

3D image guided adaptive brachytherapy in patients with locally advanced cervical cancer: experience and clinical results from a minimum of six years of follow-up

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In 2005, individualized 3D image guided brachytherapy was implemented for cervical cancer patients, in accordance with the (GYN) GEC ESTRO recommendation, at St. Olavs Hospital, Trondheim, Norway. This study reports the clinical results of sixty-five consecutive patients treated from 2005 to 2010. The patients were treated with curative intent using external beam radiotherapy, brachytherapy and cisplatin. Results of this treatment are presented, including Kaplan-Meier estimates for overall survival (OS) and cancer specific survival (CSS), as well as biological effective dose normalized to equivalent 2 Gy fractions to tumor, defined as high-risk clinical target volume (CTV_{HR}), and to organs at risk (OARs, here bladder and rectum). Morbidity was prospectively assessed and scored in accordance with the CTCAE 3.0. 92% of the patients achieved treatment response. Local control (LC) remained in all but one patient during follow-up. Five-year OS and CSS were 71% and 80%, respectively. The mean minimum dose to CTV_{HR} for all patients was 80.2 ± 7.3 Gy; 16% and 23% of the patients developed bladder and GI symptoms respectively. 14% of all symptoms were categorized as serious (CTCAE score ≥ 3). A dose-effect relationship was observed for adverse effects of the bladder, and the findings support the more recently recommended lower total dose limit for this OAR.

Keywords

Cervical cancer; Radiotherapy; Brachytherapy; Follow-up

1. Introduction

The current standard treatment of locally advanced cervical cancer includes pelvic external beam radiotherapy (EBRT), concurrent cisplatin-containing chemotherapy and intracavitary brachytherapy (BT). It is well documented that BT is a critical component of the treatment [1].

Technological improvements in imaging, treatment planning and dose delivery have led to a general advancement of radiotherapy during the last two decades. For treatment of cervical cancer, the BT dose has been traditionally prescribed to a geometrical point (point A) in the pelvis [2], using 2D

imaging. Hence, neither the individual size/shape of the tumor, nor the actual positions of the surrounding organs at risk (OARs), in particular the rectum and bladder, were taken into consideration. Now, individualized 3D image guided treatment planning has emerged as an attractive alternative also for BT. Nevertheless, many centers still use point A as the only way of specifying the dose to the target volume, and there is still a large variation in parameters used for dose prescription and dose evaluation of target volume and OARs [3]. Meanwhile, the gynaecological (GYN) GEC ESTRO working group has elaborated guidelines for image guided BT of cervical cancer, recommending individualized treatment planning, preferably based on 3D magnetic resonance imaging (MRI) [4–7]. The guidelines provide a standardized way of prescribing and reporting doses to different target volumes and OARs. Taken into use, they will ultimately provide a more evidence based approach for the treatment of cervical cancer using primary chemoradiation.

After 15 years of traditional point A, 2D BT treatment planning [8], individualized 3D image based BT planning following the (GYN) GEC ESTRO guidelines was implemented at St. Olavs Hospital, Trondheim, Norway, in 2005 [9]. This prospective study was initiated in order to share the experience and clinical progress resulting from the implementation of a new BT treatment technique. The aim was to evaluate the clinical outcomes after at least 6 years of follow-up, focusing on tumor control, survival and late treatment toxicity.

2. Materials and methods

A protocol was developed to monitor the implementation and register the treatment results including local control (LC), pelvic control (PC), distal recurrences, cancer specific survival (CSS), overall survival (OS) and toxicity.

2.1 Patient and tumor characteristics

From September 2005 to June 2010, all patients diagnosed with locally advanced cervical cancer and eligible for treatment with curative intent at St. Olavs Hospital, Trondheim, Norway, were prospectively included in this study. No patients were excluded, and informed consent was obtained from all participants. The Regional Committee for Medical and Health Research Ethics approved the study (approval number: 18603).

