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Review Article

External Beam Radiation Therapy Alone in the Treatment of Cervical Cancer: A Single-Institution Study on Efficacy and Safety

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Abstract

Purpose: The purpose of this study was to investigate the results regarding primary remission, recurrences, survival and toxicity when treating cervical cancer with external beam irradiation without addition of brachytherapy and to determine prognostic factors associated with these results.

Material and Methods: The study included 111 consecutive patients treated with External Beam Radiotherapy (EBRT) alone at our department between 1993 and 2010. Patients treated with primary hysterectomy or brachytherapy were excluded. Twenty-seven patients had either strictly palliative treatment regimens or discontinued treatment and received 60 Gy or less. Eighty-four patients completed the planned treatment to 64.8-72.0 Gy with a combination of pelvic irradiation and an external boost to the tumor. Concurrent chemotherapy was given to 38 patients (34.2%).

Results: The primary remission rate, 5-year Overall Survival (OS), and Cancer-Specific Survival (CSS) for the complete material was 62.2%, 19.5%, and 28.5%, respectively. For patients with non-metastatic cancer that received boost the primary remission rate, 5-year overall survival rate, and cancer-specific survival rate were 79.7%, 29.3% and 37.9%, respectively. The independent and significant prognostic factors for overall survival rate were: full treatment with boost, tumor histology, concurrent chemotherapy, and tumor stage. Severe early radiation reactions were reported in 12.6% of the patients and severe late reactions in 6.3%.

Conclusions: The prognosis for patients receiving EBRT alone is markedly poorer than for those who receive a combination of EBRT and brachytherapy, although, a direct comparison cannot be made because of confounding factors. Brachytherapy should be used when technically possible. Concurrent chemotherapy should always be considered.

Keywords: Boost radiotherapy; Cervix cancer; External beam radiotherapy; Prognosis

Purpose

In Sweden 549 women were diagnosed with cervical cancer in 2014, and the age-adjusted incidence was 11 per 100,000 women [1]. This is a reduction in incidence by more than one-half since the 1960s, when a general screening program was introduced [2]. However, over the last 20 years, the decrease in incidence has been very small and the relative survival has remained unchanged since the 1970s in Sweden as well as in the other Nordic countries [3]. However, during the last few years there was a new increase in incidence from 450 to 550 new cases per year. Globally, cervical cancer remains a major cause of morbidity and mortality and it causes 200,000 deaths yearly with a majority in low and middle-income countries [4]. The relative 5-year survival rate was 76.1% and the number of deaths was 135 per year in Sweden.

It is well established that the best treatment available for locally advanced cervical cancer is a combination of External Beam Radiotherapy (EBRT) and Intra-Cavitary Brachytherapy (ICBT) with addition of concurrent chemotherapy. Many studies have shown that the use of ICBT in patients primarily treated with radiotherapy is independently associated with increased local tumor control and better survival [5-7]. However, in clinical practice, some patients still receive EBRT with no addition of brachytherapy. Han et al. showed that 37% of women treated with

EBRT for locally advanced cervical cancer in the United States between 1988 and 2009 did not receive brachytherapy [5]. They also demonstrated a continuous decreasing trend in the utilization of brachytherapy since the 1980s and this was further confirmed in a large patterns of care study by Bagshaw, et al. [8].

Reasons for not giving brachytherapy included: palliative intent, inability to cover the tumor with a brachytherapy treatment volume, inability to apply the intrauterine tandem because of obliteration of the cervical canal, patient refusal, contraindication to spinal anesthesia and discontinuation of treatment before brachytherapy was given. It has been shown that older women are less likely to receive brachytherapy [5,9].

We wished to investigate the clinical outcome: primary remission, recurrences, survival and adverse events, when treating advanced cervical cancer with EBRT alone, regardless of reason for not using brachytherapy. Furthermore, we wanted to determine patient, tumor and treatment characteristics that were associated with treatment outcome.

Material and Methods

In this study we aimed to include all patients who received External Beam Radiation Therapy Alone (EBRTA) as primary treatment for carcinoma of the uterine cervix at the department of Gynecological Oncology, Örebro University Hospital, between the years 1993 and 2010. Patients who were primarily treated with hysterectomy as well as patients who received Intra-Cavitary Brachytherapy (ICBT) were excluded from this study. A total of 111 patients met the inclusion criteria for the study and their patient records were reviewed retrospectively by a single researcher (JK). Patients with tumors of all stages were included and aborted treatment or treatment with only palliative intent is not an exclusion criterion.

Tumor Staging and Evaluation

Staging was done according to the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) staging system. Patients underwent a clinical examination under anesthesia including inspection, bimanual palpation, cystoscopy and a biopsy of the tumor. All patients were evaluated for lung metastases with either a standard chest radiograph or a CT scan of the thorax. Seventy-five patients were primarily evaluated with either MRT of the pelvis or a CT scan of the abdomen or both. In the retrospective review of the patient records, we considered lymph nodes larger than 1 cm to be possibly malignant. The tumors were measured with CT, MRT or ultrasound when possible and otherwise the tumor size was estimated at the clinical examination.

