



Clinical outcomes after isolated pelvic failure in cervical cancer patients treated with definitive radiation

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HIGHLIGHTS

- Isolated pelvic failure after definitive radiation occurred in 11% of cervical cancer patients.
- FDG-avid para-aortic nodes at first diagnosis predicted for subsequent distant failure after initial isolated pelvic failure.
- Surgical salvage of isolated pelvic failure was curative in about 1/3 of patients.

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ABSTRACT

Purpose. To describe clinical outcomes in patients with isolated pelvic failures after definitive radiation treatment for cervical cancer.

Methods and materials. Cervical cancer patients with isolated pelvic failure after definitive radiation with brachytherapy boost were identified in a tertiary academic center database from 1997 to 2016. All patients received an FDG-PET scan prior to their initial treatment and at the time of their first recurrence. Isolated failures in the cervix or pelvic nodes were biopsy-proven. Distant failure and overall survival (OS) were censored outcomes.

Results. Isolated pelvic failure was detected in 67 (11%) out of 607 consecutive patients treated with external beam pelvic radiation and brachytherapy boost. The median time to isolated pelvic recurrence was 9 months (range 3–198). Median follow-up time for patients alive after isolated pelvic recurrence was 40 months (range 0.6–183). Of these 67 patients, 28 (42%) received salvage surgery, 17 (25%) received chemotherapy alone, and 22 (33%) received neither surgery nor chemotherapy. The median time to distant failure after isolated pelvic failure was 20 months (95% CI 3–37), with no significant difference between patients treated surgically vs. non-surgically. FDG-avid pelvic and para-aortic nodes at initial presentation were associated with worse distant control after isolated pelvic failure (HR = 3.4, 95% CI 1.0–12). Median OS for patients treated with surgery, chemotherapy alone, and neither surgery nor chemotherapy was 29 months (95% CI 16–41), 12 months (95% CI 3–21), and 3 months (95% CI 1–5), respectively.

Conclusions. Patients who have pelvic and para-aortic nodal disease at initial presentation are at higher risk of failing distantly after isolated pelvic failure, which should be considered when counseling patients on aggressive surgical salvage. Surgical salvage was associated with prolonged survival after isolated pelvic failure.

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1. Introduction

Definitive chemoradiation is the standard treatment for locally advanced cervical cancer [1]. Despite advances in pre-treatment imaging and radiation delivery, recurrent disease represents a significant clinical

challenge and occurs in up to one third of patients [2–4]. In over 80% of these cases, recurrent disease arises within 2 years of initial treatment, and up to 25% of recurrences are isolated local failures within the radiation field [5–7].

Management options for recurrence after chemoradiation are limited [8]. Systemic agents have yielded poor results in this setting, and re-irradiation portends significant risk of severe complications [9–11]. Salvage surgery, namely pelvic exenteration or radical hysterectomy, is the only potentially curative option for patients with isolated pelvic

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failure, and five-year survival above 30% has been achieved with this approach [12,13]. However, it is unknown if aggressive local therapy reduces the rate of distant spread in recurrent cervical cancer. In this study, we report on a cohort of patients with isolated pelvic failure after definitive radiation and describe clinical characteristics associated with distant control and survival.

2. Methods

2.1. Patients and outcomes

Cervical cancer patients with isolated pelvic failure after definitive external beam radiation with brachytherapy boost were identified in a tertiary academic center database from 1997 to 2016. All patients underwent a complete pretreatment staging workup for their initial diagnosis, including a history and physical examination, examination under anesthesia, cervical tumor biopsy, pelvic computed tomography (CT) or magnetic resonance imaging (MRI), and whole-body 18-fluorodeoxyglucose positron emission tomography (FDG-PET). Patients received external irradiation to their pelvic lymph nodes with a standard dose of 50.4 Gy in 28 daily fractions. Larger lymph nodes did not receive higher boost radiation doses in this study cohort. A brachytherapy boost was given to the primary cervical tumor either as two low-dose rate or 6 weekly high dose rate brachytherapy implants, as previously described [2]. Concurrent weekly chemotherapy, when given, was bolus cisplatin 40 mg/m².

