Universitat Autònoma de Barcelona

Vall d'Hebron Hospital

Final Degree Project

Pelvic Drainage after Total Mesorectal Excision: a multicentre study

-Degree in Medicine-

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Pelvis Drainage after Total Mesorectal Excision: a multicentre study

Drenaje Pélvico tras la Escisión Total de Mesorrecto: un estudio multicentrico

Drenatge Pelvià tras l´Escisió Total del Mesorrecte: un estudi multicèntric

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A special thanks to my family. Words cannot express how grateful I am for all of the sacrifices that you have made on my behalf¨

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SUMMARY:

Rectal cancer is the third most common cancer in men and the second most common cancer in women. Among the different treatment options the radical approach is performed with a surgical technique known as Total Mesorectal Surgery (TME). The use of prophylactic pelvic drainage after TME has been long debated. Despite most of the literature agrees about its ineffectiveness, there is still controversy over the need of using it or not: On the one hand there are articles supporting the use of drainage and on the other hand, articles questioning its use as well as studies that find no difference between using them or not.

Most of the published studies, are inconclusive owing to the heterogeneity of the included population, the small number of patients, the deficient randomization among other causes; leading to inconsistent results and conclusions. For that reason, I have proposed a multicentre study to asses the effect of pelvic drainage after Total Mesorectal Excision.

RESUMEN

El cáncer rectal es el tercer cáncer más frecuente en hombres y el segundo más común en mujeres. Entre las diferentes opciones terapéuticas, encontramos una técnica quirúrgica conocida como Escisión Total de Mesorecto (ETM). El uso de drenaje pélvico tras una ETM ha sido un tema muy debatido. A pesar del acuerdo generalizado de la literatura sobre su inefectividad, aún existe controversia sobre la necesidad o no de usarlo: Por un lado, tenemos artículos que apoyan el uso de drenaje y, por el otro lado, artículos que lo cuestionan; además de estudios que no encontraron ninguna diferencia entre ponerlo y no ponerlo.

La mayoría de los estudios publicados son inconclusos dada la falta de heterogeneidad de los mismos, o a su pequeño número de pacientes, o al déficit de randomización, entre otras causas; ocasionado así resultados y conclusiones inconsistentes. Por esta razón, he propuesto un estudio multicéntrico para verificar el efecto del drenaje pélvico tras una Escisión Total de Mesorecto.

RESUM

El càncer rectal és el tercer càncer que afecta més freqüentment als homes i el segon més freqüent a les dones. Entre les diferents opcions terapèutiques, trobem una tècnica quirúrgica coneguda com Escissió Toral de Mesorrecte. L´us de drenatge pelvic després d´una ETM ha estat un tema molt debatut. Tot i que hi ha un acord generalitzat a la literatura sobre la seva inefectivitat, encara existeix controvèrsia sobre la necessitat de fer-lo servir o no: per un costat, tenim articles que recolzen l´us de drenatge i, per un altre costat, articles que ho qüestionen, a més d´estudis que no han trobat cap diferencia entre fer-lo i no fer-lo servir.

La majoria dels estudis publicats són inconclusos donada la falta d´heterogeneïtat a l´hora d´incloure la població, o al petit numero de pacients o al dèficit de randomitzacio entre altre causes, ocasionant resultats i conclusions inconsistents. Per aquesta raó, he proposat un estudi multicentric per verificar l´efecte del drenatge pelvià després d´una Escissió Total de Mesorecte.

COLORECTAL CANCER

Colorectal cancer is the development of cancer from the colon or rectum.

Worldwide, colorectal cancer is the third most common cancer in men (746,000 cases) diagnosed in 2012 and the second most common cancer in women (614,000 cases). Annually colorectal cancer is the cause of approximately 694,000 deaths (9 per cent of all cancer deaths) across the globe. (1) The average age for colon cancer diagnosis is 70 (2)

There is wide geographical variation in incidence across the world incidence rates vary ten-fold worldwide, the highest estimated rates being in Australia, New Zealand, Europe and North America, and the lowest in Western Africa, South and Central Asia. (1) This incidence difference is believed to exist as a result of the way in which risk factors are distributed worldwide.

There are many factors that can decrease or increase the risk of suffering colorectal cancer: On the one hand, factors that decrease the risk of colorectal cancer are:

✓ Physical activity (1,3): a meta-analysis compared the highest and lowest total physical activity levels which showed a 20 per cent significant decrease in the risk.

