Curative pelvic exenteration for recurrent cervical carcinoma in the era of concurrent chemotherapy and radiation therapy. A systematic review

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Curative Pelvic Exenteration For Recurrent Cervical Carcinoma in the Era of Concurrent Chemotherapy and Radiation Therapy. A Systematic Review.

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Abstract

Objective: Pelvic exenteration requires complete resection of the tumor with negative margins to be considered a curative surgery. The purpose of this review is to assess the optimal preoperative evaluation and surgical approach in patients with recurrent cervical cancer to increase the chances of achieving a curative surgery with decreased morbidity and mortality in the era of concurrent chemoradiotherapy.

Methods: Review of English publications pertaining to cervical cancer within the last 25 years were included using PubMed and Cochrane Library searches.

Results: Modern imaging (MRI and PET-CT) does not accurately identify local extension of microscopic disease and is inadequate for preoperative planning of extent of resection. Today, only half of pelvic exenteration procedures obtain uninvolved surgical margins.

Conclusion: Clear margins are required for curative pelvic exenterations, but are poorly predictable by pre-operative assessment. More extensive surgery, i.e. the infra-elevator exenteration with vulvectomy, is a logical surgical choice to increase the rate of clear margins and to improve patient survival following surgery for recurrent cervical carcinoma.

INTRODUCTION :

Cervical cancer represents a major public health burden with 529 000 new diagnoses and 275 000 deaths annually worldwide [1]. Treatment options differ depending on the extent of tumor spread at the time of diagnosis. Early cervical cancers, defined as $\leq$ IB1 by the International Federation of Gynecology and Obstetrics (FIGO) classification [2], can be treated by surgery (radical hysterectomy and lymphadenectomy) and/or radiation therapy with equivalent results in terms of relapse-free and overall survival [3]. For cases of locally advanced cervical cancer, $\geq$ FIGO IB2, concomitant chemoradiotherapy is recommended based on the results of clinical trials from the 1990s [4-7]. Today concomitant chemoradiotherapy is the primary treatment for approximately 70% of patients [8]. Despite local control and a prolongation of disease-free survival, an estimated 20-30% of patients develop recurrent disease within the radiation field. The majority of recurrences occur 18-24 months following initial treatment. Risk of recurrence increases with FIGO stage and is estimated to be 10% for stage IB patients, 17% for IIA, 23% for IIB, 42% for III and 74% for IV [9].

When local recurrence occurs, treatment options are limited due to the frequent use of pelvic irradiation for primary cervical cancer. Reirradiation of the same anatomic site is contraindicated, and chemotherapy is ineffective at controlling tumors located within the previously irradiated tissue that tends to be less vascularized [10, 11]. A recent Cochrane review was unable to compare the effectiveness of medical (radiotherapy and/or chemotherapy) versus surgical treatment for recurrent cervical cancer given the absence of randomised controlled trials [12]. Surgical resection is often the only treatment option for disease recurrence but it is associated with a high rate of complications due to the fragility of the tissue after concomitant

radiochemotherapy [9]. Curative surgical resection of locally recurrent cervical cancer is pelvic exenteration with removal of neighboring organs such as bladder and rectum [9, 11, 13]. However, there is a lack of consensus regarding the optimal extent of the resection margins and whether the best chance of cure should include a pelvic exenteration with anterior, posterior and/or inferior exenterations. There is also no clear definition as to which patients should undergo curative versus palliative treatment. For example, lateral pelvic recurrences are considered eligible for resection by some teams, yet unresectable by others [14].

The goal of this review is to define the preoperative workup for recurret cervical cancer to guide the selection of patients for curative surgery, as well as the optimal extent of surgery in terms of morbidity and mortality.

MATERIALS AND METHODS :

The literature was reviewed for articles published during the past 25 years using the following Medical Subject Headings (MeSH): pelvic exenteration, recurrent cervical cancer, cervical cancer treatment, radiotherapy and cervical cancer. All meta-analyses, systematic reviews and original articles written in english were reviewed. The following databases were searched:

- Medline : PubMed (Internet portal of the National Library of Medicine)
http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed
- The Cochrane library: Cochrane-database 'Cochrane Reviews' and 'Clinical Trials'
http://www3.interscience.wiley.com/cgi-bin/ mrwhome/106568753/HOME
DARE

RESULTS

PRE-OPERATORY EVALUATION OF CERVICAL CANCER RECURRENCE :

Evaluating the extent of recurrent tumor growth is important for proper patient management. Recurrent cervical cancer is classified as a central pelvic recurrence when the tumor is limited to the vagina, bladder, rectum and/or parametrium, and as a lateral pelvic recurrence when it spreads to the muscles and vasculature of the lateral pelvic wall. Local tumor extension needs to be accurately defined to guide proper surgical management. It is also important to eliminate the presence of metastatic tumor, which is considered to be an incurable progression of disease. Distant recurrent cervical cancer involves para-aortic, supra-clavicular or pulmonary lymph nodes in 81%, 7%, and 21% of cases respectively [15].

