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The Effect of Prophylactic Endoluminal Vacuum Assisted Therapy (pEVAT) to Prevent Anastomotic Leakage of Ultra-low Rectal Anastomoses in High-Risk Patients with Colorectal Cancer

DISSERTATION

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Für Mona und Mhd Adib, meine Eltern.

Für Batoul, meine Frau.

Ich danke euch herzlich für eure unendliche Unterstützung!

I. Abstract

Colorectal Cancer is one of the leading causes of cancer related deaths. With a few exceptions, radical surgery offers the only chance of cure. In cases of ultra-low anterior rectal resections with intersphincteric coloanal or rectoanal anastomoses and the presence of additional risk factors, an anastomotic leak is a fearful complication and one of the main causes of patients' postoperative morbidity and mortality. In the past two decades, the endoluminal vacuum-assisted therapy (EVAT) has proven its efficacy in healing such anastomotic insufficiencies and in many cases, avoiding the need of re-surgery. We here present a novel use for prophylactic endoluminal vacuum-assisted therapy (pEVAT) to protect these difficult or "impossible" anastomoses.

Our study consisted of 33 patients divided into two groups. The control group included 20 patients who underwent an ultra-low rectal resection for colorectal cancer with an anastomosis measuring 5 cm or less from the anal verge and a diverting stoma. The study group included 13 patients who, additionally to the above-mentioned procedure, received a pEVAT with an open-pored polyurethane sponge (e.g., Endo-Sponge®) for a medium duration of 9 days (range 4-16 days), Patient characteristics and risk factors, as well as postoperative complications were retrospectively collected from medical records and analyzed.

An anastomotic leakage occurred in one (7.7%) of the 13 patients of our study group and in 6 (30%) of the 20 patients of our control group. The only patient of the study group with an anastomotic leak was treated with a therapeutic application of EVAT and healing of the anastomosis was achieved. The application of pEVAT resulted in less anastomotic stenoses (7.7% vs. 35%) and a higher rate of stoma reversal (76.9% vs. 55%) in the study group compared to their counterparts in the control group.

This novel use of prophylactic, endoluminal, vacuum-assisted therapy (pEVAT) showed promising results of preventing an anastomotic leak of ultra-low anastomoses in patients with multiple risk factors. However, further prospective studies are needed to reveal the significance of this new method.

II. Zusammenfasseung:

Das kolorektale Karzinom ist eine der führenden, krebsbedingten Todesursachen. Mit wenigen Ausnahmen bietet die operative Resektion die einzige kurative Therapie. Bei ultratiefen anterioren Rektumresektionen mit intersphinktären koloanalen oder rektoanalen Anastomosen, besonders bei Patienten mit zusätzlichen Risikofaktoren ist eine Anastomoseninsuffizienz eine gefürchtete Komplikation mit erhöhter postoperativer Morbidität und Mortalität der Patienten.

In den letzten zwei Jahrzehnten hat sich die endoluminale Vakuum-unterstützte Therapie (EVAT) als wirksam erwiesen, Anastomoseninsuffizienzen zu heilen und in vielen Fällen eine erneute Operation zu vermeiden. Wir präsentieren hier eine neuartige Anwendung für eine prophylaktische endoluminale Vakuum-unterstützte Therapie (pEVAT) zum Schutz dieser schwierigen oder „unmöglichen“ rektalen Anastomosen.

Unsere Studie besteht aus 33 Patienten in zwei Gruppen. Die Kontrolgruppe umfasste 20 Patienten, die eine ultratiefe Rektumresektion aufgrund eines kolorektalen Karzinoms mit einer Anastomose von 5 cm oder weniger vom Analrand messend sowie einem protektiven Stoma erhielten. Die zweite Studiengruppe mit 13 Patienten erhielt, zusätzlich zum oben genannten Verfahren ein pEVAT mit einem offenporigen Polyurethanschwamm (z.B. Endo-Sponge®) für eine mittlere Dauer von 9 Tagen (Range 4-16 Tage). Patientencharakteristika, Risikofaktoren sowie postoperative Komplikationen wurden retrospektiv aus den Patientenakten erhoben und analysiert.

Eine Anastomoseninsuffizienz trat bei einem (7,7%) von 13 Patienten unserer Studiengruppe und bei sechs (30%) von 20 Patienten unserer Kontrollgruppe auf. Unter Fortfühung der Endovac-Therapie heilte die Anastomoseninsuffizienz (100%) in der Studiengruppe. Außerdem, führte die pEVAT zu einer reduzierten Rate an relevanter Stenosen (7,7% vs. 35%) und einer erhöhten Rate an erfolgreicheen Stomarückverlagerungen (76,9% vs. 55%) in der Studiengruppe im Vergleich zur Kontrollgroupe.

Diese neuartige Anwendung von pEVAT zeigt erste vielversprechende Ergebnisse bei der Verhinderung der Anastomoseninsuffizien bei Patienten mit ultratiefer Anastomose und multiplen Risikofaktoren. Allerdings sind weitere prospektive Studien erforderlich, um die Bedeutung dieser neuen Methode zu bestätigen.

III. Tables' Index:

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V. Abbreviations

AL	Anastomotic leak
APE	Abdominoperineal excision
ASA	American society of Anesthesiology
cm	Centimeter
CRC	Colorectal cancer
CRP	C-reactive protein
CTX	Chemotherapy
e.g.	for example
EUR	Euro
EVAT	Endoluminal vacuum-assisted therapy
HIPEC	Hyperthermic intraperitoneal chemotherapy
i.e.	That is
kg	Kilogram
LARS	Low anterior resection syndrome
m	Meter
N/A	Not available
NPWT	Negative pressure wound therapy
pEVAT	Prophylactic endoluminal vacuum-assisted therapy
PME	Partial mesorectal excision
RTX	Radiotherapy

SSI Surgical site infection

TME Total mesorectal excision

UICC Union for international cancer control

ULAR ultra-low anterior rectal resection

VAC vacuum-assisted closure

Contents

1 Introduction:

1.1 Colorectal cancer

Colorectal carcinoma (CRC) is one of the leading causes of cancer-related morbidity and mortality worldwide. According to the German center for cancer registry data, colorectal cancer is the third most common cause of cancer-related mortality in both men and women [1]. In 2018, 60630 new cases and 24248 deaths related to colorectal cancer were registered in Germany. Rectal cancer accounted for about one third of these cases, making it the seventh most common cancer in Germany [1, 2].

Histopathologically, adenocarcinoma accounts for more than 90% of the cases of malignant rectal tumors. Other histopathologic types include neuroendocrine tumor, adenosquamous carcinoma, signet ring cell carcinoma, sarcoma, etc. [3].

The management of rectal cancer depends on its stage, its histopathologic type, grade of differentiation (grading system) and anatomic location within the rectum (upper, middle or lower third) [4].

According to the international TNM-classification of malignant tumors, CRC can be classified in 4 stages depending on its local growth and infiltration of the rectal wall or adjacent structures, its invasion of local, regional, or distant lymph nodes, and the presence or absence of distant metastases or peritoneal carcinomatosis (Table 1).

TNM Clinical Classification	
T – Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: Invasion of lamina propria [a]
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumour invades subserosa or into nonperitonealised pericolic or perirectal tissues

T4	Tumor directly invades other organs or structures[b,c,d] and/or perforates visceral peritoneum T4a Tumor perforates visceral peritoneum T4b Tumor directly invades other organs or structures
N – Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes N1a Metastasis in 1 regional lymph node N1b Metastasis in 2–3 regional lymph nodes N1c Tumor deposit(s), i.e., satellites, in the subserosa, or in non-peritonealised pericolic or perirectal soft tissue without regional lymph node metastasis
N2	Metastasis in 4 or more regional lymph nodes N2a Metastasis in 4–6 regional lymph nodes N2b Metastasis in 7 or more regional lymph nodes
M – Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis M1a Metastasis confined to one organ (liver, lung, ovary, non-regional lymph node(s)) without peritoneal metastases M1b Metastasis in more than one organ M1c Metastasis to the peritoneum with or without organ involvement

Stage			
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage II	T3, T4	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1, N2	M0
Stage IIIA	T1, T2	N1	M0
	T1	N2a	M0

Stage IIIB	T1, T2	N2b	M0
	T2, T3	N2a	M0
	T3, T4a	N1	M0
Stage IIIC	T3, T4a	N2b	M0
	T4a	N2a	M0
	T4b	N1, N2	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

[a] Tis includes cancer cells confined within the mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

[b] Invades through to visceral peritoneum to involve the surface.

[c] Direct invasion in T4b includes invasion of other organs or segments of the colorectum by way of the serosa, as confirmed on microscopic examination, or for tumors in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria.

[d] Tumor that is adherent to other organs or structures, macroscopically, is classified as cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-3, depending on the anatomical depth of wall invasion

Table 1: TNM-clinical classification and UICC-staging of colorectal cancer [5]

Surgery offers, despite major advances in neoadjuvant and adjunctive therapies, and with very few exceptions (e.g., carcinoma in-situ, where endoscopic resection is possible) the only chance of curative therapy of rectal cancer.

1.2 Surgery of the rectum

Rectal cancer is the most common indication for rectal resection. Other, less-frequent indications include anal cancer, infiltration or involvement of the rectum in a variety of malignant tumors (e.g., ovary, cervix, prostate, urinary bladder), inflammatory bowel disease, ischemia, prolapse, etc...

Rectal resection can be performed with either a primary anastomosis with or without a diverting stoma or in cases of an emergency operation with gross fecal contamination, with closure of the rectal stump and an end colostomy, the so-called Hartmann's procedure. In cases of very low tumors involving the anal sphincter, an abdominoperineal resection (APR) could be necessary to achieve adequate surgical results. The surgical therapy normally includes the removal of the tumor and the draining lymph nodes with a safety margin, depending on the location of the tumor within the rectum. The special anatomical location of the rectum in the narrow pelvis with its proximity to different organs and structures as well its distinctive biological features compared to colon cancer results in a more complex approach in surgical management.

