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11. The place of pelvic exenteration as a cytoreductive procedure in advanced gynaecologic malignancies

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Abstract. For now 60 years pelvic exenteration is in the armamentarium of pelvic surgeons for the treatment of advanced pelvic malignancies. The biology of malignant tumors originating in the pelvis - locoregional tumor progression and only late stage distant spread - was the basis for the development of a radical surgical technique removing the tumor en-bloc with the adjacent pelvic organs. The original procedure described by Brunschwig in 1948 comprised the resection of rectum and bladder followed by a "wet" colostomy with implantation of both ureters into the colon. Originally described for palliation of symptoms this procedure was initially afflicted with a high surgical mortality and morbidity, but on the other hand became the only surgical option offering cure for advanced stage and recurrent pelvic tumors. Over the years, improvements in perioperative management and surgical technique modified the procedure including continent reconstruction techniques for bowel and bladder making the operation more acceptable for patients.

To date more than 95% of patients not only survive the procedure, but may also encounter 5-year survival rates of 40% or more depending on the individual patient selection criteria. This improvement in outcome parameters is paralleled by an increase

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in continent urinary and intestinal reconstruction techniques which have made pelvic exenteration in appropriately selected cases not only acceptable but indispensable for the treatment of advanced gynaecologic malignancies.

Introducing the concept of pelvic exenteration

The concept of pelvic exenteration (PE) goes back to the 1940s when some centers in the US developed a surgical technique to treat locally advanced or recurrent pelvic cancers. The concept was based on the observation that tumors in the small pelvis, especially cervical and rectal cancers, have common biological features. They show locoregional invasion and metatastatis but distant metastasis only occur at late stage disease as tumors only rarely spread by hematogeneous route. Tumor persistence or recurrence within the pelvis is the major cause of death in patients suffering from cervical cancer (1). Patients with advanced or recurrent disease in the pelvis frequently develop infiltration of neighbouring organs like urinary bladder, ureter or intestine resulting in urinary complications including obstruction, fistula formation, uraemia or intestinal obstruction with ileus and/or fistula formation. These observations allowed the conclusion that an ultra-radical local therapy of advanced or recurrent pelvic malignancies might not only relief symptoms or prevent complications, but might also have significant impact on patients' prognosis.

The development of the concept of PE is traditionally credited to Alexander Brunschwig (*1901-†1969) (2) who published his first report on this technique in 1948 (3). He described an en-bloc resection of the pelvic viscera including rectum and anus, urinary bladder and parts of the perineum for the treatment of recurrent cervical cancer. Intestinal and urinary deviation was provided in form of a wet colostomy. Surgical mortality (death within 30 days post surgery) of this procedure at that time was high (23%) and long-term survival was short. Over the past 60 years numerous modifications to pelvic exenteration have been introduced with respect to patient selection criteria, perioperative management, surgical technique and methods for the reconstruction of bladder and bowel function. The initial "total" pelvic exenteration had been modified into a procedure preserving either the rectum (i.e. anterior PE) or bladder (i.e. posterior PE). Still, in appropriately selected patients, pelvic exenteration is considered to be the only therapeutic option offering cure.

In the following paragraphs of this chapter we are going to describe the initial surgical technique, its potential indications and modifications over time. We will summarize the published studies with special emphasis on outcome parameters and will highlight current indications and potential future

prospects for this challenging surgical procedure. As in the field of gynaecologic oncology patients with cervical and endometrial cancers represent the largest group of patients undergoing PE this review will focus on these two entities.

Original technique

Alexander Brunschwig, attending surgeon at the New York Memorial Hospital, started in 1946 to treat women with advanced pelvic malignancies with a new ultra-radical en-bloc resection of the pelvic viscera. In his first report, which was published in 1948 (3), he summarized the outcome of 22 patients who underwent exenteration for palliation of symptoms caused by locally advanced malignant disease in the pelvis. These patients were mainly suffering from cervical cancer. Although no patient died during the operation perioperative mortality was 23% with 5 patients dying from early surgery related complications.

