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Editorial Open Access

10 Reasons to Do TAPP

Radu Moldovanu[1,2]* and Gérard Pavy[3]

[1]Department of Surgery, "St. Mary" Clinic, Cambrai, France
[2]Department of Surgery, University of Medicine and Pharmacy "Gr.T. Popa" Iasi, Romania
[3]Department of Surgery, Les Bonnettes Hospital, Arras, France

Abstract

Hernia repair is the most common surgical procedure worldwide. The mesh repair is the gold standard technique for groin hernia in adults; anatomic, non-mesh repair is still indicated in contaminated wounds. The recommended techniques by the actual guidelines are: Lichtenstein and Shouldice technique for open access and TAPP (TransAbdominal PrePeritoneal) and TEP (Total ExtraPeritoneal) hernia repair for endoscopic repair. We present herein several aspects of TAPP hernia repair with highlighting its advantages. The present paper is a brief argument to do TAPP routinely in benefice of patients, residents and surgeons.

Keywords: Hernia repair; Laparoscopy; TAPP; Laparoscopic training; Surgery warm-up

Editorial

The hernia repair is the most common surgical procedure with over 2,000,000 procedures performed every year [1]. The mesh repair is the gold standard technique for groin hernia repair in adults. The exception is the risk of mesh infection in case of contaminated wounds and, the "anatomical" repair without mesh is recommended for these cases [2,3].

The actual guidelines recommend 4 techniques for groin hernia [2-4]:

- for open approach, mesh repair using Lichtestein technique and, for contaminated wounds, Shouldice technique, and
- for endoscopic hernia repair, TAPP (TransAbdominal PrePeritoneal) and TEP (Total ExtraPeritoneal)

The recent papers and guidelines didn't reveal any advantage between TAPP and TEP from point of view of postoperative morbidity and recurrence rate and only the surgeon's experience (and preference) remains the only valuable argument [2-4].

The "absolute" contraindications for TAPP are in fact the contraindications of general anesthesia and generally of laparoscopic approach: severe comorbidities (e.g. severe cardiac or respiratory dysfunction). It is also contraindicated in children (as all the mesh repair techniques). All the rest are "relative" contraindication, which depends of surgeon experience and local conditions: large inguino-scrotal hernia, history of radical prostatectomy or planned radical prostatectomy, peritoneal adhesions [2-4].

We presented below 10 reasons to do TAPP as usual technique for groin hernia:

1) TAPP is an outstanding hernia repair procedure because allows a good reinforcement of abdominal wall and the reinforcement of all the groin area with a low of recurrence. To have a low rate of recurrence is it mandatory to respect several technical tricks: wide dissection to allow a good mesh deployment and parietalization and avoid the mesh enrollment and the use of large mesh (ideally 12x15cm) to cover all the weak groin areas [1-8].

2) TAPP is associated with low risk of morbidity: less mesh infection, hematoma and recurrence [2-4]. However, TAPP is associated with a higher risk of postoperative seroma; however several technical tricks as fascia transversalis eversion and fixation in large direct hernia and Retzius space drainage allow the decrease of postoperative seroma [2-4,7,8].

3) The laparoscopic exploration during TAPP allows a rapid check-up of contralateral site with diagnosis and then treatment during the same procedure of occult contralateral hernias. We perform the bilateral repair sequentially, firstly the most important hernia and then the contralateral, and we use two separated meshes fixed together on the mid-line with absorbable tacks/staples [7,8].

4) The preperitoneal dissection during TAPP allows the diagnosis of occult obturator hernias (type I), source of chronic inguinal or pelvic pain. Using the open approach this hernias are overlooked; in this way it is important to note the high incidence of obturator hernia in women in necropsy: 60% [9]. In our experience the overall incidence of obturator hernia was 18% (32% in women and 15.5% in men respectively) [10]. The wide preperitoneal dissection also allows the diagnosis of small, incipient, femoral hernias. In this way, TAPP is highly recommended in women, especially in "skinny old ladies" with high risk of obturator, femoral or other occult hernia [4,11-14].

5) TAPP, contrary to TEP, can be performed in strangulated hernias [2-4]. In our opinion the laparoscopic exploration represents a great advantage in strangulated hernia and allows to explore the entire small bowel and to treat the small bowel ischemic lesions [2-4]. Afterwards, hernia repair can be performed using either semi absorbable mesh or anatomic (open/laparoscopic) non mesh repair according to the wound contamination.

6) TAPP, contrary to TEP, is easy to be learned with a learning curve of about 30 procedures. The anatomical landmarks are easy to be recognized. Usually a step-by-step approach with landmarks recognition is advisable: superficial landmarks (urachus, umbilical

***Corresponding author:** Radu Moldovanu, MD, PhD, Department of Surgery, "St. Mary" Clinic, 22 rue Watteau, 59400, Cambrai, France, Tel: +33 (0) 3 27 73 56 03; Fax: +33 (0) 3 27 73 56 96; E-mail: rmoldovanu@gmail.com

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folds, epigastric vessels, spermatic vessels, vas deferens or uterine round ligament) and then, deep landmarks (Cooper, Gimbernat ligaments, corona mortis and external iliac vein) [7,8].

7) TAPP allows the diagnosis and treatment of concomitant ventral hernias. In this way we are the advocates of laparoscopic mesh repair which allows a better exploration and reinforcement of abdominal wall with large prosthesis which overlaps with a minimum 5 cm in all directions the parietal defect(s), to avoid postoperative mesh shrinkage and recurrence [15,16].

8) TAPP has a low risk of postoperative pain if we respect several simple rules: use of light weight mesh, use of absorbable tacks, use of less of 10 tacks, glue fixation or adhesive mesh [1-4,7,8].

9) TAPP allows a rapid recovery with a short time to return to normal activity and work. In this way it is suitable for ambulatory or one day surgery [2-4].

10) One of the most important issues is the value of TAPP as a tool for laparoscopic training. As mentioned above, TAPP is a relatively easy to be learned especially due to the easy recognition of anatomic landmarks. Then, TAPP is an excellent exercise to learn and practice laparoscopy:

- **It allows a gain in exploration, 3D accommodation and camera manipulation:** to navigate and explore the entire abdomen, to recognize the superficial and then the deep anatomic landmarks; furthermore, in our opinion a 30 degree camera is mandatory to better perform the procedure, and TAPP is an excellent exercise for the training of 30 degree camera manipulation for the surgeon and his assistant, targeting the different superficial and especially deep anatomic landmarks.
- **Dexterity and ambidexterity:** TAPP requires good skills of dissection and tissue exposure so is an excellent training tool for dissection and navigation in narrow spaces, dissection of "fragile" structures (e.g. testicular vessels, vas deferens). It is also a valuable exercise to deploy and manipulate a mesh.
- **Knot tying:** The peritoneal closure after TAPP is very important; the actual guidelines recommend "waterproof" closure of the peritoneum using different methods: staples, glue, suture [2-4,7,8]. We usually close the peritoneum by a running suture with extracorporeal or intracorporeal knot tying or barbed sutures [7,8]. This is a very good exercise for laparoscopic sutures and knot tying and we highly recommend it as training tool before start any other more complex procedure which implies sutures (gastro-esophageal junction surgery, colic surgery, bariatric surgery).
- **Warm-up:** Warm-up concept in general surgery is relative recent. However it's value was demonstrated in different studies [17,18]. In our opinion, TAPP is useful as "warm-up" procedure before to start other more complex techniques (e.g. laparoscopic colectomy, gastric bypass) due to its complex role to train all the gestures used in minimally-invasive surgery, from 3D accommodation and camera navigation until dissection and suturing.

In conclusion, we consider TAPP an excellent procedure and in our opinion, it has to be generalized as common routine hernia repair procedure for the benefice of patients, residents and surgeons.

Conflict of interests

Authors have no conflict of interests to disclose.

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Review Article Open Access

Metastatic Colorectal Cancer: Review of Diagnosis and Treatment Options

Madalina Palaghia[1]*, Cristina Cijevschi Prelipcean[2], Elena Cotea[3], Nuțu Vlad[1], Lucian Leneschi[3], Valentin Bejan[3], Lacramioara Perianu[1], Alin Vasilescu[1] and Eugen Târcoveanu[1]

[1]Department of Surgery, First Surgical Unit "St. Spiridon" Hospital Iasi, University of Medicine and Pharmacology "Gr.T. Popa" Iasi, Romania
[2]Department of Gastroenterology, University of Medicine and Pharmacy "Gr.T. Popa" Iasi, Romania
[3]First Surgical Unit "St. Spiridon" Hospital Iasi, Romania

Abstract

Colorectal cancer (CRC) is currently considered the third most common neoplasm in the world according to the World Cancer Research Fund International with 1.4 million cases diagnosed in 2012, and the second malignity as cause of death. Approximately 1/5 of patients present directly with metastatic disease (mCRC), and 30 to 50% develop metastasis after surgical treatment for initially localized disease. The aims of the current study are to review the diagnostic particularities, treatment options and clinical evolution of mCRC. Metastatic process in CRC is long and complex, involving several mechanisms, molecular pathways and cellular types. Advances in medical imaging now allow an early and accurate diagnosis of metastatic lesions no matter their location. The progress of fundamental research in CRC led to understanding the molecular basis of the metastatic process that was further translated into novel chemotherapic and biological agents, thus increasing overall survival and and progression-free survival rates. Resection of liver, lung and brain metastases is crucial for survival when achievable and is more effective when completed by an oncological treatment and rigorous follow-up. All patients with mCRC should be discussed by a multidisciplinary team (surgeon, oncologist, radiologist, and gastroenterologist) in order to identify the most appropriate therapeutic management.

Keywords: Colorectal cancer; Metastasis; Chemotherapy

Introduction

Colorectal cancer (CRC) is currently considered the third most common neoplasm in the world according to the World Cancer Research Fund International with 1.4 million cases diagnosed in 2012, and the second malignity as cause of death [1]. In Romania, CRC registered an incidence of 17.74 cases/100.000 inhabitants in 2000, and was responsible for 19.05 deaths/100.000 inhabitants in 2002, while 8240 new cases have been diagnosed in 2006 [2].

Age greater than 50, alcohol abuse, reduced physical activity, obesity, unbalanced diet (poor in fibers, rich in fats), personal or familial history of polyps, and inflammatory bowel disease are known risk factors for the development of CRC. Histopathologically, 95% of the CRC are adenocarcinomas [3].

Approximately 1/5 of patients present directly with metastatic disease (mCRC), and 30 to 50% develop metastasis after surgical treatment for initially localized disease [4,5]. Metastatic disease involves in the order of frequency the liver, the peritoneum, the lungs, the bone and the brain, other locations being extremely rare (ovary, pancreas etc.). An advanced stage of the primary lesion with lymphatic or vascular invasion at the moment of diagnosis, high levels of the carcinoembryonic antigen (CEA), gene mutations (18q) and aggressive cellularity are important risk factors for metastatic disease [6]. The median survival interval of the mCRC without treatment is of less than 8 months, with longer intervals in case of patients with a limited number of metastases in a single organ (liver) [7]. Some metastases can be addressed surgically, but chemotherapy (single or combined with biological agents) remains the only valuable treatment in patients with inoperable metastases (most cases with mCRC). With the advance of pharmacological research, mortality from mCRC has decreased over the past decades. The aims of the systemic therapies are to increase survival rate, and to offer a good life quality. The most commonly used drugs in mCRC adjuvant therapy are the chemotherapics 5-fluorouracil (5-FU), oxaliplatin, irinotecan, capecitabine and the biological agents bevacizumab, panitumumab, cetuximab that act either against angiogenesis (bevacizumab) or inhibit the endothelial growth factor receptor (EGFR) (panitumumab, cetuximab). These drugs can be used in different combinations depending on patient's general condition, tumor histopathological and immunohistochemical characteristics, and drug availability, leading to variable survival rates [8,9].

Metastases in CRC can be syncronous (detected prior/during surgery of the primary tumor or within 3-12 months since initial intervention) or metachronous (discovered more than 1 year after surgical resection of the primary tumor). According to Slesser et al. a distinctive approach is mandatory as synchronous metastases usually are associated with a locally advanced CRC, a greater metastatic burden and a poor outcome [10]. On the other hand, metachronous metastases occur mostly in patients already treated with adjuvant chemotherapy and are more prone to be chemo resistant compared to synchronous metastases thus compensating the worse initial prognosis of synchronous metastases.

The aims of the current study are to review the diagnostic particularities, treatment options and clinical evolution of mCRC.

Metastatic Spread in CRC

The cellular and molecular pathways of metastatic process in CRC have been extensively analyzed over the last decades, and their understanding was materialized in the form of a new generation of anti-tumoral drugs like bevacizumab, an anti-VEGF antibody that has been proved to increase survival rate.

***Corresponding author:** Madalina Palaghia, MD, Department of Surgery, First Surgical Unit, "St. Spiridon" Hospital, Iași, Romania, Bd. Independenței, No 1, 700111, Iași, Romania, Tel: +40 (0) 0232-24 08 22; Fax: +40 (0) 0232-21 77 81; E-mail: madalinapalaghia@yahoo.com

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Liver Metastases

The liver is most frequently involved organ in mCRC and often the single site of metastasis in CRC, both at the time of initial diagnosis (20–25% of cases) or after resection of the primary tumor (40% of cases) [11].

Liver metastatic process in CRC involves a series of steps such as [6,12,13]:

- **Lysis of the extracellular matrix**: enzymes produced by cancer cells alter the extracellular matrix and allow cancer cells to leave the primary tumor. Cancerous cells can ignore integrin signaling and survive without contact to the extracellular matrix;
- **Cellular adhesion**: cancerous cells express adhesion molecules (cadherins, integrins, carcinoembryonic antigen - CEA) that favor their adhesion to the extracellular matrix;
- **Angiogenesis**: some CRC have an increased expression of the vascular endothelial growth factor (VEGF) and the platelet derived growth factor (PDGF), important angiogenic factors associated with a poor prognosis. The vascular network whose formation was induced by tumor cells is poorly effective, fragile and hemorrhagic. VEGF and PDGF together with fibroblastic growth factor (FGF) and hepatocyte growth factor (HGF) also promote lymphangiogenesis by circulating endothelial progenitors derived from the bone marrow. Cancerous cells adapted to the mechanical forces of the circulatory system and attach to platelets thus forming tumoral emboli, and are able to bypass immunosurveillance by an overexpression of protective acute phase proteins [8,14,15];
- **Dissemination, invasion and colonization of distant organs with subsequent growth**: the liver is the most involved organ because of the portal circulation, and the morphology of the fenestrated sinusoid network.

According to Paschos, liver metastases formation is a 4 stages process:

1) Microvascular infiltration with tumoral cells,
2) Interlobular micrometastasis phase,
3) Angiogenetic micrometastasis phase and
4) Established liver metastasis phase [6].

Cancerous cells adhere to sinusoidal endothelial cells (SEC) and resist this way to the blood stream forces [6]. Kupffer cells are able to identify and destroy tumor cells, but this is a two-ways interaction: as cancerous cells attached to Kupffer cells are arrested in the liver, Kupffer cells eventually become saturated and cancerous cells start to divide and grow inside the liver. Hepatic stellate cells (HSC) that lie in the space of Disse can be activated by cancerous cells through citokines and promote liver angiogenesis. Some members of the tumor necrosis factor (TNF) family expressed by cancerous cells make them able to resist apoptosis, and the gene for the chemokine receptor CXCR4 regulates their migration. The epidermal growth factor (EGF) is also overexpressed in mCRC and is a target for chemotherapics [16]. Formation of macroscopic metastases takes weeks or months, and cancerous cells may rest in dormancy state for a long period of time.

Peritoneal Metastases

Peritoneal metastases, detected in 7-10% of patients at the initial presentation, occur in 4-19% after surgical resection of the primary tumor. Survival rates in these cases range from 5 to 24 months [17]. Peritoneal metastases develop secondary to intraperitoneal spread caused by full thickness invasion of the colonic wall or secondary to rupture of a mucus-producing appendix cystadenocarcinoma (pseudomyxoma peritonei). Peritoneal spread may also occur during surgery under the form of tumor cells or emboli that freed from dissected vessels or bowel lumen.

Lung Metastases

Lung metastases in CRC occur in 10 to 30% of all cases at 5-60 months after resection of the primary tumor. Tumor cells reach the lungs through haematogenous dissemination (colon – portal vein – inferior vena cava – pulmonary artery) or, less frequent, through lymphatic dissemination [18]. Contrary to the liver, the lungs are the single organs involved in only 2-4% of cases [19]. Mediastinal adenopathies occur through lymphatic spread from a nearby lesion in 3.5% to 16.7% of cases [20].

Bone Metastases

The incidence of bone metastases in CRC varies from 6% to 10.4% depending on the study, with a median time of detection of 11-21 months after resection of the primary tumor. In all the reviewed studies, bone metastases were associated to lung and/or liver metastases [21-23]. Metastatic lesions, usually multiple, occur secondary to hematogenous dissemination, and most frequently involve the axial skeleton and the proximal segments of the limbs. In decreasing order, they are located in the dorsal and lumbar spine, sacrum, pelvis, ribs, sternum, proximal femur and humerus and cranium. Metastatic bone destruction is not caused by tumor cells, but by osteoclasts activated by tumor cells that secrete an osteoclast activating factor. Mundy et al. divided this process into 4 stages [21,22]: tumor cells adhere to the basement membrane; tumor cells produce proteolytic enzymes that alter the basement membrane; tumor cells migrate through the basement membrane; tumor cells stimulate osteoclasts' activity.

Brain Metastases

Brain metastases occur in 2-12% of patients with CRC during the course of the disease, and median survival rate ranges from 2.8 to 6 months without surgery and from 6 to 10 months after metastasis resection [24]. Brain metastases occur through hematogenous spread and they may locate in the cerebrum (80%), cerebellum (15%) and the brainstem (5%) [25].

Clinical Diagnosis

A series of symptoms like pain in the right upper quadrant, significant weight loss, anorexia, jaundice, nausea suggest the presence of an advanced form of CRC with a high probability of liver metastases, especially if these symptoms are associated with an elevated CEA [20]. Patients with peritoneal metastases present with nonspecific symptoms like abdominal discomfort, increased abdomen size, nausea, vomiting, weight loss, cachexia, and fatigue, symptoms indistinguishable from those that generally occur in advanced CRC [17]. By contrast, lung metastases are frequently asymptomatic and incidental radiographic findings with the exception of bronchial lesions that occur rarely and can present with cough, dyspnea, or repeated infections [18,19]. Apparition of vertigo, headache, blurred vision or hemiparesis suggests the possibility of brain metastases [24].

Diagnostic Imaging in mCRC

The purposes of medical imaging in mCRC are to quantify the number and extent of secondary lesions, to evaluate the liver prior to liver resection (residual volume), to assess tumoral response to chemotherapy and conversion of initially unresectable lesions into resectable ones, to exclude local or distal recurrence or any associated pathology [26]. Despite the multitude of available imaging methods, there is no international consensus concerning the most appropriate method for assessing recurrent disease on the operated liver.

Chest X-ray

Chest X-ray, routinely performed as part of preoperative evaluation, of limited use in detected lung metastases as small lesions (< 1 cm), is either missed or invisible.

Ultrasound (US)

Abdominal US are the most accessible and widely available imaging method. US is able to diagnose most liver metastasis >1 cm (20% sensitivity rate for metastases < than 1 cm) but its sensitivity is limited by user's experience, technical performances of the US device, and patient's characteristics (obesity, particular conformation, steatosis). Typically, CRC liver metastases present as solid lesions with a hypo echogenic halo, but iso echogenic lesions (difficult to detect) and hyper echogenic ones (differential diagnosis with hemangiomas) have also been reported. Intravenous contrast agents are not used for ultrasound examination in Romania despite the fact that their use could increase sensitivity rate to up to 87% [2,26]. Conversely, intraoperative US are used in many Romanian clinics for detecting liver lesions prior to metastasis resection.

Computed Tomography (CT)

Currently, CT is a widely available low cost method of choice for metastases screening in patients with known CRC. CT with intravenous contrast (three phase's examination–non-contrast, late arterial and portal venous) is mandatory for preoperative cancer staging in all cases except for patients with absolute contraindications to iodinated contrast material when other methods like MRI, chest X-ray, PET should be considered. In late arterial phase, liver metastases may present a rim enhancement but they are more conspicuous in the portal venous phase. Liver metastases typically present as hypovascular lesions, and CT is able to detect up to 85% of all liver metastases with false negative/positive results in case of small, indeterminate, hypo-enhancing lesions (cysts mistaken for metastases or metastases mistaken for cysts) [27]. Evaluation of vascular invasions and a liver volumetric study are mandatory when liver metastasis resection is planned. Infiltration of both portal veins and the three principal hepatic veins contraindicates liver resections. Vascular invasion of portal or hepatic veins of a single lobe does not contraindicate surgery but is associated to a poor prognosis [28].

Lung metastases are easily detected by CT, but false positive results may occur in case of benign lung nodules (non-calcified granulomas, hamartomas with low fat content or without calcifications, etc.). If the patient underwent a previous CT examination, a comparative study is mandatory for differential diagnosis.

CT is also the method to use for postoperative or adjuvant therapy follow-up according to the revised Response Evaluation Criteria in Solid Tumors (RECIST) revision 1.1, the gold standard for evaluating tumor progression [7].

Magnetic Resonance Imaging (MRI)

MRI is not the first method to be used for metastases screening except for brain metastases, due to its high costs, the length of the examination, and the necessity of repeated breath holds and long period of immobility. Despite its limitations, MRI has the advantage of a more accurate characterization (sensitivity and specificity rates of 85% and 100% respectively) of liver lesions compared to CT, especially in patients with steatosis or small lesions (MRI can precisely identify pure liquid lesions). The new diffusion sequences and the apparent diffusion coefficient (ADC) allow a better identification of metastases due to limited diffusion of water molecules in the extracellular space of tumoral tissue [26,27]. In the western world a series of liver-specific contrast agents have been introduced but they are of very limited availability in Romania.

Positron Emission Tomography (PET) with or without a CT Acquired at the Same Time (PET-CT)

PET using F-18-fluorodeoxyglucose (FDG) as a radiopharmaceutical is, taken by itself, of limited use in liver metastases diagnosis but when associated with CT (PET-CT) it can anatomically map all lesions with an increased metabolic rate. Reviewed studies report sensitivity and specificity rates inferior to MRI (71% and 93.7% respectively) in case of liver metastases. In case of CT detected lung nodules, the PET adds the metabolic information thus facilitating the differentiation between benign and malignant lesions [26,27].

Therapeutic Management

Surgical Treatment

Liver Metastases: Addition of new, multidisciplinary techniques and therapies like systemic or local chemotherapy, radiofrequency ablation (RFA), cryotherapy and radiotherapy improves the rate of liver metastases resectability but currently there is no gold standard concerning the optimal treatment of synchronous liver metastases. Neoadjuvant chemotherapy may convert up to 15% of liver metastases from inoperable to operable by tumor shrinkage and producing free margins. In case of small lesions that disappear after chemotherapy, it is still necessary to remove the containing liver as most lesions are not sterilized [29].

According to clinical studies, 10-25% of patients with hepatic metastases may be candidates for surgical resection, while the recurrence rate ranges from 60 to 80%. Historically, extrahepatic metastases were considered as a contraindication to liver resection but recent studies proved that patients undergoing both lung and liver resection (usually first pulmonary resection and then liver resection) register 5-year survival rates superior to 30% [30]. The presence of extrahepatic disease is associated to mix patterns of dissemination that lead to new metastatic foci after surgical resection.

The purpose of the surgical treatment for liver metastases is to remove all lesions with a free margin of 1 cm and to leave sufficient liver parenchyma (at least two liver segments in continuity) in order to ensure 25% of total functional liver or a remnant liver volume to body weight ratio superior to 0.5%. The residual liver has to be supplied by a portal vein, a main hepatic vein, a hepatic artery and a bile duct that can be anastomosed to the gut [29,30]. Complete metastasis resection (R0) increases 5-year survival rate to 25-40% depending on the study. Small survival intervals are expected if there are more than four metastases or involved lymph nodes at the moment of primary tumor resection or if metastases occur less than 1 year after removing the CRC [31].

Sectional medical imaging (CT, MRI) is necessary to calculate the volume of the future residual liver prior to surgery. 25% of the initial liver volume is sufficient only in patients free of cirrhosis, steatosis and hepatic disease due to chemotherapy. In cirrhotic patients, a minimum of 40% remnant liver volume has been recommend in order to prevent liver failure [27]. As most patients underwent prior chemotherapy, leaving just ¼ of total liver volume is associated to a high rate of complications and an increased postoperative mortality. Two techniques have been used in such cases, separately or combined: staged resection at one-month interval and portal vein embolization (determines atrophy of the affected lobe and hypertrophy of the healthy lobe) with resection of the embolised lobe [29,30].

Garden et al. have proposed some guidelines for resection of mCRC liver metastases. According to these guidelines, patients with mCRC should have a preoperative CT of the abdomen and pelvis, and ideally of the thorax as well (a chest X-ray may also be accepted). The entire colon has to be examined prior to surgery in order to assure that there is no recurrent disease at this level. CEA levels also have to be

determined prior to surgery. In most cases, primary tumor resection and liver metastasectomy are not to be performed at the same time, but in selected cases with superficial, small metastases, combined, synchronous resection may be considered. Recurrent liver lesions could be treated in the same way as the initial liver metastases [32].

Anatomical vascular variants should always be assessed prior to surgery, as hepatic arteries originating from the left gastric artery (left hepatic artery) or the superior mesenteric artery (right hepatic artery) together with multiple hepatic arteries require additional steps. In case of right lobe resection, the middle and left hepatic veins are to be preserved in order to prevent venous congestion or ischemia of the remnant liver. For left lobe resection, the right and middle hepatic veins should be preserved. Similarly, the presence of accessory hepatic veins requires additional surgical times. In case of trifurcation of the portal vein (the right anterior portal vein originates directly from the main portal vein), resection of the left portal vein proximal to the origin of the right anterior portal vein could lead to a compromise of the portal perfusion of the anterior segments of the right lobe (V and VIII) and of segment IV. Portal vascularization of segment IV must be accurately assessed as it can originate from the any of the two portal veins. Bile leakage may occur when resection is extended to segments I and IV. A triple confluence of hepatic ducts (right, left, a division of the right anterior and posterior ducts with the left one) occurs in up to 15% of individuals, and in 8% of individuals a right sectorial duct may confluence with the left hepatic duct. Rarely (2%) a right posterior sectorial duct joins the neck of the gallbladder. All these variants increase the risk of biliary complications [33].

When synchronous liver metastases are diagnosed, the sequence of surgical procedures remains controversial. The order of tumor resection, liver metastases or primary colorectal carcinoma first, is an issue that surgeon has to deal with taking into account the impact of new chemotherapics on tumor size, the role of portal vein embolization in increasing liver volume, and the possible association of liver resection with ablation techniques.

Traditionally, colorectal primary tumor is resected first, followed by postoperative chemotherapy for 3-6 months and liver surgery in a second stage. This approach has a significant prognostic impact as survival rate is determined by the presence of liver metastases, and the presence of postoperative complications (ex. anastomosis dehiscence) could delay the onset of chemotherapy and second stage liver surgery. In case of locally advanced rectal cancer, neoadjuvant radio-chemotherapy could be applied thus delaying second stage liver surgery with subsequent progression of metastases.

Single stage resection of both primary tumor and liver metastases seems like the perfect approach as it is associated with less physical and psychological stress, lower costs, shorter hospitalization, and faster recovery. The disadvantages are represented by the cumulative risk of two surgical procedures with increased morbidity and mortality [34].

A “liver-first” approach has been proposed by several teams [34-36] in order to prevent complications associated with liver surgery in the context of chemotherapy-associated steatohepatitis (CASH), to perform a curative R0 liver resection that could become impossible after several months of chemotherapy, and to reduce the delay between surgical and oncological treatment. Despite its advantages, this approach carries the risk of bowel occlusion.