✓ Food containing fibre (4)

✓ Wholegrains (5): this meta-analysis showed a significant 17 per cent decrease in the risk per 90 grams of wholegrains per day (RR 0.83; 95% CI 0.78–0.89)

✓ Dairy products (6): the meta-analysis showed a 13 per cent decrease in the risk per 400 grams per day of diary products

✓ Calcium supplements (7): meta-analysis which showed a six per cent decrease in the risk per 200 milligrams per day (RR 0.94 (95% CI 0.93–0.96)

✓ Fish (8): meta-analysis which showed an 11 per cent decrease in the risk per 100 grams per day (RR 0.89; 95% CI 0.80–0.99);

✓ Vitamin C (9): meta-analysis which showed a six per cent decrease in the risk per 40 milligrams of Vitamin C per day (RR 0.94 ; 95% CI 0.89–0.99)

✓ Vitamin D (10): A study concluded that there is a significant five per cent decrease in the risk per 100 IU per day of vitamin D (RR 0.95 (95% CI 0.93–0.98)

✓ Multivitamin supplements:an analysis comparing users of multivitamin supplements with non-user which showed a significant decrease in the risk (RR 0.88 ; 95% CI 0.79–0.98))

On the other hand, there are many factors that increase the risk of colorectal cancer:

- Consuming processed meat (11): Processed meats, such as sausages, are often cooked at high temperatures, which can lead to increased exposure to HCAs and PAHs, which may stimulate tumorigenesis. Processed meat is also a source of exogenously derived N-nitroso compounds which may have carcinogenic potential

- Smoking (9): smoking 40 cigarettes per day increases the risk of colorectal cancer by about 40 per cent and nearly doubles the risk of colorectal cancer death.

- Alcoholic drinks (12): study shows that significant increased risks were observed for 30 grams per day and above, where the relationship was positive and appeared linear

- Body fatness (13,14,15): Body fatness stimulates the body´s inflammatory response, promoting, that way, colorectal cancer. Also, as fat promotes cell growth and inhibits apoptosis, it has been linked to greater risk of colorectal cancer.

- Red meat (16): red meat increases risk of colorectal cancer as it is rich in fat and haem iron

- Low intakes of vegetables and of fruits (17): the meta-analysis showed a significant inverse association per 100 grams of vegetables and fruits per day (RR 0.98 (95% CI 0.97–0.99)

- Food containing haem iron (18): haem iron, which is found at high levels in red meat, has been shown to promote colorectal tumorigenesis by stimulating the endogenous formation of carcinogenic N-nitroso compounds

- Age (19): as we age, the risk of developing colorectal cancer increases. Most that 90% of people diagnosed with this type of cancer are older than 50

- Hereditary conditions: 30% of colorectal cancers run in families. About 10% of all colorectal cancers can be traced directly to specific genes.

- Polyps in bowel: since colorectal cancers develop from polyps, the more polyps a patient has, the greater risk will have to develop this cancer. There are many type of polyps. The one that has the highest chance of transforming into malignant is the adenomatous polyp. Nowadays, in order to prevent any kind of possible malignant transformation, patients who have polyps undergo endoscopic polypectomy, or even surgery in selected circumstances.(2)

The mentioned geographical variation in incidence, nowadays has no relation with the number of deaths due to colorectal cancer as a result of the introduction of screening tests (21). In several parts of Spain there are screening programs in which, from age 50 onwards and every two years everybody undergoes a physical exam that includes a take-home testing of the stool for fecal occult blood (FOBT). If positive result, it will be highly recommended to complement endoscopic tests in order for us to find and remove any polyps (2) or to diagnose a colorectal cancer in its early stages. Regular screenings starting at age 50 for people at average risk, have a very good chance of catching polyps on their way to becoming cancer, since colorectal cancer is typically slow growing, taking five to ten years to develop. That way, this screening is not just about detecting cancer early; it prevents cancer from arising.

In reference to the signs and symptoms of colorectal cancer, there are usually no symptoms in the early stages. The most common symptom is rectal bleeding (22). When a patient has rectal bleeding a differential diagnosis must be done between hemorrhoids and anal fissures. Rectal bleeding has a positive predictive value (PPV) of just 2,4% (23). Other possible symptoms of colorectal cancer include: constipation, diarrhea,

bloating, loss of weight and appetite, anaemia, vomiting, inability to pass stools due to an intestinal blockage (24,25).

To establish a definitive diagnosis, biopsy samples from the colonoscopy are needed. Moreover, since 1 out of 25 colorectal cancers present a synchronic tumour. In order for us to detect these synchronic lesions a complete colonoscopy must be performed, reaching the ileocecal valve. This allows direct identification of another synchronic tumour, histologic examination through biopsy, diagnosis and removal of synchronic polyps,… (26). The TNM classification system is used as a tool to stage colorectal cancer (2). Colorectal cancer staging is performed by using Computed Tomography Scan (this test can tell if colon cancer has spread into other organs), Ultrasounds, including abdominal ultrasounds (to look for a possible tumour spreading in liver, gallbladder, pancreas,or elsewhere in the patient´s abdomen), endorectal ultrasound (used to see how far through the real wall the cancer has grown and if it reached nearby organs or tissues such as lymph nodes), Magnetic Resonance Imaging Scan, Chest X ray (it may be done to check if colorectal cancer has spread to the lungs), Positron Emission Tomography Scan, Angiography to see the arteries that supply blood to the spread tumours and to plan treatments for cancer spread to the liver like embolisation.

