

The Role of Exenterative Surgery and Urinary Diversion in Persistent or Locally Recurrent Gynecological Malignancy: Complications and Survival

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Key Words

Cervical cancer · Exenteration · Gynecological cancer · Radiotherapy · Tumor recurrence · Urinary diversion

Abstract

Objective: Treatment options in patients with persistent or locally recurrent cervical cancer are limited. The aim of this study was to determine the chance of cure and associated morbidity following pelvic exenteration. **Patients and Methods:** Consecutive patients who underwent pelvic exenteration between January 1992 and December 2006 at the University Hospital of Bern or the Karlsruhe Medical Center were evaluated. Time to recurrence, type of exenteration and urinary diversion, pathological stage, postoperative complications and survival were assessed. **Results:** Initial therapy prior to diagnosis of persistent or locally recurrent disease included radiation therapy in 51%. Anterior exenteration was performed in 37 (86%) and total exenteration in 6 (14%). Half of the women underwent additional procedures. A continent urinary diversion was constructed in 16 and an ileal conduit in 27 patients. Early postoperative complications were generally minor and only 2 patients required surgical intervention. Four intestinal fistulas were successfully treated conservatively. Late complications were mainly tumor-related. Complication rates associated with the urinary diversion were low and there was no difference in complications be-

tween continent and incontinent diversions. The overall disease-specific 5-year survival rate after exenteration was 36.5%. Survival correlated significantly with surgical margin status. **Conclusion:** In patients with persistent or locally recurrent gynecological malignancy of the pelvis, exenteration is a viable option with long-term survival in over one third of patients. Continent urinary diversion did not show higher complication rates than an ileal conduit and should be considered even in irradiated patients. This may be of greater significance in younger patients in whom an intact body image can play an important role in quality of life.

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Introduction

Cervical cancer is the second most common cancer affecting women, with approximately 300,000 new cases and >130,000 deaths attributed to the disease in Europe in 2004 [1]. Recurrence rates are 10–20% for FIGO stages IB/IIA cervical cancers [2] and 50–70% for locally advanced cases (FIGO IIB, III and IVA) [3]. Tumor persistence or recurrence within the pelvis is the major cause of death in patients suffering from carcinoma of the uterine cervix and not metastatic disease. Treatment options for these patients are limited due to previous chemo- and/or radiation therapy in the majority. This leaves exenter-

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Table 1. FIGO classification of the initial tumors

Initial tumor stage	Patients	
	n	%
IA/B	14	32
IIA/B	15	35
IIIA/B	2	5
IVA	6	14
Unknown	6	14

ative surgery as the only palliative and in some cases possibly curative treatment available for these often young patients. Estimates of the number of patients with cancer of the lower and middle genital tract in an irradiated pelvis compared with the number of patients treated with exenteration suggest that the potential of the procedure is underused [4].

According to oncologic principles, the main goal of surgery is complete removal of the tumor mass with tumor-free margins to achieve local control and long-term survival, thus limiting the indication for pelvic exenteration to central pelvic disease. The literature on pelvic exenteration is sparse, with complication rates for radical exenterative surgery (anterior, posterior or complete) and urinary diversion ranging up to 75% for early and 83% for late postoperative complications [5, 6]. The goal of this study was to evaluate if these women profit from this extensive and mutilating surgery and if there is a chance of cure.

Patients and Methods

All patients who underwent pelvic exenteration for persistent or locally recurrent gynecological tumors at the University Hospital of Bern or the Karlsruhe Medical Center between January 1992 and December 2006 were included, and their case notes were reviewed retrospectively. Patients were followed from the day of surgery until July 2008 or until death. Persistent or recurrent disease was diagnosed by biopsy and distant metastasis was excluded in all patients by abdominal CT or MRI, plain chest X-ray and bone scan. Bimanual palpation was performed under general anesthesia and the tumor was considered to be resectable in all patients. In patients with suspected infiltration of the colon or rectum, colonoscopy was performed. All tumors were classified according to the TNM classification (6th edition, 2002).