Preoperative evaluation of the extent of cervical cancer spread traditionally involved clinical examination of the patient under general anaesthesia with endoscopic evaluation of the bladder and/or rectum as required. Magnetic resonance imaging (MRI) is now the preferred modality to evaluate the size of the tumor, and its relationship with neighboring organs (Table 1) [16]. Compared to computed tomography (CT), MRI has a higher sensitivity for detecting spread to the bladder (75%), rectum (71%), parametrium (74%) and lymph nodes (60%). The specificity of MRI is generally comparable to CT, with the exception of bladder invasion which has been found to have a specificity of 91% by MRI and 73% by CT [17]. MRI can be used to predict uninvolved surgical margins with a sensitivty of 85% and a specificity of 52%, with a positive predictive value of 60% and a negative predictive value of 80% [18]. Improvements in the ability of imaging to detect tumor extension will allow for more detailed preoperative planning. The surgeon will be better equipped to determine if curative surgery is feasible and will increase the chances of achieving uninvolved surgical margins. Currently all radiologic modalities are limited by their poor sensitivity in picking up microscopic disease, as well as their poor specificity in distinguishing tumor from radiation-induced fibrosis.

For the evaluation of distant metastases, positron emission tomography-computed tomography (PET-CT) is superior to MRI and CT [19]. PET-CT has been shown by Husain et al. to detect distant metastases with a sensitivity of 100% and a specificity of 73%, with a positive predictive

value of 55% and a negative predictive value of 100 % [20]. A meta-analysis of 1757 patients found that PET-CT has a sensitivity of 90% and a specificity of 99% in detecting distant metastases in cases of recurrent cervical cancer [21].

Currently the standard approach for evaluating patients with recurrent cervical cancer involves analyzing and correlating the findings from both MRI and PET-CT imaging. Combining the information provided by these two techniques allows for more precise evaluation of the size of the recurrence, the extent of invasion of adjacent structures and the presence of lymph node metastases (p= 0,041) [22]. Curative surgery requires complete tumor resection with uninvolved surgical margins and is a strong prognostic factor for postoperative survival. Imaging allows for better patient selection and planning of surgical procedures to increase the chances of a curative surgery, and to help avoid performing extensive surgeries, such as pelvic exenterations, for unresectable disease. In 1989 approximately 40% of pelvic exenterations were aborted intraoperatively due to unresectable disease [23].

There is minimal data regarding the accuracy of imaging in the preoperative evaluation of lymph node involvement because metastases to pelvic lymph nodes is a contraindication for curative pelvic exenterations. Preoperative imaging has been shown to detect nodal metastases with a sensitivity of 75% and a specificity of 52%, suggesting that patients should undergo lymph node dissection if there is any suspicion of involvement [18, 24]. While there are no precise recommendations in the literature, patients without preoperative evaluation of their lymph nodes should have them removed laparoscopically and evaluated intraoperatively in all cases, even if the patient received neoadjuvant radiation.

SELECTION OF PATIENTS ELLIGIBLE FOR CURATIVE SURGERY :

When Dr. Brunschwig first described the technique of pelvic exenteration in 1948, it was considered a palliative treatment to remove gastric and/or urinary fistulas with a survival rate of less than 20% at 5 years [25]. Today the goal of pelvic exenteration is curative, aiming to achieve complete tumor resection with margins that are free of microscopic disease. According to some studies, the survival rate at 5 years is now closer to 60% with an acceptable rate of postoperative morbidity (Tables 2 and 4). In patients with visceral or lymph node metastases, there is no proven benefit of attempting curative surgery. Pelvic exenterations are therefore reserved for isolated central recurrences or lateral pelvic recurrences that do not involve the

sciatic nerve, in patients whose general health and nutritional status permit such an extensive surgery [14, 26].

PROGNOSTIC CRITERIA FOR ISOLATED PELVIC RECURRENCE OF CERVICAL CANCER :

There are several prognostic factors that should be evaluated in patients with recurrent cervical cancer, that is limited to the pelvis, before considering a pelvic exenteration:

1) **Size of tumor recurrence -** lesions measuring more than 5cm in diameter have been shown by some authors to have almost no chance of remission despite complete removal of the tumor with uninvolved surgical margins [9, 10].

