Outcomes associated with treatment to all sites of disease in patients with stage IVB cancer of the cervix

Shira Peleg Hasson ,[1,2] Shira Felder,[1,3] Limor Helpman,[1,4] Alexandra Taylor ,[5] Mihal Shalamov,[1] Sireen Abuakar,[1,3] Smadar Bauer,[1,3] Ronnie Shapira-Frommer,[1,3] Inbal Greenhouse,[1,3] Jacob Korach ,[1,4] Tatiana Rabin,[1,6] Jeffrey Goldstein,[1,6] Akram Saad [1,3]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ijgc-2022-004224).

For numbered affiliations see end of article.

Correspondence to
Dr Akram Saad, Tel Aviv University Sackler Faculty of Medicine, Tel Aviv, Tel Aviv, Israel; akram.saad@sheba.health.gov.il

Received 20 December 2022
Accepted 13 February 2023
Published Online First 24 March 2023

ABSTRACT

Objective The use of chemoradiation in patients with stage IVB cancer of the cervix was evaluated to determine if definitive treatment offers benefit.

Methods A database of 546 patients with cancer of the cervix treated between January 2005 and May 2021 at a tertiary academic medical center was reviewed retrospectively to identify patients with stage IVB disease. Log rank test, regression analysis, and the Kaplan–Meier method were used to identify and compare variables and estimate progression free survival and overall survival.

Results Thirty-three patients with stage IVB cervical cancer were identified. Median age was 53 years (range 28–78). Pathology subtypes were squamous cell (n=22, 67%), adenocarcinoma (n=8, 24%), and clear cell (n=3, 9%). Metastases were classified as lymphatic (n=14, 42%) or hematogenous (n=19, 58%). Following treatment to all sites with chemoradiotherapy and selected use of surgery (n=23), six patients (26%, lymphatic n=4, hematogenous n=2) remained disease free for a median duration of 4 years (range 3–17 years). Recurrences in the remaining patients were distant (n=13) or local (n=4). All patients in the chemotherapy group (n=10, 100%) progressed. Kaplan–Meier analysis showed that median progression free survival was longer for patients treated at all disease sites than for patients treated with chemotherapy alone (19 vs 11 months, p=0.01). However, this was not the case for overall survival (49 vs 33 months, p=0.15). Patients with metastases limited to lymph nodes also had longer median progression free survival (22 vs 11 months, p=0.04) but not overall survival (p=0.68).

Conclusions Patients with stage IVB cancer of the cervix may benefit from treatment to all sites of disease, if feasible and safe, as demonstrated by improved progression free survival.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Clinical presentation of patients with stage IVB cancer of the cervix is heterogenous and includes patients with sites of disease limited to an isolated inguinal or supradiaphragmatic lymph node to widespread hematogenous dissemination.

⇒ Treatment guidelines suggest the use of systemic chemotherapy and an individualized approach to use of radiation and surgery but provide little specification for which patients may benefit from comprehensive treatment.

⇒ This retrospective review was done to better identify patients with stage IVB disease who may benefit from definitive therapy.

WHAT THIS STUDY ADDS

⇒ This retrospective analysis suggests that for patients with lymphatic or oligometastatic disease, treatment of all disease sites with definitive chemoradiotherapy or surgery to the pelvis and selected use of radiotherapy or surgery for metastases improves progression free survival compared with patients treated with palliative chemotherapy alone.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study warrants further investigation to evaluate current staging systems.

⇒ Guidelines should be reviewed to better identify patients with stage IVB cervical cancer who may benefit from definitive rather than palliative therapy.

INTRODUCTION

The prognosis of patients with stage IVB cancer of the cervix varies depending on the extent and pattern of disease dissemination. Providing local control in the pelvis is an important palliative goal despite the risks of treatment toxicity because of significant morbidity from uncontrolled tumor. Some patients may derive a survival benefit from definitive treatment to the pelvis and metastatic sites.[1] Management guidelines from the National Comprehensive Cancer Network[2] and the European Society of Medical Oncology[3] recommend use of radiation therapy based on individualized considerations, such as pattern and extent of disease spread or performance status, without providing guidance for selecting patients for definitive therapy.[3 4]

Since criteria for offering definitive therapy are undefined, investigations to identify who may benefit from local treatment are warranted. We compared outcomes in patients treated with palliative intent using chemotherapy alone or with definitive intent using chemoradiotherapy to the pelvis and radiotherapy or surgery to metastatic sites. Study

To cite: Peleg Hasson S, Felder S, Helpman L, *et al. Int J Gynecol Cancer* 2023;**33**:683–691.

endpoints included treatment toxicity, progression free survival, overall survival and local control.

METHODS

Patient Population

A retrospective observational study was conducted using a cervical cancer database of patients treated consecutively at Sheba Cancer Center between January 2005 and May 2021. Eligible participants were aged ≥18 years and had biopsy confirmed stage IVB cervical cancer according to the International Federation of Gynecology and Obstetrics (FIGO) criteria (2018).[5] Exclusion criteria were small cell histology and follow-up <90 days. Table 1 shows the clinical and pathological variables collected from medical records. Programmed death ligand 1 was considered positive if the combined positive score was ≥1. The European Society of Therapeutic Radiation Oncology (ESTRO) and the American Society of Therapeutic Radiation Oncology (ASTRO) consensus definitions of oligometastatic disease (≤5 lesions) and polymetastatic disease (>5 lesions) were used.[6] Patients with both lymphatic and hematogenous spread were considered in the hematogenous group.

