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Review and case series

Pelvic exenteration for locally advanced or recurrent pelvic malignancies – initial experience and review of the literature

[1,2]Mihai S. Mureșan, [3]Vitalie Gherman, [4]Cornel Cheregi, [1]Mihai S. Mihalcea, [1]Ion Imihteev, [1]Raul Micu-Chiș, [5]Radu Fodor, [6,7]Hassan Noor, [8]Alexandru Iliescu, [1,2]Călin Ionescu

[1]Vth Department of Surgery, Cluj-Napoca Municipal Hospital, Cluj-Napoca, Romania; [2] VIIth Department of Surgery, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [3] Department of Urology, Cluj-Napoca Municipal Hospital, Cluj-Napoca, Romania; [4] Department of Surgery, Oradea Military Hospital, Oradea, Romania; [5] Faculty of Medicine, University of Oradea, Oradea, Romania; [6] Department of Surgical Medicine, County Clinical Emergency Hospital of Sibiu, Sibiu, Romania; [7] Faculty of Medicine, "Lucian Blaga" University, Sibiu, Romania; [8] Department of Oncology, Salaj County Emergency Hospital, Zalau, Romania.

Abstract. Historically, pelvic exenterations were considered radical, mostly palliative surgeries, reserved for selected cases of pelvic gynaecologic malignancies confined to the pelvis, where radiotherapy or chemo-radiation did not offer sufficient benefit. Recently, these types of surgeries have offered improved local control and overall survival rates also for other advanced or recurrent pelvic malignancies. The aim of this study was to investigate the surgical rationale behind performing such extensive surgeries in a small case series of patients in an University hospital setting and to compare the initial results to the current standards in the literature. After an extensive literature search, we have selected the most relevant high impact papers, from which we have tried to point out the current recommendations and indications for these types of surgery. We have compared these findings with our initial experience of two advanced and recurrent rectosigmoid cancers operated radically in our institution. In a multidisciplinary setting, pelvic exenterations offer good local control of the disease confined to the pelvis, without major compromise in quality of life, low morbidity and mortality rates, for selected cases where chemo-radiation has no benefit. These outcomes could be achieved if R0 resection are obtained or facilitated, thus improving overall survival in such extreme scenarios.

Key Words: pelvic exenteration, locally advanced pelvic malignancies, pelvic recurrence

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Corresponding Author: C. Ionescu, email: ionnescu.calincj2002@gmail.com

Introduction

Pelvic exenteration (PE) is an extensive surgical procedure initially introduced for selected patients bearing pelvic malignancies of gynaecologic origin, with palliative intent, in the late 40s by Brunschwig; in the next decade, Appleby subsequently adapted PE techniques for advanced mid- and low rectal cancer (Bacalbașa and Bălescu 2015; Pawlik et al 2006; Lee et al 2017). The first case series of the aforementioned authors carried a high rate of morbidity and postoperative mortality, in such way, that for the next five decades, such types of salvage surgeries were reserved to highly selected patients. In the initial reports, such ultra-radical surgery involved an en bloc resection of the male/female internal reproductive organs, the urinary bladder, the entire/part of the rectosigmoid, with or without the perineal soft tissue; the extent of resection is in direct relation with the primary tumour's histology, initial imaging studies, performance status of the patient and distant metastases status (KD 2017).

Until the 90s, these types of procedures were rarely performed with curative intent, and were usually offered as salvage surgery for patients with either recurrent or advanced gynecologic cancers or extensive central pelvic disease, initially considered to be non-resectable or with poor response to intention-to-treat chemo-radiation (Berek et al 2005; Goldberg et al 2006). It was not until Berek et al and Goldberg et al published promising results resulted from their retrospective case series that PE redrew specialists' attention and was reconsidered. In their series, they managed to achieve 5-year overall survival (OS) rates of almost 50% with postoperative morbidity rates constantly decreasing through the reported decades from 40% to about 10%, especially for center pelvic disease (Berek et al 2005; Goldberg et al 2006; Bacalbașa and Bălescu 2015), in such manner that PE was sometimes offered as an option of salvage surgery beyond palliation for other pelvic malignancies (i.e soft tissue sarcoma, retosigmoid cancers, urologic malignancies, - both for advanced stages of the disease and for local recurrences).

PE gained wide acceptance as useful tool in the surgical oncologists' armamentarium especially when referring to locally advanced (LARC) or locally recurrent rectal cancer (LRRC). This ultra-radical surgical approach using some type of PE has been previously widely debated (Lee et al 2017). The prior poor increase of the use of PE for LARC and LRCC was mainly due to the widespread in the past four decades, of the total mesorectal excision (TME) principle, which, added to the neoadjuvant radiation/chemo-radiation protocols, has dramatically declined the percentages of LRRC, but has also contributed to better control rates for LARC (Shoup et al 2002; Hansen et al 2007; Silberfein et al 2010; Höckel 2015). Since the days when TME, as a technical concept, was added to neoadjuvant treatment, the reported 5-year local recurrence rates have dropped to 5-10% versus 20-30%, in the pre-TME era, with the majority of recurrences occurred in the first two years after the initial intention-to-treat multimodal treatment (Silberfein et al 2010; Höckel 2015; Lee et al 2017). In the event of such recurrences, additional chemo-radiation or boosts of local radiotherapy, rarely offer local symptoms' relief; in the majority of the cases has no benefit on overall survival, and only adds significant morbidity and poor quality of life (QoL) (Ito et al 2003; Hansen et al 2007; Silberfein et al 2010). For these reasons, several centers have reported excellent results in the management of LARC and LRRC, adapting their experience gained in the management of advanced or recurrent gynecologic pelvic malignancies, with promising results, offering a 5-year overall survival rates ranging from 35% to 50%, without any pelvic tumor progression (Harris et al 2015; Höckel 2015; Lee et al 2017; Bacalbasa et al 2019). Past classifications of the extent of resections, divided PE into anterior, posterior or total PE. These types of classifications focused only upon the antero-posterior axis (Kazi et al 2021b). More recently, a vertical classification was proposed, dividing the plane of PE into supralevatory, intralevatory, sublevatory (Yang et al 2013). The most recent classification, proposed by the team from Royal Marsden (Table 1), divides the pelvis in seven compartments and has its' rationale in both the embryologic development of the pelvic organs and in clear anatomical MRI visible landmarks (Georgiou et al 2013; Kazi et al 2021b). These seven compartments together to the levatori ani plane have been widely adopted when describing and standardizing the PE extent.