In his original report the technique was described as follows: In a first ‘abdominal phase’ and after a low midline incision the abdomen is palpated and the bowels are packed upwards. In Trendelenburg position the posterior parietal peritoneum is incised over aorta and the incision is carried down bilaterally to both external iliac arteries. The infundibulo-pelvic ligament is dissected and ligated and the hypogastric artery and vein are ligated and transsected at their origin. A pelvic node dissection along the iliac artery is performed. Then the mesosigmoid is divided over the left common iliac vessels and the sigmoid pushed cephalad. Analogous to the other pelvic side dissection is performed and the hypogastric vessels are cut. After division of the round ligament, on both sides the obturator space is developed and the obturater vessels and the tissue is transected and developed medially under preservation of the obturator nerve. The peritoneal reflection from the anterior abdominal wall onto the bladder is dissected and the bladder completely mobilized except its attachments at the base. Both ureters are then dissected with a sufficient distance to the tumor and the ureters are implanted into the sigmoid colon. The upper pelvic colon is transected and each cut end invaginated by a purse string suture. Then the recto-sigmoid is dissected away from the concavity of the sacrum and mobilized completely to the pelvic floor. This way the specimen is completely mobilized except its attachments to the pelvic floor. The midline incision is closed and the wet colostomy is brought out through the incision.

In the second perineal phase the vaginal introitus and the rectum are closed by continuous suture and an elliptical incision emcompassing introitus and anus preserving the clitoris is performed. The levator ani muscle is

dissected and the pelvic viscera are removed en-bloc and the perineal wound is closed.

Indications and contraindications

General indications for PE in gynaecologic oncology are advanced primary or recurrent tumors of the uterine cervix, corpus and the vulva. According to their position in the treatment concept procedures can be classified as primary, secondary or palliative. By definition the intent of exenterative procedures labelled as primary or secondary must be to cure the patient from disease.

The fact, that some studies on the outcome after PE also include ovarian cancer cases, makes results hard to compare as its distinct biology and good response to chemotherapy is not comparable with other gynaecologic malignancies. Ovarian cancer debulking can only be considered as indication if it requires a true compartimentalized resection of the inner genitals in combination with bladder and/or rectum. Due to the fact that in most ovarian cancer cases disease is limited to peritoneal cavity with infiltration of the recto-sigmoid at the

Site	Primary	Secondary	Palliative	Contra-indications
Cervix **Vagina** **Vulva**	Selected cases FIGO stage IVA, cases with fistula formation if complete resection is probable (Incidental bladder or rectum infiltration during scheduled radical hysterectomy)	- central recurrence or tumor persistence after surgery or chemo- radiation (- recurrence after primary surgery)	Probably in highly selected cases with vesico-vaginal or rectovaginal fistula formation	- Distant Metastasis - Positive pelvic lymphnodes - Local irresectability - (Pelvic sidewall infiltration)
Endometrium	-	Central recurrence		
-Soft tissue sarcoma **- Melanoma** **-Neuroendocrine cancers** **- others**	Cases with rectal/bladder infiltration and probability of complete resection, tumors with known radio-resistance	-		

Indications for primary, secondary and palliative PE.

level of the Douglas pouch it rarely requires a pelvic exenteration-like procedure by definition.

Indications for primary exenteration

The term “primary” PE describes exenterations which are performed as the initial treatment after primary diagnosis. The use of exenteration as primary treatment for advanced gynaecologic cancers has been reported by numerous centers worldwide (4-8). Potential indications for primary exenteration are classically FIGO stage IVA cancers of the uterine cervix invading the wall of the bladder or bowel mucosa, patients with bulky tumors having tumor- or therapy-associated fistula formation and such tumors, in which radiation or chemotherapy is not likely to lead to a clinical response as in soft tissue sarcomas or neuroendocrine tumors (9). According to the FIGO annual report 2006 5-year survival is 22% in stage IVA cervical cancer and 21 to 30% in endometrial cancers depending on histological grade (10, 11).