In selected cases (patients who are not eligible for resection, recurrences, small liver metastases, or need for major liver resection), several down staging techniques (chemotherapy, portal vein occlusion, local ablation) can be used as part of a single-stage or two-stage hepatectomy. Portal vein occlusion (by embolization or ligation) triggers the atrophy of the correspondent lobe and hypertrophy of the noninvolved lobe thus increasing the size of the future remnant liver volume (FRLV) and allowing lobe resection. Local ablation (radiofrequency, cryotherapy, steam thermonecrosis, microwave coagulation) can be combined to hepatic resection in order to treat metastases less than 5cm in diameter (3cm for a better control rate). Anatomic location of liver metastases can limit the use of down staging techniques like radiofrequency ablation that cannot be applied to lesions close to large vessels (heat sink effect increases the risk of incomplete ablation) or main biliary structures (risk of thermal injury).

Concerning metastases reduction chemotherapy, a French study showed similar prognosis in patients that underwent metastasis resection of initially resectable liver metastases compared to patients with initially unresectable lesions converted to resectable ones after chemotherapy [37]. The presence of < 1 cm free margins and of extrahepatic disease is the most important predictive factor of recurrence after liver metastasectomy. Characteristics of the primary tumor like lymph node involvement, grade of differentiation and location (rectum) still are considered independent prognostic factors of survival and recurrence [38,39].

Lung Metastases: Lung is the second most involved organ in mCRC after the liver, and up to 20% of lung metastases are not detectable prior to surgery [18]. The aim of the surgical treatment is complete removal of metastases without extensive lung resection. Operative approach is chosen based on the size and location of metastases. Lung metastases are most frequently located peripherally in the lower lobes thus allowing ease wedge resection. Lobectomy and pneumonectomy are avoided because of the high postoperative morbidity and mortality. Patients with adequate cardiopulmonary reserve, without extrathoracic disease except the primary tumor or with resectable extrathoracic disease, are candidates to lung resection for metastasis. Authors like Lizasa et al. consider that the number and size of lung nodules represent independent prognostic factors for survival, and that multiple or bilateral lesions can be excised [40]. Several studies have proved that preoperative carcinoembryonic antigen (CEA) is an important prognostic factor for survival after lung resection for metastasis. According to Rama et al., patients with completely resected single nodules, a disease free interval of more than 3 years prior to lung metastasis discovery, and a normal preoperative CEA register the higher survival rates [34]. A 21-63% 5-year survival rate has been registered in patients who have undergone lung resection [41]. Radiofrequency ablation (RFA) is preferred in patients with insufficient cardiopulmonary reserve, but it is not widely available.

Peritoneal Metastases: Peritoneal metastases were classically considered as a contraindication for surgery in CRC cancer and a terminal condition. However recent studies revealed that cytoreductive surgery (CRS) with peritonectomy, peritoneal resection associated with Hyperthermic Intraperitoneal Chemotherapy (HIPEC), and Early Postoperative Intraperitoneal Chemotherapy (EPIC) has promising results in selected patients. Complete CRS is achievable in patients with a Peritoneal Cancer Index (PCI) score inferior to 10, no extra-abdominal disease, a maximum of 3 small, resectable, liver metastases, no enteric or biliary obstruction, no gross mesenteric involvement [36,42]. CRS aims to completely remove macroscopic disease using visceral resection and peritonectomy procedures and can be combined to HIPEC.

Brain Metastases: Treatment recommendations from brain metastases are similar to brain primary tumors. The resection is usually indicated in case of single metastases in the absence of important comorbidities and uncontrolled disease. Surgical resection may also be performed in case of multiple (mostly double) lesions if neurological symptoms cannot be controlled with radiotherapy and steroids alone. Surgery is combined with radiotherapy and steroid administration in 1/3 of cases, improving overall survival up to 11-12 months [24,25].

Focal Therapies

Radiofrequency Ablation (RFA): RFA is indicated for patients with unresectable lesions, small recurrent metastases, severe comorbidities contraindicating extensive surgery, and as a complement to hepatic resection. RFA is restricted to a maximum of 3 metastases measuring less than 3cm [43]. Lesions located close to large vessels, extrahepatic organs or major biliary ducts cannot be treated by RFA due to the heat sink effect and the risk of thermal injury. In patients with resectable lesions and no contraindications to major surgery, RFA should not be used.

Cryotherapy: Liquid nitrogen introduced into the metastases through thin metallic probes freezes the tissue with subsequent tumor necrosis. This method is not as popular as RFA due to the risk of hemorrhage from parenchymal lesions and intravascular coagulation [43].

Stereotactic Body Radiotherapy (SBRT): SBRT can be used to treat liver, lung, lymph nodes, spinal and adrenal metastases, and postoperative pelvic recurrence. SBRT involves irradiating metastases with hypofractionated high-dose (10-20 Gy per fraction) radiation while sparing the surrounding normal tissue with a 2-year local control rate of up to 80% [44].

Stereotactic Radiosurgery: Stereotactic radiosurgery using Gamma Knife, Cyberknife or Linac can achieve control of both single and multiple brain metastases by focally applying high-dose radiation (minimum 18 Gy) with a recurrence rate of 39-52%. The procedure can be repeated if a new lesion appears and is as efficient as classical surgical resection (level I evidence) [45]. Adjacent cerebral tissue and cerebral functions are preserved.

Percutaneous Ethanol Injection (PEI): Although PEI proved to be efficient in treating small hepatocellular carcinoma, is not effective in case of CRC metastases but the only studies have been performed more than 20 years ago [46].

Microwave Ablation (MWA): MWA uses microwave frequencies of more than 900 MHz that induce coagulative necrosis similar to RFA but due to its recent availability there is a lack of extensive studies that evaluate the efficiency of this method [43].

Thermonecrosis with overheated steam implies laparoscopic or open surgery injection of overheated steam into metastases that induces coagulative necrosis similar to MWA and RFA with promising results [47].

***In Situ* Chemotherapy via the Hepatic Artery**

In case of unresectable liver metastases, chemotherapic agents (5-FU, leucovorin, oxaliplatin, irinotecan) may be administered direct into the hepatic artery with higher response rates (40-50%) compared to systemic chemotherapy, according to Lorenz [48]. This type of treatment can also be used after hepatic resection in order to prevent the recurrence of the disease. Kemeny has reported a 1-year free of disease rate of 90% in case of in situ chemotherapy after liver metastasectomy compared to 60% in case of metastasectomy alone [28]. Due to the toxicity of the chemotherapic drugs, elevated liver enzymes (transaminases, alkaline phosphatase, and bilirubin), hepatic artery thrombosis, gastritis and biliary sclerosis may occur. Also, the catheter must be left in place for 14 days and may dislodge.

Transarterial Chemoembolisation (TACE)

TACE involves supraselective injection of chemotherapeutic agents emulsified in a viscous carrier like lipiodol into the feeding artery of the tumor followed by definitive embolization with polyvinyl alcohol particles or spheric embolic agents. The aim of this procedure is to achieve a high concentration of chemotherapeutic drugs combined with tumor necrosis due to arterial occlusion. Currently, this procedure is being replaced by injection of microspheres impregnated with chemotherapeutic agents (drug-eluting beads transarterial chemoembolization) which, compared to lipiodol, allows progressive drug delivery for a long period of time [49].

Radiation Therapy

Palliative or definitive radiation therapy is indicated in metastatic or locally advanced rectal cancer. 45 to 50 Gy may be administered in 1.8 Gy fractions for 4-5 weeks. Radiation therapy cannot be used in case of patients with antecedents of ulcerative colitis, Crohn disease or prior pelvic radiation therapy for another cancer [3]. As side effects, radiation enteritis and colitis, radiation cystitis and incontinence are frequently cited. Preferably, radiation therapy is to be performed after chemotherapy, 5-FU being proved to make tumors more radiosensitive.

Adjuvant Chemotherapy

The usual cytotoxic drugs used for chemotherapy in mCRC that can be administered single or in combination: fluoropyrimidines, oxaliplatin, and irinotecan.

Fluoropyrimidines (5-fluorouracil) (5-FU) were the first ones discovered by Heidelberger in 1957who observed that cancerous tissues utilize uracil for nucleic acids synthesis. He substituted an atom in the 5th position of the uracil molecule thus acting towards division of tumor cells. Decades later, leucovorin (LV) has been associated to 5-FU as its biomodulation increases 5-FU activity with amelioration of survival rates [50].

Microsatellite instability (MSI) diminishes the chemosensitivity to 5-FU that requires a functional MMR system. Chemotherapeutic agents like oxaliplatin and LV have been added to the 5-FU in the FOLFOX regimen in order to circumvent this mechanism of 5-FU resistance [51].

In the years 2000s, oxaliplatin, and irinotecan have been added to the arsenal used to treat mCRC with increase of survival rates from 12 months (5-FU + LV) to 20 months. Oxaliplatin is platinum derivate that inhibits DNA replication and transcription, and irinotecan is a semisynthetic analogue of the natural alkaloid camptothecin that prevents DNA from unwinding by inhibition of topoisomerase 1. Irinotecan improves the median survival period from 6.5 months to 9.2 months and the 1-year survival rate (from 14% to 34%) in patients refractory to 5-FU [9].

A succession of two sequences has been proposed by the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR): FOLFOX (oxaliplatin + 5-FU + LV) followed by FOLFIRI (irinotecan + 5-FU + LV). A special regimen using all three drugs at a time (FOLFOXIRI) has been reserved to patients with a good general status (notably a good liver function) and to patient's candidate to metastasectomy as it is highly toxic. Recently, chemotherapic drugs have been associated with monoclonal antibodies in a regimen called XELOX that involves administration of oxaliplatin and capecitabine together with monoclonal antibodies that bind to VEGF and to EGFR [4,5].

Biological Agents

In addition to first and second line chemotherapics, molecular targeted agents like antibodies towards fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), mast/stem cell growth factor receptor (KIT) and epidermal growth factor receptor (EGFR) have been developed [14].

VEGF is a diffusible glycoprotein that regulates both physiological and pathological angiogenesis. The recombinant antibody targeting VEGF, Bevacizumab (Avastin, Roche, Bale, Switzerland), is used to inhibit VEGF function and thus tumor angiogenesis, indispensable

to growth and metastasis. Randomized trials have proved that adding bevacizumab to chemotherapy regimens both in first and second-line treatment slows disease progression and increases survival rates with 4.7 months in case of first-line treatment and 2.1 months in second-line treatment. When bevacizumab was added to chemoteraphy regimens, median overall survival (OS) increased from 15.6 to 20.3 months and progression–free survival (PFS) increased from 6.2 to 10.6 months compared to chemotherapy alone [38,52]. Side effects occur rarely, are dose dependent and consist of gastrointestinal bleeding and perforation, thromboembolic events, hypertension and proteinuria.

A mutation that occurs early both in adenoma-carcinoma sequence and in colorectal cancer metastatic spread is the activation of Kras (Kirsten rat sarcoma viral oncogene homologue), a small intracellular GTPase (guanosin triphosphate cleaving enzyme) which is the main transduction pathway for EGFR. Kras mutations are present in 30-60% of colorectal cancers and confer resistance to anti-EGFR antibody therapy [40]. Cetuximab (Erbitux, Merck, Darmastadt, Germany) and panitumumab (Vectibix, Amgen, Thousand Oaks, CA) are monoclonal antibodies against EGFR and can be used use in tumors that express a specific molecular marker, namely wild-type Kras and are chemotherapy refractory.

The BOND study has proved that by adding cetuximab it is possible to overcome irinotecan resistance with an increase of PFS from 1.5 to 4.1 months and of OS from 6.9 to 8.6 months. The CRYSTAL trial performed on 1198 patients with EGFR-positive tumors that were randomly assigned to receive FOLFIRI with or without cetuximab has showed that cetuximab prolonged PFS with a median of 1.5 months and OS with 3.5 months. Studies analyzing panitumumab showed similar results [52].

Several trials argued against the association of anti-angiogenetic and anti-EGFR drugs: in the CAIRO study, the addition of cetuximab to a regimen including bevacizumab leaded to a decrease of PFS by 1.3 months, results further confirmed by the PACCE trial. The mechanisms behind the negative interaction of these drugs are not known [9].

Antibodies against FGF, PDGF, and KIT are still in research and not yet approved for general use neither in USA nor in Europe.

Prognostic Factors in mCRC

Survival rate in mCRC significantly increased from the 1950s (12 months) to the 2010s (60 months) when a combination of surgery, chemotherapy and biological agents is used [31].

Traditionally, tumor size (pT), positive surgical margins, lymph node involvement (pN), lymphovascular invasion, carcinoembrionar antigen (CEA) level, poor histological differentiation (G3 grade) and tumor budding were considered the most important prognostic factors both in CRC and in mCRC.

In the last 2 decades, many studies have analyzed the survival prognostic factors in mCRC with disparate results [31,39,53]:

1983 - Lahr indicates elevated alkaline phosphatase, serum bilirubin, the presence of bilateral hepatic metastases, the number of involved lymph nodes, depressed serum albumin and the presence of an unresectable primary tumor as negative prognostic factors for survival;

2005 – Schindl adds the Dukes Stage, the number of metastases and the serum CEA levels to the list of prognostic factors;

2009 – Luo states that increased histopathological grade and CEA level are associated with an unfavorable prognosis;

2010- Zacharakis reports that combination chemotherapy and an improved performance status lead to an increase in survival rates, and that increase C-reactive protein, influenced performance status, anemia, cachexia, anorexia, hypoalbuminemia, necessity of blood transfusions indicate unfavorable survival.

High CEA levels indicate an advanced disease and a high risk of recurrence after metastasectomy. Liver metastasectomy with a > 1 cm free margin led to a 5-year survival rate of approximately 40% that has increased to 50% when combination chemotherapy (5-FU, irinotecan, oxaliplatin, biological agents) has been added. Chemotherapy alone is associated with significantly lower survival rates at 5 years (25%) [31].

However, traditional factors are unable to predict the outcome in case of advanced CRC and therefore additional markers have to be evaluated in order to improve therapeutic management.

Histological Factors

Mucinous adenocarcinomas represent 4-19% of CRC and are commonly encountered in older patients and in the right colon. These tumors are often microsatellite-unstable and associated to a poor prognosis.

Signet ring-cell carcinomas represent almost 1% of CRC, occur most commonly on the right side, and are associated with a lymphatic invasion and poor differentiation, markers of a poor survival.

Micropapillary adenocarcinomas are very rare, have an infiltrative pattern and are associated with lymphovascular and perineural invasion. The presence of a micropapillary adenocarcinoma indicates a poor survival [54].

Tumor infiltrating inflammation corresponds to host antitumoral response, the presence of lymphocytic and macrophagic infiltrate predicting high recurrence and poor survival both in hepatocellular carcinoma and in CRC with liver metastases [55,56].

Dedifferentiation represents clusters (buds) of undifferentiated cancer cells located at the tumor invasive front and is associated with an increased recurrence rate of liver metastases in CRC [56,57]. Dedifferentiation presents a desmoplastic reaction and important neovascularization thus increasing tumor invasiveness.

Lymph and blood-vessel invasion are considered major prognostic factors in CRC and are associated to an increased risk of liver metastases [54].

Cell Proliferation Indices

Immunohistochemical methods allow detection of antibodies that bind to nuclear proteins associated with tumor proliferation and are a marker of malignity. Proliferating cell nuclear antigen (PCNA), Ki-67, Mib-1, MCM-2, Bcl-2 have been investigated in order to evaluate their role as prognostic factors and proved to indicate the development of lymph node metastases. On the other hand, no association was found between their expression and distant metastasis [58].

p53, a tumor suppressor gene, is involved in cell cycle regulation and its abnormal nuclear accumulation can be detected by immunohistochemical methods. Overexpression and abnormal nuclear accumulation of p53 are associated with an advanced T stage, lymph node metastases, and local recurrences in the liver and decreased survival rate [58].

Angiogenesis

Angiogenesis is crucial to metastasation process and VEGF is the main angiogenic stimulator. VEGF expression can be assessed by immunohistochemical methods with anti-VEGF antibodies or by mRNA analysis. VEGF expression holds an independent prognostic role and is associated to an increased metastatic spread and a poor prognosis.

Genetic Factors

Microsatellite Instability (MSI) is present in 15% of CRC and involves inactivation of the Mismatch Repair Genes. This anomaly is found in hereditary CRC and some sporadic forms. MSI predicts 5-FU resistance in mCRC [59]. Currently, routine evaluation of MSI is still a subject of debate with no general consensus.

Recent studies demonstrate that right-sided CRC follow different molecular pathways of carcinogenesis compared to left-sided CRC and are more prone to MSI, diploidy and gene mutations. Left-sided CRC mostly involve chromosomal instability and aneuploidy. Overall and progression-free survival rates are better in patients with left-sided tumors, and bevacizumab is less efficient in case of right-sided tumors [60].

The genotype of the primitive tumor also holds a significant impact on mCRC prognosis. Patients with Kras mutations (30-60%) do not respond to monoclonal antibody treatment and this pattern is maintained by CRC metastases [61]. On the other hand, the presence of a special genotype called wild type-Kras is associated with a good response to cetuximab and panitumumab therapy. Identifying such patients could lead to a reduction of hepatotoxic chemotherapics administration and avoidance of additional side effects. BRAF mutations are rare (only 10% of all CRC) and associated with diploid, microsatellite-unstable tumors that carry a poor prognosis. Almost 30% of patients with mCRC present a CpG island methylator phenotype (CIMP), exhibiting promoter methylation at multiple sites. This phenotype contributes to CRC progression and is associated to Kras/BRAF mutations. CIMP-High tumors that are MSI and BRAF mutation positive have a good prognosis compared to MSI negative tumors which are positive for CIMP and BRAF mutation and carry a poor prognosis [59].

Conclusions

CRC metastatic spread is long and complex, involving several mechanisms, molecular pathways and cellular types. Advances in medical imaging now allow an early and accurate diagnosis of metastatic lesions no matter their location. The progress of fundamental research in CRC led to understanding the molecular basis of spreading process that was further translated into biological agents like anti-VEGF and anti-EGFR antibodies. The combination of classic and recent chemotherapies and biological agents increased OS and PFS rates.

Resection of liver, lung and brain metastases is crucial for survival when achievable and is more effective when completed by an oncological treatment and rigorous follow-up.

All patients with mCRC should be discussed by a multidisciplinary team (surgeon, oncologist, radiologist, and gastroenterologist) in order to identify the most appropriate therapeutic management.

Conflict of interests

Authors have no conflict of interests to disclose.

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Review Article Open Access

Intravenous Acetaminophen: Assessment of Medication Utilization Evaluation Data in Peri-operative Pain Management

Mark A Malesker[1], Anne L Bruckner[1], Brian Loggie[2] and Daniel E Hilleman[1]*

[1]Creighton University School of Pharmacy and Health Professions Omaha, Nebraska, USA
[2]Creighton University School of Medicine Omaha, Nebraska, USA

Abstract

Intravenous (IV) acetaminophen has become an accepted component of a multimodal analgesic strategy in perioperative patients. It is currently a branded drug (Ofirmev®) in the United States. The purchase price of the drug is greater than oral and rectal acetaminophen, intravenous ketorolac, and parenteral opioids. As a result, a large number of medication utilization evaluations (MUEs) have been conducted to evaluate the appropriateness of IV acetaminophen use. Many of these MUEs have failed to demonstrate the expected benefits observed with the use of IV acetaminophen in randomized, controlled trials. This review summarizes the major methodological flaws seen in many of these MUEs. The most common flaws of the available MUEs were inclusion of inadequate numbers of patients, failure to adequately define the timing and duration of IV acetaminophen use, and failure to adequately match characteristics of patients receiving IV acetaminophen with control patients. An appropriately designed MUE for IV acetaminophen should take into consideration the identified methodological flaws described in this review. A template for a comprehensive MUE of IV acetaminophen is provided in the review. This template can be modified to meet institution specific criteria applied to the use of IV acetaminophen.

Keywords: Acetaminophen; Acute pain management; Medication utilization evaluation

Introduction

The objective of this review is to provide a brief overview of the therapeutic profile of intravenous (IV) acetaminophen, to summarize appropriate use criteria for the parenteral route of the drug, and review methodologies and results of IV acetaminophen medication utilization evaluations (MUEs) that are available in the public domain. Based on methodological problems that have been identified in many IV acetaminophen MUEs, recommendations will be provided concerning the standards of conduct of scientifically optimal MUEs for IV acetaminophen in the peri-operative setting, including a template for data collection as part of an appropriate MUE for IV acetaminophen.

Therapeutic Profile of Intravenous Acetaminophen and Appropriate Use Criteria

Acetaminophen has been used as a FDA approved oral analgesic and antipyretic since the 1950's. The IV formulation of acetaminophen was approved for use in Europe in 2002 and in the United States in November 2010 [1,2]. Acetaminophen is a centrally acting drug although its exact analgesic mechanism of action remains unknown [1]. Acetaminophen crosses the blood-brain barrier via passive diffusion [3]. Cerebrospinal fluid concentrations have been shown to be significantly greater following IV acetaminophen administration compared to the oral or rectal route. The maximum plasma concentration (Cmax) of acetaminophen is a critical factor which dictates the drug's analgesic efficacy [3]. Oral acetaminophen is often poorly absorbed in the post-operative setting [4-7]. The primary differences in absorption characteristics are a lower Cmax and a longer time to peak plasma concentration (Tmax) with oral and rectal acetaminophen compared to IV acetaminophen [3,4-7]. The reduction in the Cmax and increase in Tmax with oral acetaminophen has been shown to result from a delay in gastric emptying often ascribed to the concomitant use of opioids [7]. These pharmacokinetic changes with oral acetaminophen may also result from other physiologic alterations associated with surgery which may be related to the administration of anesthetic agents or other perioperative drugs [8]. As a result, oral or rectal acetaminophen is generally not recommended for pain relief in the first 24 hours following surgery or in settings where the bioavailability of these routes is suspected to be compromised [7]. IV acetaminophen is preferred in the perioperative setting as it achieves peak analgesic activity at approximately 1 hour following administration and has duration of action up to 6 hours [1,2,9]. The duration of IV acetaminophen therapy may exceed 24 to 48 hours in circumstances where delayed or reduced oral absorption of drugs is known to occur (i.e. small or large bowel resection). The most common dosage regimen for adults weighing more than 50 kg is 1000 mg given every 6 hours [1]. A less commonly used dosage regimen is 650 mg administered every 4 hours. Dosing and drug administration recommendations for IV acetaminophen are summarized in Table 1.

In 2011, the manufacturer of branded oral acetaminophen (Tylenol®) voluntarily reduced the maximum daily dose of the 500 mg extra strength tablet to 3000 mg per day [10]. The manufacturer also indicated it would change the recommended maximum daily dose of the 325 mg tablets to 3250 mg per day. Generic manufacturers have not changed the labeling for the maximum dose of oral acetaminophen. Since this unilateral decision by the manufacturer of branded oral acetaminophen, there has been increased confusion regarding the total maximum daily dose when IV/oral acetaminophen is used in the same patient. In the absence of risk factors for the development

***Corresponding author:** Daniel E Hilleman, Professor of Pharmacy, Creighton University School of Pharmacy and Health Professions, 2500 California Plaza, Omaha, Nebraska 68178, USA, Tel: +402-280-4288; E-mail: hilleman@creighton.edu

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Table I: FDA approved dosing of IV acetaminophen [1]

Age Group	Dosing given every 4 hours	Dosing given every 6 hours	Maximum single dose	Maximal total daily dose of acetaminophen (by any routes)
Adults and adolescents (13 yrs and older) weighing ≥ 50 kg	650 mg	1000 mg	1000 mg	4000 mg in 24 hours
Adults and adolescents (13 yrs and older) weighing < 50 kg	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)
Children ≥ 2 to 12 yrs of age	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)

of hepatotoxicity, hospital policies restricting the maximal daily dose of IV acetaminophen to 3000 mg per day solely out of concern for an increased risk of hepatic toxicity is unnecessary [10]. When IV acetaminophen is used, the maximal daily dose of acetaminophen administered via all routes remains at 4000 mg per day [1]. No oral acetaminophen containing products should be administered while patients are receiving IV acetaminophen. Depending on the dosing regimen used for IV acetaminophen, transition to oral acetaminophen or acetaminophen containing products should occur 4 to 6 hours after the last IV acetaminophen dose. Acetaminophen is contraindicated in patients with a known history of hypersensitivity to the drug, severe hepatic impairment, or severe active liver disease. IV acetaminophen should be used with caution in patients with hepatic impairment or active hepatic disease, in cases of alcoholism, chronic malnutrition, severe hypovolemia, or severe renal impairment. In cases of severe renal impairment, longer dosing intervals and a reduced total daily dose of acetaminophen may be warranted [1].

The labeled indication for IV acetaminophen is in the management of mild-to-moderate pain (as monotherapy), in the management of moderate-to-severe pain with adjunctive opioid analgesics, and for the reduction of fever [1]. A substantial number of randomized, controlled trials have demonstrated the clinical efficacy and safety of IV acetaminophen in a variety of settings [2,11]. Unless contraindicated, IV acetaminophen may be considered as a primary analgesic in a multimodal analgesic regimen with opioids reserved only for breakthrough pain or to fill analgesic gaps. IV acetaminophen should always be given via a scheduled dosing regimen and not on an as needed basis. Studies have found IV acetaminophen to be an effective part of a multimodal analgesic strategy in cesarean section, total abdominal hysterectomy, lumbar discectomy, open-heart surgery requiring sternotomy, oral surgery, mastectomy, retinal surgery, laparoscopic cholecystectomy, and orthopedic surgery [2,11]. Although many of the studies evaluating the peri-operative use of IV acetaminophen have used durations of therapy of 24 hours, the FDA approved label for IV acetaminophen does not limit the duration of its use [1].

A number of studies using IV acetaminophen as part of a multimodal analgesic strategy were able to demonstrate reductions in the amount of opioids required for pain relief and/or a delay in the use of rescue opioids [2,11]. This favorable effect was often accompanied by a reduction in the frequency and severity of opioid related adverse reactions. A recent meta-analysis found that the use of prophylactic IV acetaminophen was associated with significantly less nausea and vomiting when compared to placebo in surgical patients [12]. Preliminary data from over 23,000 patients undergoing total knee or hip replacement surgery found that the use of IV acetaminophen was associated with significantly fewer side effects, a shorter length of hospital stay, and lower hospital costs compared to matched controls not receiving IV acetaminophen [13].

IV acetaminophen is currently a branded drug (Ofirmev®) in the United States. It is substantially more costly than either oral and rectal acetaminophen or IV ketorolac. It is also more costly than parenteral opioids which are available at generic prices. As a result, there is substantial interest in pharmacoeconomic outcomes data with IV acetaminophen. No formal published studies have directly examined the pharmacoeconomic effect of intravenous acetaminophen. However, randomized controlled trials designed with primary or secondary endpoints to determine total hospital length of stay (LOS), time spent in the post-anesthesia recovery unit (PACU), time to extubation, time to ambulation, and patient satisfaction surveys, suggest that IV acetaminophen may be a cost-effective part of a multimodal peri-operative analgesic strategy [2,11]. As a result, numerous institutions have sought to address this issue by conducting MUEs for IV acetaminophen.

Intravenous Acetaminophen Medication Utilization Evaluations

A literature search was conducted to identify published MUEs evaluating the use of IV acetaminophen. The guidelines defined by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) were used to develop this systematic review [14]. In addition, the methodology recommended by Cook, et al. and Counsell were followed to identify relevant studies and to evaluate study quality [15,16]. The on-line databases of Pubmed (Medline), EBSCO Host, and the Cochrane Library were searched for the time periods from January 2000 through December 2013 for MUEs including IV acetaminophen. The Medical Subject Headings (MeSH) terms used in the search included acetaminophen, IV acetaminophen, paracetamol, propacetamol, multimodal analgesia, and peri-operative pain control. A manual search of the bibliographies from the identified publications and reviews was also performed. In addition, a search of published pharmacy and nursing conference abstracts and programs was conducted during this same time frame. Only studies available in the public domain were included in the analysis.

A total of 33 IV acetaminophen MUEs were identified in the public domain. None of the MUEs were published in a peer-reviewed journal as a manuscript. All MUEs appeared as abstracts and/or presentations at educational conferences. A variety of utilization criteria and patient populations were included in these MUEs. Although the primary objective of these MUEs was heterogeneous, many MUEs evaluated the efficacy and safety of IV acetaminophen. In the remainder of the MUEs, the primary objective was to assess the appropriateness of IV acetaminophen using institution specific criteria. The objective of some of these MUEs also included an education process to change institutional prescribing behavior and/or to correct inappropriate use of IV acetaminophen if detected.