Treatments

Treatment parameters collected were use of systemic treatments, radiotherapy, and surgery. Treatment decisions were based on multidisciplinary tumor board review. Patients unfit for chemoradiotherapy were offered chemotherapy alone. Bevacizumab was added according to the Moore criteria.[7] Immunotherapy was offered starting in 2019. Radiotherapy and high dose rate brachytherapy were given according to EMBRACE II (Image Guided Intensity Modulated External Beam Radiochemotherapy and MRI Based Adaptive BRAchytherapy in Locally Advanced CErvical Cancer) contouring recommendations[8] and ESTRO guidelines.[9] Metastatic sites were treated concurrently with pelvic radiotherapy by modifying or adding additional radiotherapy fields. Radiotherapy doses were converted to biological equivalent dose using an alpha/beta ratio of 10.[10] In selected cases, the primary tumor or metastatic lesions were resected.

Follow-Up and Clinical Outcome

Follow-up examinations and imaging studies with computed tomography (CT) or fluorodeoxyglucose positron emission tomography were done at 3–6 month intervals during the initial 2 years post-treatment or as indicated. First recurrence was recorded as local, regional, or distant. Toxicity was assessed according to Common Terminology Criteria for Adverse Events V.5.[11]

Statistical Analysis

Patients were divided into two groups for comparison of outcomes: chemotherapy group that received palliative chemotherapy alone and chemoradiotherapy group that received definitive treatment to all disease sites. Descriptive statistics, including proportions, means, medians, and standard deviations, were used to assess patient and treatment parameters. Duration of progression free survival and overall survival were calculated from date of diagnosis until progression, death, or were censured at the last evaluation. Time to event data were analyzed using the Kaplan–Meier method. The log rank test was used to compare outcomes between treatment groups. A significance threshold for p values was set at 0.05. Cox univariate and multivariate analyses were used to predict the hazard ratio (HR) for patient, disease, and treatment variables associated with progression free survival and overall survival. Multivariate analysis models included variables with a p value <0.2 in the univariate analysis. Variables correlating ($p \leq 0.05$) with progression free survival or overall survival were excluded from the multivariate analysis. Computed values reported include 1 year, 2 year, and median progression free survival and overall survival, HRs, 95% confidence intervals (CI) and p values. All analyses were performed using IBM SPSS 25.0 software (SPSS, Chicago, Illinois, USA).

RESULTS

Patient Population

Review of the cervical cancer database (n=546) identified 35 patients with stage IVB disease (online supplemental Figure 2). Patients were excluded due to small cell histology (n=1) and follow-up <90 days (n=1). Patient characteristics are shown in Table 1. Performance status in most patients was 0 when beginning treatment (70%). Comorbidities were present in almost half of patients (48%). Post-coital or post-menopausal bleeding (73%) was the most common symptom at diagnosis. Most patients had oligometastatic disease (n=25). The number of lesions per patient were: one (n=8), two (n=8), three (n=7), four (n=1), five (n=1), and >5 (n=8). Oligometastatic disease was more common in the chemoradiotherapy group (n=22/23) than in the chemotherapy group (n=3/10, p<0.001). Sites of lymph node metastases (n=14) were inguinal (n=5) or supradiaphragmatic (n=9), which included supraclavicular (n=3), axillary (n=3), and mediastinal (n=3) locations. Sites of hematogenic metastases (n=19) included bone (n=5), ovary (n=3), visceral organs (n=6), brain (n=4), and peritoneum (n=7).

Treatments

Patients available for analysis (n=33) were treated with either chemotherapy (n=10, 30%) or chemoradiotherapy (n=23, 70%).

Chemotherapy

Chemotherapy regimens used are summarized in online supplemental Table 1. All patients received singlet or doublet platinum based chemotherapy. Some patients in the chemoradiotherapy group received neoadjuvant chemotherapy (n=6) for three cycles (range 2–6) with or without bevacizumab (n=3) or adjuvant chemotherapy (n=5) for two cycles. One of eight patients with polymetastatic disease had a good response to chemotherapy and then received chemoradiotherapy. One patient received pembrolizumab in a first line setting and 14 patients (chemotherapy=7, chemoradiotherapy=7) received immunotherapy in second and advanced line settings.

Radiation Therapy

All patients were treated with definitive intent. Median time from diagnosis to starting radiotherapy was 1 month (range 1–4.25 months). The pelvis (n=27) and, when involved, the para-aortic lymph nodes (n=13) were treated with 45 Gy (biological equivalent dose=53.1 Gy). Enlarged or metabolically active pelvic lymph