When performing a PE, it is mandatory to achieve a R0 en bloc resection, irrespective of the multivisceral (MVR) extent of the surgical resection (Courtney et al 2014; Ress et al 2015; Kazi et al 2021b). En bloc dissection and resection is recommended, avoiding dissecting the adhesions between the tumor and other visceral or parietal structures, since approximately 40-85% of these adhesions carry malignant invasion (Hyman et al 2005). By achieving these prerequisites, improved local recurrence (LR) rates (15 vs. 69 % for R0 vs. R1 resection) ($p < 0.001$) (Smith et al 2012; Courtney et al 2014) and 5-year overall survival (OS) rates can be obtained (Derici et al 2007; Courtney et al 2014). Worse outcomes have been reported when PE is performed for recurrent pelvic cancers than for primary locally advanced ones (Law et al 1998; Courtney et al 2014; Ress et al 2015). The most common indications for PE can be observed in Table 2 (Adapted from (Pawlik et al 2006)).

When planning to perform a curative intent PE, the surgical team should also take into account the absolute contra-indications of when not to offer this type of salvage surgery. These absolute contra-indications include (Law et al 1998): poor performance status, bilateral sciatic nerve involvement or circumferential bone involvement. Historically, some absolute cotra-indications have become relative contraindications, where the benefit of PE is uncertain; these include: $>180^{o}$ encasement of the iliac vessels, sacral bone invasion cephalad of the S2 vertebrae, tumor spread beyond the sciatic notch, unresectable extrapelvic metastases or R1/R2 predicted resection (Law et al 1998; Harris et al 2015). Even so, some high-volume centres successfully perform PE for these scenarios, bearing in mind the fact that constant technical and logistic novelty is brought in the reconstructive and rehabilitation systems.

Table 1. Definition of the seven intrapelvic compartmens (Adapted from (Georgiou et al 2013))

Definition of the seven intrapelvic compartments demonstrating the organs that are included in each compartment.

Compartment	Included organs and boundaries of compartment	Operations
Peritoneal reflection (PR)	Level of the rectovesical pouch or recto-uterine pouch of Douglas	Peritoniectomy
Anterior above PR	Ureters and iliac vessels above the peritoneal reflection, sigmoid colon, small bowel and lateral side wall fascia	Small bowel loop resection, sigmoidcolectomy, ureterectomy, iliac vessels resection/reconstruction
Anterior below PR	Genitourinary system (seminal vesicles, prostate, uterus, vaginal vault, bladder, urethra) and pubic symphysis	Prostatectomy, hysterectomy, vaginal wall resection and reconstruction, cystectomy, urethrectomy, sympysectomy
Central	Includes the rectum or neo-rectum, intra-luminal, extra-luminal or/ and perirectal fat or mesorectum recurrence	Local resection
Posterior	Coccyx, pre-sacral fascia, retro-sacral space and sacrum up to the upper level of S1	Coccycectomy, sacrectomy
Lateral	Ureters, external and internal iliac vessels, lateral pelvic lymph nodes, sciatic nerve, sciatic notch, S1 and S2 nerve roots and the piriformis or obturator internus muscle	Ureterectomy, iliac vessels resection/reconstruction, pelvic sidewall lymphadenectomy
Inferior	Levator ani muscles, external sphincter complex, perineal scar (if previously APER) and the ischio-anal fossa	Abdominoperineal resection of the rectum (APER)

Abbreviations: PR = peritoneal reflection, APER = abdomino-perineal excision of rectum.

Table 2. Frequent indications for performing PE

Most common indications for pelvic exenteration
Cervical carcinoma—recurrence after irradiation
Cancer of rectum or sigmoid—primary
Cervical carcinoma—primary
Endometrial cancer—persistent or recurrent
Vaginal cancer—primary or recurrent
Adenocarcinoma of the cervix—primary or recurrent
Squamous cell carcinoma of the vulva—recurrent
Squamous cell carcinoma of the anus—recurrent
Cervical carcinoma—palliative treatment
Prostate carcinoma—palliative treatment
Postirradiation fibrosis, necrosis, or fistula

The aim of the present paper is to briefly review the current recommendations, evidence and indications for performing PE and to compare the findings with our initial experience in the field.

Patients, Materials and Methods

1. Review strategy

Original published studies of pelvic exenteration for pelvic cancers were identifed by electronically searching Medline, Pubmed, and Cochrane library databases from January 2000 to January 2021. The following MeSH terms were used to perform the search: "exenteration," "pelvic exenteration," "cancer," "pelvic,". Studies were screened for information on surgical technique, type of tumor, mortality, morbidity, local recurrence rates, and survival rates. All relevant articles were assessed by two different reviewers. Related articles found on Pubmed were also reviewed to look for relevant articles. The reference lists of all articles that met our inclusion criteria as well as recent systematic reviews and meta-analyses were manually reviewed to identify potentially relevant studies. Only articles in English that were accessible in extenso (not only in Abstract form) were selected. The final number of reviewed articles was 190, out of which, we have selected the 40 most relevant guidelines, consensus papers, official Specialists' Societies Statements, systematic reviews, editorials and original articles.

2. Case presentations –(Note: both patients have consented for sharing their medical data and for potential academic purposes use)

Patient no. 1 – 71 years old male, ECOG 0, with no relevant family or personal history of malignancy, with mild hypertension, was referred to our institution with a recto-sigmoid junction moderately differentiated (G2) stenotic adenocarcinoma, invading the urinary bladder. He has initially diagnosed in December 2020, CT scan staged as cT4bNxMx. Prior to neoadjuvant chemotherapy (8 cycles of Xelox regime January-June 2021), he was subjected to a laparoscopic sigmoid colon loop colostomy for bowel obstruction prevention. During his chemotherapy treatment (March 2021), he was diagnosed with a synchronous urothelial bladder cancer (resected via cystoscopy – pT1R0). In August 2021, he was re-evaluated via a contrast-enhanced CT scan, without any signs of tumor downsizing or down-staging, with high suspicion of prostate and seminal vesicle involvement (Figures 1-3). No distant metastases to the liver, no signs of carcinomatosis and no ipsilateral hydronephrosis were seen; few mezocolic-enlarged lymph nodes were noted. CEA levels remained constant at 120 ng/ml, moderate leukocyt-uria with bacteriuria was noted, with negative bacteriology. Pelvic MRI scans (Figures 4 and 5) revealed no invasion in the levatori ani plane. Our clinical exam revealed an important uncomplicated and reducible stoma prolapse, with positive digital rectal exam (DRE) – tumor palpable at 10 cm from the anal verge, without any mobility of Douglas' pouch towards the urinary bladder. In-hospital cystoscopy did not identify intra-luminal bladder invasion, only mucosal protusion towards the neck of the bladder. The patient was discussed in a multidisciplinary team meeting, and was consented for supra-levatory total PE. Nutritional and physical prehabilitation started 2 weeks prior to hospital admission. Mechanical bowel preparation (per os and with enemas) associated to antibio-prophylaxis (Eritromycin + Metronidazole - per os) and trombo-prophylaxis, were undertaken on the pre-operative evening.