Patients were followed with clinical examinations approximately every 2 months for the first 6 months, every 3 months for the next 2 years, and then every 6 months. FDG-PET was performed 3 months after completion of treatment in 60/67 (90%) patients and then as indicated by clinical examination or symptoms. Patients with persistent FDG-uptake 3 months after completion of therapy received a second follow-up FDG-PET in 2–3 months and were biopsied at that time if there was evidence of persistent disease. Patients who had initial response to radiation on FDG-PET and later recurred were staged at that time with another FDG-PET. Isolated failures in the cervix or pelvic nodes were confirmed and dated at time of biopsy. Time to distant failure from the date of initial pelvic failure, following observation or salvage treatment, was our primary outcome. Overall survival (OS) from date of initial pelvic failure and site(s) of distant failure were secondary outcomes. This retrospective analysis was approved by our institutional Human Research Protection Office with waiver of informed consent (IRB# 201808184).

2.2. Treatment for isolated pelvic failure

Patients were considered for curative pelvic exenteration or radical hysterectomy if they had recurrent disease localized to the cervix only. Pelvic sidewall involvement, rectum/bladder involvement, hydronephrosis, or spread to new lymph nodes was considered a relative contraindication for radical surgery. Patients with aborted radical surgery due to intraoperative findings were included in the surgery group. Five patients with persistent pelvic nodal disease after initial chemoradiation received radical surgery (4 radical hysterectomy with lymph node dissection, 1 total pelvic exenteration with lymph node dissection). Three patients with isolated pelvic nodal failure without cervix recurrence received lymph node dissection alone at the surgeon's discretion.

2.3. Statistical analyses

The Fisher's exact test was used to compare categorical data and nonparametric Mann-Whitney *U* test was used for continuous variables. Kaplan-Meier survival analyses were performed, with statistical significance calculated by log-rank test. Cox regression analysis was done for both univariable and multivariable modeling of distant failure and

death. Factors significant on univariable analysis ($p < 0.1$) were entered in a backward-conditional multivariable model. Final significance was defined as $p \leq 0.05$, and all tests were two-tailed. Statistical analyses were done in SPSS, version 23 (IBM, Armonk, NY).

3. Results

3.1. Patient and tumor characteristics

There were 607 cervical cancer patients who completed curative intent radiation with a brachytherapy boost from 1997 to 2016. Of these

Table 1
Patient and tumor characteristics stratified by patients selected for surgery vs. no surgery.

	Total No. of patients (%) n = 67	No surgery No. of patients (%) n = 39	Surgery No. of patients (%) n = 28	p value
Median age at initial diagnosis	48 (26–90)	50 (26–90)	46 (35–81)	0.52
Initial histology				0.09
Squamous	60 (90%)	37 (95%)	23 (82%)	
Adenocarcinoma	7 (10%)	2 (5%)	5 (18%)	
Initial FIGO stage				0.66
IB1	9 (13%)	5 (13%)	4 (14%)	
IB2	14 (21%)	7 (18%)	7 (25%)	
IIA	1 (1.5%)	1 (2.5%)	0 (0%)	
IIB	26 (39%)	15 (38.5%)	11 (39%)	
IIIA	1 (1.5%)	0 (0%)	1 (4%)	
IIIB	16 (24%)	11 (28%)	5 (18%)	
Initial PET lymph node involvement				0.87
None	31 (46%)	17 (43.5%)	14 (50%)	
Pelvic	28 (42%)	17 (43.5%)	11 (39%)	
Pelvic and para-aortic	8 (12%)	5 (13%)	3 (11%)	
Initial treatment				0.13
Chemoradiation	54 (81%)	29 (74%)	25 (89%)	
Radiation alone	13 (19%)	10 (26%)	3 (11%)	
Site of initial pelvic recurrence/persistent disease				0.07
Cervix only	39 (58%)	23 (59%)	16 (57%)	
Pelvic lymph nodes only	13 (19.5%)	9 (23%)	4 (14.5%)	
Both cervix and pelvic lymph nodes	7 (10.5%)	1 (3%)	6 (21.5%)	
Vagina/bladder/uterus	8 (12%)	6 (15%)	2 (7%)	
Time to initial pelvic recurrence				0.09
Median (months)	9 (3–198)	10 (4–198)	7 (3–94)	
≤6 months	21 (32%)	10 (26%)	11 (39%)	0.25
6.1–12 months	23 (34%)	13 (33%)	10 (36%)	
12.1–24 months	8 (12%)	4 (10%)	4 (14%)	
>24 months	15 (22%)	12 (31%)	3 (11%)	
Median age at initial pelvic recurrence	50 (27–90)	55 (27–90)	47 (36–83)	0.25
Chemotherapy after failure				0.004
Yes	20 (30%)	17 (44%)	3 (11%)	
No	47 (70%)	22 (56%)	25 (89%)	
Surgery type				–
Pelvic exenteration	10 (36%)	–	10 (36%)	
Radical hysterectomy	12 (43%)	–	12 (43%)	
Lymph node dissection only	3 (10.5%)	–	3 (10.5%)	
Aborted surgery	3 (10.5%)	–	3 (10.5%)	
Reason surgery not performed				
Local invasiveness (ureter, bowel, sidewall)	–	17 (43.5%)	–	
Nodal spread	–	12 (31%)	–	
Patient preference	–	4 (10%)	–	
Patient lost to follow up	–	1 (2.5%)	–	
Patient got brachytherapy salvage	–	1 (2.5%)	–	
Comorbid disease	–	3 (8%)	–	
Second malignancy	–	1 (2.5%)	–	