Since its first description by Heald in 1979, the introduction of total mesorectal excision (TME) for tumors of the middle and distal third of the rectum has led to a significant reduction in local recurrence rates [6]. The TME entails the removal of the whole mesorectum along with the rectum down to the pelvic floor including the perirectal fatty tissue and the pararectal lymph nodes, which are the first to be involved by direct invasion or nodal spread of rectal cancer, respectively. The extent of rectal and mesorectal excision depends mainly on tumor localization in relation to anal verge [7]. Thus, for tumors localized in the upper third (>10-15 cm from the anal verge) an anterior resection a partial mesorectal excision (PME) and a primary anastomosis is the tailored surgical therapy. For adenocarcinoma in the middle third (>5-10 cm from the anal verge), a low anterior resection with TME and 5 cm safety margin, a primary anastomosis and a diverting stoma is the treatment of choice. For tumors of the lower third (up to 5 cm from the anal verge) without involvement of the anal sphincter, a rising tendency in the past two decades has become to perform an ultra-low, intersphincteric rectal resection with a coloanal anastomosis and a diverting stoma (figure 1). Thus, the traditional and more radical abdominoperineal resection (APR) with a permanent stoma can be avoided. An exception to the above-described procedures are tumors in an early stage, which are amenable to transanal resection, either endoscopically or surgically. As stated earlier, for very low rectal tumors with direct invasion of adjacent structures or involving the anal sphincter, the abdominoperineal resection with a permanent colostomy continues to be the appropriate surgical management to obtain an adequate safety margin [7, 8].

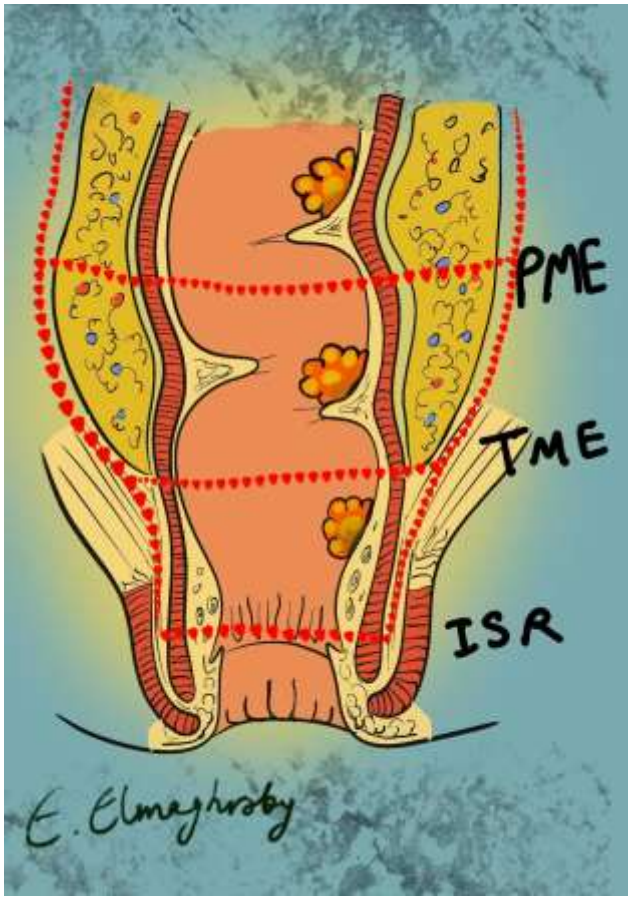

Figure 1: Standard oncological procedures related to the position of rectal tumor (i.e., upper, middle or lower third), PME: partial mesorectal excision, TME: total mesorectal incision, ISR: intersphincteric resection

1.3 Anastomotic Leakage

The most important postoperative complications related to low or ultra-low anterior resection include: anastomotic leakage, bleeding, fistula, stenoses, fecal incontinence and low anterior resection syndrome (LARS). Anastomotic insufficiency is the most feared postoperative complication and direct cause of patients' substantial morbidity and mortality. It also imposes a negative impact upon the oncologic outcome, delaying or even excluding the possibility of adjuvant therapy and adversely affecting the patients' overall survival [9, 10]. Moreover, it causes a prolonged hospital stay with additional cost for the treatment of complications and consequently increasing the burden of the health system. The terms anastomotic insufficiency, leakage, leak or failure were all used throughout the literature to imply the same entity [11].

The low colorectal or coloanal anastomosis is usually considered as “critical”. Removing the mesorectum to minimize the risk of local recurrence along with ligation of the inferior mesenteric artery to ensure a tension-free anastomosis could result in an insufficient blood supply at the level of the anastomosis, impairing the normal healing and resulting in various degrees of insufficiency [12].

The risk factors affecting the healing of these low or ultra-low anastomoses and predisposing the development of an anastomotic insufficiency were extensively studied [12-18]. They can be categorized into:

- General factors affecting the healing process:
  - advanced American Society of Anesthesiologists fitness grade (above II)
  - advanced age
  - sex
  - diabetes mellitus
  - steroid, immune suppressive therapy or chemotherapy
  - chronic arterial atherosclerosis
  - chronic renal or hepatic insufficiency
  - obesity or cachexia
  - preoperative anemia, perioperative blood loss or transfusion
  - chemotherapy (CTX)

- Local factors affecting the healing process:
  - extensive scarring (so-called frozen pelvis)
  - previous pelvic irradiation (RTX)
  - infection or peritonitis
  - intraoperative chemotherapy (HIPEC)

- factors related to the operation itself:
  - preoperative bowl preparation
  - emergency operation (obstruction or perforation)
  - level of the anastomosis, especially ultra-low anastomosis measuring ≤ 5cm from the anal verge

- type of the anastomosis (colorectal or coloanal)
- technique used for the anastomosis (handsewn, stapler)
- high ligation of the inferior mesenteric artery
- tension upon the anastomosis
- length of the operation

In the literature, the occurrence of an anastomotic insufficiency has been reported from 2-26%, depending on the severity of the insufficiency and the level of the anastomosis, i.e., the distance from the anal verge [11-20]. In cases of ultra-low anastomoses (intersphincteric), the risk for anastomotic leakage was found to be more than six folds higher compared to higher anastomoses [16].

The variation in the incidence rates of AL can, at least partially, be ascribed to the fact that there has never been a universally accepted definition of anastomotic leakage, resulting in different criteria to patients with different forms of anastomotic leaks including for example patients with merely radiologic evidence of leakage. In 2010, Rahbari et al from the international study group of rectal cancer proposed a standardized definition and grading system of anastomotic insufficiency after low anterior rectal resection [11]. They defined anastomotic leakage as a defect of the intestinal wall integrity at the colorectal or coloanal anastomotic site (whether it is a suture or stapler line) leading to a communication between the intra- and extraluminal compartments. The severity of anastomotic leak was arranged in three levels:

- Grade A: Anastomotic leaks requiring no further therapy (asymptomatic).
- Grade B: Symptomatic leaks (with clinical, laboratory and radiologic findings), which require active interventional measures other than a re-laparotomy.
- Grade C: Anastomotic leakage with signs of peritonitis which requires a re-laparotomy [11]

Most of the patients undergoing a low anterior rectal resection receive a diverting or a defunctioning stoma (either a colostoma or an ileostoma) to ensure that the healing of the anastomosis is undisturbed from increased intraluminal pressure and bacterial

contamination as fecal material passes through. It was believed that a defunctioning stoma would decrease the incidence of anastomotic insufficiency. However, it remains controversial, with plenty of studies depicting that a fecal diversion via a stoma does not influence the rate of anastomotic leakage. Nevertheless, fecal diversion does decrease the impact of such leaks in terms of sepsis, fecal peritonitis and the need for a re-laparotomy, so that patients undergoing a low or an ultra-low anterior rectal resection (uLAR) routinely receive a defunctioning stoma [14-17, 21-24].

The management of anastomotic leak (AL) depends on its severity and its clinical presentation. Thus, for minor AL (represent grade *A* according to the above-mentioned system) in an otherwise asymptomatic patient, clinical observance with no further therapeutic measures is sufficient. In a grade *B* leakage, presenting as a turbid or faecal discharge from the drains, abdominal pain, laboratory signs of acute infection and accompanied by radiologic evidence of AL or a presacral abscess, therapeutic intervention such as antibiotics, radiologic-guided drainage of the abscess or transanal lavage with a prolonged hospital stay are mostly successful. Grade C anastomotic insufficiencies require a re-laparotomy and probably a Hartmann's procedure [11, 25].

In the past decades, surgeons have tried different approaches to protect the new anastomosis and promote its healing. Transanal drains, temporary percutaneous ileostomy, or intraluminal bypass device all aimed at reducing the incidence of AL. Apart from a defunctioning stoma, none of the different methods gained a widespread acceptance to be routinely applied after LAR or especially uLAR [26-30].

1.4 Vacuum-assisted therapy

1.4.1 Background

The first description of a vacuum system for wound therapy with the use of a polyurethane foam was done by Bagautdinov in 1986, in which a sterile petrolatum and an antiseptic was used to seal the dressing [31]. It was then for Argenta and Morykwas to present the vacuum assisted wound closure (VAC) similar to the dressing we know today. First in an

animal and later in a clinical study, a sub-atmospheric pressure was used in a controlled manner, with positive results ascertaining the role of sub-atmospheric pressure in accelerating wound healing [32, 33]. Since the introduction of a commercial VAC dressing by Kinetic Concept Inc (KCI®), this method of vacuum assisted wound therapy has rapidly extended and been applied in almost every surgical field for an accelerated management of acute, chronic and septic wounds and it is now a well-established therapeutic option for simple and complex wounds. In the last decade, an increasing trend was directed toward a prophylactic use of VAC therapy (e.g., PREVENA®) to decrease the rate of surgical site infection (SSI) in surgeries, where its rate is inevitably high (e.g., colorectal surgery) or where SSI would have devastating consequences (e.g., after problematic joint-replacement) [34].

1.4.2 Application and mechanism of action:

This method involves the application of sub-atmospheric pressure via a specialized device and a dressing made of an open-pore foam, which can be cut down to fit the wound size and secured with an adhesive drape. Various forms of foam were developed to deal with special organs or tissues (e.g., soft tissues, vessels, bone, bowel, etc.).

