Survival and Toxicity Following Chemoradiation for Carcinoma of the Cervix – Impact of Multiple-phase Treatment and Shielding

SUNDUS YAHYA¹, LUBNA BHATT², MARGARET KING³, SARAH PIRRIE⁴, RUTH WYATT¹,
MUHAMMED SUHAIL ANWAR¹, AHMED EL-MODIR¹ and INDRAJIT FERNANDO¹

¹Hall Edwards Radiotherapy Research group, Cancer Centre, Queen Elizabeth Hospital, Birmingham, U.K.;

²Christie Hospital, Manchester, U.K.;

³Deansley Centre, New Cross Hospital, Wolverhampton, U.K.;

⁴Cancer Research UK Clinical Trials Unit, Institute for Cancer Studies,
The University of Birmingham, Birmingham, U.K.

Abstract. *Aim: We report on outcomes and significant grade 3-4 late toxicities between January 1999 and October 2006 following introduction of multi-phase treatment and effect of shielding in treatment of cervical cancer with concurrent chemoradiation. Patients and Methods: Radiotherapy dose by phase, recurrence, survival and toxicity data was collated by a retrospective review of clinical notes. Shielding information was retrieved from original planning films. Results: 3-year survival for stages I, II and III disease were 89%, 76% and 51% respectively. Local pelvic failure was 9%. Overall significant late toxicity (SLT) rate was 13%, with lower rates for post-operative treatment than primary chemoradiation (4% vs. 16%). SLT with single phase treatment was 29% versus 12% following multiphase EBRT and 16% when <2 areas were shielded versus 6% with ≥3 shielded areas (p=0.01). Conclusion: Shielding and multi-phase treatment not only reduce dose to organs at-risk but can also reduce late toxicity without compromising local control or survival.*

Concurrent chemoradiation is standard-therapy for patients with carcinoma of the cervix, with strong evidence for efficacy (1-8), and a consensus of medical opinion (9, 10) resulting in increasing use since 1999. In September 2010 the Royal College of Radiologists (RCR) published its national audit (11), demonstrating a survival benefit of 11% at 5 years over radiotherapy-alone.

Correspondence to: Dr. Sundus Yahya, The Cancer Centre, Queen Elizabeth Hospital, Birmingham, B15 2TH, U.K. Tel: +44 7840172851, e-mail: drsundusyahya@yahoo.co.uk

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One of the main goals for the future is reduction of late toxicity, which is of particular concern for patients who may suffer significant morbidity from even low-grade toxicity (12).

In 2006 we published outcome and toxicity data for 79 patients treated at the University Hospital Birmingham between 1999 and 2002 (13). At that time, with a median follow-up of 35 months we reported an overall survival of 87% with a 10% serious late-toxicity rate. We now give an update on that original cohort and add patients treated up to 2006. During this period (2002 onwards) radiotherapy techniques have progressed with the use of multi-phase treatment and increased shielding using multi-leaf collimators, reducing radiotherapy dose to bowel and other organs at risk. We look at the effect of these changes on local control, survival and late toxicity.

We are aware of the recent trend towards employing intensity-modulated radiotherapy across all tumor sites. Huge potential of reducing normal tissue toxicity and dose escalation lies in Intensity-modulated Radiotherapy however patient-specific organ motion necessitates for careful introduction of this technique. It may be necessary to employ techniques of Image-guided Radiotherapy to ensure adequate planning target volume coverage due to risk of organ motion (uterine motion by bladder filling) and cervical motion by rectal motion.

Patients and Methods

Data collection and statistics. Patients were identified from the local radiotherapy database and original patient data from the original study (13). Retrospective review of case notes and radiotherapy planning films was used to obtain patients' characteristics, treatment details and data related to overall and disease-free survival, local and distant recurrence and late toxicity. Patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) system of 1995 (14). Late toxicity was scored

using the RTOG/EORTC late-radiation morbidity scoring system and was defined as complications present at or after 90 days from completion of radiotherapy. Overall survival (OS) was defined as date of diagnosis to date of death from any cause (patient alive or lost to follow-up at the time of analysis were censored at the date last known to be alive). Progression-free survival (PFS) was defined as date of diagnosis to the earliest date of progression or death. Patients alive and progression-free or lost to follow-up at the time of analysis were censored at the date last known to be progression free. OS and PFS was analyzed using the Kaplan–Meier method and Hazard’s Ratio generated through Cox regression analysis. Differences in SLT rates between groups was analysed using the chi-squared and Fishers exact tests as appropriate.