Table 1 Baseline characteristics

	Stage IVB (total, n=33)	CT only (n=10)	CRT (n=23)	P value
Age (years) (median (range)	53 (28–78)	46 (34–76)	57 (28–78)	0.4
Performance status (n (%))				
ECOG 0	23 (70)	7 (70)	16 (70)	>0.9
ECOG 1	10 (30)	3 (30)	7 (30)	
Symptoms at diagnosis (n (%))				
PCB/PMB	24 (73)	4 (40)	20 (87)	0.01
Other	9 (27)	6 (60)	3 (13)	
Histology (n (%))				
Adenocarcinoma	8 (24)	3 (30)	5 (22)	0.7
Squamous cell carcinoma	22 (67)	7 (70)	15 (65)	
Other	3 (9.1)	0 (0)	3 (13)	
Grade (n (%))				
Well differentiated	4 (12)	0 (0)	4 (17)	0.2
Moderately differentiated	7 (21)	1 (10)	6 (26)	
Poorly differentiated	22 (67)	9 (90)	13 (57)	
PD-L1 CPS status (n (%))				
≥1%	7 (21)	2 (20)	5 (22)	0.001
<1%	7 (21)	6 (60)	1 (4)	
Unknown	19 (58)	2 (20)	17 (74)	
Para-aortic lymph nodes (n (%))				
No	12 (36)	2 (20)	10 (43)	0.3
Yes	21 (64)	8 (80)	13 (57)	
Pelvic lymph nodes (n (%))				
No	3 (9)	0 (0)	3 (13)	0.5
Yes	30 (91)	10 (100)	20 (87)	
Pattern of metastasis (n (%))				
Hematogenous spread	19 (58)	6 (60)	13 (57)	>0.9
Lymphatic spread	14 (42)	4 (40)	10 (43)	
Oligometastatic vs polymetastatic (n (%))				
Oligometastatic disease	25 (76)	3 (30)	22 (96)	<0.001
Polymetastatic disease	8 (24)	7 (70)	1 (4)	
Systemic treatment with CRT (n (%))				
Adjuvant	5 (15)	NA	5 (22)	0.028
Neoadjuvant	6 (18)	NA	6 (26)	
No	22 (67)	NA	12 (52)	
Brachytherapy (n (%))				
Yes	20 (61)	NA	20 (87)	<0.001
No	13 (39)	NA	3 (13)	
Duration of RT treatment (median (range)) (days)	59 (18–93)	NA	59 (18–93)	
Time to completion of RT (n (%))				
<8 weeks	9 (39)	NA	9 (39)	>0.9
≥8 weeks	14 (61)	NA	14 (61)	
Recurrence (n (%))				
Yes	27 (82)	10 (100)	17 (74)	0.14

Continued

Table 1 Continued

	Stage IVB (total, n=33)	CT only (n=10)	CRT (n=23)	P value
No	6 (18)	0 (0)	6 (26)	
Pattern of failure (n (%))				
No recurrence	6 (18)	0 (0)	6 (26)	0.3
Distant recurrence	20 (61)	10 (100)	10 (43)	
Regional recurrence	3 (9)	NA	3 (13)	
In-field recurrence	4 (12)	NA	4 (18)	
Best response after CRT (n (%))				
CR	14 (43)	2 (20)	12 (52)	0.03
PR	9 (27)	6 (60)	3 (13)	
PD	10 (30)	2 (20)	8 (35)	
Death (n (%))				
Death related to cervical cancer	19 (58)	8 (80)	11 (48)	0.13

CPS, combined pathology score; CR, complete response; CRT, chemoradiation; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; NA, not applicable; PCB, post-coital bleeding; PD, progressive disease; PD-L1, programmed death ligand 1; PMB, post-menopausal bleeding; PR, partial response; RT, radiation therapy.

nodes (n=20) and para-aortic lymph nodes (n=13) were boosted to 55 Gy (biological equivalent dose=67.1 Gy) using a simultaneous integrated boost. The parametrium was given a supplementary dose to bring the pelvic sidewall dose to 50.4–54 Gy (biological equivalent dose=61.5–66 Gy). High dose rate brachytherapy was given twice weekly. Dose to the high risk clinical tumor volume was 27.5 Gy (biological equivalent dose=42.6 Gy). The median number of brachytherapy fractions was 5 (range 3–5). Brachytherapy was deferred (n=3) in patients who underwent surgery following neoadjuvant chemotherapy.

Surgery

Six patients underwent radical hysterectomy (n=4) or pelvic exenteration (n=2) before chemoradiotherapy (n=3) or after chemoradiotherapy (n=3).

Treatment of Metastatic Sites

Lymph nodes

Most patients with lymph node metastases (n=14) were treated with definitive (n=10) rather than palliative intent (n=4). Inguinal lymph nodes (n=5) were treated with chemoradiotherapy to 55 Gy (biological equivalent dose=67.1 Gy) with two patients (40%) remaining disease free at 37 and 57 months post-treatment. Supraclavicular lymph nodes (n=3) were treated with chemoradiotherapy (n=2) to 45 Gy (biological equivalent dose=58.5 Gy) and 54 Gy (biological equivalent dose=63.7 Gy), respectively, or with lymphadenectomy (n=1). Both patients treated with radiotherapy recurred (20 months and 42 months). The patient who underwent lymphadenectomy remains disease free 17 years post-treatment.

Mediastinal lymph nodes (n=3) were treated with chemoradiotherapy (n=1, 60 Gy, biological equivalent dose=72 Gy) or chemotherapy (n=2). Although progression free survival was longer (21 months vs 7.5 months) in the patient treated with chemoradiotherapy, overall survival was shorter (24 months vs 30 months) because this patient died soon after recurrence, while the other two patients received immunotherapy within a clinical trial. Axillary lymph nodes (n=3) were treated surgically with axillary lymph node dissection (n=1) or chemotherapy only (n=2). The patient who underwent axillary lymph node dissection remains disease free 6 years post-treatment.

