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## Pelvic Lymphedema in Rectal Cancer

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### 1. Introduction

Clarke's Second Law is: "The only way of discovering the limits of the possible is to venture a little way past them into the impossible" (Clarke, 1962). Pelvic lymphedema issues this challenge.

The prognosis for pelvic malignancies has improved in recent years mainly due to advanced technologies and better knowledge of the pathways of cancer spread. Lymphadenectomy is the most important prognostic factor in pelvic malignancies, a finding that has substantially changed surgical approaches from a "quantitative" premise to a more "qualitative" nature giving priority to the psycho-physical integrity of cancer patients by limiting the surgical intervention (Breyer et al, 2008; Mills et al, 2006; Desnoo & Faithfull 2006; Greco et al, 2006).

However, despite progress made by the conservative surgical approach for rectal cancer, the development of functional abnormalities in patients undergoing conservative surgery has become more evident (Ortiz & Armendariz, 1996). These dysfunctional pathology are associated with symptoms similar to those of the pre-surgery pelvic pathology. Most importantly these problems are considered a major public health issue representing one third of costs of colorectal cancer treatment, even if the massive economic burden of disability has received limited attention (Selke, 2003). Although theories including neural damage, reduction of capacity and compliance of organs, and sensory loss have been already proposed, no clear evidence of a direct correlation between such symptoms and surgical damage exists. Additionally, such disabilities do not depend on the extent of the surgical intervention (conservative versus radical), on the use of concomitant post-operative radio-chemotherapy or the gender (Kakodkar et al, 2006). Fortunately, patients have been shown to respond to biofeedback reeducation of the pelvic floor, with or without added psychotherapy (Devroede, 1999).

We hypothesized that pelvic surgery, regardless of the extra-peritoneal organs, results in the loss of continuity of the pelvic region, as key event with the following reduction in fatty tissue where the lymph node stations are mostly concentrated. Therefore we suggest that pelvic lymphadenectomy should be followed by a pelvic lymphedema (Vannelli et al, 2009).

Once identified, lymphedema does not undergo significant reabsorption and may lead to serious chronic pathology with severe functional impairment of pelvic organs ((Zermann et al, 2001). Yet, the mechanisms and pathways that involve lymphedema in pelvic pathology are still unknown and needs to be investigated. We examined, by chance, post surgery

lymphedema in 13 patients submitted to our hospital for colorectal adenocarcinoma, by comparing MRI of the abdominal area of the pre and post surgery. Interestingly, comparison of dynamic MRI images obtained in different phases of the patient's management enabled identification of pelvic floor lymphedema after surgical intervention for colorectal adenocarcinoma.

## 2. Vannelli's theory

The complete description of the lymphatic vessels goes back to 17th century. However, some investigators have only recently recognized the impact of lymphology on the treatment of tumours, both from research and clinical points of view. This sudden increased interest has led to study oncological and functional lymphatic disease, in particular related to lymphedema. It is known that each lymphadenectomy is associated to a lymphedema. Lymphedema is defined as a chronic and debilitating condition and it is correct to suggest the presence of a lymphedema also in the pelvic area related to the oncological surgery treatment: a pelvic lymphedema, that we will call blind lymphedema, i.e. with symptoms but with no signs. We make an introduction. Are we sure to know the meaning of lymphedema? Lymphedema is what we know because we can see it: upper limbs, lower limbs, even neck, scrotum or pubis (Thorat, 2006; Fang et al, 2008; Vignes & Trévidic, 2005). Probably there is a lymphedema that we do not know only because we cannot see it. The Roman playwright Terentius wrote: "But 'even if the old masters have discovered everything, one thing will be always new, - the application and the scientific study and classification of the discoveries made by others.'" (Gummere, 1917-28). To clear our mind of any doubt, it is necessary to make a step backwards. In the scientific discussion lymphedema is not a "meaning" that does not define or indicate a disorder. It is rather defined by its characteristics, i.e. what determines a lymphedema: interstitial retention of proteins, tissue inflammation, fatty tissue hypertrophy, fibrosis, progressive pathological condition, but this is not lymphedema (Warren et al, 2007). The only acceptable definition of lymphedema should be the alteration of the lymphatic vessels due to a (primary) malformation or a (secondary) mechanical damage. Basing on this definition, a new model of lymphedema can be therefore assumed: pelvic lymphedema, that is the alteration of lymphatic vessels associated to a pelvis mechanical damage. The pelvic disorders are extremely frequently and occur regardless of gender, type of surgery or concomitant medical treatment (pre- or post-operative radiotherapy). The study on pelvic disorders immediately is found to be of difficult execution and even without instrumental evidence of any damage, an important symptomatology can be present. The available examinations for the study of the various pelvic components are numerous: uroflowmetry and cystography to investigate the bladder; rectomanometry or electrical stimulation by means of evoked potentials of pudendal nerve; defecography for the investigation of the rectum, just to mention some of them. However, the available data in the literature do not give any satisfactory response concerning the patients with negative tests but with clinically relevant disorders (Antolak et al, 2002). Perineology has acquired higher importance in the recent years: a multispecialistic discipline of multifactorial interest of pelvic diseases with rehabilitation purpose (Peters et al, 2008). After a careful follow-up of the patients operated for pelvic tumours, we observed that all the patients referring to the perineology centres had a relevant benefit from the rehabilitation treatment reducing the complications rate and, in some cases, preventing them (Bai et al, 2006; Brown & Seow-Choen, 2000). This could

answer the question “how does pelvic lymphedema occur?” During surgery the main responsible of the damage should be detected because if, not promptly treated, it can result in a chronic disease. However, to promptly institute the most suitable therapy, we should understand “why does the lymphedema occurs?” and identify the first action. When we talk about postoperative disorders of pelvic surgery, two areas are identified: perineum and extraperitoneal region (Corton, 2005). Perineum consists of soft tissues which close the lower pelvic cavity. This region is sited between the upper portions of the two thighs, to which anal canal, extraperitoneal rectum and external genitals are connected. An ideal transversal line joining the two ischiatic eminences divides the region into two triangles: one anterior, or urogenital perineum, and the other, posterior or anorectal perineum. The subcutaneous layer is bulky in the side walls and posteriorly where it continues with the fat of the ischiorectal fossae.

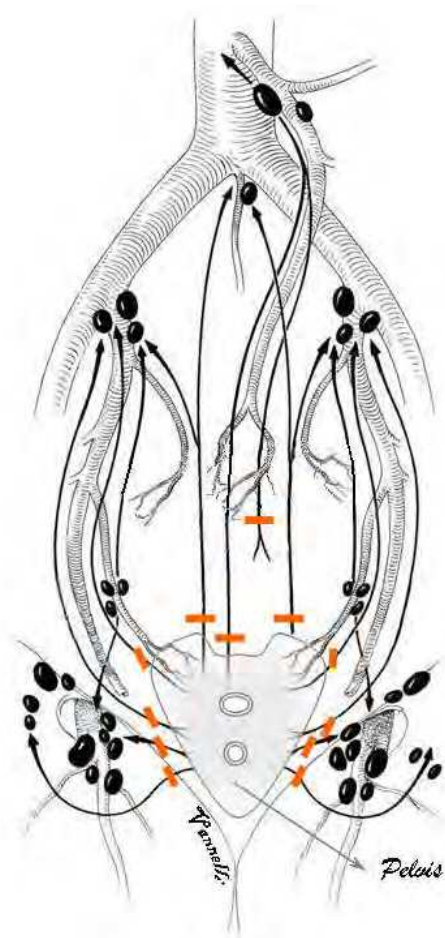


Fig. 1. Illustration of the drainage pathways of the lymphatic vessels in the pelvic area (orange lines correspond to lymphadenectomy and eventually lymphatic spread).