The applied negative pressure has been described to promote wound healing via direct and indirect mechanisms [35]. The direct effect is achieved through wound sealing, providing adequate moisture needed for the healing process. The continuous suction on the other side ensures that the excessive wound exudate and the edema in the surrounding tissues are actively pumped out of the wound. The open-pore nature of the sponge guarantees that the pressure applied by the pump is equally distributed across the whole surface of the wound. Moreover, the mechanical traction applied to the edges leading to the so-called wound deformity is an important stimulus for the formation of a new granulation tissue [32, 35].

The indirect effect of negative pressure wound therapy is achieved through alteration of the local blood flow at the level of the wound, thereby creating a kind of transient ischemia, which in turn stimulates the production of various growth factors and angioneogenesis, resulting in the formation of the granulation tissue. The continuous suction also reduces the bacterial load as well as the cellular and biochemical mediators

of the inflammatory response (cytokines, monocytes) in the wound, thus eliminating microorganisms and dead tissue preventing or slowing down the healing process [32, 35].

1.4.3 Endoluminal vacuum-assisted therapy (EVAT)

In 2003, Weidenhagen *et al* first described a new method of endoluminal vacuum-assisted therapy (EVAT) of anastomotic leakage after (low) anterior rectal resection [36, 37]. They reported later that EVAT treatment resulted in 96% healing of anastomotic leak without signs or symptoms of peritonitis between 2002 and 2004, pointing out the important role of this novel method [38]. Nagell *et al* also proved the efficacy of this method in treating anastomotic insufficiency and controlling the development of a pelvic sepsis with a noticeable reduction in hospital stay and treatment time [39]. This led to a revolutionary evolution in the treatment of anastomotic leaks. Since then, a numerous, well controlled studies have ascertained the value of this treatment, so that it has become the standard management of AL with or without a pelvic abscess (grade *B* leakage) [39-52]. The application of this method has spread out to include patients with perforation or anastomotic leak in the upper GI-tract, so that it has become the standard treatment in most centers as well [53, 54]. The incidence and treatment of grade *C* leakage remains, nonetheless, predominantly the same, i.e., a re-laparotomy and mostly a Hartmann's procedure [25].

1.5 Aims of the study

The aim of this study is to evaluate the novel use of prophylactic EVAT (from now on mentioned to as pEVAT) and its role at reducing the rate of anastomotic insufficiencies in a subgroup of patients with multiple risk factors receiving an uLAR with a primary anastomosis measuring less than 5 cm from the anal verge and a diverting stoma. To the best of our knowledge, we were the first to present the novel indication of prophylactic EVAT in a case series to prevent anastomotic leakage of high-risk anastomoses in colorectal surgery, which has never been described before [55]. In this study, we wanted to extend our findings with more patients and a matching control group to evaluate the effect of the prophylactic use of EVAT.

Furthermore, we questioned whether pEVAT treatment provokes an anastomotic stenosis compared to the present literature. Moreover, other complications, the total hospital stay and the rate of stoma reversal were compared between the two groups.

With this study we hope to present pEVAT as a reliable method to protect high-risk low colorectal anastomoses, reduce related morbidity and mortality and improve the patient's quality of life.

2. Materials and Methods

2.1 Devices:

Material	Manufacturer
Endo-SPONGE®	B. Braun Medical BV, Melsungen, Germany
Redyrob® Trans Plus suction device	B. Braun Medical BV, Melsungen, Germany
Fiber optic light head 36019 (for proctoscope)	Welchallyn GmbH, Hechingen Germany
UniSpec Disposable Proctoscopes	Heine Optotechnik GmbH & Co. KG. Gilching, Germany

2.2 Patients' selection

Our collective consisted of 33 patients, who underwent surgery for colorectal cancer with an ultra-low resection (including the TME-layer) followed by a colorectal or a coloanal anastomoses measuring 5 cm or less from the anal verge and a defunctioning stoma between 2016 and 2020. All surgical and other procedures took place at the Department of Surgery, Heinrich-Heine-University Hospital in Dusseldorf, Germany. Excluding criteria were: indication for surgery other than colorectal cancer, anastomosis distance from the anal verge >5 cm or missing documentation regarding the level of the anastomosis, or mortality within 30 postoperative days for causes that cannot be ascribed to be related to anastomotic leakage, with or without evidence of an AL at the time of death.

The distance of the anastomosis from the anal verge was either measured intraoperatively or on subsequent proctoscopic or colonoscopic examination. All surgical procedures were done by one of our two senior colorectal surgeons.

2.3 Prophylactic endoluminal vacuum-assisted therapy (pEVAT)

Of the above-mentioned collective, and after performing an uLAR, 13 patients received a prophylactic endoluminal vacuum-assisted therapy (pEVAT) at the end of the operation. The decision to place a pEVAT was based on the judgement of our senior colorectal surgeons upon the condition of the anastomosis and aligned risk factors. In the above-mentioned cases, the anastomosis was considered as high-risk one so that the decision to place a pEVAT was made. An open-cell polyurethane foam (Endo-SPONGE®) was intraoperatively, transanally placed under direct visualization of the anastomosis at the end of the operation to assure a correct placement and was left in place for a mean duration of about 9 days (figure 2).

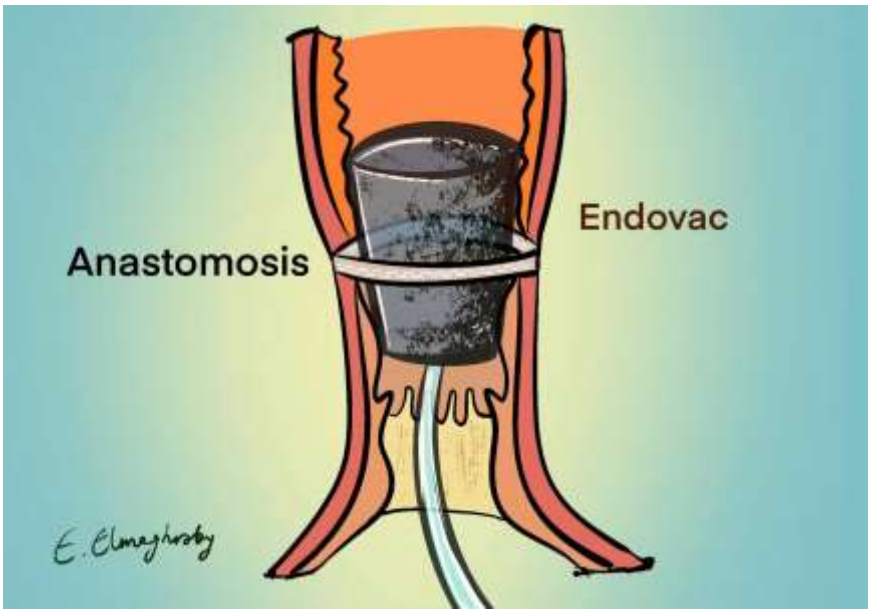

Figure 2: Placement of prophylactic endoluminal vacuum-assisted therapy (pEVAT)

2.3.1 Changing of the endosponge

The endosponge was postoperatively changed every 3-6 days to prevent sponge adhesion to the mucosa. This was done by the operating surgeon himself or an experienced resident, under local anesthesia or sedation and in either the operating room, on the proctology examination chair, or at the bedside depending on the patients` condition and preference.

Figure 3: Endo-sponge® set with a rigid rectoscope and Redoryb® suction device

The draining tube was first disconnected from the bottle to abolish the negative pressure. Then, normal saline with local anesthetic (e.g., lidocaine) was administered over the draining tube to allow the sponge to detach from the adherent mucosa, followed by the removal of the sponge.

The anastomosis was then examined using a proctoscope for integrity, signs of insufficiency or active bleeding. The new sponge was afterwards customized to the diameter of the anastomosis, placed in the introducing tube before it was carefully transanally positioned over the proctoscope at the level of the anastomosis (distance from the anal verge previously measured), and the pushed out of the introducing tube. Finally, the tube and the proctoscope were removed. At the end, the correct placement at the level of the anastomosis was ascertained by careful digital palpation to exclude dislocation of the sponge after removing the introducing tube. The endosponge was then connected to a drain bottle with a constant negative pressure (Redyrob® Trans Plus suction device level one, which matches 150-200 mbar vacuum power).

2.3.2 Termination of the pEVAT

The removal of the pEVAT was based on the local finding of the anastomosis (good healing, no signs of leakage, healthy mucosal lining, no visible stapler line) as well as the absence of local or systemic signs of sepsis, peritonitis or abscess. The decision was made by the operating surgeons.

2.4. Data collection

The data was retrospectively collected from patients' medical records at the Heinrich-Heine university hospital-Dusseldorf / Germany. This included the endoscopic, radiological and laboratory findings, surgical reports, daily clinical charts, discharge letters and post-operative follow-up documentations. The collected data was examined for patients' characteristics, presence of risk factors for anastomotic insufficiency, total hospital stay, total duration of pEVAT in the study group, the rate of anastomotic leakage and other complications, the type of defunctioning stoma used and the total duration of EVAT in patients with an anastomotic leakage.

All data was collected according to the guidelines established by the Declaration of Helsinki and has been approved by the local ethics committee (2020-840).

2.5. Statistical data analysis

Descriptive statistics were used to determine the arithmetic mean, standard deviation of the variables included in the tests and the percentages and frequencies. The odd ratio was used to further reveal the role of PEVAT as an effective method in preventing an AL or reducing other complications such as anastomotic stenosis. Moreover, the same test was used to identify whether a pEVAT application resulted in an increased rate of stoma reversal.

All the statistical analyses performed in this study were done using the Software statistical package for social science (SPSS) for Windows (Version 25.0; SPSS, Inc., Chicago, IL,

USA). The figures were drawn using Procreate 5.3.4., Savage Interactive Pty Ltd., Tasmania.

3. RESULTS:

3.1. Patients' characteristics

Between January 2016 and December 2020, 33 patients were treated in our department and received an ultra-low anterior resection for colorectal cancer. All patients received an ultra-low colorectal or coloanal anastomosis measuring 5 cm or less from the anal verge. In addition to the above-mentioned procedure, all of the patients received a defunctioning stoma, either an ileostoma (n= 7, 21.2%), rarely a jejunostoma (n= 3, 9.1% (, or, in the majority of cases, a colostoma (n= 23, 69.7%(. Of these 33 patients, 31 patients (94%) presented with rectal cancer and two (6%) had colon cancer. Of these two, one patient had a history of rectal cancer and had already undergone a LAR years ago, so that his colon cancer was located deep in his pelvis, anatomically resembling rectal cancer. The other patient had a history of colon cancer and received a right hemicolectomy in the past but suffered a recurrence of his colon cancer with peritoneal carcinomatosis with some lesions invading his rectum, so that an uLAR additionally to the cytoreductive surgery and HIPEC was needed.