Regarding the treatment of colorectal cancer, a multidisciplinary team is needed. This team includes colorectal surgeons, general surgeons, hepatobiliary surgeons, gastroenterologists, medical oncologists, radiation oncologists, radiologists, pathologists, geneticists, social workers, oncology and surgical nurses and nurse practitioners, enterostomal therapists, and a team coordinator. An interactive discussion is undertaken and a consensus built as to the most appropriate plan of treatment and care. (27)

Treating a colorectal cancer has the main objective of curing the patient as well as preserving , when feasible, the sphincter, bladder and sexual function. If not possible, then we must try and calm the symptoms moving towards a palliative management. (28)

We can find 5 different treatment options:

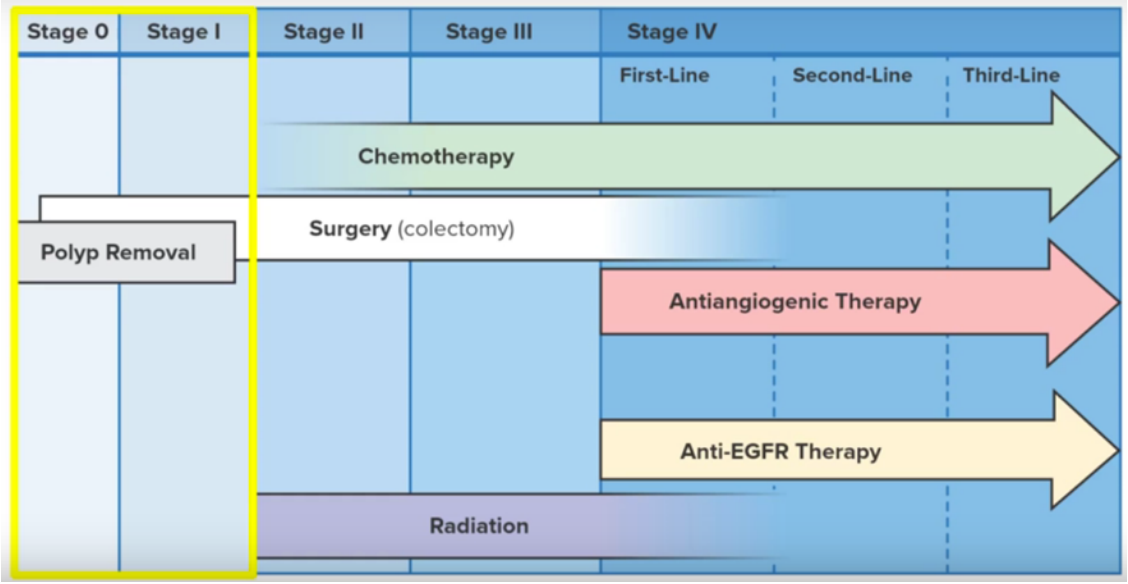
1.Surgery

2.Radiotherapy

3.Chemotherapy

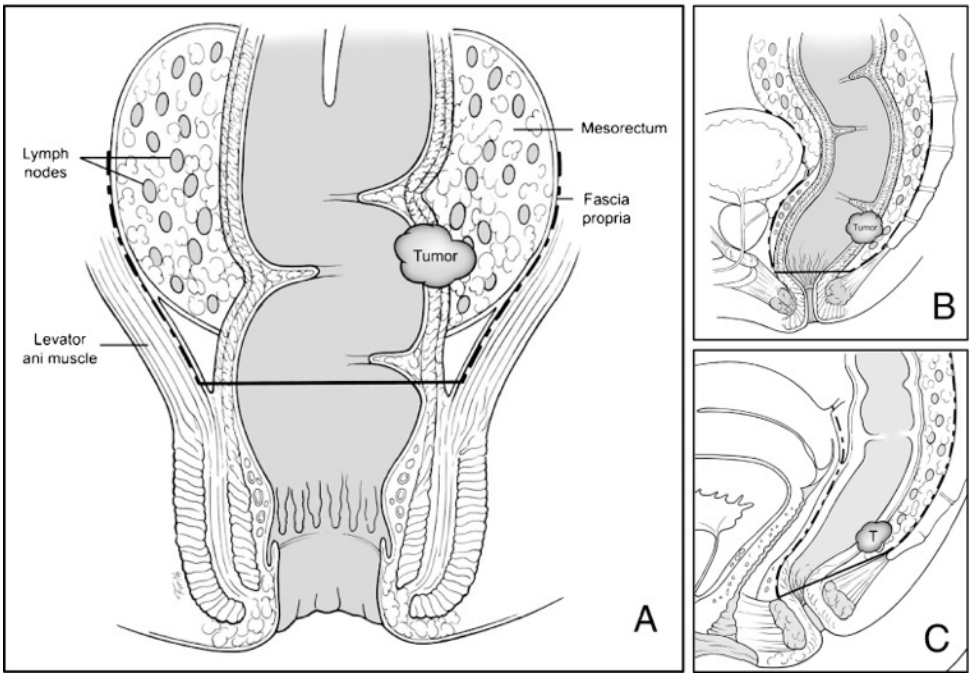
4.Antiangiogenic Therapy

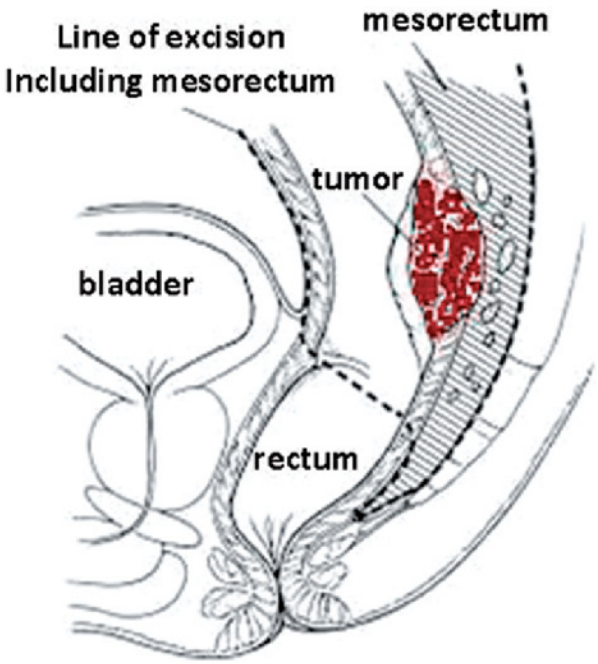
5.Anti-EGFR Therapy



Stage 0	Very early cancer on the innermost layer of the intestine
Stage 1	Cancer is in the inner layers of the colon
Stage 2	Cancer has spread through the muscle wall of the colon
