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Surgical Management of Recurrent Cervical Cancer

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The majority of patients with recurrent cervical cancer are incurable and treatment is based on the type of primary therapy delivered. Only a very small percentage of the patients with recurrent cervical cancer following primary radiotherapy will have central pelvic recurrences that are amenable to surgical resection and curable by pelvic exenteration. These procedures should be undertaken only after the completion of exhaustive attempts to exclude extrapelvic disease.

Key Words: Cervix neoplasms, pelvic exenteration, recurrent cervical cancer, treatment outcome, quality of life, prognosis, survival rate, urinary diversion, colonic diversion, vaginal reconstruction, preoperative care, postoperative complications

INTRODUCTION

Patients with cervical cancer, in general, are treated primarily with surgery if they have less than stage IIB disease and with radiation therapy (RT) if they have greater than stage IIA disease. Patients may undergo postoperative irradiation if they are initially treated surgically, depending on the presence of poor prognostic factors such as positive lymph nodes, positive margins, or lymphovascular space involvement.[1]

Despite advances in early detection, surgical treatment, and RT, cervical cancer still recurs. Recurrence rates of 1.5% for early small tumors and 20 to 40% for more advanced lesions have been reported.[2,3] Detection sufficiently early to lead to better prognosis is not achieved by routine follow-up in the vast majority of patients.[4,5] Symptoms (87%), and signs (9%) are the most important diagnostic tools to detect recurrent disease. Vaginal cytology is of little value for the detection of recurrent disease, because despite high specificity, it has poor sensitivity.[5,6]

Recurrent cervical cancer is a difficult clinical problem because of its poor outcome, regardless of initial treatment.[7,8] Recurrence after surgical treatment is treated with RT, but options for patients already irradiated are limited to chemotherapy or radical surgery, including exenteration.

Chemotherapy for advanced or recurrent cervical cancer

Multiple Gynecologic Oncology Group studies have evaluated chemotherapy for cervical cancer, but all have found poor response rates. Its use should therefore be considered palliative. Cisplatin has shown reasonable activity of 20 to 38% in recurrent carcinomas of the cervix; however, median survival is short at 6 months.[9,10] Combination chemotherapy regimens have been evaluated in recurrent cervical cancer, and response rates of up to 50% have been noted.[10,11] Nevertheless, no significant difference in overall survival has been shown, and toxicity is greater with combination regimens. In a review of the role of chemotherapy in carcinoma of the cervix, Vermorken concluded that combination chemotherapy regimens offer no survival benefit over cisplatin alone.[12]

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Primary factors affecting management options for recurrent carcinoma of the cervix

Prior treatment

Treatment of recurrent cervical cancer is determined by the site of recurrence(s) and the primary therapy. Patients who initially undergo surgery are candidates for RT and chemotherapy; those who initially receive RT should be considered for surgery or chemotherapy depending on the recurrence location. Most recurrences occur in patients with advanced-stage disease. Most patients already treated with primary RT are not good candidates for repeat radiation.

Anatomical involvement

Following radical hysterectomy, about one fourth of recurrences occur locally in the upper part of the vagina or the area previously occupied by the cervix. In an often quoted, but dated study from 1949, the location of recurrence after RT was 27% occurrence in the cervix, uterus, or upper vagina; 6% in the lower two thirds of the vagina; 43% in the parametrial area, including the pelvic wall; 16% distant; and 8% unknown. Less than 15% of patients with recurrent cervical cancer developed pulmonary metastasis.[13]

Recurrent cervical cancer may occur in one of three general sites. Commonly, it recurs in the pelvis on the sidewall, presumably in lymph node bearing areas. It may also be seen in distant sites, such as para-aortic or other distal lymph node metastasis, or bony metastasis, most commonly to the vertebral bodies. Finally, a few patients will have a central pelvic recurrence.

Patients with locally recurrent disease after simple or radical hysterectomy should be treated with pelvic RT, resulting in anticipated survival at 5-years of 22 - 44%.[14,15] The role of concomitant chemotherapy in these cases has not been defined.