This novel technique of a prophylactic endoluminal vacuum-assisted therapy (pEVAT) was applied in thirteen (39.4%) patients. These patients (study group) consisted of nine)69.2%) men and four (30.4%) women. The control group consisting of 20 (60.6%) patients (thirteen [62.5%] men and seven [37.5%] women) with a comparable risk profile, also underwent an uLAR with an anastomosis measuring 5 cm or less from the anal verge (Table 2).

		Study group		Control group	
		n	%	n	%
Gender	male	9	69.2%	13	62.5%
	female	4	30.8%	7	37.5%
Total		13	100 %	20	100%

Table 2: Gender of patients in study and control group

The study group showed a mean age of 65 (range 44-85) years. The mean body-mass-index was 26.2 kg/m² (range 20.7-31.4 kg/m²). Twelve (92.3%) patients had rectal cancer while one (7.7%) had cancer of the sigmoid colon and history of rectal cancer, for which he already underwent a LAR years before (Table3).

In the control group, the mean age was 66 (range 34-88) years and the mean body-mass-index was 25.3 kg/m² (range 14.7-33 kg/m²). Of the 20 patients in this group, 19 (95%) patients had rectal cancer and one (5%) suffered from colon cancer. There was no significant difference in the mean age (p = 0,88), nor in the mean BMI (p = 0,58) between both groups.

	Study group			Control group		
	Minimum	**Maximum**	**Mean**	**Minimum**	**Maximum**	**Mean**
Age	44	85	65	34	88	66
BMI (kg/m²)	20.7	31.4	26.2	14.7	33	25.3

Table 3: Age and BMI in study and control group

3.2. Risk factors

In this study, the major risk factor rendering the anastomosis at risk for leakage was the ultra-low anastomosis measuring 5 cm or less from the anal verge. Patients with an anastomosis of more than 5 cm were excluded from the study. The mean distance of the anastomosis from the anal verge measured 3.5 cm (range 2-5 cm). The mean distance of the anastomosis in the study group was 3.4 cm, whereas in the control group, the mean distance of the anastomosis from anal verge measured 3.6 cm. No significant difference was found between the two groups (p = 0.78) (Table 4).

	Study group		Control group	
Distance of the anastomosis from the anal verge in cm	**n**	**%**	**n**	**%**
2	2	15.4	2	10.0
3	6	46.2	7	35.0
4	2	15.4	9	75.0
5	3	23.1	2	10.0
Total	13	100.0	20	100.0
Mean distance	3.4		3.5	
Median of distance	3		3.7	

Table 4: Distance of the anastomosis from the anal verge in study and control groups

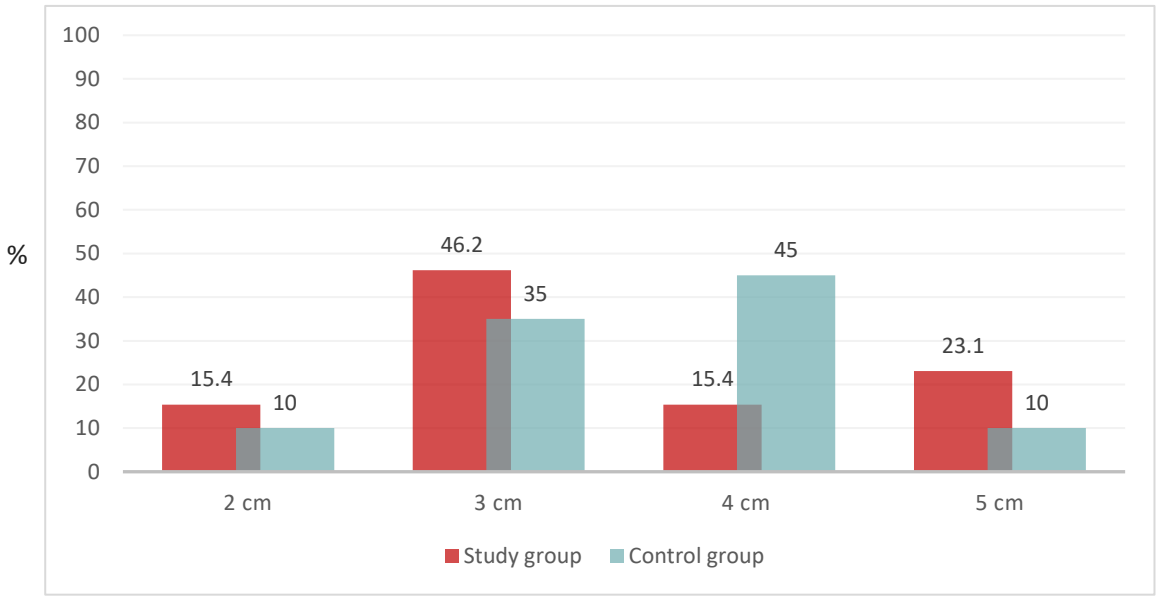

Figure 4: Diagram showing the distance of the anastomosis from the anal verge in both groups

The additional risk factors for anastomotic leak taken into consideration included advanced age, cardiovascular disease (CHD), American Society of Anesthesiologists fitness score (ASA-score) ≥3, cachexia (defined as a body-mass-index ≤ 18,5 kg/m²), overweight (defined as a body-mass-index ≥ 25 kg/m²), intraoperative blood transfusion, duration of surgery > 4 hours, diabetes mellitus, preoperative irradiation of the pelvis, perioperative chemotherapy, acute local infection, sepsis or peritonitis, extensive adhesions (the so-called frozen pelvis), pharmacological immune suppression known to affect wound healing or mechanical dysfunction of stapler device (Table 5).

Number of risk factors the patient has	Study group		Control group	
	n	%	n	%
1	0	0	1	5
2	0	0	2	10
3	3	23	4	20
4	4	30	4	20
5	3	23	3	15
6	0	0	3	15
7	1	7.7	2	10
8	1	7.7	1	5
9	1	7.7	0	0

Table 5: Subgrouping of patients in each group according to the sum of the risk factors for anastomotic leakage

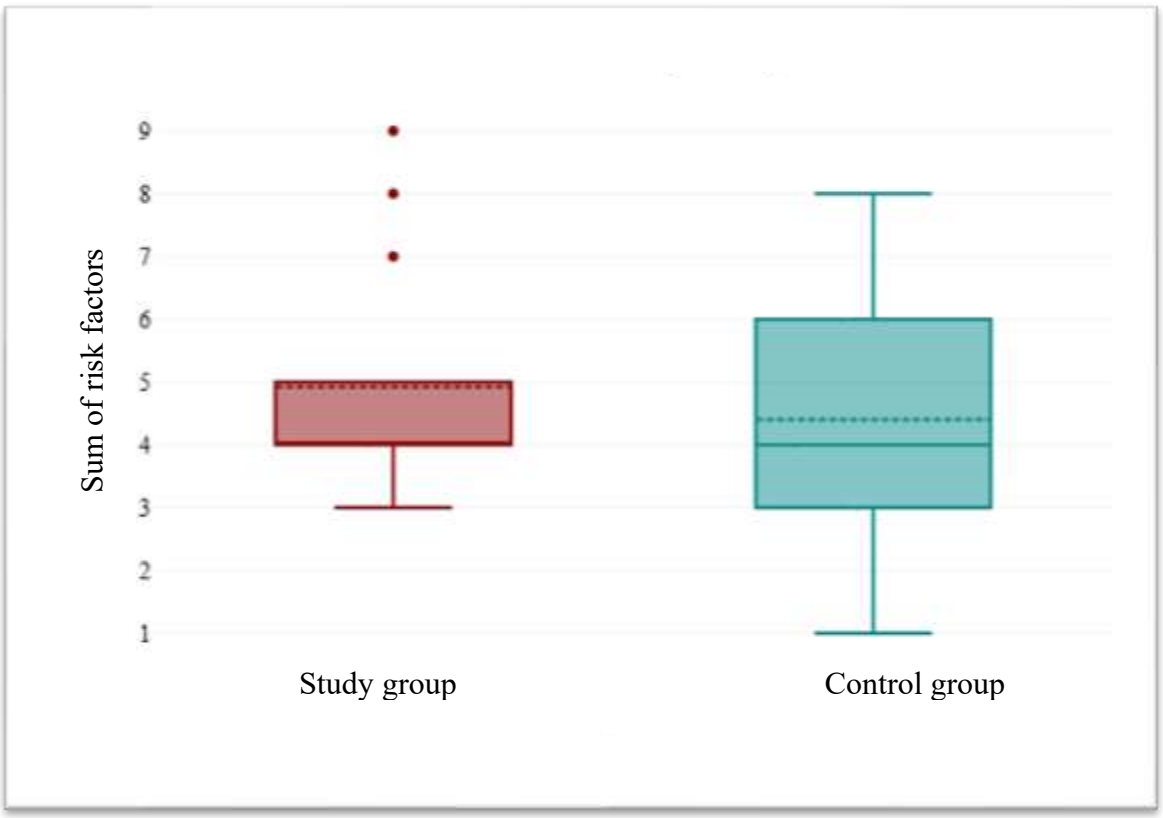

Figure 5: Boxplot of the sum of risk factors in both groups

Patients in the study group showed an average sum of risk factors of 4.92, while patients in the control group had a mean sum of risk factors of 4.4, with no significant difference between the two groups ($p = 0.44$). These increased risk factors made these patients particularly prone to develop an AL at increased incidence when compared to the existing literature. Figure 5 summarizes this difference between the patients in both groups regarding the number of risk factors.

By looking at the individual risk factors, a similar distribution across both groups was observed with three exceptions: cardiovascular disease (46.2% vs. 15%, $p = 0.05$), frozen pelvis (30.8% vs. 5%, $p = 0.04$) and stapler dysfunction (23.1% vs 0%, $p = 0.02$), which were significantly dominant in the study group (Table 6). On the other hand, the control group displayed an insignificant higher rate of neoadjuvant chemoradiotherapy (38.5% vs 50%, $p = 0.51$). Moreover, the control group included one patient with cachexia state and one patient with perioperative sepsis.