Stage 3	Cancer has spread to the lymph nodes
Stage 4	Cancer has spread to other organs

Firstly, regarding Surgery, it is the standard treatment when the tumor is considered local (from Stage I to III). When undergoing surgery, modern proctectomy for colorectal cancer is based on a sharp, meticulous extirpation of the all the mass with its surrounding pericolorectal lymphatic tissue contained within a thin fascial layer, referred to as total mesorectal excision (TME):





The following figures show the way how the Total Mesorectal Excision technique has to be done:

At the end of the surgery, the healthy sections are reconnected (if this is not possible, the surgeon will perform a colostomy). Proper nutrition before and after surgery is important for healing and speeding recovery. (29)

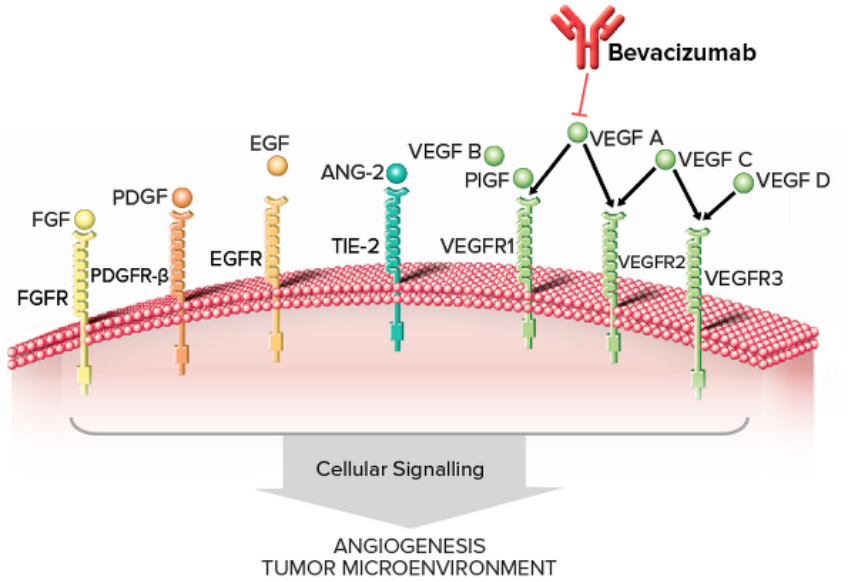
Secondly, in respect to Radiotherapy, It may be used alone or in combination with other therapies to shrink tumours before surgery or to destroy any remaining cancer cells after chemotherapy.(30) Radiation can also be used to reduce the tumour size to make a patient more comfortable, even when the cancer cannot be removed in locally advanced colorectal cancer.