Blood Evaluation and Toxicity Scoring

Standard laboratory work including a blood count was done weekly during radiotherapy. We recorded nadir levels for thrombocytes and leukocytes. Toxicity was registered according to the RTOG/EORTC [10] radiation morbidity scoring criteria. We focused on lower intestinal, urinary, leukocyte and thrombocyte toxicity.

Patient and Tumor Characteristics

Table 1 shows the characteristics of the patients and their tumors. The age at diagnosis ranged between 27 and 91 years with a mean of 66.3 years. The tumors were generally large with a mean maximum diameter of 6.7 cm. In 80.2% of the patients, the cancer was in stage III-IV.

		Number of patients	%
Age at diagnosis	≤ 50 years	22	19.8
	51-70 years	33	29.7
	> 70 years	56	50.5
FIGO Stage	IB	4	3.6
	IIA	4	3.6
	IIB	14	12.6
	IIIA	11	9.9
	IIIB	30	27
	IVA	31	27.9
	IVB	17	15.3
Histology	Squamous cell carcinoma	90	81.1
	Adenocarcinoma	15	13.5
	Adenosquamous	2	1.8
	Other	4	3.6
Smoking	At diagnosis	37	33.3
	Previous	16	14.4
	Minimal	2	1.8
	Non-smoker	41	36.9
	Unknown	15	13.5
Pathological regional	Yes	31	27.9
lymph nodes	No	80	72.1
Pathological para aortic	Yes	17	15.3
lymph nodes	No	94	84.7

Table 1: Patient and tumor characteristics.

Radiotherapy Technique

Table 2 shows characteristics of the treatment given. For all patients CT was used for treatment planning. Radiotherapy was given with one fraction daily, five days a week, with a linear accelerator at energies of 10-18 MV.

		Number of patients	%
Boost treatment > 60 Gy	Yes	84	75.7
	No	27	24.3
Treatment time >50 days*	Yes	29	26.1
	No	55	49.5
Concurrent chemotherapy	Complete	18	16.2
	Incomplete	20	18
	None	73	65.8
*of those who received boost			

Table 2: Treatment characteristics.

For patients where the intent of treatment was curative or, in case of stage IVB cancer, to achieve complete local remission, standard external pelvic irradiation, covering pelvic lymph nodes, was given. In addition to this treatment, an external boost to the gross tumor volume was given as a substitute for ICBT. The irradiation boost was always given after the whole pelvic irradiation.

Eighty-four patients received full treatment with pelvic irradiation and boost to a final dose of at least 64.8 Gy. For this group, the tumor doses for the complete treatment ranged between 64.8 and 72.0 Gy, with a mean of 68.0 Gy. The whole pelvic doses ranged between 46.0 and 62.0 Gy with a mean of 58.0 Gy. The boost doses ranged between 6.0 and 22.0 Gy with a mean of 9.9 Gy. In a majority of cases, a four-field box technique was used for the pelvic irradiation (n = 72) as well as for the boost (n = 69). In the remaining cases, the number of radiation fields was either three, two and in one case, six. The most common treatment was 60.0 Gy pelvic irradiation plus 8.0 Gy boost given as 2.0 Gy fractions (n = 70) and the second most common one was 46.8 Gy pelvic irradiation plus 21.6 Gy boost given as 1.8 Gy fractions (n = 10). For the pelvic irradiation, the mean height and width of the anterior-posterior fields were 22.3 cm and 17.3 cm, respectively, and for the lateral fields 22.4 cm and 13.9 cm, respectively. For the boost fields the corresponding measures were 11.4 cm, 12.8 cm and 11.4 cm, 9.6 cm, respectively. The length of the treatment time varied between 44 and 77 days with a mean of 50.1 days.

For the 84 patients that was given full treatment with boost the reason to not give brachytherapy was in the majority of cases that it was not considered technically possible (n = 76), mainly because the tumor was too bulky or irregularly shaped and, in some cases, because of inability to insert the intrauterine tandem in the cervical canal. In six cases, the reason for not giving brachytherapy was comorbidity and in two cases, it was unknown.

Twenty-seven patients received 60.0 Gy or less and no addition of boost, either because the treatment was discontinued (n = 21) or because the treatment plan was strictly palliative (n = 6). In this group, the final radiation dose ranged between 2.0 and 60.0 Gy with a mean dose of 33.0 Gy. The main reasons to interrupt radiotherapy were comorbidity or bad performance status (n = 11), toxicity (n = 5), progression during treatment (n = 3), patient noncompliance (n = 1) and in one case the boost was omitted by mistake. However, in most cases the reason to discontinue treatment was multifactorial.

Concurrent Chemotherapy

Thirty-eight patients (34.2%) were given Concurrent Chemotherapy (CCT). The mean age of this group was 58.8 years compared to 70.2 years for the patients that did not receive chemotherapy (t-test, $p < 0.001$). Eighteen patients received a complete regime of CCT. This was defined as six or more cycles since the time for a full treatment with boost for the regimens used included at least six whole weeks. CCT mostly consisted of single-agent weekly cisplatin, but in a few cases, other drugs where given in combination with cisplatin.