Patients’ characteristics. Seventy-nine patients were included in the original article reporting on women treated between 1 January 1999 and 1 May 2002. A further 96 patients were treated up to October 2006. Thus, 175 patients are included in the final analysis. Median age at diagnosis was 45 years (22-76). Median follow-up for patients alive at time of analysis was 46.4 months. One hundred and twenty-eight patients (73%) underwent chemoradiation as their primary therapy, whilst 47 (27%) were treated post-operatively. Sixty-three (36%) had lymph node involvement on imaging or operative pathology (Table I).

Treatment.

Chemotherapy. Standard chemotherapy was weekly cisplatin (40 mg/m²) for 5 cycles, with the dose capped at a maximum of 70 mg. Forty-three patients (25%) received less than the planned 5 cycles. Eight patients (5%) received 6 cycles. In those receiving less than the planned treatment, this was due to toxicity in 33 cases (77%), two patients experienced hypersensitivity, two chose not to complete treatment, and in four cases (9%) the cause was not documented. One patient died from myocardial infarction after 14 fractions of radiotherapy and two cycles of chemotherapy. Twenty-eight patients (16%) also received 2 cycles of cisplatin/fluorouracil chemotherapy following chemoradiation. This was given at the discretion of the clinician due to positive lymph nodes on imaging or surgery.

Radiotherapy. One hundred and twenty-eight patients (73%) underwent chemoradiation as their primary therapy. Standard primary treatment was external beam radiotherapy (EBRT) 45-50 Gy in 25-28 fractions of 1.8 Gy followed by one medium dose rate (MDR) brachytherapy insertion of dose 20-30 Gy to point A. This gives a resulting biological effective dose (BED) of 77.5-95.6 to point A. The median selectron dose actually received by this group was 25 Gy with a median total BED received of 90.0 Gy (calculated using $BED = n \cdot d \cdot [1 + d/(\alpha/\beta)] \cdot f(\mu, t)$ where n is the number of fractions, d is the dose per fraction, assuming α/β ratio of 10 Gy for tumour, t is the duration of the treatment, f (μ, t) is a correction for β -mediated cell kill, given by $2/\mu \cdot t [1 - (1/\mu \cdot t)]$, is the recovery constant related to the repair half-time $T_{1/2}$ by $\mu = 0.693/T_{1/2}$ where $T_{1/2} = 0.5$ h).

However, 20 patients of those receiving primary chemoradiation (16%) did not receive their planned brachytherapy treatment. One was patient died during EBRT due to acute myocardial infarction. 4 cases had no reason documented, 4 had stenosed cervix, and 2 had vesico-vaginal fistula. One procedure was abandoned due to pyometrium, 2 due to the bulk of residual disease and 1 due to uterine perforation. Two patients did not tolerate the treatment and

Table I. *Patients’ characteristics.*

Characteristic	Number (%)
Treatment	
Primary	128 (73)
Post-operative	47 (27)
Stage	
1	41(23)
2	96 (55)
3	31 (18)
4	6 (3)
Unknown	1
Nodal status	
Positive	63 (36)
Negative	111 (63)
Unknown	1
Histology	
Squamous	124 (71)
Adenocarcinoma	28 (16)
Adenosquamous	11 (6)
Other	11 (6)
Unknown	1
Shielding block	
0-2	110 (63)
≥ 3	58 (33)
Unknown	7 (4)

3 refused brachytherapy prior to the attempt. Out of these cases 15 underwent a third phase of EBRT at 10-20 Gy in 5-10 fractions. This resulted in total EBRT dose of 60 Gy in 7 patients, 62 Gy in 1 patient, 65 Gy in 6 patients and 70 Gy in 1 patient. Five patients had salvage hysterectomy and the results of this are discussed elsewhere (15).

Forty patients (27%) were treated post-operatively. Standard post-operative treatment was with EBRT at 45-50 Gy in 25-28 fractions (16 patients). For those with positive or close margins this was followed either by a further 15 Gy in 8 fractions of EBRT (15 patients) or a single MDR brachytherapy insertion (15 patients) of dose 13-20 Gy to 0.5 cm (median BED received 83.8). One patient stopped EBRT after 32.4 Gy at her own request due to abdominal pain.

Dose rate for medium dose rate brachytherapy of this period was approximately 1.6 Gy per hour and treatment used an intrauterine tube and ovoids. Ovoids without intra-uterine tube were used for postoperative treatment.