The oncologic follow-up was performed according to institutional preferences at 3- to 6-month intervals and included ultrasonography, abdominal CT and chest radiography. Bone scans were performed either routinely after 1 year, or in case of new on-

Table 2. Treatment before recurrence

Previous treatment	Patients	
	n	%
Surgery only	19	44
Radiation only	5	12
Surgery + radiation	10	23
Surgery + chemotherapy	2	5
Radiation + chemotherapy	3	7
Surgery + radiation + chemotherapy	4	9

set of pain or elevated alkaline phosphatase levels. Patient charts were retrospectively reviewed focusing on early (≤ 30 days) and late (>30 days) surgery-related postoperative complications, requirement of re-operation as well as tumor recurrence and survival. When necessary follow-up was updated by the authors either by a questionnaire sent to the patients or telephone interview. Postoperative fever $<39^{\circ}\text{C}$ for <36 h, wound infection and hematoma treated conservatively were classified as minor complications. Cancer-specific survival was determined from the date of surgery to the date of death from cancer or censored at the last follow-up. Survival probabilities were estimated using the Kaplan-Meier method. The effect of age, clinical stage, margin status, lymph node status and type of urinary diversion on outcome was determined by the log-rank test, and multivariate analysis was performed using the Cox proportional hazards model.

Results

A total of 43 patients with a median age of 57.0 years (range: 30–79) underwent pelvic exenteration for persistent or locally recurrent disease: 2 for endometrial and 41 for cervical cancer (table 1). First-line treatment prior to diagnosis of persistent or recurrent disease consisted of surgery alone in 19/43 (44%) patients. In 16/43 (37%) patients, surgery was combined with either radiation therapy (23%), chemotherapy (5%) or combined radio-chemotherapy (9%). Of the remaining 8 patients, 5 (12%) underwent radiation monotherapy and 3 (7%) combined radio-chemotherapy (table 2). Overall 51% of the patients underwent some form of radiation therapy before diagnosis of persistent or recurrent disease. The median interval from initial treatment until diagnosis of persistent or recurrent disease was 16 months (range: 1–240 months). Of the 43 patients, 37 (86%) underwent anterior and 6 (14%) total pelvic exenteration including rectosigmoid resection. Pelvic exenteration was combined with other procedures in 26 (60%) patients: nephrectomy because of non-functioning kidneys in 3, colon resection because of

Table 3. Surgery performed at the time of exenteration

Surgery	Patients	
	n	%
Type of exenteration		
Anterior	37	86
Complete (including rectosigmoid)	6	14
Additional surgical procedures		
None	17	40
Nephrectomy	3	7
Recto/colonic resection	9	21
Colostomy	10	23
Sigma/ileum neovagina	4	9
Urinary diversion		
Ileal conduit	27	63
Continent ileocecal/ileal pouch	12	28
Orthotopic ileal bladder	4	9

Table 5. Early postoperative complications in 22 patients (51%)

Complications	Frequency	
	n	%
Fever	13 ^a	30
Wound infection	7 ^a	16
Sepsis	1	2
Pelvic abscess	3	7
Hematoma	2 ^a	5
Ileus	1	2
Intestinal fistula	4	9
Deep vein thrombosis	3	7
Pulmonary embolus	2	5

^a Classified as minor complications.

colonic infiltration in 9 and colostomy in 10 (table 3). Four younger patients underwent vaginal reconstruction with sigma or ileum. A continent urinary diversion was constructed in 16: 4 ileal orthotopic bladder substitutes, 2 continent ileal reservoirs, 10 continent ileocecal reservoirs (Mainz pouch I) and 1 ileal conduit in 27 patients.

Histopathology of the recurrent disease showed squamous cell carcinoma in 78% of the patients and adenocarcinoma in 22%. Advanced disease (pT \geq 3a) was seen in 36 patients (84%) and 9 (21%) had positive margins (n = 43; table 4). Despite previous surgical treatment in the majority of the patients, lymph node metastases were found in 18 of the 43 (42%) patients, of whom 14 had negative surgical margins. Of the 9 patients (21%) with posi-

Table 4. Histopathological data at recurrence

TNM stage (AJCC 2002)	Frequency	
	n	%
pT0	1	2
pT2b	6	14
pT3a	2	5
pT3b	7	16
pT4	27	63
Nodes		
Negative	25	58
Positive	18	42
Surgical margin		
Negative	34	79
Positive	9	21

Table 6. Late postoperative complications in 15 patients (35%)

Complications	Frequency	
	n	%
Pelvic abscess	4 ^a	9
Deep vein thrombosis	3	7
Pulmonary embolus	1	2
Sepsis	1	2
Ileus	6 ^a	14
Intestinal fistula	3 ^a	7
Ureter obstruction	2 ^a	5

^a Related to tumor recurrence.

tive surgical margins, 4 (44%) had positive lymph nodes. One specimen was tumor-free in the final histopathology although tumor recurrence had been confirmed by biopsy preoperatively.

