RESEARCH ARTICLE

Definitive Concurrent Chemoradiotherapy in Cervical Cancer - a University of Malaya Medical Centre Experience

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Abstract

Background: The efficacy of concurrent chemoradiotherapy in the treatment of locally advanced cervical cancer is well established. We aimed to investigate the long-term efficacy of definitive concurrent chemoradiotherapy for cervical cancer in the University of Malaya Medical Centre. Materials and Methods: A cohort of 60 patients with FIGO stage IB2-IVA cervical cancer who were treated with definitive concurrent chemoradiotherapy with cisplatin followed by intracavitary brachytherapy or external beam radiotherapy (EBRT) boost between November 2001 and May 2008 were analysed. Patients were initially treated with weekly intravenous cisplatin (40mg/m^2) concurrent with daily EBRT to pelvis of 45-50Gy followed by low dose rate brachytherapy or EBRT boost to tumour. Local control rate, progression free survival, overall survival and treatment related toxicities graded by the RTOG criteria were evaluated. Results: The mean age was 56. At the median follow-up of 72 months, the estimated 5-year progression-free survival (PFS) (median PFS 39 months) and the 5-year overall survival (OS) (median OS 51 months) were 48% and 50% respectively. The 5-year local control rate was 67.3%. Grade 3-4 late gastrointestinal and genitourinary toxicity occurred in 9.3% of patients. Conclusions: The 5-year PFS and the 5-year OS in this cohort were lower than in other institutions. More advanced stage at presentation, longer overall treatment time (OTT) of more than fifty-six days and lower total dose to point A were the potential factors contributing to a lower survival.

Keywords: Cervical cancer - concurrent chemoradiotherapy - progression free survival - overall survival

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Introduction

Cervical cancer is the third most common female malignancy with estimated 529,800 new cases in 2008 (American Cancer Society, 2011). It is still the second most common female malignancy in Malaysia with 847 new cases (8.4%) reported in the National Cancer Registry in 2007 (Zainal and Nor, 2011). While a decline in incidence and mortality were observed in developed countries owing to successful screening and the introduction of human papillomavirus (HPV) vaccines, it remains a major health problem in developing countries with an estimated 275,100 cancer-related deaths in 2008 (American Cancer Society, 2011).

Although prognosis and survival are dependent on the cancer stage, the quality of care provided also influence the overall outcome. Surgery alone provides excellent cure rates for microinvasive disease and FIGO (International Federation of Gynecology and Obstetrics) stage IA with 5-year survival rate greater than 95% (Haffty et al., 2009). For localised disease (FIGO IB1 and non-bulky stage IIA) radical surgery or radical radiotherapy (RT) offers similar 5-year survival rate of 85-90% (Landoni et al., 1997). Concurrent irradiation with cisplatinum-based chemotherapy (CCRT) as the gold standard for treatment of locally advanced stage FIGO IB2-IVA has been established since almost 15 years with results from several randomized trials and meta-analyses that confirmed the benefit. In 1999, the National Cancer Institute issued an announcement that 'strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women requiring radiation therapy for treatment of cervical cancer' (National Cancer Institute, 1999). This was based on collective evidence from four pivotal phase III trials, which demonstrated superior local control, a 30-50% decrease in risk of death and 10-12% improvement in overall survival with CCRT compared to RT alone (Morris et al., 1999; Rose et al., 1999; Peters et al., 1999; Whitney et al., 1999). A more recent Cochrane meta-analysis reported improvement in 5-year survival by 6% overall absolute benefit. Chemoradiotherapy reduces local and distant recurrence rate in addition to increasing progression-free-survival (PFS) but all these are achieved at the expense of an increased rate of acute toxicity (Chemoradiotherapy for Cervical Cancer Meta-analysis

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Collaboration, 2010).

The superiority of this radical approach was demonstrated in trials conducted primarily in developed countries, involving selected patients and in well-equipped health facilities. In an actual clinical setting in a developing country like Malaysia, varied patients' background, disease and treatment factors such as poor performance status and limited resources for optimum management of treatment toxicities may affect patient tolerance to treatment. The safety and benefits of such treatments remain untested and under-reported. A recent published local data from University of Science Malaysia Hospital (HUSM) in Kelantan, Malaysia reported a 5-year overall survival of 39.7% with median survival of 40.8%. However, the specific survival of patients treated with definitive CCRT was not reported (Nuradhiaty et al., 2013).

Treatment with CCRT for cervical cancer in University of Malaya Medical Centre (UMMC) was fully commenced in 2001. We herein examine the effectiveness of CCRT in treating locally advanced cervical cancer patients in our institution over a seven-year period from 2001-2008.