At advanced cancer stages surgical treatments traditionally compete with chemo- and or radiation therapy either in a neoadjuvant or primary setting. There are numerous trials showing the efficacy of radiation therapy in combination with cis platinum based chemotherapy for advanced stages of cervical cancer (12-15). Several investigators have been favouring primary exenteration as a reasonable first-line therapy (6, 7, 16-18). However, no prospective randomized clinical trial has been performed yet to directly compare the outcome after chemo-radiation and after primary exenteration for FIGO IVA cervical cancers. The only available data so far is based on observational studies and retrospective analyses (7, 8, 17, 18). This is due to some drawbacks related to the design of such a trial:

1. The number of potential patients to be enrolled into a surgery arm is limited due to some basics characteristics that need to be present like tumor-free pelvic sidewall, the absence of lymph node involvement or extrapelvic spread and a physical performance status which allows major surgery.
2. Screeening programs in many developed countries, which in general provide the vast majority of clinical studies, have led to a decrease in the total number of advanced stage cases so that a monoinstitutional trial even in major referral centers is unlikely to recruit a sufficient number of patients to detect potentially significant differences in survival and morbidity.

Especially in cases with bulky tumors radiation therapy is likely to result in tissue necrosis potentially leading to fistula formation which impairs

patients' quality of life (13, 19). The success rate of a local attempt to surgically repair radiation-related fistula is low so that these cases have to be considered for primary PE.

It remains debatable if PE is a reasonable option for FIGO IVA endometrial cancer as patients mostly present with metastatic disease. There is no survival data after surgical therapy for this rare subset of patients available so that indication for PE might be limited only to a highly selected subset of patients.

Indications for secondary exenteration

Exenterations are termed "secondary" if they are performed for recurrent or persistent disease after prior radiation or chemo-radiation therapy. Patients with FIGO IB to IIA cervical cancer undergoing radical hysterectomy (Wertheim-procedure) show a recurrence rate of 10-15% with a pelvic localization of the recurrence in 60% of cases. Patients with stage II to stage III cervical cancer primarily treated by radiation relapse in 20-50% (20). Approximately 70% of patients with locally advanced cervical cancer relapse and most of them die from uncontrollable disease in the pelvis (18, 21). It is commonly accepted that PE is a valid treatment option for patients with a central recurrence or persistent disease after (chemo-) radiation therapy. The survival rates for secondary exenterations are reported between 16 and 60%.

Another unanswered question is the role of PE for the treatment of a local recurrence after surgery without prior radiotherapy. There are no studies available comparing the outcome of PE for this indication with the results of chemo-radiation, so that PE cannot be generally recommended. Some authors suggest that if the recurrence appears to be completely respectable and is not likely to respond to chemo-radiotherapy (cervical adenocarcinoma, tumor size >3cm tumor extension to the pelvic side wall) pelvic exenteration should be considered (4).

Patients with endometrial cancer usually present at an early stage with excellent survival rates after treatment. However, approximately 11% relapse, half of which with a local pelvic recurrence. PE for central recurrence in endometrial cancer without evident lymph node metastasis is also a therapeutic option offering cure with 5-year survival rates between 20 and 40% (22, 23).

Indications for palliative exenteration

Although initially developed for the palliation of symptoms of advanced and non-curable pelvic cancers especially its use for palliation remains

debatable (24, 25). Because of the high postoperative morbidity and mortality rates associated with this procedure some authors do not believe in the use of PE for palliation (26-31). Other authors advocate that PE can improve quality of life and therefore in appropriately selected cases is indicated for palliation (32, 33).

Frequently presented palliative indications are 1) pelvic **pain** due to infiltration of the nerval plexus, refractory to medical treatment, 2) recurrent severe **hemorrhage**, 3) entero-vesical, entero-vaginal and vesico-vaginal **fistula** formation and its related symptoms, 4) **abscess** formation on the basis of infected tumor necrosis and 5) subtotal or total intestinal **obstruction**.

Many investigations on palliative exenterations were performed at a time when currently established options for palliation of symptoms were not available. Nowadays novel chemotherapeutics and re-irradiation in combination with surgical suprapelvic diversion can be considered. Patients predominantly suffering from deep visceral pain can benefit from local and systemic analgesia and acute hemorrhage can be addressed by interventional angiographic supra-selective particle embolization techniques so that the by itself questionable concept of palliative exenteration has to be re-evaluated considering alternative current treatment options.