2) **Length of time between initial cancer treatment and the recurrence -** Marnitz et al found a correlation between the length of time to recurrence and patient survival such that a recurrence at less than 2 years, between 2 to 5 years and more than 5 years after initial treatment is associated with a 5-year survival rate 16.8%, 28.0% and 83.2% respectively [10]. Recently, Chiantera et al also determined that a recurrence occuring more than two years after initial treatment is associated with better overall patient survival rates (p= 0,012) [27]. The prognostic value of time to recurrence is still debated because some authors have found no association with survival [28, 29].

3) **Histologic type of recurrence -** squamous cell carcinomas are associated with a significantly worse prognosis than adenocarcinomas of the cervix (p= 0,003). The poorer prognosis may be a reflection of the fact that perineural invasion is more frequently present in squamous cell carcinomas (p= 0,004) [30].

4) **Presence of lymph node involvement at initial presentation -** the prognostic value of lymph node involvement is controversial and has been evaluated in only a few studies. It has been found that patients presenting with lymph node metastases have a worse prognosis [31, 32]. Recently this notion was challenged by Been et al in a study that showed no significant difference in survival rates [33].

The size of the cervical cancer recurrence, the interval of time to recurrence and the histologic type of the tumor are important elements to consider preoperatively before offering patients a

potentially curative pelvic exenteration surgery. The age of the patient has not been found to influence overall, or disease-free, survival rates [34, 35].

Postoperatively, histopathologic evaluation of the tumor provides additional prognostic information.

1) **Metastasis to mesorectal lymph nodes** is significantly associated with a shorter median disease-free survival interval of 2.4 months, compared to 7.3 months in patients without mesorectal lymph node involvement (p= 0,005) [27, 36, 37].

2) **Lymphovascular space invasion (LVSI)** is an independent prognostic factor which negatively impacted overall survival [38]. Assessing the presence of vascular emboli on pretherapeutic biopsies could facilitate the selection of patients eligible for curative pelvic exenterations [39].

3) **Surgical resection margins involved by invasive carcinoma** is a major significant and independent prognostic factor associated with decreased survival of patients [23]. Postoperative survival at two years drops from 55.2% with uninvolved margins to 10.2% with positive margins (p= 0,0057) [10]. Some authors have found that the survival rate in patients with positive margins falls to 0% after three years [28, 40].

In conclusion, patient survival depends on numerous pre and postoperative factors of which only one is modifiable, the achievement of surgical margins that are confirmed to be uninvolved by invasive carcinoma after histologic evaluation.

DISEASE-FREE AND OVERALL SURVIVAL IN PATIENTS FOLLOWING EXENTERATION FOR RECURRENT CERVICAL CANCER :

Since the initially reported cases of exenteration in 1948, the rate of five-year survival has increased considerably from 20% in the 1970s to 64% in recent series where patients were better selected.

In 1989, based on the analysis of a large series of cervical cancer patients treated by pelvic exenteration, Shingelton et al estimated that the median delay to cancer recurrence was 12 months, with death typically ensuing 3 to 5 months later [23]. More recent studies, in the era of concurrent chemoradiotherapy, have found that the median time interval to recurrence is 6.1 to 7

months [33, 36]. The relatively short time interval to cancer recurrence highlights the importance of assessing prognostic factors preoperatively to select patients that are best suited for exenterations.

Cervical cancer recurs locally, in the pelvis or perineum, in approximately 35-60% of relapsed patients. While 20-40% of patients with recurrent disease present with distant metastases mainly involving the lungs, lymph nodes and bone. The tendancy towards local recurrence has not changed since the introduction of concomitant chemoradiotherapy. In 1999, a review of the literature by *Estape et al* found that the rate of local recurrence and distant metastases is 50-64% and 19% respectively [41]. *Shingleton et al* did not find an association between the type of exenteration and the type of recurrence (local vs distant) [23].

In general, for patients where exenteration is the final therapeutic option, studies have found an encouraging rate of survival. However it is difficult to compare the results of the different studies since there is a large heterogeneity with respect to the type of procedure that was performed and the type of cancer that is being investigated (cervical, endometrial, vulvar or ovarian). Studies rarely focus uniquely on cervical cancer and even more rarely on cervical cancer recurrences. As shown in table 3, anterior, posterior, total, supra or infralevator exenterations are all described in the literature but authors rarely explain how or why a given procedure was chosen. Since uninvolved surgical margins is such an important prognostic factor that is potentially modifiable, it would be useful to understand the reasons surgeons opt for one procedure over another.