Of the identified MUEs evaluating IV acetaminophen, 6 reported no results. In the majority of the MUEs, the types of surgery included either an unspecified mix of procedures or grouped different surgical procedures together (n=15) [17-31]. The other most common study populations reported in the MUEs included total knee and/or hip replacement surgery (n=3) and cardiothoracic surgery (n=3) [32-37]. The remaining study populations included unspecified orthopedic surgery in two MUEs and individual MUEs in patients with hip fracture, spine surgery, gynecologic surgery, and bariatric surgery [25,31,38-42]. The most commonly reported outcomes included changes in opioid use in 16 MUEs, length of stay (LOS) in 16 MUEs, pain scores in 12 MUEs, frequency of opioid related adverse reactions in 11 MUEs, and

institution specific criteria in 8 MUEs. None of the MUEs reported follow-up data indicating changes in the use of IV acetaminophen after education or institutional policy changes. The numbers of patients included in the MUEs reporting results were generally small. One study reported only the number of doses of IV acetaminophen administered at its institution, but total number of patients receiving the drug was not reported [19]. Of the remaining MUEs, 9 (35%) included ≤ 100 patients [17,20,23,28,31,33,34,38,43]. Seven (27%) MUEs included ≥ 200 patients with 5 (19%) of these MUEs including a total of ≥ 300 patients [18,24,27,30,35,36,42].

The majority of the IV acetaminophen MUEs included multiple methodological problems (Table 2). Many of the MUEs are limited by missing data which includes not reporting the numbers of patients in each treatment group, the total daily doses of IV acetaminophen used, and what drugs were used in the usual analgesic protocol. The primary purpose of an IV acetaminophen MUE should be to document that the drug is being used appropriately based on FDA approved prescribing information or protocols published in appropriately designed randomized clinical trials. In MUEs evaluating institution specific use criteria, most of those criteria were either not consistent with the FDA approved prescribing information or not consistent with methods and materials described in the randomized, controlled trial literature. Some examples of institutional restrictions for IV acetaminophen were: exclusion of its use in certain types of surgeries; use limited to ≤ 24 hours; use limited to a single dose; exclusion as a first-line analgesic; use only when other analgesics were contraindicated; limiting total daily IV acetaminophen doses to 3000 mg; and use only by prescription from an attending physician, excluding consultant physicians, fellows, or residents.

MUEs collecting data to evaluate the impact of IV acetaminophen to reduce opiate consumption, opiate related adverse effects, improvement in pain scores, or reductions in length of stay were largely underpowered to reach valid conclusions. Length of stay as a measure of quality of care is impacted by a large number of variables and cannot be easily linked to quality of care unless large numbers of patients are evaluated. LOS in the post-anesthesia care unit (PACU), which is typically the most common LOS parameter reported in surgical studies and in the MUEs, can also be impacted by several variables unrelated to quality of patient care including bed availability and staffing changes. Another methodological flaw observed in many of the MUEs included the failure to adequately evaluate and report on the specifics of the IV acetaminophen dosing regimen [17,19,23,25,27-29,31,33,35-38,40,41,43]. This information should have included the timing of the initiation and discontinuation of IV acetaminophen as well as the dose used. Several MUEs evaluated surgical patients who received only a single preoperative or intraoperative IV acetaminophen dose, yet evaluated pain scores and concomitant opioid use over 24 to 48 hours after surgery. It is inappropriate to evaluate the impact of IV acetaminophen on these outcomes at 24 to 48 hours when the duration of the drug's effect is only six hours. Evaluation of pain control with IV acetaminophen should be based only on the time period during which it is administered. In addition, timing of acetaminophen dosing was not adequately detailed in the majority of MUEs and it is not possible to determine if IV acetaminophen was initiated pre-operatively, just prior to anesthetic induction, intra-operatively, in the PACU, or after transfer to a general post-operative ward. The timing and duration of IV acetaminophen use is critical when pain scores, opiate use, and opiate-related adverse reactions are being assessed. When assessing the ability of IV acetaminophen to reduce the need for opioids, the use of IV and oral opioids other than morphine should preferably be converted to IV morphine equivalents. The conversion used to calculate the morphine equivalent dose should be included in the MUE to allow for comparisons made across different healthcare institutions.

Several MUEs failed to adequately control for differences in baseline patient characteristics, types of surgical procedures, or concomitant use of other drugs or procedures (spinal/epidural anesthesia) that may impact outcomes [17-20,22,34]. The groups of patients receiving IV acetaminophen were either substantially different from patients not receiving IV acetaminophen or data was not provided to allow for assessment of baseline characteristics between the treatment groups. Another common limitation observed in several of the MUEs is development of institutional use criteria for IV acetaminophen based on the assumption that if patients can swallow oral medication that those medications are being adequately absorbed. There is substantial evidence that in the 24 hours following many types of surgery that the bioavailability of orally administered medications is compromised [4-7]. The use of a patient's ability to swallow oral medication as an indirect indicator of adequate drug absorption may be an erroneous assumption [4-7]. It appears that concomitant administration of opioids is the most common cause of pharmacokinetic changes with enteral administration of acetaminophen. Petring, et al. found that acetaminophen was poorly absorbed in orthopedic surgery patients following the use of IM morphine with spinal anesthesia compared to patients receiving IM ketorolac with spinal anesthesia [5]. Administration of morphine has also been shown to decrease the absorption of other drugs such as clopidogrel with resultant reductions in antiplatelet activity [44]. Other methodological flaws include the failure to consider pre-operative opiate use as a baseline characteristic. Patients with a tolerance to opiates may inherently require more opiate for pain relief than an opiate-naïve patient. Other medications such psychotropic agents, anti-emetics, and sedative-hypnotics also need to be considered when comparing groups of post-operative patients. The use of post-operative anti-emetic agents or other drugs used to manage opiate-related adverse reactions should not be used as a surrogate for the frequency of opiate-related nausea and vomiting. This would be especially true if the anti-emetics are given on a scheduled basis for prevention of nausea and vomiting rather than on an as needed basis.

Conclusion

This review summarizes appropriate use criteria for IV acetaminophen and describes the methodological flaws seen in many of the IV acetaminophen MUEs conducted to date. Methodological errors noted in these IV acetaminophen MUEs limit the validity of their conclusions. A total of 27 MUEs with results have been presented as posters or abstracts and have been reviewed here. No MUE has been published in a peer-reviewed journal. The most common flaws of the available MUEs were inclusion of inadequate numbers of patients, failure to adequately define the timing and duration of IV acetaminophen, and failure to adequately match characteristics of patients receiving IV acetaminophen with control patients. An appropriately designed MUE for IV acetaminophen should take into consideration the identified methodological flaws described in this review. The MUE is a tool that can allow healthcare institutions to evaluate the appropriateness of medication use [45]. Supplementary file serves as a template for a comprehensive MUE of IV acetaminophen. This template can be modified to meet institution specific criteria applied to the use of IV acetaminophen. Institutional use criteria for IV acetaminophen should be based on approved prescribing information or on methods that have been validated in published, randomized controlled trials.

IV acetaminophen is an effective analgesic that when used as a component of a multimodal analgesic strategy can reduce opiate consumption, reduce opiate related adverse effects, and potentially shorten recovery times. Currently available guidelines recommend a multimodal approach for the management of pain in the peri-operative period [46-48]. These guidelines indicate that all patients, unless contraindicated, receive an around-the-clock regimen of a non-steroidal anti-inflammatory drug (NSAID), a COX-2 selective NSAID,

Table II: Common Methodological Errors Observed in IV Acetaminophen Medication Utilization Reviews

1. Failure to specify the timing and number of IV acetaminophen doses. Failure to identify specifics regarding timing of doses makes it impossible to accurately assess the impact of IV acetaminophen on pain scores, opioid consumption, and other important clinical outcomes. Many MUEs determine total opioid consumption and total hospital length of stay in settings where a single preoperative or intraoperative dose of IV acetaminophen is administered.
2. Failure to balance the characteristics of surgeries between patients receiving IV acetaminophen compared to other analgesic regimens. The type, duration, and intensity of surgical procedures should be similar in the different treatment groups. Combining patients undergoing a variety of surgeries into a single group also makes it more difficult to reach valid conclusions about the utility of a specific analgesic regimen, which may be different based on the type of procedure.
3. Failure to balance patient characteristics such as opioid-tolerance, gender, age, weight, and the concomitant use of preoperative and postoperative medications used to treat or prevent nausea, itching, constipation, or other surgery or drug-related adverse events.
4. Use of total hospital length of stay or post-anesthesia care unit length of stay as an efficacy measure of analgesia with IV acetaminophen without evaluating the time of readiness for discharge or transfer. Lengths of stay in any setting in the hospital may be influenced by a large number of variables, many of which may be not related to quality of patient care.
5. Evaluating the change in opioid use based on the number of doses of opioid administered rather than evaluating the total amount of opioid administered in patients receiving IV acetaminophen. Total opioid consumption in mg is probably more relevant than the actual number of doses. Failure to capture the use of bolus opioids given on an as needed basis and the use of patient controlled opioid analgesia may lead to differences in analgesic utility of different treatment regimens. Failure to document opioids administered during surgery may also lead to incorrect assessments of clinical outcomes. Failure to define conversion from different opioids to a morphine equivalent dose can lead to confusion about relevance of outcomes. Different types of opioid conversion formulas are available. MUEs should provide the opioid conversion used.
6. The exclusive reliance on the use of electronic health records (ICD-9 codes) to determine rates of opioid-related adverse events or to determine analgesic response (pain scores) should be reviewed; opioid-related adverse events and pain scores may not be properly coded.
7. Reliance exclusively on the use of electronic health records using billing records for naloxone, antipyretics, laxatives, or anti-emetics as a surrogate marker of adverse reactions may not be an accurate measure of such reactions.
8. Reliance on increases in serum transaminase levels as a marker of hepatotoxicity secondary to IV acetaminophen may not accurately represent actual drug-induced hepatotoxicity. A number of factors such surgical trauma, antibiotic use, and inhalational anesthetics may be associated with changes in serum transaminase levels.
9. Failure to document the use of other non-opioid multimodal interventions including oral celecoxib, pregabalin, or regional anesthesia.
10. Institution-specific appropriate use criteria may be considered in an MUE with IV acetaminophen, but should not be inconsistent with either the FDA approved prescribing information or must at least be consistent with data collection methods from published and properly designed clinical trials. As just one example, administering IV acetaminophen at a dose of 1000 mg every 8 hours to limit the total daily acetaminophen dose to 3000 mg is not consistent with either the prescribing information or the published literature. The duration of action of IV acetaminophen is no longer than 6 hours. Giving the drug at longer intervals would inherently limit the drug's clinical efficacy. In addition, there is no published data to show that using IV acetaminophen at a daily dose of 4,000 mg increases the risk of adverse effects vs placebo.

or acetaminophen. Gabapentin or carbamazepine may also be considered part of a multimodal management strategy in patients with neuropathic pain. Regional spinal or epidural administration of local anesthetics or opioids may also be considered as part of a multimodal pain management strategy. Opioid use would be individualized based on the type of surgical procedure and the severity of pain [46]. In some instances where only mild-to-moderate pain occurs, the use of IV acetaminophen may obviate the need to administer any opioid [1,49]. For more invasive procedures with a greater severity of pain, IV acetaminophen in combination with other non-opioid analgesics often reduces the amount of opioid needed to achieve adequate pain control [11,50,51]. This reduction in opioid dose has been demonstrated to reduce the frequency and severity of adverse effects of opioids [51,52]. Since IV acetaminophen is a branded analgesic (Ofirmev®) with cost of $14-$15 per 1000 mg dose, it has become a focus of many MUEs intended to allow healthcare institutions to evaluate the appropriateness of its use [53]. We propose the use of a template to identify appropriate data elements as a basis for conducting future MUEs with IV acetaminophen. Improvements in standardizing future MUEs will ensure the optimal use of this non-opioid intravenous analgesic.

Conflict of interests

Dr. Hilleman is on the speaker's bureau for Bristol Myers-Squibb, Cadence, and Pfizer.

Drs. Malesker, Bruckner, and Loggie report no conflict of interests.

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Research Article Open Access

Current Concepts of Bone Regeneration in Implant Dentistry

Reena Rodriguez*, Nico Hartmann and Dieter Weingart

Department of Oral and Maxillofacial Surgery, Katharinen Hospital, Klinikum Stuttgart, Germany

Abstract

The use of dental implants for the rehabilitation of missing teeth has broadened the treatment options for patients and clinicians equally. As a result of advances in research in implant design, materials and techniques the use of dental implants has increased dramatically in the past two decades and is expected to expand further in the future. However the clinical complexity of the patient who present with limited bone volume often requires additional biomaterials and surgical procedures to ensure successful implant treatment. This review outlines the various biomaterials used in augmenting bone deficiencies encountered and the different surgical techniques that are used in order to achieve a predictable long term success of dental implants.

Keywords: Dental implants; Bone regeneration; Current concepts

Introduction

Success of dental implants depends largely on the quality and quantity of available bone in the recipient site [1]. This however may be compromised or unavailable due to tumor, trauma or periodontal disease etc., which in turn necessitates the need for additional bone augmentation. Successful regeneration requires the essential components of cells, scaffold and signaling molecules. This is effectively achieved with the use of autologous bone and is thus considered the gold standard of bone regeneration against which all other types of bone regenerative materials are compared. However autologous bone grafting is associated with morbidity of the recipient site. With the tremendous advances in the field of regenerative biomaterials, a wide range of biomaterials have been tested as an alternative to autologous bone. This review outlines the present scenario in bone regenerative therapy in implant dentistry, the various biomaterials, surgical techniques employed to circumvent different clinical situations and the future directions in the field of bone regeneration.

Autogenous bone grafts

One of the most difficult challenges in implant dentistry is the treatment of large bone defects or deficiencies. Autologous bone offers a wide pool of growth factors that can induce mesenchymal stem cells to differentiate into osteogenic progenitor cells [2]. They also help in the osteoconduction by acting as a scaffold on which further apposition may occur [3]. Furthermore, there is no risk of immune rejection and the long term studies indicate excellent long term results. The preferred site for intraoral bone harvesting is the retromolar, angle of the mandible and chin. Extra orally the iliac crest and tibia are employed for bone harvesting. The quantity of autologous bone however may often be limited to avoid extensive morbidity of the donor site. Several techniques have been developed in order to circumvent this problem [4-6]. They maybe by the use of a modified surgical technique, volume expansion of the autologous graft or by the addition of a non allogenic graft material .The ultimate decision for the choice of the graft material is dictated by the complexity of the deficiency and the approval of the treatment option by the patient.

Allograft

An allograft is a tissue graft between individuals of the same specimen but of non-identical genetic composition. The source is usually cadaver bone, which is subjected to a treatment sequence which renders it neutral to immune reactions and helps to avoid cross contamination of host diseases. Human bone material in the form of freeze dried bone or demineralised freeze dried bone (DFDB) has been used in periodontology and implant dentistry. The disadvantages are an increased risk of immunogenicity, a rather quicker resorption rate compared to autogenous bone and a risk of disease transmission [6].

Xenografts

Xenografts are tissue grafts between two different species. Deproteinized bovine bone matrix (DBBM) is a well-documented bone substitute for intraoral bone grafting [7]. Other materials in use are of coral source and porcine sources.

Alloplast

Graft material which is synthetically derived and do not originate from humans or animals. Calcium phosphate materials have attracted particular interest due to the similiarity in the mineral composition of natural bone. Materials such as hydroxyapatite and alpha tricalcium phosphate, beta tricalcium phosphate have widely been used as fillers on their own or combined with autogenous bone [8]. They provide an osteoconductive scaffold for the osteogenic cells but are not by themselves osteoinductive. The use of alloplastic grafting materials on their own is not routinely recommended. However, their use with bone promoting agents has been widely studies in the recent years with predictable outcome.

Growth factors

Various growth factors have widely been tested in animal models. Of these, Bone Morphogenic Proteins (BMPs) requires special mention as they induce osteogenic precursor cells into osteogenic cells and have shown tremendous bone growth in many animal and

***Corresponding author:** Reena Rodriguez, Department of Oral and Maxillofacial Surgery, Katharinen Hospital, Klinikum Stuttgart, Kriegsbergstrasse 60, D 70174 Stuttgart, Germany, Tel: 0711-2783301; Fax: 0711-2783309; E-mail: drreenajoseph@gmail.com

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also human clinical studies. Extensive research is being undertaken to develop injectable formulations for minimally invasive application with novel carriers for prolonged and targeted local delivery [9]. Other growth factors besides BMPs that have been implicated during bone regeneration are also being investigate [10], including platelet-derived growth factor, transforming growth factor-β, insulin-like growth factor-1, vascular endothelial growth factor and fibroblast growth factor, among others [11].

Guided bone regeneration

Guided bone regeneration (GBR) also known as "membrane protected bone regeneration" refers to the use of barrier membranes in the treatment of alveolar ridge defects. It helps to separate the hard tissue compartment (bone, bone marrow and bone defect) from the soft tissue compartment thereby enabling bone regeneration by space creation [12]. It also effectively stabilizes the blood coagulum and thereby allows for faster healing to occur. This technique can be used before or at the same time as implant placement. Barrier membranes may be non-resorbable (eg: expanded poly tetrafluoroethelene e-PTFE) or resorbable. Although non-resorbable have shown the most bone volume gain, they are associated with a higher incidence of complications such as membrane exposure due to soft tissue dehiscence [13]. The different techniques for bone augmentation are as below:

Graft and membrane

Depending on the amount of localized deficiency, implants may be placed at the same stage as augmentation (1 step surgery) or following bone regeneration (2 step surgery).

When the localized deficiency is a dehiscence or fenestration type, particulate autograft or bone substitute covered with a membrane is indicated. Horizontal and vertical ridge augmentation procedures often require the use of autologous bone block graft combined with a membrane or a particulate autograft with a bone substitute and a membrane. A healing period of 3 to 6 months before the second stage surgery is undertaken is recommended as delays greater than 6 months may result in resorption of the graft.

Onlay grafts

Onlay grafts have been used with great success and predictability in the augmentation of severely resorbed edentulous ridges for the treatment with dental implants [6]. Both intra oral (mental symphysis, body of the mandible and ramus, maxillary tuberosity) and extra oral (iliac crest, calvarium,tibia)donor sites may be used depending on the amount of bone that is required for reconstruction. Modelling of the bone graft and fixation of the grafts is done by miniscrews or miniplates and the use of particulated autograft and other forms of bone substitutes maybe used in combination with a bioresorbable membrane (Figure1). A tension free closure of the overlying flap is also critical for the success of the augmentation.

Maxillary sinus lift using lateral approach

The loss of posterior maxillary teeth causes resorption of the alveolar process in the oral side, by expansion of the sinus cavity into the alveolar process, or both these methods. This results in a lack of sufficient quality and quantity of bone for implant placement. Bone deficiencies in the posterior maxillary regions are one of the most challenging situations in implant dentistry. This can be circumvented with bone augmentation following a sinus floor elevation which involves elevating the schneiderian membrane from the maxillary sinus floor (Figure 2). This technique is often used as a pre-implant procedure when the residual alveolar ridge has is inadequate to a point where initial implant stability is compromised. Implant placement can be done after 3-6 months. Maxillary sinus grafting may also be combined with nasal inlay grafting if the bone volume in the sub nasal area for placement of implants also needs to be increased.

Maxillary sinus elevation by using the transalveolar approach

This method is less invasive and involves moving the sinus floor by gently fracturing it with the use of osteotomes [14]. Maxillary sinus elevation using the transalveolar approach can be recommended in sites with adequate alveolar crest width, initial bone height of at least 5 mm and a relative flat sinus floor anatomy.

Split–Ridge /Ridge –expansion technique

Split ridge/ridge expansion technique refers to the creation of a linear groove in the middle of the ridge with rotary burs or a piezosurgery device and deepening this groove with an osteotome chisel. The lingual or palatal cortical bone is used as a guide and careful tapping with a mallet will advance the chisel into the cancellous part of the bone [15,16].

This technique is indicated in cases of the atrophy of the edentulous ridge has developed horizontally and the cancellous bone is present between the oral and facial cortical plates and the presence of adequate residual height exists. A split ridge with conventional implant placement or a split ridge with interspersed bone graft material may be used.

Vertical distraction osteogenesis

It is the creation of new bone and adjacent soft tissue after gradual and controlled displacement of a bone fragment obtained by surgical osteotomy. This technique is used to increase the height of the alveolar ridge. It is indicated in cases with vertical deficient ridges (minimum 3 mm height) with adequate residual width [6]

Le-fort I Osteotomy with interpositional autologous bone grafts

This is a technique indicated in cases of extremely severe alveolar ridge resorption and there is an unfavourable intermaxillary relationship in the horizontal and vertical plane [6].

Discussion and Conclusion

The recent advancements in nanotechnology and biomaterial engineering have led to several advancements in the field of implantology and regenerative medicine. An improved implant design, surface and material modification at a nanoscale have greatly contributed in the success and predictability of dental implant treatment [17]. Various bone regenerative materials in the form of gels, particle and scaffolds have also been designed with the help of

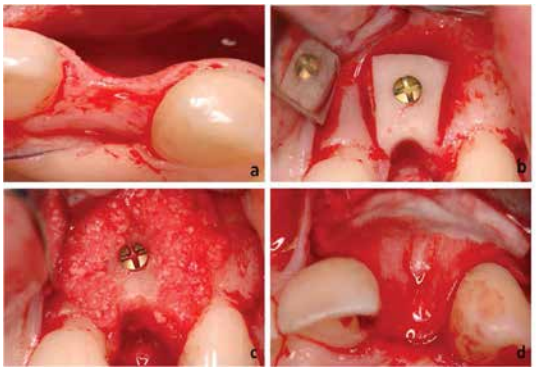

Figure 1:
a.Extensive alveolar ridge atrophy in left lateral incisor region.
b.Bone block augmentation with transplant from angle of the mandible.
c.Bone augmentation using autologous bone particles .
d.Guided bone regeneration with Biogide membrane.

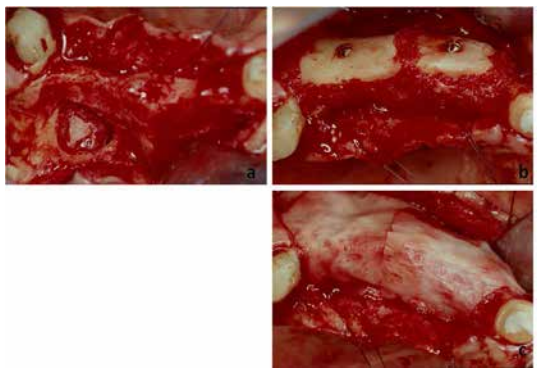

Figure 2:
a. Osteoplastic flap elevation to access the maxillary sinus for an external sinus lift in region 24-26.
b. Horizontal mandibular augmentation with autologous bone block transplant from the angle of the mandible and fixation with titanium screws.
c. Adaptation of Biogide membrane.

nanotechnology and engineering and have opened up a new horizon for bone regeneration [18].

Many studies have shown that nanometer-controlled surfaces can influence early events such as the adsorption of proteins, blood clot formation, and cellular migration and differentiation of mesenchymal stem cells [19-21]. Novel drug delivery systems are being studied for the local delivery of compounds that can enhance osseointegration and bone regeneration [22]. However, several factors such as resorption rate and drug release kinetics are important considerations. An optimum release of the drug is important as the development of tissues is orchestrated by the coordinated interactions of multiple growth factors along spatial and temporal gradients.

In tissue engineering, mesenchymal stem cells (MSCs) are isolated from the patient, expanded and seeded onto a synthetic scaffold and allowed to produce extracellular matrix on the scaffold in controlled culture conditions. This is finally implanted into the bone defect in the patient. The clinical significance of tissue engineering lies in our ability to predictably direct cells to differentiate into the right phenotypes in a spatially and temporally defined pattern.

However, the cost, technical difficulties, failure of the tissue engineered bone to vascularize are still impediments for the routine use of tissue engineered bone in the clinical situation.

The clinical outcome of any regenerative procedure is a combination of the influences from systemic factors, the osteogenic, osteoinductive and osteoconductive properties of the biomaterial, as well as the regenerative potential of the surrounding tissue. The clinician should therefore be mindful to choose the biomaterial based on the 1.diagnosis of the overall health condition of the patient, 2.complexity of the clinical situation at hand and also 3.the long term clinical results of the biomaterial and use the treatment protocol that are simple ,involves the least risk with minimal intervention.

Conflict of interests

Authors have no conflict of interests to disclose.

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Research Article Open Access

Does the Type of Initial Biopsy Method Determine Re-Excision Rate of Cutaneous Melanoma?

Ramya Vangipuram[1], Mary Ramirez[1], Yasir Al Abboodi[2] and Subhasis Misra[1]*

[1]*Department of Surgery, Texas Tech University Health Sciences Center School of Medicine, Texas, USA*
[2]*Department of Internal Medicine, Texas Tech University Health Sciences Center School of Medicine, Texas, USA*

Abstract

Background: Various biopsy types are used to diagnose melanoma, after which wide local excision (WLE) is the gold standard for treatment. Depending on the final pathology report, further re-excision may be necessary despite an initial, presumably adequate, WLE. In this study, we analyzed the impact of initial biopsy type (shave, punch, or excision) on the management of melanoma.

Methods: A retrospective chart review of 243 patients with clinically node-negative melanoma was completed. Evaluated variables included the initial biopsy type, initial and final peripheral and deep margin status, further re-excision rates, tumor site, and clinician specialty performing the biopsy. Univariate and multivariate analyses tests were performed using SPSS software.

Results: 29.5% of specimens with both positive peripheral and deep margins underwent further excisions. Overall, 14.6% of cases had re-excision regardless of initial biopsy type after initial WLE. There was higher rate of re-excision with an initial excision biopsy (28.6%) than with initial punch (13.3%) or shave biopsies (11.2%) Dermatologists, Surgeons, and Primary Care Physicians performed 13%, 34%, and 32% of the excision biopsies respectively. Neither the anatomic location of the tumor nor the survival rates were significantly correlated to the biopsy type, margin status, or re-excision rates.

Conclusion: Both shave and punch biopsies showed high rates of residual tumor in either peripheral or deep margins but this does not translate into a higher re-excision rate. Although the biopsy type is important, the clinical specialty performing the biopsy could be influential. Surprisingly, there was a higher positive peripheral margin than deep margin with shave biopsy.

Keywords: Melanoma; Wide local excision; Shave biopsy; Punch biopsy; Re-excision rate

Introduction

Melanoma is one of the few cancers whose incidence and mortality has been increasing in the U.S. [1-3]. Approximately 77, 000 new cases of melanoma were diagnosed in the United States in 2013 [3]. In the same year, 9,480 deaths were attributed to melanoma [3]. The lifetime risk for the development of melanoma is now 1 in 35 for males and 1 in 54 for females [4]. Suspicious pigmented lesions must be biopsied in order to diagnose melanoma. Although excisional biopsy is the recommended diagnostic procedure for melanoma, clinicians commonly use other methods such as a shave or punch biopsy [2,4-7]. Moreover, the proportion of cutaneous melanomas diagnosed by non-excisional biopsy techniques is increasing [4]. Wide local excision (WLE) is the gold standard for treatment after an initial diagnosis [2,4-7]. Thus, a proper initial biopsy is necessary for accurate preoperative tumor staging, which in turn is critical for determining appropriate treatment options for patients with confirmed cancer. These include selection of appropriate resection margins, the need for sentinel lymph node biopsy, and consideration of adjuvant therapy [4]. However, despite presumably sufficient margins after a WLE, re-excision of the tumor site is ultimately dependent on the findings described in the final pathology report. The current management of melanoma begins with performing an initial biopsy for suspicious lesions. For biopsies with confirmed melanoma, the depth of tumor invasion determines the appropriate surgical margins in the consequent WLE. If this excision shows inadequate margin resection, then another re-excision is performed to assure that all margins are free of tumor. In this study, we analyzed the effect of initial biopsy method (shave, punch, or excision) on the management of melanoma, with a particular focus on re-excision rates.

Methods

After IRB review and approval, 337 patients were initially identified through the Cancer Registry and selected for inclusion. Then, a retrospective chart review of each patient who presented with clinically node-negative melanoma (stages cTI-4N0) from 2008 to 2013 was completed. Patients excluded from the study included those who were lost to follow-up and those without complete pathology reports. Ultimately, 243 eligible patients were included. Evaluated variables included age at time of diagnosis, sex, race, Breslow's depth, presence of ulceration, mitoses on initial or consequent biopsies, Clark's level, location of tumor on the body, initial biopsy type, initial and final peripheral and deep margin status, further re-excision rates, and clinician specialty performing the biopsy. Univariate and multivariate analyses tests were performed using SPSS software.