The next day, surgery was performed as planned (supra-levatory total PE, with en bloc segmental enterectomy, terminalisation of the loop colostomy, end-to-side uretero-ureteral left-to-right by-pass, right iliac fossa cutaneous ureterostomy – double stented, omental flap to the pelvis) (Figures 6-9). Intraoperative, the following findings were noted: caudal from the loop colostomy – a pelvic tumor block encompassing the terminal sigmoid colon, superior and mid rectum, the dome of the urinary bladder – also bearing small deposits of carcinomatosis, a loop of the terminal ileum, the seminal vesicles and proximal capsule of the prostate and deep in the retroperitoneum, the ilio-lumbar left ureter. We have to mention the fact the we have performed a "high-tie" of the inferior mesenteric artery (IMA), that the lower rectum was stapled-closed using blue 60-mm cartridges, and that the omental flap was made from left to right with the right gastro-epiploic artery as arterial pedicle. The total duration of surgery was 420 minutes, with approximately 600 cc intraoperative blood loss. The postoperative pathology report concluded the specimen to be a poorly differentiated mucinous adenocarcinoma with urinary bladder, left seminal vesicle and left ureter invasion, ypT4bN1b<<2/19>>M0L0V0Pn0R1 (left ureter – which was intraoperatively re-excised with negative margins).

Patient no. 2 - 67 years old male, ECOG 1, with no relevant family or personal history of malignancy, with moderate hypertension and type II diabetus mellitus, was referred to our institution with a known upper and mid rectal moderately differentiated (G2) stenotic adenocarcinoma (May 2020), with positive invasion of the posterior mesorectum and urinary bladder, positive lymph nodes (cT4b<<MRF+>>N2M0). At initial diagnosis, a PET scan was performed (not shown), which did not detect distant metastases, but only the intense metabolism of the primary tumour. Prior to neoadjuvant chemo-radiotherapy (8 cycles of CapeOX regime + 50Gy/25fr/32 days IMRT, July 2020-May 2021), he was subjected to an open sigmoid colon loop colostomy for bowel obstruction prevention. During his chemotherapy treatment (April 2021), he was diagnosed with a synchronous urothelial bladder cancer (resected via cystoscopy – pT1aR0). In July 2021, he was scheduled for radical surgery (other Institution). Then, a suboptimal anterior resection of the rectum was performed, with terminalisation of the loop colostomy (ypT3Nx-only 2 lymph nodes harvested-M0V0L0R2<<distal

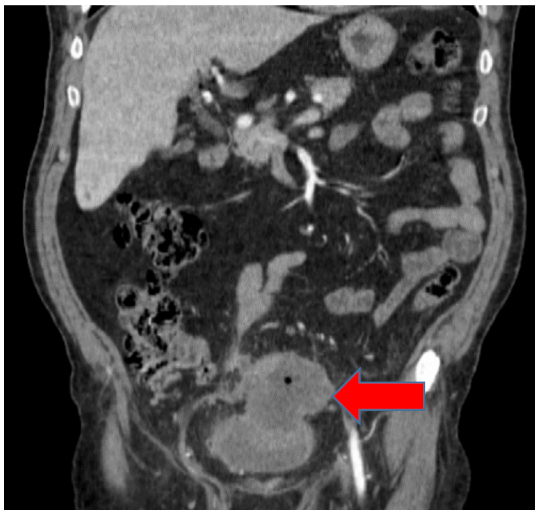

Figure 1. Contrast-enhanced abdominal CT scan (arterial phase; arrow pointing towards the tumor, invading the urinary bladder) – frontal view

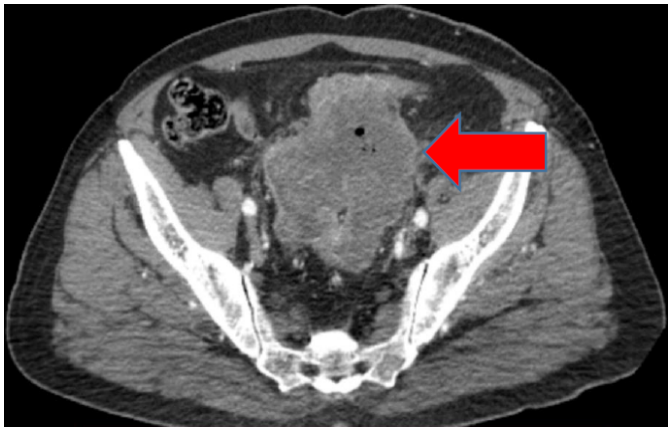

Figure 2. Contrast-enhanced abdominal CT scan (arterial phase; arrow pointing towards the tumor, invading the urinary bladder) – coronal view

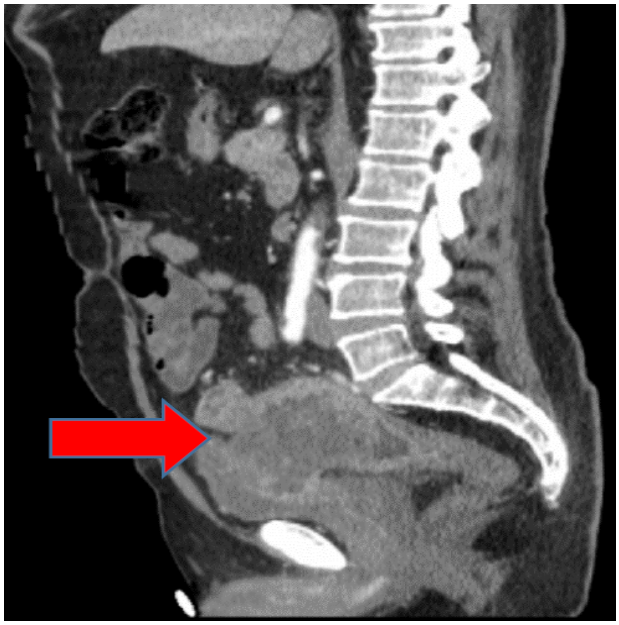

Figure 3. Contrast-enhanced abdominal CT scan (arterial phase; arrow pointing towards the tumor, invading the urinary bladder) – sagittal view