A total of 36 early complications occurred in 22/43 (51%) patients, the majority being considered minor (22/36, 61%) (table 5). Two patients required surgical revision for hematoma and abscess. Four intestinal fistulas were observed in the early postoperative period following urinary diversion via ileum conduit. Two of these patients had undergone additional colonic resection. All 4 patients had prior radiation therapy and were successfully managed conservatively. Late complications occurred in 15/43 (35%) patients and were associated with

Fig. 1. Disease-specific survival of all patients undergoing exenterative surgery for recurrent gynecological malignancy (n = 43).

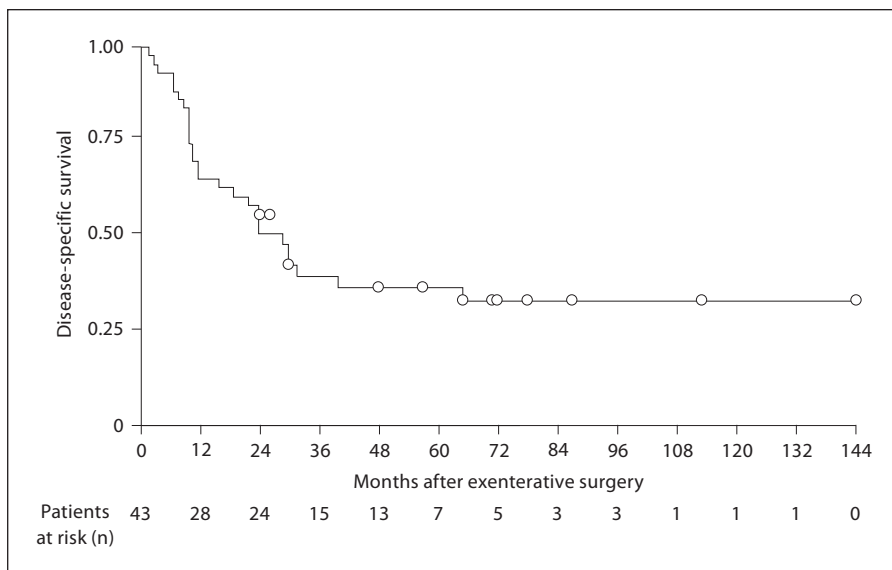
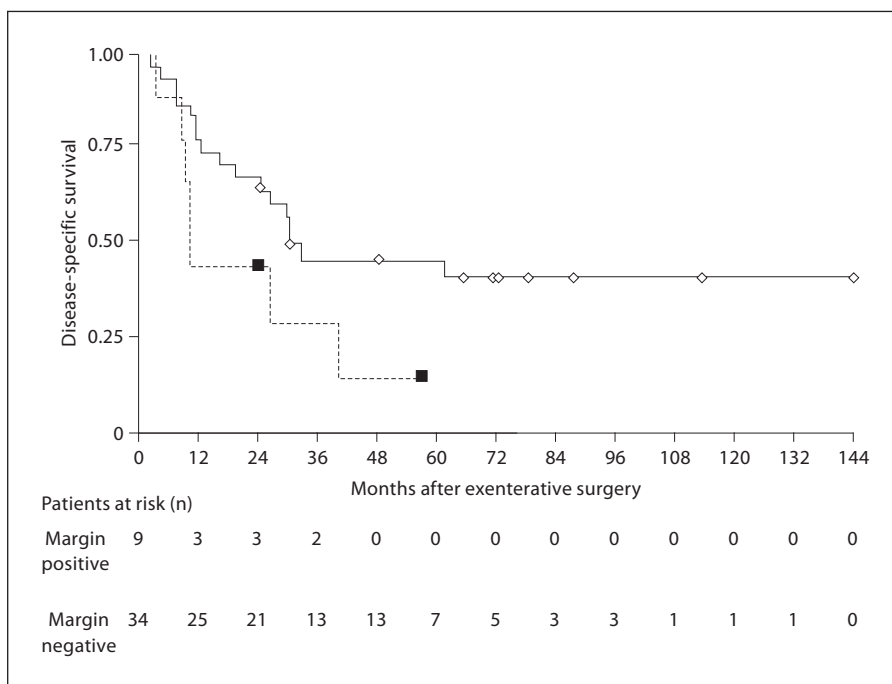