The patients underwent a gynecological examination under general anaesthesia at the time of diagnosis, and were clinically staged according to the International Federation of Gynaecology and Obstetrics (FIGO) classification system (1994). In addition, all patients underwent diagnostic computer tomography (CT) examinations of the chest and abdomen, and MRI of the true pelvis.

2.2 Treatment characteristics

All patients received a combination of EBRT with weekly concomitant cisplatin, 40 mg/m², for 5-6 courses if no contraindications occurred. BT was given twice weekly during the last two weeks of the EBRT. No EBRT was given on the days of BT. Throughout the study, and before every BT treatment, the same specialist in gynecological oncology delineated the target volumes and OARs based on the (GYN) GEC ESTRO guidelines. A summation of the doses from BT and EBRT gave an estimate of the total radiation doses given to these volumes. All radiation doses were normalized to biologically equivalent doses in 2 Gy fractions (EQD2), using the linear-quadratic model with $\alpha/\beta = 3$ (EQD2₃) for OARs and $\alpha/\beta = 10$ (EQD2₁₀) for tumor.

2.3 Prescription, planning, and treatment of EBRT

EBRT planning was performed using the treatment planning system Oncentra (Elekta Instrument AB, Stockholm, Sweden) and based on CT images (Siemens Somatom Emotion spiral-CT, Munich, Germany), with support from diagnostic MRI for the volume delineation. The standard prescription was 2 Gy \times 25 = 50 Gy to the planning target volume (PTV), including tumor, uterus and pelvic lymph nodes. However, 12 patients received EBRT of 1.8 Gy \times 25 due to comorbidity and age. 3D conformal 4-field box technique was applied with 15 MV photons to obtain the desired dose distribution. If enlarged lymph nodes in the pelvic or paraaortic region were present at the time of diagnosis, an additional radiation boost of 4-14 Gy in 2 Gy fractions was further prescribed to the lymph nodes and given by opposing radiation fields. An Elekta Synergy linear accelerator (Elekta Instrument AB, Stockholm, Sweden) delivered the EBRT.

2.4 Prescription, planning and treatment of BT

BT treatment planning was performed using PLATO or Oncentra Brachy (Nucletron, Elekta AB, Veenendahl, the Netherlands), and an individual treatment plan was made before each BT fraction. For most patients (44 out of 65), BT was planned using MRI (SPACE, Magnetom Avanto, Siemens Healthcare AG, Germany) as the basis for volume

delineation and treatment planning. However, for the first 21 patients (treated before 2007), BT planning was based on CT images. Details of the treatment planning, as well as dosimetric aspects of this initial CT-based group of patients, were presented previously [9].

The BT prescription dose was 6 Gy \times 4 to the high risk clinical target volume (CTV_{HR}). The minimum dose to 90% of the delineated volume (D90) represents the dose delivered to CTV_{HR}. Calculation of total dose to CTV_{HR} assumes both a homogeneous external dose distribution and that the minimum BT dose occurs at the same spot for every BT fraction.

The interpretation of the CTV_{HR} concept and corresponding prescribed dose changed during the study period due to the transition from CT to MRI. However, the treatment dose was maintained throughout the study, by changing the prescription from 5 Gy \times 4 for the first patients (when using the CTV concept) to 6 Gy \times 4 when the CTV_{HR} concept was introduced [9]. The precise D90 given to the volume representing CTV_{HR} is not known for the CT based patients as the tumor tissue cannot be separated from normal cervical tissue in CT scans; D90 for CTV_{HR} for these patients are therefore excluded from the detailed dosimetric analysis. Data from OARs based on CT delineation are, however, included in the analysis as the OARs can easily be defined in CT scans as well as in MRI.

Each BT fraction was optimized to avoid violation of the dose limits for OARs, while at the same time trying to maintain the dose coverage of the target volume. The employed dose limits for OARs were given in terms of equivalent EQD2₃, and reflect the minimum dose to the most exposed 2 cm³ of the OARs (D_{2cm3}). These total dose limits were 90 Gy for bladder and 75 Gy for rectum and sigmoid.