DIFFERENT TYPES OF PELVIC EXENTERATIONS :

Radical pelvic exenteration was initially described by Brunschwig as a palliative procedure for central pelvic recurrences of cervical cancer. Recurrences that are limited to the cervix and/or upper vagina are amenable to a total hysterectomy with pelvic lymph node dissection. He defined three additional categories of local disease recurrence and suggested the following types of resection [25] :

4) **Anterior:** With invasion of the bladder it is recommended that the entire bladder, uterus and vagina be removed.

5) **Posterior:** Invasion of the rectum is amenable to complete excision of the vagina, uterus and involved segment of bowel.

6) **Total:** Invasion of the bladder and rectum requires removal of bladder, vagina, uterus and rectum.

Lateral pelvic extension was considered a contraindication to surgical exenteration for a long time because it was not possible to achieve tumor-free surgical margins [28]. In 2008, *Höckel et al* demonstrated that patients with recurrent cervical cancer involving the pelvic side wall can benefit from a laterally extended endopelvic resection (LEER) [32]. To date, their series includes 91 patients with a overall survival rate of 61% at 5 years [14]. The LEER technique involves the resection of some, or all, of the following lateral pelvic structures : obturator internus muscle, pubococcygeus muscle, iliococcygeus muscle, coccygeus muscle, internal iliac vessels and the lumbosacral nerve plexus. The only contraindication to the LEER procedure is involvement of the sciatic nerve [26, 42].

Pelvic exenterations are now subclassified into type I (supralevator), type II (infralevator), and type III (infralevator with vulvectomy) exenterations based on the extent of surgical resection. The extent of tumor extension dictates the type of exenteration that is required to obtain uninvolved surgical margins. A study by *Magrina et al* found that there was no significant difference in patient survival between the three types of exenteration, provided that no cancer was present at the resection margins [43]. Recently, these results were confirmed by *Berek et al* et *Yoo et al* [28, 36]. Currently, a type III resection is feasible for any recurrence but is preferentially performed in patients with a recurrent lesion larger than 5cm or one that has invaded the anal canal, the lower part of the vagina and/or the vulva [43].

Given the strong prognostic significance of uninvolved surgical margins, several pre and intraoperative evaluations are performed, such as preoperative imaging to select patients with resectable lesions, intraoperative exploration to ensure complete surgical removal of all macroscopically visible tumor and intraoperative evaluation of the status of surgical resection margins. Despite these measures, 7-35% of exenterations performed with a curative intent, are found to have tumor present at the surgical resection margin after thorough pathological evaluation (Table 3). To reduce this risk, a type III exenteration can be proposed to patients. With the improvement of perineal and pelvic reconstruction techniques, the rate of intra and

postoperative complications is reasonable (Table 4) and the quality of life is comparable for all types of exenterations.

MORBIDITY AND MORTALITY ASSOCIATED WITH PELVIC EXENTERATIONS :

Pelvic exenterations are complex surgeries that are associated with a significant risk of morbidity. Resection of previously irradiated pelvic tissue leaves a large cavity that is prone to perineal leaking, poor primary wound healing and complications secondary to the obstruction of the ureters or bowel.

The rate of early postoperative complications (within 30 days of the surgery) varies from 16-71%. One of the most frequent complications is gastrointestinal fistulas with connections to the skin, urinary system or vagina. Other common complications include blood clots and leaking anastomoses. There are two main factors influencing the rate of early complications: preoperative radiation-induced tissue damage and the length of the operation [44]. The rate of late postoperative complications (occuring more than 30 days after surgery) ranges from 36-61%. Late complications include enterocutaneous and vaginal fistulas, ureteral obstruction, bowel obstruction and pyelonephritis. These complications arise secondary to postoperative adhesions, tumor recurrence and urinary tract infections precipitated by self-catheterization [36]. *Magrina et al* did not find a significant difference between the rate of early or late complications and length of hospital stay among the different types of exanterations [43]. These findings were recently confirmed by *Yoo et al* [36]. The mortality asscoiated with intra and postoperative complications varies from 0-12% depending on the study (Table 4). *Benn et al* found that survival time is significantly reduced in patients that develop postoperative complications that are considered complex (p=0,03) [33].

The morbidity associated with type III exanterations has been shown to be reduced in patients with pelvic floor reconstructions. The rate of bowel obstruction, pelvic abscess and fistula formation is decreased when musculocutaneous flaps are used to fill the pelvis for vaginal reconstructions [24, 44]. *Miller et al*, found that filling of the pelvic cavity led to a decrease in the rate of fistula formation from 16 to 4.5% [45].

The rates of postoperative complications vary widely in the literature. *Dindo et al* proposed a grading system for the classification of complications as a comparison tool, but few authors have

adopted it [46]. Certain severe complications appear to occur significantly less often when pelvic reconstruction is performed, which is an argument in favor of type III exanterations. Type III exanterations may also increase the probability of tumor-free resection margins.