Statistically significant p values are bolded.

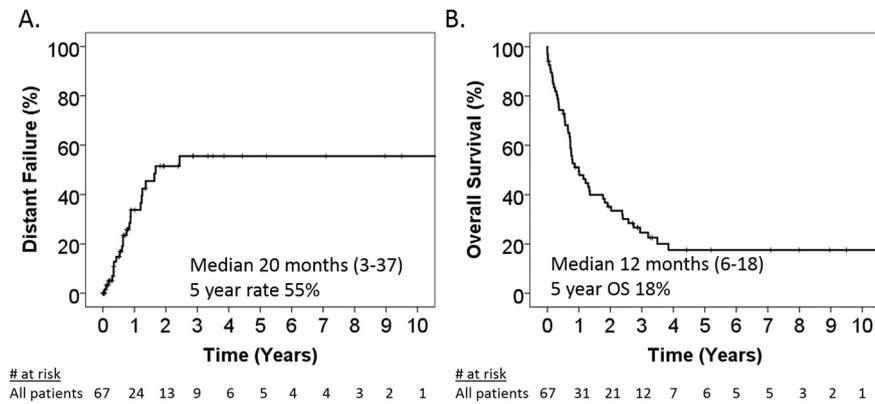


Fig. 1. Kaplan-Meier curves of distant failure (A) and OS (B) in cervical cancer patients with an isolated pelvic failure. Estimated median time (with 95% confidence interval) to distant failure or death after isolated pelvic failure is shown.

607 patients, 241 (40%) had a cancer recurrence; 49 (20%) had both pelvic and distant metastases at first failure, 125 (52%) had distant only metastases at first failure (of which only 1 (0.8%) developed pelvic metastasis subsequently), and 67 (28%) had isolated pelvic disease at first failure. The median time to isolated pelvic recurrence was 9 months (range 3–198), with a third of patients recurring before 6 months. Of the 29 patients with incomplete response on the first post-treatment PET, 15 (52%) had a biopsy-proven recurrence with the second PET scan 2–3 months later. There were no significant differences in baseline tumor or initial treatment factors between patients that received salvage surgery vs. no surgery (Table 1). Of the 14 patients with records of their chemotherapy regimen, 8 received carboplatin/paclitaxel, 5 received carboplatin/paclitaxel/bevacizumab, 2 received cisplatin/topotecan, and 1 received cisplatin/paclitaxel. The median number of cycles given was 6 (range 1–11). Of the 11 patients receiving pelvic exenteration, 8 (73%) were total pelvic exenteration, 2 (18%) were anterior pelvic exenteration, and 1 (9%) was abandoned after finding intraperitoneal metastasis during surgery. Patients that received salvage surgery were less likely to receive salvage chemotherapy ($p = 0.004$).