BT was given using the GammaMed 12i high dose rate (HDR) afterloading equipment (Varian, Palo Alto, USA) with an Ir¹⁹² stepping source. Fletcher applicators with standard colpostat segment of the ovoids were used. Further details of the BT procedure are described elsewhere [9].

2.5 Follow-up

The patients were followed up from the end of radiotherapy until May 1st, 2017 or until death if the patient died before that date. Clinical examinations and morbidity scoring were performed before starting treatment and for every third month after the end of treatment for the first two years, for every sixth month the third year, and thereafter yearly. CT (thorax and abdomen) and MRI (true pelvis) imaging were performed three months and one year after the end of treatment. The primary treatment response was recorded three months after the end of treatment. Absence from local recurrence was monitored by physical examinations and any radiographic imaging at later follow-ups, and defined as no evidence of disease in the cervix (LC) or pelvis (PC). At every follow-up, injuries and symptoms of adverse effects related to the bladder and gastrointestinal (GI) tract were recorded according to the Common Terminology Criteria for Adverse

Table 1. Patient and tumor characteristics.

Parameters		Mean \pm SD	Range	Number of patients	%
Eligible patients				65	100
Age (years)		57 \pm 18	24-91		
Tumor size at diagnosis	Largest diameter (mm)	51 \pm 16	10-90		
Pathological lymph node (s)	Pelvis			28	43
	Pelvis and paraaortic			7	11
Histologic type	Squamous			55	84
	Adenocarcinoma			8	12
	Adenosquamous			1	2
	Undifferentiated carcinoma			1	2
FIGO stage	IB			6	9
	IIA			6	9
	IIB			31	48
	IIIB			21	32
	IVA			1	2

Events (CTCAE) version 3.0 scoring system. Manifest symptoms occurring at least three months after treatment were recorded as late effects.

2.6 Data analysis

Descriptive statistics were used to characterize the patient population, disease, and treatment features as well as toxicity associated with the treatment. OS and CSS probabilities were estimated using the Kaplan-Meier product limit method. A nonparametric two-independent samples test (Mann-Whitney) was used to evaluate whether the total dose given to the OARs was different between patients with and without reported late effects. The analyses were performed using SPSS (statistics 23, IBM), Microsoft Excel 2010 or Sigmaplot (Systat Software).

3. Results

Table 1 lists the baseline characteristics of the 65 patients. The majority of the patients were diagnosed with FIGO stage IIB (48%) and IIIB (32%). 52% and 67% of the patients in these groups had nodal disease at diagnosis, respectively.

98% of the patients received the prescribed BT fractions, whereas 94% received the prescribed EBRT. The incomplete treatments were due to acute side effects resulting in 1-2 BT or EBRT fractions being omitted. 12% of the patients received EBRT with extended paraaortic fields. The mean overall treatment time (OTT) was 41 days (range 32-50), and no prolonging due to acute side effects was registered. 75% of the patients received chemotherapy during radiotherapy.

3.1 Disease control and results from follow up

The median follow-up of the participants was 7.2 years (range 0-11.6 years), with a mean of 6.6 \pm 3.3 years. At the end of the study period, the median follow-up time was 8.6 years (range 6.7-11.6) for the surviving patients, and 3.3 years (range 0-8.8) for the deceased patients. The completeness of follow-up was 100%.

Primary treatment response was achieved for 60 of the 65 patients (92%). Table 2 presents the sites of progression

for the five patients without primary response. One patient had progression of the primary tumor during treatment, and three patients were diagnosed within 3 months with lymph node metastases in the paraaortic region, not included in the primary radiation fields. The fifth patient received paraaortic irradiation, but progressed within the external radiation fields. Four of these patients died from cervical cancer, and one died from other causes after the successful treatment of nodal disease outside the primary radiation field.