***Corresponding author:** Subhasis Misra, Department of Surgery, Texas Tech University Health Sciences Center School of Medicine, 1400 Coulter Street, Amarillo, Texas 79106, USA, Tel: + 806 414 9558; Fax: + 806 351 3787; E-mail: subshasis.misra@ttuhsc.edu

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Results

Overall, 36 (14.6%) patients underwent re-excision after WLE, irrespective of initial biopsy type. 72 (29.5%) biopsies with both positive peripheral and deep margins underwent further excisions. 181 (74.5%) cases were diagnosed by shave biopsy, 59.7% of which had positive peripheral margin, 34.8% had positive deep margin, and 19% had both positive margins. 16 (6.6%) cases were diagnosed with punch biopsy, 68.8 % of which had a positive peripheral margin, 31.3% had positive deep margin, and 25% had both positive margins. 46 (18.9%) cases were diagnosed with excision biopsy, 39.1% of which had a positive peripheral margin, 21.7% had positive deep margin, and 13% had both positive margins. There was a significantly higher rate of re-excision with initial excision biopsy (28.6%) than with initial punch (13.3%) or initial shave biopsies 11.2% (P=0.01). Dermatologists, Surgeons, and Primary Care Physicians did 13%, 34% and 32% of the excision biopsies respectively. Melanoma location and survival rates were not significantly correlated to the biopsy type, margin status, or re-excision rates (Tables 1-3).

Discussion

Because surgical excision is the primary treatment of biopsy-proven melanoma at any site, the initial biopsy is critical in determining the appropriate surgical strategy, including the calculation of optimal surgical resection margins, and the necessity of a sentinel lymph node biopsy. These decisions are largely based on the thickness, ulceration status, and mitotic rate of the primary melanoma [3,6-10]. Re-excision is performed when residual tumor is identified in either peripheral or deep margins. In our study, 29.5% of cases with both positive peripheral and deep margins underwent further excisions. Overall, 14.6% cases had re-excision regardless of initial biopsy type after initial WLE.

The majority of cases (74.5%) in our study were diagnosed by shave biopsy. We found that 59.7% of all shave biopsies had a positive peripheral margin, 34.8% had a positive deep margin and 19% of had both positive peripheral and deep margins. It is surprising that shave biopsies had a higher rate of positive peripheral margins than the rate of positive deep margins. This could be attributed to two plausible theories: the field defect phenomenon and saucerization of the specimen. The field defect phenomenon accounts for microscopic lateral invasion that would not be visible to the clinician performing the biopsy. Typically, melanocytes initially undergo transformation into atypical melanocytes and then further convert into cancerous cells. These changes would not be visible to the unaided eye, and thus could explain the higher positive peripheral margin rate. In addition, the use of a deep scoop shave to obtain tissue leads to saucerization of the biopsy specimen, and renders the shave biopsy with a thicker depth than would be expected with the use of traditional blades for shave biopsies.

Dermatologists, Surgeons, and Primary Care Physicians did 13%, 34% and 32% of the excision biopsies respectively. In our study, dermatologists preferred shave biopsies for suspected melanomas, whereas surgeons and primary care practitioners preferred excision biopsies. Given our finding that initial excision biopsies were associated with the highest rate of re-excision, it is worth investigating if the clinician's field of practice influences the re-excision rate, and ultimately the outcome of complete removal of the tumor.

Some literature suggests that shave biopsies are not recommended when melanoma is suspected because these biopsies may limit the amount of specimen available for adequate pathologic assessment and microstaging, especially in regard to tumor thickness [4-6,11]. However, our data proposes that shave and punch biopsies may be a sufficient means of initial diagnosis because these methods are not associated with a higher rate of re-excision. Even though both of these types of biopsies had positive peripheral and deep margins, the resulting WLE performed was adequate enough to remove the melanoma completely. In addition, shave and punch biopsies are simpler and less expensive to perform, and cosmesis becomes less of a concern.

46 (18.9%) cases were diagnosed with excision biopsy, 39.1% of which had a positive peripheral margin, 21.7% had a positive deep margin, and 13% had both positive margins. The high positive rate of peripheral margin may be attributed to the use of excision biopsy when the suspicion for melanoma is high, compared to the preference for a shave or punch biopsy when the suspicion for melanoma is low. By the time the patient had presented with a cutaneous lesion that looked suspicious enough to warrant an initial excisional biopsy, the tumor may have already exhibited microscopic lateral spreading, which is not identifiable without a histopathological examination.

16 (6.6%) cases were diagnosed with punch biopsy, 68.8 % of which had a positive peripheral margin, 31.3% had positive deep margin, and 25% had both positive margins. Although punch biopsies may sample enough tissue depth, they do not provide enough information to assess the lateral growth of melanocytic tumors, which is also essential for proper diagnosis [12]. Our findings support the statement that punch biopsies are seldom used in the diagnosis of a suspected melanocytic tumor.

Newer literature suggests that simpler types of initial biopsies may be sufficient for diagnosing and staging melanoma and providing sufficient information for consecutive management plans [10,11,13-15]. A study by Hieken et al, with a similar design to that of ours, found that only 2% of its patients were diagnosed by excisional biopsy, and only 23% of patients diagnosed by biopsies with positive deep and lateral margins needed additional cancer treatment after final pathology

Table I: Patient Characteristics.

Characteristics	Patients	(n=243)
Gender		
Male	148	60.90%
Female	95	39.15%
Race		
White	238	98.00%
Non-White	2	0.01%
Unknown	3	0.01%
Age (years)		
10-19	2	0.01%
20-29	6	0.02%
30-39	13	0.54%
40-49	39	16%
50-59	57	23.50%
69-69	52	21.40%
70-79	50	20.10%
80-89	12	4.90%
90-99	1	0.00%
Median Age	60	
Stage		
0	55	22.60%
IA	81	33.30%
IB	39	16.00%
I NOS	15	6.17%
IIA	9	3.70%
IIB	9	3.70%
IIC	1	0.00%
IIIA	3	1.23%
IIIC	6	2.05%
III NOS	5	2.05%
IV	11	4.52%
Unknown	8	3.29%

Table II: Biopsy Characteristics.

Characteristics	Patients	(n=243)
Breslow's Depth (mm)		
0 < x < 1	129	53.09%
1 < x < 2	34	13.99%
2 < x < 4	16	6.58%
> 4	11	4.12%
Unknown	53	21.81%
Clark's Level		
I	52	21.40%
II	62	25.51%
III	31	12.76%
IV	46	18.93%
V	5	2.05%
Unknown	47	19.34%
Site of Tumor		
Head and Neck	84	34.57%
Trunk	51	20.10%
Upper Extremity	72	29.63%
Lower Extremity	36	14.81%
Ulceration Present		
Initial Biopsy	78	11.52%
Final Biopsy	24	24%
Mitoses Present		
Initial Biopsy	78	32.10%
Final Biopsy	24	9.88%

Table III: Survival Rates.

Variable	p -Value
Location	0.991
Margin Status	
Positive Peripheral	0.00
Positive Deep	0.826
Re-excision	0.083

at WLE [4]. Moreover, the study discovered that most diagnostic biopsies were margin positive regardless of biopsy technique, and that more than one third of patients had residual melanoma on WLE [4]. These literature findings, along with ours, propose that less invasive techniques such as shave and punch biopsies are an adequate means of accurately diagnosing suspected melanocytic tumors.

Conclusion

Both shave and punch biopsies showed high rates of residual tumor in either peripheral or deep margins; however, this is not correlated with a higher re-excision rate. Although the biopsy type is important, clinical specialty performing the biopsy could be influential. Surprisingly, there was a higher positive peripheral margin than deep margin with shave biopsy, which could be due to the field defect phenomena in melanoma.

These data suggest that shave or punch biopsies are preferable to excision biopsies for an initial biopsy when a primary cutaneous melanoma is initially suspected. Although they may be associated with a higher likelihood of residual tumor, they were not correlated with an increased risk of re-excision. Also, initial WLE removes a wider area of skin, which can lead to increased healing time, increased cost, and is less cosmetically appealing. The limitations of our study include the biases innate to retrospective chart reviews, including the need to exclude some patients because of incomplete data for analysis. Our study is unique in that it suggests that a simpler, less invasive, and less expensive method of biopsy can provide the same level of information, as does an excisional biopsy, while decreasing the rate of re-excision.

Conflict of interests

Authors have no conflict of interests to disclose.

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Research Article Open Access

Assessment of Tumor Parameters as Factors of Aggressiveness in Colon Cancer

Ana-Maria Todosi[1]*, Ionut Huțanu[1], Mihaela Mădălina Gavrilescu[1], Mihaela Moscalu[2], Dan Ferariu[3] and Viorel Scripcariu[1]

[1]*Department of Surgery, First Surgical Unit "St. Spiridon" Hospital Iasi, University of Medicine and Pharmacology "Gr.T. Popa" Iasi, Romania*
[2]*Department of Gastroenterology, University of Medicine and Pharmacology "Gr.T. Popa" Iasi, Romania*
[3]*First Surgical Unit "St. Spiridon" Hospital Iasi, Romania*

Abstract

Background: Colorectal cancer is a major public health problem worldwide. Tumor volume associated with the number of positive lymph nodes may be a new predictor of 5-year survival in colon cancer.

Material and Methods: We conducted a retrospective study of a prospective database that included all patients diagnosed with colon cancer (CC) between May 2012 and September 2013 in the Surgical Oncology Clinic of the Iasi Regional Cancer Institute. The patients underwent surgical resection and two tumor sizes were recorded. Tumor characteristics and their potential role in tumor aggressiveness were analyzed.

Results: The study group included 138 patients, of which 38 (27.54%) with metastases and 100 (72.46%) without metastases. Maximum tumor diameter showed significant differences depending on the degree of differentiation and histological type, and was significantly correlated with the total number of evaluated and positive lymph nodes (p=0.009 and p=0.00, respectively). Tumor volume was influenced by male gender (p=0.0404), tumor stage (p=0.0192), and type of tumor invasion (p=0.0159) in 23.02 % of cases (p=0.02809). Maximum tumor diameter and tumor volume had poor discriminatory power in predicting survival.

Conclusions: A statistically significant association was found between the metastatic group and advanced disease stages. Maximum tumor diameter and tumor volume could not predict overall survival of patients.

Keywords: Colon cancer; Tumor volume; Maximum tumor diameter; Predictive factors

Introduction

Colorectal cancer (CRC) is a major public health problem worldwide, representing a leading cause of mortality and morbidity. It is the third most common cancer and the fourth leading cause of death worldwide [1]. Surgery is the only treatment with radical intent. Tumor staging (UICC-TNM) is a preocondition for multimodal treatment [2]. Adjuvant chemotherapy is necessary for metastatic cancers (lymph nodes, parenchymal organs, stages III, IV), however approximately 30% of localized cancers (stage II) will recur [2,3]. Currently, TNM staging [4] is the best prognostic factor for CRC, with a mean 5-year survival of 93%, 78%, 60% and 8% for stages I, II, III and IV, respectively. For adequately staging a colon cancer AJCC (American Joint Committee on Cancer) recommended a minimum of 12 lymph nodes to be harvested [5]. Tumor volume associated with the number of positive nodes may be a new predictor of 5-year survival in colon cancer [6].

Material and Methods

The aim of this study was to analyze the tumor characteristics and their potential role in assessing tumor aggressiveness. Another aim was to determine whether increased tumor parameters may influence tumor stage and therefore the presence of lymph node and distant metastases.

Patient Selection

We conducted a retrospective study of prospective database that included all patients diagnosed with colon cancer (CC) between May 2012 and September 2013 in the Surgical Oncology Clinic of the Iasi Regional Cancer Institute. The patients underwent surgical resection and at least two tumor sizes were reported.

The histological type, total lymph nodes evaluated, number of positive lymph nodes, tumor stage according to the TNM staging, T and N stage, and presence of vascular, lymphatic and perineural invasion were analyzed. Maximum tumor diameter was considered as the largest tumor diameter reported by the pathologist. Tumor volume was calculated by multiplying the two largest dimensions reported for each tumor. Tumor volume was related to the percentage of positive nodes (tumor node ratio). The percentage of positive nodes was calculated by dividing the number of positive nodes identified to the total number of nodes in the surgical specimen, multiplied by 100. Depending on the presence or absence of distant metastases, we identified two groups of patients who were subjected to comparative statistical analysis. Patients with metastases were operated on either to improve the quality of life (clinically manifest tumor) or to approach the metastases at a later time. Data were obtained from analysis of clinical observation sheets, medical records and pathology reports. Date of death was obtained from the database of the National Health Insurance Company.

Preoperative Evaluation

All patients received preoperative staging that included medical history, physical examination, chest radiography, abdominal-pelvic ultrasound, computed tomography (CT), colonoscopy with biopsy,

***Corresponding author:** Ana-Maria Todosi MD, General Henry Mathias Berthlot Street, 2-4, Regional Cancer Institute Iasi, 1st Clinic of Oncologic Surgery, 700483, Iași, Romania, Tel: +40 (0) 741 66 76 83; E-mail: todosi_anamaria@yahoo.com

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carcinoembryonic antigen (CEA) and in some patients CA19.9. Complete blood count and EKG were done in all patients. All patients were operated by surgeons experienced in colorectal surgery. The diagnosis was confirmed by histological assessment of both the diagnostic biopsies and surgical resection specimens. Tumor staging was done according to the latest AJCC/UICC TNM classification [4]. No patients received neo-adjuvant therapy. The objective of radical surgery was tumor resection without macro or microscopic residue. Postoperatively, the management included surveillance in the intensive care unit, treatment of pain, and monitoring of abdominal drainage and passage of stool and gas.

Exclusion Criteria

Were excluded the patients in which radical surgery was not possible, those with tumor recurrence, and the patients diagnosed with rectal cancer due to different patient management.

Statistical Analysis

The database was created using Microsoft Excel 2010version. Data were analyzed in SPSS V.19.0. Data analysis included: descriptive statistics and analytical statistics. Continuous variables were reported as mean/median and standard deviation. Categorical variables were expressed as percentages. The study on the influence of some parameters on the value of maximum tumor diameter was based on the results of multiple correlation for which a generalized regression model was used. The significance level (p-value) (maximum probability of error) was considered 0.05 (5%) with a probability (confidence interval) of 95%. Survival analysis was performed using Kaplan Meier curve. To assess the discriminatory power of the values of a parameter on patient survival we used ROC curve (Receiver Operator Characteristic Curve) to express the relationship between sensitivity and specificity of the prediction method and to characterize the test performance.

Results

Demographic Data and Evaluation of T, N and VELIPI Categories

The study group consisted of 138 patients of which 38 patients (27.54%) had one or more tumor metastases at the time of diagnosis of clinically and clinically manifest tumor. In the remaining 100 patients (72.46%) the preoperative and intraoperative investigations did not detect metastases. The study patients had a mean age of 65.2 years ± 10.64SD, range 35-87 years. The number of male patients was substantially equal to that of females (47.1% and 52.9 %, respectively).

Metastases were more frequently present in advanced stages of disease ($p << 0.01$) 53.62% of the patients with metastases were T3 and 39.8% T4. The presence of metastases was significantly correlated with T stage (p=0.00001) and the progressive involvement of regional lymph nodes in 78.95% of the cases (p=0.00004) with a significant correlation between the presence of distant metastases and lymph node invasion ($p << 0.01$). In the metastatic group, vascular invasion was present in 84.21% compared to 47%, significantly less, in the nonmetastatic group (p=0.00008). Nonparametric analysis demonstrated a significant correlation between vascular invasion and the presence of metastases (p=0.00006), with a risk of vascular invasion presence of 1.8 (RR=1.79) and a 6-fold increased probability. Lymphatic invasion was significantly present in 81.58 % found in a significant proportion of patients (81.58%) (p=0.00037) with a 4.8-fold higher risk of occurrence (OR=4.8) in the group with secondary lesions. Perineural invasion was found in a small number of cases (17.39%) and was associated statistically significant with the presence of metastases 34.21% (p=0.00131). The probability the patients with metastases to present perineural invasion is 4-times higher (OR=4.21) with a prospective risk of occurrence of 3 (HR3.1) (Table I).

Evaluation of the Maximum Tumor Diameter

In the patients with metastases (F=5.95, p=0.0023) the maximum tumor diameter showed significant differences depending on the degree of differentiation and histological type (adenocarcinoma versus mucinous adenocarcinoma). A statistically significant correlation was found between maximum tumor diameter and the total number of evaluated nodes (r=0.422, p=0.009) in both study groups, and the number of positive nodes (p=0.007) in the group with metastases. In the group without metastases, maximum tumor diameter showed a slight tendency to increase in relation with the number of positive lymph nodes, but this was not statistically significant. In the case of bone metastases maximum tumor diameter was significantly larger than in other locations (liver (p=0.0011), peritoneal (p=0.0017), and lung (p=0.00438)). No significant differences in age, sex, serosal invasion, histological type and tumor invasion, or tumor topography in the colon were found (Table II).

Table I: General Characteristics of Cohort Patients.

	Metastasis Group	No Metastasis Group	Spearman-rank	Chi -square
Patient number	38 (27.54%)	100 (72.46%)		
Tumor stage				
1	0%	5 (5%)		
2	0%	50 (50%)		
3	1 (2.63%)	45 (45%)		
4	37 (97.37%)	0 (0%)	p<<0.01	p<<0.01
T stage			r=0.726; p<<0.01	
T1	0 (0.00%)	2 (2%)		
T2	1 (2.63%)	6 (6%)		
T3	9 (23.68%)	65 (65%)		
T4	28 (73.68%)	27 (27%)	p<<0.01	p=0.00001
N stage			p<<0.01; r=0.641	p=0.00004; $\chi 2$=22.79
N0	7 (18.42%)	55 (55.00%)		
N1	13 (34.21%)	32 (32.00%)		
N2	17 (44.74%)	12 (12.00%)		
Nx	1 (18.42%)	1 (1.00%)		
Vascular invasion			r=0.714, p=0.00006, 95%CI	p=0.00008; χ^2=15.57
Present	32 (84.21%)	47 (47.00%)		
Absent	6 (15.79%)	53 (53.00%)		
Lymphatic invasion			r=0.65, p=0.0003, 95%CI	p=0.00037, χ^2=12.68
Present	31 (81.58%)	48 (48.00%)		
Absent	7 (18.42%)	52 (52.00%)		
Perineural invasion				p=0.00131, χ^2=10.32
Present	13 (34.21%)	11 (11.00%)		
Absent	25 (65.79%)	89 (89.00%)		
Degree of differentiation			r=-0.1025, p=0.231, 95%CI	
Gx	9 (23.68%)	15 (15.00%		
G1	8 (21.05%)	24 (24.00%)		
G2	19 (50.00%)	48 (48.00%)		
G3	2 (5.26%)	11 (48.00%)		
G4	0 (0.00%)	2 (2.00%)		

Analysis of the Influence of Predictive Parameters on Maximum Tumor Diameter, Tumor Volume, and Tumor Volume Rate

The maximum tumor diameter was influenced by the histologic type (p=0.043), type of tumor invasion (p=0.0253), and the number of positive lymph nodes (p=0.0339) in 40.13% of the patients (p=0.038). Tumor volume was influenced by male sex (p=0.0404), tumor stage (p=0.0192), and invasion type (p=0.0159) in 23.02% of cases (p=0.02809). The presence of metastases had no influence on tumor volume. Tumor volume rate was influenced by male gender (p=0.0026), tumor stage (p=0.0005), presence of metastases (p=0.0404), and total lymph nodes (p=0.0017) (Table III).

Evaluation of the Predictive Value of Maximum tumor Diameter for Survival

To determine the discriminatory power of maximum tumor diameter values in predicting survival of study patients a ROC curve was obtained. The results showed an AUC value of 0.575 (p=0.394, 95% CI: AUC→0436-0713), demonstrating a poor discriminatory power of maximum tumor diameter for survival. Maximum tumor diameter did not significant influence the survival of study patients (Figure 1 and Table IV).

Cutt-off values were used to assess the predictive power of maximum tumor diameter for survival. The study results indicated a cut-off value of 4.40 in predicting survival time with a sensitivity of 40% and a specificity of 83% (Figure 2).

Evaluation of Tumor Volume in Predicting Patient Survival

To assess the discriminatory power of tumor volume in the survival of the study patients a ROC curve was obtained. The results showed AUC value of 0.594 (p=0.484, 95% CI: AUC→0406-0782), which showed poor discriminatory power values of tumor volume on survival (Figure 3 and Table V).

Cut-off value of tumor volume in predicting patient survival time was 15.40, with a sensitivity of 52% and a specificity of 80%, which showed that survival time of study patients was not influenced by tumor volume (Figure 4).

Discussion

The course of cancer is usually predicted by assessing the tissue samples taken during the surgical resection of primary tumor, mainly focused on histological features. So far, tumor staging (AJCC/UICC-TNM classification) includes data on tumor stage and size (T), presence of tumor cells along drainage ducts and in the regional lymph nodes (N), and evidence of metastases (M). Statistical data available for patients with similar progression features and current progression parameters, such as disease-free survival (DFS) and overall survival are used to make estimates. These estimates were used to predict cancer progression [7-9]. However, it is known that cancer progression may vary significantly among patients with the same tumor stage. The progression of locally advanced cancer may remain stable for years

Table II: Statistical Indicators of Maximum Tumor Diameter.

Metastases	Degree of Differentiation	Mean max. diameter	Mean			Median	p
			-95%	95%	SD		
Absent	Gx	6.9	5.56	8.24	2.41	6	**0.026047**
	G1	4.78	4.05	5.51	1.73	4.05	
	G2	5.09	4.34	5.84	2.58	4.65	
	G3	6.13	4.54	7.72	2.22	6	
	G4	6.85	4.12	7.82	2.33	6.85	
Present	Gx	6.39	4.4	8.37	2.58	6	**0.002323**
	G1	3.75	2.51	4.99	1.49	3.75	
	G2	4.55	4.01	5.08	1.11	4.5	
	G3	0.7			0	0.7	
Absent	ADK.	5.23	4.71	5.76	2.43	5	**0.036433**
	Mucinous ADK	6.73	5.59	7.87	1.89	6	
Present	ADK	4.31	3.54	5.08	1.98	4	**0.02308**
	Mucinous ADK	6	4.95	7.05	1.37	6	
Present	Hepatic	4.38	3.53	5.24	1.72	4.25	**0.010395**
	Peritoneal	4.62	3.74	5.51	1.53	4.75	
	Pulmonary	4.75	2.86	6.64	1.19	4.25	
	Bone	12			0	12	

Table III: Multivariate Analysis and Partial Correlation between Variables and Maximum Tumor Volume, Maximum Tumor Diameter and Tumor Volume Rate.

Partial Correlation *vs.*	P (volume T) 95% confidence interval	P(ø max T) 95% confidence interval	P (volume rate T) 95% confidence interval
Intercept	0.030779	0.087216	0.004428
Sex (male)	**0.040422**	0.097637	**0.002674**
Age	0.831834	0.207553	0.2047
Tumor location	0.424817	0.615374	0.247058
Metastases type	0.470563	0.258878	0.425377
Serous invasion	0.351947	0.592135	0.071775
Histological type	0.946217	**0.043613**	0.844324
Degree of differentiation	0.396712	0.694775	0.266766
Invasion	**0.015949**	**0.025329**	0.635929
Metastases	0.961018		**0.040478**
Tumor stage	**0.019287**		**0.000563**
No. total lymph nodes evaluated	0.360405	0.492002	**0.001787**
No. positive lymph nodes	0.79246	**0.033966**	0.053011

Table IV: Parameters Estimated in ROC Curve Analysis.

Area Under the Curve					
Test Result Variable(s)	Area Under the Curve (AUC)	Std. Error	Asymptotic Sig.[b] (p)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Maximum tumor diameter	**0.575**	0.071	0.394	0.436	0.713

[b]Null hypothesis: true area = 0.5

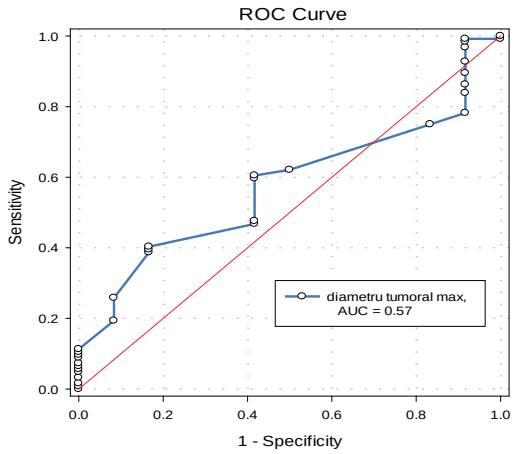

Figure 1: ROC Curve (Receiver Operating Characteristic) for Maximum Tumor Diameter for Survival.

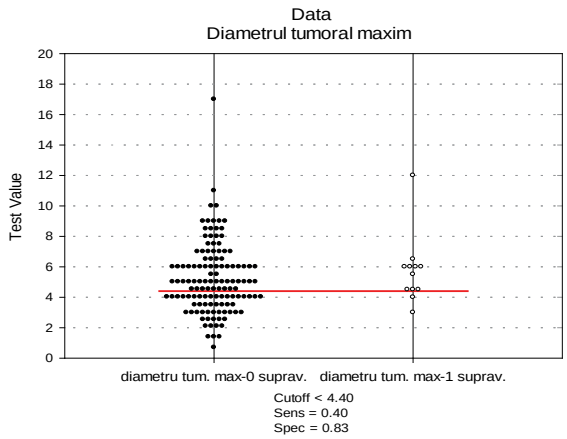

Figure 2: Point-Pair Histogram for the Cut-off Values of Maximum Tumor Diameter vs. Survival.

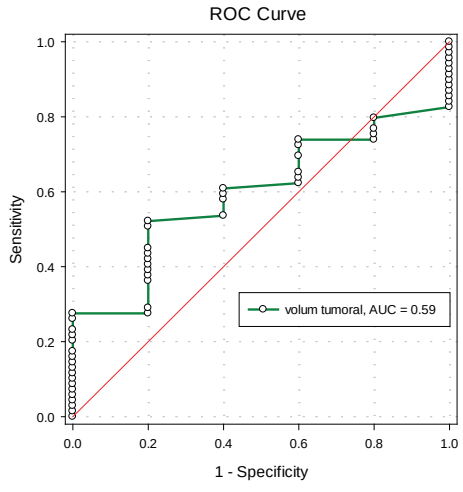

Figure 3: ROC Curve (Receiver Operating Characteristic) Tumor Volume in Predicting Patient Survival.

and partial or complete regression of large metastatic lesions may also occur spontaneously [10-12].

According to international guidelines, the key determinant in the management of colon cancer is histopathologic stage, so specific strategies are recommended for each stage separately [13-15]. As to surgical treatment, one of its goals is the resection of the involved colon segment together with the draining lymph nodes [14].

According to the 7th AJCC/UICC edition, for a good staging of both colon and rectum cancer it is recommended that a minimum of 12 lymph nodes to be evaluated pathologically [16]. As to the favorable prognosis and survival of patients with colon cancer, a very important role it played by the number of harvest nodes [5,17]. Thus, it is considered that the surgical gesture can have an impact on the harvest nodes. The total number of nodes found in the surgical excision specimen can vary according to age, sex, degree of tumor differentiation, or tumor site. The number of positive lymph nodes plays an important role in TNM system, but N stage is slightly influenced by the extent of lymph node removal, technique used by the surgeon, and thoroughness of the pathologist [18-21]. Stage migration can occur due to these factors. In some cases, such as stage T4, as many as possible lymph nodes should be examined for a better assessment of the disease stage. Patients without lymph node involvement (N0) but in which less than 12 nodes were identified and analyzed are under staging and can be considered high risk patients [13]. Until now, no other TNM independent prognostic factors able to predict the progression of colon cancer have been identified. Nowadays trend is to find as many as possible predictive markers for this disease. For a predictive marker to be incorporated into a staging system it has to have a strong and reproducible impact on the clinical outcome of patients, independent of tumor invasion [22]. The markers can be obtained by analyzing the surgical specimens or diagnostic biopsy samples [23,24].