Due to constraints involving the radiation tolerance of other pelvic structures such as the small intestine, bladder, and rectum, re-irradiation is generally not possible in patients with persistent or recurrent cervical cancer after maximal radiation. In these patients, therapy depends on the site and extent of the disease. Patients with distant metastases are essentially incurable and are candidates for palliative chemotherapy only. In a review of 849 patients with cervical cancer treated with irradiation alone, Perez and colleagues observed a total pelvic failure rate of 19%.[16] Yet, the majority of these patients presented with distal failure, leaving only 7% with isolated pelvic recurrences. With the advent of sophisticated RT methods, including improved methods of brachytherapy and supervoltage external RT, patients with pure central recurrence have become even rarer. For this small subset of patients, exenterative surgery remains the only treatment modality that can provide curative potential. In selected cases, the successful completion of pelvic exenteration is associated with a 5-year survival rate of 20 to 60%.[17] Occasionally, however, there are patients with small central recurrences (2 cm or less in diameter) whose disease could conceivably be cleared by a less extensive procedure such as radical hysterectomy.[17]

An operative technique for the resection of different types of pelvic side-wall recurrences has now been developed and is known as laterally extended endopelvic resection (LEER).[18] Exenteration en bloc with the parietal endopelvic fascia and the adjacent pelvic wall muscles leads to clear margins in the majority of cases. In cases of resection with microscopic residual disease, guide tubes for postoperative brachytherapy are implanted on the tumor bed at the pelvic wall. By transposition of nonirradiated autologous tissue from the abdominal wall or from the thigh, a compartmentalization of the tumor bed is achieved. This pelvic wall plasty also provides therapeutic angiogenesis and creates a protective distance of several centimeters to the remaining hollow organs in the pelvis. The complete therapy is known as combined operative radiotherapeutic treatment (CORT). The rate of severe complications is 25%. Local control rates between 80 and 90% and 5-year survival rates between 30-40% can be achieved.[18-20]

Isolated lung metastases from pelvic malignancies have responded in selected cases to lobectomy. A surgical attack for isolated pulmonary recurrence should be considered, especially if the latent period has been greater than 3

years.[21]

Recurrent cervical cancer in the pelvis: ominous signs and symptoms

Most authors agree that the triad of unilateral leg edema, ureteral obstruction, and pelvic pain in the distribution of the sciatic nerve suggest unresectable pelvic sidewall disease.[3] Leg edema is usually the result of progressive lymphatic obstruction, or occlusion of the iliofemoral vein system, or both. The clinician should consider the possibility of thrombophlebitis, but recurrent cancer is more likely. Although ureteral obstruction can be caused by radiation fibrosis, this is relatively rare and 95% of such obstructions are caused by progressive tumor. Patients may describe pain that radiates into the upper thigh either to the anterior medial aspect of the thigh or posteriorly into the buttock. Other patients describe pain in the groin or deep-seated central pelvic pain. Also, obese patients and heavily irradiated patients may have higher morbidity and mortality rates.

Table 1. Patient Selection for Exenteration

Minimal Benefit From Exenteration
Hydronephrosis
Leg edema
Hip pain
Weight > 200lb
> 6000 cy of radiation to pelvis

Confirm diagnosis

In every case, the diagnosis of recurrent cervical cancer must be confirmed histologically. Despite extensive investigation including CT scans, CT-guided biopsies, lymphangiogram, examination under anesthesia, and tru-cut biopsies, preoperative confirmation of tumor recurrence and resectability often remains unsettled. Exploratory laparotomy is thus the logical next step, but unfortunately, inoperable disease is frequently discovered. In most series, the reported rate of aborted exenterations varies between 40 and 63%, depending upon the extent of preoperative investigation.

Table 2. Preoperative Work-up and Evaluation

Patient Assessment
Tumor Recurrence Must be Confirmed by Histology:
Radiation necrosis of cervix and vagina can masquerade as central recurrence
Radiation injury to bowel/ureters can masquerade as abdominal recurrence
Exclude Distant Recurrence:
Chest radiograph
CT scan of abdomen and pelvis
Pelvic examination
Patient Education:
Explanation of the procedure
Colostomy, pouch (continent)
Vaginal reconstruction

Surgical options for recurrent cervical cancer after definitive RT

1) Radical Hysterectomy type 2 or 3 (limited to cervix, < 2 cm, original stage IB/IIA).
2) Pelvic Exenteration (if central recurrence not amenable to radical hysterectomy).
3) Radical surgical resection combined with intra-operative radiotherapy (IORT) "to exclude normal tissues from the treatment are a" (locally recurrent disease involving the pelvic sidewalls and/or nodal draining areas).[22]
4) LEER, sacral resections, hemipelvectomy and CORT "for positive or close margins" (if extending to pelvic sidewall).