RECONSTRUCTION :

Various techniques for urinary, gastrointestinal and pelvic reconstruction have been developed for the different types of pelvic exenteration to improve the quality of life of patients [24, 44].

Urinary reconstruction :

The technique used for urinary reconstruction depends on the preference of the surgeon and the anatomical condition of the pelvis following radiation therapy. A cutaneous ureterostomy is the least technically challenging approach, but it has become obsolete due to problems with the required equipment [47]. Currently, two techniques are performed :

- Bricker non-continent ileal conduit urinary diversion involves anastomosing the ureters to a 15-20cm segment of unirradiated ileum that opens into a cutaneous stoma of the right iliac fossa

- Miami Pouch continent ileocolic urinary diversion consists of anastomosing the ureters to a low-pressure reservoir using distal ileum, right colon or proximal transverse colon. A high pressure valve at the skin's surface helps avoid incontinence. Rome, Indiana and Mainz 1 and 2 are all modified version of the Miami pouch.

The major early postoperative complications are similar for both types of urinary reconstruction, and are primarily ureteral and gastrointenstinal anastomotic leaks. *Goldberg et al* described a complication rate of approximately 14% [48]. *Houvenaeghel et al* found that preoperative radiation increases the risk of postoperative complications and they suggest using a nonirradiated segment of bowel for the conduit to reduce this risk [47]. The main late postoperative complications are urinary tract infections and ureteral obstruction in 19 and 22% of cases, and are more frequently associated with continent diversions [49].

There is no consensus as to which technique of urinary diversion should be performed. The Miami technique is appealing because it provides continence, but it can lead to other complications (catheterization difficulties 19% to 33% of cases [58, 59]) that negatively affect

the patient's quality of life, which is why the non-continent Bricker approach is still an important alternative.

A newer surgical technique was developed in which a segment of ileum is used to construct an orthotopic bladder, which avoids the need for a stoma and was hoped to increase the patient's quality of life. This technique has a 50% rate of continence with a complication rate of 12.5%, compared to a complication rate of 2.9% for "standard" diversions [50]. This technique is rarely performed and is reserved for type I or II exenterations. So far it has not been shown to improve quality of life and thus should not be used as an argument against a type III exenteration.

Gastrointestinal reconstruction :

The standard reconstruction of rectal resections during pelvic exenterations is a definitive left-sided colostomy. Direct anastomoses are preferable in terms of quality of life, but despite advances that facilitate this procedure, such as automatic suturing devices, this technique is associated with a high rate of major complications which is thought to be related to prior pelvic irradiation. Failure of the anastomosis is the most common complication, even in patients with proximal protective stomas [49, 51]. A recent study by *Chiantera et al* found that the complication rate increases from 14.5 to 20.4% when a colostomy reversal is performed [50]. In addition, *Goldberg et al* suggest that this technique should be avoided based on the finding that 45% of their patients suffered from early tumor recurrence at the site of colorectal anastomosis [48]. Currently there is no accepted technique for colostomy reversal in patients undergoing pelvic exenterration for recurrent cervical cancer.

Vaginal and Perineal Reconstruction :

Several different techniques have been developed for vaginal and perineal reconstruction [24, 44]. As previously discussed, pelvic reconstruction reduces the risk of postoperative morbidity by filling the cavity that is created during pelvic exenteration and lowering the incidence of gastrointestinal fistulas and obstruction. It can also improve quality of life by restoring female body image. For pelvic exenterations without perineal resections, there are two main techniques for vaginal reconstruction:

- A pedicle graft of greater omentum, using either of the gastroepiploic arteries, can be introduced into the pelvis for vaginal reconstruction. To achieve a tubular shape the

tissue is placed around an inflatable device that is fixed to the vulvar vestibule. This is a simple surgical technique associated with a 35% risk of vaginal stenosis [52].

7) Bowel neocolpoplasty involves using a portion of the sigmoid or caecum to reconstruct the vagina. The segment of bowel that is used depends on the field of previous irradiation. The main complication of this technique is diversion colitis which can lead to frequent discharge requiring vaginal irrigation [53].

The most reliable techniques for pelvic exenterations with perineal resections involve musculocutaneous flaps that fill the pelvic cavity and allow for vaginal reconstruction when necessary. Currently, two main techniques are practiced:

8) Gracilis flaps were the first reconstruction to be described and are associated with a rate of skin paddle necrosis that varies from 14-25% depending on the study [54]. When vaginal reconstruction is desired, bilateral gracilis flaps are used [55].