	Study group		Control group		Significance P-value
	N	%	N	%	
ASA score ≥3	7	53.8	8	40.0	0.43
Advanced Age (>65 years)	7	53.8	12	60.0	0.727
Cachexia	0	0.0	1	5.0	0.41
Overweight	7	53.8	10	50.0	0.82
cardiovascular diseases	6	46.2	3	15.0	0.05
Diabetes mellitus	3	23.1	4	20.0	0.83
RTX	6	46.2	12	60.0	0.43
CTX or HIPEC	5	38.5	10	50.0	0.51
Immunosuppression	1	7.7	1	5.0	0.75
Acute infection or sepsis	0	0.0	1	5.0	0.41
Duration of surgery>300 min	10	76.9	16	80	0.83
Intraoperative blood transfusion	5	38.5	9	45.0	0.71
Frozen pelvis	4	30.8	1	5.0	0.04
Stapler dysfunction	3	23.1	0	0.0	0.02

Table 6: Different risk factors for anastomotic leakage in each group

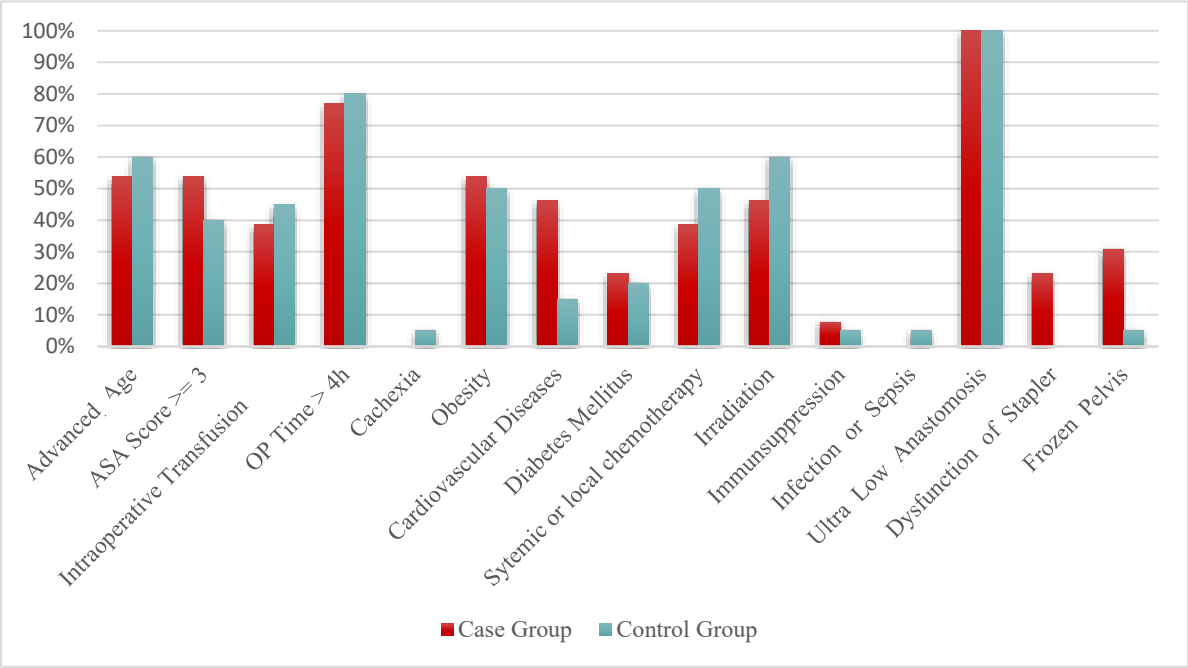

Figure 6: Distribution of different risk factors across both groups

All the patients were submitted to an open ULAR-procedure with a primary anastomosis, either a colorectal or a coloanal and a defunctioning stoma. Additionally, all patients in the study group received a pEVAT at the end of the operation. The anastomoses were stapled in eleven (84.6%) and hand-sewn in two (15.4%) patients in the pEVAT group, whereas in the control group, the anastomoses were stapled in 16 (80%) and hand sewn in four (20%) patients. Again, no significant difference was noticed between both groups ($p = 1$).

In the study group, stool diversion was conducted via a colostomy in seven (53.8%), an ileostomy in four (30.8%) or a jejunostomy in two (15.4%). In the control group, fecal diversion was ensured in the majority of patients via a colostomy, with 16 patients (80%) receiving a colostoma, three patients (15%) an ileostoma and one patient (5%) a jejunostoma (Table 7). Although the control group had remarkably more colostomas, the was no significant difference between the two groups ($p = 0{,}27$).

The decision to apply a pEVAT was primarily based on the intraoperative evaluation of the anastomosis done by one of our senior colorectal surgeons, but also taking into consideration that the patients in our study group had many of the earlier mentioned risk factors for an anastomotic leakage.

		Study group		Control group	
		N	%	N	%
Type of anastomosis	**Hand-sewn**	2	15	4	20
	Stapler	11	85	16	80
Protective stoma diversion	**No stoma**	0	0	0	0
	Colostomy	7	54	16	80
	Ileostomy	4	31	3	15
	Jejunostomy	2	15	1	5

Table 7: Type of anastomosis and stoma conducted in both groups

The mean duration of the total application of the pEVAT was 9 days (range 4-16 days). The dressing change was performed under local anesthesia or sedation. The dressing was changed every 3-4 days or pEVAT was ended by sponge removal (Table8). The decision to end the pEVAT was based on the local finding during the proctoscopy (intestinal integrity, absence of local ischemia or wall defect) and after consulting one of our two colorectal surgeons.

	Minimum	Maximum	Mean	Std. deviation
Total time of pEVAT	4	16	8.77	3.811
Frequency of dressing change	0	4	1.23	1.235

Table 8: Total time of pEVAT and frequency of pEVAT change

3.3. Postoperative complications

3.3.1. Anastomotic leak

This novel technique of prophylactic endoluminal vacuum-assisted therapy was successfully applied in twelve patients from our study group (92.3%). Only one patient (7.7 %) developed an anastomotic leak and with a presacral abscess. In the control group, complete healing of the anastomosis was observed in 14 patients (70%), while six patients developed an anastomotic leak (30%). One patient in the study group and three in the control group presented a grade *B* anastomotic leak, necessitating EVAC treatment without the need for a relaparotomy. The other three in the control group showed a grade *C* anastomotic leak and underwent a re-laparotomy (Table 9). There was a remarkable difference in the rate of AL between both groups. However, the difference was not significant (p = 0.12).

	Anastomotic leak									
	No		**Yes**							
			Total		**Grade of anastomotic leak**					
					Grade *A*		**Grade *B***		**Grade *C***	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Study group	12	92.3	1	7.7	0	0.0	1	7.7	0	0.0
Control group	14	70	6	30	0	0.0	3	15	3	15

Table 9: Frequency of Anastomotic leak in both groups. Grade *A*: radiologic diagnosis in an asymptomatic patient, Grade *B*: anastomotic leak requiring active therapeutic intervention without re-laparotomy, Grade *C*: anastomotic leak with peritonitis requiring a relaparotomy [11]

The patients with an anastomotic leak developed signs and symptoms related to an acute systemic infection (i.e., fever, lethargy, tachycardia, elevated white blood count and C-reactive protein). Additionally, many of them had specific signs indicative for an anastomotic leak (accumulation of air, purulent or fecal secretion in the drainage bag).

All patients with clinical suspicion of an anastomotic leak received a computer tomography of the abdomen, which revealed extraluminal air around the anastomosis and\or presacral abscess. These findings were confirmed via proctoscopic examination, in which a wall defect at the anastomotic line was visible. On average, the anastomotic leak was diagnosed on the 11th postoperative day (Table 10).

	N	Minimum	Maximum	Mean	Std. Deviation
Day on which AL was diagnosed	7	6	23	11.57	6.024

Table 10: day on which the anastomotic leak in was diagnosed in both groups.

The only anastomotic insufficiency in our study group was treated by CT-guided drainage of the abscess and endoluminal vacuum-assisted therapy (EVAT) for one week, until no clinical or radiological signs of anastomotic insufficiency were any longer present, so that EVAT could be ended. Thus, a complete healing of the anastomosis could be achieved in all patients of the pEVAT group (100%).

In the control group, three patients were managed with EVAT and the other three who developed signs of peritonitis, required a re-laparotomy. Of those six patients, one patient had extensive peritonitis and needed a Hartmann's procedure. The other five patients with a diagnosed anastomotic leak were managed with EVAT. Here, a complete healing of the anastomosis was achieved in three patients (60%) with restoration of the gastrointestinal tract continuity. In two patients the EVAT failed. One patient underwent an abdominoperineal resection due to ischemia of the rectal remnant. The other one developed a rectovaginal fistula, which persisted despite EVAT.

3.3.2. Anastomotic stenosis

Since the new anastomosis in the study group was subjected to constant negative pressure, pulling the rectal wall together, we wanted to examine if this approach would lead to an

increased scaring of the anastomosis, resulting in a relevant stenosis at this level. One patient (7.7%) of the study group and seven patients (35%) of the control group suffered a relevant stenosis, necessitating a balloon dilatation with a variable degree of success (Table 11). The control group had considerably more cases of anastomotic stenosis, but no significant difference was noticed between the two groups ($p = 0.15$). Unfortunately, three patients (23.1%) of the study group and five patients (25%) of the control group were lost in the follow-up, so that no further information could be obtained regarding the later patency of the anastomosis, limiting the interpretation of these findings.

3.3.3. Other complications

The following postoperative complications were addressed: bleeding from the anastomosis, surgical site infection, sepsis and fistula formation (Table 11). By looking at the individual complications, one patient (7.7%) of the study group suffered from bleeding. One patient of the control group (5%) and none of the study group suffered from sepsis because of an anastomotic leak. Surgical site infection was noticed in five patients (38.5%) of the study group and six (30%) of the control group, with no significant difference ($p = 0.71$). One patient (5%) of the control group developed a rectovaginal fistula. In five patients (38.5%) of the study group and eight patients (40%) of the control group, no complication was documented. Complications, which were not related to anastomotic leak nor the use of pEVAT or EVAT (e.g., pneumonia, myocardial infarction, urinary tract infection, etc.) were beyond the scope of this research and were excluded from this list.