Central recurrence - limited to cervix

If a patient has a very small cervical recurrence after primary RT, radical hysterectomy has been used as a less radical alternative to pelvic exenteration.[17] Patients must be carefully selected for this approach because the potential for complications is high. Because the normal pelvic tissues have been irradiated, healing after surgery is impaired. Dissection through tissue planes, especially when mobilizing the ureters, is often difficult and occasionally impossible. Most patients with a central recurrence of cervical cancer following RT should be considered for pelvic exenteration. Coleman's series of 50 patients from the MD Anderson Hospital was treated with radical

hysterectomy (type II or III).[23] Severe postoperative complications occurred in 42% of the patients, of whom 28% developed urinary tract injury. Survival was 90% at 5-years for patients with lesions less than 2 cm as opposed to 64% in patients with larger lesions. Excessive morbidity can be limited if an omental pedicle is placed at the operative site at the end of the procedure, bringing new blood supply to the operative field that has undergone previous RT.

Pelvic exenteration

Historically, almost all patients whose cervical tumor failed to be eradicated by RT faced a hopeless prognosis. In 1948, Dr. Alexander Brunschwig reported on 22 patients (15 of whom had cervical cancer) who underwent "the most radical surgical attack so far described for pelvic cancer".[24] The procedure involved a one-stage abdominoperineal operation with complete excision of the pelvic viscera, end colostomy, and bilateral ureteral implantation into the colon above the colostomy. When first described by Brunschwig, the peri-operative mortality rate was over 23% with no long-term survivors. Peri-operative morbidity was almost universal, particularly before the advent of the ileal conduit for urinary diversion.[25] Today, 90 to 95% of patients undergoing pelvic exenteration for advanced pelvic malignancy can expect to survive surgery and 20 to 60% of them will be alive 5-years later.[26]

This surgical procedure was initially envisioned as a palliative measure for women with large ulcerating necrotic lesions. Today, pelvic exenteration is a potentially curative operation for women with recurrent pelvic carcinomas.[27]

The use of exenterative procedures has become more common because of advances in the intraoperative and postoperative management of these patients. The rate of fistula formation has decreased with improvements in pelvic floor reconstruction. The use of stapling devices has decreased operative time. The surgical learning curve, in addition to new broad-spectrum antibiotics, hyperalimentation, and critical care units, has contributed to a decrease in mortality rates to 5-10%.

Hockel et al have developed the CORT regimen that involves planned postoperative re-irradiation after exenteration.[19] IORT also has been used for both locally advanced primary rectal cancer and recurrent rectal cancer after exenteration.[28] The preliminary results of these new modalities require confirmation with larger, long-term studies.

As total exenteration became a more established procedure, surgeons observed that the cancerous extension did not always involve all of the pelvic organs. Partial exenterations (anterior and posterior) were developed to spare viable, noncancerous organs. When the cancer extended anteriorly into the bladder but did not involve the rectum, the rectum could be spared, thus preserving rectal function. When cancer extended posteriorly into the rectum, without involvement of the urinary tract, posterior pelvic exenteration could be done to remove the rectogenital organs, leaving a functioning urinary system.[29] For very small, high lesions around the cervix, lower uterus and bladder it may be possible to carry out a more limited procedure (supralevator exenteration) retaining considerable parts of the pelvic floor.[30] In addition, the extent of resection could be enlarged to improve the chance for cure, e.g., when cancer spread involved the sacrum and abdominal-sacral resection could increase the chance of obtaining clear margins.[31]

Preoperative assessment for pelvic exenteration

Before considering exenteration, distant metastasis must be excluded, preferably by noninvasive techniques. Physical examination, chest radiograph, and CT scan of the abdomen and pelvis are sensitive tests in the evaluation of distant disease. A tissue diagnosis is essential prior to embarking on exenterative surgery, and needle biopsy, aspiration cytology or even open biopsy at laparotomy may be required. As distant metastases tend to occur with recurrent and residual disease, it is sometimes helpful to perform scalene node biopsies and radiological assessment of the pelvic and para-aortic lymph nodes together with fine- needle aspiration. A major part of preoperative counseling is an explanation of the procedure, including colostomy, urinary diversion, and possible vaginal reconstruction.

Intraoperative steps

The final decision to proceed with exenteration will not be made until the abdomen has been opened and explored for evidence of metastatic cancer. The lymph nodes surrounding the aorta are the first to be sampled if the abdominal exploration has revealed no evidence of disease. If the aortic area findings are negative, a bilateral pelvic lymphadenectomy is performed, if possible. On occasion the residual fibrosis from prior RT precludes meaningful safe lymphadenectomy within the radiation field. The para-aortic lymph nodes and pelvic sidewall nodes are sent for frozen section examination. Avascular spaces (prevesical, pararectal, and paravesical) must be opened and explored to evaluate the lateral pelvic attachments and the sidewall.