9) A pedicled vertical (VRAM) and transverse (TRAM) rectus abdominis myocutaneous flap are approaches with several advantages due to the vascular reliability of the inferior epigastric artery. *Houvenaeghel et al* described only one case of necrosis among twenty patients that underwent the procedure [56]. Additionally, *Soper et al* found that only 12% of patients developed vaginal strictures or stenosis [57]. I realize you described vascular stenosis but I did not see any mention of vascular stenosis in reference 66 but they did describe a 12% rate of vaginal stenosis. A rectus myocutaneous flap is larger than a gracilis, which permits easier vaginal reconstruction using a single flap. The disadvantage of this technique is that it creates an abdominal wall weakness with 6-10% of patients developing incisional hernias [44].

10)   Of note, free flaps anastomosed to iliac vessels have been described using abdominal or latissimus dorsi muscles, but this requires significant surgical experience [44].

In 1996, a study found that 95% of patients were satisfied with the vaginal reconstruction even though only 47% of them were sexually active [58]. Similarly, *Goldberg et al* described the rate of satisfaction and sexual activity as 85% and 56% respectively [48].

In general, the improvement in reconstruction techniques allows for type 3 exenterations that do not significantly alter the quality of life of patients. Unfortunately, colorectal anastomoses for gastrointestinal reconstruction are associated with a risk of morbidity that is too significant to be used regularly. Currently there is not enough evidence about patient outcome following ileal bladder reconstruction following type 3 exenterations. In contrast, pelvic reconstruction is associated with high levels of patient satisfaction [43].

NEOADJUVANT AND ADJUVANT TREATMENT :

The efficacy of neoadjuvant and adjuvant treatments are currently being evaluated to improve patient outcome.

Intraoperative Radiation Therapy:

High dose intraoperative radiation therapy was initially used when the margins of a laterally extended endopelvic resection were found to be involved with cancer by intraoperative pathologic assessment. This technique was shown to increase patient 5-year survival from 11 to 42% [59]. It was also found to cause significant gastrointestinal and nervous system toxicity in 25% and 30% of patients respectively [60].

Neoadjuvant Chemotherapy:

A recent study by *Landoni et al* investigated the role of preoperative chemotherapy for patients presenting with poor prognostic factors such as tumor size larger than five centimeters, lateral pelvic extention of tumor and recurrence less than a year after initial treatment. The chemotherapy was prescribed as three cycles of Taxol, Ifosfamide and Cyclophosphamide. While the study only involved 31 patients, the results were encouraging with tumor shrinkage in 61% of patients with a rate of uninvolved margins, complications, overall and disease-free survival comparable to patients who initially presented with a better prognosis [61].

Complete surgical excision remains the gold standard treatment for cervical cancer recurrence. As not all patients are eligible for curative surgery, it is hoped that the trials investigating radiation and chemotherapy will lead to improved patient care.

CONCLUSION :

Pelvic exenteration is a complex surgical procedure that remains the sole curative therapeutic option for recurrent cervical cancer in patients that received prior radiation therapy. Preoperative patient selection requires MRI and PET-CT imaging that does not demonstrate any evidence of tumor metastasis. There is a lot of heterogeneity in the design of studies in the literature in terms of patient selection (exenteration for cervical, endometrial, vulvar and/or vaginal cancer recurrence), procedure type (anterior, posterior or total, supra or infralevator exenterations with or without perineal resection) and the recording of postoperative complications (lack of standardized classification). Two large studies from 1989 and 1997 found that the type and level of resection did not influence patient survival [23, 43]. Many large studies have found that the strongest independent and modifiable prognostic risk factor is final surgical margins that are free of cancer. Since the preoperative workup does not allow for accurate prediction of postoperative margin status, it is prudent to offer type 3 exenterations (infralevator with perineal resection) to increase the chance of uninvoled surgical margins, and thus improve patient survival, in cases of recurrent cervical cancer following pelvic radiation therapy with or without chemotherapy, especially if quality of life can be improved by using reconstructive techniques that protect against postoperative complications such as occlusion, fistulas and pelvic abscesses.

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Table 1 : Performance of MRI in detecting extent of pelvic tumor invasion and presence of nodal metastases in patients with primary and/or recurrent cervical cancer.