Contraindications

Like for other procedures, PE should not be considered if the physical performance status and co-morbidities do not allow a major operation. In addition, classical contraindications for PE are the presence of distant metastasis, peritoneal spread or preoperatively assessed local irresectability. Some authors advocate that the presence of an isolated distant metastasis in case of recurrent disease is not a contraindication per se as the metastasis could be resected at the time of PE. Also the presence of tumor positive pelvic lymph nodes is associated with a decrease in postoperative survival so that some authors conclude that this condition can be considered as a contraindication for PE (8, 34-38). If complete resection seems unlikely from pelvic examination or imaging studies PE should not be attempted. Especially pelvic sidewall involvement, which is a major reason for irresectability, can be difficult to evaluate and sometimes can only be detected if the procedure is already at an advanced stage so that this condition still represents and obstacle in identifying eligible candidates for this procedure.

Höckel developed a surgical technique allowing a laterally extended endopelvic resection (LEER) especially for patients with recurrent cervical carcinomas involving the side wall of an already irradiated pelvis (39). In his feasibility study he showed that extending the lateral resection plane of pelvic

exenteration to the medial aspects of the lumbosacral plexus, sacrospinous ligament, acetabulum, and obturator membrane enables the complete removal of locally advanced and recurrent tumors fixed to the pelvic wall with free margins (R0) (39). In his series of 36 cases including 7 cases of primary advanced gynaecologic cancers he found a remarkable 5-year survival rate of 49%. Future studies have to demonstrate if this technique will also provide local control for cases with significant parametrial involvement. Albeit the positive initial results of the LEER procedure most authors consider a fixation of the tumor to the pelvic sidewall as contraindication for secondary exenteration (34, 40-43). Along these lines the presence of hydronephrosis and pain caused by infiltration of the lumbar plexus suggests local irresectability and therefore must be considered as contraindications for PE.

Technical modifications

Over the last 60 years pelvic exenteration underwent numerous modifications regarding perioperative management and surgical technique.

Modified exenterations

The initially described operation termed ‘pelvic exenteration’ comprised the en-bloc resection of the inner genitals the bladder and the bowel (i.e. “**total pelvic exenteration**”). Over time surgeons tailored this procedure to the amount of disease to be removed. Procedures where resection was limited to the inner genitals in combination with the bladder preserving the rectum were termed “**anterior PE**”, in combination with recto-sigmoid preserving the bladder “**posterior PE**”. Some authors also introduced the term ‘**composite PE**’ to describe cases involving bony resections like the sacrum-coccyx, ischium, pubic symphysis and others.

Intestinal reconstruction

The reconstruction of bladder and bowel function is a central part of exenterative procedures. The decrease in postoperative morbidity and mortality over time resulted in an increase in long-term survivors. There for attention had been directed to improve quality of life aspects. Various technical modifications and improvements in urinary and intestinal reconstruction techniques have been introduced aimed to improve quality of life and patients’ acceptance of this initially mutilating procedure. Traditionally total and posterior exenteration required a permanent colostomy which impaired the acceptance of this procedure for affected women (44). The introduction of

supralevator rectal resections with low colo-rectal anostomosis with or without protective proximal transient colostomy has avoided permanent colostomy in curatively and non-curatively resected patients with total or posterior exenteration (36, 45). Hatch and co-workers first described the preservation of a rectal stump for selected cases and performed a low rectal anastomosis using automated circular stapler devices. In some cases the anastomosis was secured by an omental wrap, some patients also had protective colostomies. In their analysis they showed the feasibility of this intestinal reconstruction technique with acceptable morbidity (32%), mortality (no operative deaths) and survival (68% overall survival). At least in their series protective colostomies did not improve the healing rate of the anastomosis. As a conclusion, the preservation of faecal continence should be considered in every case of PE requiring bowel resection.