This allows the proliferation of a rich and branched lymphatic net with numerous lymph nodal stations. The extraperitoneal pelvic space is sited between the peritoneum covering the pelvic organs, and the pelvic diaphragm. In the pelvic cavity the peritoneum is separated from the walls which delimit the cavity by the surrounding and supporting fatty extraperitoneal tissue. This creates a sort of floating effect of the organs contained in the pelvis. The fatty tissue forms the two thirds of the total volume and contains important

lymph node stations. The pelvic floor can be considered as the centre supporting the perineal layer. It consists of a complex of muscles which are twisted together and close the pelvis in the bottom.

These muscles wrap the urinary (urethra and bladder) and reproductive (vagina in females and prostate in men) systems and form the anterior floor down to the anorectal apparatus (anus, rectum) which makes the posterior floor. Perineum is a dynamic organ and is continuously subject to our body weight. It especially has the duty to support the increases in intra-abdominal pressure due to the increases in loads, chronic conditions and natural events, such as the childbirth (Van der Putte, 2005). Pelvic surgery, regardless of the involved organs, results in the loss of continuity of the pelvic region as key event with the following reduction in fatty tissue where the lymph node stations are mostly concentrated (Andrade & Jacomo, 2007). Therefore, the occurrence of pelvic disorders, even though of difficult etiology, could be possible due to a surgery which is associated to a lymphadenectomy (Fig. 1). The presence of a lymphadenectomy, that can be considerably wide in some cases, should be followed by a lymphedema.

### **3. Materials and methods**

#### **3.1 Patients**

Between March 1990 and January 2010, 6975 patients were operated for colo-rectal carcinoma in the Division of Colorectal Surgery at the Fondazione IRCCS "Istituto Nazionale dei Tumori", a non university teaching hospital in Milan, the Italy.

For the purpose of the study, information was collected both from medical records and a computerized database of patients admitted to our Division, between May 2008 and January 2010. To discriminate pelvic lymphedema we compared the extra-peritoneal adenocarcinoma (cases) with intra-peritoneal adenocarcinoma (controls) staging with MRI examination. Excluded from the analysis were patients with preoperative treatment, those patients with locoregional recurrence, previous pelvic surgery or patients with distant metastases and with more than one primary cancer. We regarded the rectum cut-off within 15 cm from the anal verge and intraperitoneal cut-off more than 12 cm from the anal verge. We identified a cohort of 13 patients with sigmoid colon and rectal adenocarcinoma. Bowel preparation and surgical techniques have been described in details (Leo et al, 2009). All patients had a pre-operative (one week before surgery) and post-operative (six months following discharge from the hospital) MRI examination. This study was approved by the institutional review board.

#### **3.2 Nuclear magnetic resonance**

In details, a 1.5-T high-resolution MRI system (Avanto; Siemens Medical Systems, Erlangen, Germany) was used for the pre operative stages and the follow-up of the patients. For the purpose of our study, the 13 patients were examined in the supine position with feet forward and measurements were obtained using the same system and by the same technician.

We consider the common features of lymphedema, usually observed in an MRI examination: circumferential edema, increased volume of subcutaneous tissue, and a

honeycomb pattern above the fascia between muscle and subcutaneous fat, with evident thickening of the dermis (Witte, 2002). Although it is generally difficult to differentiate primary from secondary lymphedema, MRI is able to discriminate lymphedema from lipoedema and phlebedema (Lohrmann et al, 2009; Aström et al, 2001). Our standard procedure for pre-operative patients is an MRI with Gadolinium. On the other hand, for follow-ups, the MRI is indicated only for a suspicious local recurrence. Thirteen patients were selected for our study to be evaluated with MRI but with a different approach. In details, along with the above described standard procedures, a sequence of fat-suppressed T2-weighted (FST2) and diffusion weighted T2-weighted (DIT2) were performed, as those are the most efficient techniques to evaluate lymphedema. Specifically, to evaluate lymphedema using FST2 the signal should be increase as the presence of increasing degrees of edema related to active inflammation (Delfaut et al, 1999). Additionally, DIT2 has been found to improve the detection of edema and herein introduced to detect the lymphedema degree (Ebisu T, et al 1993). Moreover when lipoedema occurs, MRI is able to confirm that the peripheral lymphatic system is normal while soft tissue swelling consists solely of fat, and subcutaneous edema is absent.

#### 4. Result

At the time of the analyses thirteen patients were admitted to our department, for colo-rectal adenocarcinoma. Five were male and eight females with a median age of 66, ranging from 45 to 72 years. In all patients, a whole body mass index (BMI) was calculated: range 25-35, mean 29.9. Cases included patients with adenocarcinoma of the sigmoid colon without metastases and rectum without metastases. Four patients have been affected by intra-peritoneal adenocarcinoma: one sigmoid and three upper third rectal cancer (one male and three female) and nine extra-peritoneal adenocarcinoma: four middle third rectal cancer and five lower third rectal cancer (four male and five female). The patients affected by intra-peritoneal adenocarcinoma has been submitted to: one resection of sigmoid colon and three anterior resection of upper rectum. Three patient presented stage IIa and one stage I. The patients affected by extra-peritoneal adenocarcinoma has been submitted to seven anterior resection of the rectum and two total resection of the rectum with colo-endo anal anastomosis. Seven patient presented stage I and two stage 0. Nine patients with an extra-peritoneal lesion underwent a resection of middle and lower third of rectum with regional lymphadenectomy, while the other patients with an intra-peritoneal lesion required resection of sigmoid colon and upper third of the rectum with regional lymphadenectomy. A sagittal and coronal T1 MRI, as well as FST2 and DIT2 images on the axial plane were requested for the seven patients who underwent anterior rectal resection, which involved the pelvic floor, as a result of extra-peritoneal location of the adenocarcinoma (middle and lower third of the rectum). There is no clear evidence of the pelvic lymphedema or lymphatic alterations in the pre-operative MRI performed 1 week prior to surgery for all patients. However, a post-operative MRI follow-up performed six months flowing discharge from the hospital revealed in seven patients a lymphatic 'stipes-like' elements within the presacral adipose tissue with compression of the sacro-sciatic ligaments and bladder, all indicative of lymphatic alterations. Moreover in nine patients, the area of edema and venous congestion of pelvis together with compression of pelvic organs indicated by MRI signals, were located far from the area of surgical intervention. Furthermore, in eight patients, with the phase of T1 acquisition, epifascial "lakes" related to the muscular bands located outside