3.2. Distant failure after isolated pelvic failure

The median time to distant failure after isolated pelvic recurrence was 20 months (95% CI 3–37) (Fig. 1A). Of the 23 patients found to have distant failure, 22 (96%) failed within 2 years of the initial isolated pelvic failure. Median time to distant failure did not significantly differ by treatment (Fig. 2A), but death was a significant competing risk in

patients not receiving surgery nor chemotherapy. The sites of distant failure are shown in Table 2. The most common sites of distant failure for non-surgical patients were the lung (36.5%) and para-aortic nodes (27.5%); for surgical patients, they were the peritoneum (33.3%), lung (16.5%) and bone (16.5%). Patients who presented initially with both pelvic and para-aortic lymph nodes were more likely to eventually develop distant failure (Table 3). Compared to pelvic exenteration, patients receiving radical hysterectomy did not have a significantly different risk of distant failure (Hazard Ratio HR = 1.6, 95% CI 0.4–5.6). For the 28 patients that underwent surgery after initial isolated pelvic recurrence, the rate of distant failure was 6/18 (33%) for initial central failures, 4/6 (67%) for initial central and lymph node failures, and 2/4 (50%) for initial lymph nodes alone failures.

3.3. Overall survival after isolated pelvic failure

Median OS for the whole cohort was 12 months (95% CI 6–18) (Fig. 1B). Median OS for patients treated with surgery was 29 months (95% CI 16–41); median OS for patients treated with chemotherapy alone was 12 months (95% CI 3–21); median OS for patients treated with neither surgery nor chemotherapy was 3 months (95% CI 1–5) (Fig. 2B). Patients who were initially treated with definitive radiation alone without chemotherapy and patients that did not get surgery nor chemotherapy for their pelvic recurrence had worse OS (Table 4). For patients salvaged with surgery, radical hysterectomy did not have a significantly higher risk of death compared to pelvic exenteration (HR = 1.3, 95% CI 0.5–3.8).

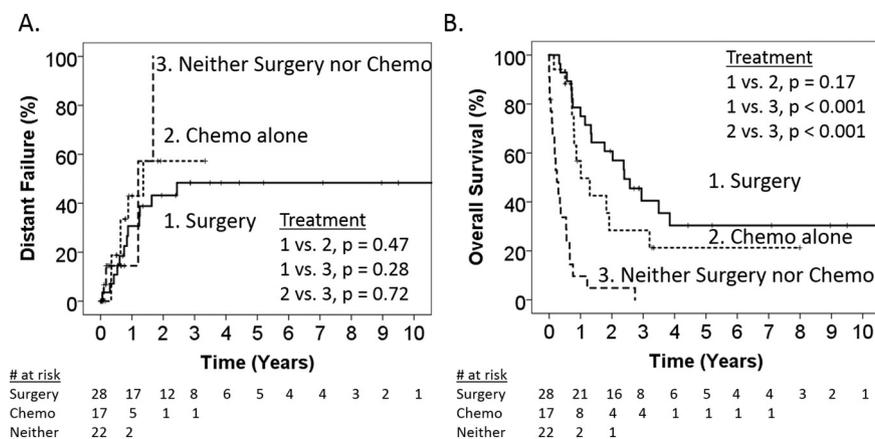


Fig. 2. Kaplan-Meier curves of distant failure (A) and OS (B) in cervical cancer patients with an isolated pelvic failure stratified by treatment.

Table 2
Sites of subsequent distant failure after isolated pelvic failure.

	Total No. of patients (%) n = 67	No surgery No. of patients (%) n = 39	Surgery No. of patients (%) n = 28
Lung	6 (26%)	4 (36.5%)	2 (16.5%)
Para-aortic nodes	4 (17%)	3 (27.5%)	1 (8.3%)
Peritoneal	4 (17%)	0 (0%)	4 (33.3%)
Peri-rectal	2 (9%)	1 (9%)	1 (8.3%)
Liver	2 (9%)	2 (18%)	0 (0%)
Bone	2 (9%)	0 (0%)	2 (16.5%)
Multiple sites	2 (9%)	1 (9%)	1 (8.3%)
Infraclavicular node	1 (4%)	0 (0%)	1 (8.3%)
Distant failure/total	23/67 (34%)	11/39 (28%)	12/28 (43%)