Materials and Methods

Data collection was initiated following the University of Malaya Medical Centre Ethics Committee approval (UMMC MEC Ref. No: 685.19). All patients with biopsy proven, stage IB2-IVA cervical cancer who received definitive CCRT were identified. Pretreatment assessment included a complete medical history and full physical examination, complete blood count, renal and liver function tests, and review of histopathology reports. Staging was based on clinical evaluation and procedure as per International Federation of Gynecology and Obstetrics (FIGO) recommendations (Bernadet et al. 2000). Tumour staging consists of a minimum of chest x-ray, liver ultrasound and intravenous urography of the kidneys or contrasted computed tomography (CT) scan or magnetic resonance imaging (MRI) of the pelvis as well as further imaging for distant metastases when deemed appropriate. All patients received whole pelvic external beam radiotherapy (EBRT) to a total dose of 45Gy to 50Gy in 1.8Gy to 2Gy per fraction delivered over five to six weeks with either four-field box technique or anterior posterior parallel opposing portals using 6-10MV x-rays. This was followed by intracavitary brachytherapy prescribed to Manchester point A, defined as 2 cm above the lateral vaginal fornices and 2 cm lateral to central uterine tube. Whenever brachytherapy was not possible, EBRT boost dose to the primary tumour was prescribed. Overall treatment time (OTT) was aimed at not exceeding 56 days. Four to six doses of intravenous cisplatin at 40 mg/m^2 were administered to all patients. Patients were assessed weekly for acute toxicity. Acute side effects were graded according to National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) version 2.0.

Follow up and statistical analysis

Patients were reviewed at six weeks after completing treatment and subsequent follow-up involved alternate clinic visits between Oncology and Gynaecology Oncology clinic every three months in the 1st year, six monthly in the 2nd and 3rd years and yearly thereafter. Late radiation toxicity was scored using the European Organization for Research and Treatment of Cancer and Radiation Therapy Oncology Group (EORTC/RTOG) scoring system. Clinical, histological and radiological evidences of tumour recurrence or radiotherapy-related complications were also assessed. The PFS was defined as, time from the date of the treatment commenced to time of relapse or death, whichever comes first. The OS was defined as time from the date of treatment commenced to death from any cause. The PFS, OS and local control (LC) were analysed using the Kaplan Meier method. Risk factor for death was estimated using univariate and multivariate analysis.

Results

From November 2001 to December 2008, 60 patients were treated with definitive CCRT in UMMC. The mean age was 56 years (range 34-77 years). All patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 prior to therapy. Patients' characteristics are depicted in Table 1.

Mean EBRT dose to target volume was 71.5Gy (range 45Gy-88Gy). Forty-six patients received LDR brachytherapy while 14 patients were deemed not suitable for the procedure and these patients received boost to the tumour with EBRT to a mean point A dose of 56.7Gy (range 45Gy-70Gy). Mean brachytherapy dose was 24.3Gy with median 30Gy. Treatment details are shown

Table 1. Patient Characteristics

Characteristic		No. of Patients (%) n=60
Age	<60	40 (66.7)
	≥60	20 (33.7)
Race	Malay	13 (21.7)
	Clinese	33 (55)
	Indian	11 (18.3)
	Others	3 (5)
FIGO	I	1 (1.7)
	II	27 (45)
	III	24 (40)
	IV	8 (13.3)
*ECOG performance status	0	30 (50.5)
	1	17 (28.3)
	2	13 (21.7)
Nodal status	Negative	34 (56.7)
	Positive	21 (35.0)
	Unknown	5 (8.3)
Treatment details	EBRT alone	14 (23.3)
	EBRT+brachytherapy	46 (76.7)
EQD2 to point A	<80Gy (range 45Gy-78Gy)	45 (75)
	≥80Gy (range 80Gy-88Gy)	15 (25)

*ECOG indicates the eastern cooperative oncology group

Table 2. Acute and Late Toxicity Effects

Site/RTOG grade (3-4)		No. of patients (%)
Acute	Gastrointestinal	3 (5)
	Bladder	2 (3.3)
	Hematology	2 (3.3)
Late	Rectum	5 (8.3)
	Bladder	8 (13.3)

in Table 2.