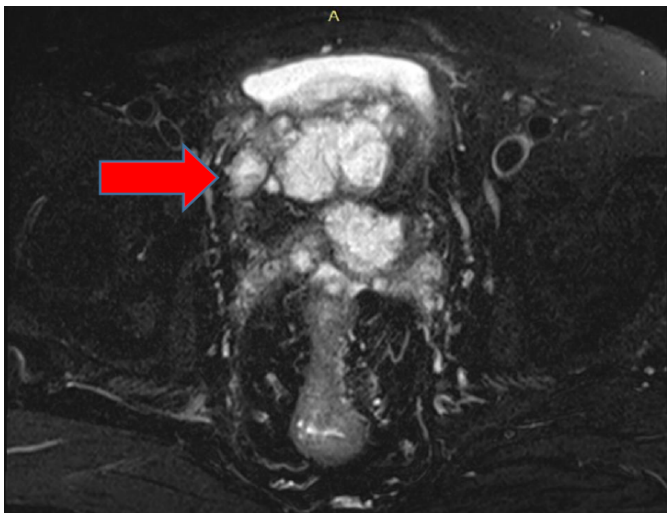

Figure 4. T2 fat suppression pelvic MRI (arrow pointing towards the tumor, invading the urinary bladder and prostate) – coronal view

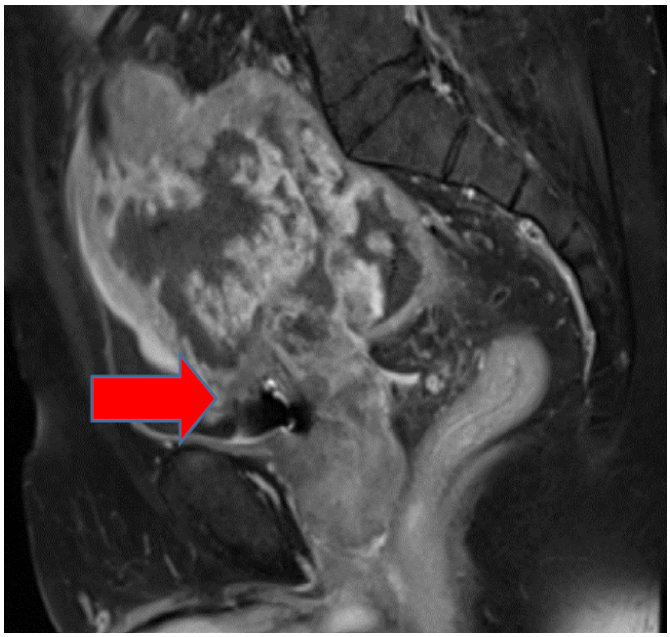

Figure 5. T1 TSE pelvic MRI(arrow pointing towards the tumor, invading the urinary bladder and prostate) – sagittal view

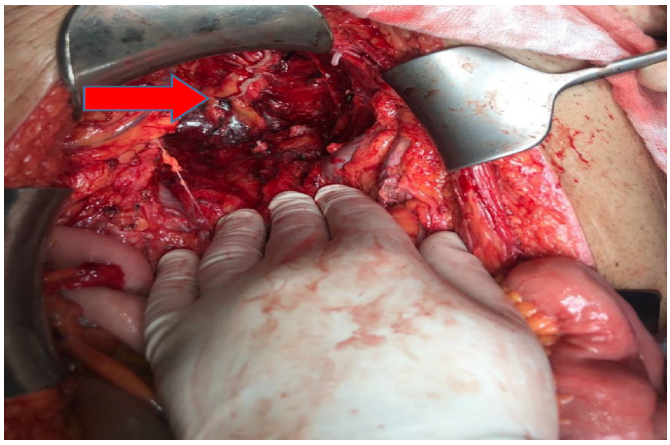

Figure 6. Post PE intraoperative aspect (arrow pointing towards stapled lower rectum; head of the patient towards the bottom of the picture)

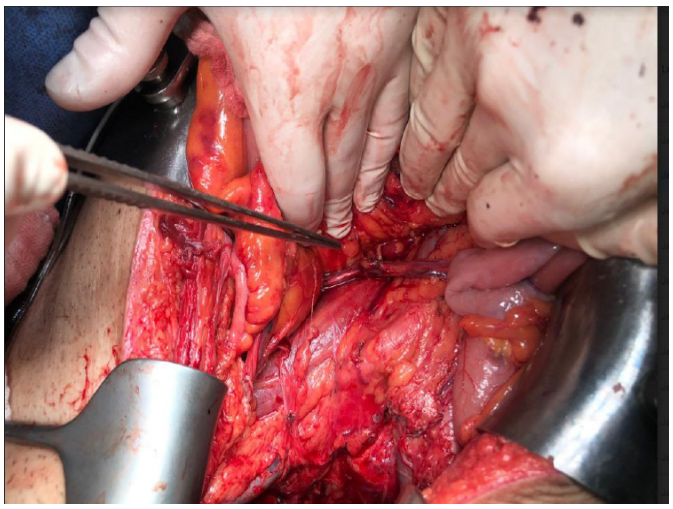

Figure 7. Post PE intraoperative aspect (forceps pointing towards the end-to-side uretero-ureteral bridging, with stents already in the lumen of both ureters; patient's feet towards the bottom of the picture)

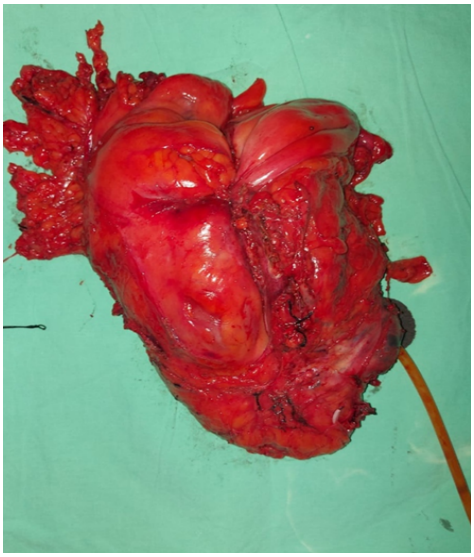

Figure 8. Post PE specimen (note the urinary catheter still in place, used for traction during the dissection)