Thirdly, apropos the Chemotherapy (highlighting FOLFOX, CapeOX and FOLFIRI), it is used in advanced cases (stage II, III and IV). There are many different types of chemotherapy drugs, and often, they are used in combination to, that way, achieve a more aggressive effect. This is known as ¨combination therapy,¨ which can also reduce the likelihood that the cancer would become resistant to any single chemotherapeutic drug. (31).

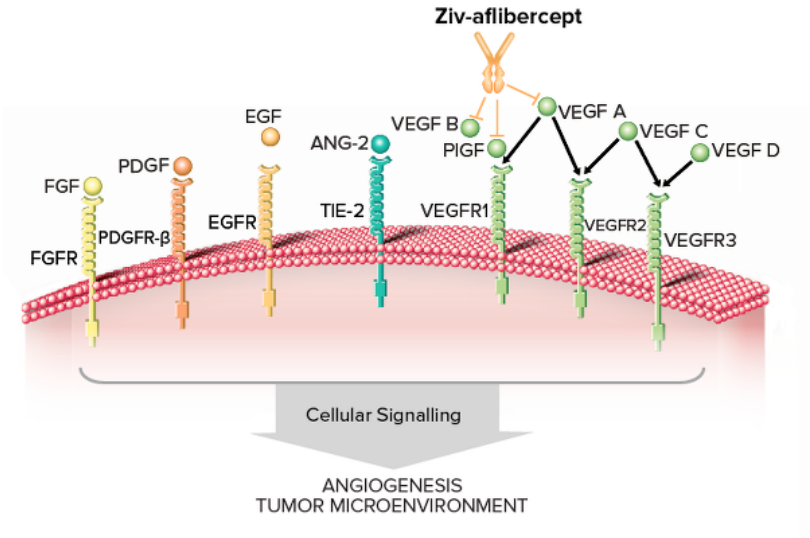
Since 2004, new treatments have been developed called "Targeted Therapies," which are designed to attack specific cell pathways used by cancers to survive and grow such as angiogenesis and apoptosis-resistance. These new treatments are improving our ability to treat metastatic colorectal cancer. (32). We can find the following Targeted Therapies:

- Antiangiogenic treatments:

- **Bevacizumab (Avastin):** it is an antibody drug that binds and neutralizes a protein called VEGF-A. Based on the results of the randomized, placebo-controlled, double blind clinical trial called AVF 2107, Bevacizumab + FOLFOX improved median overall survival compared to those treated with chemotherapy alone.

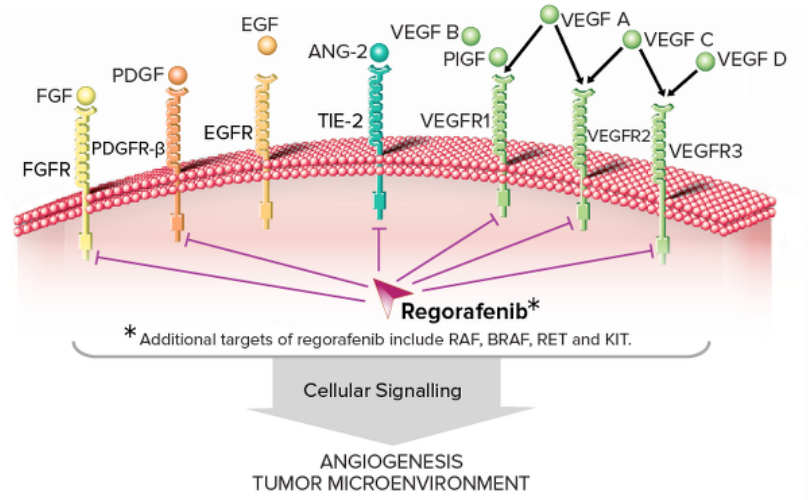


- **Ziv-aflibercept (Zaltrap):** it targets proteins VEGF-A, VEGF-B (angiogenic factors) and the placental growth factor (PlGF). A randomized, double-blind, placebo-controlled clinical trial called VELOUR which studied 1226 patients with metastatic colorectal cancer whose disease progressed during or within 6 months of receiving FOLFOX or FOLFOX + Bevacizumab, found a significant improvement in median overall survival if patients were treated with Ziv-aflibercept combined