Among the 60 patients with primary treatment response, 12 patients (20%) recurred during the time of observation. 17%, 25% and 16% of the patients staged as IIA, IIB, IIIB respectively, recurred. Among the 35 patients with nodal disease at diagnosis, 11 progressed or recurred during follow up. Among the 10 patients with adeno/adenosquamous carcinoma, 7 patients had nodal disease at diagnosis, and 5 of these progressed/recurred during the period of follow-up.

The mean tumor size (largest diameter measured on MRI) at diagnosis was 51 \pm 16 mm. The mean of the largest tumor diameters were 53 mm, 58 mm and 61 mm for patients without progression/recurrence, patients with primary response but later recurrence, and patients with progression, respectively.

The median time from the end of treatment to the detection of recurrence was 16 months (range 6-46 months). The sites for recurrence are presented in Table 2, showing that nine of the recurrences observed were distant, while two patients recurred in the pelvic lymph nodes. Local control in the cervix was obtained for all but one of the patients with recurrences during follow-up. At the end of observation, all but one of the recurring patients had died.

Kaplan-Meier estimates are presented in Fig. 1. The merged data from all stages show that percentages of OS at three and five years were 82% and 71% respectively, and of CSS, 88% and 80%, respectively. The three years CSS for FIGO subgroups IB + IIA, IIB and IIIB + IVA were 92%, 94% and 84% respectively, while 5 years CSS were 92%, 84%, 72% respectively Fig. 1B.

Table 2. Time and site of relapse.

Progression/recurrence	Site of progression/first recurrence	Number of patients	FIGO stage	Time to progression/recurrence (months)
Progression	Cervix	1	IIIB	< 3
	Paraortic region, not primary irradiated	3	IIB, IIB, IIIB	< 3
	Paraortic region, primary irradiated	1	IIB	< 3
Recurrence versus primary irradiated volume				
· Inside	Cervix	1	IIIB	18
	Both inside and outside	1	IIIB	6
· Both inside and outside	Pelvic/paraortic lymph node, primary irradiated	1	IIA	8
	Pelvic/paraortic lymph node, primary no paraaortal irradiation	1	IIA	8
· Outside	Abdomen	1	IIB	25
	Adrenal gland	1	IIB	12
	Groins and bone	1	IIB	13
	Paraortic region	1	IIB	6
	Lung	3	IIIB, IIB, IIB	18, 30, 46
	Abdominal wall	1	IVA	20
	Sacrum	1	IIB	13

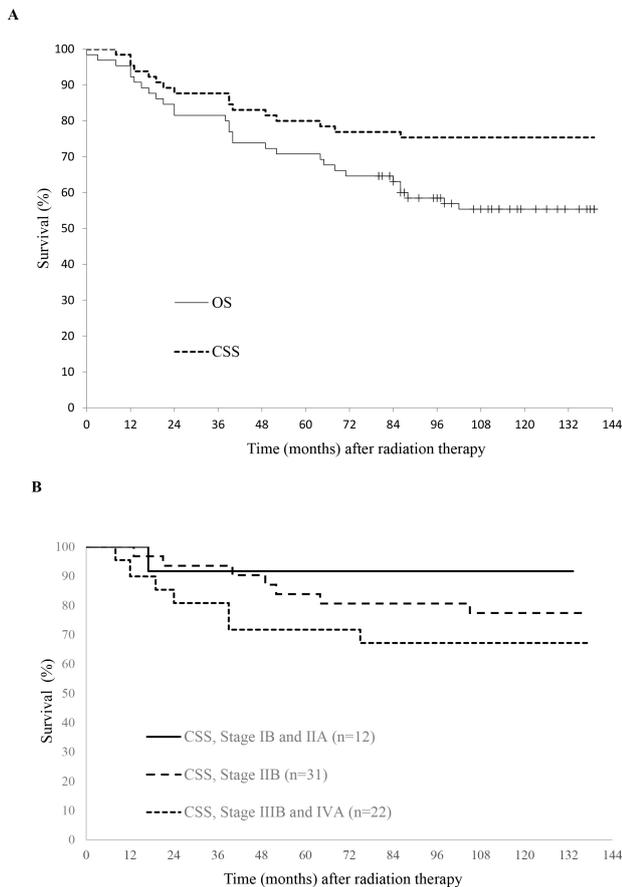


Fig. 1. A: Kaplan-Meier plots of OS and CSS (%) for the whole population. The vertical tick marks represent censored patients. B: Kaplan-Meier plots of CSS for patients in different FIGO stage subgroups.