In terms of radiotherapy technique, phase 1 radiotherapy (45 Gy in 25 fractions) was given with 6-15MV photons using anterior, posterior and lateral fields. The superior margin was at the level of L5/S1 junction, the inferior margin at the inferior edge of the obturator foramen, the lateral margins were at 1.5 cm beyond the bony pelvic brim, the anterior margin was at the anterior symphysis pubis and the posterior margin was at S2/S3 junction. All these margins were modified according to staging MRI and examination under anaesthetic to ensure both the tumour and regional nodes were encompassed within the clinical target volume. For those patients undergoing treatment in 2 phases, phase 2 (5 Gy in 3 fractions or 15 Gy in 8 fractions for post-operative treatment with no

Table II. *Pattern of recurrence.*

Stage at diagnosis	Pelvic		Paraortic	Distant
	Central	Nodal		
1	4	1	0	4
2	5	2	8	12
3	5	2	3	4
4	2	1	0	2
All stages	16(9%)	6(3%)	11(6%)	22(13%)

brachytherapy) was given with reduced fields based upon radiological or surgical findings. 10 patients (6%) received their treatment in 3 phases with further reduction in field size for the final phase at the discretion of the planning oncologist. 49 patients (28%) had treatment in a single phase only.

Shielding with multi-leaf collimators was used with increasing frequency from 2000 onwards. For the purposes of clarity each area shielded is referred to as a shielding “block”. Shielding was typically to the superolateral/inferolateral corners of the anterior and posterior fields and to three corners of the lateral fields to shield small bowel, rectum and sacrum. An example case is shown in Figure 1. 63 patients (36%) had no shielding, 47 (27%) had 2 shielding blocks and 58 (33%) had 3 or more blocks during their treatment. In seven cases the original planning films were unavailable so shielding is unknown. Radiotherapy planning in the vast majority of cases was using orthogonal films with virtual simulation being introduced during 2006.

Twenty (11%) patients received an additional boost to the parametrium matched to the 60 Gy isodose, with a typical dose of 5.4 Gy in 3 fractions. Two patients with involved paraortic nodes on imaging also received para-aortic radiotherapy.

Results

Median follow-up was 36.4 months (1.8-108.6) with median follow-up for those alive at time of analysis of 46.4 months. Thirty-eight patients (22%) had died at the time of analysis. Five patients were alive with disease. Overall survival at 3 years (Figure 2) was 73.7% (95% Confidence Interval (CI)=65.9-79.9%), with 3-year survival for stage I of 89% (Hazard Ratio (HR), reference group=stage 1). Stage 2 of 76% (HR=1.81; CI=0.80-4.12) and stage 3 of 51% (HR=4.86; CI=2.07-11.40). Recurrence-free survival (RFS) at 3 years (Figure 3) was 71.6% (CI=63.3-78.4), with RFS for stage 1 of 85% (HR, reference group), stage 2 of 74% (HR=1.72; CI=0.80-3.71) and stage 3 of 41% (HR=4.05; CI=1.81-9.08). Pattern of recurrence is shown in Table II. This correlates with a central control rate at 3 years of 91% overall, 99% for stage 1, 95% for stage 2 and 84% for stage 3.

Late toxicity. In total 22 (out of 175) patients experienced 28 episodes of grade 3-4 late toxicity, giving a significant late toxicity (SLT) rate of 13% overall. Grade 1 and 2 toxicities

Table III. *Incidence of late complications in the study population.*

	0-2 shielding blocks (n=110)	≥3 shielding blocks (n=58)	Total	
Grade 3	4 (4%)	5 (9%)	9 (5%)	
GI	1	4	5	
GU	3	1	4	
Grade 4	17 (15%)	2 (3%)	19 (11%)	
GI	6	1	7	
GU	6	0	6	
Bone	4	1	5	
Renal	1	0	1	
Total	15 patients (14%)	7(6%)	22 (13%) patients	
	1 phase (n=17)	2 phase (n=73)	Post-op N=47	Primary n=128
Grade 3	1	4	2	5
Grade 4	4	5	0	15
Total	5 (29%)	9 (12%)	2 (4%)	20 (16%)

are not presented herein as they were unreliably documented in the notes. There were no treatment-related deaths.

The incidence of SLT by site and severity is shown in Table III. 5.7% of patients had grade 3 or 4 genitourinary, 0.5% renal, 6.9 % had grade 3 or 4 bowel and 2.9% had grade 4 skeletal complications. 5 (2.9%) patients had grade 3 or 4 complications affecting more than one organ.