TNM staging is based on tumor invasion into colonic wall, lymph node status, presence of lymphatic, vascular, and perineural invasion, and of distant metastases. Tumor size and tumor volume were not found useful in this staging system and in predicting the clinical outcome of patients. Although TNM staging is the only strong prognostic marker for identifying patients at high risk of recurrence, however, it can not discriminate patients in the same stage of disease [2,3]. Category N in the TNM classification appears to have the greatest prognostic power, well-known being the fact that the presence of vascular-lymph node invasion is a negative prognostic factor [5].

This study represents an attempt of identifying tumor parameters as potential predictive factors in colorectal cancer. Statistical analysis was based on comparing two groups of patients: group 1 included patients with metastases at the time of admission, and group 2 patients without metastases at diagnosis. In our study, the analysis of maximum tumor diameter showed a statistically significant association with the degree of differentiation, number of invaded lymph nodes, and the number of positive nodes in both study groups. The comparative analysis of the two study groups showed differences in depth of colon tumor invasion, vascular and lymph node invasion. In the group of patients with metastases the results showed a statistically significant higher frequency of T4 tumors with a significant presence of lymph node and vascular invasion. According to the obtained results, the presence of metastases increases the risk of vascular invasion by 6 times with a 5-fold risk of lymphatic invasion. Histologic type and number of

Table V: Parameters Estimated in ROC Curve Analysis.

Area Under the Curve					
Test Result Variable(s)	Area Under the Curve (AUC)	Std. Error	Asymptotic Sig.[b] (p)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Tumor volume	0.594	0.096	0.484	0.406	0.782

[b]Null hypothesis: true area = 0.5

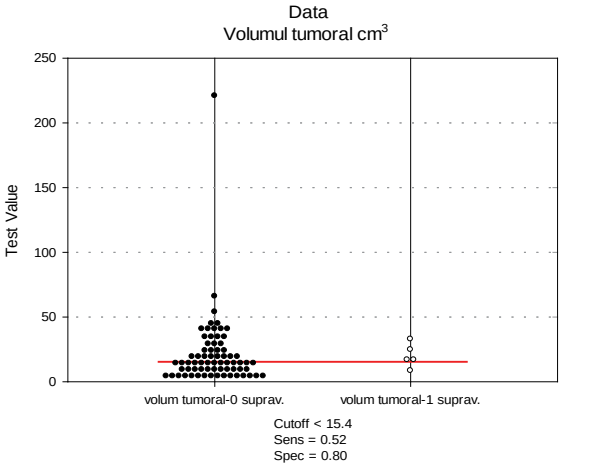

Figure 4: Point-Pair Histogram for Tumor Volume Cut-off Values vs. Survival.

positive lymph nodes were analyzed and they proved to be important factors influencing the maximum tumor diameter. Tumor volume was influenced by male gender, type of invasion, and tumor stage. To use tumor volume and maximum tumor diameter as predictive factors, their cutt-off values were calculated. The obtained statistical results were insufficient for predicting overall survival of the study cohort.

The short follow-up period represents a disadvantage of our study as it did not allow the obtaining of disease-free survival curves. As a perspective of our study is an enlarge cohort with a follow-up according to the international guidelines recommendations with a review of statistical analysis.

Conclusions

Prognostic factors in colon cancer are numerous, but number of lymph nodes is the most powerful in predicting clinical evolution. Tumor dimensions are not included yet in the category of prognostic factors. Nevertheless tumor parameters represent the characteristics that may be used to evaluate tumor aggressiveness. In order to be considered factors with prognostic value, these parameters should be analyzed and validate in larger prospective studies.

Conflict of interests

The authors have no conflict of interests to declare.

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Research Article Open Access

Early and Late Complications after Hepatic Arterial "Port-a-Cath" Implantation in the Treatment of Hepatic Metastasis from Colorectal Cancer

Simona Ruxandra Volovat[1]*, Serban Negru[2], Vasile Maciuc[3] and Viorel Scripcariu[1]

[1]*Regional Cancer Institute Iasi, "Gr.T. Popa" University of Medicine and Pharmacy Iasi, Romania*
[2]*Department of Oncology, University of Medicine and Pharmacy Timisoara, Romania*
[3]*"Ion Ionescu de la Brad" University of Agricultural Sciences and Veterinary Medicine Iasi, Romania*

Abstract

Background and Aim: In metastatic colorectal cancer, in the last 10 years, hepatic arterial infusion (HAI) was proposed as an alternative using various chemotherapy agents. The insertion of a port-a-cath in the hepatic artery is needed and there are various methods to do that, from classical to interventional approach.

Patients and Methods: Patients were selected with metastatic colorectal cancer with inoperable liver metastasis only and were treated with oxaliplatin HAI, combined with systemic intravenously chemotherapy. The port-a-cath insertion was done using the classical approach in the same surgical time with the subclavicular vein port insertion.

Results: Thirty-two patients were treated. During our experience we did not encounter intra-operative complications. Among the immediate post-operative complications mainly consisted of metabolic complications (6.2%) and infection was the most common late complication (9.4%). In one case we removed the port-a-cath, thus the patient was not able to continue the treatment.

Conclusion: When talking about the safety of the procedure, we didn't find it to be more at risk for the patients compared to the literature. Even though the antibiotic prophylaxis is done regularly, the risk of infection remains, especially as a late complication

Keywords: Metastatic colorectal cancer; Hepatic arterial infusion; Hepatic port-a-cath implantation

Background

The colorectal cancer (CRC) still represents in the modern era a major health problem, being the second cause of cancer related mortality, despite the major scientific progresses and the emerge of many new biological agents currently used in the treatment. The liver is known to be the first metastatic site in CRC and approximately 60-70% of patients develop them during the course of the disease, out of which only 10% are eligible for a partial liver resection, the only curative treatment in this disease.

Nowadays, the modern systemic treatment with or without biological agents has the purpose to switch the patients with an un-resectable liver disease to a resectable stage.

Regional hepatic arterial infusion of chemotherapy (HAI) aims to deliver higher local drug concentration to un-resectable liver tumors, leading to fewer significant systemic side effects compared to standard chemotherapy. The theoretical basis for treating liver tumors with HAI is that hepatic neoplasms receive ~95% of their blood supply from the hepatic artery, unlike normal hepatocytes, which are perfused mainly by the portal vein [1]. It has been proved that patients treated with HAI have a better response rate than those on systemic chemotherapy, despite the low impact on overall survival [2,3]. When it is associated with systemic chemotherapy, the use of HAI could offer a better control of the extra-hepatic disease. Therefore, it remains an important treatment option in patients with advanced, inoperable primary or metastatic hepatic tumors.

A rather large experience with the HAI technique has been obtained in patients with isolated liver metastases of colorectal cancer. There are several randomized trials on HAI using FUDR or 5-FU in patients with non-resectable colorectal liver metastases that have been performed since the 1980, but achieved inconsistent results. This fact could be explained on one side by the inadequate study designs at the time and on the other side by the technical problems with the application of the devices [4-6].

This last issue was significantly improved in the last decade by introducing different techniques of placing the catheter. Most of the studies with HAI have been performed on the colorectal cancer patients with un-resectable liver metastasis [7] and not on primary liver cancer patients.

This administration of cytotoxic agents to the liver requires catheters connected to subcutaneous ports in order to allow an easy and repetitive infusion of chemotherapy directly to liver tumors. Surgically implanted hepatic catheters have shown to have considerable complication rates and the repair or replacement of the malfunctioning port systems often require further surgery procedures. The aim of this article is to provide a comprehensive review of early and late complications of surgical implanted catheter-port systems for HAIC.

In order to define the safety and the practicability of the HAI approach, we included patients with colorectal cancer and non-resectable liver metastasis in a prospective study that took place in our hospital. The patients were further included in a study that compared

***Corresponding author:** Simona Ruxandra Volovat, MD, Regional Cancer Institute Iasi, General Berthelot Street No. 24, 700483, Iasi, Romania, Tel: +40 (0) 374 27 88 10; E-mail: simona_v2002@yahoo.com

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the standard chemotherapy regimen FOLFIRI with FOLFIRI associated with the local administration of Oxaliplatin using the hepatic inserted port. The primary objectives of the study were progression free survival; among the secondary objectives, which will be detailed in this article, are "complication rates" and "safety of the device and regional therapy".

Material and Method

Study Design, Patient´s Collective and Eligibility Criteria

Patients with colorectal cancer with non-resectable liver metastasis were enrolled into a prospective phase II study that aimed to compare the administration of FOLFIRI vs. FOLFIRI and Oxaliplatin administered in the hepatic artery. The FOLFIRI regimen consisted of irinotecan 160 mg m^{-2} IV in 90 minutes, leucovorin 200 mg m^{-2} IV in 90 minutes (concurrently with leucovorin in separate bags via y-line connection) and 5-FU 2400 mg m^{-2} in 48 hours (with an ambulatory elastomeric pump), repeated at 14 days. Oxaliplatin was administered 85 mg m^{-2} infused in day 1 over 2 hours, combined with systemic chemotherapy. Apart from the primary endpoints like progression free survival and response rate, we also considered evaluating the technical complications and safety associated with the use of implanted port catheter systems. The study was performed from 2011 to 2013. The local ethics committee of the University of Medicine and Pharmacy Iasi, Romania and Victoria Hospital Iasi, Romania approved the protocol, and a detailed written informed consent was obtained from every patient prior to treatment.

The patients included in the trial met the following inclusion criterias:

- Age over 18 years-old;
- Proven histology of colorectal adenocarcinoma
- Stage IV colorectal cancer,
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2
- Estimated life expectancy of ≥ 3 months.

Leukocyte count of at least 3.5×109/L, neutrophils count of at least 1.5×109/L, platelet count of at least 100X109/L, satisfactory biochemical results (serum creatinine of 1.3 mg/dL or less, serum bilirubin less than 1.5 mg/dL)

Measurable disease (hepatic lesion with longest diameter of minimum 20 mm) according to RECIST 1.1 criteria with liver invasion assessed by computed tomography (CT) as less than 50% of the liver.

The main exclusion criteria were:

- Detectable extra-hepatic disease (including during laparotomy for catheterization of hepatic artery)
- Hepatic artery thrombosis,
- Peripheral neuropathy,
- Active infections,
- Inflammatory bowel disease,
- Total colectomy,
- Heart failure,
- Respiratory insufficiency,
- Severe coronary artery disease or failure of other organs.

Previous adjuvant chemotherapy including irinotecan or oxaliplatin were excluded, but previous fluoropyrimidine-based adjuvant chemotherapy was allowed if it ended more than 6 months before random assignment.

We have subcutaneously placed hepatic arterial ports in our Surgical Unit on 32 patients aged between 37 and 75 years old, which were eligible for the protocol of systemic chemotherapy with FOLFIRI and hepatic arterial infusion with Oxaliplatin. Most of the patients had no prior chemotherapy for metastatic disease, but some had adjuvant chemotherapy before becoming metastatic, but neither had chemotherapy less than 6 months prior to entering the study.

The protocol involved also the placement of a subclavian catheter in order to administer the systemic chemotherapy that consisted in FOLFIRI protocol during a longer period of time and with better tolerance for the patients.

Interventions–Port Implantation Procedure

After identifying the right gastroepiploic artery, using as reference the proximity to the inferior margins of the duodenal bulb, we continue with the careful dissection of the artery from the vein located in the immediate vicinity. The right gastroepiploic artery at this level has a caliber that will allow the catheterization of the gastro-duodenal artery and then of the hepatic artery. After the distal ligature of the right gastroepiploic artery we can puncture the artery in the proximal segment and an arteriography can be made in order to visualize the hepatic artery and its entire course (Figure 1). This arteriography is not a compulsory maneuver because it will be accomplished after placing the catheter.

A small transversal incision of the right wall of the gastroepiploic artery is made and the guide wire is introduced (Teflon guide wire 0.35"), which ascends afterwards by pushing it into the hepatic artery, passing through the gastro-duodenal artery. At this moment, palpating the hepatic artery in the hepatic pediculum in the same time with ascending the guide wire will allow us to place the catheter properly.

Afterwards, we proceed to the insertion of the silicon radio-opaque catheter in the proper hepatic artery and ascending as much as possible in the hepatic artery towards the hepatic hilum, carefully feeling by hand the artery in the hepatic pediculum (Figures 2-4). During this step or in the moment of the introduction of the guide wire, it may be possible that there is the tendency to engage towards the celiac trunk through the common hepatic artery. If this happens, the guide wire or the catheter is retracted and we try to re-position it.

At this point, after the correct positioning, a hepatic arteriography is made through the introduced catheter in order to verify its position.

After the correct positioning of the catheter in the hepatic artery we will proceed to the chamber positioning (capsule, the "infusional

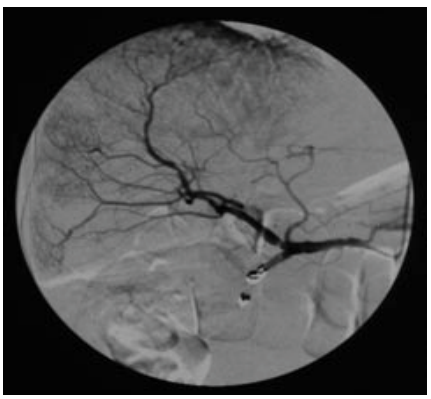

Figure 1: The Arteriography made Indicates the Correct Position of the Catheter in the Common Hepatic Artery.

Figure 2: Port-a-Cath Insertion in the Hepatic Artery.

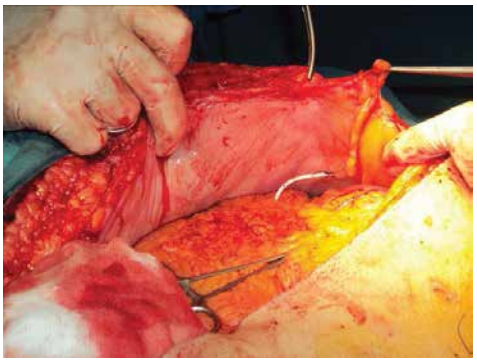

Figure 3: Port-a-Cath Insertion in the Hepatic Artery.

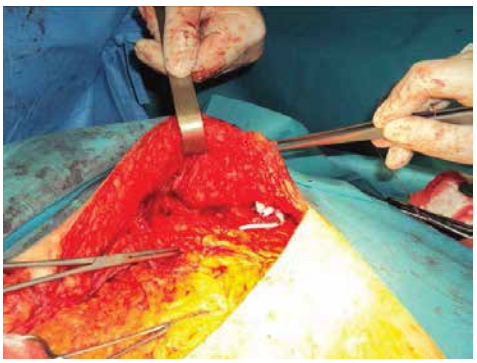

Figure 4: Port-a-Cath Insertion in the Hepatic Artery.

port") on the inferior part of the right rib cage on the same layer as the medial-clavicular line, taking into consideration the fact that the entire capsule should be placed on the hard layer of the last ribs of the rib cage. In order to accomplish this separate skin incision made, at approximately 3-5 cm proximal to the chamber's positioning spot and the dissection of the subcutaneous layer to the muscular-aponeurotic layer of the costal margin of the last ribs. This dissection is done distally of the incision, in order to avoid the over-positioning of the incision, and so of the future scar, over the spot of the future injections of the capsule. Through dissection, a subcutaneous pocket is created in which we will place the capsule and fix it with three suture points to the muscular-aponeurotic layer. The maneuver is necessary in order to avoid a possible migration or subcutaneous torsion of the capsule, thus being impossible to use it for injections in the future.

Afterwards a subcutaneous tunnel is being created to the peritoneal cavity, using the metallic perforator from the port-a-cath's kit and the already positioned in the hepatic artery catheter is being brought through this subcutaneous tunnel right to the proximity of the capsule. Using sealing fixing elements of the catheter to the port-a-cath's capsule, the catheter is being connected to the chamber. The physical functionality is being verified and also using arteriography, after which, the procedure is being considered closed.

Surgical Incidents and Accidents

The impossibility to identify the right gastroepiploic artery in a well-represented fat tissue covering the epiplones. The dissection is being made in a more proximal position, closer to the gastro-duodenal artery.

A hematoma situated at the dissection site can be an impediment in appreciating the anatomy and the trajectory of the right gastroepiploic artery to the emerging point from the gastro-duodenal artery. The dissection is made in a more proximal position, closer to the gastro-duodenal artery.

Guide wire or catheter malposition towards the celiac trunk. The positioning procedure is retried and an arteriographic control for an eventual anatomic variant is done.

The malposition of the capsule in the thickness of the abdominal wall and not on the hard layer of the costal margin. Another subcutaneous pocket will be made.

A bleed of a hematoma where the capsule is situated. The hemostasis must be carefully controlled in order to avoid the hematoma, which can be a source of infection for the capsule.

Late Complications

Infection where the subcutaneous capsule is located. It is a severe complication and antibiotic treatment according to the antibiogram is needed. The repositioning of the capsule or even the removal of the port-a-cath is compulsory. The repositioning of the port-a-cath is made under large-spectrum antibiotics administered in prophylaxis, according to the existent protocols for a surgical procedure.

Port-a-cath malfunction and its blockage through blood cloth obstruction. We try a de-obstruction or, if not, the port-a-cath is suppressed. This incident must be avoided by a proper maintenance with heparin after the procedure or after the chemotherapy, once a week or in between administrations.

In the same time with placing the catheter in the hepatic artery, a port-a-cath in the subclavian or jugular vein can be placed, in order to be able to administer the concomitant systemic chemotherapy. The technique is the classic Seldinger technique, percutaneously, by finding the subclavian or jugular vein and placing the capsule in a pre-pectoral subcutaneous pocket. The radiologic control is necessary after positioning the catheter, in order to avoid the complications due to the catheter malposition.

Evaluations

Pretreatment Evaluation and Follow-up

We recorded each patient's history; clinical examination and routine laboratory status were performed at least 10 days before the first chemotherapy application. Basic imaging consisted of an abdominal CT, chest-X-ray or CT. Before every HAI-application a clinical evaluation, a full blood count and chemistry were repeated. Assessment of toxicity was performed according to WHO-criteria. Response evaluation was performed according to RECIST 1.1 criteria and repeated in 3-monthly intervals using CT evaluations. In case of progression (end of treatment), patients were seen at least every

3 months. The treatment was interrupted in case of grade IV WHO toxicity, irreversible loss of port function or disease progression.

Port Complications

Port-related adverse events were assessed from the date of implantation. The duration was defined as functional device with or without revision, but without the requirement for removing the entire system.

Statistical Evaluations

Our data was analyzed by using SPSS 16.00 for Windows. We determined the frequency, the regression coefficient, Pearson correlation and relative risk (RR) assessment. We also used in our study Chi-Square tests and "p" significance test. A two-sided p-value less than 0.05 were considered to prove significance for all tests performed.

Results

Patient's Characteristics

During 2011-2013 a number of 32 patients underwent the surgical implantation of port-a-cath, as described, in the subclavian vein and hepatic artery. The patients were aged between 37 and 75 years old, but with a higher age frequency between 51-70 years old (n=21). 71.9% (n=23) were diagnosed with rectal adenocarcinoma, 15.6% (n=5) were colon adenocarcinoma, 9.4% (n=3) had double colo-rectal localization and one patient had a different histology (neuroendocrine tumor) after resection. Most patients had a well-differentiated (grade 2) adenocarcinoma (46.9%, n=15), only 25% (n=8) being undifferentiated.

In our lot of patients 6.2% (n=2) had a unique hepatic lesion, un-resectable due the large dimension (>5 cm) or due to the proximity with large vessels. In most cases (56.2%, n=18), our patients had multiple hepatic lesions between 2-5 cm. 84.4% (27) of the patients had synchronous hepatic metastasis and in these cases the primary tumor was resected at the same time with implanting the port-a-cath. A large proportion (65.6%, n=21) hadn't had previous chemotherapy for metastatic disease (especially irinotecan or oxaliplatin based chemotherapy), but some patients with rectal cancer had previous peri-operative radio-chemotherapy with capecitabine, ended more than 6 months before random assignment. (Table I)

Complications

During our study, all patients received peri-operative antibiotic treatment for 7 days according to internal guidelines. During the surgery, we did not encounter any intraoperative complications. The immediate port-related complications mainly consisted of metabolic complications, post-surgery pre-renal insufficiency, which had a fast response to medical treatment. Infectious problems (such as sepsis) and also fistulae were less frequent (only one case) and were resolved without compromising the oncological treatment (Table II).

Late complications were mainly infectious (9.4%, n=3), which needed hospitalization and complex antibiotic treatment, as all patients were at the moment under chemotherapy, thus being at a higher infectious risk due to post-chemotherapy induced neutropenia. In all cases, all complications were resolved. In one case, a patient had a port-a-cath infection that obliged us to remove it (Figure 5). From that point on, the patient did no longer receive the HAI perfusions with oxaliplatin.

Discussion

The oncological patients sometimes need long-term systemic or local chemotherapy, which can be achieved through an access system connected to an access port. An implantable device, which consists of a reservoir, a capsule connected to a catheter, will allow the continuous access for the treatment and can lead to an increased quality of life for the patients.

Among different techniques used in order to insert a port-a-cath into the hepatic artery [8-10], the fixed catheter tip method [11] has proven the advantage of preventing catheter dislocation and hepatic artery obstruction, thus being used in most centers performing this technique.

A review of large studies involving the percutaneous placement of port-a-cath for HAI administration using the fixed-catheter method described a rate of catheter dislocation between 2-8% [1,12].

The present study evaluated a heterogeneous group of 32 patients diagnosed with metastatic colorectal adenocarcinoma limited to the liver. For these patients a curative approach of the hepatic involvement was not feasible due to the number (>2 lesions), size (>2-5 cm) or localization (the unique lesions were located close to major vessels and, as a consequence, metastasectomy could not be performed). In these cases we opted for an interventional approach in order to obtain a better local response and control. A protocol consisting of systemic chemotherapy by FOLFIRI protocol and an intra-arterial

Table I: Patient's Characteristics.

Patient's characteristic	N (%)
Sex	
Male	16 (50)
Female	16 (50)
Age at diagnosis	
< 50 years-old	9 (28.1)
51-70 years-old	21 (65.6)
> 70 years-old	2 (6.2)
Histology	
Colon adenocarcinoma	5 (15.6)
Rectal adenocarcinoma	23 (71.9)
Double localization (colon and rectum)	3 (9.4)
Tumor grade	
Poorly-differentiated	8 (25)
Moderately-differentiated	1 (3.1)
Well-differentiated	15 (46.9)
N/A	8 (25)
Hepatic lesion(s)	
Unique lesion > 5 cm	2 (6.2)
Multiple lesions > 5 cm	9 (28.1)
Multiple lesions 2-5 cm	18 (56.2)
Multiple lesions < 2 cm	3 (9.4)
Metastasis	
Synchronous	27 (84.4)
Metachronous	5 (15.6)
Previous chemotherapy	
Yes	11 (34.4)
No	21 (65.6)

Table II: Intra and Postoperative Complications.

Complications	N (%)
Intra-operative complications	0 (0)
Early surgical complications	
None	28 (87.5)
Metabolic complications	2 (6.2)
Infectious complications	1 (3.1)
Fistulae	1 (3.1)
Late surgical complications	
None	28 (87.5)
Infectious complications	3 (9.4)
Dislocation of catheter's chamber	1 (3.1)

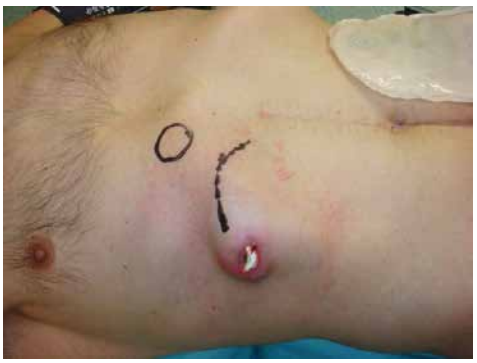

Figure 5: Infected Port-a-Cath that needed to be Removed.

administration in the hepatic artery of Oxaliplatin was implemented for these patients. In the present study, among the primary objectives such as response rate and progression free survival, we also considered secondary objectives such as toxicity profiles, safety and, in some cases, the target was the ulterior possibility of resectability of the hepatic metastasis in case of a good response to chemotherapy. The present paper addresses one of the secondary objectives that of the safety of the procedure, taking into account the fact that it is not a standardized treatment option for these patients.

It was found that the implantation of port-a-cath in the hepatic artery was feasible in all patients, and that the rate of device related-complications was relatively low. In addition, the proportion of patients with treatment discontinuation due to port-failure compares favourably with the literature [13,14] (only one patient out of 32).

In our study, the rate of catheter dislocation was comparable with the data from the literature (3.1%) and the correction was possible without further complications. Even though other studies mention the difficulty in catheter removal as a major issue, we had a 100% rate of success. Tajima et al. describes in his study a withdrawal method of the port-a-cath implanted using the fixed-tip method [15]. He reported several cases of catheter removal due to infection, catheter obstruction, hepatic artery obstruction or catheter dislocation and 14 of 15 cases were successful and 10 out of 15 patients underwent reinsertion of the port-catheter system. He also developed a new system called the self-retaining indwelling catheter system that required a special device.

In this study, the percutaneous positioning of arterial port is a safe and effective technique to deliver loco-regional treatment for hepatic tumors. Complication rates are similar to literature reports, being in an acceptable range. Additionally, the occurrence of infectious complications or chamber dislocation was low and the difficulty of removal was rare. In conclusion, this percutaneous approach in the hands of a skilled team allows intra-arterial infusion in a wide percentage of patients.

Conclusions

The insertion of a port-a-cath in the hepatic artery remains an experimental procedure, with limited indications. However, we find this procedure to be more and more used in clinical trials or as part of a local treatment of the hepatic metastasis.

Although there are multiple techniques described in the literature, we prefer the fixed catheter tip method due to its advantages and to the fact that it has been widely utilized.

In our study, we can conclude that the insertion of the port-a-cath into the hepatic artery is a safe procedure, with limited complications during or after surgery. Moreover, these complications were manageable in all cases and this percutaneous approach, in the hands of a skilled team, allows intra-arterial infusion in a wide percentage of patients.

Conflict of interests

Authors have no conflict of interests to disclose

Acknowledgement

The first author, Simona Ruxandra Volovat is PhD student of "Gr.T. Popa" University of Medicine and Pharmacy Iasi, Romania. The present study is the result of research program during PhD thesis studentship.

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Journal of Surgery
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Case Report Open Access

Diagnosis and Treatment of Mesenteric Cystic Lymphangioma: Case Report

Călin Molnar[1], Vlad Latiş[1], Victor Iosif Neagoe[1], Doina Milutin[2], Vlad-Olimpiu Butiurca[1], Cosmin Nicolescu[1], Daniel Popa[1], Adrian Tudor[1] and Constantin Copotoiu[1]

[1]*First Surgery Unit, Târgu Mureş Emergency County Hospital Romania*
[2]*Department of Pathology, Târgu Mureş Emergency County Hospital Romania*

Abstract

Background: Mesenteric cysts, and particularly lymphangiomas, occur very rarely in adult patients. Due to this low incidence and their non-specific symptomatology, they often present a difficulty in diagnosis.

Case report: We present the case of a patient aged 58 years admitted to the Surgical Clinic 1, Târgu Mureş Emergency County Hospital accusing diffuse abdominal pain and tenderness in the epigastrium. Abdominal ultrasound revealed a fluid cystic tumor, multi-septated, located in the root of the mesentery and the abdominal computer tomography confirmed this diagnosis. Surgery consisted of total cystectomy without compromising the intestinal segment and sparing the vascular structures in its vicinity. Cyst dimensions were approximately 70x50x30 mm and contained lymphatic fluid. The histopathological report confirmed a mesenteric cystic lymphangioma. The postoperative evolution was uneventful, with quick recovery and no postoperative complications.

Conclusions: The diagnosis of mesenteric cyst should be included in the differential diagnosis of intra-abdominal tumors in patients with nonspecific symptoms. Once this diagnosis is established histological differentiation between lymphangiomas and simple lymphatic cyst is essential. The total excision minimizes the recurrence rate, and their early removal can prevent complications caused by the compression and invasion of neighboring organs.