Treatment toxicity

Majority of the documented acute toxicity were grade 2 and lower with acute all grade for gastrointestinal (GI) toxicity of 95%, acute hematological toxicity 96.7%, and acute genitourinary (GU) 96.7%. Seven patients required hospitalization; two for ileus, one for acute diarrhoea, two for acute cystitis complicated by urinary tract infection and two for grade 3 anaemia requiring blood transfusion. There was no treatment related death. Grade 3 and 4 acute and late toxicity effects are listed in Table 2. Vaginal stenosis was the most common late effect observed affecting almost half of the study cohort. Five patients developed grade 3 and 4 radiation proctitis necessitating surgery for permanent stoma. Grade 3 and 4 radiation cystitis affected five patients with four patients requiring ileal conduit diversion surgery.

About 28.3% of the patients exceeded the recommended OTT of 7 weeks due to various reason including the unplanned public holiday, patients' compliance, and time taken to re-planning for EBRT boost for those patients deemed unsuitable for brachytherapy.

All patients received at least four cycles of chemotherapy.

Table 3. Pattern of Treatment Failure in the Study Population

Characteristics		No of patients *n=29 (%)
Type of recurrence	Local only	13 (21.7)
	Local and distant metastases	6 (10.0)
	Distant metastases only	10 (16.7)
Local recurrent pattern	In field	13 (21.7)
	Outside field	3 (5)
	Both in-field & outside field	1 (1.7)
#Distant metastatic site	Liver	5 (8.3)
	Lung	4 (6.7)
	Bone	4 (6.7)
	Other sites	4 (6.7)

**note: total number of patients is only for the total recurrence

Table 4. Multivariate Analysis of Risk of Death

Risk factor	p-value	HR	95% CI
Age (<60 vs ≥60)	0.04	2.35	1.04-5.30
Stage (I vs II vs III vs IV)			
Overall treatment time (<56 vs ≥56)	0.82	0.91	0.41-2.039
BED EQD2 at point A (<80Gy vs ≥80Gy)	0.45	0.72	0.30-1.71
Lymph node status	0.11	0.51	0.23-1.15

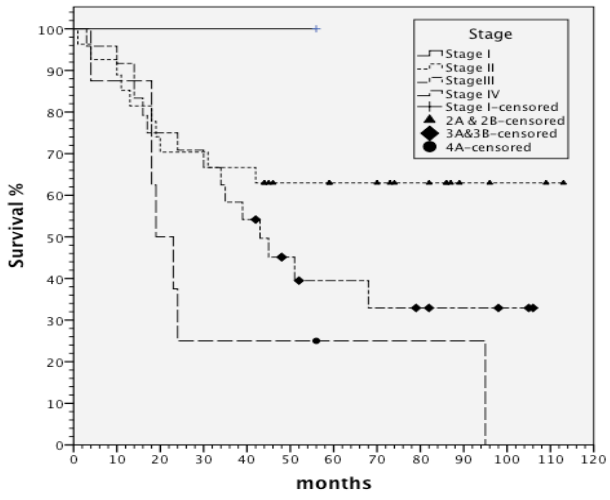

Figure 1. Overall Survival Based on Clinical Stage

Outcomes and Survival Analysis

At median follow-up of 79 months we observed disease relapse in a total 21 patients (35%). These patients received further palliative treatment either with systemic chemotherapy, local radiotherapy or best supportive care. Eleven patients were lost to follow up and thus were censored in the analysis.

Three local recurrences occurred outside the radiation fields at the introitus. The most common sites of distant metastases were liver followed by lungs and bones. Details of the treatments failure pattern are shown in Table 3.

The estimated 5-year PFS for the study population was 44% with median PFS of 39 months. The estimated 5-year OS in this study cohort was 48% with median survival of 51 months. The risk factor for death was estimated using univariate and multivariate analysis. The factor considered includes age (<60 years, ≥60 years), FIGO staging (FIGO I-IV), overall treatment time (≤ 49 days, >49 days), BED of EQD2 to point A (<80Gy, ≥80Gy) and lymph node involvement are shown in Table 4. Kaplan Meier plot for the overall survival based on clinical stage and age are shown in Figure 1 & 2.