3.2 Target volume characteristics and dosimetry

The mean CTV_{HR} volumes for all actual patients and all fractions were $38.3 \pm 16.3 \text{ cm}^3$, while the mean dose to CTV_{HR} (EQD2₁₀) for the total radiation (BT and EBRT) was $80.2 \pm 7.3 \text{ Gy}$. Due to technical difficulties, four patients were omitted from the dosimetric analysis.

Fig. 2 shows the total dose to CTV_{HR} as a function of the mean CTV_{HR} volume for each patient. The two patients with local progression and recurrence in the cervix, receiving a total dose of 86.3 Gy and 83.3 Gy, respectively, are highlighted in the figure. For five of the patients, the total dose to CTV_{HR} was less than 70 Gy. Three of these patients received a lower total external radiation dose (less than 50 Gy), and for two of those there were a combination of low external dose and a large mean tumor volume making target dose coverage with BT difficult. For one of the patients, the rectum position limited the CTV_{HR} dose, and the fifth patient received only two BT fractions. One of the patients with recurrence in the pelvis received an external dose lower than prescribed (EBRT EQD2₁₀ = 44.4 Gy vs. 50 Gy).

Generally, a shrinkage of the CTV_{HR} was observed during BT. The mean volume for all patients at BT fraction 1 was $41.8 \pm 22 \text{ cm}^3$, whereas the mean volume was reduced to 35.5 cm^3 at fraction 4, which represents a decrease of 18%. This effect was most pronounced for the largest volumes.

3.3 Late adverse side effects

During follow-up, 34% of the patients reported persisting symptoms from the urinary and/or GI tract. Bladder/GI symptoms were seen in 16%/23% of the patients, respectively. 14% of the patients developed serious symptoms with a CT-CAE score ≥ 3 (Table 3). From Table 3 it can also be seen that 3 patients with grade 3-4 adverse effect were registered with pre-treatment morbidity, making the patients predisposed to

Table 3. Observed late effects.

CTCAE score grade	Description	Number of patients (%)
3 and 4		9 (14%)
	Treated for rectovaginal fistula*	1
	Treated for ileus, faecal incontinence*	1
	Brickerbladder and sigmoidostomy	1
	Reimplant of ureter, no symptoms today	1
	Bilateral hydronephrosis removed one kidney*	1
	Severe symptoms of diarrhea and stomach cramps in periods	2
1 and 2	Severe urinary incontinence	2
		13 (20%)
	Bowel symptoms in periods, diarrhea and urgency	7
	Bowel and urinary symptoms	3
	Urinary symptoms	3

* Severe pre-treatment symptoms.

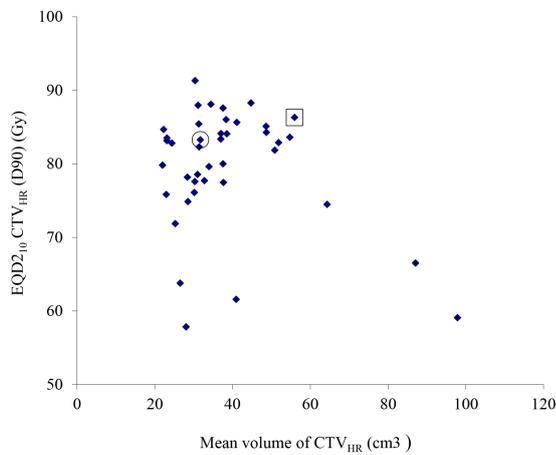


Fig. 2. Total EQD₂₁₀ for CTV_{HR} D90 (Gy) as a function of mean CTV_{HR}-volume during BT (fraction 1-4) for each patient. The one patients with recurrence (□) and the one patient with progression (○) in primary tumor volume are marked.

post-irradiation damage.