Only 32% of patients receiving post-operative treatment required brachytherapy, as opposed to 84% receiving primary chemoradiation. SLT in patients receiving chemoradiotherapy as primary therapy was 16%, as opposed to 4% treated post-operatively shown in Table III. The difference was significant ($p=0.03$) using Chi-squared analysis. Table IV shows the effect of shielding and phases on toxicity. 15 patients (14%) developed grade 3 or 4 toxicity with <2 shielding blocks compared to (6%) if ≥3 blocks were used. There is a statistically significant decrease in late toxicity with the use of shielding ($p=0.01$; Chi-square test). The effect of phases is examined for patients who received standard 50.4 Gy of EBRT without parametrial or paraortic treatment. Thus, these patients are largely primary treated. Although there appeared to be a slight trend towards decreased late toxicity with two-phase treatments showing serious toxicity rates of 13%, as opposed to 27% of single-phase treatment, this finding was not significant ($p=0.58$; Fisher's Exact test).

Discussion

The present study is, to date, the largest retrospective review of chemoradiation for cancer of the cervix from a single UK centre.

Figure 1. Virtual simulation images for primary treatment illustrating the use of shielding and phases of EBRT (Phase 1=a+b, Phase 2=c+d). The specific patient was recorded as having five shielding “blocks” based on phase 1 shielding.

Table IV. Effect of phases and shielding on late toxicity.

	1 phase (n=17)	2 phase (n=73)	0-2 shielding blocks (n=110)	≥3 shielding blocks (n=58)
Grade 3	1	4	2	5
Grade 4	3	5	13	2
Total	4(27%)	9(13%)	15 (14%)	7(6%)
	$p=0.58$ (Fisher's Exact test)		$p=0.01$ (Chi-square test)	

In the original report by King *et al.* 3-year survival rate was reported as 87% with a 3-year RFS of 75%. Ten percent of patients experienced serious late grade 3-4 toxicities. In this cohort patients were categorised as early (IIA or less)- or late-stage with 3-year survival for early-stage of 100% and of 79% for late-stage and RFS of 90% for early-stage *versus* 66% for late-stage disease. As this method of categorisation is not consistent with other published work we have chosen

to report survival data by FIGO stage. There has been little change in patient characteristics at our Centre in terms of stage, nodal status, histology and the percentage of patients being treated post-operatively since 1999.

Comparison of our results with the original randomised trials of chemoradiation is hindered by differences in treatment, patients' characteristics, and methods of reporting. However our overall and disease-free survival is broadly consistent with,

Figure 2. Overall survival.

Figure 3. Progression-free survival.

or better than those found in these trials. The GOG 120 update (16) reports 30-month OS of 70% for the cisplatin CRT arm and PFS of 63%, but the trial did not include stage 1b and IIa and over 40% of patients were stage 3 or above. The RTOG 90-01 trial results, which were updated in 2004 (17), revealed an OS of 73% at 5 years, but stage 1b was again excluded. Significant late toxicity was identical to ours.

Other non-randomised studies have reported patients treated with HDR or LDR brachytherapy along with concurrent chemoradiation. All studies included less than 100 patients. Tan and Zahra (18) reported on 74 patients treated in Cambridge between 1999 and 2003. They reported 5-year survival by stage of 58.3% (I) 69.9% (II) and 20.8% (III), with an overall 5-year survival of 54.6%. Median duration of follow-up was longer than our own (64 vs. 46.4 months for surviving patients), but this cannot explain this discrepancy. Thirty-eight percent of the Cambridge patients were node-positive at diagnosis compared to 21% of our own and this may account for poorer outcomes. However, this is not borne-out by the difference in pelvic control rates, particularly in stage 3 patients (33.3% versus 71%), although numbers in this stage are very small. It is possible that the difference is caused by the higher BED of our brachytherapy due to higher dose rate.

Parker *et al.* in Cardiff reported on 92 patients treated with HDR brachytherapy (four 6-Gy insertions) (19). OS rate was 72% at 2 years and 55% at 5 years. The Local control (LC) rate was 76% at 2 years and 67% at 5 years. Spensley *et al.* (20), reported on 70 patients treated between 2000 and 2003. Overall survival was 70% for all groups and PFS 67/71/66%, with pelvic control rate of 83/78/74% for stages I, II and III respectively. Thus, control rates for our study are comparable and indeed better for early-stage disease, possibly due to higher BED of treatment. Similarly the local control rates for patients having surgery and post-operative chemo-radiation were very high. The RCR audit reports 5-year overall survival of 55% but 3-year figures are very similar to our own (74, 71 and 51% for stages I, II and III). Stage 1 survival was better in our cohort and this may be reflective of a better local control rate overall (91% vs. 80%).