Sixty-six patients started radiotherapy after February 1999 when a clinical alert was issued by the National Cancer Institute (USA) with the recommendation that CCT should be considered when treating cervical cancer patients with radiotherapy [11]. In this group, CCT to some extent was given in 35 cases.

Follow-up Routines

Patients had, by routine, a follow-up visit one month after completed radiotherapy and then every third month during the first year. During years 2-3 follow-up visits were every 4 months, during years 4-5 every six months, and during years 5-10 once per year. Patients were in a majority of cases followed-up at our clinic. If the home clinic handled the follow-up, copies of the records of the patients were routinely sent to us.

Statistical Methods

For comparison of mean values of independent samples, Student's t-test was used. Differences in proportions were tested with Pearson chi-square test. Kaplan-Meier survival analysis was used to calculate the 5-year survival rates and to plot survival curves. Differences between survival curves were tested with the log-rank test. To define predictive factors for primary remission and recurrences, we used binary logistic regression analysis. Cox proportional hazard regression analysis was used to analyze prognostic factors for survival. We began with univariate regression analyses for variables of interest and those with a p-value of < 0.1 were included in a multivariate analysis.

Results

Primary Tumor Control and Recurrences

In the complete material 69 (62.2%) patients were considered to be in complete remission after radiotherapy. In 42 cases it was known or suspected that there was remaining disease, locally or in

the form of distant metastases. In the boost group, the primary remission rate was 72.6% (61/84) and, excluding patients with FIGO stage IVB tumors, the primary cure rate was 79.7% (59/74).

Table 3 shows the results of the univariate and the multivariate analyses of predictive factors for primary remission. The strongest significant and independent predictive factor for primary cure was whether the patient received a complete treatment > 60 Gy, including boost or not. Type of tumor histology, tumor in stage IVB, and age of the patient also came out as significant and independent predictive factors.

Characteristic	**Univariate**			**Multivariate**		
	Odds Ratio (95%CI)		p	Odds Ratio (95%CI)		p
Age (per year increment)	1.024	(1.000-1.049)	0.054	1.043	(1.006-1.081)	0.022
Size (per cm increment)	0.820	(0.700-0.961)	0.014	0.855	(0.668-1.094)	0.212
Smoking						
No		1				
Yes	1.179	(0.502-2.771)	0.705			
Enlarged regional lymph nodes						
No		1				
Yes	0.619	(0.266-1.441)	0.266			
Enlarged para aortic lymph nodes						
No					1	
Yes	0.131	(0.039-0.435)	0.001	0.387	(0.062-2.403)	0.308
Histology						
Adenocarcinoma/Other		1			1	
Squamous cell cancer	3.598	(1.341-9.658)	0.011	5.162	(1.486-17.930)	0.01
Treatment						
Incomplete/Palliative		1			1	
Full including boost	5.304	(2.087-13.482)	0.000	13.297	(3.386-52.217)	0.000
Concurrent chemotherapy						
Incomplete/None		1				
Complete(≥6cycles)	1.207	(0.416-3.505)	0.730			
Time for completed treatment						
≤50days		1				
>50days	0.457	(0.170-1.224)	0.119			
FIGO stage						
I-II		1			1	
III	0.537	(0.150-1.922)	0.339	0.681	(0.148-3.127)	0.621
IVA	0.467	(0.125-1.746)	0.258	0.376	(0.077-1.833)	0.226
IVB	0.030	(0.005-0.185)	0.000	0.042	(0.004-0.440)	0.008

Table 3: Predictive factors for Primary remission

Of the 69 patients who achieved primary remission, 32 (46.4%) had a confirmed recurrence. The sites of recurrences were 8 (11.4%) local, 6 (8.6%) regional, and 21 (30.0%) distant. Some patients had a recurrence in more than one location. We tested for the same factors as we did for primary remission, but none came out as significant predictive factors for risk of tumor recurrences, not even in univariate analyses.

Survival

Follow-up time ranged between 1 and 252 months (median: 17 months) for all patients and between 32 and 206 months (median: 97 months) for the surviving patients. One patient moved abroad and was lost to follow-up. At the end of follow-up 11 (9.9%) of the patients were alive. Median survival, 5-year overall survival (OS) and 5-year Cancer-Specific Survival (CSS) for the entire group was 1.4 years, 19.5 % and 28.5%, respectively. In the subgroup of patients who received full external radiation including a boost, median survival, 5-year OS and 5-year CSS was 1.9 years, 25.8% and 33.8%, respectively. When excluding patients with stage IVB disease from this group, median survival was 2.2 years, 5-year OS was 29.3% and 5-year CSS was 37.9%. For the patients who received 60.0 Gy or less and no addition of boost the 1-year and 5-year and survival was 33.3% and 0%, respectively. Figures 1-3 show survival plots for cancer-specific survival grouped for histology, FIGO-stage and treatment given.