Fig. 2. Disease-specific survival of surgical-margin-positive (—■—; n = 9) and -negative (—◇—; n = 34) patients after exenterative surgery for recurrent gynecological malignancy. Log-rank test: p = 0.0749.



tumor recurrence in 10/15 (67%) patients (table 6). In 10 of the 15 patients with late complications, early postoperative complications were also present. None of the patients required any form of intervention for complications associated with the urinary diversion either in the early or late phase.

The median duration of follow-up was 30.5 months (range: 2–144) following exenteration. Fourteen patients (33%) remained free of disease after a median follow-up

of 52 months (range: 12–144). Twenty-nine patients (76%) developed a recurrence after a median time of 15 months (range: 8–31 months), of whom 27 died after a median time of 12 months (range: 2–61).

The overall disease-specific survival after pelvic exenteration was 36.5% at 5 years (fig. 1), being 46 and 30% in margin-negative and -positive patients after 3 years, respectively. There was a significant association between surgical margin status and survival (p = 0.0749; log-rank

test, fig. 2). In 31 patients with tumor-free margins, median survival was 32 months (range: 2–144), compared to a median survival of 10 months (range: 3–40) for patients with positive surgical margins. The Cox proportional hazards model revealed surgical margin status as the only factor with a significant effect on disease-specific survival ($p = 0.0781$ with a hazard ratio of 2.193).

Discussion

The care of patients with persistent or locally recurrent gynecological tumors after previous multimodality treatment can be challenging, and without further treatment the survival rate is <6% after 3 years [7]. Treatment options vary depending on the prior therapy and range from chemotherapy and radiation therapy to radical surgery, e.g. pelvic exenteration with bladder substitution. Staging computerized tomography has limited accuracy in detecting advanced local tumor extension and pelvic lymph node metastasis [8].

In the series presented here, the overall 5-year survival rate following pelvic exenteration was 36.5%, with 46% in patients with negative surgical margins, indicating the possibility of prolonged survival after radical surgery. Radiotherapy, if given as first-line therapy, is another treatment option with 5-year survival rates of 33% [9]. Generally, only small recurrent tumors (<2–3 cm) are deemed potentially curable. This was not an option in the 51% of our patients who had already received radiation therapy. The remaining alternative is chemotherapy. Many different chemotherapy agents have been investigated as single or combined regimes for advanced or recurrent disease and are generally considered as palliative treatment [10]. Response rates in multicenter phase II trials average at 10–40%; complete responses are rarely seen and are of short duration. Cisplatin is the most active single agent in recurrent disease. Combining cisplatin with paclitaxel in a phase II study resulted in a median progression-free survival of 10 months in patients with advanced or recurrent disease [11]. A randomized, phase III study compared cisplatin as a single agent with the cisplatin-paclitaxel combination. The combined regime was superior to cisplatin monotherapy in terms of response rate and survival, with a higher rate of reversible toxic effects on the bone marrow [12]. However, the survival benefit was modest (a few weeks). One factor that apparently negatively affects the response to chemotherapy is recurrence occurring within a previously irradiated field. About 25% of patients with recurrence outside the irradiated field

respond to chemotherapy versus only 5% if the tumor recurs within the irradiated field [13].