		Study group		Control group	
		N	%	N	%
No complication	**No**	8	61.5	12	60.0
	Yes	5	38.5	8	40.0
Surgical site infection	**No**	8	61.5	14	70.0
	Yes	5	38.5	6	30.0
Bleeding	**No**	11	92.3	20	100.0
	Yes	1	7.7	0	0.0
Sepsis	**No**	13	100.0	19	95.0
	Yes	0	0.0	1	5.0
Fistula formation	**No**	13	100.0	19	95.0
	Yes	0	0.0	1	5.0
Stenosis	**0**	9	69.2	8	40.0
	1	1	7.7	7	35.0
	N/A	3	23.1	5	25.0

Table 11: Other postoperative complication

3.3.4. Reversal of the stoma

Stoma reversal usually takes place three to six months after the initial operation, mostly after ending the adjuvant therapy. The integrity of anastomosis plays a major role in determining whether the protectively conducted stoma can be reversed.

In the study group, the stoma could be successfully reversed in ten patients (76.9%), whereas in the control group, a stoma reversal was carried out in only 11 patients (55%). However, no significant difference was found between the two groups ($p = 0.44$). One patient of the pEVAT group (7.7%) and three of the control group (15%) were lost in the follow-up group, so that no sufficient documentation regarding the stoma reversal was found (Table 12).

	Study group		Control group	
	N	%	N	%
No stoma reversal	2	15.4	6	30.0
Successful stoma reversal	10	76.9	11	55.0
N/A	1	7.7	3	15.0

Table 12: Rate of stoma reversal

3.4. Risk estimate

By comparing both groups and estimating the risk for complications, we noticed that the probability of having an anastomotic leak in a patient who receives a pEVAT after an uLAR with an anastomosis measuring 5 cm of less from the anal verge was lower compared to a person without pEVAT (OR 0.26, 95% CI 0.35-1.89), pointing out a protective role of pEVAT against the incidence of an anastomotic leak. The incidence of an anastomotic stenosis without pEVAT was higher in comparison to a patient with pEVAT (OR 0.21, 95%CI 0.03-1.49).

Moreover, the probability of having a successful stoma reversal after pEVAT is higher compared to no pEVAT treatment (OR 1.28, 95% CI 0.83-1.98), depicting a further advantage of pEVAT and positive long-term effect on patients` quality of life (Table 13).

Risk estimation			
	Value	95% Confidence interval	
		Lower	Upper
Odds ratio (study group / control group) For cohort anastomotic leak = Yes	0.256	0.035	1.892
N of valid cases	33		
Odds ratio (study group / control group) For cohort stenosis = Yes	0.214	0.031	1.486
N of valid cases	25		
Odds ratio (study group / control group) For cohort reversal of stoma = Yes (successful stoma reversal)	1.288	0.835	1.985
N of Valid Cases	29		

Table 13: Risk estimation via odd ratio (OR) for anastomotic leak, stenosis and stoma reversal

3.5. Hospital length of stay

Regarding the total hospital length of stay, the study group patients spent on average 26 days (range 12-47 days), while the mean hospital stay was 36 days (range 11-242 days) in the control group. No significant difference was noticed between the two groups ($p = 0.48$).

4. Discussion

The anastomotic leak after colorectal procedures, especially in colorectal cancer patients, is considered a major factor for patients' morbidity and mortality, oncologic outcome, and quality of life. The novel prophylactic use of endoluminal vacuum therapy (pEVAT) proved to be an effective method in reducing postoperative anastomotic insufficiency.

4.1. Why pEVAT?

We were looking for an effective method that can protect these high-risk anastomoses and lead to undisturbed healing. We were inspired by the idea of negative wound pressure used on a prophylactic base to decrease the rate of SSI, especially in contaminated or clean-contaminated operation, which apply for colorectal surgeries. After two decades of successful NPWT for SSI as well as chronic, complicated or dirty wounds, the novel idea

of a preemptive application of equally distributed negative pressure (e.g., PREVENA®) to the wound surface was developed to ensure adequate drainage of wound`s fluids, reducing the bacterial load in the wound and promoting a rapid wound healing. There have been many publications revealing the positive role of prophylactic NPWT in effectively reducing the rate of SSI [34, 56, 57]. Sahebally et al showed in a meta-analysis of 1266 patients from 9 studies that the NPWT was able to significantly reduce the rate of SSI (12.4% vs. 27.1% for standard wound dressing) in closed laparotomy for general and colorectal surgery [34].

On the other hand, the role of EVAT is nowadays well-established, and many studies in the last decade have increasingly spotted the light to this revolutionary solution. A systematic review from 2017 analyzing 17 studies and 276 patients revealed a mean rate of healing success of about 85%, which reduced the need for re-operation, and resulted in a shorter total therapy duration to complete healing [58]. Kühn et al have showed positive results regarding the efficacy of EVAT in 41 patients for different applications (AL, Hartman`s stump insufficiency or rectal perforation), with success rates ranging from 79-90% [47]. In another article from 2020, Kühn also demonstrated the significant superiority of endoluminal vacuum assisted therapy over the other conventional methods

in terms of healing of the anastomosis in patients with a diagnosed AL. Furthermore, it was also showed that EVAT resulted in a shorter total hospital stay without a significant reduction in total therapy duration [59]. Regarding the best time to begin with EVAT, it was previously shown that an early application of EVAT was crucial to complete closure of the anastomotic leak. Several studies showed that the healing rate of the anastomosis was significantly higher when EVAT was started within the first 3-6 weeks after the diagnosis of AL compared to those when EVAT was initiated after 6 weeks [59].

Taken this into consideration, we postulated to apply the endoluminal negative pressure therapy as early as possible, i.e., intraoperatively as a form of prophylaxis to stimulate the healing of the vulnerable anastomosis as well as to seal any invisible defect at the stapler line or between the stitches in hand-sewn anastomoses via continuous negative pressure.

4.2. Role of pEVAT in reducing AL

This novel method of pEVAT did not lead to a reduction of the rate of anastomotic leak when compared to the existing literature regarding colorectal anastomoses. However, it did reduce the rate of AL when compared to our control group (7.7% vs. 30%), as well as subgroups of patients who received an ultra-low anastomosis in various studies [16, 18, 60]. The rate of anastomotic leak in our control group was 30%, which is higher than the rate of relevant AL described in the literature, ranging from 2-26%, however not significantly [11-20]. Nevertheless, these studies reported the rate to be more than six folds higher (nearly 19%) in ultra-low anastomoses as a risk factor. Given the fact that both our groups consisted of patients with multiple risk factors, many of them are well-known as independent risk factors for anastomotic leak, this could at least in part explain this variance of results in the rate of AL. The risk factors for AL and their significance were extensively studied, but to the best of our knowledge, there is no previous description in the literature about the incidence of anastomotic leak in patients with multiple risk factors simultaneously.

4.3. Treatment duration

The prophylactic use of endoluminal vacuum therapy was considerably shorter than the time needed to effectively treat patients suffering from an anastomotic leak. According to

Shalaby *et al*, the duration of therapy in cases of AL ranged 11-244 days (median 47 days), whereas in our study group the mean duration for pEVAT was 8.7 days (range 4-16 days) [58]. In our control group, the EVAT was performed for a mean time of 12.75 days (range 6-19 days). It is unclear why the control group in our study demonstrated a considerably shorter duration of EVAT until complete healing of the anastomosis compared to the existing literature. Furthermore, the small collective of patients who received EVAT therapy in our study is not sufficient to draw a definite conclusion and needs to be warranted in larger studies.

The patients in the study group required considerably less sponge changes until a complete healing of the anastomosis was achieved. On average, the sponge in the pEVAT group was changed 1.23 times (range 0-4). In the literature when patients were treated with EVAT for AL, the sponge was changed on average 7 times until a complete healing. This difference was easily reflected in terms of the total hospital stay. The pEVAT group stayed on average for 26 days, with the most common cause for a prolonged stay being SSI, which was treated with VAC, while in the control group, the mean total hospital stay was 36 days. Reviewing the existing literature, it was difficult to find a matching comparison. Since EVAT for patients with AL started during hospitalization but was continued as outpatient, it is hard to compare our findings to others. In these studies, the term ″duration of treatment to complete healing″ was frequently used. However, it remains unclear whether this term comprises the total duration since the admission of patients or probably doesn’t include the perioperative period before the EVAT therapy was started. As previously mentioned, Shalaby et al described a duration of treatment ranging from 11 to 244 days and a median of 47 days [58].

4.4. Complication of PEVAT

The complications which could be directly related to pEVAT were bleeding from the anastomosis in one patient and one case of stenosis. The patient who suffered from bleeding is the same one who suffered from AL. As mentioned earlier, endoluminal therapy was carried out as EVAT to treat the AL, combined with CT-guided percutaneous drainage of a presacral abscess. The EVAT has probably resulted in an erosion of a small blood vessel at the level of the anastomosis, which caused the bleeding. The bleeding was managed operatively and EVAT was terminated as there were no more signs of an

anastomotic leak. Since this patient had AL and later a bleeding, it is difficult to state if bleeding is a potential complication of pEVAT. However, there was no mortality reported within our pEVAT group throughout the duration of the intended follow up.

Since this is a novel method, no comparison to the existing literature was possible. For EVAT therapy, the related complications are well-known. These include: bleeding, stenosis, fistula formation, sepsis and/or peritonitis, formation of a para-anastomotic abscess or chronic sinus, or migration of the sponge intraperitoneally. Kühn *et al* in detail reviewed most of these complications in a meta-analysis of 24 publications [61]. Here, a complication rate of 12.1% (64 of 628 patients) was documented. The most common was the anastomotic stenosis. Other mentioned complications included fistula formation, presacral abscess, chronic sinus and bleeding. No mortality which could be ascribed to EVAT was registered. Popivanov et al reported in another review of 19 studies and a total of 295 patients a complication rate of 19%, with para-anastomotic abscess being the most common (11.5%), followed by stenosis (4.4%) [49].