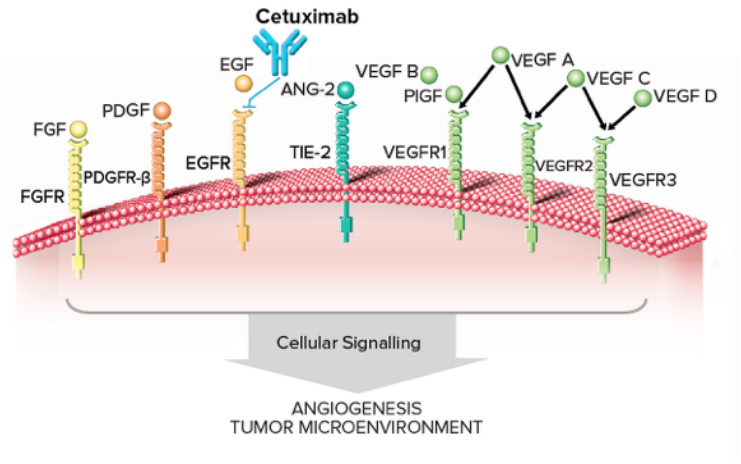
with the FOLFIRI chemotherapy, compared to those who received chemotherapy alone.

- **Regorafenib**: it is a tyrosine kinase inhibitor that targets multiple growth factors involved in tumor angiogenesis, including VEGF receptors, Fibroblast Growth Factor (FGF) receptors, Platelet-Derived Growth Factor (PDGF) receptors, and the angiopoietin receptor TIE-2. Regorafenib was approved in 2012 based on the results of the randomized, double-blind, placebo-controlled CORRECT trial, which enrolled 760 patients with metastatic colorectal cancer previously treated with multiple lines of therapies. The results showed a significant improvement in median overall survival among patients treated with Regorafenib versus those who received placebo.

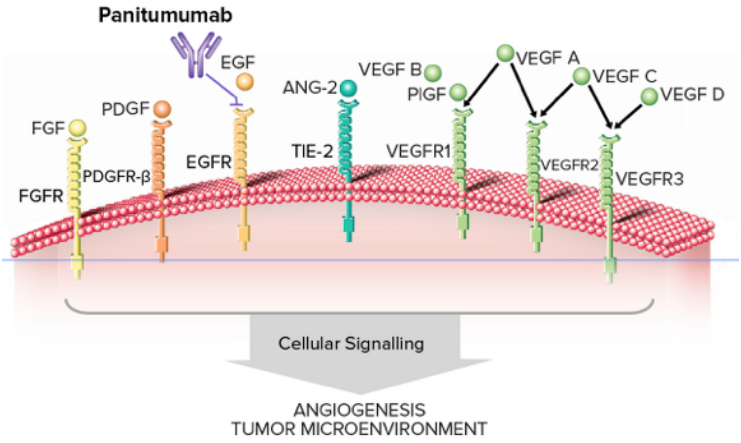


- <u>Anti-EGFR treatment:</u> KRAS gene helps doctors customise therapy for patients with metastatic colorectal cancer. KRAS tests determine the target therapies for which you may be eligible. The drugs Cetuximab and Panitumumab are ineffective in tumours that carry mutations of the KRAS gene. Roughly 40% of colorectal cancers have KRAS mutations while the non-mutated KRAS gene (also known as “wild type”) is found in the remaining 60%. Identifying KRAS mutation status avoids unnecessary expenses and toxicities from anti-EGFR inhibitors, which are ineffective in KRAS mutated colorectal cancers.

- **Cetuximab**: It is mainly used as a single agent in patients who have failed previous chemotherapies. (it may also be used with chemotherapy for first line treatment of patients who have KRAS mutation-negative (wild-type), EGFR-expressing mCRC. (33)



- **Panitumumab**: is used as a single agent for treating patients with EGFR-expressing mCRC who have experienced progression of their disease while or after taking a chemotherapy regimen.(34)



In summary, surgery is the standard treatment of rectal cancer. In advanced cancer of the middle and lower third of the rectum a radical surgery named Total Mesorectal Excision (TME) should be performed. Although it is a standardized procedure that can be performed in an open, laparoscopic or robotic approach, there are still some controversies in its management. One of these controversies is if a drainage must be placed or not after TME.