Hematogenous Metastases

Patients with hematogenous metastases (n=19) were treated using palliative chemotherapy (n=6) or with chemoradiotherapy to the pelvis (n=13) plus stereotactic body radiation therapy (n=5), hypofractionated radiotherapy (n=5), or surgical resection (n=3) to the metastases. Single site oligometastatic disease (n=6) was treated with oophorectomy (n=2), pulmonary segmentectomy (n=1), or radiotherapy to the peritoneum (57.5 Gy, biological equivalent dose=70.7 Gy), the abdominal wall (52.5 Gy, biological equivalent dose=63.5 Gy), or a pelvic bone (stereotactic body radiation therapy, 30 Gy, biological equivalent dose=48 Gy). Two patients remain disease free >3 years post-treatment.

Response to Therapy

Following chemotherapy, responses were: complete response (n=2, 20%), partial response (n=6, 60%), or progressive disease (n=2, 20%). Following chemoradiotherapy, responses were: complete response (n=12, 52%), partial response (n=3, 13%), or progressive disease (n=8, 35%).

Survival

Median duration of follow-up was 45 months (range 32–not reached). Following treatment, six patients remain alive and disease free for a median duration of 4 years (range 3–17). Four patients had lymph node metastases (inguinal n=2, supraclavicular n=1, and axillary n=1) and two had hematogenous metastases (peritoneum and abdominal wall). All patients in the palliative chemotherapy group recurred. Deaths were more common in the chemoradiotherapy group (8/10) than in the chemoradiotherapy group (11/23). Recurrences following chemoradiotherapy were distant (n=13) or within the radiation field (n=4). Univariate analysis showed that the

Table 2 Univariate and multivariate analysis for progression free survival and overall survival

			Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
			Progression free survival				Overall survival			
Parameter	CRT/CT only	n=33	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Performance status	ECOG 0	23	NR				NR			
	ECOG 1	10	1.23 (0.55 to 2.77)	0.61			1.03 (0.38 to 2.76)			
Systemic CT+CRT	No	22	NR				NR			
	Adjuvant CT	5	0.91 (0.29 to 2.81)	0.867			0.88 (0.25 to 3.09)	0.845		
	Neoadjuvant CT	6	0.66 (0.24 to 1.80)	0.413			0.53 (0.12 to 2.35)	0.406		
Symptoms at diagnosis	Other	9	NR				NR			
	PCB/PMB	24	0.48 (0.21 to 1.11)	0.085			0.47 (0.18 to 1.23)	0.126		
Histology	Adenocarcinoma	8	NR				NR			
	Squamous cell carcinoma	22	1.07 (0.42 to 2.73)	0.883			1.60 (0.46 to 5.60)	0.458		
	Other	3	2.08 (0.51 to 8.41)	0.306			1.44 (0.24 to 8.74)	0.695		
Grade	Moderately differentiated	7	NR				NR			
	Well differentiated	4	0.97 (022 to 4.32)	0.963			0.83 (0.08 to 8.16)	0.872		
	Poorly differentiated	22	2.0 (0.67 to 5.89)	0.212			1.84 (0.53 to 6.46)	0.338		
PD-L1 CPS status	Unknown	19	NR				NR			
	<1%	7	5.20 (1.85 to 14.60)	0.00176			0.74 (0.20 to 2.64)	0.638		
	≥1%	7	2.57 (0.98 to 6.76)	0.05588			0.43 (0.15 to 1.26)	0.124		
Para-aortic lymph nodes	No	12	NR				NR			
	Yes	21	1.29 (0.58 to 2.89)	0.529			2.61 (0.92 to 7.38)	0.071		
Pelvic lymph nodes	No	3	NR				NR			
	Yes	30	1.05 (0.30 to 3.60)	0.944			2.88 (0.38 to 21.7)	0.304		
Pattern of metastasis	Hematogenous spread	19	NR				NR			
	Lymphatic spread	14	0.45 (0.20 to 0.99)	0.049	0.43 (0.19 to 1.0)	0.0502	0.82 (0.33 to 2.06)	0.673	0.65 (0.21 to 1.97)	0.4437
Oligometastatic vs polymetastatic	Oligometastatic disease	25	NR				NR			
	Polymetastatic disease	8	2.22 (0.95 to 5.18)	0.065	1.12 (0.33 to 3.74)	0.8598	1.09 (0.39 to 3.08)	0.867	0.32 (0.06 to 1.74)	0.1903
Brachytherapy	Yes	20	NR				NR			
	No	13	0.40 (0.75 to 3.57)	0.219			1.0 (0.39 to 2.56)	0.995		
RT to all sites	No	10	NR				NR			
	Yes	23	0.38 (0.17 to 0.86)	0.019	0.38 (0.12 to 1.17)	0.0917	0.51 (0.20 to 1.31)	0.162	0.25 (0.06 to 1.03)	0.0544

Continued

Table 2 Continued

Parameter	CRT/CT only	n=33	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
			Progression free survival				Overall survival			
			HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Time to completion of RT	≤8 weeks	9	NR				NR			
	>8 weeks	14	0.81 (0.29 to 2.24)	0.684			0.90 (0.24 to 3.31)	0.868		
Best response after CRT	CR	14	NR				NR			
	PR	9	6.67 (2.23 to 19.9)	0.0006			4.76 (1.12 to 20.2)	0.034		
	PD	10	4.60 (1.64 to 12.9)	0.003			14.1 (3.52 to 59.9)	0.0001		

CPS, combined pathology score; CR, complete response; CRT, chemoradiation; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; NR, not reached; PCB, post-coital bleeding; PD, progressive disease; PD-L1, programmed death ligand 1; PMB, post-menopausal bleeding; PR, partial response; RT, radiation therapy.