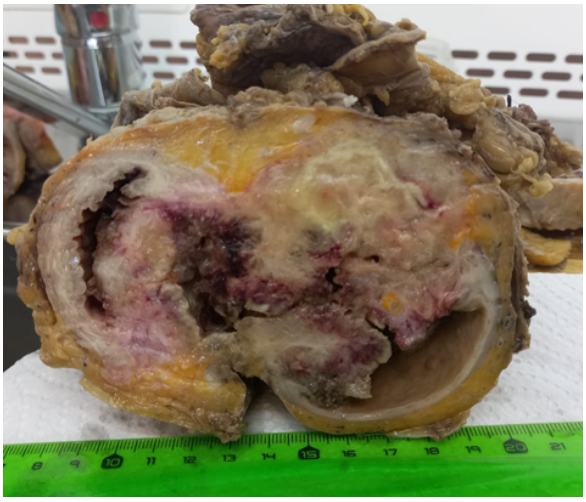

Figure 9. Post PE formalin-fixed specimen – transected at the level of the urinary bladder and prostate

Figure 10. Contrast-enhanced abdominal CT scan (arterial phase; arrow pointing towards the tumor, invading the urinary bladder) – sagittal view

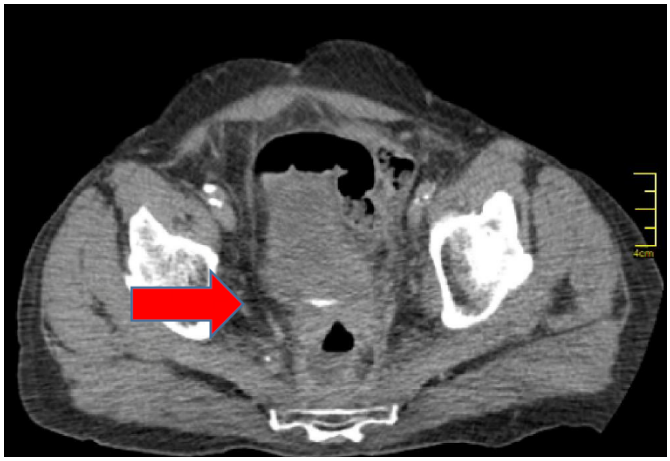

Figure 11. Contrast-enhanced abdominal CT scan (arterial phase; arrow pointing towards the tumor, invading the urinary bladder) – coronal view

margin>>), without any subsequent systemic therapy given. In September 2021, his rectoscopy re-evaluation identified the remnant mid rectal stump evolving tumour, with clear signs on CT (Figures 10 and 11) and pelvic MRI scans (not shown), of prostate and posterior mesorectal invasion.

On the contrast-enhanced CT scan, signs of tumor progression were seen, with high suspicion of prostate and seminal vesicle involvement, but without any distant metastases to the liver, no signs of carcinomatosis and no ipsilateral hydronephrosis seen; few mezocolic-enlarged lymph nodes were noted. CEA levels remained constant at 86 ng/ml. Our clinical exam revealed an important uncomplicated and reducible parastomal hernia in the left iliac fossa, with positive digital rectal exam (DRE) – tumor palpable at 8 cm from the anal verge, without any mobility of Douglas' pouch towards the urinary bladder, nor towards the sacrum. In-hospital cystoscopy did not identify intra-luminal bladder invasion or tumour recurrence. The patient was discussed in a multidisciplinary team meeting, and was consented for total PE. Nutritional and physical prehabilitation started 2

Figure 12a. Enterectomy and completion proctectomy specimens

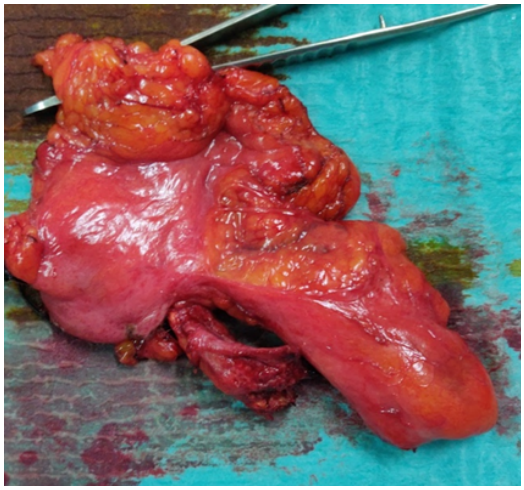

Figure 12b. Completion distal sigmoid colectomy + IMA lymph nodes staging specimen

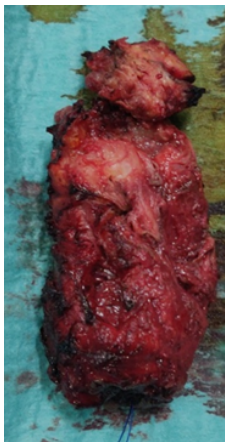

Figure 13. Completion distal proctectomy specimen

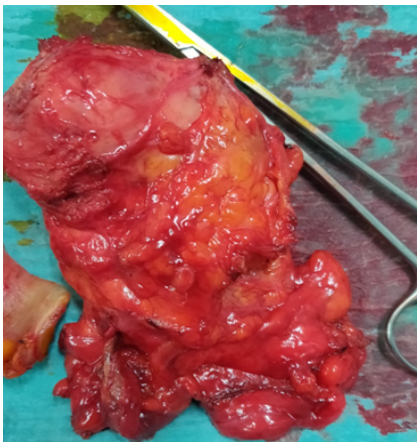

Figure 14. Completion cysto-prostatectomy specimen

weeks prior to hospital admission. Mechanical bowel preparation (per os and with enemas) associated to antibio-prophylaxis (Eritromycin + Metronidazole - per os) and trombo-prophylaxis, were undertaken on the preoperative evening.