TO DRAIN OR NOT TO DRAIN AFTER TME

The introduction of the Total Mesorectal Excision (TME) by Heald in 1982 was a major advance in the surgical strategy for rectal cancer, resulting in a reduction of local recurrence without adjuvant therapy. In radically operated patients, the local recurrence rates with TME after 5 and 10 years have been reported to be <10% with a 5-year of survival rate of 80% (35,36,37,38). As a result of this procedure, patient satisfaction and quality of life has increased since it allows sphincter preservation in a high percentage of patients (39)

Despite all this progress, significant morbidity and mortality may occur. The primary concern after a TME surgery is the anastomotic deshicence and leakage: its incidence varies from 2 to 25% depending on the level of anastomosis (40), tumour diameter, tumour location, and absence of protective stoma(41) or method of reconstruction (42,43,44). Also it increases the incidence of other deeper complications such as abscesses, peritonitis and hematoma. Therefore, among the colorectal surgeons there is a major goal to detect any early leak and as a result, prevent the complications that it brings. For all these reasons, drainage has been proposed to drain the pelvis after colorectal anastomosis (45, 46, 47, 48).

On the one hand, the surgeons who routinely use pelvic drains believe that will help detect an early anastomosis leakage (49,50,70). At the same time, they defend that the drain avoids the retentions and contamination of postoperative pelvic fluid and the consequent sepsis (51,52,53)

On the other hand, according to the surgeons who are against the routine use of drains, believe that drainage increase the rate of some complications (54,55,56), including anastomotic leakage, peritonitis, hemorrhage and hematoma. Moreover they argue that also can provoke

complications related to the operative wound: abscess, disruption or incisional hernia, as well as pulmonary complications (57,58) and intestinal obstruction (59). In addition, drains are thought to promote infection from the outside (60), as well as intestinal adhesions (59). Furthermore, they are associated with pain, decreasing thoracic compliance leading to microatelectasia (57,58). Likewise, they can cause ulcerations of the gastrointestinal tract through the drain (61,62),hemorrhage (63), infection of the drainage tract (64), intrabdominal retention of the drain (57, 65) hampering its removal and wound disruption through the drainage tract (65).

As result of its unclear function, many studies have been made in order to objectify if placing a drainage makes a positive impact or not after TME surgery.

Firstly, we will focus in the studies that support the use of prophylactic drainage after TME.

Study	Type of study	Number of patients (n)	Main conclusions
Peeters et al. (66)	Retrospective	924 patients	•Lower rate of anastomotic leakage in patients that were drained than in the patients were not (9.6% versus 23.5%) after TME for rectal cancer located 15 cm or less from the anal verge. •Drains decrease the rate of reoperation.
Que et al. (67)	Meta-analysis of 14 studies (7 prospective and 7 retrospective)	4580 patients	Anastomotic leakage was 5,3% in the darán grup, versus 23,5% in the non drained group.
Rondelli et al (68)	Meta-analysis of 8 studies (3 randomised clinical trials and 5 non-randomised clinical trials)	2277 patients	•Lower incidence of extraperitoneal colorectal anastomotic leakage in drained patients (OR = 0.51; 95% CI: 0.36–0.73). •Lower reintervention rate in drained patients (OR = 0.29; 95% CI: 0.18–0.46).

Study	Type of study	Number of patients (n)	Main conclusions
Tsujinaka et al. (69)	Retrospective	196 patients	Pelvic drainage acts as an early detector of anastomotic leakage and reduces the need for reoperation

On the other hand, many studies have shown that drains can be an independent risk factor for anastomotic leakage and other serious complications, inducing more harm than benefit.

Study	Type of study	Number of pariente (n)	Main conclusions
Urbach et al. (71)	Meta-analysis of 4 randomised controlled trials.	414 patients	•Drain group has higher rates of wound infection and mortality than the non drained group. •20 of 223 drained patients (8,9%) developed anastomotic leakage versus 12 of 188 non- drained patients (6,4%)
Petrowsky et al. (72)	Meta-analysis of 8 randomised controlled trials	1390 patients	The overall rate of anastomotic leakage in drained patients was 4,2% (30 of 717 patients) versus 2,4% (16 of 673 patients) in non-drained patients
Karliczek et al. (73)	Meta-analysis of 6 randomised controlled trials	1140 patients	Drain group has higher rates anastomotic leakage, reintervation rates
Zhang et al. (74)	Meta-analysis of 11 randomised controlled trials	1803 patients	•Anastomotic leakage rate is higher in drained patients (67 of 939 ;7,1%) than in non-drained patients (50 of 864; 5,7%)
Menahem et al. (75)	Meta-analysis of 3 randomised controlled trials	660 patients	The drained group has higher incidence of small bowel obstruction (18,7% versus 12,6%)

There are studies that showed that placing a drainage after a TME surgery makes absolutely no difference: it is neither harmful or protective.