Fig. 3 illustrates the distribution of the total maximum dose for bladder and rectum in patients with persisting symptoms from the urinary or GI tract, compared to those showing no symptoms. All patients received treatment within the dose limit for bladder (90 Gy); however, three patients were given a slightly higher total dose than the dose limit for rectum (75 Gy). None of these patients was among those associated with late side effects.

No statistically significant difference was seen when comparing the maximum doses given to OARs in patients having persisting symptoms in the OARs vs. patients with no symptoms. The results remain the same when the OAR doses for patients with a CTCAE score 3-4 (severe damage) were compared to the OAR doses in the patients without symptoms. However, for bladder adverse effects, a dose-effect relationship was observed; the relative number of patients with

symptoms (grade 1-4) increases with increasing total dose, as shown in Fig. 3. 73% of the patients who developed bladder symptoms received bladder doses > 80 Gy.

In the three patients where the rectum late side effects were grade 3-4, the mean totalrectum dose was 67.6 ± 7 Gy.

4. Discussion

This study adds evidence of the efficacy of chemoradiation in the treatment of locally advanced cervical cancer. By following the (GYN) GEC ESTRO recommendations, including adaptive BT, high rates of local tumor control and CSS were achieved. In our limited material of 65 patients, we experience, like others, that adenocarcinoma and the presence of pathological lymph nodes increase the risk of recurrence. 75% of the recurrences were distal; the role of (neo) adjuvant treatment to reduce the risk is still uncertain.

Compared to a retrospective analysis of 107 cervical cancer patients treated in our institution between 1987-2001 [8], the patients in our current study have had a substantial improvement in survival. 5-year OS and CSS for all stages for the historical data were 36% and 45%, respectively, in contrast to the current figures of 71% and 80%. However, the proportion of patients diagnosed with more advanced disease (stage \geq III) was higher in the historical cohort (56% vs. 34%). Furthermore, the use of chemotherapy has increased from 14% in the study from 1987-2001, to 75% in the current study. We believe earlier detection of the disease, more use of chemotherapy and the establishment of guidelines for the prescription of radiotherapy altogether have contributed to the improved treatment outcome.

Among the patients experiencing recurrence during the time of observation, only one patient had the first recurrence in the cervix, while two more patients were diagnosed with recurrences in the pelvic region (Table 2). The results are comparable with the outcome of several mono-institutional reports as well as the multicenter RetroEMBRACE study [10]. In the RetroEMBRACE study, the local and pelvic control was associated with an overall survival benefit of about