ORGAN EVALUATED		BLADDER	RECTUM	LATERAL PELVIC COMPARTMENT	NODAL METASTASES
Popovitch [19]	Se	67%	67%	80%	
	Sp	93%	93%	76%	NA
	PPV			50%	
Bipat [17]	NPV			100%	
	Se	75%	71%		60%
	Sp	91%		NA	
	PPV				
Rockall [16]	NPV				
	Se	100%	100%		
	Sp	88%	91%	NA	NA
	PPV	100%	100%		
Forner [18]	NPV	7%	17%		
	Se			75%	75%
	Sp	NA	NA	65%	52%
	PPV			65%	56%
Donati [20]	NPV			75%	69%
	Se	87%	75-81%	75-87%	
	Sp	93-100%	97%	94-97%	NA
	PPV	91-100%	92%	75-87%	
	NPV	90%	89-91%	94-97%	

Se : sensitivity, Sp : specificity, PPV : positive predictive value, NPV : negative predictive value, NA : Not available

Table 2 : Overview of patient survival and site of recurrence following pelvic exenteration.

Authors	Date Range of Cases Analyzed	Number of Curative Pelvectomies	Average (a) or Median (m) Duration of Patient Follow-up (months)	Average (a) or Median (m) Time to Recurrence (months)	Average (a) or Median (m) Time to Death (Months)	Survival Rate for Patients Following Exenterations for Gynecologic Malignancies	Survival Rate for Patients Following Exenterations for Cervical Cancer	Site of recurrence
Shingleton [23]	September 1969 to January 1986	NA	NA	m: 9.6 - 12	NA	OS : 50% at 5 years	Idem	64% pelvic 12% lymph nodes 9% abdomen 7% lung
Berek [28]	1956- 2001	75 (100%)	a : 45.5 m: 50	NA	NA	NA	OS : 57% at 3 years and 54% at 5 years	NA
Goldberg [42]	January 1987 to December 2003	103 (100%)	NA	NA	NA	OS : 47 % at 5 years	OS : 48% at 5 years	For the 6 patients alive at 5 years: 2 lung 1 liver 3 para-aortic lymph nodes
Maggioni [43]	June 1996 to April 2007	99 (97%)	m: 22.3 (1.6-117)	NA	NA	OS at time of median follow-up : 34%	OS at time of median follow-up : 52%	NR
Been [33]	January 1990 to August 2009	47 (87%)	m: 12.5 (0-158)	m: 7 (0-33)	m: 29 (12-42)	OS : 44% at 2 years OS : 34% at 5 years	NA	10% distant metastases 31% locoregional recurrence (vagina, perineum, abdomen)
Vergote [44]	June 1999 to April 2010	36 (100%)	m: 78	m: 11 (3-58)	NA	OS : 44% and DSS : 52% at 5 years	OS : 38% and DSS : 44% at 5 years	35% local recurrence
Baiocchi [45]	January 2000 to September 2010	107 (100%)	m: 23.7 (1-122)	NA	NA	OS : 49.9% at 2 years OS : 27.4% and DSS : 41.1% at 5 years	OS : 24.7% at 5 years	NA
Yoo [36]	January 2001 to April 2011	61 (100%)	m: 22 (1-60)	m: 6.1 (0.7-7.8)	m: 6.5 (0.1-58.2)	OS : 56% and DFS : 49% at 5 years	Idem	28 distant metastases (lung, liver, bone, lymph node) 8 local recurrences
Schmidt [46]	NA	156 (73.5%)	a: 45 m: 17	NA	NA	OS : 41% DFS : 61% at 5 years	OS : 64% at 5 years	NA
Tanaka [47]	August 2002 to August 2011	12 (100%)	m: 22 (3-116)	NA	NA	SG : 42.2% at 5 years	NA	NA
Chiantera [48]	1998-2011	223 (97%)	m: 68	a: 13.4	a: 19	OS: 38% at 5 years	NA	NA

OS : Overall Survival, DSS : Disease Specific Survival, DFS : Disease Free Survival.