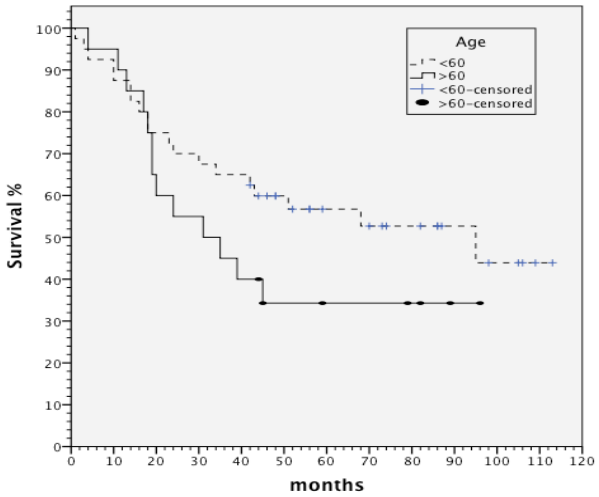

Figure 2. Overall Survival Based on Age

Discussion

Cervical cancer is a significant health concern for women in Malaysia. The Malaysian government has advocated the conventional pap-smear screening programme since 1969 but until today, it is still based on opportunity. Resource limitation and lack of knowledge was the main barrier to its success. Vaccination against HPV subtypes 6,11,16 and 18 was only recently implemented as a national healthcare policy under the National HPV Immunisation Programme in 2010. Free vaccines are now provided to the girl aged 13 and above (Information and Documentation System Unit, Malaysian Ministry of Health, 2010). Prior to 2001, RT alone was the primary treatment offered at our centre

to patients with non-metastatic cervical cancer. Limited resources prohibited us from offering CCRT despite the emergence of robust evidence showing the superiority of this approach against RT alone as early as 1999 (Morris et al., 1999; Peters et al., 1999; Rose et al., 1999; Whitney et al., 1999).

The chemotherapy used in our study was single agent weekly intravenous cisplatin 40mg/m^2. Some other agents have been tested included 5-fluorouracil, hydroxyurea, bleomycin, mitomycin, etoposide, gemcitabine, paclitaxel and docetaxel either as single agent or in combination with cisplatin but at the expense of increased acute toxicity (Morris et al., 1999; Whitney at al., 1999; Rose et al., 1999; Peters et al., 2000; Farnaz et al., 2013; Qing-Hua et al., 2013). The study by Qing-Hua et al (2013) has shown that combination of cisplatin and docetaxel gave higher response rate with 64.3% complete response (CR) rate as compared to radiotherapy alone with CR rate of 32.1%. The only setback for this trial was the comparison arm was radiotherapy alone, which was not considered the standard treatment for cervical cancer in this concurrent cisplatin-based radiotherapy era. Amourzegar Hashemi et al (2013) has conducted a study using the combination of low dose gemcitabine and cisplatin in the treatment of locally advanced cervical cancer (stage IIB to stage IVA) in the Imam Khomeini Hospital Tehran, Iran and thirty patients were recruited from September 2009 to September 2010. The total radiotherapy dose to point A given was between 85-90Gy. The complete response rate was 73% with the combination gemcitabine, cisplatin and radiotherapy regime. The toxicity rate was also high as evidenced by the need for treatment interruptions in 26.7% of the patients and the hospitalization rate due to hematologic toxicity was 16.7%. The survival rate was not reported and results are still pending (Amouzegar Hasemi et al., 2013). A study in Thailand by Pesee et al. (2013) has tested the usage of thai herbal medicine (Vilac Plus G716/45) in combination with radiation therapy in treating poor performance status cervical cancer stage IIIB and stage IV as palliative treatment. Thirty patients were recruited in this trial between March 2003 to June 2006, and the 5-year survival for stage IIIB was 52% when compared with 34-54.8% from historical data (Arai et al., 1992; Lorvidhaya et al., 2000; Rose et al., 2007; Pesee et al., 2010). However, all patients received good radiation therapy dose to point A with a mean of 86Gy which could have explained the good 5-year OS in addition to the radiation sensitivity and antioxidant effects produced by the Thai herbs (Pesee et al., 2013).

All surviving patients were followed-up for at least five years. At median follow up of 79 months, 5-year PFS was 44%. The previous studies (Morris et al., 1999; Rose et al., 1999; Whitney et al., 1999) reported a higher 5-year PFS ranging from 56-65%. The 5-year OS from our study was 48%. These results were also lower compared to the results reported by (Morris et al., 1999; Rose et al., 1999; Whitney et al., 1999) which, showed 5-year OS of 60 - 70%. In 2007, a multicentre study involving countries like Malaysia, Japan, China, Indonesia, Philippines, Thailand and Vietnam reported a 5-year OS rate of 53.3% (Takashi et al., 2007). The more recent in publication by Shingo et al. (2013) in their multi-institutional phase 2 study of CCRT for locally advanced cervical cancer in East and Southeast Asia also involving countries such as Malaysia, Japan, Indonesia, Korea, Vietnam, Philippines, China and Thailand, reported a 5-year OS of 55.1%. We observed inferior results compared to studies done by Takashi et al. (2007), and Shingo et al. (2013), which involved treating similar population with with CCRT in a similar study population. The difference observed was, their study enrollment was based on tumour size, as compared to FIGO staging used in our study. There was a higher proportion of FIGO stage III and IVA (i.e. 53.3%) in our study population (53.3%) as compared to other studies (range 30-50%), which was very likely to have affected the outcome (Morris et al., 1999; Rose et al., 1999; Whitney et al., 1999; Shingo et al., 2013). Our study showed a clear inferior result compared to the other study done previously. Furthermore, the other studies comparatively have higher proportion of younger patients age <60 years (range 75-85%) as compared to our study populations 66.7% with patients age <60 years, which in turn resulted in poorer survival.