The next day, surgery was performed as planned (total sublevatory PE, without an en bloc segmental enterectomy, totalisation of the abdominal perineal resection, with completion lymph node staging – "high tie" of the IMA, terminalisation of the loop colostomy, bilateral cutaneous ureterostomy – stented, omental flap to the pelvis) (Figures 12-14). Intraoperative, the following findings were noticed: pelvic tumoral bloc encompassing the remnant superior rectum, mid and low rectum, with urinary bladder invasion, prostate, seminal vesicles, distal ileum, left ureter (dilated), presacral fascia (from S2-S5), left internal iliac vessels. The presacral fascia and left interal iliac vessels – were marked with metal clips, in order to facilitate future boosts of radiotherapy. The procedure was performed in two settings – abdominal and perineal stage. Since the post-radic and previously operated pelvis was not favorable for an en bloc resection, all resected organs were dissected separately. The total duration of surgery was 390 minutes, with approximately 300 cc intraoperative blood loss. The postoperative pathology report concluded the specimen to be a moderately differentiated tubular adenocarcinoma with urinary bladder, left seminal vesicle prostate invasion, ypT4bN0<<0/34>>M0L0V0Pn0R2 (macroscopically positive posterior mesorectum, which was in contact to the presacral fascia).

Results and cases discussions

When planning a PE with curative intent, irrespective of primary tumor histology, several authors have underlined the importance of performing a full panel of imagining studies (Memon et al 2014; Harris et al 2015; Lee et al 2017). Extensive contrast-enhanced CT scans are useful for determining distant metastatic disease; pelvic contrast-enhanced MRI is the most accurate in determining the local resecability, vascular structure involvement and bony invasion (with or without intra-rectal/intravaginal gel administration); furthermore, 18FDG-PET scans have proven their utility especially for central pelvic disease derived from gynecologic malignancies (Memon et al 2014; Harris et al 2015; Kazi et al 2021b), with focus on differentiating between tumor invasion or desmoplastic post-radiation fibrosis. 18FDG-PET is moreover the most accurate tool for determining the presence of occult distant metastases (Memon et al 2014; Ng and Lee 2021). For all of the above-mentioned studies, rectal endoscopic ultrasound examination (EUS) can be added when the surgical team has inconsistent data concerning sphincter involvement (Kazi et al 2021b), thus offering more preoperative information regarding the plan of whether to perform a supra/intra/extra-levatory PE, or a total PE.

The tumor involving the lateral pelvic wall (vascular structures) was considered in the past to be a relative contraindication for performing PE, especially in the recurrent setting of the disease (Courtney et al 2014; Kazi et al 2021b; Ng and Lee 2021). To this day, vascular reconstruction can be achieved either via a primary suture/anastomosis, or by graft interposition or graft/saphenous vein bypasses (Kazi et al 2021b; Ng and Lee 2021), without affecting LR or OS rates. However, R0 resections are achieved in lower number of cases when lateral walls of the

pelvis are involved (Courtney et al 2014). Some specialized centers (Höckel 2015; Lee et al 2017; Ng and Lee 2021) even perform, in a preoperative setting, vascular embolization of the internal iliac artery, advocating the fact that such strategy could come to aid the surgical team, via either downsizing the primary tumor, and offer intraoperative vascular control (especially for tumor centrally located in close proximity to the iliac vessels, or partially encasing them).

Posterior, sacral involvement, was, in the past, also considered a relative contraindication for performing PE (Moore et al; Ito et al 2003; Salom and Penalver 2003). Mixed approaches (abdominal + prone jack-knife lithothomy) with subsequent composite lumbar fusion or titanium rod reconstructions covered by synthetic meshes or local flaps, have offered promising results, as long as the sciatic nerve is spared by tumor involvement (Lee et al 2017; Kazi et al 2021b; Ng and Lee 2021).

PE attempts have also benefited from the introduction in the past decades of intraoperative radiation methods (IORT) or hyperthermic intraperitoneal chemotherapy (HIPEC), with some benefit for selected cases for subsequent local control of the disease or for reducing residual tumor burden, in the case of R1 resections (Shoup et al 2002; Wibe et al 2004). Novel local advancement (gluteal) or pedicled myo (cutaneous) flaps (especially Vertical Rectus Abdominis Muscle – VRAM, gracilis muscle or superior/inferior gluteal artery muscle flap – SCAP/IGAP) used for pelvic wall and vaginal reconstruction, add some increase in the QoL and sexual function preservation of the patients in the postoperative setting (Goldberg et al 2006; Pawlik et al 2006; Rodriguez-Bigas et al 2010; Devulapalli et al 2016; Kazi et al 2021b; Radwan et al 2021). In this matter, several authors have reported that in total PE, the use of flaps (irrespective of perioperative radiotherapy), have a lower morbidity rate consisting in pelvic surgical site infections (SSIs), chronic wounds or wound dehiscence, perineal fistulae or bowel obstruction, when compared to primary suture of the remnant pelvic myocutaneous structures (Salom and Penalver 2003; Goldberg et al 2006; Kaur et al 2014; Devulapalli et al 2016; Radwan et al 2021). The use of VRAM flaps, even if it is a very elegant strategy in preventing the potential development of perineal complications, has a major disadvantage when multiple ostomies formations are required, since it compromises the integrity of the anterior abdominal wall; for this reason, many centers advocate for the use of bilateral gluteal advancement flaps (Lee et al 2017; Ng and Lee 2021). Depending on the primary tumor's location and invasiveness, in some cases sphincter-preserving resections can be achieved, without the need of pelvic reconstructions, thus offering the possibility of primary colorectal/colo-anal anastomoses, with lower morbidity rates and better QoL scores, when some type of reservoirs/pouches are tailored (Goldberg et al 2006; Kaur et al 2014; Höckel 2015; Lee et al 2017; Kazi et al 2021b). When urinary diversion strategies rely on continent ileal conducts for urinary reconstructions, the QoL in the postoperative setting, was better than when using direct cutaneous ureterostomies (Rodriguez-Bigas et al 2010; Bacalbaşa and Bălescu 2015; Höckel 2015; Kazi et al 2021b). Vascular sealing devices have added much aid in reducing intraoperative blood loss and duration of surgeries (Martin et al 2012; Courtney et al 2014; Kazi et al 2021b), and have become an useful tool in the armamentarium of the surgeon.