Urinary reconstruction

Brunschwigs' way of urinary diversion was the implantation of both ureters into the sigmoidostomy. Patients frequently suffered from postoperative episodes of pyelonephritis and hypochloremic acidosis so that other options were tested. Bilateral percutaneous urostomies were technically easy to perform but committed patients to a lifetime of double urinary stomas which impairs daily activities and is associated with a high long-term morbidity rate (46, 47). The first milestone in urinary reconstruction was Bricker's development of the ileal conduit (1950) which separated the urinary and faecal stoma (48). Both ureters are implanted into a pouch formed by an isolated segment of the terminal ileum. However, patients still need to wear a bag as the urinary flow was constant. To overcome this issue the use of various other methods of creating a continent urinary conduit have been described including the Indiana pouch (49), the Kock pouch (50), the Florida pouch (51) and the Miami pouch (52). E.g. the Miami pouch has a mean urinary reservoir volume of 650 ml and provides the patient with a convenient emptying frequency. But continent urinary diversion techniques might be limited by extensive adhesion formation, prior bowel operation or irradiation. Especially in cases with prior radiation therapy this technique is afflicted with a high morbidity rate. Therefore the use of various intestinal segments like the transverse, sigmoid and right colon has been described for pouch formation (27, 53-55) with different postoperative morbidity rates.

Nowadays in many centers the creation of an orthotopic neo-bladder has become the urinary diversion technique of choice (8, 41). The pros of the neobladder are the continence and preservation of the body image especially for younger patients. This technique enables patients to perform their routine

daily activities without the necessity of wearing bags or performing self-catheterization. Conditions are at least 70 cm of intact small bowel, a tumor-free trigonum and urethra and the absence of preoperative stress incontinence. The cons of this form of reconstruction technique are that it is technically difficult to perform and that neobladders have a relatively high postoperative complication rate. Approximately 15% of patients suffer from postoperative hypercontinence.

Vaginal reconstruction

Another problem that female patients face and which is a considerable source of postoperative psycho-sexual morbidity is the loss of their vagina and thereby the chance of having vaginal intercourse (56, 57). Therefore after careful consideration of both, oncologic and psychologic aspects and after discussing this aspect with the patient vaginal reconstruction should be part of the operative strategy and should be offered whenever possible and reasonable. There are several options for vaginal reconstruction which can be performed either at the time of the exenteration or as a separate delayed procedure. Beemer and co-workers reported their experience with split-thickness skin grafts, which requires a delayed procedure 2 to 8 weeks after the initial operation during which an adequate granulation tissue forms (58). Alternatively myocutaneous flaps involving the gracilis and the rectus abdominis muscles can be used at the time of the initial operation (59-61). These flaps do not only allow immediate reconstruction but also help to address the issue of filling the “empty pelvis” which predisposes to abscess and fistula formation and which is source of perineal wound healing problems and intestinal obstruction (30). Accordingly creating a neovagina using myocutaneous flaps has been shown to reduce postoperative morbidity and to decrease pelvic abscess formation (62, 63). However, there is only limited information available with respect to quality and quantity of sexual activity of patients who underwent vaginal reconstruction as part of their treatment concept for gynaecologic cancers.

Minimal-invasive techniques

The preoperative assessment of localization and extension of the disease can be challenging as non-invasive imaging techniques like CT or MRI have limited validity especially for the detection of positive lymph nodes (64-66). Koehler and colleagues estimated that 40-60% of patients who are potential candidates for PE by clinical examination and preoperative staging undergo “aborted” laparotomy due to intraoperative detection of unresectability or distant metastasis (67).

Aborted exenteration is a situation that needs to be avoided as it is not only source of additional frustration and unnecessary morbidity for the patient but it may also result in a delayed initiation of alternative treatment options like radiation therapy. In their series they performed laparoscopy prior to exenteration. By laparoscopy they excluded macroscopic peritoneal disease and performed pelvic and periaortic lymph node dissection. Nodes and other biopsy were sent for frozen section and then the cervico-vesical septum, the cul-de-sac and the rectal pillars were explored and biopsy taken. Then the perivesical and perirectal space were opened and evaluated for tumor involvement. Surgery was discontinued if extrapelvic disease was confirmed. If laparoscopy suggested complete tumor resectability the procedure was converted to laparotomy and PE was performed. Analyzing their series of 41 patients irresectability was correctly identified with a specificity of 95.2% and resectability with a specificity of 90.4%. Still, like for the exploration in an open procedure, the laparoscopic exploration of the pelvic sidewall is the most difficult aspect of the procedure and remains a challenge. However, in centers performing PE which also have an expertise in advanced laparoscopy a minimal-invasive staging procedure prior to exenteration might be beneficial to identify eligible patients and to avoid unnecessary laparotomies.