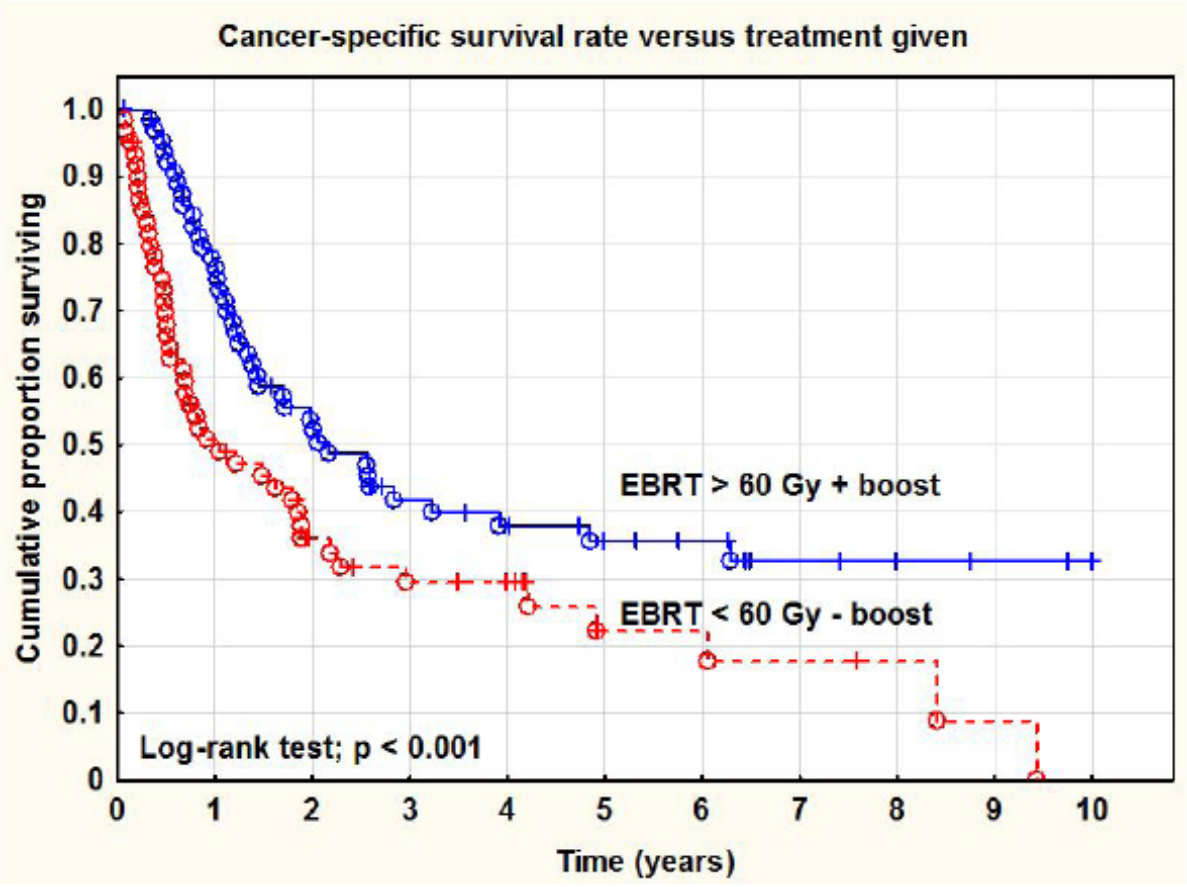

Figure 1: Cancer-specific survival rate versus treatment given.

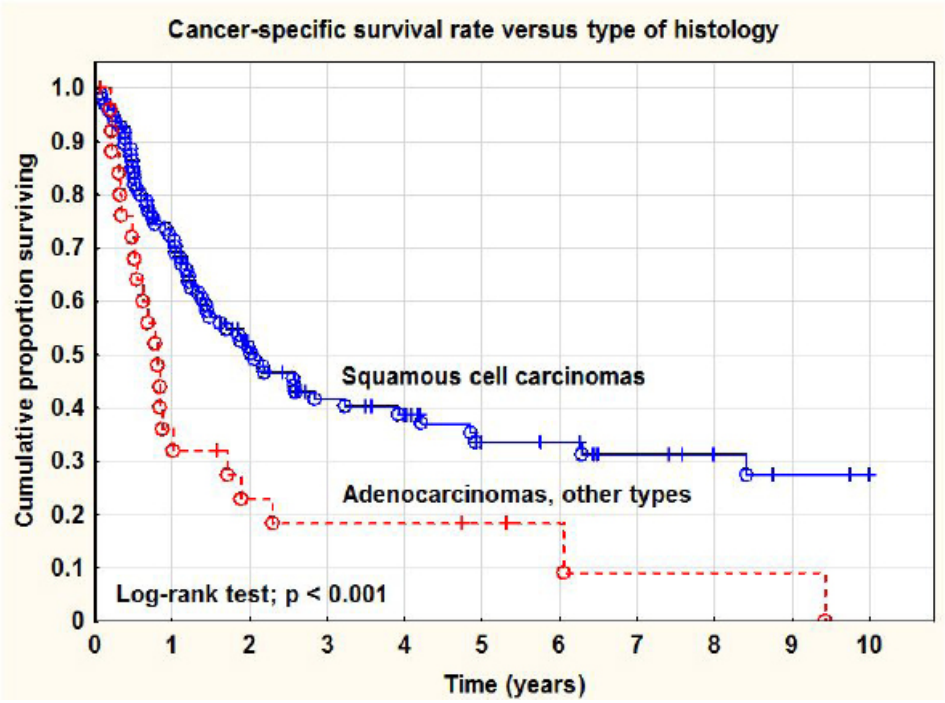

Figure 2: Cancer-specific survival rate versus type of histology.

