J Cancer Prev*, **12**, 487-90.
- Li Y, Yan PW, Huang XE, et al (2011). MDR1 gene C3435T polymorphism is associated with clinical outcomes in gastric cancer patients treated with postoperative adjuvant chemotherapy. *Asian Pac J Cancer Prev*, **12**, 2405-09.
- Liu J, Huang XE, Tian GY, et al (2013). Phase II study on safety and efficacy of Yadanzi® (Javanica oil emulsion injection) combined with chemotherapy for patients with gastric cancer. *Asian Pac J Cancer Prev*, **14**, 2009-12.
- Liu W, Li SY, Huang XE, et al (2012). Inhibition of tumor growth in vitro by a combination of extracts from *rosa roxburghii* tratt and *fagopyrum cymosum*. *Asian Pac J Cancer Prev*, **13**, 2409-14.
- Liu YC, Zhou SB, Gao F, et al (2013). Phase II study on breast conservative surgery plus chemo- and radiotherapy in treating Chinese patients with early staged breast cancer. *Asian Pac J Cancer Prev*, **14**, 3747-50.
- Liu YC, Zhou SB, Gao F, et al (2013). Chemotherapy and late course three dimensional conformal radiotherapy for treatment of patients with stage III non- small cell lung cancer. *Asian Pac J Cancer Prev*, **14**, 2663-5.
- Lu YY, Huang XE, Xu L, et al (2013). Potential predictors of sensitivity to pemetrexed as first-line chemotherapy for patients with advanced non-squamous NSCLC. *Asian Pac J Cancer Prev*, **14**, 2005-8.
- Martínez D, Vermeulen M, Trevani A, et al (2006). Extracellular acidosis induces neutrophil activation by a mechanism dependent on activation of phosphatidylinositol 3-kinase/Akt and ERK pathways. *J Immunol*, **176**, 1163-71.
- Martínez D, Vermeulen M, von Euv E, et al (2007). Extracellular acidosis triggers the maturation of human dendritic cells and the production of IL-12. *J Immunol*, **179**, 1950-9.
- Matthiessen P, Henriksson M, Hallböök O, et al (2008). Increase of serum C-reactive protein is an early indicator of subsequent symptomatic anastomotic leakage after anterior resection. *Colorectal Dis*, **10**, 75-80.
- Mileski WJ, Joehl RJ, Rege RV, et al (1988). Treatment of anastomotic leakage following low anterior resection. *Arch Surg*, **123**, 968-71.
- Millan M, Garcia-Granero E, Flor B, et al (2006). Early prediction of anastomotic leak in colorectal cancer surgery by intramucosal pH. *Dis Colon Rectum*, **49**, 595-601.
- Ortega-Deballon P, Facy O, Binquet C (2013). C-reactive protein and procalcitonin as predictors of anastomotic leak. *Dis Colon Rectum*, **56**, 395.
- Ortega-Deballon P, Radais F, Facy O, d'Athis P, et al (2010). C-reactive protein is an early predictor of septic

- complications after elective colorectal surgery. *World J Surg*, **34**, 808-14.
- Park SY, Bae DJ, Kim MJ, et al (2012). Extracellular low pH modulates phosphatidylserine-dependent phagocytosis in macrophages by increasing stabilin-1 expression. *J Biol Chem*, **287**, 11261-71.
- Paun BC, Cassie S, MacLean AR, et al (2010). Postoperative complications following surgery for rectal cancer. *Ann Surg*, **251**, 807-818.
- Riss S, Stremitzer S, Riss K, et al (2011). Pelvic organ function and quality of life after anastomotic leakage following rectal cancer surgery. *Wien Klin Wochenschr*, **123**, 53-57.
- Shandall A, Lowndes R, Young HL (1985). Colonic anastomotic healing and oxygen tension. *Br J Surg*, **72**, 606-9.
- Sheridan WG, Lowndes RH, Young HL (1987). Tissue oxygen tension as a predictor of colonic anastomotic healing. *Dis Colon Rectum*, **30**, 867-71.
- Shu J, Li CG, Liu YC, et al (2012). Comparison of Serum Tumor Associated Material (TAM) with Conventional Biomarkers in Cancer Patients. *Asian Pac J Cancer Prev*, **13**, 2399-403.
- Sun MQ, Meng AF, Huang XE, et al (2013). Comparison of psychological influence on breast cancer patients between breast-conserving surgery and modified radical mastectomy. *Asian Pac J Cancer Prev*, **14**, 149-52.
- Wu XY, Huang XE, You SX, et al (2013). Phase II study of pemetrexed as second or third line combined chemotherapy in patients with colorectal cancer. *Asian Pac J Cancer Prev*, **14**, 2019-22.