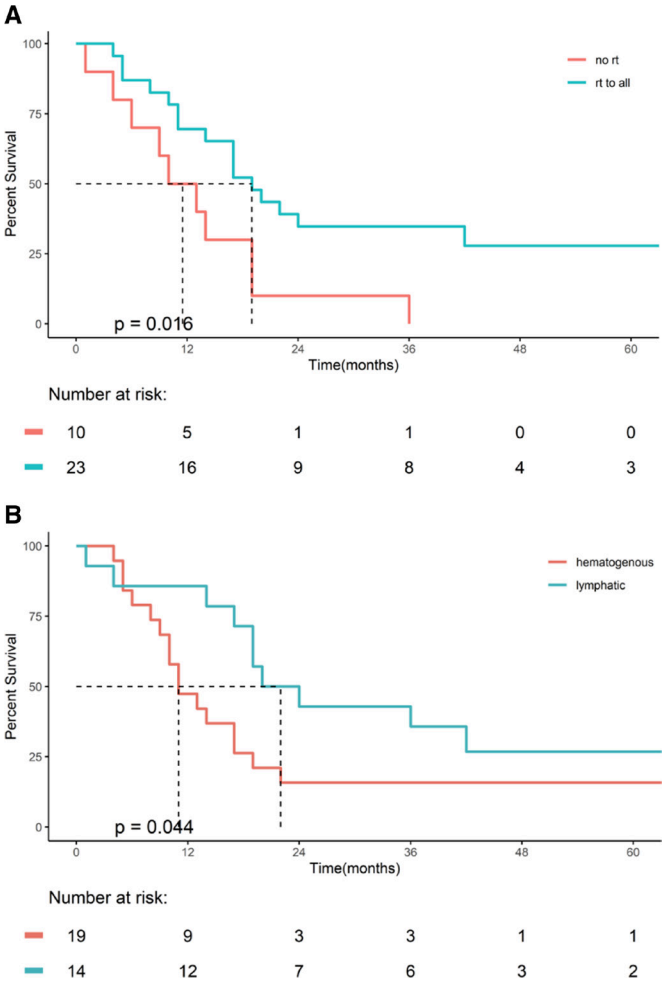

Figure 1 (A) Progression free survival according to definitive chemoradiotherapy (RT) vs chemotherapy alone. (B) Progression free survival according to lymphatic versus hematogenous spread.

use of neoadjuvant (n=6) or adjuvant chemotherapy (n=5) had no effect on duration of progression free survival or overall survival (Table 2).

Table 2 shows that progression free survival on univariate analysis was associated with programmed death ligand 1 status <1% (p=0.0018), pattern of metastasis (p=0.049), treatment to all sites (p=0.019), and tumor response (partial response, p=0.0006 and complete response, p=0.003). Overall survival on univariate analysis was associated with tumor response (partial response, p=0.034 and complete response, p=0.0001). Kaplan–Meier estimates of median progression free survival and overall survival for the cohort (n=33) were 17 months (95% CI 11 to 24) and 45 months (95% CI 32 to not reached), respectively. Figure 1A shows that median progression free survival was longer for patients treated with chemoradiotherapy than chemotherapy (19 months, 95% CI 14 to not reached vs 11.5 months, 95% CI 6 to not reached, p=0.016). Figure 1B shows that median progression free survival was longer in patients with lymphatic versus hematogenous spread (22 months, 95% CI 19 to not reached vs 11 months, 95% CI 10 to 22, p=0.044). Figure 2A shows that there was no difference in median overall survival in patients treated with chemoradiotherapy or chemotherapy (49 months, 95% CI 40 to not reached,