Not only does radical surgery show comparably good results, it may also have a positive effect on quality of life. This is currently under investigation in a prospective phase II trial (Gynecologic Oncology Group, National Cancer Institute, No. NCT00217633). Despite these encouraging results, there are only a limited number of reports on exenterative procedures [5, 6, 14, 15]. The reason for the reluctance to perform radical surgery is unclear. Salvage surgery is extensive and mainly involves the urinary tract (bladder, urethra and ureters) requiring urinary diversion, but interdisciplinary collaboration is a prerequisite. However, mortality rates of up to 11% reported in earlier series may be discouraging [5, 6, 10, 13]. Indeed, complications do occur, especially when taking the 51% of patients who underwent previous radiation therapy into account [5, 6, 14, 15], but the majority of these complications can be managed conservatively and do not require additional surgery. In the series presented here, the rate of early postoperative complications was 51%. The four intestinal fistulas reflect the difficulties associated with irradiated bowel segments in reconstructive surgery. None of them was related to an orthotopic diversion and all of them were effectively managed conservatively. Only two re-interventions were necessary and no patient in our series died perioperatively, which may reflect the standardized operative and perioperative management. We did not analyze the effect of body mass index on complications and outcome in our patients, but in a recent large radical cystectomy series intra- and postoperative morbidity was not significantly elevated in overweight patients, and overall survival was not reduced [16]. Late complications were strongly associated with further tumor recurrence, often resulting in bowel or ureteral obstruction (table 4). In the one third of patients remaining tumor-free, late complications were a rare event.

An attempt should always be made to use non-irradiated bowel, and several authors have suggested using either jejunum or a transverse colon segment for urinary diversion to reduce the risk of complications [17–19]. However, severe electrolyte and acid base disturbances are encountered when jejunum comes into prolonged contact with urine and its role for diversion is limited. Ravi et al. [20] reported on a series of 30 irradiated patients treated with a transverse colonic conduit. Early diversion-associated postoperative complications occurred in 16% and late complications in 20%, and as a result they recommended transverse colonic conduit in case of pre-

vious radiation therapy. If the colon is used, the ileocecal valve should be left intact, or patients will develop diarrhea. In addition, all patients will experience acidosis, however this is often only of mild degree [17]. Ileal and colonic conduits are most frequently applied and reported in the literature, however they are not continent diversions and require dependence on an external appliance, which may negatively affect the patient's body image.

Quality of life issues are becoming increasingly important, and an improvement in the body image in patients with a continent reservoir compared with those with an ileal conduit is well known [18]. The increased use of different continent urinary diversions and orthotopic bladder substitutes has led to their application even in irradiated patients. In a study by Salom et al. [6], 82 patients with recurrent gynecological cancer were subjected to some form of exenterative surgery and urinary diversion with a continent ileocolonic urinary reservoir. The most common reservoir-related complications were urinary tract infections (40%), ureteral stricture (20%) and difficulty in self-catheterization (18%). More than 80% of these complications were resolved by conservative treatment. Leissner et al. [19] reported on the use of a transverse and descending colonic pouch (Mainz pouch III) in irradiated patients respecting the 'stay-away' principle and using a more proximal ureterocolonic anastomosis. However, even in this series, 11% developed ureteral obstruction. In contrast to the literature, we did not find any radiation-induced ureteral obstruction in our patients. This may be the result of using an afferent ileal tubular segment which allows more proximal resection (stay-away principle) leaving a non-irradiated ureteric segment

to perform a direct, non-refluxing uretero-intestinal anastomosis.

Some limitations of our study have to be outlined. We have reported on a selected cohort of patients with recurrent gynecological cancer who had undergone different treatments prior to their recurrence. The patients were evaluated retrospectively and a direct comparison to other modern treatment modalities is not available.

Conclusion

Pelvic exenteration and urinary diversion is a viable and in some cases the only option for cure in patients with recurrent cervical cancer confined to the center of the pelvis, with acceptable complication rates and long-term survival in approximately one third of all patients and almost half of the patients with negative surgical margins. Margin-free resection is of utmost importance as tumor recurrence is the factor limiting survival in these patients. Complication rates are higher in patients with prior radiation therapy but can be minimized by adhering to surgical principles, such as the 'stay-away principle', which still holds true. Continent urinary diversion did not show higher complication rates compared to ileal conduit and should be taken into account, especially in younger patients, as this may result in a better quality of life and body image. Patient selection is the silent partner of successful oncological treatment. Not all patients can be offered pelvic exenteration, but if deemed feasible, good results, with no operative mortality, can be achieved in patients with no or limited alternatives for curative treatment.

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