of the pelvic floor in gluteal muscles were identified. Additionally, in six patients, the DIT2 enabled the detection of moderate lymphatic stasis in the presacral space. On the other hand, the four patients who underwent resection of the sigmoid colon and upper third of the rectum (without pelvic involvement due to intra-peritoneal adenocarcinoma located more than 12 cm from the anal verge), had a different MRI outcome. In details, the axial second planes were amplified with acquisition of T1, FST2 and DIT2- weighted sagittal and coronal images through subtraction of adipose tissue signals on the axial planes. Pre-operative MRI revealed no pelvic lymphedema or alterations of the pelvic lymphatics in these patients. Also the post-operative follow-up performed six months after discharge from the hospital, showed no evidence of pelvic wall edema. Two patients, submitted to resection of the sigmoid colon, presented mild signal intensification in the lower part of the rectal abdominal muscle (figure 6). Overall, there are no signs of lymphatic congestion anywhere within the pelvic wall were noted in the four patients with intra-peritoneal surgery. Table I summarizes surgery information for each patient. Thirteen patients were admitted to our department for colo-rectal adenocarcinoma. Five were males and 8 females with a median age of 66, ranging from 45 to 72 years. In all patients, a whole body mass index (BMI) was calculated: range 25-35, mean 29.9.

Number patient	Age	Sex	Body Mass Index	Site of cancer	Surgical procedure	Cancer classification
1	45	female	25	Sigmoid colon	RSC	Ila
2	72	male	35	URC	ARR	Ila
3	68	female	31,6	URC	ARR	Ila
4	70	female	25,8	URC	ARR	I
5	55	female	29,9	URC	ARR	I
6	60	male	28,8	MRC	ARR	I
7	59	female	29,6	LRC	ARR	0
8	71	female	29,9	LRC	ARR	I
9	66	male	28,9	MRC	ARR	I
10	65	female	31,2	MRC	CEAA	0
11	64	female	33,5	LRC	ARR	I
12	67	male	34,5	LRC	CEEA	I
13	67	male	33,3	LRC	ARR	I

Upper third rectal cancer (URC), Middle third rectal cancer (MRC), Low third rectal cancer (LRC), Resection of the sigmoid colon (RSC), Anterior resection of the rectum (ARR), Total resection of the rectum with colo-endo anal anastomosis (CEAA); Cancer classification with American Joint Committee on Cancer Staging 2010

Table 1. Characteristics of patients from May 2008 to January 2010

Cases included patients with adenocarcinoma of the sigmoid colon without metastases and of the rectum without metastases. Four patients have been affected by intra-peritoneal adenocarcinoma: one sigmoid and 3 upper third rectal cancer (1 male and 3 female) and 9 extra-peritoneal adenocarcinoma: 4 middle third rectal cancer and 5 lower third rectal cancer (4 male and 5 female). The patients affected by intra-peritoneal adenocarcinoma have been submitted to: one resection of sigmoid colon and 3 anterior resection of upper rectum. Specifically, 3 patients presented stage Ila and one stage I. The patients affected by extra-

peritoneal adenocarcinoma have been submitted to 7 anterior resection of the rectum and 2 total resection of the rectum with colo-endo anal anastomosis. In details, 7 patients presented stage I, and 2 stage 0. Nine patients with an extra-peritoneal lesion underwent a resection of middle and lower third of rectum with regional lymphadenectomy, while the other patients with an intra-peritoneal lesion required resection of sigmoid colon and upper third of the rectum with regional lymphadenectomy. Table II summarizes the MRI characteristics for each patient using 4 paramenters: stipes-like, edema and venous congestion, epifascial ‘lakes’, lymphatic stasis in presacral space.

Patient	Stipes like		Edema and venous congestion		Epifascial “lakes”		Lymphatic stasis in presacral space	
	MRI pre	MRI post	MRI pre	MRI post	MRI pre	MRI post	MRI pre	MRI post
1	no	no	no	no	no	no	no	no
2	no	no	no	no	no	no	no	no
3	no	no	no	no	no	no	no	no
4	no	no	no	no	no	no	no	no
5	no	yes	no	yes	no	yes	no	yes
6	no	no	no	yes	no	yes	no	yes
7	no	no	no	yes	no	yes	no	no
8	no	yes	no	yes	no	no	no	no
9	no	yes	no	yes	no	yes	no	yes
10	no	yes	no	yes	no	yes	no	no
11	no	yes	no	yes	no	yes	no	yes
12	no	yes	no	yes	no	yes	no	yes
13	no	yes	no	yes	no	yes	no	yes

Table 2. MRI characteristics

A sagittal and coronal T1 MRI, as well as FST2 and DIT2 images on the axial plane were requested for the 7 patients who underwent anterior rectal resection, which involved the pelvic floor, as a result of extra-peritoneal location of the adenocarcinoma (middle and lower third of the rectum). There is no clear evidence of the pelvic lymphedema or lymphatic alterations in the pre-operative MRI performed 1 week prior to surgery for all patients (figure 2).

However, a post-operative MRI follow-up performed 6 months flowing discharge from the hospital revealed in 7 patients a lymphatic 'stipes-like' elements within the presacral adipose tissue with compression of the sacro-sciatic ligaments and bladder, all indicative of lymphatic alterations (figure 3). Moreover in 9 patients, the area of edema and venous congestion of pelvis together with compression of pelvic organs indicated by MRI signals, were located far from the area of surgical intervention (figure 4). Furthermore, in 8 patients, with the phase of T1 acquisition, epifascial "lakes" related to the muscular bands located outside of the pelvic floor in gluteal muscles were identified (figure 5). Additionally, in 6 patients, the DIT2 enabled the detection of moderate lymphatic stasis in the presacral space (figure 6). On the other hand, the 4 patients who underwent resection of the sigmoid colon and upper third of the rectum (without pelvic involvement due to intra-peritoneal adenocarcinoma located more than 12 cm from the anal verge), had a different MRI outcome. In details, the axial second planes were amplified with acquisition of T1, FST2 and DIT2- weighted sagittal and coronal images through subtraction of adipose tissue signals on the axial planes. Pre-operative MRI revealed no pelvic lymphedema or alterations of the pelvic lymphatics in these patients. Also the post-operative follow-up performed six months after discharge from the hospital, showed no evidence of pelvic wall edema. Two patients (number 1 and 4), submitted to resection of the sigmoid colon, presented mild signal intensification in the lower part of the rectal abdominal muscle (figure 7). Overall, there are no signs of lymphatic congestion anywhere within the pelvic wall were noted in the four patients with intra-peritoneal surgery.