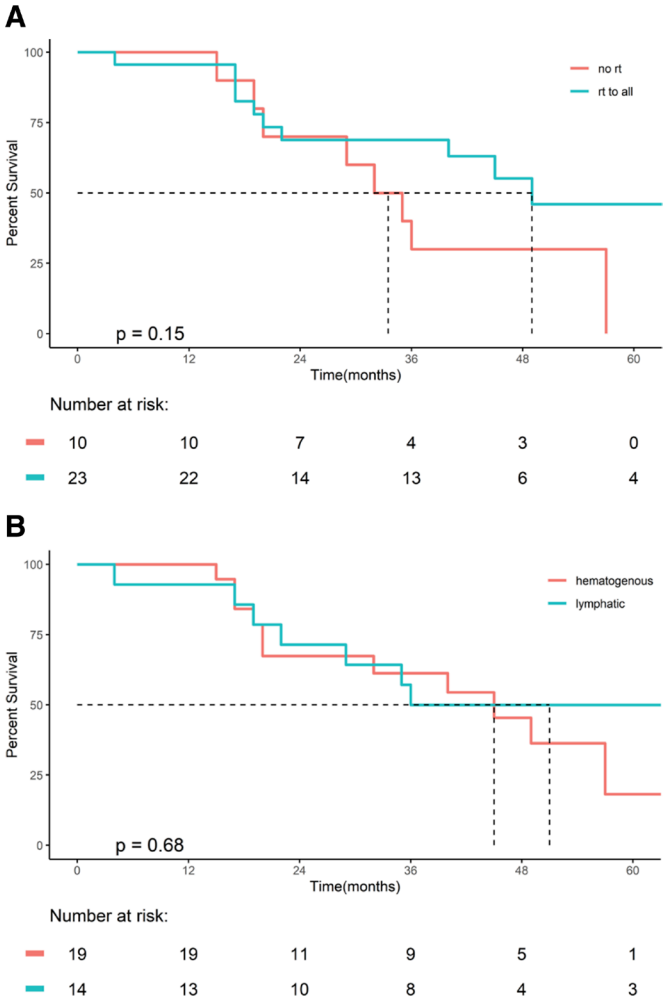

Figure 2 (A) Overall survival according to definitive chemoradiotherapy (RT) vs chemotherapy alone. (B) Overall survival according to lymphatic versus hematogenous spread.

vs 33 months, 95% CI 20 to not reached, p=0.15). Figure 2B shows that the difference in median overall survival for lymphatic versus hematogenous spread was not significant (51 months, 95% CI 29 to not reached vs 45 months, 95% CI 20 to not reached, p=0.68).

Toxicities

Table 3 lists the toxicities associated with chemoradiotherapy and chemotherapy. Two patients developed fistulae (vesicovaginal and vesicorectovaginal) treated with bilateral nephrostomies (n=2) and diverting colostomy (n=1). The fistulae in both patients were attributed to progression of pelvic disease rather than chemoradiotherapy, although chemoradiotherapy could not be excluded as a cause. Other grade 3 late toxicities were fatigue and pelvic pain (n=3) and gastrointestinal (n=3), genitourinary (n=1), or gynecological symptoms (n=1).

Table 3 Toxicities associated with chemoradiotherapy and chemotherapy

Toxicities (CTCAE grade)	Adverse events (CRT) (n=23) Events (n (%))
No of patients reporting adverse events	10 (43)
Total adverse events reported	19 (83)
Pelvic pain	5 (22)
Fatigue	5 (22)
Gastrointestinal symptoms	3 (13)
Genitourinary symptoms	1 (4)
Vaginal stenosis	3 (13)
Fistula	2 (9)

CRT, Chemoradiation; CTCAE, Common Terminology Criteria for Adverse Events.

DISCUSSION

Summary of Main Results

This retrospective analysis suggests that some patients treated with definitive intent using chemoradiotherapy or surgery to the pelvis and selected use of radiotherapy and surgery for metastatic lesions may remain disease free for extended periods and even achieve long term survival compared with patients treated with palliative chemotherapy alone. In this series, long term survivors were treated with definitive intent and had either lymphatic only metastases or hematogenous spread with an oligometastatic lesion involving a single site.

Results in the Context of Published Literature

Our findings are consistent with other studies comparing outcomes for patients with stage IVB disease treated with chemoradiotherapy with chemotherapy alone (online supplemental Table 2). Kim et al and Perkins et al showed that the use of chemoradiotherapy versus chemotherapy alone was associated with longer progression free survival (40.5 vs 7.8 months, p<0.01) and overall survival (63.7 vs 18.4 months, p<0.01),[12] and progression free survival (13 vs 5.9 months, p=0.0006) and overall survival (41.6 vs 17.6 months, p=0.0005),[13] respectively. Two sequential reports using the National Cancer Database showed that treatment with chemoradiotherapy or surgery was associated with longer median overall survival than treatment with chemotherapy only (19.2 vs 10.1 months, p<0.001,[14] and 14.4 vs 10.6 months, p<0.001,[15] respectively). Several other single institution studies as well as two recent SEER (Surveillance, Epidemiology, and End Results) database studies also showed a survival benefit with the addition of pelvic radiotherapy to chemotherapy.[13 16–18]

Our results are consistent with reports showing that patients with lymphatic metastases alone have better outcomes than patients with hematogenous dissemination.[19–21] Inguinal lymph node involvement was treated with curative intent to 55 Gy (biological equivalent dose=67.1 Gy), with 2/5 patients (40%) remaining disease free for 37 and 56 months, consistent with other reports describing long term survival.[19 22 23] In contrast, only 2/9 patients (22%) with supradiaphragmatic lymph nodes achieved long term survival. While these results are consistent with the 5 year overall survival rate of 16.5% for patients with supraclavicular lymph node metastasis reported by Qiu et al,[24] other investigators reported better outcomes with higher radiotherapy doses. Kim et al reported a median overall survival of 32 months[25] in patients receiving a

mean dose of 59.4 Gy to the para-aortic lymph nodes and supraclavicular lymph nodes compared with 7.5 months when 50% of patients received chemotherapy alone.[26] Lee et al reported 5 year overall survival and progression free survival of 55.6% and 44.4%, respectively, in patients who received a median radiotherapy dose of 66.6 Gy (range 60–75.6)[27] to supraclavicular lymph nodes. The unfavorable outcomes for patients with supradiaphragmatic lymphatic involvement in our cohort may be due to a less aggressive treatment approach using palliative chemotherapy alone or low radiotherapy doses. We adjusted treatment protocols to deliver >60 Gy to supradiaphragmatic lymph node metastasis.