4.5. Anastomotic Stenosis

One of the concerns regarding EVAT therapy is the formation of a stricture or stenosis at the level of the anastomosis. As the healing of the anastomosis under EVAT occurs, a scar tissue is formed to close the wall defect, followed by the mucosal covering of this scar and restoration of the intestinal continuity. Prior to the intraluminal application of an endoluminal vacuum with continuous negative pressure in the setting of pEVAT, we were also concerned that it could lead to retraction of the rectal/anal wall at the level of the anastomosis and eventually to stenosis, but we were encouraged by many publications regarding the successful intraluminal application of EVAT in the upper GI for treating AL after esophagus/gastric surgery with a low rate of anastomotic stenosis [62, 63]. Unfortunately, three patients of pEVAT group were lost in the follow-up. Of the ten remaining, only one patient developed a relevant anastomotic stenosis, which was successfully treated with endoscopic dilatation. In our control group, five patients were lost in the subsequent follow-up. Of the 15 remaining, seven patients suffered from stenosis.

Weidenhagen *et al* reported in their very first description of EVAT for AL a relevant anastomotic stenosis in 10 out of 29 patients. All patients were successfully treated with bougienage or balloon dilatation [38]. In the meta-analysis by Kühn *et al*, 24 out of 628 patients suffered from an anastomotic stenosis, which was described as the most common EVAT-related complication [61].

4.6. Other complications

As mentioned earlier, the study group demonstrated a complete healing of the anastomosis (100%) with a very low complication rate. With one anastomotic leak, one bleeding from the anastomosis, one para-anastomotic abscess and one relevant stenosis, this novel method appears to be promising and relatively safe when compared to the control group as well as the literature, not only for colorectal surgery with ultra-low anastomoses , but also for patients managed with EVAT after developing AL, with an EVAT-related comorbidity rate of 12.1% in many publications [61, 64, 65].

4.7. Reversal of Stoma

As mentioned before in the introduction, a huge debate existed regarding the routine conduction of a defunctioning stoma in colorectal surgery over the past 40 years. Many authors recommended at first the routine use of a diverting stoma, arguing that the rate of AL is higher in patients who didn't have a stoma, especially in cases of extraperitoneal anastomoses [14, 16, 66]. Rondelli *et al* presented a meta-analysis with a total of 1529 patients comparing loop ileostomy vs. loop colostomy to determine the advantages of each one and found that loop ileostomy was superior to loop colostomy regarding a lower incidence of prolapse and sepsis but on the other hand a higher incidence of dehydration and stenosis with obstruction after stoma reversal. No significance was found regarding other stoma-related complications such as retraction, stenosis, necrosis or parastomal hernia [67].

This contrasts with our experience and belief. Since we regularly conduct stomas for different indications, we experienced that the comorbidities associated with ileostomy were high, especially dehydration with acute renal failure as well as stoma prolapse and

peristomal skin irritation. Thus, we prefer, whenever possible, to use a diverting loop colostomy.

However, in the last two decades, the value of stoma diversion in colorectal surgery was questioned by many surgeons. Wong *et al* reported that the use of a diverting stoma did not lead to a reduction in the rate of AL, carried itself the risk for stoma-related complications and raising the cost of the operation. Hence he advised against its routine use in colorectal surgery [23]. In a meta-analysis by Ahmad *et al*, the evidence supporting the protective role of diverting stomas against AL was found to be weak [68]. Kong et al also reported in a series of 66 patients who underwent an ultra-low resection due to rectal cancer a lower incidence of anastomosis-related complications in patients who did not receive a diverting stoma, considering a single-stage operation without a stoma and reserving stomal diversion for selected cases [20].

However, most authors agree that diverting stomas, leading to a reduced incidence of AL or not, does attenuate the impact of AL by reducing the rate of peritonitis, sepsis and reoperation. The current practice recommends the use of a diverting stoma in colorectal surgery, especially in patients undergoing an ultra-low resection or possessing risk factors for AL [13-17, 19, 21, 22, 24].

There rate of stoma reversal varies according to the level of the anastomosis and the presence of anastomotic leak. David *et al* reported a stoma reversal rate of loop ileostomy of 75.1% after low anterior resection in 964 patients in the UK [69]. A decade later, in a similar report from Denmark, Jørgensen described a stoma reversal rate of 70.3% after one year and 74.3% after three years of restorative rectal cancer resection in 2449 patients [70]. Both of them recognized adjuvant therapy and postoperative complication as negative predictors for delayed reversal. In the case of clinical leakage, Shalaby et al reported in their systematic review a stoma reversal rate of 75.9% compared to rate of 30–40 % for clinical leakage in the literature. In our study, the rate of stoma reversal in pEVAT group was 76.9% compared to a reversal rate of 55% in the control group, with one patient (7.7%) in the pEVAT group and three patients (15%) in the control group lost in the follow-up. These findings indicate that the application of pEVAT did not adversely affect the rate of stoma reversal.

4.8. Limitation of the study

This retrospective study describes the novel use of EVAT on a prophylactic base (pEVAT) in colorectal cancer surgery, which has to the best of our knowledge never been described before in the literature. We published this very first description of pEVAT in a case series for colorectal surgery, not only for colorectal cancer but rather for a variety of indications.

The pEVAT study shows promising results. However, our study has some limitations. The major limitation of our study was the low number of the patients collective. Although the novel prophylactic EVAT approach seems to improve the postoperative outcome of this high-risk anastomoses in colorectal surgery, this technique needs to be validated in a larger series of patients in a controlled prospective trial. This should elucidate which patients benefit from pEVAT and provide long-term results. Moreover, our decision about which patient is eligible to a pEVAT carries the risk of selection bias, as it was done based on the subjective clinical judgement of our senior colorectal surgeon upon the anastomosis. Also, the duration of pEVAT was an individual decision depending on the endoscopic finding.

Another limitation of our study was that there were many international patient enrolled in the study, who were lost in the subsequent follow-up and were thus unable not eligible for the analysis for anastomotic stenosis or stoma reversal.

5. Conclusion

This novel use of endoluminal vacuum assisted therapy on a prophylactic base appears to effectively protect ultra-low colorectal or coloanal anastomoses in patients with colorectal cancer, especially those with multiple risk factors for anastomotic leak. It may also play a significant role in reducing patients' morbidity as well as total hospital stay. However, more prospective, well controlled studies with larger patients' collective are required to reveal the significance of this novel method. Since pEVAT is a safe method, it may also be considered for use of low-risk anastomoses in the future.

6. Reference

1. Koch-Institut, Z.f.K.i.R., *Krebs in Deutschland für 2017/2018.* 2018.
2. Emrich, K. and K. Kraywinkel, *Epidemiologie des Rektumkarzinoms in Deutschland.* Der Onkologe, 2020. **26**(12): p. 1085-1094.
3. Hamilton, S.R. and L.A. Aaltonen, *Carcinoma of the colon and rectum. In: WHO Classification of Tumours of the Digestive System.* 2010, Lyon: IARCPress.
4. Li, F.Y. and M.D. Lai, *Colorectal cancer, one entity or three.* J Zhejiang Univ Sci B, 2009. **10**(3): p. 219-29.
5. Brierley, J.D., M.K. Gospodarowicz, and C. Wittekind, *TNM Classification of Malignant Tumours. 8th Edition*. 2017, John Wiley & Sons, Ltd. p. 84-87.
6. Heald, R.J., *A new approach to rectal cancer.* Br J Hosp Med, 1979. **22**(3): p. 277-81.
7. Rajput, A. and K. Bullard Dunn, *Surgical management of rectal cancer.* Semin Oncol, 2007. **34**(3): p. 241-9.
8. Shirouzu, K., N. Murakami, and Y. Akagi, *Intersphincteric resection for very low rectal cancer: A review of the updated literature.* Ann Gastroenterol Surg, 2017. **1**(1): p. 24-32.
9. Ptok, H., et al., *Impact of anastomotic leakage on oncological outcome after rectal cancer resection.* Br J Surg, 2007. **94**(12): p. 1548-54.
10. Jung, S.H., et al., *Risk factors and oncologic impact of anastomotic leakage after rectal cancer surgery.* Dis Colon Rectum, 2008. **51**(6): p. 902-8.
11. Rahbari, N.N., et al., *Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer.* Surgery, 2010. **147**(3): p. 339-51.
12. Trencheva, K., et al., *Identifying important predictors for anastomotic leak after colon and rectal resection: prospective study on 616 patients.* Ann Surg, 2013. **257**(1): p. 108-13.
13. Buchs, N.C., et al., *Incidence, consequences, and risk factors for anastomotic dehiscence after colorectal surgery: a prospective monocentric study.* Int J Colorectal Dis, 2008. **23**(3): p. 265-70.
14. Peeters, K.C., et al., *Risk factors for anastomotic failure after total mesorectal excision of rectal cancer.* Br J Surg, 2005. **92**(2): p. 211-6.
15. Lee, M.R., et al., *Risk factors for anastomotic leakage after resection for rectal cancer.* Hepatogastroenterology, 2006. **53**(71): p. 682-6.
16. Rullier, E., et al., *Risk factors for anastomotic leakage after resection of rectal cancer.* Br J Surg, 1998. **85**(3): p. 355-8.
17. McDermott, F.D., et al., *Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks.* Br J Surg, 2015. **102**(5): p. 462-79.
18. Karanjia, N.D., et al., *Leakage from stapled low anastomosis after total mesorectal excision for carcinoma of the rectum.* Br J Surg, 1994. **81**(8): p. 1224-6.
19. Zarnescu, E.C., N.O. Zarnescu, and R. Costea, *Updates of Risk Factors for Anastomotic Leakage after Colorectal Surgery.* 2021. **11**(12): p. 2382.
20. Kong, A.P., et al., *Selective treatment of rectal cancer with single-stage coloanal or ultralow colorectal anastomosis does not adversely affect morbidity and mortality.* International Journal of Colorectal Disease, 2007. **22**(8): p. 897-901.
21. Hanna, M.H., A. Vinci, and A. Pigazzi, *Diverting ileostomy in colorectal surgery: when is it necessary?* Langenbecks Arch Surg, 2015. **400**(2): p. 145-52.