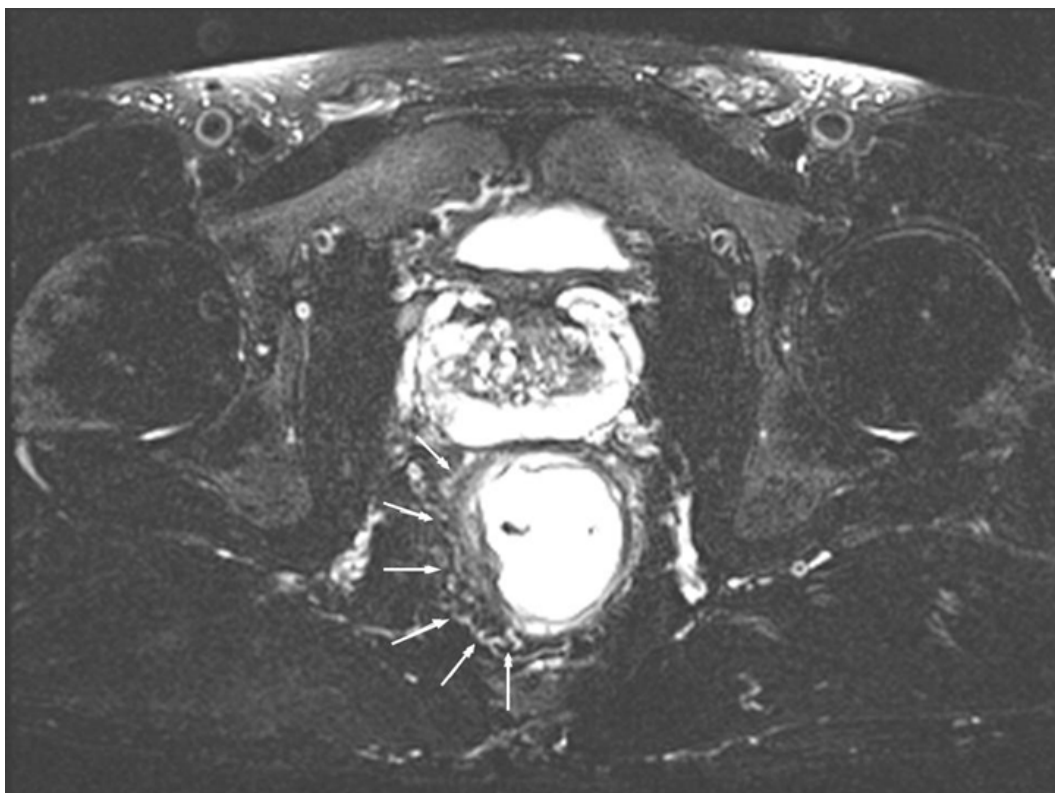


Fig. 2. Phase of FST2 acquisition in pre-operative period, revealing no evidence of lymphedema. Arrows indicate the primary lesion.

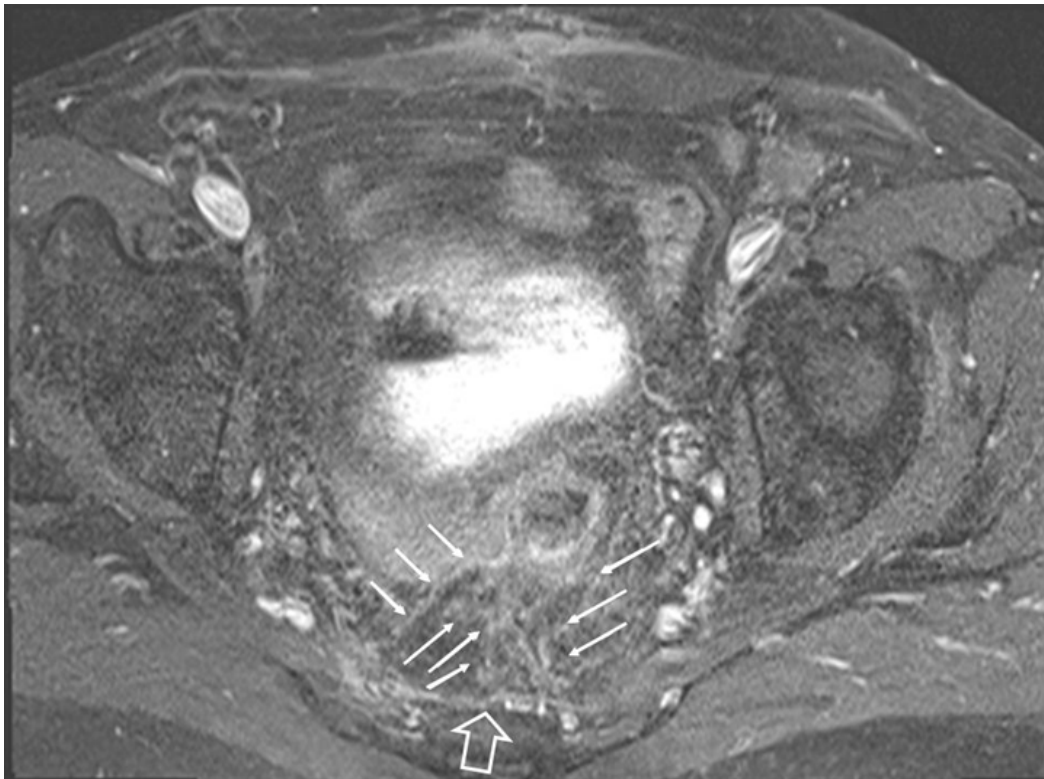


Fig. 3. Post-operative period. Phase of FST2 acquisition. White arrows indicate lymphangitis in the sacral area; large open arrow indicates presacral fibrosis.