As a logical consequence of the general advances in the use of laparoscopic techniques for the treatment of gynaecologic malignancies few centers showed the feasibility of a laparoscopic approach for PE. There are sporadic case reports and small series published on the successful performance of total laparoscopic or laparoscopically assisted PE for various indications (68-71). Considering the potential benefits of minimal-invasive procedures in general like lower blood loss, shorter hospital stay, and decreased postoperative pain, these procedures are of considerable interest. It will be almost impossible to statistically compare reliable outcome parameters like morbidity and survival between laparoscopic and open exenterative procedures considering the case number needed for a valid prospective trial. Also, considering the importance of modern continent urinary and intestinal reconstruction techniques it does not only require a laparoscopic surgeon who is skilled to perform the resection but also various reconstructive techniques by laparoscopy. These prerequisites are currently given only in very few oncology centers worldwide.

Outcome and selection criteria

Mortality

The high perioperative mortality of more than 20% highlighted in the initial reports (72) was result of infectious, metabolic and surgical complications. Improvements in perioperative management in combination with modifications

Table 1. Mortality, morbidity and survival in various series investigating the outcome after pelvic exenteration. NR= not reported, NA= not applicable, n= number of included patients (number of gynaecologic patients) (modified after (4)).

Authors	Years analyzed	n	Mortality	Morbidity		R0	5-year survival				Reference
				Early	Late		All	Primary	Persistent or recurrent disease		
									Post radiation	No radiation	
Brunschwig et al. 1965	1947-1957	430	18%	NR	NR	NR	22%	27%	15%	NA	(72)
Kiselow et al. 1967	1950-1965	207	8%	44%	39%	NR	35%	NA	NR	NA	(78)
Ingiulla et al. 1967	1957-1961	100	37%	NR	NR	NR	16%	NA	NR	NA	(42)
Ketcham et al. 1970	1954-1969	162	17%	NR	NR	NR	38%	48%	28%	NA	(17)
Symmond et al. 1975	1950-1971	198 (169)	8%	92%	88%	NR	33%	50%	30%	16%	(6)
Karlen et. al 1975	1957-1974	87 (83)	25%	75%	NR	NR	22%	NA	NR	NA	(80)
Rutledge et al. 1977	1955-1976	296 (255)	14%	63%	27%	92%	42%	NA	NR	NA	(81)
Averette et al. 1984	1966-1981	92 (87)	24%	67%	NR	69% (75%)	37%	NA	NR	NA	(82)
Rodriguez Cuevas et al. 1988	1962-1982	252	17%	45%	NR	NR	39% (3-year)	NA	NR	NA	(83)
Lawhead RA et. al. 1989	1972-1981	65	9%	NR	NR	83%	23%	NA	NR	NA	(37)
Soper et al. 1989	1970-1987	69 (63)	7%	38% surgical 46% non-surgical	NR	NR	48%	NA	NR	NA	(27)
Morley et al. 1989	1964-1984	100	4%	49%	NR	NR	61%	NA	NR	NA	(77)
Shingleton et al. 1989	1969-1986	143	6%	NR	NR	84%	50%	NA	50%	NA	(76)
Robertson et al. 1994	1974-1992	83 (79)	4%	47%	NR	NR	42%	NA	NR	NA	(5)
Lopez et al. 1994	1940-1989	232 (189)	20%	45%	NR	NR	42%	NA	NR	NA	(84)
Shepherd et al. 1994	1982-1992	61 (53)	5%	31%	27%	85%	44%	NA	NR	NA	(85)
Magrina et al. 1997	1977-1986	133 (NR)	7%	36%	22%	NR	41%	NA	NR	NA	(38)
Berek et al. 2005	1956-2001	75	4%	NR	NR	88%	55%	NA	55%	NA	(40)
Roos EJ et al. 2005	1989-2000	62 (49)	2%	75%	83%	82%	42%	NA	NR	NA	(86)
Goldberg et al. 2006	1987-2003	103 (98)	2%	NR	NR	NR	47%	NA	47%	NA	(87)
Höckel et al. 2006	1996-2005	74	3%	49%	19%	97%	56%	80%	51%	59%	(4)
Fleisch et al. 2007	1983-2002	203	1%	33% surgical 43% non-surgical	NR	43%	21%	NA	NR	NA	(8)

in surgical technique have contributed to a significant decrease in mortality over the last 40 years. The introduction of perioperative antibiotic and thrombosis prophylaxis has reduced the number of infectious and thromb-embolic events after major surgery in general. Improvements in medical care and intensive care therapy have impacted patient selection criteria and improved postoperative surveillance, respectively. All major studies on the outcome after PE published between 1989 and 2007 now report a proportion of postoperative deaths ranging from 1 to 9% (4, 5, 8, 27, 35, 38, 40, 73-77) (see table 1).