22. Shiomi, A., et al., *The indications for a diverting stoma in low anterior resection for rectal cancer: a prospective multicentre study of 222 patients from Japanese cancer centers.* Colorectal Dis, 2011. **13**(12): p. 1384-9.
23. Wong, N.Y. and K.W. Eu, *A defunctioning ileostomy does not prevent clinical anastomotic leak after a low anterior resection: a prospective, comparative study.* Dis Colon Rectum, 2005. **48**(11): p. 2076-9.
24. Wu, S.W., C.C. Ma, and Y. Yang, *Role of protective stoma in low anterior resection for rectal cancer: a meta-analysis.* World J Gastroenterol, 2014. **20**(47): p. 18031-7.
25. Blumetti, J. and H. Abcarian, *Management of low colorectal anastomotic leak: Preserving the anastomosis.* World J Gastrointest Surg, 2015. **7**(12): p. 378-83.
26. Kawada, K., et al., *Impact of transanal drainage tube on anastomotic leakage after laparoscopic low anterior resection.* Int J Colorectal Dis, 2018. **33**(3): p. 337-340.
27. Wang, F.G., et al., *Comparison of anastomotic leakage rate and reoperation rate between transanal tube placement and defunctioning stoma after anterior resection: A network meta-analysis of clinical data.* Eur J Surg Oncol, 2019. **45**(8): p. 1301-1309.
28. Challine, A., et al., *Does a transanal drainage tube reduce anastomotic leakage? A matched cohort study in 144 patients undergoing laparoscopic sphincter-saving surgery for rectal cancer.* Tech Coloproctol, 2020. **24**(10): p. 1047-1053.
29. Rondelli, F., et al., *Temporary percutaneous ileostomy versus conventional loop ileostomy in mechanical extraperitoneal colorectal anastomosis: a retrospective study.* Eur J Surg Oncol, 2012. **38**(11): p. 1065-70.
30. Bakker, I.S., et al., *Randomized clinical trial of biodegradeable intraluminal sheath to prevent anastomotic leak after stapled colorectal anastomosis.* Br J Surg, 2017. **104**(8): p. 1010-1019.
31. Bagautdinov, N.A., *Variant of External Vacuum Aspiration in the Treatment of Purulent Diseases of Soft Tissues.* 1986.
32. Morykwas, M.J., et al., *Vacuum-assisted closure: a new method for wound control and treatment: animal studies and basic foundation.* Ann Plast Surg, 1997. **38**(6): p. 553-62.
33. Argenta, L.C. and M.J. Morykwas, *Vacuum-assisted closure: a new method for wound control and treatment: clinical experience.* Ann Plast Surg, 1997. **38**(6): p. 563-76; discussion 577.
34. Sahebally, S.M., et al., *Negative Pressure Wound Therapy for Closed Laparotomy Incisions in General and Colorectal Surgery: A Systematic Review and Meta-analysis.* JAMA Surg, 2018. **153**(11): p. e183467.
35. Gestring, M., et al,. *Negative pressure wound therapy*. 2022, January 03; Available from: https://www.uptodate.com/contents/negative-pressure-wound-therapy.
36. Weidenhagen, R., et al., *A NEW METHOD FOR SEPSIS CONTROL CAUSED BY ANASTOMOTIC LEAKAGE IN RECTAL SURGERY-THE ENDO-VAC®: 608.* 2004. **21**: p. 152.
37. Weidenhagen, R., et al., *Endoluminal vacuum therapy for the treatment of anastomotic leakage after anterior rectal resection.* Rozhl Chir, 2008. **87**(8): p. 397-402.
38. Weidenhagen, R., et al., *Endoscopic vacuum-assisted closure of anastomotic leakage following anterior resection of the rectum: a new method.* Surg Endosc, 2008. **22**(8): p. 1818-25.

39. Nagell, C.F. and K. Holte, *Treatment of anastomotic leakage after rectal resection with transrectal vacuum-assisted drainage (VAC). A method for rapid control of pelvic sepsis and healing.* Int J Colorectal Dis, 2006. **21**(7): p. 657-60.
40. Arezzo, A., et al., *Endoluminal vacuum therapy for anastomotic leaks after rectal surgery.* Tech Coloproctol, 2010. **14**(3): p. 279-81.
41. Arezzo, A., et al., *Long-term efficacy of endoscopic vacuum therapy for the treatment of colorectal anastomotic leaks.* Dig Liver Dis, 2015. **47**(4): p. 342-5.
42. Bemelman, W.A., *Vacuum assisted closure in coloproctology.* Tech Coloproctol, 2009. **13**(4): p. 261-3.
43. Borstlap, W.A.A., et al., *Vacuum-assisted early transanal closure of leaking low colorectal anastomoses: the CLEAN study.* Surg Endosc, 2018. **32**(1): p. 315-327.
44. Huisman, J.F., et al., *Effectiveness of endosponge therapy for the management of presacral abscesses following rectal surgery.* Tech Coloproctol, 2019. **23**(6): p. 551-557.
45. Jimenez-Rodriguez, R.M., et al., *A New Perspective on Vacuum-Assisted Closure for the Treatment of Anastomotic Leak Following Low Anterior Resection for Rectal Cancer, Is It Worthy?* Surg Innov, 2018. **25**(4): p. 350-356.
46. Keskin, M., et al., *Effectiveness of Endoluminal Vacuum-assisted Closure Therapy (Endosponge) for the Treatment of Pelvic Anastomotic Leakage After Colorectal Surgery.* Surg Laparosc Endosc Percutan Tech, 2015. **25**(6): p. 505-8.
47. Kuehn, F., et al., *Endoscopic Vacuum Therapy in Colorectal Surgery.* J Gastrointest Surg, 2016. **20**(2): p. 328-34.
48. Pliakos, I., et al., *The value of vacuum-assisted closure in septic patients treated with laparostomy.* Am Surg, 2012. **78**(9): p. 957-61.
49. Popivanov, G.I., et al., *Endoluminal negative pressure therapy in colorectal anastomotic leaks.* Colorectal Dis, 2020. **22**(3): p. 243-253.
50. Rottoli, M., et al., *Endoluminal vacuum-assisted therapy as treatment for anastomotic leak after ileal pouch-anal anastomosis: a pilot study.* Tech Coloproctol, 2018. **22**(3): p. 223-229.
51. Strangio, G., et al., *Endo-sponge therapy for management of anastomotic leakages after colorectal surgery: A case series and review of literature.* Dig Liver Dis, 2015. **47**(6): p. 465-9.
52. van Koperen, P.J., et al., *The Dutch multicenter experience of the endo-sponge treatment for anastomotic leakage after colorectal surgery.* Surg Endosc, 2009. **23**(6): p. 1379-83.
53. Reimer, S., et al., *Evolution of endoscopic vacuum therapy for upper gastrointestinal leakage over a 10-year period: a quality improvement study.* Surg Endosc, 2022. **36**(12): p. 9169-9178.
54. Kuehn, F., et al., *Endoscopic vacuum therapy for various defects of the upper gastrointestinal tract.* Surg Endosc, 2017. **31**(9): p. 3449-3458.
55. Lehwald-Tywuschik, N.C., et al., *The "impossible" rectal anastomosis: a novel use for endoluminal vacuum-assisted therapy.* Tech Coloproctol, 2021. **25**(1): p. 125-130.
56. Cheong Chung, J.N., et al., *Closed incision negative pressure wound therapy is associated with reduced surgical site infection after emergency laparotomy: A propensity matched-cohort analysis.* Surgery, 2021. **170**(5): p. 1568-1573.
57. Curran, T., et al., *Prophylactic closed-incision negative-pressure wound therapy is associated with decreased surgical site infection in high-risk colorectal surgery laparotomy wounds.* Colorectal Dis, 2019. **21**(1): p. 110-118.

58. Shalaby, M., et al., *Systematic review of endoluminal vacuum-assisted therapy as salvage treatment for rectal anastomotic leakage.* BJS Open, 2019. **3**(2): p. 153-160.
59. Kühn, F., et al., *Comparison Between Endoscopic Vacuum Therapy and Conventional Treatment for Leakage After Rectal Resection.* World Journal of Surgery, 2020. **44**(4): p. 1277-1282.
60. Akasu, T., et al., *Risk factors for anastomotic leakage following intersphincteric resection for very low rectal adenocarcinoma.* J Gastrointest Surg, 2010. **14**(1): p. 104-11.
61. Kühn, F., et al., *Endoscopic vacuum therapy for the treatment of colorectal leaks — a systematic review and meta-analysis.* International Journal of Colorectal Disease, 2022. **37**(2): p. 283-292.
62. Kuehn, F., et al., *Surgical Endoscopic Vacuum Therapy for Defects of the Upper Gastrointestinal Tract.* Journal of Gastrointestinal Surgery, 2016. **20**(2): p. 237-243.
63. Virgilio, E., D. Ceci, and M. Cavallini, *Surgical Endoscopic Vacuum-assisted Closure Therapy (EVAC) in Treating Anastomotic Leakages After Major Resective Surgery of Esophageal and Gastric Cancer.* Anticancer Research, 2018. **38**(10): p. 5581.
64. Paun, B.C., et al., *Postoperative complications following surgery for rectal cancer.* Ann Surg, 2010. **251**(5): p. 807-18.
65. Straja, N.D., et al., *Morbidity after Ultra Low Anterior Resection of the Rectum.* Chirurgia (Bucur), 2015. **110**(3): p. 231-6.
66. Köhler, A., et al., *Long-term results of low anterior resection with intersphincteric anastomosis in carcinoma of the lower one-third of the rectum: analysis of 31 patients.* Dis Colon Rectum, 2000. **43**(6): p. 843-50.
67. Rondelli, F., et al., *Loop ileostomy versus loop colostomy for fecal diversion after colorectal or coloanal anastomosis: a meta-analysis.* International Journal of Colorectal Disease, 2009. **24**(5): p. 479-488.
68. Ahmad, N.Z., et al., *A meta-analysis of the role of diverting ileostomy after rectal cancer surgery.* International Journal of Colorectal Disease, 2021. **36**(3): p. 445-455.
69. David, G.G., et al., *Loop ileostomy following anterior resection: is it really temporary?* Colorectal Dis, 2010. **12**(5): p. 428-32.
70. Jørgensen, J.B., et al., *Stoma reversal after intended restorative rectal cancer resection in Denmark: nationwide population-based study.* BJS Open, 2020. **4**(6): p. 1162-71.

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