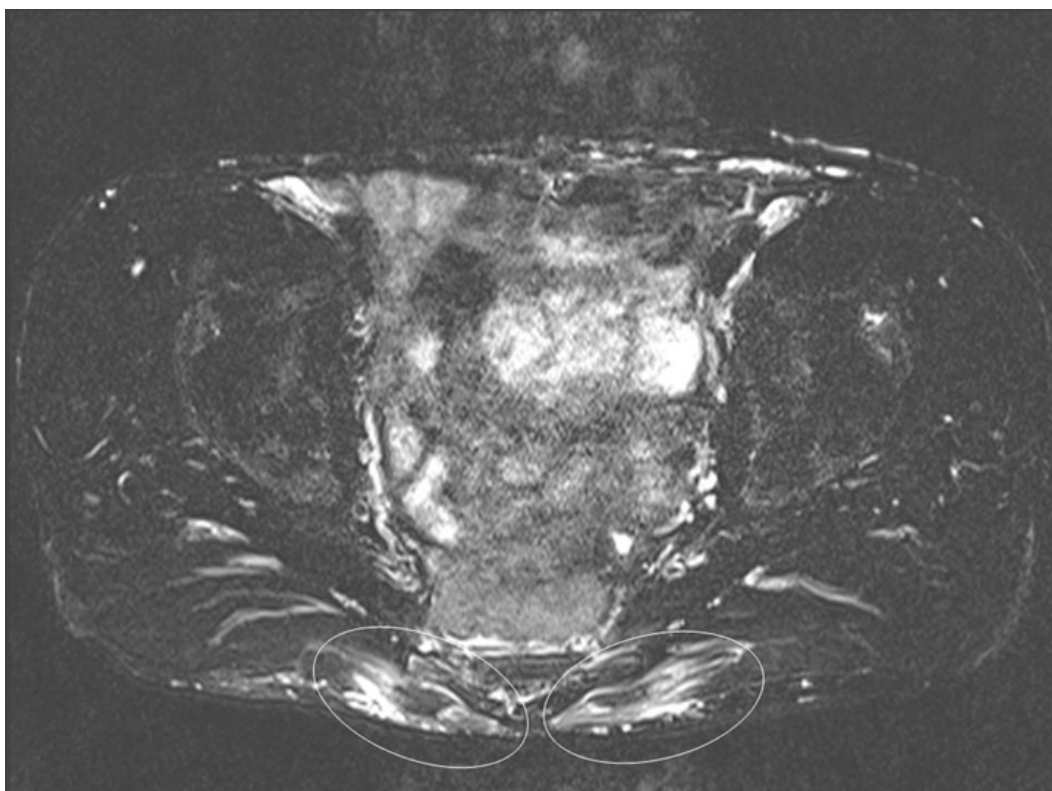


Fig. 4. Post-operative period. Phase of FST2 acquisition. Note lymphedema and venous congestion in presacral area.

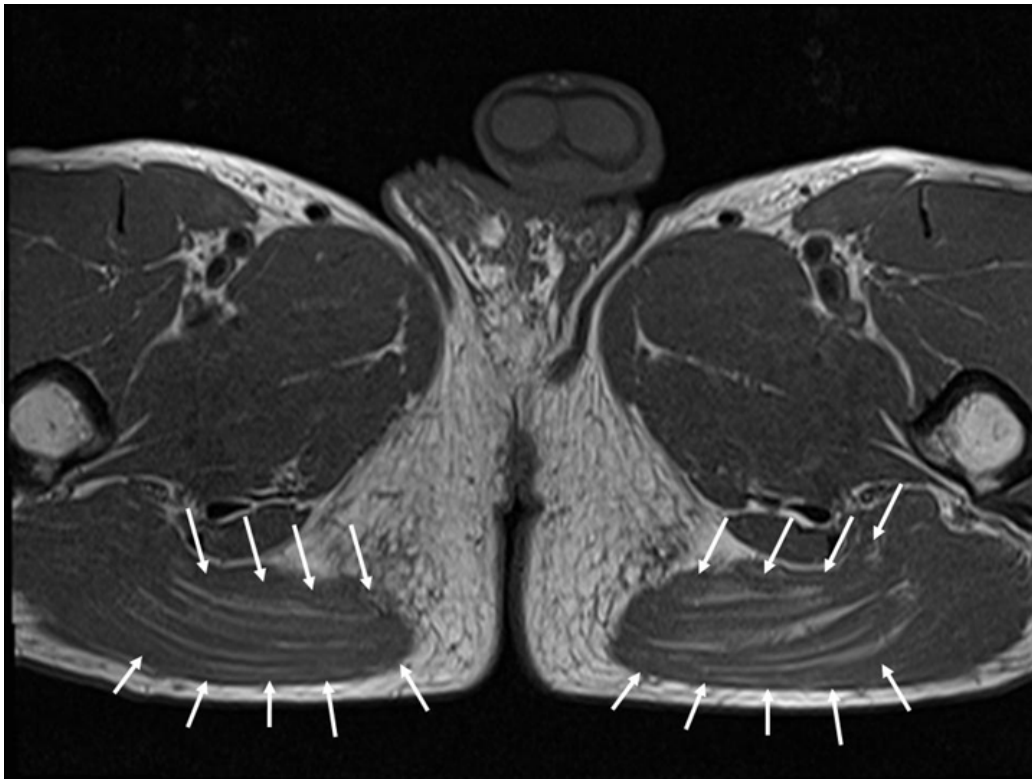


Fig. 5. Post-operative period. Phase of T1 acquisition. Arrows surrounding muscular fascia indicate the epifascial "lakes".

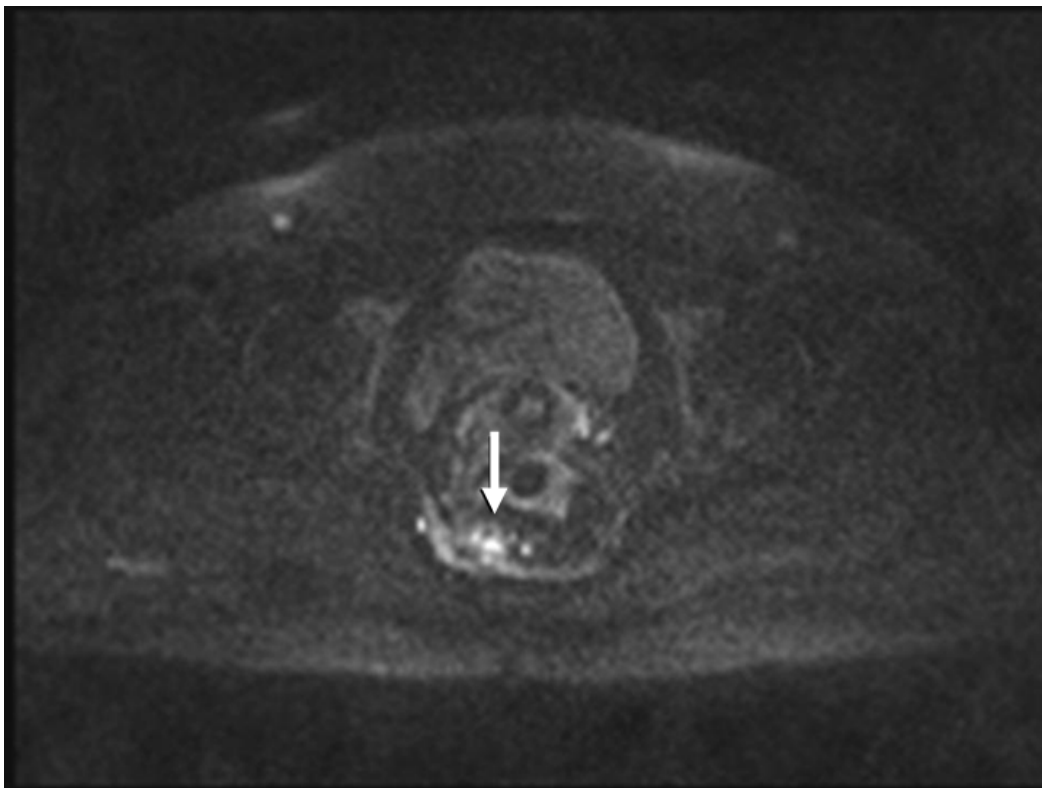


Fig. 6. Post-operative period. Phase of T2WI. Arrow indicates lymphedema in the presacral space.