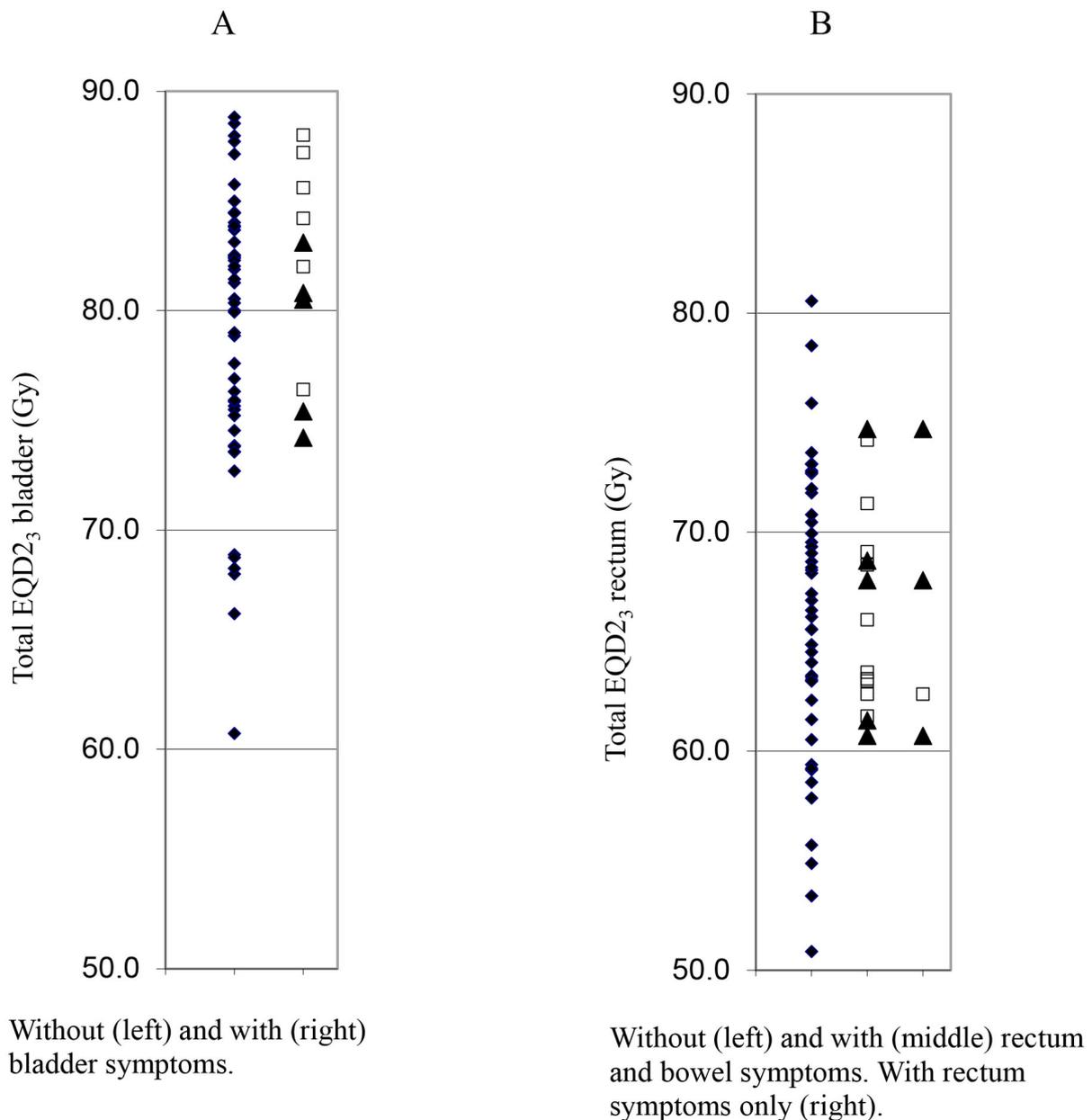


Fig. 3. Total EQD₂₃ (Gy) for bladder (A) and rectum (B) (D_{2cm^3}). ♦ represents patients without tissue damage or symptoms in either the bladder (A) or GI tract/rectum (B). □ represents patients with tissue damage or symptoms grade 1 or 2; ▲ represents grade 3 or 4 damage.

10% compared to historical cohorts [11], and similar benefits were also observed in several mono-institutional reports [10].

Based on the high degree of local tumor control in our study, the mean total dose delivered seems to be sufficient to treat the primary tumor for this patient group. The high local control may be somewhat surprising since the patients on average received a lower dose to the tumor compared to the RetroEMBRACE patients [11]. However, the systematic target contouring and less variation in CTV_{HR}/target volume in the present study might explain this finding. The true adaptive approach, delineating the CTV_{HR} on MRI for every BT fraction, ensures the best possible dose distribution

throughout the treatment. Adaptation is particularly important in those cases where we see a large reduction in tumor volume throughout the course of treatment. The mean OTT was 41 days, which is favorable and may also contribute positively to the obtained local control [12]. Compared to the RetroEMBRACE data [11], the present study showed higher values of 5 years CSS (80% vs. 73%) and OS (71% vs. 65%).