- Trevani AS, Andonegui G, Giordano M, et al (1999). Extracellular acidification induces human neutrophil activation. *J Immunol*, **162**, 4849-57.
- Tjandra JJ, Kilkenny JW, Buie WD, et al (2005). Standards practice task force; American society of colon and rectal surgeons. Practice parameters for the management of rectal cancer (revised). *Dis Colon Rectum*, **48**, 411-423.
- Veenhof AA, Kropman RH, Engel AF, et al (2007). Preoperative radiation therapy for locally advanced rectal cancer: a comparison between two different time intervals to surgery. *Int J Colorectal Dis*, **22**, 507-513.
- Welsch T, Müller SA, Ulrich A, et al (2007). C-reactive protein as early predictor for infectious postoperative complications in rectal surgery. *Int J Colorectal Dis*, **22**, 1499-507.
- Wei GL, Huang XE, Huo JG, et al (2013). Phase II study on pemetrexed-based chemotherapy in treating patients with metastatic gastric cancer not responding to prior palliative chemotherapy. *Asian Pac J Cancer Prev*, **14**, 2703-6.
- Woeste G, Muller C, Bechstein WO, et al (2010). Increased serum levels of C-reactive protein precede anastomotic leakage in colorectal surgery. *World J Surg*, **34**, 140-6.
- Xu JW, Li CG, Huang XE, et al (2011). Ubenimex capsule improves general performance and chemotherapy related toxicity in advanced gastric cancer cases. *Asian Pac J Cancer Prev*, **12**, 985-7.
- Xu HX, Huang XE, Li Y, et al (2011). A clinical study on safety and efficacy of Aidi injection combined with chemotherapy. *Asian Pac J Cancer Prev*, **12**, 2233-6.
- Xu HX, Huang XE, Qian ZY, et al (2011). Clinical observation of Endostar® combined with chemotherapy in advanced colorectal cancer patients. *Asian Pac J Cancer Prev*, **12**, 3087-90.
- Xu T, Xu ZC, Zou Q, Yu B, Huang XE (2012). P53 Arg72Pro polymorphism and bladder cancer risk--meta-analysis evidence for a link in Asians but not Caucasians. *Asian Pac J Cancer Prev*, **13**, 2349-54.
- Xu X, Wang L, Xu HQ, Huang XE, et al (2013). Clinical comparison between paclitaxel liposome (Lipusu®) and paclitaxel for treatment of patients with metastatic gastric cancer. *Asian Pac J Cancer Prev*, **14**, 2591-4.
- Yan PW, Huang XE, Yan F, et al (2011). Influence of MDR1 gene codon 3435 polymorphisms on outcome of platinum-based chemotherapy for advanced non small cell lung cancer. *Asian Pac J Cancer Prev*, **12**, 2291-4.
- Yang L, Huang XE, Zhou JN (2013). Risk assessment on anastomotic leakage after rectal cancer surgery: an analysis of 753 patients. *Asian Pac J Cancer Prev*, **14**, 4447-53.
- Yin HT, Zhang DG, Wu XL (2013). In vivo evaluation of curcumin-loaded nanoparticles in a A549 xenograft mice model. *Asian Pac J Cancer Prev*, **14**, 409-12.
- Yin HT, Tian QZ, Guan L (2013). In vitro and in vivo Evaluation of the Antitumor Efficiency of Resveratrol Against Lung Cancer. *Asian Pac J Cancer Prev*, **14**, 1703-6.
- Yu DS, Huang XE, Zhou JN, et al (2012). Comparative study on the value of anal preserving surgery for aged people with low rectal carcinoma in Jiangsu, China. *Asian Pac J Cancer Prev*, **13**, 2339-40.
- Zhang LQ, Huang XE, Wang J (2011). The cyclin D1 G870A polymorphism and colorectal cancer susceptibility: a meta-analysis of 20 populations. *Asian Pac J Cancer Prev*, **12**, 81-5.
- Zhan YP, Huang XE, Cao J et al (2012). Clinical study on safety and efficacy of Qinin® (cantharidin sodium) injection combined with chemotherapy in treating patients with gastric cancer. *Asian Pac J Cancer Prev*, **13**, 4773-6.
- Zhan YP, Huang XE, Cao J, et al (2012). Clinical safety and efficacy of Kanglaite® (Coix Seed Oil) injection combined with chemotherapy in treating patients with gastric cancer. *Asian Pac J Cancer Prev*, **13**, 5319-21.
- Zhang XZ, Huang XE, Xu YL, et al (2012). Phase II study on voriconazole for treatment of Chinese patients with malignant hematological disorders and invasive aspergillosis. *Asian Pac J Cancer Prev*, **13**, 2415-8.