Keywords: Mesenteric lymphangioma; Mesenteric cysts

Introducere

Limfangioamele chistice sunt tumori angiomatoase benigne, localizate mai ales la nivelul capului, gâtului (70-75%) şi regiunii axilare (20%) [1]. Doar în 5% din cazuri acestea au alte localizări, la nivelul abdomenului cel mai adesea fiind localizate în mezenter, mezocolon şi retroperitoneu [2]. Raportul adulţi/copii este de 1/5 pentru pacienţii spitalizaţi, incidenţa la vârsta adultă fiind de aproximativ 1:100.000-250.000 [1], cu o predominanţă de trei ori mai crescută la sexul masculin [2].Chisturile mezenterice pot apărea în orice parte a mezenterului şi mezocolonului, cel mai frecvent fiind întâlnite în mezenterul ileal şi mezocolonul drept (aproximativ 60% porţiunea ileală şi 40% mezocolonul ascendent)[3].

Mennemeyer şi Smith elaborează cea mai acceptată clasificare, bazată pe particularităţile histopatologice [4]:

1) Chisturi de origine limfatică (Chisturile mezenterice simple şi limfangioamele mezenterice)

2) Chisturi de origine mezotelială (beningne sau maligne)

3) Chisturi enterice

4) Chisturi de origine urogenitală ;

5) Chisturi dermoide (Teratoame chistice);

6) Pseudochisturi-de origine infecţioasă sau traumatică.

Chisturile mezenterice simple şi mezoteliale evoluează lent şi sunt simptomatice în timp, pe când limfangioamele şi mezotelioamele chistice dobândesc proprietăţi invazive şi implicit evoluţie agresivă.[3]

Etiologia limfangioamelor este incertă, probabil determinată de o anomalie congenitală a sistemului limfatic ce cauzează sechestrarea ţesutului limfatic în timpul dezvoltării embriologice [5]. Această teorie explică apariţia limfangioamelor mai ales la copii [6]. Există autori care sugerează că traumatismele abdominale, obstruarea canalelor limfatice, procesele inflamatorii, intervenţiile chirurgicale în antecedente sau radioterapia pot duce la apariţia acestor entităţi patologice [7,8].

Prezentarea Cazului

Prezentăm cazul unui pacient în vârstă de 58 de ani, din mediul urban, internat în Clinica Chirurgie nr. 1 din cadrul Spitalului Clinic Judeţean de Urgenţă Târgu-Mureş, acuzând dureri abdominale difuze de aproximativ 5 luni. Durerea a fost descrisă ca fiind de intensitate moderată, intermitentă, localizată preponderent în epigastru şi mezogastru. Din antecedentele patologice ale bolnavului reţinem o hepatită cronică virală B (confirmată in anul 2003) şi gastrită cronică hiperacidă (recent diagnosticată) pentru care a urmat tratament cu inhibitori de pompă de protoni, lamivudină şi hepatoprotectoare.

Examenul ecografic(13.01.2014) efectuat în spitalul teritorial pune în evidenţă un ficat de dimensiuni normale, omogen, fără dilatări ale venei porte şi ale canalelor biliare intrahepatice, colecistul fiind de aspect normal. Pancreasul este greu apreciabil, însă inferior de corp se decelează o formaţiune transonică, neregulată de 73 x 36 mm cu ecouri lineare declive în interior (septuri fine) (Figura 1).

Tomografia computerizată abdominală efectuată nativ şi cu substanţă de contrast (15.01.2014) tranşează dignosticul, descriind o masă cu densităţi lichidiene, omogenă, la nivelul mezenterului, median şi paramedian drept, cu dimensiuni maxime de 69x27x53mm, bine delimitată, contur regulat (Figura 2). De asemenea se mai vizualizează câteva imagini limfo-ganglionare la nivelul mezenterului,

***Corresponding author:** Calin Molnar MD, PhD, First Unit of Surgery, Târgu Mureş Emergency County Hospital, Nicolae Grigorescu Street, No 31, 540136, Târgu Mureş, Mureş, Romania, Tel: +40 (0) 722 69 66 10; E-mail: molnar.calin@yahoo.comyahoo.com

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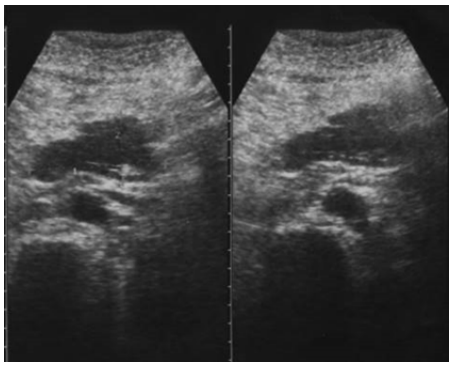

Figura 1: Imaginea ecografică a chistului mezenteric (formațiune de 73x36mm, transonică, septată).

cu dimensiuni de până la 9 mm.

Examenul obiectiv general și local, efectuat în ziua internării, arată un pacient afebril, acuzând dureri abdominale minime, ușoară distensie, moderată sensibiltate la palpare în etajul superior, fără semne de iritație peritoneală, murmur intestinal prezent.

Paraclinic se constată valori normale, însă markerii antigenici HBs au fost mult crescuți (peste 17,3 la un interval de referință de 0-1,1).

După o pregătire preoperatorie adecvată se intervine chirurgical (24.02.2014) prin laparotomie mediană; la inspecția cavității peritoneale se confirmă diagnosticul de chist mezenteric corespunzător cadrului jejunal (Figura 3), situat în vecinătatea trunchiului venei mezenterice superioare. S-a practicat excizia formațiunii tumorale chistice mezenterice, cu ajutorul pensei Harmonic Focus Ultrasonic®, împreună cu tesutul grăsos adiacent, menajând structurile vasculare din vecinătate (Figura 4) și păstrând viabilitatea intestinală. Se asociază și prelevarea unui limfonodul mezenteric pentru o eventuală stadializare.

Breșa mezenterică restantă a fost închisă cu fire separate, pentru a preveni o hernie internă. Inspecția minuțioasă a cavității peritoneale nu a pus în evidență prezența de alte modificări, intervenția încheindu-se prin laparorafie în planuri anatomice. Examinarea macroscopică a formațiunii excizate arată un chist unilocular cu dimensiuni de aproximativ 70x50x30 mm, de formă ovalară, culoare brun-gălbuie, cu perete subțirie (3-5mm), tapetat la interior de o membrană bine vascularizată, transparentă (Figura 5). La secționarea longitudinală a masei chistice s-au exteriorizat aproximativ 30 ml de lichid alb-deschis, opalescent, cu aspect lăptos, calități caracteristice limfei.

Examenul microscopic pune în evidență o formațiune cu aspect chistic delimitată de un perete conjunctivo-muscular, tapetat pe alocuri de endoteliu aplatizat, iar adiacent agregate limfoide și focare de histiocite cu citoplasmă spumoasă. Examinarea microscopică din limfonodulul mezenteric denotă histiocitoză sinusală. Diagnosticul histopatologic fiind de limfangiom chistic mezenteric (Figura 6).

Evoluția postoperatorie a bolnavului a fost favorabilă, cu reluarea tranzitului în a doua zi postoperator și externare în ziua a 5-a.

Discuții

Chisturile mezenterice au fost descrise prima dată de în 1507 de Benevieni, în timpul unei autopsii la o fetiță de 8 ani. Prima decriere a unui chist mezenteric limfatic este legată de numele lui Rokitansky (1842), iar Tillaux a efectuat în 1880 prima excizie a unei formațiuni tumorale chistice [3]. Limfangioamele pot apărea fie ca leziuni unice, fie sub formă de formațiuni tumorale multiple de-a lungul intestinului [2].

Acestea sunt de obicei asimptomatice la adulți, fiind descoperite incidental, cu ocazia unor investigații pentru alte patologii, deseori constituind o surpriză intraoperatorie [5]. Clinic pacienții cu acestă entitate rară se prezintă acuzând un tablou nespecific (dureri abdominale nesistematizate, meteorism grețuri, vărsături) [1]. Deși benigne, limfangioamele mezenterice pot crește semnificativ morbiditatea sau mortalitatea în cazul în care ating o anumită dimensiune și comprimă structurile adiacente. Au fost raportate complicații redutabile ale acestor formațiuni cum ar fi infecții secundare, ruptura chistului cu hemoragie, volvulus, sau ocluzie intestinală [9-12].

Examenul obiectiv urmat de ultrasonografie și computer-tomografie sunt pașii de bază în elucidarea diagnosticului [1-7]. Ecografia evidențiază structuri lichidiene, chistice, septate și ecouri caracteristice detritusurilor, hemoragiilor sau infecțiilor. Conținutul are de obicei o densitate similară cu cea a apei [13]. Secțiunile computer tomografice native pot ajuta la stabilirea punctului de origine, iar folosirea substanței de contrast evidențiază peretele chistului și septurile acestuia [14].

Diagnosticul diferențial al limfangioamelor include: chisturile mezenterice limfatice simple [3], pseudochistul pancreatic [12], chistul hidatic [13], colecțiile ascitice loculare (maligne sau infecțioase- de exemplu în tuberculoză) [13], chisturile de incluziune peritoneale [15], paniculita chistică mezenterică (mezenterita sclerozantă)[16].

Elementul caracteristic histopatologic limfangiomului este reprezentat de prezența fibrelor musculare netede în interiorul peretelui acestuia; chisturile mezenterice limfatice sunt căptușite de un strat fibros și conțin doar celule endoteliale spre cavitatea chistului [17].

Excizia chirurgicală completă este metoda chirurgicală ideală în chisturile mezenterice, în special în cazul limfangioamelor [1-6]. Benigne histologic, limfangiomele se comporta de multe ori agresiv și tind să atingă dimensiuni enorme [13], unii pacienți necesitând o rezecție intestinală pentru îndepărtarea completă a chistului (înglobarea vaselor sangvine sau relația de imediată vecinătate cu acestea) [1-3].

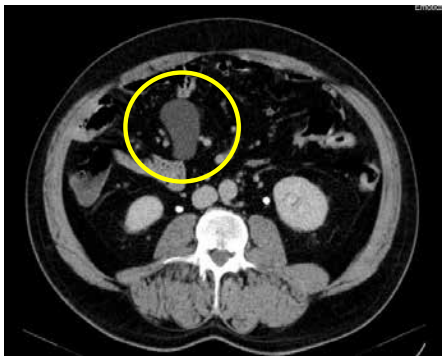

Figura 2: Aspectul computer tomografic al leziunii mezenterice.

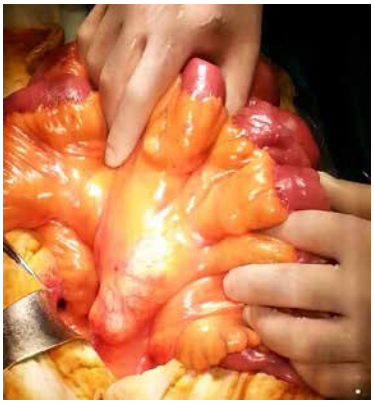

Figura 3: Imaginea intraoperatorie a chistului mezenteric.

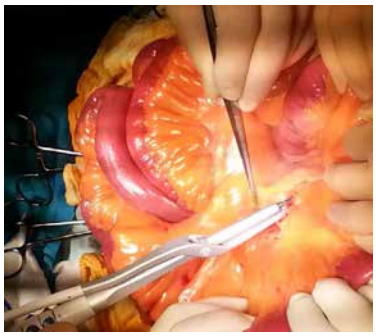

Figura 4: Îndepărtarea chistului cu ajutorul penei Harmonic Focus Ultrasonic®.

Figura 5: Aspectul macroscopic chistic al limfangiomului mezenteric.

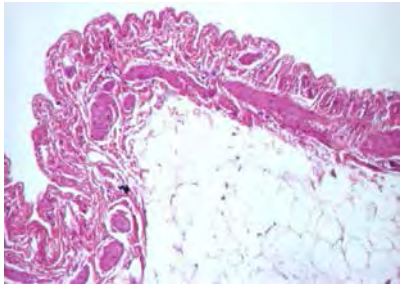

Figura 6: Imagine microscopică (hematoxilină-eozină): limfangiom chistic; de notat prezența fibrelor musculare netede în peretele chistului.

Urmărirea postoperatorie include monitorizare clinică, ecografică şi computer tomografică.

Concluzii

Un chist mezenteric, fie el limfangiom sau de altă natură, trebuie suspectat în prezența unei tumori abdominale palpabile, însoțită de dureri abdominale difuze,în condițiile unor examinări de laborator normale, la un pacient în stare generală relativ bună. În cazurile simptomatice, durerile abdominale acute sau cronice sunt cea mai comună caracteristică; alte acuze "de împrumut" depind de localizarea, dimensiunea şi existența fenomenelor compresive a organelor de vecinătate (ocluzie intestinală, volvulus, infecţii secundare, hemoragie, hidronefroză etc). Dintre investigațiile imagistice ecografia abdominală şi computer-tomografia sunt metodele standard de diagnostic şi de diferențiere față de alte suferințe abdominale ce îmbracă aceeași simptomatologie. Diferențierea intraoperatorie între chistul limfatic şi limfangiom este de cea mai mare importanță, şi poate fi realizată doar prin examinarea histopatologică a peretelui chistului. De aceea chistectomia totală este opțiunea terapeutică de elecție în tratamentul acestei patologii fie pe cale deschisă, fie prin metoda laparoscopică, având în vedere prezumția de malignitate a acestora şi potențialul acestor chisturi de a se extinde spre structurile învecinate. Odată îndepărtate, chisturile mezenterice rareori recidivează, iar pacienții au un prognostic excelent.

Conflict de interese

Autorii nu au niciun conflict de interes.

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Case Report Open Access

Pulmonary Neuroendocrine Tumor with Thyroid Gland Metastasis: Case Report

Cristina Corina Pop Radu*

Department of endocrinology, University of Medicine and Pharmacy Târgu Mureș, Romania

Abstract

Neuroendocrine tumors (NET) represent approximately 20% of all primary neoplasms of the lung. Histologic confirmation is important for treatment and prognosis determination. NET are classified according to four subtypes in the lung: typical carcinoid tumor (TC), atypical carcinoid tumor (AC), small cell carcinoma (SCC), and large cell neuroendocrine carcinoma (LCNEC). TC is low-grade, AC is intermediate-grade, and SCC and LCNEC are high-grade malignancies.

Case report: A 57 years old woman, affected by a cervical anterior tumor and a proliferative tissue below the glottis was referred to our Endocrinology Department from ENT service for a second opinion. An ultrasound scan of the neck showed a polynodular goiter with bilaterally lymph nodes enlargement with suspicious malignancy characters. She had undergone surgery for the cervical anterior mass and for the laryngeal biopsy. Histopathological examination results were consistent with a SCC; neoplastic cells showed immunoreactivity to synaptophysin, neuron specific enolase and chromogranin. The serum levels of serotonin, cromogranin A, calcitonin, carcinoembryonic antigen, ACTH, PTH, TSH, FT4 were normal. Fine needle aspiration biopsy of her left thyroid lobe nodule was performed and the cytopathological exam was compatible with a neuroendocrine tumor metastasis. Thoracic and abdominal computed tomography was normal at that moment. Chest CT revealed the primary pulmonary tumor at 6 months after presentation. The therapeutic option for advanced or metastatic NETs is mainly palliation of symptoms; options need to be individualized and, therefore, rely on the knowledge of multidisciplinary teams.

Keywords: Pulmonary neuroendocrine tumor; Small cell lung carcinoma; Thyroid metastasis

Introducere

Tumorile pulmonare neuroendocrine (TPNE) reprezintă aproximativ 20% dintre toate tumorile primare ale plămânilor. Confirmarea histologică este importantă pentru tratament și determinarea prognosticului. În 2004, OMS a introdus sistemul de clasificare histologică a tumorilor anterior clasificate împreună drept „carcinoide" pulmonare. Acest sistem cuprinde patru subtipuri: tumori carcinoide tipice (CT) – cu grad mic de malignitate, tumori carcinoide atipice (CA) – cu grad intermediar, carcinomul cu celule mici (CNECm) și carcinomul cu celule mari (CNECM), ultimele două cu grad înalt de malignitate. CT și CA sunt clasificate împreună ca și „carcinoide", CNECM este considerat un subgrup, iar CNECm este o categorie independentă (Tabel I) [1].

Deși tiroida are o vascularizație bogată, metastazele de tumori solide în tiroidă sunt raportate rar (1,4%). Incidența acestora stabilită clinic este mai mică de 1%, dar studii pe atopsii seriate au evidențiat faptul că metastazarea în tiroidă a apărut până la 24% dintre pacienții care au decedat prin cancer [2]. Leziunile tiroidiene metastatice sunt datorate în majoritatea cazurilor carcinoamelor de sân, plămân, stomac, esofag, renal și melanomului [2,3]. Cele mai frecvente tipuri histologice de cancer pulmonar raportate cu metastazare în tiroidă sunt adenocarcinomul și carcinomul cu celule squamoase, urmate de CNECM. CNECm care reprezintă 15-20% dintre TPNE metastazează rar în tiroidă, în literatură fiind raportate cazuri izolate [3].

Prezentare de caz

Prezentăm cazul unei paciente în vârstă de 57 de ani care a fost internată în Clinica de Endocrinologie în 2009 pentru investigarea unei guși polinodulare însoțită de adenopatii latero-cervicale bilaterale, fiind trimisă din serviciul ORL. Laringoscopia directă efectuată în serviciul ORL a evidențiat țesut proliferativ subglotic. Principalele acuzele subiective au fost: disfonie intermitentă, tuse și dispnee la eforturi medii. Examenul obiectiv endocrin: IMC – 29,8 kg/m2, curbă ponderală constantă, gușă polinodulară, cu consistență crescută, mobilă la deglutiție, nedureroasă, cu multiple adenopatii latero-cervicale și supraclaviculare bilateral în conglomerat, ferme, aderente, imobile, nedureroase. Superior de glanda tiroidă, prelaringian formațiune tumorală de aproximativ 2/1,5 cm, fermă, mobilă. Fără alte modificări clinice obiective. Tensiune arterială – 120/75 mmHg, AV- 72/minut. Fără sindrom tumoral hipofizar și fără semne clinice de disfuncții endocrine, menopauza la 39 de ani, examenul senologic – fără formațiuni nodulare la palpare și fără secreție la exprimarea mameloanelor.

Ecografia regiunii cervicale anterioare (Figura 1) a confirmat prezența unei guși polinodulare însoțită de multiple adenopatii latero-cervicale și supraclaviculare bilateral cu caractere suspecte de malignitate. În regiunea cervicală anterioară, superior de glanda tiroidă conglomerat nodular hipoecogen, inomogen cu vascularizație peri- și intranodulară de 25/10mm. S-a intervenit chirurgical în serviciul ORL pentru extirparea formațiunii prelaringiene și s-a efectuat biopsie din țesutul proliferativ subglotic.

***Corresponding author:** Cristina Corina Pop Radu MD, Medic Primar Endocrinolog, Department of Endocrinology, University of Medicine and Pharmacy Târgu Mureș, Gheorghe Marinescu Street, No 38540139, Târgu Mureș, Romania, Tel: +40 (0) 265 21 44 10 / 236; E-mail: ccorinaradu@yahoo.com

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Tabel I: Clasificarea Histologică a TPNE [1].

Tipul tumorii	Aspecte histologice	Imunohistochimie	Grad de malignitate
CT	Arhitectură carcinoidă; < 2 mitoze/10HPF	Cg A; SNF; ENS; RS	Grad 1; scăzut
CA	Arhitectură carcinoidă; 2-10 mitoze/10HPF; necroză focală	Cg A; SNF; ENS; RS	Grad 2; intermediar
CNECM	Morfologie neuroendocrină (rozete organoide, cuiburi palisade, trabecule); celule mari cu raport nucleu/citoplasmă scăzut, cromatină veziculară sau fină; necroză	Expresie slabă a SNF și a ENS; mutații ale genei p 53	Grad 3; mare
CNECm	Dimensiuni mici; citoplasmă insuficientă; nucleu cu cromatină fin-granulară, nucleol absent sau vag conturat	Expresie slabă a SNF și a ENS; mutații ale genei p 53	Grad 3; mare

CT carcinod tipic; CA carcinoid atipic; CNECM carcinom neuroendocrin cu celule mari; CNECm carcinom neuroendocrin cu celule mici; CgA cromogranina A; SNF sinaptofizina; ENS enolaza neuron-specifică; RS receptori la somatostatină; HPF high-power field.

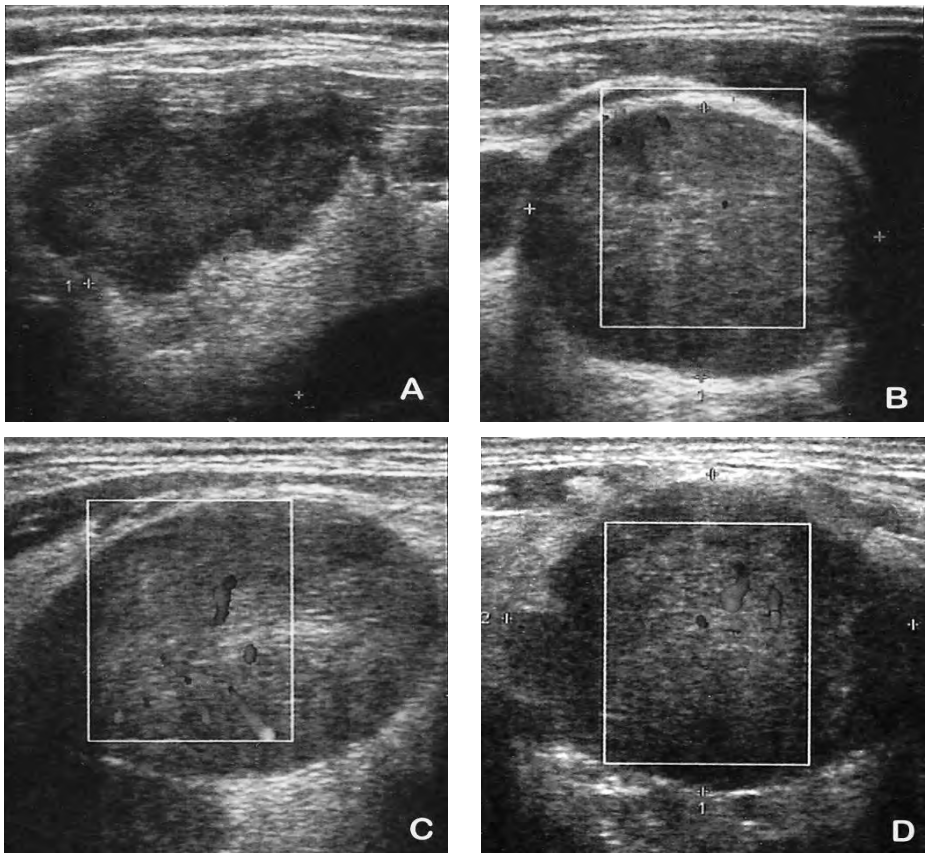

Figura 1: Ecografia tiroidiană A) Lob tiroidian stâng: anterior și inferior - macronodul cu dimensiuni de 27x14,4 mm, hipoecogen, inomogen, cu margini neregulate și vascularizatie intranodulara intensă la examinarea color flow-Doppler, ce invadează capsula anterioară. B, C, D) bilateral multiple formațiuni nodulare latero-cervicale și supraclaviculare hipoecogene, inomogene, cu vascularizație intranodulară, cu dimensiuni de 28,6x25,3 mm.

Examenul histopatologic (laringe și nodul limfatic) a evidențiat carcinom cu celule mici de tip neuroendocrin (celule cu citoplasma redusă, nuclei rotunzi-ovalari, fără nucleoli vizibili, cu atipie citonucleară marcată, dispuse în placarde sau trabecule, uneori cu formare de rozete), cu imunohistochimie pozitivă pentru sinaptofizină, enolaza neuron specifica (ENS) și focal pozitivă pentru cromogranină. Nivelele serice de CgA, serotonină, calcitonină, antigen carcinoembrionar (ACE), corticotropină (ACTH), parathormon (PTH), tireotropină (TSH), tiroxină liberă (FT4), prolactină (PRL) au fost normale. Acidul 5 hidroxi-indol-acetic urinar (5 HIAA) a fost de asemenea în limite normale (Tabel II).

Examenul citopatologic al punctiei tiroidiane cu ac fin a confirmat prezența carcinomului neuroendocrin cu celule mici la nivelul tiroidei (Figura 2 A-D).

Computer tomografia cervico-toraco-abdominală a evidențiat îngroșarea marcată a mucoasei peretelui posterior al traheeei în regiunea incipientă cu reducerea lumenului la jumătate. Multiple adenopatii supraclaviculare și latero-cervicale bilaterale cu dimensiuni până la 25 mm, în rest aspect pulmonar și abdominal normal. Examenul cardiologic cu ecocardiografie a diagnosticat o cardiopatie ischemică cronică cu angină pectorală de efort și minimă colecție pericardică. Radiografia de șa turcească: șa cu dimensiuni normale, cu contur inferior dublu și fin neregulat, cu osteoporoza dorsului selar și infraselar; calcificări supraselare de 8/5 mm. Pacienta a fost remisă serviciului de oncologie pentru efectuarea tratamentului de specialitate chimioterapie- radioterapie. Tumora primară pulmonară a fost vizualizată la 6 luni de la diagnosticul metastazelor tiroidiene prin examen computer tomografic toracic. Decesul a survenit la 1 an de la diagnostic.

Discuții

CNECm reprezintă 15-20% dintre TPNE. În ultimii ani incidența globală a CNECm a fost în scădere, datorită renunțării la fumat, dar s-a observat pe de altă parte o creștere a acesteia la sexul feminin, cu un raport pe sexe de 1:1. Prezintă mai multe subtipuri histologice și este adesea însoțit de activitate neuroendocrină [1]. Localizat cel mai adesea central, în 80 % din cazuri prezintă metastaze în momentul stabilirii

Tabel II: Markeri tumorali şi dozări hormonale.

Parametru	Rezultat	Interval de referinţă	Unitate de măsură
Cromogranina A	37	19 - 98	µg/l
Serotonina	68,9	117 - 190	µg/l
Calcitonina	4,22	< 13	pg/ml
ACE	1,2	< 3,4	ng/ml
ACTH	20	7,2 – 46	pg/ml
PTH	46	Jul-76	pg/ml
TSH	1, 89	0,4 – 3,45	µUI/ml
FT4	1,3	0,8 – 1,7	ng/ml
PRL	23	2,39 - 25	ng/ml
5 HIAA	4,3	9-Feb	mg/24 ore

ACE antigen carcinoembrionar; ACTH corticotropina; PTH parathormon; TSH tireotropina; FT4 tiroxina liberă; PRL prolactina; 5 HIAA acidul 5 hidroxi-indol-acetic urinar.

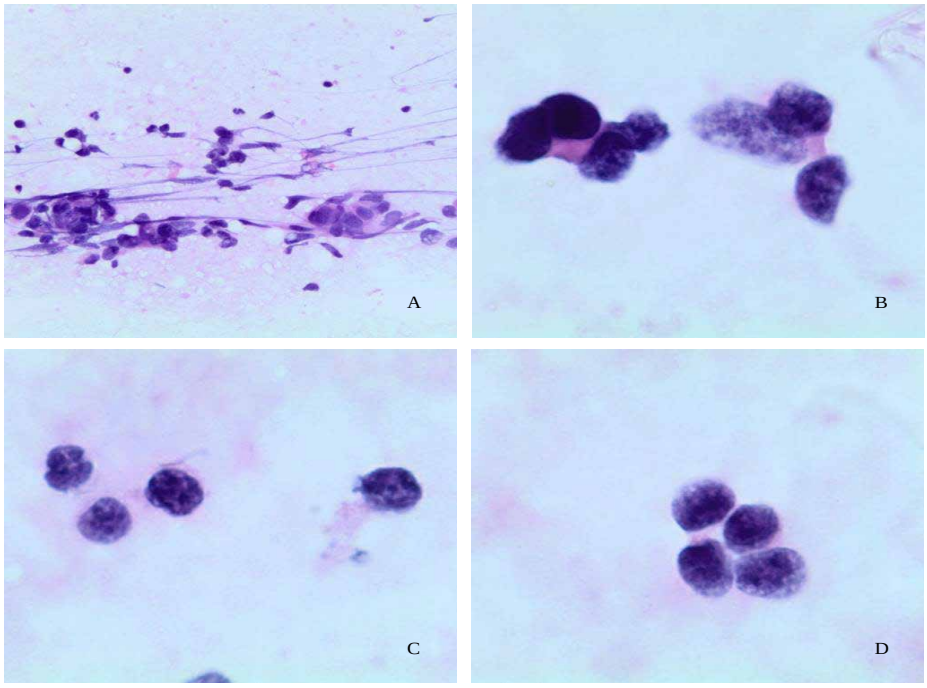

Figura 2: Examenul citopatologic al puncţiei tiroidiene - colorație Papanicolau. A) celularitate abundentă într-o metastază de tumoare neuroendocrină în tiroidă. B) celule cu nucleu mărit de volum și citoplasmă foarte puțină. Cromatină nucleară cu aspect granular. C, D) celule izolate, foarte discret pleomorfe, cu nuclei măriți de volum și cu aspect de tip endocrinoid al cromatinei nucleare.

diagnosticului. Metastazează preponderent pe cale hematogenă în plămânul controlateral, ficat, glande suprarenale, creier, oase, măduva osoasă [2,3]. Prezența metastazelor tiroidiene reprezintă este un semn de stadiu avansat de boală, adesea fiind asociate cu metastaze și în alte organe (rar evidențiabile clinic), pentru majoritatea pacienților decesul survenind în următoarele 9 luni de la diagnosticul acestora [2].