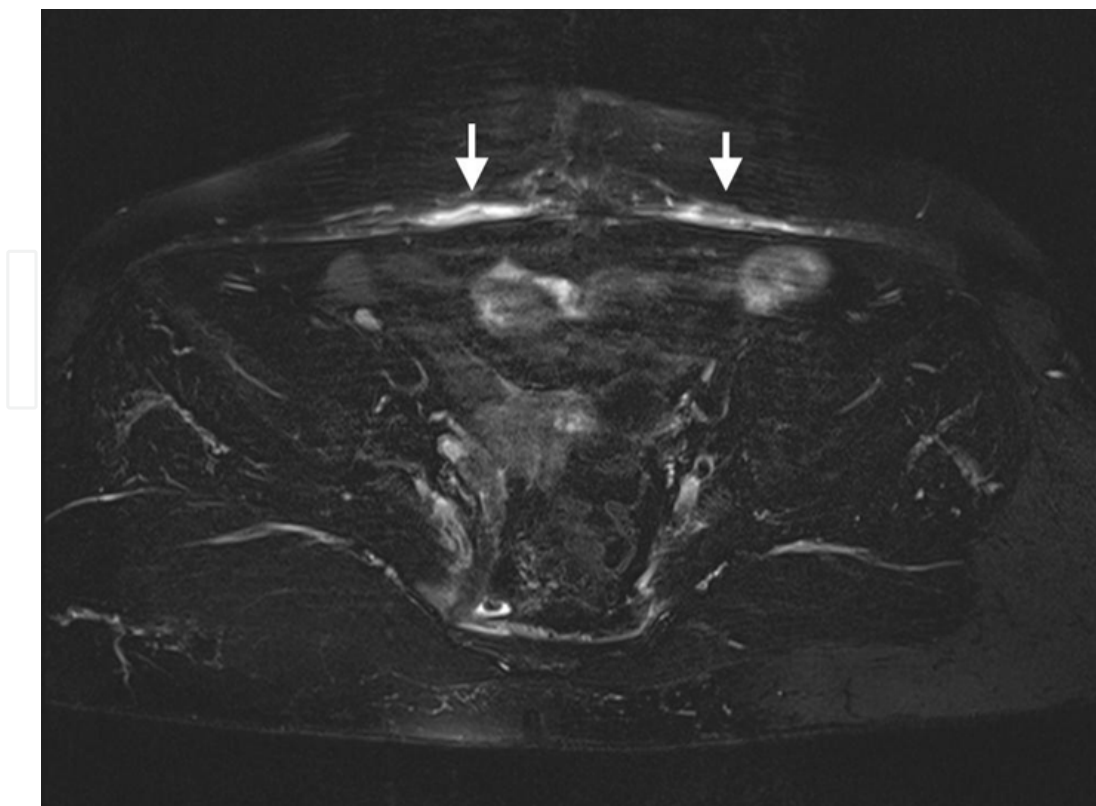


Fig. 7. Post-operative period. Phase of FST2 acquisition. Arrows indicate mild hyperintensity in the area of abdominal rectal muscles.

## 5. Discussion

### 5.1 Pathophysiology of the pelvis

Pelvic cavity is a large region. The pelvic bone walls are completed with layered muscles: internal by pyriform and obturators, and closed in the bottom by levator ani and ischiococcygeal muscles which form the pelvic diaphragm or floor. In the pelvic cavity, like in the remaining abdominal cavity, peritoneum is separated from the walls which delimit the cavity by the extraperitoneal connective tissue. Peritoneum surrounds the organs contained in the pelvis is connected backwards with the extraperitoneal tissue, anteriorly with the connective tissue of the anterior compartment of the thigh through the obturator canals, laterally with that of the gluteal regions through the supra- and sub-pyriform canals of the great ischiatic foramen. The extraperitoneal connective tissue occupies the spaces free of viscera. In some points, such as around the rectum and bladder, it looks like a loose fatty connective tissue, while in others it gets thicker and forms septa and ligaments. These are, sometimes, provided with small bundles of smooth muscle cells which have the duty to support the pelvic viscera. These septa are the weak points of the whole pelvis. The septa, that can be hardly delimited from the adjacent loose tissue, surround the vessels directed to viscera or pelvic walls and are rich in lymphatic vessels and lymph nodes too (Wilting et al, 2004). It is, therefore, evident that any surgery in this area should be necessarily associated to a loss of potentially vital substance to perform a really radical lymphadenectomy. The female pelvic cavity has a different aspect from the male cavity due to the particular development of the genital apparatus. While the male genital apparatus is hidden by the

bladder, in the female uterus and its appendages acquire a considerable development: they rise from the extraperitoneal areal tissue and raise the serosa forming ligaments.

Uterus and ligaments, therefore, form a transversal septum which divides the pelvic cavity into an anterior portion, where bladder is sited, and a posterior one occupied by the rectum. Some lymphatic vessels of the rectal ampulla join at the root of the superior rectal vein to reach the anorectal and superior sacral lymph nodes, while others go up to the hypogastric lymph nodes. The bladder lymphatic vessels mouth into the hypogastric and external iliac lymph nodes.

In males the lymphatic vessels of the deferent canal and seminal vesicles are confluent of the external and internal iliac lymph nodes.

The prostate lymphatic vessels mouth into the hypogastric ones, while those of the anterior face of the prostate are confluent of anterior vesical lymph nodes or obturator lymph nodes. Regarding females, the lymphatic vessels of uterus are the following: the fundus uteri lymphatic vessels follow the ovarian vessels and are confluent to lumboaortic lymph nodes sited at the level of the renal hilus; some of the corpus and fundus uteri follow the round ligaments and reach inguinal lymph nodes, whereas those of the corpus and neck reach the internal iliac lymph nodes like those of vagina. In the pelvic extraperitoneal region lymphatic vessels follow the course of parietal and visceral veins and present lymph nodes alternating along their course.

Those distributed along the internal iliac vessels that receive lymphatic collectors of pelvic viscera and walls are particularly relevant. Finally, the pelvic cavity is externally closed by the perineum which is made by a diamond-shaped layer rich in fatty tissue. The most superficial lymphatic vessels are confluent of inguinal lymph nodes, while the internal ones go along the blood vessels and anastomose with the anal ones. The perineum in the posterior portion is crossed by anus whose lymphatic vessels which come from the columnar area and haemorrhoidal ring are confluent of internal iliac lymph nodes. The vessels of the anal orifice are confluent of the anorectal lymph nodes and inguinal lymph nodes of the medial group. The perineum in the anterior portion has a similar structure in both genders.

The constituting layers are, however, modified by the different conformation of the genital organs. In male two lymphatic pathways for the penis can be identified. The first consisting of superficial lymphatic vessels which join together in a unique trunk which flows with the dorsal superficial vein and mouths into the superficial inguinal lymph nodes and then bifurcates together with those coming from the scrotum. The second is constituted by deep lymphatic vessels which join in an unpaired dorsal trunk which goes with the anonymous vein and join the external iliac lymph nodes. The lymphatic vessels of testicle follow the spermatic cord and flow into lumboaortic lymph nodes. In the female, the lymphatic vessels of the mons of pubis, labia majora and minora are confluent of superficial inguinal lymph nodes. The lymphatic vessels of erectile organs are confluent of deep inguinal lymph nodes or external iliac vessels. It is evident how the pathways of lymphatic outflow of pelvis are extremely branched and the lymph node stations constitute a closely inter-connected complex.