Although the prognosis for patients with hematogenous metastasis is poor, with a 5.3-fold higher risk of death than lymphatic metastasis,[28] when disease involves only a single site, we found that long term survival may be possible. Our results are consistent with other series showing long term disease free survival in patients with oligometastatic disease treated at metastatic sites using stereotactic body radiation therapy or surgery.[29 30] An international effort (ESTRO-ASTRO consensus) is in progress to better define oligometastatic disease that may benefit from an intensified treatment approach.[6]

The late effects of chemoradiotherapy include incidence of rectovaginal or vesicovaginal fistulae in 1–2% as well as gastrointestinal, urological, female genital, skeletal, and vascular toxicities, secondary malignancies, and quality of life issues[31] In our study, a higher fistula formation rate was found (2/33, 6%), probably due to the small sample size and advanced pelvic disease at diagnosis. The addition of bevacizumab to pelvic radiotherapy in patients with cervical cancer has been associated with an increased risk of fistula formation.[32] In our study, fistula formation was not associated with bevacizumab treatment.

Strengths and Weaknesses

We collected and reviewed comprehensive clinical and pathological information, detailed treatment plans, and long term outcomes in patients treated with modern radiotherapy techniques. In comparison, large database studies, such as SEER or the National Cancer database, often provide insufficient information for analysis of treatment details that may influence outcomes. For example, detailed review of dosimetric data enabled us to identify a subgroup of patients (lymphatic spread to the thorax) that had a higher than expected rate of failure, possibly due to omission of radiotherapy or treatment with a sub-therapeutic radiotherapy dose.

The small cohort size limits the statistical power of the results. For example, conclusions on how treatment with bevacizumab or immunotherapy affected progression free survival or overall survival could not be reached due to the small numbers. Selection biases, inherent to retrospective studies, may result in patients with good performance status or favorable prognostic variables receiving more aggressive treatments. This was apparent in our study where patients with more advanced and perhaps more biologically aggressive disease were predominantly in the chemotherapy group rather than in the chemoradiotherapy group. In consideration of the multiple analyses performed in this limited cohort, caution must be undertaken when interpreting results specifically considering selection bias for patients with favorable clinical parameters who received chemoradiotherapy rather than chemotherapy. Information bias from incomplete record entries may have led to underestimation of treatment toxicities.

Implications for Practice and Future Research

Patients with stage IVB cervical cancer treated with chemoradiotherapy and selected use of surgery had longer progression free survival and trended towards longer overall survival compared with patients treated with chemotherapy alone.

CONCLUSIONS

Patients with stage IVB cancer of the cervix who receive treatment to all sites of disease may have improved progression free survival compared with patients treated with palliative chemotherapy alone. Patients presenting with lymph node metastasis or oligometastatic disease and treated with definitive intent may have an opportunity for long term survival with a limited risk of toxicity.

Author affiliations
[1]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[2]Oncology Division, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[3]Sheba Cancer Center and Institute of Oncology, Tel-Hashomer, Israel
[4]Gynecologic Oncology, Sheba Medical Center, Tel-Hashomer, Israel
[5]Department of Clinical Oncology, The Royal Marsden, London, UK
[6]Department of Radiation Oncology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Correction notice This article has been corrected since it was first published to correct author name Mihal Shalamov.

Contributors SPH analyzed the data and drafted and revised the paper. JG monitored the data collection for the whole trial, analyzed the data, and drafted and revised the paper. AS designed the data collection tools, monitored data collection for the whole trial, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. AS accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. All other authors revised the draft paper.

Funding SPH received financial support from the Parasol Foundation.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The institutional ethics committee approved the study (identifier SMC-5899–19).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Shira Peleg Hasson http://orcid.org/0000-0002-3707-1107
Alexandra Taylor http://orcid.org/0000-0001-8100-5388

Jacob Korach http://orcid.org/0000-0003-0483-4582
Akram Saad http://orcid.org/0000-0002-3803-4754