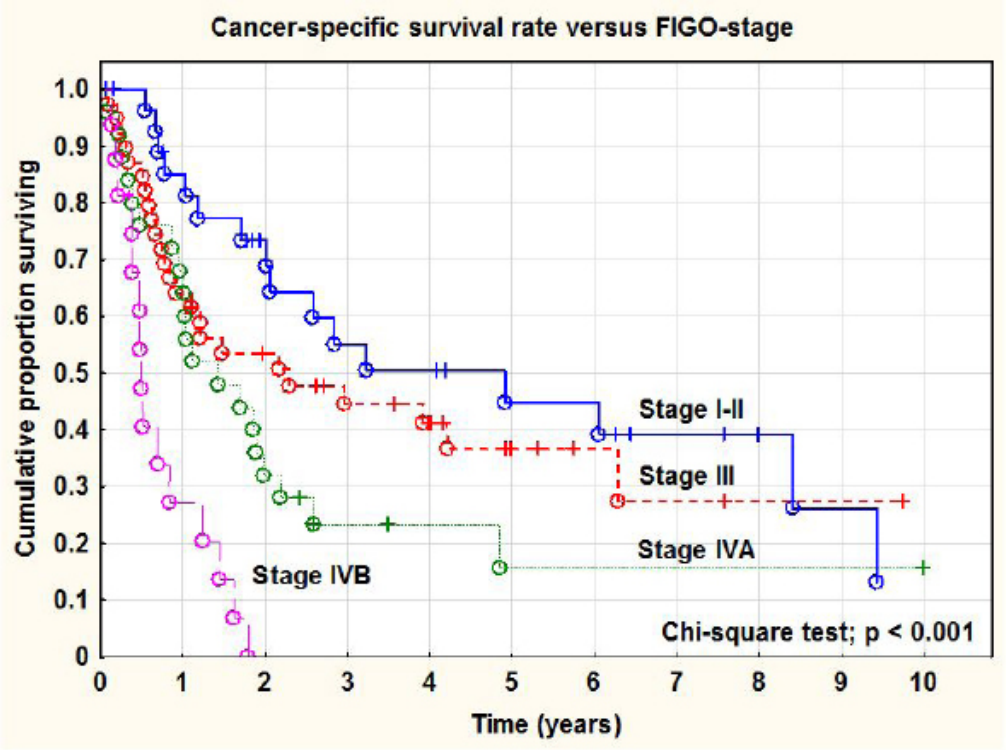

Figure 3: Cancer-specific survival rate versus tumor stage (FIGO).

Complete treatment, tumor histology, tumor stage IVB and full concurrent chemotherapy emerged as independent and significant prognostic factors for overall survival. Enlarged para aortic lymph nodes was a highly significant prognostic factor in the univariate analysis ($p < 0.001$), but it became non-significant in the multivariate analysis. Likewise, a treatment time of more than 50 days was a significant ($p = 0.031$) prognostic factor univariate but lost the significance ($p = 0.073$) in multivariate analysis. The results of the analyses of the prognostic factors for cancer-specific survival were similar to that of overall survival, with the difference that concurrent chemotherapy did not remain a significant ($p = 0.091$) factor in the multivariate analysis. Tables 6-7 show the results of the prognostic factor analyses.

Toxicity

Acute lower intestinal toxicity occurred in 85 patients (76.6%) and out of those, 14 (12.6 %) had a severe, grade 3 or higher toxicity. Grade 2 toxicity was common (48.6%), because treatment with loperamide was standard even for mild diarrhea. Twenty-seven (24.3%) patients had an acute urinary tract toxicity of any grade and one of those was a serious grade 3. Forty-two patients had any grade of late, lower intestinal or urinary tract, toxicity and seven patients had a severe late toxicity. In two cases the outcome was lethal. One patient died of bowel obstruction and one of bowel necrosis and infection In Table 4, lower intestinal and urinary tract toxicity is presented separately.