Moreover, contrary to the remaining areas, these lymphatic pathways are exposed to a high pressure for two reasons: to counteract the pressure difference between endo-abdominal and endo-thoracic values and due to the calibre of the outflow vessels, which are particularly large (cisterna of Pecquet, lumbar right and left lymphatic trunks). The oncological surgery in the pelvic area always involves a remarkable radical operation of lymph nodes, which is partially necessary (lymphadenectomy), but also unavoidable. The removal of extraperitoneal tissue occupying the areas free from viscera is, as mentioned above, abundantly supplied by lymphatic vessels. The lymphatic pathway on the transected area is completely removed without having any alternative outflow pathways (Taneja & Cady, 2005). It is appropriate to assume that the lymphedema related to lymphadenectomy appears in the same way as it occurs in other body areas. However, due to its completely internal nature and its site within the bones of the pelvis, it cannot be immediately viewed during the inspection (Sallustio et al, 2000). Moreover, it is logic to presume that there is a histological picture related to the lymphedema which is comparable to that of other areas: interstitial retention of proteins, tissue inflammation, fatty tissue hypertrophy, fibrosis, progressive pathological condition (Warren et al, 2007). The progressive pathological condition should underlie the disease of the pelvic floor. As above mentioned, pelviperrineology is a recent discipline and it is still subject to complex evaluations by many specialists: gynaecologists, urologists, proctologists, sexologists (Jones et al, 2008). The benefits resulting from the treatments of rehabilitation proposed by these specialists indirectly ensure the decongestive action typical for the physical exercise of the other body districts, beyond stimulating the correct recovery of the muscular activity. This should mean that the treatments of rehabilitation of pelvis result in the evident reduction in the edema and the related cohort of symptoms. Indeed, the best way to treat lymphedema and the related disorders seems to be the increase in the force of lymphatic circulation (Swartz et al, 2001). The filtration pressure in the tissue spaces ensures that lymph can move with force and this resulting liquid pressure in the tissue draws the blood from capillaries. The movement of the lymphatic valves provides to lymph the direction from the smaller lymphatic vessels into the lymphatic ducts. The automatic contraction of lymphatic vessels is one of the explanations of the lymphatic circulation and accelerates the formation of the lymph itself. The pressure resulting from the contraction of the adjacent muscles can compress the lymphatic vessels and push the lymphatic circulation towards the valves. It is easy to assume that a pelvic surgery irremediably impairs this fragile balance whereas the rehabilitation offered by the specialists studying the pelvic disorders produces a beneficial decompressing effect on the lymphedema, acting directly on the muscular structure. If this can explain the etiopathogenesis of lymphedema, it is not yet clear why the distribution of this disorder can be so variable. Some peculiar characteristics of the lymphatic vessels in the pelvic area need therefore to be considered. The normal function of the lymphatic vessels is to remove the portion of liquid leaked from the capillaries, which accumulates in the interstice, so that the interstitial pressure can be kept constant (Stachowska-Pietka et al, 2006). The venous capillaries reabsorb 90% of the liquid in the interstice, while the remaining fluid is transported to the blood by the lymphatic vessels in the form of lymph. Under normal conditions, the portion transported to the interstice is the same as that transported in the opposite direction. However, this balance is destroyed in the lymphadenectomy due to the reduction in the lymph transport capacity. As a result, there is a liquid retention and swelling like in any other body organs after a lymphadenectomy.

Moreover, the pelvic lymphatic vessels serve to remove macromolecules, such as proteins, from interstice. Unlike other anatomical regions, the particular structure of the pelvis with its parallelepiped shape and semirigid shell, the abundant distribution of venous plexus as well as the tight bond with the intestinal lymphatic tissue make the role of the lymphatic vessels even more specific (Barret et al, 2006). When the proteins diffuse through the arterial capillary wall, they are downgraded by the macrophages, which allow them to come back to the blood circulation through the venous capillary circulation, or are reabsorbed through the lymphatic vessels (Greitz, 2002). During pelvic surgery it is easy to assume that the resulting inflammatory picture will be so widespread that a remarkable number of macrophages will be recruited through the activation of different cell lines and partially contrast the effect of the resulting lymphedema. Moreover, in case of obstructed, abnormal or absent lymphatic system, a lymphatic stasis can occur, leading to retention of proteins and liquid in the interstice. Another element contributes to counteract this effect, namely the close inter-connection with the venous plexus present in the pelvis micro-circulation which acts by mimicking the role of the lymphatic vessels. According to the classical theory, this increase in protein concentration leads to an increase in the tissue colloido-osmotic pressure, which draws liquids into the interstice and causes edema and clinical outbreaks of lymphedema. On the other hand, the intra-abdominal pressure, which ranges from 3 to 5 mm Hg in the postoperative period, contributes to strengthen the effect of lymphedema. Although the intra-abdominal pressure is distributed on the whole cavity, it leads to a higher effect of venous stasis in the operated pelvis, adding to lymphatic pressure. The clinical occurrences of lymphedema occur following the retention of edematogenic liquid in the fatty and subcutaneous tissue. The inflammatory response appears with the liquid retention in the interstitial space. In addition to the inflammation, the slowed lymphatic flow is also associated to an increase in the lipogenesis and fat deposition, to the increase in the activation of fibrocytes and expansion of connective tissue. The patient would progressively develop a subcutaneous hard tissue as a result of the consequent fibrosis in addition to hypertrophy of the fatty tissue. These pathological changes will initially develop as simple swelling, but later on their persistence would lead to a higher state of hardening. Unlike the other regions, the performance of an intra-abdominal surgery, with no contact with the external environment, will never cause the classical signs which are normally visible in another body region. In these terms, it is less difficult to suggest a pelvic lymphedema. Pelvis is a functional unit, therefore, after a surgery (conservative or radical, with or without post-operative treatment); the patients develop pelvic dysfunctions, probably due to lymphedema. We believe that this disorder without an appropriate rehabilitation leads to an inflammation with interstitial liquid retention with high protein concentration, which results in fatty tissue hypertrophy and fibrosis, and develops as a progressive pathological condition. We can therefore agree with the hypothesis that the lymphatic damage leads to pathology of progressive malfunctioning that, if not properly treated, can become chronic within few weeks and result in a severe chronic disease. The pelvic lymphedema can be a difficult condition to be treated and one of those causes with significant morbidity for the patient both from the clinical and psychological points of view. The clinical evidence shows that the lymphatic vessels play a relevant role in the pathology of the pelvic floor and perineum.

## 5.2 Clinical evidence of pelvic lymphedema

In this pilot study using abdominal MRI we hypothesized that pelvic surgery, regardless of the extra-peritoneal organs, results in the loss of continuity of the pelvic region as key event with the following reduction in fatty extra-peritoneal tissue where the lymph node stations are mostly concentrated; the consequent pelvic lymphadenectomy, should be followed by a pelvic lymphedema (Vannelli et al, 2009). As lymphedema been discovered often by chance and has no reported common elements, it has been difficult to create an experimental model (Savoye-Collet et al, 2008). Here, we attempted to generate a diagnostic model by exploiting the radiological resources available in our laboratory.