REFERENCES

1 Usami T, Takahashi A, Matoda M, *et al*. Review of treatment and prognosis of stage ivb cervical carcinoma. *Int J Gynecol Cancer* 2016;26:1239–45.
2 NCCN. Guidelines detail. Available: www.nccn.org/guidelines/guidelines-detail [Accessed 12 May 2022].
3 Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up† - annals of oncology. Available: www.annalsofoncology.org/article/S0923-7534(19)42148-0/fulltext [Accessed 12 May 2022].
4 Abu-Rustum NR, Yashar CM, Bean S, *et al*. NCCN guidelines insights: cervical cancer, version 1.2020. *J Natl Compr Canc Netw* 2020;18:660–6.
5 Bhatla N, Aoki D, Sharma DN, *et al*. Cancer of the cervix uteri. *Int J Gynaecol Obstet* 2018;143 Suppl 2:22–36.
6 Lievens Y, Guckenberger M, Gomez D, *et al*. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. *Radiother Oncol* 2020;148:157–66.
7 Tewari KS, Sill MW, Monk BJ, *et al*. Prospective validation of pooled prognostic factors in women with advanced cervical cancer treated with chemotherapy with/without bevacizumab: NRG oncology/GOG study. *Clin Cancer Res* 2015;21:5480–7.
8 Pötter R, Tanderup K, Kirisits C, *et al*. The embrace II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the embrace studies. *Clin Transl Radiat Oncol* 2018;9:48–60.
9 Haie-Meder C, Pötter R, Van Limbergen E, *et al*. Recommendations from gynaecological (GYN) GEC-ESTRO working group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol* 2005;74:235–45.
10 Fowler JF. 21 years of biologically effective dose. *Br J Radiol* 2010;83:554–68.
11 Common terminology criteria for adverse events (CTCAE). 2017. Available: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm
12 Kim HS, Kim T, Lee ES, *et al*. Impact of chemoradiation on prognosis in stage ivb cervical cancer with distant lymphatic metastasis. *Cancer Res Treat* 2013;45:193–201.
13 Perkins V, Moore K, Vesely S, *et al*. Incorporation of whole pelvic radiation into treatment of stage ivb cervical cancer: a novel treatment strategy. *Gynecol Oncol* 2020;156:100–6.
14 Venigalla S, Guttmann DM, Horne ZD, *et al*. Definitive local therapy is associated with improved overall survival in metastatic cervical cancer. *Pract Radiat Oncol* 2018;8:e377–85.
15 Wang Y, Farmer M, Izaguirre EW, *et al*. Association of definitive pelvic radiation therapy with survival among patients with newly diagnosed metastatic cervical cancer. *JAMA Oncol* 2018;4:1288–91.
16 Xu J-Y, Chen J-N, Lei J, *et al*. Local treatment improves survival in patients with stage ivb cervical cancer. *Gynecol Oncol* 2022;165:538–45.
17 Ding L, Bi Z, Pan Z, *et al*. Brachytherapy-based radiotherapy is associated with improved survival for newly diagnosed metastatic cervical cancer. *Brachytherapy* 2021;20:361–7.
18 Wiley RL, Bondre IL, Jalloul R, *et al*. Definitive vs palliative pelvic radiation for patients with newly diagnosed stage IVB cervical cancer treated with bevacizumab - an exploratory study. *Gynecol Oncol Rep* 2022;40:100963.
19 Oishi S, Kudaka W, Toita T, *et al*. Prognostic factors and treatment outcome for patients with stage IVB cervical cancer. *Anticancer Res* 2016;36:3471–5.
20 Sasano T, Mabuchi S, Kuroda H, *et al*. Predictors of survival in patients with FIGO stage ivb cervical cancer. *Int J Gynecol Cancer* 2016;26:528–33.
21 Im JH, Yoon HI, Kim S, *et al*. Tailored radiotherapeutic strategies for disseminated uterine cervical cancer patients. *Radiat Oncol* 2015;10:77:77.:.
22 Mukai Y, Yokota NR, Sugiura M, *et al*. Outcome of radiation therapy for stage ivb uterine cervical cancer with distant lymph nodes metastases; sequential irradiation for distant lymph nodes metastases. *In Vivo* 2021;35:1169–76.
23 Chino J, Annunziata CM, Beriwal S, *et al*. Radiation therapy for cervical cancer: executive summary of an ASTRO clinical practice guideline. *Pract Radiat Oncol* 2020;10:220–34.
24 Qiu JT, Ho KC, Lai CH, *et al*. Supraclavicular lymph node metastases in cervical cancer. *Eur J Gynaecol Oncol* 2007;28:33–8.
25 Kim J-Y, Kim J-Y, Kim JH, *et al*. Curative chemoradiotherapy in patients with stage ivb cervical cancer presenting with paraortic and left supraclavicular lymph node metastases. *Int J Radiat Oncol Biol Phys* 2012;84:741–7.
26 Tran BN, Grigsby PW, Dehdashti F, *et al*. Occult supraclavicular lymph node metastasis identified by FDG-PET in patients with carcinoma of the uterine cervix. *Gynecol Oncol* 2003;90:572–6.
27 Lee SH, Lee SH, Lee KC, *et al*. Radiation therapy with chemotherapy for patients with cervical cancer and supraclavicular lymph node involvement. *J Gynecol Oncol* 2012;23:159–67.
28 Kim K, Cho SY, Kim B-J, *et al*. The type of metastasis is a prognostic factor in disseminated cervical cancer. *J Gynecol Oncol* 2010;21:186–90.
29 Mangaj A, Chopra S, Nout RA. Defining the role of high-dose radiation in oligometastatic & oligorecurrent cervical cancer. *Indian J Med Res* 2021;154:303–18.
30 Ning MS, Ahobila V, Jhingran A, *et al*. Outcomes and patterns of relapse after definitive radiation therapy for oligometastatic cervical cancer. *Gynecol Oncol* 2018;148:132–8.
31 Maduro JH, Pras E, Willemse PHB, *et al*. Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. *Cancer Treat Rev* 2003;29:471–88.
32 Kim N, Choi SH, Chang JS, *et al*. Use of bevacizumab before or after radiotherapy increases the risk of fistula formation in patients with cervical cancer. *Int J Gynecol Cancer* 2021;31:59–65.