În combinație cu aspectul histologic, marker-ul de proliferare celulară Ki-67 pare să fie fie cel mai util marker de distincție între carcinoidele pulmonare (CT, CA) și formele cu grad înalt de malignitate (CNECm și respectiv CNECM). În determinarea diagnosticului diferențial o varietate de alți markeri tumorali pot fi de asemenea utili. Astfel, Cg A este exprimată 100% de carcinoidele pulmonare, 74% de varianta cu celule mari și 34% de CNECm. SNF în 97% de CT, 89% de CA, 65% de CNECM și 25% de CNECm. ENS este exprimată frecvent de toate carcinoidele (CT – 99%, CA – 85%, CNECM – 69%, CNECm – 100%). Serotonina este în mod obișnuit exprimată de CT și CA (67%, respectiv 50%) și rar de CNECm (11%) [4].

Tumorile agresive pot determina apariția de noduli tiroidieni dureroși cu creștere rapidă, simptome de compresie locală și uneori tireotoxicoză de însoțire determinată de tiroidita de distrucție [5]. Creșterea lentă a TNE bine diferențiate poate fi responsibilă pentru absența simptomelor locale și a tireotoxicozei prin distrucție, metastazele tiroidiene fiind diagnosticate și la 2-3 ani după diagnosticul TNE primare. Perioada medie de latență raportată în literatura de specialitate, între diagnosticul tumorii primare și cel al metastazelor tiroidiene a fost de 9 luni [3]. În cazul pacientei prezentate în acest articol modul de prezentare și respectiv diagnosticul CNECm a fost prin metastazele la distanță localizate în tiroidă, trahee, limfonoduli cervicali (anterior și latero-cervical bilateral), supraclavicular, tumora primară fiind vizualizată imagistic la 6 luni de la diagnostic.

Dacă diagnosticul tumorii primare nu este evident, metastazele tiroidiene de carcinom neuroendocrin poate duce la confuzii de diagnostic. Leziunile tiroidiene metastatice de TNE pot mima carcinomul medular pe citologie sau pe examen histopatologic (EHP). Markerii imunohistochimici: Cg A, ENS și SNF sunt pozitivi atât pentru carcinomul medular tiroidian, cât și pentru TNE metastatice [6]. TNE metastatice ar trebui să fie imunohistochimic negative pentru calcitonină și ACE, în timp ce carcinomul medular tiroidian este pozitiv la acești markeri tumorali (la colorare) [6,7]. Uneori, imunocolorarea pentru calcitonină poate fi pozitivă în TNE. A fost raportat faptul că în special, varianta cu celule mici de carcinom tiroidian medular seamănă cu CNECm [8,9].

Într-un studiu radiologic efectuat pe 11 cazuri de CNECm s-a constatat că toți pacienții au prezentat leziuni cu aspect radiologic similar, caracterizat de mase centrale asociate cu adenopatii coalescente cu aspect heterogen și infiltrativ, cu invadarea structurilor vasculare și a arborelui traheo-bronșic adiacent. Toate cazurile au prezentat și alte modificări toracice: leziuni pulmonare secundare, pneumonie, atelectazie, pleurezie și îngroșare pleurală. Pe radiografii caracterizarea maselor tumorale a fost în general mai dificilă, în special datorită prezenței atelectaziei și revărsatului pleural important. Metastaze la distanță au fost găsite la 10 pacienți (90%) la momentul diagnosticului, mai ales în oase și abdomen superior (ficat și glande suprarenale), evidente de la prima evaluare computer tomografică toracică. Leziunile care au putut fi măsurate au fost mai mari de 5 cm în diametrul lor cel mai mare, unele dintre ele fiind mai mari de 10 cm. Nu au fost identificate calcificări în nici o leziune. Toți pacienții au fost trimiși pentru tratament local sau sistemic cu evoluție progresivă nefavorabilă și deces în următoarele luni după confirmarea diagnosticului histopatologic [10].

Alegerea metodei de tratament depinde de: stadiul tumorii, tipul histologic, condiția clinică și biologică a pacientului. CNECm care nu este extins în afara cavității toracice are o rată de răspuns la combinația chimioterapie–radioterapie de 80– 90%. Pentru CNECm metoda de tratament de elecție este radio-chimioterapia, chirurgical intervenindu-se doar în cazuri selecționate de cancer localizat. Acest tip de cancer are o mare capacitate de diseminare, iar chirurgia nu îi poate opri evoluția [11,12]. Tratamentul cu analogi de somatostatină (Lanreotid, Octreotid) reprezintă un tratament pentru controlul simptomatologiei clinice produsă de secreția aminelor biogene și pentru reducerea nivelului unor markeri hormonali; are efect limitat în reducerea volumului tumoral, și aceasta la tumorile bine/moderat diferențiate, care prezintă receptori de somatostatin sensibili. Noi agenți terapeutici (aflați în studii privind eficacitatea) includ radioterapia cu analogi radioactivi de somatostatină și chimioterapia cu inhibitori de receptori tirozin-kinazici. Tratamentul pentru TPNE avansate sau metastatice fiind în principal paleativ, trebuie să fie individualizat și presupune echipe multidisciplinare [13-15].

Concluzii

Este important de a considera existența posibilității metastazelor la pacienții cu noduli tiroidieni, și mai ales atunci când există istoric de tumoră malignă primară. Nodulii tiroidieni detectați în timpul monitorizării pacienților cu TNE trebuie investigați cu atenție. Puncția tiroidiană cu ac fin poate confirma diagnosticul, în cele mai multe cazuri și poate preveni abordări inutile de tratament.

Conflict de interese

Autorul nu declară nici un conflict de interese.

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Journal of Surgery
[Jurnalul de Chirurgie]

Case Report Open Access

Spontaneous Osteonecrosis of the Medial Femoral Condyle: Case Report

Ovidiu Alexa[1]*, Dan Cionca[2], Samir Albetar[2] and Bogdan Veliceasa[1]

[1]Department of orthopedics and traumatology, "Gr.T. Popa" University of Medicine and Pharmacy Iași, Romania
[2]Department of orthopedics and traumatology, "St. Spiridon" Emergency Hospital Iași, Romania

Abstract

Spontaneous osteonecrosis of the knee presents with acute onset of severe pain in elderly patients, usually females, without a history of trauma. Originally described as idiopathic osteonecrosis, the exact etiology is still debated. Evidence suggests that an acute fracture occurs as a result of chronic stress or minor trauma to a weakened subchondral bone plate. We report one case of spontaneous osteonecrosis of medial femoral condyle in a 71-year-old female with no evidence of trauma involving a 4 cm weight bearing surface. According to Koshino this case can be classified as stage II. Various types of treatment have been reported, including conservative treatment with physical exercise and non-steroidal anti-inflammatory drugs, arthroscopy alone, arthroscopy and drilling, valgus high tibial osteotomy, and total knee arthroplasty. Total knee arthroplasty was considered the appropriate management strategy in this case.

Keywords: Medial femoral condyle; Osteonecrosis; Bone infarction

Introduction

Spontaneous osteonecrosis of the knee (SONK), first described in 1968, has been thought to be a distinct type of osteonecrosis. The lesion occurs most commonly in women 60 years of age and older [1-3]. SONK is characterized by acute onset of knee pain and can be differentiated from secondary osteonecrosis, which occurs secondary to such factors as corticosteroid therapy, systemic disorders, alcoholism, and Caisson disease [4].

Although the exact etiology of SONK remains unknown, two theories have been proposed: vascular insufficiency and trauma [1,2,5,6]. In a recent study, the primary pathology of SONK was demonstrated to be a subchondral insufficiency fracture and, in some cases, focal osteonecrosis confined the area between the fracture line and the articular surface [7].

The lesions can be classified into four stages according to Koshino's radiographic classification: stage I, no abnormalities on radiographs, stage II, a radiolucent oval area in the subchondral region or flattening of the medial femoral condyle (MFC), stage III, expansion of the radiolucent area with a sclerotic halo, and stage IV, secondary degenerative changes including osteophytes and osteosclerosis on both the tibial and femoral sides [8].

Various types of treatment have been reported including conservative treatment with physical exercise and non-steroidal anti-inflammatory drugs (NSAIDs), arthroscopy alone, arthroscopy and drilling, valgus high tibial osteotomy, and total knee arthroplasty [9,10].

Case Report

We report a case of spontaneous osteonecrosis of the knee investigated radiologically (X-ray and MRI) and arthroscopically.

A 71-year-old woman complaining of severe knee pain in the absence of a history of significant trauma and not responding to NSAIDs and physiotherapy was referred to our clinic in September 2013. Palpation of the medial femoral condyle elicited pain and a mild knee effusion was present.There was no varus or valgus malalignment.

Plain x-rays showed an osteolytic lesion in the weight bearing area of the medial femoral condyle with no sclerotic delimitations or articular degenerative changes (Figure 1).

Magnetic resonance imaging (MRI) showed a high intensity subchondral area in the weight bearig surface of medial femoral condyle surrounded by low signal intensity in the femoral condyle with undulating hypointense lines demarcating bone infarction (Figure 2).

Based on the diagnosis of stage 3 spontaneous osteonecrosis of the medial femoral condyle, arthroscopy was performed under spinal anesthesia in October 2013.

A partially detached fragment of articular cartilage with a 4 cm lesion on the weight-bearing area of the medial condyle which was excised and the other unstable small fragments and coexisting degenerative lesion of medial meniscus posterior horn were debrided (Figure 3). No other intraarticular injuries were identified.

Discussion

It is well known that the clinical course of this disease varies from remission with conservative treatment to severe dysfunction requiring surgical treatment [11].

The early form of SONK in middle aged patients usually resolves without surgical intervention. Yates et al. [12] have reported MRI prognostic criteria that indicate a benign course in the absence of a focal depression of the epiphyseal lining and the absence of deep, low signal intensity lines on the condyles. However, in the advanced stage of this condition some patients need surgical treatment. Locouvet et al. [13] concluded that initial MRI imaging characteristics indicative of an early irreversible osteonecrosis included a subchondral area of low signal intensity on T2-weighted images with a thickness of more than 4 mm or a length of more than 14 mm, focal epiphyseal contour depressions, and lines of low signal intensity located deep in the affected condyle.

***Corresponding author:** Ovidiu Alexa, MD, PhD, Department of Orthopedics and Traumatology, "St. Spiridon", Emergency Hospital Iași, Independenței Street No 1, 700111, Iași, Romania, Tel: +40 (0) 722 45 80 78; E-mail: ccorinaradu@yahoo.com

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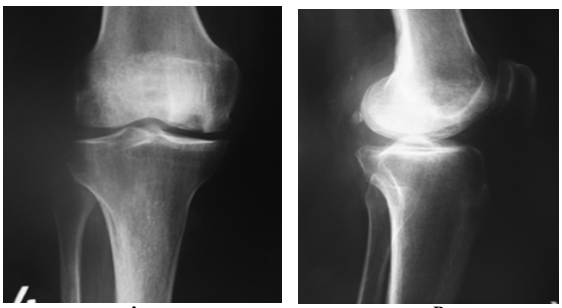

Figure 1: Knee X-ray (A: Antero-Porterior View, B: Lateral View): Osteolytic Lesion of Medial Femoral Condyle.

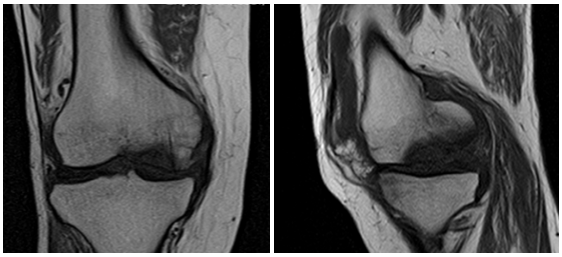

Figure 2: Knee MRI: Bone Infarction in the Medial Femoral Condyle.

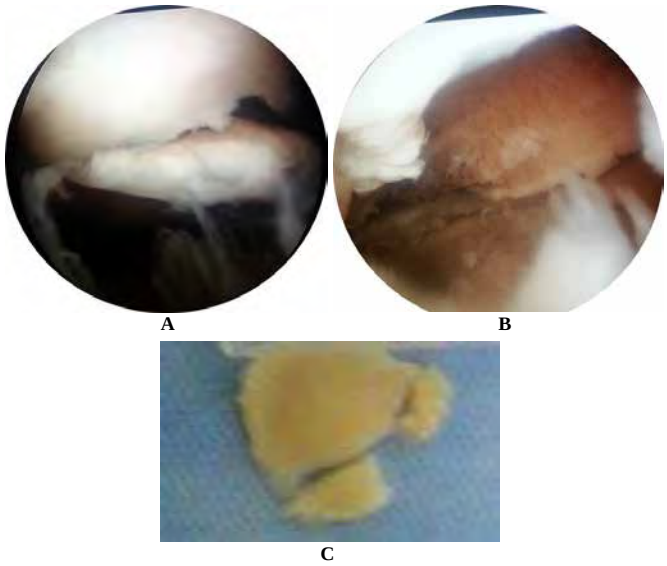

Figure 3: A&B: Operative Arthroscopic Imagines; C: Detached Articular Cartilage Fragment.

In stage II or higher stages when these radiographic findings are visible on X-rays, the clinical course and prognosis were reported to depend on the radiographic size of the lesion. Some authors reported that when a more than 50% of the occupied ratio of the lesion, and more than 5 cm square of the lesion area, the patient had a poor clinical and radiographic prognosis with rapid development of osteoarthritis and surgical treatment was recommended [14,15].

In the early stage of the disease, the non-operative treatment is indicated, and many patients, if diagnosed early, have a benign course with satisfactory pain relief and good knee function [15]. Conservative treatment is also supported by evidence that lack of immobilization and continued weight bearing could eventually result in further displacement, subchondral collapse and subsequent extension of necrosis.

Soucacos et al. [9]. suggested that patients in stages 1 and 2 be treated by conservative management and in stages 3 and 4 be treated by surgery according to the size of the lesion. Lotke et al. [11]. suggested that surgical treatment should be considered when femoral condyle rate is over 50%. Aglietti et al. [2]. suggested that prognosis is poor when femoral condyle rate is over 40% and the lesion is over 5 cm^2.

Koshino et al. [8] employed arthroscopy to evaluate knees with spontaneous osteonecrosis. They concluded that in the early stages of osteonecrosis, fissures and flattening of the articular cartilage, with or without formation of a cartilage flap, were useful findings in choosing intra-articular surgical procedures. Similarly, in the late stages the presence of loose bodies and regeneration of fibro-cartilaginous tissue over the necrotic lesion also helped in the selection of surgical intervention [16].

Core decompression by extra-articular drilling into the femoral condyle has been recommended as an effective treatment in the initial stages [17,18]. Akgun et al. [19] evaluated the microfracture technique and concluded that it is safe, simple, and cost-effective, and may be an alternative procedure for treatment of SONK, especially in young patients, before possible subsequent replacement surgery.

The best results are achieved with osteotomy combined with arthrotomy, or by knee replacement arthroplasty. If the stage of SONK is 3 or higher, the treatment of choice is arthroplasty [17]. Arthoplasties of the knee can be either total or unicompartmental. Reports have shown variable results of each method [14,20,21]. Marmor [22]. obtained good clinical results in 30 cases of 34 patients who had unicompartmental knee arthroplasty. However, two patients got revision arthroplasty due to depression around where they had surgery and two patients got revision arthroplasty due to newly forming lesions in the lateral condyle of the femur. Radke et al. [21] reviewed 39 cases. Of these, 23 underwent unicompartmental knee arthroplasty and 16 total knee arthroplasty. With and average follow-up of more than 5 years, they reported better clinical ourcomes in the patients who underwent total knee arthroplasty. In patients who underwent unicompartmental knee arthroplasty, four had a revision arthroplasty. However, they reported that the main causes of poor results of unicompartmental knee arthroplasty are inadequate operative technique and patient selection. Recently, good clinical results and high long-term survival rates of unicompartmental knee arthroplasty have been reported due to improvement of surgical technique, component design, and strict selection criteria [20,23].

Our case can be classified as Koshino stage II with no sclerosis halo but with a big defect-4 cm, 71-year-old pacient, so we thought total knee arthroplasty to be the appropriate management method.

Conclusion

Osteonecrosis of the knee is a debilitating disease that is poorly understood. Typically, initial treatment involves nonsurgical measures, such as limited weightbearing, for small and medium lesions. Surgical options are used with large lesions. We need more prospective, randomized studies, which may be difficult to conduct due to the small number of patients. We need to maintain a high index of suspicion for these disorders because early diagnosis and treatment may allow for an improved clinical outcome. Continued study of patients with SONK is needed in an effort to identify specific risk factors that predispose certain patients to their development.

Conflict of interests

Authors have no conflict of interests to disclose.

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Journal of Surgery
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Case Report Open Access

Laparoscopic Cholecystectomy in a Patient with Portal Cavernoma

Nilanjan Panda[1]*, Ruchira Das[2], Subhoroto Das[1], Samik K Bandopadhyay[1], Dhiraj Barman[1] and Ramakrishna Mondol[2]

[1]Department of Surgery, R.G. Kar Medical College & Hospital, Kolkata, West Bengal, India
[2]Department of Surgery, Bankura Sammilani Medical College and Hospital, Gobindonagar, Bankura, West Bengal, India

Abstract

Portal cavernoma (network of collateral vessels around the portal vein) is found in one-third of patients with thrombotic portal vein. Management of Cholecystitis in such a patient is problematic. Laparoscopic cholecystectomy is usually contraindicated due to risk of haemorrhage.

A 32 year old female presented with symptomatic calculous cholecystitis and portal cavernoma without portal hypertension. Liver functions were normal (non-cirrhotic, no jaundice). Conservative treatment failed. Imaging assessment was by Ultrasound Doppler, followed by CT and MRCP, MRI and MRA.

We performed laparoscopic cholecystectomy was successfully performed. Operative time 210 minutes, blood loss 50 ml. Extreme caution and painstakingly meticulous dissection around the cavernoma was the key to success. Although open cholecystectomy may assume to be safer in such patients; enhanced magnified vision, access and maneuverability made laparoscopy a preferred option. Standby laparoscopic and open vascular instruments facility is essential.

Keywords: Portal cavernoma; Laparoscopic cholecystectomy; Portal thrombosis

Introduction

The network of collateral vessels around the portal vein, a so-called portal cavernoma, is typical of chronic portal vein thrombosis (PVT) with or without portal hypertension. They surround the Calot's triangle and gallbladder fossa, making management of calculous cholecystitis in such patients controversial [1]. We report successful laparoscopic cholecystectomy in such a case.

Case Report

A 32 year old female presented with history of pain upper abdomen for two years without jaundice or upper GI bleeding. Physical examination showed no feature of acute cholecystitis or hepatosplenomegaly. Blood investigations including liver function tests were normal. Ultrasonography revealed thick walled gall bladder with multiple calculi. Multiple vascular collaterals were seen at porta hepatic. Bile duct was normal. Liver was non cirrhotic and there was no portal hypertension. A portal vein Doppler showed extensive cavernoma with normal hepato-portal flow in collaterals. A Computed Tomography (CT) of abdomen suggested no definite main portal vein (proximal splenic and superior mesenteric vein visualized) with extensive collaterals from the head of the pancreas extending to root of the mesentery below and right and left branch of portal vein above. A MRCP (Magnetic Resonance Cholangio Pancreatography) with MR angiography was done (Figures 1 and 2). It showed partial extrinsic compression on the CBD (common Bile Duct) by collaterals. There was occlusion of the main portal vein from the spleno-portal confluence to portal bifurcation. Cavernous transformation was covering Calot's triangle. Upper Gastrointestinal endoscopy was normal. The cause for cavernoma formation was unknown. The patient was posted for laparoscopic cholecystectomy.

Standard four port technique was used. Falciform ligament was carefully avoided to prevent umbilical vein trauma. Gall bladder was free in the fundus area where traction was applied. There was no adhesion around the gall bladder. As anticipated, the cavernous transformation was mainly covering the neck and Hartmann's pouch. A fundus first approach was used to gently free the gall bladder from the few cavernous veins coursing along the gall bladder body into GB fossa (Figure 3). Near the Calot's triangle, gentle dissection between the peritoneal folds separated cystic artery and duct from the cavernoma. Duct and artery was clipped and gall bladder dissected out. A prophylactic drain was placed in hepato-renal pouch of Morrison. Operating time was 210 min, blood loss was approximately 50 ml. Postoperative recovery was uneventful. Patient was discharged on first postoperative day.

Discussion

Cavernous transformation of portal vein is the development of a network of tortuous collateral vessels bypassing the obstructive area due to PVT. It is seen in one-third of patients with thrombotic portal vein [1]. The transformation can take place as early as a week although it usually takes months. Localised abdominal inflammations like cholecystitis, pancreatitis, hydatid cyst, duodenal ulcer and iatrogenic injury predisposes to this condition [2]. Laparoscopic cholecystectomy is usually contraindicated in these patients due to multiple collaterals near the gall bladder, which increases the risk of intraperitoneal haemorrhage. On literature review, we found only one such case report [3]. In our patient, favourable factors were normal liver architecture without cirrhosis and no portal hypertension.

Pulsatile collaterals suggesting high intravascular pressure seen intra-operatively was challenging. Extreme caution and painstakingly meticulous dissection around the cavernoma was the key to success.

***Corresponding author:** Nilanjan Panda MS, P 318 b, CIT Road, Scheme 6 M, Kankurgachi, Kolkata, West Bengal, India, Pin – 700054, Tel: +91 97 48 77 49 42; +91 33 23 62 90 07; E-mail: mailto:npanda05@aol.com

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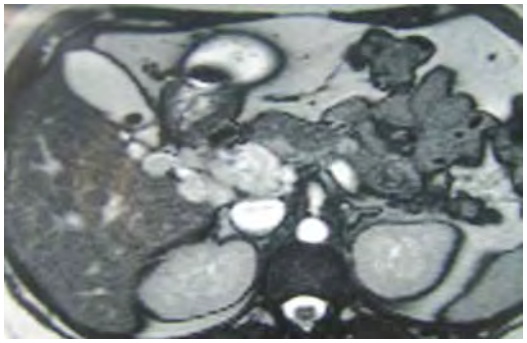

Figure 1: MRI Picture Axial Cut.

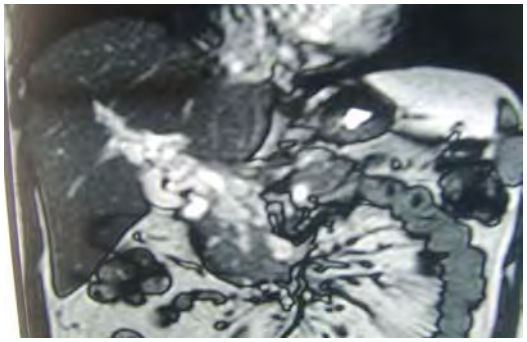

Figure 2: MR Angiography Reconstruction - Coronal Cut.

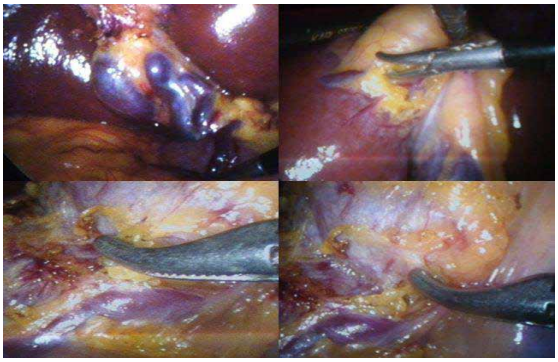

Figure 3: Intra-Operative Picture.

Harmonic energy source and taking very small bites of tissue at a time was helpful. Patient was discharged on first post-operative day. Although open cholecystectomy may assume to be safer in such patients; enhanced magnified vision, access and maneuverability made laparoscopy a preferred option.

For diagnosis ultrasound with Doppler showing absent portal vein with high echo (diamond sign) and multiple serpentinous channel is sufficient but for operative planning MRCP and MRI and MRA / venography /dynamic CT is essential [4].

In the absence of cirrhosis and neoplasia, portal cavernoma is usually asymptomatic until the first variceal bleeding and has a better prognosis [5]. Intestinal ischemia or portal biliopathy may rarely develop. No treatment for the cavernoma per-se is warranted.

Conclusion

We conclude that with careful dissection and experience, laparoscopic cholecystectomy is a safe procedure in patients with portal cavernoma and symptomatic cholelithiasis. Standby laparoscopic and open vascular instruments facility is essential.

Conflict of interests

Authors have no conflict of interests to declare

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Journal of Surgery
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Method Open Access

New Vascular Ligation Technique Applied in Liver Transplantation

Radu Zamfir[1]*, Vladislav Brașoveanu[1], Leonard David[1], Cristian Lupașcu[2], Florin Cristian Blăjuț[1], Tudor Stoian[1], Luiza Țircă[1] and Irinel Popescu[1]

[1]Fundeni Clinic Institute, Center of General Surgery and Liver Transplantation "Dan Setlacec" București, "Carol Davila" University of Medicine and Pharmacy București, Romania

[2]Department of Surgery, "Gr.T. Popa" University of Medicine and Pharmacy Iași, Romania

Abstract

Liver procurement is a race against time, which is mainly focused on obtaining a good quality of liver grafts with an ischemia time as short as possible. The actual procurement time definitely influence cold ischemia time, a reduction of it leading to shorter graft cold ischemia time.

Methods: We examined the use of tire-ups in the liver procurement, in terms of improving the procurement time (calculated as the time between incision and the time of starting infusing portal vein and aorta with cold preservation solutions).

Results: We enrolled in our study two groups of 30 donors each. In the first group we included patients on which we did not use the tire-ups, and in the second patients on which the tire-ups were used for dissection and rapid clamping of the infrarenal aorta and the portal vein. Procurement time in group 1 averaged 121.6 minutes (+/- 20.2 minutes) and in the second batch averaged 88 minutes (+/- 16.2 minutes), with statistical significance ($p<0.05$). We observe a reduction of about 30 minutes between batches, reduction which was possible using tire-ups in rapid dissection and clamping of the portal vein and aorta.

Conclusions: The use of tire-ups are a simple, cheap and feasible to shorten operative time in liver procurement. It can be successfully applied to all donors shortening the actual time of sampling, with direct consequences to cold ischemia time.

Keywords: Liver transplantation; Liver procurement; Tire-up; Vascular ligation

Introducere

Prelevarea hepatică, de obicei parte a prelevării multiorgan, reprezintă etapa premergătoare transplantului hepatic și are ca obiectiv furnizare unei grefe hepatice cât mai bune, în condițiile preexistente legate de donator, cu un timp de ischemie cât mai scurt. Mai multe studii retrospective, analizând variabile legate atât de primitor cât și de donator, au identificat factori de risc predictivi pentru supraviețuirea grefei și a pacientului după transplantul hepatic de la donator aflat în moarte cerebrală.

Factorii de risc legați atât de donator cât și de primitor care au influențat negativ supraviețuirea includ vârsta donatorului, sexul, testele funcționale hepatice, durata spitalizării în secția de Terapie Intensivă, folosirea de agenți vasopresori, scorul MELD al primitorului, insuficiența renală, timpul de protrombină (PT) crescut și nu în ultimul rând durata prelevări [1-4]. Timpul efectiv de prelevare influențează categoric timpul de ischemie rece, o reducere a acestuia ducând la scurtarea timpului de ischemie rece a grefei [5].