Indications to abort surgical procedure

Absolute contraindications

If there are metastases in extrapelvic lymph nodes, abdominal viscera, lungs or bones, then the value in performing such major surgery is low. However, there is evidence that patients with pelvic lymph node metastases may survive, and good quality of life (QoL) is reported in a small but significant percentage of such patients.

Relative contraindications

If the tumor has extended to the pelvic sidewall either in the form of direct extension or nodal metastases, then the prospects for cure are extremely small and the surgeon must decide whether the procedure will improve the patient's QoL. Encouraging results have been reported in these patients with the relatively new application of IORT, LEER and CORT.[32]

Obesity is a problem with all surgical procedures producing many technical difficulties, especially with regard to the creation and location of stomas. It also increases postoperative respiratory and cardiovascular complications as well as the risk of wound infection.[33]

Surgical techniques

Once the exploration is complete and the decision to proceed is made, there are two parts to the procedure: exenteration and reconstruction. Reconstruction is divided into four parts: the pelvic floor, the perineum and vagina, the gastrointestinal tract, and the urinary reservoir.

Table 3. Reconstructive Advances in Exenterative Procedures

Basic Reconstructive Elements (have improved quality of life)
Closure of large perineal defects with an appropriate myocutaneous flap
Successful vaginal reconstruction with myocutaneous graft
Continent low colorectal anastomoses
Continent urinary pouches

Evolution of urinary diversion

Brunschwig's original pelvic exenteration technique involved bilateral ureteral implantation into the colon above the colostomy, creating a "wet colostomy" (high morbidity and mortality; problems with infection and electrolytes) with both fecal material and urine being diverted into the same stoma.[24] However, the ileal conduit described by Bricker soon replaced the wet colostomy as the preferred means of urinary diversion.[25] In the 1970s, the transverse colon urinary conduit was introduced as an alternative to the ileal conduit. The proposed advantage of the transverse colon conduit was that it used an intestinal segment not previously irradiated, thereby decreasing the potential risk of complications such as anastomotic leakage.[34,35]

Subsequently, urologists introduced continent urinary diversions such as the Kock, Indiana and Miami pouches. The modified Indiana and Miami pouches both utilize a colonic reservoir tapered distal ileal segment, and plication of the ileocecal valve to improve urinary continence.[36,37]

Colonic diversion

In the past, most patients subjected to exenterative surgery required permanent colostomy. Recent experience encourages primary re-anastomosis of the colon in patients whose recurrences are amenable to a supralevator approach. Low colorectal anastomosis is possible with technical

ease and is achieved safely with the end-to-end anastomosis (EEA) stapler in irradiated patients. Hatch and associates reported a primary healing rate of 70% in their experience with 20 patients undergoing low rectal anastomosis at exenteration.[38] Anastomotic leaks were more common when the rectal stump was less than 6 cm in length. The authors recommended the use of an omental J-wrap to provide the requisite vascular support necessary to augment healing. In their series, the complete healing rate was 85% when omental wrap was possible.

In a survey of patients treated with coloanal anastomosis for rectal cancer, 81 of 90 eligible patients responded to a questionnaire evaluating current anorectal function. The median stool frequency was two per day and 22% of patients reported four or more stools per day. Of the patients surveyed, fecal continence was complete in 51%, incontinence to gas occurred only in 21%, minor leakage in 23%, and significant leakage in 5%. Complete evacuation of the neorectum was problematic in 32%. Overall function was excellent in 28%, good in 28%, fair in 32%, and poor in 12%. No surgical technique correlated with improved or impaired outcome. Time since surgery (reduced stool frequency) and use of postoperative adjuvant RT (increased stool frequency, increased difficulty with evacuation) appeared to adversely influence functional outcome.[39]

To evaluate the QoL in patients undergoing anterior resection (AR) or abdominoperineal extirpation (APE) for rectal cancer, Grumann and colleagues treated fifty patients with AR and prospectively followed up 23 patients treated with APE. Patients who underwent low AR had a lower QoL than those who underwent APE (preservation of anal sphincter does not result in improved QoL compared to permanent colostomy).[40]

Vaginal reconstruction

Sexual adjustment is helped when vaginal reconstruction is attempted: just under 50% of patients resume sexual activity postoperatively and 70% of patients are assessed as having a potentially functional neovagina.[41] Neovaginal creation also serves the function of filling the large, denuded dead space cavity created by radical pelvic resection. A variety of methods for achieving creation of a neovagina have been described, including split-thickness skin grafting, omental grafting, the use of sigmoid colon, and myocutaneous flaps.[42,43] Both gracilis and rectus abdominis flaps can block bowel entry into the residual pelvic space, revascularize irradiated pelvic-cavity walls, and decrease the occurrence of pelvic infections, fistula, and chronically open perineal wounds, as well as restore sexual capacity.[44,45]