Looking at toxicity, our rates are again comparable to other published data, with an overall serious toxicity rate of 13% compared to 10% in both our original report and the RCR audit. Cambridge reported serious toxicity rate of 18.3%, and Chen *et al.* 14.3% in their CRT arm. Both Manchester and Cardiff reported lower late toxicity rates (9.3 and 4%) but neither reported pelvic fracture as a late toxicity. Both groups treated to a lower BED than ourselves (87 and 91.5), and this is reflected in the lower local control rates, particularly for early-stage disease.

It is of note that our results are consistent with the RCR audit in demonstrating lower SLT rates in patients treated post-operatively than those receiving primary chemoradiation,

despite a commonly held belief that combined surgery and radiotherapy result in an increase in morbidity. This may partly be due to patients having surgery when being in earlier-stage than those having upfront chemoradiation.

We demonstrated a significant improvement in toxicity with increased shielding and a trend in favour of multi-phase treatment. It is perhaps significant that Cambridge, who treated single-phase with no shielding and a BED similar to our own, reported higher toxicity rates of 18.3%. Our in-field recurrence rate of 13% overall and central control rate of 9% remain consistent with those reported in the 2006 study. Thus, changes in radiotherapy technique have not resulted in any deterioration in local control.

We were unable to identify any other reports of this information and our results suggest that any future comparison of intensity-modulated radiotherapy (IMRT) against conventional planning should take shielding and phases into account.

Thus far, we were unable to identify any published randomised controlled trials of IMRT *versus* conventional therapy in cancer of the cervix, and we are aware of only one that is currently recruiting (21). Numerous studies have reported on the benefit of IMRT in terms of reduction in dose to organs at-risk and acute toxicity (22-24) and two comparative studies have reported late toxicities. The University of Chicago group (25) compared chronic GI toxicity in 36 patients treated with IMRT to the whole pelvis for cervical or endometrial cancer with 30 patients treated with conventional radiotherapy prior to implementation of IMRT at the Centre. Cervix and endometrial patients were included. Treatment fields and any shielding/phasing for the conventional radiotherapy group are not defined in the report. The grading system for toxicity was not RTOG/EORTC but grade 3 under the system used (severe symptoms, hospitalization, surgery required) approximates to grade 3-4. No IMRT patients complained of grade 3 toxicity and only one of the conventional RT group (3%). Toxicity of all grades was significantly higher in the conventional group (50% vs. 11.1%). However, duration of follow-up in the IMRT group was only 19.6 months as opposed to 30.2 months.

Memorial Sloan Kettering (26) has shown no grade 3 or higher toxicities in 34 patients with a median follow-up of 44 months. They reported 3-year and 5-year disease-free survival (DFS) of 91.2% with overall survival (OS) 91.1% in patients treated with post operative IMRT (Median dose of 50.4 Gy) and concurrent CRT (cisplatin). Other groups (27, 28, 29) have also shown lower grade 3 or higher toxicity with 3 year OS of 78% in stage I-IVA cervical cancer treated with IMRT with DFS of 69% and 67.6%.

Inter-fraction organ motion (uterine /cervical mobility) poses a high risk of geographical miss with IMRT (29, 30) and there is not long-term data yet to show no significant detriment to local control. In addition cautious interpretation of these results is required as no skeletal events have been

reported by most groups with short follow up and retrospective nature of these studies being the limitations.

Several phase I/II/III trials comparing IMRT with concurrent cisplatin (dose escalation studies) *versus* conventional chemo radiotherapy are currently underway and recruiting. The results however are not expected to be available in the near future and even longer until long term toxicity, survival and loco-regional control rates will be available. Any future trials comparing IMRT to conventional/virtual simulation should ensure that 2-phase technique and shielding are used in the control arm. We acknowledge the limitation of the present study in its retrospective nature and the application of the grading scores to the available documentation which is a potential source of bias.

Conclusion

Chemoradiotherapy is now established as an effective and well-tolerated therapy for cancer of the cervix. Our results provide further confirmation of this fact with a large real-life series. We also demonstrated that shielding of bowel and sacrum, as well as the use of multiple phases in EBRT not only reduce dose to organs at-risk, but that this can be correlated with a reduction in late toxicity without compromising local control or survival. Recent evidence from feasibility and dosimetric studies for the use of intensity-modulated radiotherapy in cervical cancer treatment is promising, although careful consideration needs to be given to contouring, organ motion, setup, simulation and the use of image-guided radiotherapy. Long-term follow-up of results need to be examined before adoption of intensity-modulated radiotherapy for management of cervical cancer.

Conflicts of Interest

Sundus Yahya, Lubna Bhatt, Margaret King, Sarah Pirrie, Ruth Wyatt, Muhammed Suhail Anwar, Ahmed El-Modir and Indrajit Fernando declare that they have no conflicts of interest.

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