Morbidity

PE has historically been afflicted with a high perioperative complication rate ranging between 32-84% as presented by various investigators (8, 26-28, 30, 74, 78, 79).

Table 2. Typical early and late complications after various intestinal, urinary and vaginal reconstruction techniques for PE (modified after (4)).

	Early complications	Late complications
Intestinal reconstruction		
Terminal colostomy	Stoma necrosis, retraction, abscess in the denuded pelvis	Stoma necrosis, dermatitis, peristomal hernia, stomal prolapse
Colorectal anastomosis		
-no additional means -Omental wrap -musculocutaneous flap -Rectal J-pouch	Anastomotic insufficiency (abscess, fistula, peritonitis, obstruction)	Incontinence, tenesmus, high defecation frequency
Urinary reconstruction		
Conduits		Stoma stenosis, retraction, hydronephrosis, stone formation, parastomal hernia, renal unit loss
-Ileum -Transverse Colon	Stoma necrosis, retraction, urinary leak, fistula, urinoma, early hydronephrosis, bowel anastomosis breakdown	
Pouches		Incontinence, stomal stricture, pouch perforation, fistula, diarrhoea
-Ileocolonic		Incontinence, hypercontinence, hydronephrosis, stone formation, renal unit loss
-Transverse Colon		
Neobladder		
Vaginal, vulvar and perineal reconstruction		
Musculocutaneous flap	Flap necrosis, infection, donor site dehiscence, seroma, infection	Stenosis, obliteration, dyspareunia, failure of cohabitation, abdominal wall hernia, persistent seroma

PEs are major surgical procedures with an average OR time ranging between 5 to 14h, a mean blood loss of 2300 to 4000 cc and historically with a mean hospital stay between 19 to 37 days. Although overall quality of life does not seem to be affected after PE patients tend to develop postoperative physical, sexual and social problems (18).

The most frequent general postoperative complications associated with this procedure are wound infections, hemorrhage and thromboembolism. Depending on the type of exenteration performed specific early and late complications can occur affecting urinary, intestinal and vaginal reconstruction (table 2). Typical early complications for urinary and intestinal reconstruction include necrosis, retraction, leakage, and fistula formation. Late complications are stoma and pouch stenosis, hernia, or prolapse (54). Especially after total PE patients may suffer from severe infectious pelvic complications like abscess formation in the denuded pelvis. Cases with radiation of the pelvis prior to PE are generally afflicted with a higher surgical morbidity rate than primary cases.

Ureteral stricture should be corrected surgically either immediately or after transient percutaneous nephrostomy to preserve renal function. Intestinal obstruction occurs both as early and as late complication and continues to be a significant source of morbidity in 10-15% of PE patients. Mostly paralytic ileus problems, which are also partially a consequence of the denuded pelvis, respond to medical therapy in combination with nasogastric decompression. Small anastomotic leaks often heal spontaneously; if major leakage is found or patients suffer from pelvic infection a protective transient colostomy should be performed. Also enteral fistulas often resolve spontaneously under bowel rest and iv-hyperalimentation (88).

Survival

In 1965 Brunschwig reported a series more than 430 patients treated by PE which still is the biggest published series to date on this procedure (72). The overall 5-year survival rate in this mixed cohort was 21%.

Definitive conclusions regarding the survival after primary exenteration for advanced pelvic malignancies cannot be easily drawn due to the paucity of reliable data published. However, the same applies to other treatment options: There is only limited data on survival rates after primary chemo-radiation for stage IVA cervical cancer (13, 15, 89, 90) and no data from large randomized trials is available. Marnitz, Deckers and Numa reported a 5-year survival from 43% to 52,5% in selected patients undergoing PE for FIGO IVA cervical cancer (7, 18, 91) and also the results of other small series reporting survival data after primary PE for advanced gynaecologic

malignancies are in this range (table 1). These results are even better than the 5-year overall survival after chemo-radiation for stage IVA cervical cancer as listed in the latest FIGO annual report (36%) (10).