Unul din timpii importanți din cadrul prelevării hepatice îl constituie disecția și canularea arterei aorte și a venei mezenterice inferioare [4]. Acest pas asigură izolarea, din punct de vedere vascular, a grefei, ce împiedică distribuirea soluției de prezervare către alte organe [6]. Tehnica actuală presupune disecția și ulterior ligatura aortei infrarenale și cu fir de Silk 2. Vom prezenta în acest studiu o metoda modernă de reducere semnificativă a timpului de ischemie rece folosind benzile de plastic tire-up (Figura 1).

Material și metodă

Am analizat două loturi a 30 de donatori de grefă hepatică. În cel de-al doilea lot au fost incluși pacienții la care s-a folosit metoda de disecție și ligaturare cu tire-up-uri. Cei 30 de donatori din primul lot au fost selectați retrospectiv din totalul donatorilor la care s-a practicat prelevare hepatică în perioada ianuarie 2013-aprilie 2014. Au fost analizate vârsta, sexul, IMC astfel încât să existe un case-match între cele două loturi de donatori (Tabel I).

Metoda de disecție și ligaturare a arterei aorte și a venei mezenterice inferioare

În cadrul prelevării hepatice, după disecția ficatului, pentru izolarea vasculară a grefei hepatice se ligaturează și canulează artera aortă infrarenală și vena mezenterică inferioară (pentru perfuzarea cu soluție de prezervare pe vena portă) și se ligaturează artera aortă deasupra trunchiului celiac. Ligaturarea și fixarea canulelor în artera aortă și în vena mezenterică inferioară se realizează clasic cu fir de Silk 2. Acest timp al prelevării poate fi scurtat prin folosirea benzilor de plastic tire-up (Figura 1).

Pentru disecția și canularea arterei aorte infrarenale, se introduce un tire-up de 4 mm grosime pe sub artera aortă infrarenală și se strânge. În continuare, pentru canularea arterei se introduce în aceiași manieră

***Corresponding author:** Radu Zamfir, MD, Fundeni Clinic Institute, Center of General Surgery and Liver Transplantation "Dan Setlacec" Șoseaua Fundeni, No. 258, Sector 2, București. Romania, Tel: +40 (0) 744 34 00 70; E-mail: rdzamfir@yahoo.com

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Tabel I: Datele Donatorilor.

	Lot 1	Lot 2
Vârsta (ani)	42 ± 10	44 ± 8
Sexul (B / F)	18-Dec	17-Dec
IMC (kg/m²)	29 ± 3	30 ± 3

Figura 1: Banda de plastic tire-up.

un tire-up (tot de 4 mm) 2 cm mai sus, se strânge parţial şi se incizează aorta urmând a se introduce canula.

După introducerea canulei se strânge complet şi cel de-al doilea tire-up, în acest mod realizându-se canularea aortei. Tot procesul durează în medie 20 secunde (Figura 2-4).

Pentru canularea venei porte via vena mezenterică inferioară (VMI), se introduce un tire-up de 2 mm grosime pe sub vena mezenterică inferioară şi se realizează ligaturarea. Cel de-al doilea tire-up se introduce şi se strânge parţial. Apoi se realizează o incizie la acest nivel pe unde se introduce canula de portă, ulterior se strânge complet tire-up-ul în acest mod realizându-se canularea venei porte. Tot procesul durează în medie 15 secunde (Figura 5-7).

Înainte de începerea perfuzării cu soluţie de prezervare a grefei hepatice se ligaturează artera aortă deasupra emergenţei trunchiului celiac. Clasic acest pas se realizează tot cu fir de Silk 2. Pentru acest studiu am folosit tire-up-uri de 4 mm lăţime care au fost plasate pe aorta descendentă toracică, deasupra hiatusului esofagian (Figura 8).

În cursul dezvoltării acestei metode am observat o mai bună ligaturare a arterei aorte în special în cazul aortelor ateromatoase sau calcificate, lăţimea mai marea a tire-up-urilor faţă de firul clasic de Silk 2 asigurând distribuirea forţelor de strângere pe o suprafaţă mai mare, ce reduce semnificativ riscul de rupere a vasului.

Rezultate

Am analizat timpul de prelevare, calculat ca fiind timpul dintre incizie şi începerea perfuziei cu soluţii reci a portei si a aortei. Durata medie a prelevării la donatorii din lotul 1 a fost de 121,6 ± 20,2 minute. Prelevarea la donatorii din lotul 2 a durat în medie 88 ± 16,2 minute (Figura 9).

Această diferenţa este semnificativă statistic (p=0.036), demonstrând că noua metodă reduce cu mai mult de 30 minute durata prelevării şi deci a ischemiei reci.

De asemenea am mai analizat şi siguranţa ligaturilor cu fir de Silk 2 şi cu tire-up-uri; în cazul a 10 pacienţi (33,3%) din lotul 1 (prelevare hepatică în metoda clasică) şi a 12 pacienţi (40%) din lotul 2 (prelevare hepatică folosind tire-up-uri) arterele aorte infrarenale prezentau calificări. Aceste calcificări au impus un al doilea fir de Silk 2 pentru ligatura în siguranţă a aortei în cazul donatorilor din lotul 1. Pentru donatorii din lotul 2 tire-up-ul a fost suficient pentru ligatura în siguranţă a aortei.

Discuţii

Procedura de transplant hepatic poate fi divizată în trei faze: prelevarea, ischemia rece şi implantarea. Îmbunătăţirile aduse celor trei faze, aduce cu sine şi o creştere a supravieţuirii grefei [7,8].

Există actual trei tehnici de prelevare a ficatului pentru transplant: tehnica clasică, tehnica rapidă (aplicată donatorilor instabili) şi o tehnică care le îmbină pe cele două anterior amintite. De cele mai multe ori condiţiile clinico-biologice ale donatorului impun folosirea unei anumite tehnici.

Utilizarea tire-up-urilor pentru disecţia şi ligatura vasculară reprezintă o metoda rapidă de control vascular al grefei hepatice, care poate fi utilizată în toate procedeele de prelevare hepatică.

Aplicabilitatea utilizării tire-up-urilor poate fi extinsă în cazul confecţionării acestora din materiale inerte, şi la alte tipuri de intervenţii chirurgicale, de la chirurgia deschisă (pentru controlul vascular rapid) la chirurgia laparoscopică.

Timpul de ischemie influenţează semnificativ calitatea grefei, iar uneori, datorită unor factori extrinseci procesului de prelevare hepatică, aceasta poate fi compromisă definitiv [9,10]. Aceşti factori

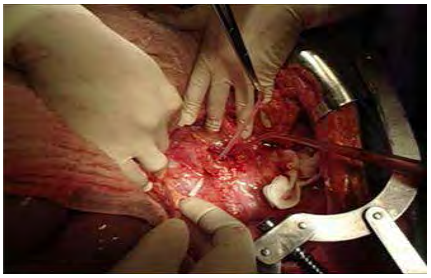

Figura 2: Montarea primului tire-up–ligatura aortei infrarenale.

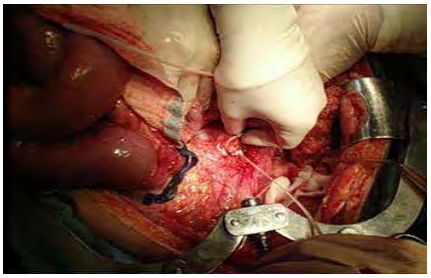

Figura 3: Montarea şi strângerea parţială a celui de-al doilea tire-up la nivelul arterei aorte infrarenale.

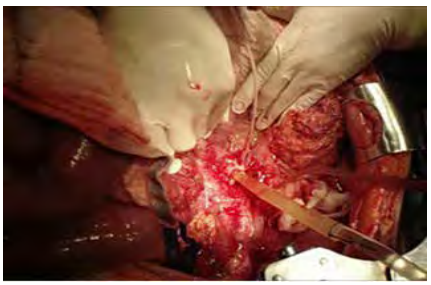

Figura 4: Aspect final–ligatura şi canularea artera aortă infrarenală.

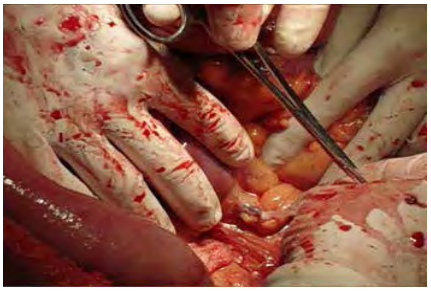

Figura 5: Ligatura venei mezenterice inferioare folosind tire-up-ul.

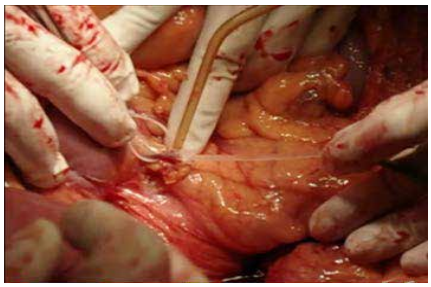

Figura 6: Introducerea celui de-al doilea tire-up la nivelul VMI și strângerea lui parțială.

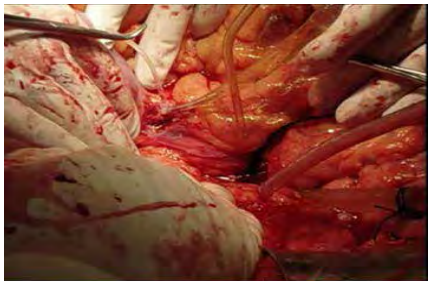

Figura 7: Ligatura și canularea VMI–aspect final.

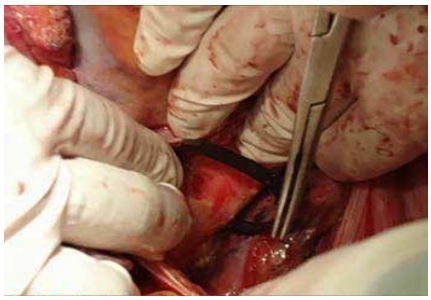

Figura 8: Ligatura aortei supradiafragmatice.

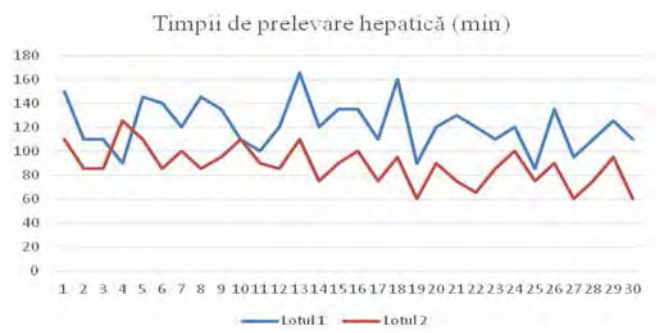

Figura 9: Timpul operator pentru cele două loturi de pacienți.

extrinseci, care țin de cele mai multe ori de metoda de transport a grefei din centrul de prelevare în centrul de implantare nu pot fi tot timpul controlați.

De aceea trebuie controlați factorii intrinseci procesului de prelevare și anume o disecție rapidă a grefei și un control vascular sigur si rapid, in condițiile pe care le "impune" donatorul [11].

Concluzii

Utilizarea tire-up-urilor reprezintă o metoda simplă, ieftină și fezabilă de scurtare a timpului operator în prelevarea hepatică. Ea poate fi aplicată cu succes la toți donatorii scurtând timpul efectiv de prelevare, cu consecințe directe asupra timpului de ischemie rece. Deasemenea ea poate fi aplicată cu succes la donatorii instabili sau Non-heart-beating donor NHBD scurtând timpul de ischemie caldă a grefei hepatice, oferind o grefă de mai bună calitate datorită începerii mai rapide a perfuzării cu soluţii reci de prezervare.

Conflict de interese

Autorii nu au niciun conflict de interese.

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Current Possibilities of Treatment in Pelvic-Perineal Floor Dysfunctions

Simona Niculescu[1]*, Ana Maria Enăchescu[2], Dan Niculescu[2] and Mircea Onofriescu[3]

[1]Department of Obstetrics and Gynecology, 3rd Obstetrics and Gynecology Unit, Elena Doamna Hospital of Obstetrics and Gynecology, Gr.T. Popa University of Medicine and Pharmacy Iaşi, Romania
[2]Department of Surgery, St. Spiridon Hospital Iaşi, Romania
[3]Department of Obstetrics and Gynecology, 3rd Obstetrics and Gynecology Unit, Cuza Vodă Hospital of Obstetrics and Gynecology, Gr.T. Popa University of Medicine and Pharmacy Iaşi, Romania

Abstract

To support through personal experience the use on a large scale of the modern techniques of correction of the pelvic floor disorders by using polypropylene prosthetic devices.

Objectives: To specify the technical details regarding the correct placement of prostheses in feminine genital prolapse. Show the personal casuistry in order to highlight the indications techniques and results of these types of surgeries. Plead for expending the modern techniques in pelvic-perineal floor dysfunctions.

Material and Methods: The study was performed between July 2007 and July 2013, in the second surgical Clinic St.Spiridon Hospital Iasi, on 138 cases with different pelvic floor dysfunctions. Different procedures were practiced, isolated or associated, on the patients in the lot, depending on symptoms, the prolapse type and degree, age, local anatomical situation and the existence or absence of sexual life. Thus they were performed: strip urethrocystopexy or "hammock" device, with four arms transobturator - 68 cases; The sacrosciatic posterior colposuspension or the anal levator floor restoration–29 cases; abdominal colpopexy in 41 cases, 18 of which with hysterectomy or resection of residual cervix. In 5 cases a polypropylene mesh implant has been associated with this procedure at anal levator level; and in 11 cases the doctors used a suburethral transobturator vaginal strip for stress urinary incontinence (SUI). The abdominal approach allows the correct path of skeletonization of the internal genitalia and also of the vagina which is turned inside-out like a glove finger, avoiding damage on the ureters and bladder. The vaginal vault is secured to the promontory with a polypropylene device and it ensures the results maintain in time.

Results: The treatment of the different pelvic-perineal floor disorders that are associated or not with stress urinary incontinence has benefited lately from new indications and techniques by using different prosthetic devices made of polypropylene, which are especially conceived and placed through minimally invasive procedures. Generally, all the cases had an immediate simple postoperatory evolution with only two haematomas that required surgical evacuation and 3 cases of vaginal mucosa necrosis, one of them requiring the removal of the device implanted. The anatomical and functional results were good.

Conclusions: The use of strips, nets and polypropylene devices in correcting different pelvic floor disorders, shows certain advantages, as it is relatively easy tom implement, the hospitalization period is shortened and there are very good results that pass the test of time.

Keywords: Pelvic-perineal floor dysfunctions; Stress urinary incontinence; Prosthetic devices

Introducere

Tulburările de statică pelviperineală apar prin deplasarea organelor susținute în mod normal de planșeul pelviperineal, perete vaginal anterior, uter, bolta vaginală, perete vaginal posterior, eventual antrenând și organele învecinate – vezică urinară, uretră , rect [1].

Bump et al consideră [2]:

- Prolaps de compartiment anterior – coborârea joncțiunii uretro-vezicale la mai puțin de 3 cm deasupra inelului himeneal.
- Prolaps de compartiment mijlociu – coborârea bolții vaginale la mai puțin de 2 cm de inelul himeneal.
- Prolaps de compartiment posterior cu coborârea – jumătății peretelui vaginal posterior la mai puțin de 3 cm de inelul himeneal [3].

Deseori acestor tulburări de statică pelviperineală li se asociază incontinența urinară de efort (IUE) [4].

Scopul acestei lucrări este de a sustine prin experienta personală a utilizării pe scară cât mai largă a tehnicilor moderne de corectare a tulburărilor de statică pelviperineală prin protezare cu dispozitive de polipropilenă.

Material și metodă

În perioada Iulie 2007-Iulie 2013 au fost rezolvate prin protezări diverse un număr de 138 de cazuri cu diferite tulburări de statică pelvină. La bolnavele cuprinse în lot sau practicat izolat sau asociat diferite procedee în funcție de diagnostic, simptomatologie, tipul și gradul prolapsului, vârsta, situație anatomică locală, existența sau nu a vieții sexuale.

Diagnosticul a fost stabilit prin anamneză, examen clinic, ecografie și probe funcționale. Anamneza a evaluat:

***Corresponding author:** Simona Niculescu, MD, PhD, Elena Doamna Obstetrics and Gynecology Hospital, Iasi, Elena Doamna Street, No 29, 700398, Iasi, Romania, Tel: +40 (0) 232 21 03 90; E-mail: enachescu_anamaria@yahoo.com

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factorul declanşator – naşteri, intervenţii chirurgicale, menopauza, accidente neurologice,

vechimea tulburării,

gradul de invaliditate, răsunetul socioprofesional şi sexual,

evoluţia în timp a simptomatologiei,

tratamente efectuate anterior.

Examenul clinic, principalul nostru mijloc de diagnostic a fost efectuat în ortostatism şi în poziţie ginecologică, cu ambele valve dar mai ales cu o singură valvă folosind manevre cunoscute pentru provocarea pierderii de urină sau care sa simuleze corecţia chirurgicală a incontinenţei [5].

Diagnosticul cuprinde în afară de evaluarea biologica generală, dimensionarea ecografică a poziţiei joncţiunii vezico-uretrale, examenul citobacteriologic vaginal, urocultură, stabilirea în final a riscului anestezico- chirurgical [5].

Uretrocistopexia transobturatorie [6,7] s-a realizat pe cale vaginală printr-o incizie longitudinală pe peretele anterior al vaginului, până la 1 cm de meat urmată de disecţia laterală a peretelui vaginal şi vezicii urinare până la eliberarea marginii inferioare a găurii obturatorii.

O mica incizie de 3 mm situată la 3-4 cm de linia mediană, aproximativ la mijlocul distanţei dintre meat si clitoris, permite introducerea perforatorului ghid dinafară-înauntru străbătând membrana obturatorie la rasul marginii osoase superioare a ramului ischiopubian, până în vagin prin breşa special pregătita. Aici este ataşat braţul protezei care este tras apoi dinăuntru-înafara şi exteriorizat transobturator la tegument [8]. Procedând similar de partea controlaterală o bandeletă suburetrală este montată si peretele vaginal poate fi închis prin surget continuu de fir lent rezorbabil, după verificarea hemostazei.

Pentru amplasarea unui dispozitiv cu patru braţe în "hamac" suburetral, intervenţia urmează aceeaşi pasi [9] doar că disecţia laterală a peretelui vaginal se face pe o lungime mai mare, cu eliberarea marginii ischio-pubiene pe o lungime mai mare iar la tegument se mai face o mica incizie la aproximativ 4 cm mai jos de prima, ce va permite perforatorului sa străbată din nou membrana obturatorie pentru exteriorizarea braţului "hamacului" de polipropilenă. Dispozitivul se tensionează treptat prin tracţiuni pe braţele exteriorizate la piele si având în vedere respectarea unui spaţiu de 2 mm suburetral [10]. Închiderea plăgii vaginale se face similar ca în cazul bandeletei simple.

Colposuspensia posterioară reprezintă soluţia optimă pentru prolapsul de compartiment posterior. Prin incizia longitudinală a peretelui vaginal posterior se disecă lateral cu evidenţierea peretelui rectal până la ridicatori şi se împinge rectul către partea mediană progresiv în sus până la evidenţierea spinei sciatice şi sub aceasta a ligamentului sacrosciatic. Printr-o mică incizie situată la 4 cm lateral de anus, se introduce perforatorul ghid prin spaţiu pararectal creat cu străbaterea ligamentului sacrosciatic şi apoi cu ancorarea şi tragerea dinăuntru-înafară a braţului dispozitivului protetic de polipropilenă. Acesta are forma unui ”maieu” ale cărui ”bretele” se exteriorizează cu ajutorul perforatorului paraanal drept şi stâng, marginea superioară fiind fixată la limita colpocervicală posterioară iar marginea inferioară eventual ajustată, la centrul de rezistenţă perineală. Hemostaza si închiderea tranşei vaginale finalizează procedeul.

Nu în ultimul rând, informarea completă a bolnavei este obligatorie si consimţământul informat al acesteia este semnat pe un formular special conceput.

Rezultate şi discuţii

În ceea ce priveste vârsta, bolnavele au fost încadrate între 30 si 85 de ani cu predominanţă clară a decadelor V, VI, VII, în peste 50% din cazuri.

La bolnavele noastre am apreciat gradul de incontinenţă ca fiind:

gradul I – la efort brusc (manevra Valsalva) în 21 de cazuri,

gradul II – în ortostatism sau la efort mare (ridicări greutăţi , alergare, etc.) în 27 de cazuri,

gradul III incontinenţa în repaus (clino sau ortostatism) în 20 de cazuri (Figura 1).

Ca indicaţie apropiată fiecărei situaţii, la bolnavele din lotul menţionat, au fost realizate următoarele procedee:

Uretrocistopexie cu bandeletă sau dispozitiv ”in hamac” cu patru braţe transobturator - 68 de cazuri,

Colposuspensie posterioară (Figura 2) sacrosciatică sau uneori colpoperineorafie posterioară cu refacerea planşeului ridicătorilor anali - 29 de cazuri,

Colpopromontopexia cu proteză de polipropilenă pe cale abdominală - 41 de cazuri.

Colpopromontopexia pe cale abdominală a fost efectuată in 41 de cazuri dintre care 18 cu histerectomie sau rezecţia colului restant. În 11 dintre aceste cazuri a asociat amplasarea pe cale vaginală a unei bandelete transobturatorii pentru incontinenţă şi în alte 5 cazuri a fost amplasată şi o proteză trapezoidală la muşchii ridicători anali evidenţiaţi retrovaginal. Prezenţa colului uterin în cazurile de prolaps de boltă vaginală posthisterectomie subtotală au impus (dupa test Papanicolau) ablaţia acestuia. Preferăm rezolvarea acestor cazuri prin abord abdominal care permite [11] scheletizarea corectă a uterului sau/şi a colului restant cu evitarea lezării ureterovezicale. Abordul abdominal [12] urmează gesturi standardizate.

După viscerolizăîn micul bazin cu separarea fundului de sac Douglas, de obicei aderent pe vechea cicatrice şi separarea bontului colului uterin restant anterior de peretele vezical şi posterior de peretele rectal se disecă bontul vaginal în absenta colului, este de obicei mai dificilă şi trebuie realizată cu hemostază progresivă şi intercepţia vaselor din plexurile cervicovaginale pe măsură ce acestea sunt întâlnite. Vaginul se scheletizează pe o porţiune, care ajunge anterior până în apropierea joncţiunii vezicouretrale posterior până la evidenţierea completă a

Figura 1: Prolaps genital total.

Figura 2: Prolaps compartiment posterior introducere "tuneller" pentru suspensie sacrosciatica.

marginilor musculare, a diafragmului urogenital și a ridicătorilor anali. Lateral, scheletizarea va intercepta eventualele bonturi ligamentare (ligamente rotunde sau/ și utero-sacrate) va evidenția ureterele terminale care trebuie cu grija evitate și dacă este cazul se va relua ligatura și rezecția pediculilor vasculari uterini. Lungimea bontului vaginal astfel creat este foarte diferită de la un caz la altul, impunând colpohisterectomie sau totalizare histerectomie pentru situațiile cu col uterin restant. Tranșa vaginală se sutureză cu dublu surget continuu de material foarte lent resorbabil (preferabil monofilamentar). După ce bontul vaginal este astfel pregătit și eliberat circumferențial pe circa 2 cm înălțime, se repereză promontoriul, lateral dreapta de peretele rectal se incizeaz[pe 2-3 cm peritoneul parietal posterior deasupra promontoriului și se diseca un tunel subperitoneal care lasă medial peretele rectal, menajează lateral ureterul și in partea inferioară parcurge baza ligamentelor largi până când se detașează complet rectul și se evidențiază bontul vaginal. Tunelul astfel creat se repereză printr-o meșă care completează hemostaza și îl menține accesibil timpilor următori. Se pregătește proteza de polipropilenă pentru suspendarea colpopromontorială aceasta realizându-se prin croirea dintr-o plasă obișnuită de protezare parietală a unui dispozitiv în formă de diapazon sau T inversat, a cărui ramuri orizontale înconjoară și se fixează pe fața anterioară și posterioară a bontului vaginal (folosim două rânduri de puncte separate cu fir neresorbabil, monofilamentar 3-0). Brațul vertical situat la marginea dreaptă si posterioară a bontului vaginal se ascensionează prin tunelul subperitoneal creat anterior. Brațul vertical al protezei se ridică până la nivelul feței anterioare a promontoriului si lungimea sa se ajusteaz astfel încât bontul vaginal să fie bine ascensionat și susținut fără însă a tensiona excesiv montajul. Fixarea capătului superior al dispozitivului o facem cu patru puncte de fir nerezorbabil la periostul promontorial (câte doua puncte de fiecare parte a bandeletei). După controlul riguros al hemostazei și poziției rectului față de implant, breșa peritoneală se închide și cu alt fir se peritonizează zona parametrilor disecați. Uneori înainte de închiderea peritoneală inferioară , este posibilă plasarea unui implant la nivelul marginii ridicătorilor anali fixat inferior la centrul tendinos și care va întări peretele vaginal posterior în porțiunea sa inferioară. Închiderea tranșei peritoneale va realiza concomitent și o ascensionare a fundului de sac Douglas până deasupra nivelului tranșei vaginale. La sfârșitul intervenției se controlează pe cale vaginală poziția actuală a vaginului și dacă este necesar se poate adăuga pe această cale o bandeletă suburetrală pentru incontinența urinară.

Această intervenție comportă riscuri chirurgicale de mică importanță și cu o corectă îngrijire pre, intra și post-operatorie poate fi folosită cu succes chiar și la bolnavele înaintate în vârstă.

In corectarea prolapsului de compartiment anterior si a incontinentei urinare, rezultatele au fost bune si foarte bune cu mici complicații intra si postoperatorii (2 hematoame, 2 necroze de mucoasa vaginală și o supurație care a impus tardiv suprimarea protezei).

In prolapsul de compartiment posterior evoluție foarte bună și fără complicații semnificative.

In prolapsul compartimentului mijlociu rezultatele în general au fost bune, amintind doar 3 cazuri, unde postoperator s-a instalat o incontinență urinară care a impus după 30 de zile efectuarea intervenției complementare de plasare pe cale vaginală a unei bandelete suburetrale transobturatorii.

Spitalizarea postoperatorie a fost în medie de 10 zile, iar controalele ulterioare la 2, 6 și 12 luni au demonstrat evoluția favorabilă din punct de vedere anatomic si functional.

Societatea Internațională de Continență încadrează ca IUE „relatarea oricărei pierderi involuntare de urină" (2002). Se apreciază că aproximativ 30% din populația feminină prezintă pierderi involuntare de urină [13].

Tratamentul prolapsului genital asociat cu IUE a beneficiat în timp de peste 100 de procedee imaginate [14]:

- Tehnici de susținere (colporafia anterioara, plicatura suburetrala Kelly, Marion 1914)
- Suspensia transvaginală a colului vezical (Pereyra 1950, Raz, Stamey, Gittes.)
- Suspensie retropubiană (Burch 1961, Marshall – Marchetti – Krantz 1949).
- Suspensie cu bandelete suburetrale pubovaginale (T.V.T) și transobturatorii (T.O.T).

Actual indicații și tehnici noi utilizează diferitele dispozitive protetice de polipropilenă special concepute în corectarea diverselor tulburări de statică pelvină izolate sau asociate cu o eventuală incontinență urinară [15].

Marea majoritate a tehnicilor de plasare a acestor dispozitive sunt minim invazive cu exceptia abordului abdominal pentru colpopromotopexie.

In afara de rata mică a complicațiilor utilizarea acestor tehnici ofera rezultate anatomice si functionale bune și persistente în timp [16].

Concluzii

Evoluția favorabilă imediată și la distanță a cazurilor confirmă utilizarea tehnicilor diferențiat, adaptate fiecarui caz în parte și susține ideea că folosirea în tratamentul incontinenței urinare de efort și a tulburărilor de statică pelvină a diferitelor dispozitive de polipropilenă prin tehnica minim invazivă este deplin justificată.

Conflict de interese

Autorii nu declară nici un conflict de interese

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