Type and time of toxicity	Lower intestinal		Bladder	
	Number of patients	%	Number of patients	%
Acute (< 90 days after start of radiotherapy)				
No reported toxicity	26	23.4	84	75.7
Mild toxicity (RTOG grades 1-2)	71	64	26	23.4
Severe toxicity (RTOG grades 3-4)	14	12.6	1	0.9
Lethal Toxicity (RTOG grade 5)	0	0	0	0
Late (≥ 90 days after start of radiotherapy)				
No reported toxicity	74	66.7	95	85.6
Mild toxicity (RTOG grades 1-2)	31	27.9	14	12.6
Severe toxicity (RTOG grades 3-4)	4	3.6	2	1.8
Lethal Toxicity (RTOG grade 5)	2	1.8	0	0

Table 4: Lower intestinal and bladder toxicity.

Of the analyzed patients with regard to treatment characteristics, follow-up time and total EQD2-dose were positively and significantly associated with increased risk of late urinary tract or lower intestinal toxicity of any grade. Concurrent cardiovascular disease was not significantly ($p = 0.054$) associated with late toxicity. There was a positive association (odds ratio 2.174) between concurrent chemotherapy and risk for late toxicity, but it was likewise non-significant ($p = 0.059$). In the multivariate analysis only total EQD2-dose remained as an independent and significant ($p = 0.040$) predictive factor for any grade of late toxicity Tables 6,7.

Fifty-six patients (50.5%) had any grade of leukocyte toxicity and 17 patients (15.3%) had any grade of thrombocyte toxicity. In the group that received concurrent chemotherapy 86.8% and 31.6% had any grade of leukocyte and thrombocyte toxicity, respectively, compared to 31.5% and 6.8% in the group with no concurrent chemotherapy. These differences were highly significant (Pearson chi-square test; $p < 0.001$ and $p = 0.001$, respectively). Table 5 shows hematological toxicity by grade.

	Number of Patients	%
Leukocyte toxicity		
No toxicity (nadir ≥ 4.0*)	51	45.9
RTOG grade 1 toxicity (nadir 3.0-< 4.0*)	17	15.3
RTOG grade 2 toxicity (nadir 2.0-< 3.0*)	18	16.2

RTOG grade 3 toxicity (nadir 1.0-< 2.0*)	15	13.5
RTOG grade 4 toxicity (nadir < 1.0*)	6	5.4
Missing data	4	3.6
Thrombocyte toxicity		
No toxicity (nadir ≥ 100*)	91	82
RTOG grade 1 toxicity (nadir 75-< 100*)	7	6.3
RTOG grade 2 toxicity (nadir 50-< 75*)	6	5.4
RTOG grade 3 toxicity (nadir 25-< 50*)	4	3.6
RTOG grade 4 toxicity (nadir < 25*)	0	0
Missing data	3	2.7
* x 10^9 per L		

Table 5: Hematological toxicity.

Characteristic	Univariate			Multivariate		
	Hazard Ratio (95% CI)		p	Hazard Ratio (95% CI)		*p*
Age (per year increment)	1.008	(0.995-1.021)	0.217			
Size (per cm increment)	1.071	(0.989-1.160)	0.090	1.031	(0.943-1.127)	0.500
Smoking						
No		1				
Yes	0.770	(0.492-1.207)	0.255			
Enlarged regional lymph nodes						
No		1				
Yes	1.136	(0.730- 1.767)	0.573			
Enlarged paraaortic lymph nodes						
No		1			1	
Yes	2.855	(1.655-4.925)	0	1.018	(0.472-2.193)	0.964
Histology						
Adenocarcinoma/Other		1			1	
Squamous cell cancer	0.47	(0.285-0.774)	0.003	0.554	(0.329-0.935)	0.027
Treatment						
Incomplete/Palliative		1			1	
Full including boost	0.306	(0.192-0.488)	0.000	0.317	(0.180-0.556)	0.000
Concurrent chemotherapy						
Incomplete/None		1			1	
Complete (≥ 6 cycles)	0.460	(0.251-0.845)	0.012	0.511	(0.263-0.993)	0.048
Time for completed treatment						
≤ 50 days		1			1	
> 50 days	1.721	(1.052-2.816)	0.031	1.598	(0.958-2.666)	0.073
FIGO stage						
I-II		1			1	
III	1.154	(0.660-2.018)	0.616	1.262	(0.692-2.302)	0.447
IVA	1.263	(0.694-2.297)	0.445	1.319	(0.689-2.523)	0.404
IVB	4.627	(2.303-9.294)	0.000	4.842	(1.889-12.408)	0.001

Table 6: Prognostic factors for overall survival.