4. Discussion

Distant control following isolated pelvic failure in previously irradiated cervical cancer patients is not well characterized in the literature. To our knowledge, this study is the first to detail patterns of subsequent distant failure and clinical characteristics influencing its likelihood. Overall, 23 of 67 patients (34%) experienced distant failure following pelvic relapse. Over 95% of distant failures occurred within 2 years of local failure. There was no difference in time to distant failure after isolated pelvic failure between patients receiving surgical vs. non-surgical management. Among patients receiving salvage surgery, we observed a distant control rate of 53% at 5 years post recurrence. This compares favorably to a recent study of 61 recurrent cervical cancer patients treated with pelvic exenteration that reported a 5-year disease free survival of 49% [14].

Our data suggests that micrometastases may have already seeded at the time of isolated local failure. Pelvic and para-aortic nodal involvement

Table 3
Cox regression for factors associated with developing distant failure after isolated pelvic failure.

	Univariable hazard ratio (95% CI)	p value	Multivariable hazard ratio (95% CI)	p value
Initial histology				
Squamous	Ref			
Adenocarcinoma	1.3 (0.4–4.4)	0.68		
Initial FIGO stage				
IB1–IB2	Ref			
IIB–IIIB	1.1 (0.5–2.5)	0.89		
Initial PET lymph node involvement				
None	Ref		Ref	
Pelvic	1.3 (0.5–3.1)	0.62	1.3 (0.5–3.1)	0.62
Pelvic and para-aortic	3.4 (1.0–12)	0.05	3.4 (1.0–12)	0.05
Initial treatment				
Chemoradiation	Ref			
Radiation alone	2.1 (0.7–6.4)	0.19		
Site of initial pelvic recurrence/persistent disease			Included but not significant in final MVA	
Cervix only	Ref			
Pelvic lymph nodes only	2.1 (0.7–5.7)	0.16		
Both cervix and pelvic lymph nodes	3.1 (1.0–9.8)	0.06		
Vagina/bladder/uterus	1.4 (0.4–5.4)	0.56		
Age at initial pelvic recurrence	1.0 (0.98–1.04)	0.55		
Time to initial pelvic recurrence	1.0 (0.99–1.01)	0.64		
Treatment after failure				
Surgery	Ref			
Chemotherapy alone	1.5 (0.6–3.9)	0.41		
Neither surgery nor chemotherapy	1.9 (0.6–6.2)	0.28		

Statistically significant p values are bolded.

Table 4
Cox regression for factors associated with death after isolated pelvic failure.

	Univariable hazard ratio (95% CI)	p value	Multivariable hazard ratio (95% CI)	p value
Initial histology				
Squamous	Ref			
Adenocarcinoma	1.2 (0.5–2.7)	0.73		
Initial FIGO stage			Included but not significant in final MVA	
IB1–IB2	Ref			
IIB–IIIB	0.6 (0.3–0.99)	0.05		
Initial PET lymph node involvement			Included but not significant in final MVA	
None	Ref			
Pelvic	0.6 (0.3–1.1)	0.09		
Pelvic and para-aortic	1.3 (0.6–3.0)	0.57		
Initial treatment				
Chemoradiation	Ref		Ref	
Radiation alone	2.5 (1.3–4.9)	0.007	2.3 (1.1–4.5)	0.02
Site of initial pelvic recurrence/persistent disease				
Cervix only	Ref			
Pelvic lymph nodes only	1.1 (0.6–2.2)	0.77		
Both cervix and pelvic lymph nodes	1.2 (0.5–3.2)	0.70		
Vagina/bladder/uterus	1.0 (0.4–2.5)	0.95		
Age at initial pelvic recurrence	1.0 (0.98–1.02)	0.69		
Time to initial pelvic recurrence	1.0 (0.99–1.01)	0.50		
Treatment after failure				
Surgery	Ref		Ref	
Chemotherapy alone	1.6 (0.8–3.3)	0.14	1.6 (0.8–3.4)	0.21
Neither surgery nor chemotherapy	7.9 (3.9–16)	<0.001	7.8 (3.8–16)	<0.001

Statistically significant p values are bolded.

has previously been linked to increased odds of developing distant metastatic disease in several studies of locally-advanced cervical cancer [15–17]. The results of our study suggest that this observation holds true when predicting subsequent distant control in the setting of isolated pelvic recurrence. In one report of 133 surgically-treated locally advanced or recurrent cervical cancer patients, the highest 5-year survival rate was achieved in those without lymph node metastases at initial presentation [18]. Thus, the risk of early distant failure must be weighed against local control for patients who initially presented with FDG-avid pelvic and para-aortic lymph nodes.