In order to prevent the development of either perineal hernia, neo-vaginal/remnant vaginal vault prolapse, or even intestinal obstruction, several strategies have been proposed for the management of the empty pelvis. The most frequently used autologous flap for filling the empty pelvis in the reconstructive phase of PE, is the greater omentum. This flap can be tailored using as vascular pedicle the right or the left gastroepiploic arteries (when the stomach's greater curvature vascular arch is ligated on one of the vascular partners), or outside the gastroepiploic arch, if the greater omentum is of abundant volume (Harris et al 2015; Ng and Lee 2021). Polyglicolic acid (Vicryl®) meshes have also been reported to add additional pelvic cephalad border, when fixed at the pelvic brim, thus preventing the descent of small bowel loops inside the pelvis with a subsequent small bowel obstruction (Ng and Lee 2021). Biologic meshes (bovine or porcine acellular dermal matrixes – ADM) have sometimes been used for offering additional perineal support, especially in the cases of an intralevatory or total PE, reducing the risk of perineal wound dehiscence, perineal incisional hernias chronic sinuses, in the event where other pedicled flaps have not been used (Byrnes et al 2011; Courtney et al 2014; Kazi et al 2021b; Ng and Lee 2021)

Some high-volume centers advocate that in carefully selected patients (i.e center pelvic disease, primary locally advanced pelvic malignancies, local recurrence confined to the lateral lymph nodes of pelvis, no extensive prior radiotherapy, planned supralevatory PE), minimally invasive surgery (robotic or laparoscopic), could be taken into consideration as a viable option. Even if this proposal is generally not the rule, but the exception, one general consent is that every PE attempt should start with an exploratory laparoscopy, since approximately 30% of the planned PE patients have peritoneal carcinomatosis, undetected at preoperative imaging studies (Iavazzo and Gkegkes 2014; Lee et al 2017; Kazi et al 2021b, 2021a).

Our initial experience

In our initial experience, since major surgery was planned at initial outpatient consultation (both of the patients), we decided to offer extensive nutritional prehabilitation using Fresubin® Energy drink/Nutridrink® – 200 ml bid for 14 days prior to hospital admission (thus offering elemental intake, enriched protein diet and polysaccharides); physical prehabilitation recommendations included at least a 20 minutes light jog daily.

Both patients were preoperatively assed clinically with digital rectal exam (DRE), per-stomial digital exam and transrectal/per-stomial flexible endoscopy. The only imaging studies performed were a contrast-enhanced thorax-abdomen-and pelvis CT scan and a pelvic MRI. The drawback of these scans for both of the patients is that they were performed prior to hospital admission (cca. 4 weeks) and not during the perioperative setting, setting which somehow proved to be misleading when choosing the surgical approach and planning. Unfortunately, no 18FDG-PET scans were performed, which would have been useful for both patients (except the initial PET scan performed at the moment of diagnosis for patient no. 2). Patient no. 1 would have potentially benefited in differentiating between tumor involvement of the ileum versus local desmoplastic reaction; whereas for patient no. 2, a new PET scan could have been useful in determining the true invasion of the prostate, thus helping our surgical team

to plan only a posterior PE, and not a total one. Both patients underwent a preoperative flexible cystoscopy due to their recent history of bladder urothelial carcinomas (both T1, resected endoscopic); this approach was very cautious since for patient no.1 bladder invasion was suspected on interval scans during the neoadjuvant setting that was not confirmed intraluminal.

Since both patients had previous open surgeries, in a multidisciplinary setting, we have decided to perform an upfront laparotomy, without any exploratory laparoscopy to begin with, since our strategy was that of curative intent.

When comparing our initial cases to the case series reported in the literature, none of the two cases benefited from IORT or HIPEC, even though, at the time of surgery, patient no. 2 would have been an excellent candidate for the former (macroscopic intraoperative R2 resection).

Patient no. 1 did not need a pelvi-perineal reconstruction, since the type of PE performed was a supra-levatory one, and his empty pelvis was managed via an omental pedicled flap; however, even if the same use of the omentum was performed for patient no.2, his perineal partial wound dehiscence (Clavien-Dindo Grade I complication) might have been prevented if either a VRAM, SGAP/IGAP myocutaneous flap would have been used; our decision was to abandon the creation of such a flap, mainly because we had suspected a macroscopic intraoperative R2 resection.

For patient no. 1, our intraoperative decision was to not perform a colorectal primary anastomosis, considering it to by a risky one, since we have already performed a segmental enterectomy of the suspected area of tumor invasion in one of the distal ileal loops, where primary end-to-end hand-sewn single layer extramucosal anastomosis using continuous PDS 3.0 USP suture, was performed. In the near future, patient no. 1 could be a candidate for bowel continuity restoration, if no local recurrence occurs. Patient no. 2, had his loop colostomy converted to a terminal colostomy per primam (suspected intraoperative R2 resection) with clear prostate invasion, where we have upfront decided to undertake a total PE. The latter had a similar suspected ileal invasion, handled identically as per patient no. 1.

Both patients benefited from vascular sealing devices intraoperative; both the LigaSure ® Maryland 5 mm and 10 mm devices were used for patient no. 2, whereas patient no. 1 benefited from the use of the new Enseal X1 10 mm device. These devices truly facilitated deep pelvic dissection and haemostasis, and, it is to our best belief that they have contributed to a decrease in operative time.

For patient no. 1, during the reconstructive steps of the procedure, we had decided to perform a uretero-ureteral left to right internal bypass, thus facilitating one single double stented cutaneous ureterostomy in the right iliac fossa; the rationale for doing this type of "bridging" was in direct relation to the fact that the left remaining lumbar ureter was significantly shorter than the right one, since its' tumour invasion by the sigmoid colon was in close proximity to it. For patient no. 2, upfront bilateral cutaneous ureterostomies were performed, bearing in mind the fact that an ileal Bricker/Wallace continent conduit would have been at risk for urinary fistula in the event of additional radiation boosts given for the suspected R2 sacral involvement.

For both patients, we have mobilized the greater omentum (patient no. 1 from left-to-right, patient no. 2 from right- to- left), inside the greater curvature's vascular gastro-epiploic arch, and descended the resulted omental flap to fill the empty pelvis. We did not use any Vicryl® Mesh sutured at the evel of the pelvic brim, because of financial reasons. We indeed agree, that for patient no. 2 an acellular-dermal matrix biologic mesh (ADM), or a completely absorbable synthetic mesh (such as the new Phasix ST®) would have added substantial benefit in preventing future perineal incisional hernias or, bowel protection against the development of post-radiation enteritis, in the event of sacral radiotherapy. Again, this was not undertaken, for the same financial restrictions.