Severe GI and bladder complications are feared consequences of chemoradiation when treating locally advanced cervical cancer [13, 14]. Although the present study reports relatively low acute toxicity, several patients reported persisting symptoms after treatment.

For rectum side effects, results from the large, prospective multicenter study, EMBRACE [15] show that low total local dose to the rectum (< 65 Gy) is associated with less frequent and minor morbidity, whereas high total local dose (> 75 Gy) is associated with more frequent and major rectal morbidity. With three exceptions, the doses given to rectum in the present study were generally lower than the clinical cutoff levels predicting severe rectal morbidity. However, patients with rectal symptoms thought to arise from focal injury due to a high local dose were not among those who received the highest rectum doses in our study. It is, however, not possible to draw any conclusions due to the limited numbers of patients.

Adverse effects from the GI-tract may also be a result of EBRT, as the doses given are relevant [16]. EBRT using 1.8 Gy × 25 fractions, in contrast to the current study using 2 Gy × 25 fractions, may reduce the late side-effects caused by the external treatment, and is now incorporated in our current practice. GI complications may arise from the small intestine and sigmoid colon. Since they were not delineated as OARs, we have no dose information and are not able to evaluate any dose effect relationships. Our data suggest that it is of equal importance to focus on these organs, as on the rectum, to avoid late adverse effects.

Compared to published results using the same dose constraints for planning [13], the percentage of patients experiencing severe bladder symptoms was higher in this study, and the percentage of milder symptoms was lower. The data showed that the bladder symptoms occurred more frequently among the patients receiving the higher bladder doses. The number of adverse effects supports the more recently proposed lower dose limit for bladder EQD_{2,3} < 80 Gy [10].

The incidence of grade 3 or 4 late adverse effects in the urinary or GI tract including rectum (14%), was somewhat higher compared to patients treated in our institution before 2002 (8%) [8]. We believe part of the difference is due to a more systematic registration in our prospective evaluation of the patients. The inclusion of patients in our study was unselected, there was a large spread in age and several had significant comorbidity.

Three out of the 65 patients, were diagnosed with progression in paraaortic lymph nodes outside the primary irradiated region within three months after the end of treatment. These patients might have benefited from even more aggressive external radiation, but this subgroup is challenging to identify in advance. Diagnostics utilizing PET-CT may reduce the problem of both under- and over-treating patients [17]. PET-CT for diagnosis of affected lymph nodes for cervical cancer patients is now standard practice in our department, and will further improve the treatment efficacy.

Our data represent improved outcomes; however, there is still a potential for improvement, especially regarding a reduction of treatment toxicity. To further reduce the probability of late side effects for the OARs, and simultaneously optimize the dose to the tumor, more sophisticated tech-

niques, such as the use of interstitial needles, have been shown to be feasible [18–20]. During the last decade, more conformal EBRT, resulting from intensity modulated radiation techniques, has significantly reduced the treatment toxicity compared to traditional box-techniques used in this study [21, 22]. Further improvement is expected when implementing adaptive techniques for external radiation [23].

5. Conclusions

Our study shows that chemoradiation including 3D adaptive BT results in high rates of local control and survival. The survival in this prospective study is favorable compared to treatment results from larger patient cohorts in other countries, as well as historical results from our own institution.

Still, many patients experience adverse side effects caused by radiation damage. Our data support the recently proposed lower dose limit for bladder irradiation. Further studies are needed to delineate and evaluate doses to the small intestine and the sigmoid colon.

The potential for increasing the treatment efficacy for both BT and EBRT by utilizing more advanced radiation treatment techniques needs to be more fully explored.

Author contributions

M.S. was the responsible physician, and performed the placement of the brachytherapy applicators. M.S., A.B.L.M., S.D. and A.D.W. analyzed the data and wrote the paper. M.D.A. and B.H. contributed in the writing process. A.B.L.M., M.S. and A.D.W. contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

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