Characteristic	Univariate			Multivariate		
	Hazard Ratio (95% CI)		p	Hazard Ratio (95% CI)		p
Age (per year increment)	0.999	(0.985-1.013)	0.845			
Size (per cm increment)	1.115	(1.023-1.215)	0.013	1.059	(0.964-1.164)	0.23
Smoking						
No	1					
Yes	0.744	(0.449-1.232)	0.250			
Enlarged regional lymph nodes						
No	1					
Yes	1.316	(0.814- 2.129)	0.262			
Enlarged paraaortic lymph nodes						
No	1			1		
Yes	3.296	(1.891-5.745)	0.000	1.531	(0.678-3.458)	0.306
Histology						
Adenocarcinoma/Other	1			1		
Squamous cell cancer	0.392	(0.232-0.665)	0.001	0.472	(0.271-0.822)	0.008
Treatment						
Incomplete/Palliative	1			1		
Full including boost	0.374	(0.224-0.626)	0.000	0.414	(0.221-0.778)	0.006
Concurrent chemotherapy						
Incomplete/None	1			1		
Complete (≥ 6 cycles)	0.462	(0.230-0.928)	0.030	0.515	(0.239-1.111)	0.091
Time for completed treatment						
≤ 50 days	1			1		
> 50 days	1.705	(0.991-2.933)	0.054	1.432	(0.813-2.522)	0.214
FIGO stage						
I-II	1			1		
III	1.388	(0.683-2.821)	0.365	1.390	(0.655-2.948)	0.391
IVA	1.982	(0.970-4.052)	0.061	1.937	(0.898-4.177)	0.092
IVB	6.084	(2.736-13.528)	0.000	4.545	(1.571-13.151)	0.005

Table 7: Prognostic factors for cancer-specific survival.

Discussion

For patients with non-metastatic cancers that fulfilled the treatment with external boost, the five-year OS and CSS were 29.3% and 37.9%, respectively. This must be considered a poor outcome compared with studies on brachytherapy. In an earlier study at our department on patients, not candidates for surgery, treated between 1993 and 2006 that received brachytherapy, the OS at five years was 50% [12]. More recent studies on newer techniques show better results. A study on the combination of intensity-modulated pelvic radiation and brachytherapy showed 3-year OS rates of 77.4% for stages I-IIA and 61.4% for stages IIB-IVA [13]. Other studies in the last years have shown 5-years OS rates of 64.5-67.0% [14-17]. However, it must be taken into consideration that the patients in our material were not given brachytherapy for certain reasons. The fraction of patients with stage III-IV cancer was considerably higher in our material than in the above mentioned, studies and the tumors were generally large. Moreover, a noticeably low percentage of our patients received concurrent chemotherapy. There could also be a selection bias of other unknown factors that negatively affected the outcome.

Several studies have been made during the last decades on the application of EBRT alone in treatment of cervical cancer with varying outcomes. Akine, et al. showed a 5-year OS of 17% for all patients with stage II-IV cancer treated with EBRT alone with curative intent at a single institution from 1962 to 1979 [18]. Lei and He showed more promising results with a 5-year OS of 56.7% and CSS of 59.8% for patients with stage IIB cancer given 60 Gy pelvic irradiation with addition of 10 Gy boost, a treatment regime

similar to ours [19]. This is remarkably better than in our study where patients with stage I-II disease that completed treatment with boost had an estimated five-year OS as well as CSS of 41.2%. A study in 1999 by Ferreira et al. on stage IIIB cancer treated with either EBRT alone with a median dose of 70 Gy, or EBRT + ICBT showed a five-year OS of 25.8% for the EBRT alone group [20]. This agrees with our results with an estimated 5-year OS and CSS for patients with cancer stage IIIA-IIIB that completed treatment with boost of 30.0% and 48.8%, respectively. More recently, Saibish Kumar, et al. showed more unsatisfactory results where patients with mainly stage IIIB-disease that was treated with EBRT alone in doses of 60-66 Gy had a five-year OS of 15.1% [21]. A small study conducted by Matsuura et al. in 2012 on EBRT alone using two different fractionation schedules with doses ranging between 60 Gy and 73 Gy showed a 3-year OS of 43.8% [22].

It is noteworthy that tumor size did not emerge as a prognostic factor for survival in this study despite it was a strong prognostic factor for CSS in our earlier study on EBRT + ICBT [12]. Other studies on brachytherapy have also shown an independent and significant association between tumor size and survival [14,17]. One can speculate that the absence of such an association in this study is due to the generally large tumor sizes (mean 6.7 cm). It is possible that the impact of tumor size as a prognostic factor is stronger with smaller tumors. However, in the study by Logsdon and Eifel including patients treated with EBRT alone as well as with addition of brachytherapy, tumor diameter of more than 8 cm was independently and significantly associated with rate of CSS [7]. The tumors in our study were measured with radiological methods when possible but otherwise with clinical estimates so the results must be interpreted with some care.

It is well established that the addition of concurrent chemotherapy improves survival for cervical cancer patients treated with radical radiotherapy [11,23,24]. In the present study, 6 cycles or more of cisplatin-based concurrent chemotherapy was an independent and significant prognostic factor for OS while it lost its' significance in the multivariate analysis of CSS. This is a clear indication that concurrent chemotherapy is important even if an EBRT alone regime is used. We can also conclude that having a tumor histology that is not pure squamous cell cancer was negatively associated with primary remission as well as OS and CSS. Poorer treatment response and survival for patients with adenocarcinomas and adenosquamous carcinomas compared to squamous cell cancers has also been demonstrated in previous studies [12,25,26].