The median OS of 12 months for this cohort is consistent with other reports of locally-recurrent pelvic disease [3,7]. Patients who received surgery for management of recurrence had a median overall survival of 31 months. Legge et al. reported a median survival of 46 months in patients with complete resection of relapsed pelvic disease [7]. In another cohort, 22 patients salvaged with hysterectomy or radiotherapy survived significantly longer than those treated with chemotherapy alone, with a median survival of 34 months [19]. The 5-year survival of our surgically-treated cohort was 32%, similar to other surgically-treated cohorts of recurrent or locally advanced disease [17,20,21]. These findings indicate that surgical salvage offers cure for about a third of patients.

The Gynecologic Oncology Group (GOG) has conducted multiple clinical trials investigating optimal chemotherapy regimens in the treatment of advanced, recurrent, and metastatic cervical cancer. GOG 179 was the first such trial to demonstrate a significant survival advantage in patients treated with cisplatin and topotecan compared to cisplatin alone (median OS of 9.4 versus 5.4 months) [22]. GOG 204 showed no statistical difference in outcomes between 4 combinations of cisplatin doublets [23]. More recently, GOG 240 demonstrated that the addition of bevacizumab to combination chemotherapy achieved an increased

median OS of 17 months [11]. Many enrolled patients exhibited distant metastatic disease at the time of these trials, complicating comparison with our cohort of patients with recurrent disease limited to the pelvis. In future prospective investigations, rigorous comparison of treatment modalities for recurrent cervical cancer requires delineation by recurrence type.

The Moore Criteria have previously been described to predict outcomes in women treated with cisplatin-based chemotherapy for recurrent or metastatic locally advanced cervical cancer [24]. African American race, performance status >0, pelvic disease, prior cisplatin exposure, and time interval from diagnosis to first recurrence <1 year were proposed to be poor prognostic factors. Investigators of GOG 240 prospectively validated the Moore Criteria, finding patients with at least two factors benefited from the addition of bevacizumab to cisplatin-based chemotherapy [25]. In our cohort, the majority of patients would have at least two Moore Criteria factors. Distant control and OS may have been underestimated in the salvage chemotherapy group, since addition of bevacizumab was not standard of care until after 2014.

The present retrospective study has a number of limitations. Patients selected for surgery had limited pelvic disease and inferred good performance status, which may overestimate survival rates compared to patients that did not get surgical salvage. Though we did not see a significant difference in distant control or OS with radical hysterectomy vs. pelvic exenteration, the patient numbers in each group were limited and further study will be needed to determine the optimal surgery for isolated pelvic recurrence. Lastly, a large number of patients in this study received neither surgery nor chemotherapy, due to intolerance to therapy or patient choice. These patients rapidly progressed and died of their disease, which competed with analysis of developing distant metastatic disease.

In conclusion, our data corroborates previous descriptions of poor clinical outcomes following relapse in an irradiated pelvis but shows a third of surgically-treated patients have long-term disease control. Patients who had initial pelvic and para-aortic nodal disease had a higher risk of distant failure regardless of salvage treatment. Future prospective studies are necessary to validate the best treatment approach in patients with isolated pelvic failure.

Conflicts of interest

The authors report no conflicts of interest with this work.

Author contributions

Alexander Lin: Data curation, methodology, formal analysis, writing-original draft. Sirui Ma: Data curation, writing-original draft. Stephanie Markovina: review and editing. Julie Schwarz: review and editing. David Mutch: review and editing. Matthew Powell: review and editing. Perry Grigsby: Conceptualization, review and editing.

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