Table 3 : Summary of recent studies on pelvic exenterations

Author and Year Published	Location of Cancer [Number (%)]	Number (%) of Patients That Received Preoperative Radiation	Number (%) of Curative Surgeries	Number (%) of Palliative Surgeries	Number (%) of Types of Exenteration	Number (%) Patients With Cancer Present at Surgical Resection Margins	Time to Cancer Recurrence (Months) Before Exenteration
Berek 2005 [28]	Cervix= 53 (70%) Vagina= 14 Endometrium= 8	NR	75 (100%)	0	Total : 46 (61%) Anterior : 23 (31%) Posterior : 6 (8%) or 67 (89%) supralevator 8 (11%) infralevator	9 (12%)	Average : 45.5
Golberg 2006 [44]	Cervix= 95 (97%) Endometrium= 2 Vulva= 1 Rectum= 5	98 (95%)	98 (95%)	0	Total : 98 (100%)	NR	NR
Maggioni 2009 [45]	Cervix= 62 (61%) Vagina= 21 Vulva= 9 Endometrium= 9 Ovary= 4	99 (97%)	99 (97%)	2 (3%)	Total : 48 (45%) Anterior : 53 (49%) Posterior : 6 (6%) or 21 (20%) supralevator and 85 (80%) infralevator	7 (7%)	Median : 16.7
Been 2011 [33]	Cervix= 40 (74%) Vulva=9 Vagina= 5	47 (87%)	52 (96%)	2 (4%)	Total : 36 (67%) Anterior : 13 (25%) Posterior : 5 (10%)	7 (13%)	Median : 32
McLean 2011 [46]	Cervix= 29 (66%) Vulva= 4 Vagina= 5 Endometrium= 6	44 (100%)	44 (100%)	0	Total : 34 (77%) Anterior : 5 (11.5%) Posterior : 5 (11.5%)	3 (7%)	Average : 74
Vergote 2012 [47]	Cervix= 18 (50%) of which 17 were recurrences Endometrium= 9 Vagina= 8 Ovary= 1	32 (89%) ovarall and 17 (100%) Of recurrences	36 (100%)	0	Total : 15 (88%) Anterior : 2 (12%) for reccurent cervical cancer of which 11 (65%) supralevator 6 (35%) infralevator	6 (16%)	Median : 34.8
Baiocchi 2012 [48]	Cervix=73 (68%) of which 69 were recurrences Endometrium= 17 Vagina=10 Vulva= 7	NR	107 (100%)	0	Total : 56 (52.3%) Anterior : 31 (29.3%) Posterior : 10 (9.3%) LEER : 10 (9.3%)	8 (7.9%)	Median : 18.8
Yoo 2012 [36]	Cervix= 61 (100%)	60 (98%)	61 (100%)	0	Total : 42 (69%) Anterior : 17 (28%) Posterior : 2 (3%)	9 (14.7%)	Median : 34.1
Schmidt 2012 [49]	Cervix= 282 (100%) Of which 212 were recurrences	156 (73.5%)	106 (50%)	106 (50%)	Total : 262 (93%) Anterior : 14 (5%) Posterior : 6 (2%)	76 (36%)	Median : 18
Tanaka 2013 [50]	Cervix= 12 (100%) Of which 10 were recurrences	10 (100%) of recurrences	10 (100%) of recurrences	0	Total : 3 (25%) Anterior : 8 (67%) Posterior : 1 (8%)	4 (33%)	NR
Chiantera 2014 [51]	Cervix= 177 (77%) Endometrium= 28 Vulva= 16 Vagina= 9 Of which 192 were recurrences	135 (70.3%)	223 (97%)	7 (3%)	Total : 131 (57%) Anterior : 68 (29.6%) Posterior : 31 (13.5%) or 169 supralevator (73.5%) and 61 infralevator (26.5%)	64 (27.8%)	Median : 14

Table 4 : Overview of major postoperative complications.

Authors	Early Complications [number of cases (rate)]	Type	Late Complications [number of cases (rate)]	Type	Perioperative Death [number of cases (rate)]
Berek [28]	NR	NR	NR	17 gastrointestinal fistulas	3 (4%)
Goldberg [47]	NR	NR	NR	NR	1 (0.9%)
Maggioni [48]	48 (44.8%)	NR	52 (48,5%)	NR	0
Benn [33]	27 (50%)	10 cardiorespiratory, 6 ileus, 1 ureteral obstruction	33 (61%)	15 ileus, 11 ureteral, 15 hernias	0
McLean [49]	NR	15 pelvic wall infections, 8 pelvic abscesses, 6 sepsis	NR	NR	1 (2%)
Vergote [50]	21 (58%)	2 pelvic abscesses, 14 leaking stomas and sepsis	18 (50%)	5 pyelonephritis 14 fistulas	1 (2%)
Baiocchi [51]	57 (53.3%)	13 fistulas, 17 pelvic infections	48 (44.8%)	8 fistulas, 9 occlusions, 16 urinary obstructions	13 (12%)
Yoo [36]	10 (16%)	4 skin infections, 1 ileus 5 fistulas, 3 wound dehiscences	22 (36%)	10 fistulas (7 enterocutaneous, 2 rectovaginal, 1 ureteroenteric)	0
Schmidt [52]	143 (51%)	42 rectovaginal fistulas, 20 pelvic abscesses, 10 pulmonary emboli	NR	NR	14 (5%)
Tanaka [53]	10 (83%)	5 ileus, 3 leaking gastrointenstinal anastomoses	NR	NR	0
Chiantera [54]	48 (21.3%)	23 sepsis, 15 cardiorespiratory, 39 wound dehiscences, 22 urinary, 29 gastrointenstinal	NR	NR	7 (3%)