Study	Type of study	Number of pariente (n)	Main conclusions
Rolph et al. (76)	Randomised controlled trial	908 patients	No difference in anastomotic leakage rates, mortality, reintervention and wound infection.
Denost et al. (77)	Randomised controlled trial	469 patients	No difference in anastomotic leakage rates, mortality, reintervention and wound infection,
Sakr et al. (78)	Multivariate analysis	224 patients	No difference in anastomotic leakage rates, mortality, reintervention and wound infection.

In summary, there is not enough evidence to support or discard the routine use of drainage after TME surgery, so we propose a multi centric study to try to bring high quality evidence on this subject.

PELVIC DRAINAGE AFTER TOTAL MESORECTAL EXCISION: MULTICENTRE STUDY PROPOSAL

Objective:

To asses the effect of pelvic drainage after Total Mesorectal Excision.

Background:

Although many studies have confirmed infectiveness of drainage, there is still a controversy after TME. Moreover, many of the published studies are not conclusive as a result of the heterogeneity of the chosen sample, as well as due to the limited sample size and the exclusion of the neo-adjuvant therapies which are used in these days in more than 50% of these patients.

Hypothesis:

Pelvic drainage after Total Mesorectal Excision does not confer any benefits to the patient within the first 30 postoperative days.

Study design:

A multicenter, open label, randomised study among patients treated for rectal cancer is suggested. The patients that fit out inclusion and exclusion criteria will be randomized in 2 arms with a ratio 1:1: On the one hand, arm ¨A¨ will have patients with pelvic suction drain; and on the other hand, arm ¨B¨ patients without pelvic drain. The patients´ randomization to one of these two groups will be achieved by using a sealed envelope, which for each case was opened in the operating room just before finishing the procedure.

After surgery, patients must be followed during a 6 month period in order to check, verify and objectify our endpoints.

Endpoints:

Primary endpoints:

-Evaluate the rate of pelvic sepsis within 30 days after surgery(process which results of an anastomotic leakage)

Secondary endpoints:

-Asses the rate the postoperative mortality within 30 days after surgery.

-Check the number of bowel obstruction cases within 30 days after surgery

-Objectify the reoperation cases due to pelvic sepsis

-Classify the time between rectal excision and the reoperation between the drain and no drain patients.

-Evaluate the length of hospital stay between both groups.

Methods:

Inclusion criteria:

✓ Total Mesorectal Excision (TME)

✓ Rectal adenocarcinoma, histopathologically proved

✓ Stage II and III

✓ With or without chemotherapy or radiotherapy neoadjuvant treatment

✓ Stapled or hand-sewn anastomosis

✓ Open, laparoscopic or robotic approach

✓ 18 or more years old

✓ Information of the patient and signature of informed consent

Exclusion criteria:

- Partial mesorectal excision
- Colonic cancer (>15 cm from the anal verge)
- Abdominoperineal resection
- Simultaneous liver resection
- Multivisceral resection (prostate, seminal bladder, vagina…)
- Total proctocolectomy
- Emergency procedure
- Infected rectal tumor
- Pregnant women
- Women currently nursing

Preoperative staging:

Preoperative evaluation includes physical examination, colonoscopy with biopsy, pelvic magnetic resonance imaging and abdominal computed tomography scan.

Surgery:

All patients must have had a preoperative bowel preparation. The operative technique could be achieved by open, laparoscopic or robotic approach and must include excision of the mesorectum. At the end of the procedure a suction pelvic drain will be placed posterior to the anastomosis (in the pre-sacral area) for patients randomized in arm A.

Patients in all groups will be treated according the postoperative protocol, which includes: evaluation of C-reactive protein at day 3, a computed tomography scan when abscess or anastomotic leakage was clinically (fever, discharge of pus by the anus or discharge of pus, gas or stools by the vagina or drain) or biologically suspected (C-reactive protein >140mg/L).

The pelvic drain will be removed when the output of the drain will be clear and lower than 100 mL/24hours.

Sample Size:

Our study´s main objective is to compare the postoperative pelvic sepsis between the 2 arms within 30 days after surgery. According to literature, 12% of patients who undergo TME suffer from pelvic sepsis. Moreover the levels of significance must maintain an overall P value of 0,05 according to the O´Brien-Fleming stopping boundaries. With a 2-sided 5% significance level and a power of 80%, an expected rate of 3% of patients for whom a pelvic drain would be used even if they were randomized in arm B (due to complications during the surgical procedure) and an expected rate of 2% of postoperative mortality, an initial sample size of 466 patients is needed (software Nquery Advisor v 6.0).

Statistical analysis

Qualitative variables will be described as numbers (percentages) and quantitative variables as mean standard deviation. Differences between groups will be assessed by x^2 tests or Fisher exact tests when appropriate and by Student t test P value less than 0.05 is considered as statistically significant. Analyses will be by intention to treat.

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