Complications of pelvic exenteration

Although operative mortality has been decreased to less than 5%, operative morbidity in terms of life-threatening complications remains between 30 and 50%.[46,47] Complications surrounding exenterative procedures are innumerable and depend in large part on the extent of the surgery and the type of reconstructions performed. Additionally, co-morbidity including nutritional status and history of previous pelvic RT influence the complication rate. Most patients who undergo exenteration experience a complication, and half of these are considered major. Recently, Morrow and Curtin summarized the more common operative complications from a compilation of several series in the literature.[48] They found intraoperative hemorrhage to average a median of 3000 mL, and the most common complications included wound sepsis and dehiscence (12%), pelvic sepsis (10%), intestinal leak (8%), urinary fistula and obstruction (6%), small bowel obstruction (5%), postoperative hemorrhage (2.5%) and pulmonary embolus (1.5%).

One of the most serious postoperative complications of exenteration is small-bowel obstruction related to the denuded pelvic floor. When this occurs, it is appropriately treated with conservative therapy. However, half of the patients require reoperation, and the mortality of this group is approximately 50% in some series.[33] In the 1980s, various techniques for filling the empty pelvis were developed. Procedures such as the omental pedicle flap, mesh reconstruction of the pelvic inlet, colonic advancement, and the myocutaneous flap began to be used, with good results.

Early postoperative complications have been reported in up to 44% of patients, the most common being bowel and urinary problems. Late postoperative complications happen less frequently but still occur in up to 35% of patients. The long-term morbidity from exenteration is predominantly related to urinary diversion. Urinary infections are most common, but obstructions and fistulas can produce morbidity and mortality. Pyelonephritis is common and should be treated promptly and vigorously. Periodic IVPs can be obtained to assess the collecting system for hydronephrosis. Averette and colleagues reported on 88 patients who had urinary diversion at the time of pelvic exenteration.[49] Urinary fistulas developed in 12% of these patients, with a 45% mortality on surgical correction.

Singleton et al. reported a 48% recurrence rate.[50] Recurrences were distributed equally among the various types of exenteration. The most common site of recurrence was the pelvis (64%), followed by the lung and other distant organs (19%), and was associated with a median survival of 1.1 years.

Survival

Most series show that the 5-year survival rate after pelvic exenteration ranges from 34 to 61%; these figures depend on case selection and criteria to abort procedures.[46,47] Patients who undergo pelvic exenteration as a primary procedure have a 5-year survival rate 20 - 25% higher than a similar group of patients with recurrence following irradiation. Survival rates can be improved by excluding the elderly, the obese, the heavily irradiated, and other high-risk patients. The triad of unilateral uropathy, renal nonfunction or ureteric obstruction together with unilateral leg edema and sciatic leg pain is an ominous sign and the prospects for cure are poor. Cumulative survival rates are always improved when patients who have positive pelvic nodes at staging are not subjected to exenteration. Rutledge et al reported their experience with pelvic exenteration in 296 patients with cervical cancer during a 21-year period.[46] The 5-year survival rate was 39.8%. Of the 206 patients who underwent nodal dissection, 30 (14.6%) were found to have nodes that contained tumor. Twenty-six of these 30 patients died of recurrent disease. They also noted a 100% recurrence rate if the surgical margin contained disease. The value of exenteration procedures in patients who have lymph node involvement has been shown to be low but significant, and now most clinicians proceed with an exenterative procedure even in circumstances where one or two pelvic lymph nodes are involved by tumor.

Indications for pelvic exenteration

Pelvic exenteration has been used for cervical cancers because these tumors are usually slow growing and late metastasizing.[51] This procedure, however, can be used for any pelvic tumors that meet the required criteria. Occasionally, patients with fistulas or purulent tumors who are young and do not meet the typical criteria undergo exenteration for palliation.[52]

CONCLUSIONS

The pelvic exenterative procedure is the only possible curative therapy for many women with recurrent or persistent central pelvic malignancy after RT. Recent improvements in perioperative support and reconstructive surgery have decreased operative morbidity and mortality, increased long-term survival, and enhanced the quality of life for survivors. Recent advances in the use of adjuvant RT are likely to improve local control rates and present the possibility for survival even in patients with small volume disease remaining in the pelvis.

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