As mentioned before there is no data available on the survival outcome after PE for FIGO IVA endometrial cancer so that this potential indication remains questionable.

PE for patients with recurrent cervical cancer after chemo-radiation therapy fulfilling the mentioned eligibility criteria results in survival rates between 16 and 60% (1, 7, 8, 18, 36, 37, 40, 77, 92).

Analyzing the literature there are some commonly identified negative prognostic factors in patients undergoing PE. The tumor-involvement of pelvic lymph nodes, tumor fixation to the pelvic side wall and tumor-positive margins of the surgical specimen have been shown to result in a shorter survival (8, 18). In our own mono-institutional analysis of 203 patients undergoing PE for various gynaecologic cancers over 20 years we found that the mean survival of completely resected patients was approximately 2 years longer than in patients with positive margins (8). Mean survival was approximately 3 years, in the series of Berek et al. and Shingleton et al. no patient survived longer than 3 years (40, 76). The use of intraoperative radiation therapy (IORT) might be beneficial for cases with microscopic residual disease (93). The impact of other factors on survival rate like lymphovascular space invasion, histological type and grade, time to recurrence and tumor size is controversely discussed.

Different investigators have different definitions when PE has to be considered as palliative. Magrina considers PE to have a palliative intent if tumor is present in pelvic or periaortic lymph nodes or at the lateral pelvic wall (38). Lambrou considers tumor-associated fistula, therapy-resistant hemorrhagic cystitis and/pr proctitis as indications for palliative PE (94), Stanhope also includes bone involvement or distant metastasis (95). Accordingly depending on the definition 5-year survival rates range between 10.5 and 27% (18). The reported median survival rates for patients undergoing palliative chemotherapy for recurrent cervical cancer are between 8 and 11 months (18).

The place of pelvic exenteration in the treatment of advanced pelvic malignancies – past, presence and future

60 years after its conceptual introduction and according to the current literature PE offers cure for approximately 50% of patients with advanced primary or recurrent cancer of the female genital tract eligible for this procedure. Treatment-related morbidity remains high but mortality has fallen below 5%. The experiences of various investigators have highlighted the selection criteria

for patients which will potentially benefit from this procedure. Considering the numerous unanswered questions regarding indications for PE and the outcome parameters in comparison with alternative treatment options the performance of PE should underlie some restrictions.

First, the performance of PE should be limited to referral centers with high case volume. Performing centers should provide all therapeutic options including all forms of continent urinary and intestinal reconstruction techniques and an up-to-date radiation therapy facility. Second, the indication for primary, secondary and palliative exenteration should be the individual decision of an interdisciplinary tumor board conference as some centers advocate (9, 18) and should be approved after discussing all available treatment options. The tumor board should at least consist of a gynaecologic oncologist, urologist, GI surgeon, radiation therapist and a pathologist. The recommendation of the tumor board should then be discussed with the patient along with the other available therapeutic options, the procedure related morbidity and mortality rate in order to get his informed consent.

If individual surgeons, like in most institutions, are not capable of offering all reconstructive techniques and in order to provide high standard of care the procedure should be performed in an interdisciplinary approach involving other disciplines as needed (96).

Minimal-invasive techniques to determine extent and resectability of advanced or recurrent tumors can potentially contribute to identify eligible candidates for PE. Laparoscopic approaches are not only limited to diagnostic purposes. A few expert centers have already shown that performing PE by laparoscopy is feasible and might offer specific advantages compared to the conventional approach. Results of numerous studies over the past 40 years show that the significant improvements in perioperative management and surgical technique have not only led to decreased perioperative mortality and increased survival but also improved postoperative quality of life in this group of patients.

In lack of new treatment modalities for locally advanced cancers in the pelvis and considering the potential advantages of a surgical approach in selected patients it is likely that suggests that also in the future PE will have a significant role for the treatment of advanced pelvic malignancies.

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