Lymphedema results from an alteration of lymphatic vessels as a consequence of malformation (primary) or mechanical damage (secondary) (Warren et al, 2007), consistent with an equal distribution in the upper and lower limbs, neck, scrotum and pubis (Purushotham et al, 2007; Fang et al 2008). Analogously, pelvic lymphedema might be a consequence of mechanical pelvic injury or of the altered lymphatic system caused by such injury. The extra-peritoneal pelvic area is sited between the peritoneum covering the pelvic organs, and the pelvic diaphragm. In the pelvic cavity the peritoneum is separated from the walls which delimit the cavity by the surrounding and supporting fatty extra-peritoneal tissue. Pelvic lymphadenectomy might in itself lead to damaged lymphatic vessels with subsequent pelvic malfunction, within a few weeks post surgery if undiagnosed and untreated, can progress to a chronic pelvic dysfunction. Our post-operative MRIs evidenced injuries involving different pelvic structures and areas, whereas no venous congestion or alteration of lymphatic vessels was detected preoperatively (Table II). Therefore it is of critical importance to investigate the mechanisms of lymphedema in pelvic pathology to limit the consequences of functional abnormalities in patients who undergo conservative surgery. Thus, despite the benefits of surgery, our results support the notion that lymphadenectomy can cause damage of the pelvic lymphatic system as a direct result of surgery. Unlike the common clinical skin signs that characterized all other sites of lymphedema, pelvic lymphedema is "hidden" or silent, with no skin changes or any single symptom manifested (Vannelli et al, 2009). The lack of signs is not surprising, considering that the shell structure of bones of the sacral area provides a structural system capable of containing almost three-fourths of the total volume alterations inside the pelvis without any external manifestations. Moreover, the perineum, which contains no bone structures and thus enables direct and unrestricted internal pelvic communication, is particularly vulnerable to damage caused by lymphadenectomy. This alteration of lymphatic vessels would produce lymphedema or progressive dysfunctional pathology manifesting as muscular deficiency, particularly defective sphincter control. As shown in our MRIs of the bone-tendineal space interposed within a deep plane of the pelvic floor, surgical intervention involving perineal skin "hidden" (Figure 5,6) lymphedema, despite the lymphatic congestion after lymphadenectomy and eventually the conditions for neural and muscular structural malfunction (Handa et al, 2009). In this series, the use of MRI has made it possible to emphasize the pre-operative period in which the presence of the cancer is not associated with any pelvic lymphedema. Moreover, our MRIs showed that pelvic illness alone is accompanied by lymphedema related exclusively to venous congestion, which can be attributed to the neoangiogenesis typically concurrent in these carcinomas. In the post-operative period the effects of lymphadenectomy and opening of the pelvic peritoneum are

characterized by specific signs of lymphedema, such as lymphangitis with local fibrosis formation. Actually, the identification of epifascial “lakes” over gluteus muscles in the absence of edema inside of the muscular girdles demonstrates that surgical intervention sets off a domino effect within the pelvic area. The observed venous congestion in areas distant from the interventional area both in patients surgically treated with opening of the extra-peritoneal space and in those without pelvic involvement, further confirms an alteration of pelvic structures following pelvic surgery. Our series of MRIs also identified other common features of lymphedema: accumulation of liquid in adipose tissue or lipedema. The estimate of body fat indicate an average BMI of 29.9 (so called overweight), since reduction of adipose tissue, where lymph nodes are predominantly concentrated, might contribute to the loss of pelvic structural continuity. Moreover, the specific structure of pelvic lymphatics must be considered, since it is ubiquitously and homogeneously distributed as a thick net and conveys a "three-dimensional" appearance of volume, unlike the generally single long dimension that characterizes the upper or lower limb lymphatics. Surgery leads not only to the limitation of volume, but also to the involvement of all pelvic structures. To date, lymphedema is frequently undiagnosed even in teaching centers (Schuchhardt C, 1997), and it seems likely that many surgical interventions have not been adequately studied with respect to lymphatic damage and their consequences. Although it could be argued that such studies are not essential when colorectal surgery is only limited to an internal pelvic space, and that any radiological image is only one indicator of type of surgical intervention, we detected signs of venous congestion in all pelvic areas, demonstrating that each surgical procedure implicates involvement of the entire pelvic structure. Thus, it is not the type of surgical intervention that creates favourable conditions for lymphedema, but rather the specific location of the pelvic floor where surgery occurs. The pelvis is a dynamic functional unit endowed with an elastic memory continually responding to changes of: body weight, intra-abdominal pressure due to increased loads caused by chronic conditions, and by the natural events of pregnancy and delivery. Elastic memory of the pelvis contributes in inhibiting the onset of lymphedema. However, surgical disruption of this functional unit, in particular impairment of the pelvic memory capability is exceeded can lead to hidden lymphedema. Overall this can be the key factor in explaining pelvic dysfunction.

## 6. Conclusion

Clinical evidence obtained by MRI in our pilot study indicates that lymphatic vessels play a significant role in surgeries that involve perineum and the pelvic floor (Boekhuis et al, 2009; Campisi, 1991). This pilot study could answer the question “how does pelvic lymphedema occur?”. During surgery the primary cause responsible for the damage should be detected otherwise if, not promptly treated, it can result in a chronic disease. However a better understanding of pelvic lymphedema could be the key to improving therapeutic strategies, including the routine use of biofeedback re-education of the pelvic floor, for functional abnormalities after pelvic surgery (Striefel & Glazer, 2008).

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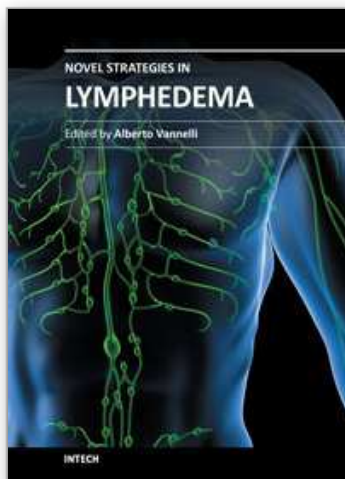
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## **Novel Strategies in Lymphedema**

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Lymphedema is a swelling caused by the abnormal accumulation of lymphatic fluid in the skin. Lymphedema can be caused by burns, injury, surgery, radiation therapy or cancer treatment that cancer survivors undergo. Risk of developing lymphedema is high especially in those with breast or prostate cancer. It is hereditary and can appear without warning at any time of life and is related to obesity and circulatory problems. If not treated, lymphedema can be painful and lead to life-threatening infections. This book will help physicians who deal with lymphedema. It will help you understand how the lymphatic system works, how lymphedema is diagnosed, how to cope with the challenges of lymphedema, how to find treatment, and how to deal with insurance issues. Novel Strategies in Lymphedema is for those with, or at risk of, developing lymphedema, and the healthcare professionals who care for them.

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