Not surprisingly, the survival rates were not optimal for patients that received 60 Gy or less. This group consisted of some patients that were given lower doses because the intent of treatment was strictly palliative, but a majority were patients where the treatment was discontinued before 60 Gy. This shows the importance of having good prerequisites for managing acute toxicity and thus making it possible for more patients to get through radiotherapy. At the same time, the argument could be made that this emphasizes the need of carefully assessing the patient's performance status and discussing with the patient and relatives before starting such an extensive radiotherapy regime.

The lower survival rates achieved when using external irradiation alone could partly be explained by a lower rate of primary remission. For the patients that received brachytherapy, as a part of radical radiotherapy, at our institution we saw a primary cure rate of 92% compared to 62% for the whole series in this study and 80% for the locally advanced cases that received boost. There was also a higher rate of recurrences in this study. Of the patients that went into primary remission, 46% had a confirmed recurrence at any location compared to 32% in the brachytherapy material. The frequencies of local and of distant recurrences were slightly higher, 11% compared to 7% and 30% compared to 19%, respectively whereas the frequency of regional recurrences was slightly lower, 9% compared to 12% [12]. Saibish Kumar, et al. do not distinguish between failure to achieve primary remission and recurrences and look instead on overall patterns of failure and they present a high, 78.1%, rate of pelvic failure [21]. Moreover, Ferreira et al. shows a higher rate of loco regional failures in the EBRT alone group, 65.1%, compared to the brachytherapy group, 49.4% [20]. The inferiority of EBRT alone when it comes to rate of local failure is likely explained with the fact that brachytherapy is capable of achieving much higher radiation doses, 80-90 Gy, directly to the tumor and even higher doses in the central part of the cervix, as has been pointed out by other researchers [27].

Newer radiation techniques that instead of photons utilize hadron particles, such as protons and ions have more advantageous dose distribution properties and can be used to give higher doses to the target without surpassing dose constraints in nearby organs [28]. One such technique is carbon ion beam therapy that also has been indicated to have favorable radiobiological effects in clinical studies, specifically in cervical cancer [29,30]. In a study by Wakatsuki, et al. carbon ion beam radiation alone was used to treat locally advanced cervical adenocarcinomas and adenosquamous cell carcinomas with a dose-escalation protocol resulting in total doses to the tumor between 62.4 GyE (Gy equivalent) and 74.4 GyE, or 68.3 GyE and 86.4 GyE, using EQD2. They showed a 5-year OS rate of 38.1%, which must be considered high, with regard to the tumor histology, but no significant correlation between dose escalation and local response could be shown [31]. The same researchers showed impressing results with a 5-year local control rate and OS of 83.6% and 68.2%, respectively, in a subsequent study on squamous cell carcinoma stage IIB-IVA using carbon ion beam radiation in 3.0 GyE fractions plus a boost with two 9.0 GyE fractions to a final dose of 72.0 GyE in the tumor [32]. In the two above-mentioned studies, the frequency of grade 3

or higher toxicity, excluding hematological toxicity, was 1.5% and 0% respectively.

The rate of grade 3 or higher acute lower gastrointestinal toxicity in our study was notably high, 12.6%. In most of the cases, it concerned profuse diarrhea, sometimes in combination with vomiting that required parenteral fluid therapy. There was one case of a rectovaginal fistula and one case of bowel obstruction during radiotherapy. This high frequency could, at least partially, be explained with the fact that patients that discontinued treatment due to toxicity were included in the study. In seven patients, a severe late radiation reaction was reported, all in the group that completed treatment with boost, amounting to a rate of 8.3% in the boost group and 6.3% in the whole material. This was lower than reported with patients receiving brachytherapy at our department (11.2%) [33]. Thus, the use of external boost instead of brachytherapy does not seem to result in a higher frequency of severe late reactions, at least not with the doses used in the present study. Likewise, Ferreira et al. reported a slightly lower rate of complications in the EBRT alone group compared to the brachytherapy group [20]. The fact that two patients in our material had a late reaction with lethal outcome should be pointed out and it is of course of great concern. It should also be mentioned that the relatively poor survival for the patients in the present study could contribute to a lower frequency of late radiation toxicity since more patients die before they have time to develop it.

In conclusion, the survival rates in this study were, in average, in agreement with other studies on EBRT alone and consistently poorer than in studies on the combination of external irradiation and brachytherapy. There is most likely a selection bias in a patient material like this that can partially explain the relatively poorer prognosis and thus an outright comparison with brachytherapy cannot be made. However, the fact that even patients with stage I-II disease that received boost had a rather poor prognosis (OS: 41.2%) supports the already substantial evidence that standard photon EBRT alone is an inferior treatment when managing locally advanced cervical cancer. Newer brachytherapy techniques with interstitial needles make it possible to cover larger tumors and thus to utilize brachytherapy in more cases [34]. We believe that the usage of EBRT alone has subsided at our department over the last years because of this. A proton radiotherapy clinic connected to our institution is under development with the first patient to be treated this year. The possible future prospect of treating cervical cancer patients unsuitable for brachytherapy with proton radiotherapy is promising to consider, the results of carbon ion radiotherapy. The EQD2-doses to the tumor will, in view of the results of the current study, likely have to be considerably higher than 68 GyE.

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