One special consideration needs to be addressed for patient no. 2, where sacral involvement was suspected. Since our multidisciplinary team did not include an Orthopaedic Surgeon and no frozen sections specimens from the sacral bone were obtained, we have decided intraoperatively, only to place metal clips on the sacral bone, thus facilitating the planned radiation boosts on the suspected macroscopic invasion, and not to perform a below-S2 sacrectomy.

In-hospital ICU stay for both patients was 4 days, uneventful, except for patient no.1 whose bowel movements, per-stomial flatus and stool output only happened on day 3 (partially obstructing ileus – managed in a conservative fashion). Same patient had 2 postop blood transfusions, since his intraoperative blood loss was approximately 600 cc. No 30-days major morbidity events have been reported with our patients. Renal sonography was performed on day 2 and 7 postop, revealing no signs of hydronephrosis, nor of urinary fistulae. Patient no. 1 was discharged on day 7, whereas patient no. 2 was hospitalized for 11 days (ICU + ward), mainly because of his conservative management of the perineal wound partial dehiscence. RO resections were achieved for both patients, even if intraoperatively, patient no. 2 was assessed as a macroscopically R2 resection (presacral/sacral tumor deposits). The enterectomy specimens for both patients were tumor free; the suspected tumor invasion was, in fact, desmoplastic fibrotic local reaction. Ureteral stents were changed, as planned at 6 weeks postop. At 90-days control CT scans, both patients were without any local pelvic recurrences. Patient no. 1 presented with oligometastatic infra-centimetric liver and lung progression for which he received second line systemic therapy with FOLFIRI regimens plus Bevacizumab (KRAS mutant). Patient no. 2 received subsequent 3x5 Gy sacral bone boosts and is currently under the same second line systemic therapy.

Our first cases of successful PE have two major particularities. First of all, both patients have been previously operated in a different setting with palliative intent (loop colostomies) and have received palliative systemic therapies, baring tumors considered to be unresectable. Patient no. 2 was re-operated after neoadjuvant systemic treatment (without radiation therapy): suboptimal R2 anterior resection, with macroscopic residual mid rectal tumor, without any TME, nor regional lymphadenectomy performed (initial 2 lymph nodes harvested). Our surgical team's effort addressed a posterior compartment advanced rectosigmoid cancer with bladder, left ureter and ileal involvement (Patient no. 1) and a progression of an advanced mid-rectal cancer (a mix of LRRC and LARC – patient no. 2) – with prostate and small bowel involvement. For patient no. 2 a completion ELAPE APR was of necessity, since staging and curative lymph node

dissection on the IMA was not previously done. It is to our best belief that young teams, interested in pelvic surgery, the first attempts of PE should be undertaken in either LRRC or LARC patients, especially when situated on the learning curve. The rationale behind this is that in most of the cases, embryologic spaces are not previously violated, as described by several other teams (Ito et al 2003; Palmer et al 2005; Goldberg et al 2006; Pawlik et al 2006; Kazi et al 2021b; Ng and Lee 2021). For gynecologic cancers primary advanced or recurrent, to our best initial knowledge, the expertise of a Plastic Surgeon should be taken into account, since in most of the cases, some type of perineal/vaginal reconstruction is needed (Goldberg et al 2006; Devulapalli et al 2016; Radwan et al 2021).

Conclusions

PE remains a radical procedure, which can be safely performed with a multidisciplinary approach (Surgical Oncologist, Uro-Oncologist, Anaesthesiology and Intensive Care Physicians, Plastic Surgeon, Orthopedic Surgeon, Radiologists). Our initial experience of two selected cases with historically uncommon indication for PE (advanced and recurrent rectosigmoid cancers), offers promising results for the implementation of this technique for other pelvic pathologies (i.e urological cancers, soft tissue sarcoma, gynaecologic malignancies). Each PE should be offered and performed in a tailored fashion according to clinical and imaging findings and tumour characteristics. Total PE im most of the cases an overtreatment, and compartmental (anterior/posterior/lateral) or sphincter-preserving (supra/intra-levatory) strategies should be offered in order to improve the patient's postoperative QoL without any oncologic compromise, furthermore facilitating targeted oncologic treatment to prevent relapses.

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Authors

•Mihai Ștefan Mureșan, Department of Surgery, Cluj-Napoca Municipal Hospital, 11-13 Tăbăcarilor Street, Cluj-Napoca, Romania, VIIth Department of Surgery, Vth Surgical Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy, 8 Victor Babes Street, Cluj-Napoca, Romania, email: mihai.stefan.muresan@gmail.com

•Vitalie Gherman, Urology Department – Cluj-Napoca Municipal Hospital, 11-13 Tăbăcarilor Street, Roamania, e-mail: vitaliegherman@yahoo.com

•Cornel Cheregi, Surgery Department – Oradea Military Hospital, 3 Dunărea Street, Oradea, Romania, e-mail: cheregicorneldragos@gmail.com

•Mihai Sebastian Mihalcea, Department of Surgery, Cluj-Napoca Municipal Hospital, 11-13 Tăbăcarilor Street, Cluj-Napoca, România, e-mail: mihalcea.sebastian@gmail.com

•Ion Imihteev, Department of Surgery, Cluj-Napoca Municipal Hospital, 11-13 Tăbăcarilor Street, Cluj-Napoca, România, e-mail: imihteevion@gmail.com

•Raul Micu-Chiș, Department of Surgery, Cluj-Napoca Municipal Hospital, 11-13 Tăbăcarilor Street, Cluj-Napoca, România, e-mail: micuchisrauldaniel@gmail.com

•Radu Fodor, Faculty of Medicine, Univeristy of Oradea, 10 Piața 1 Decembrie, Oradea, Romania, e-mail: dr.radu.fodor@gmail.com

•Hassan Noor, Department of Surgical Medicine, County Clinical Emergency Hospital of Sibiu, Sibiu, Romania, Faculty of Medicine, "Lucian Blaga" University, 10 Victoriei Boulevard, Sibiu, Romania, e-mail: nmfhassan@gmail.com

•Alexandru Iliescu, Oncology Department, Salaj County Emergency Hospital, 67 Simion Bărnuțiu Street, Zalau, Romania, e-mail: iliescu_zone@yahoo.com

•Calin Ionescu, Department of Surgery, Cluj-Napoca Municipal Hospital, 11-13 Tăbăcarilor Street, Cluj-Napoca, Romania, VIIth Department of Surgery, Vth Surgical Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy, 8 Victor Babes street, Cluj-Napoca, Romania, email: ionnescu.calincj2002@gmail.com

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