Nuradhiathy et al. (2013) reported a 5-year survival rate of 39.7% for patients diagnosed with cervical cancer for all stages and receiving at least one form of treatment in their hospital in Kelantan, Malaysia. However, their study analysed all patients with diagnosed cervical cancer regardless of the mode of treatment and not specifically pertaining to CCRT. Similar analysis on survival for cervical cancer patients in Indonesia and in Manila, reported a 5-year survival of 40.3% and 34% respectively but did not specify the mode of treatment received by the patients (Sirait et al., 2003; Laudico et al., 2011).

With 17 local recurrences, the 5-year local control (LC) rate of 68%, which was also inferior when compared to figures from the other study (range 76% to 91%). Greater LC rate was obtained in FIGO stage IB2 to IIA cancer with more advanced stage IIB to IVA showed higher trend to recur locoregionaly and/or distantly. Distant failure rate of 26.7% were also higher than other studies (8% to 19%) (Morris et al., 1999; Peters et al., 1999; Rose et al., 1999; Whitney et al., 1999; Takashi et al., 2007; Shingo et al., 2013).

The recurrence pattern was predominantly locoregional (28.4%) with a high rate of in-field recurrence (21.7%). This is not surprising since 14 patients did not undergo brachytherapy suggesting suboptimal dose to the primary tumour. The commonest metastatic sites in our study cohort were the lung and bone. Most published trials did not specifically mention the sites of distant metastases, except for the studies by Rose et al. (1999) and Whitney et al. (1999), which was the lung.

Several reasons may account for the apparent inferior results in this study. Brachytherapy allows delivery of high dose radiotherapy directly to the tumour, which results in increased probability of cell kill and improved local control. The delivery of EBRT alone cannot compensate for the absence of brachytherapy, due to dose-limiting toxicity of organs such as small bowel, bladder and rectum. Lower overall total dose may have contributed to the poorer outcome in our population. Based on the

recommendation by American Brachytherapy Society (ABS), the recommended dose to point A for stage IB2 onwards is 80 to 90Gy (Akila et al., 2012). The mean total dose received by our study cohort was 71.5Gy, which was lower by 10-20Gy to the recommended dose thus may result in a lesser tumoricidal effect. In larger studies, most patients received brachytherapy in addition to EBRT, bringing the total dose to Point A to 65 to 95Gy (De Vita et al., 2011). In contrast, only 75% of our patients had brachytherapy as brachytherapy had to be deferred in patients with bulky persistent tumour or had poor general condition. The estimated total radiotherapy dose to point A in our study was lower, ranging from 45 to 88Gy.

The latest recommendations by ABS suggested the implementation of 3D-imaging for treatment planning in addition to the documentation of dose at point A. The goal should be good coverage of the involved region (i.e. a D90-isodose that covers 90% of the tumour target volume, Gyα/β10) with EQD2 of ≥80Gy for patients with good or partial response and tumour less than 4cm and dosage of ≥85- 90Gy for non responders or if the tumour is more than 4cm by the time of brachytherapy to either point A or the D90 to optimized local control (The Royal College of Radiologists, 2009; Akila et al., 2012).

The duration from the initiation of treatment to completion is typically between 8-10 weeks in many large studies. The ideal OTT of the entire course of EBRT and brachytherapy should be kept within 7-8 weeks to offset accelerated tumour repopulation that may occur during prolonged treatment breaks. The importance of OTT as a factor affecting treatment outcomes is well established from various radiobiology and clinical studies. Prolonged course of radiation results in a lower pelvic tumour control and survival. Perez et al highlighted the impact of prolonging OTT beyond seven weeks. They estimated loss of local tumour control probability (TCP) by 0.37% per day in stages IB and IIA, 0.68% per day in stage IIB, and 0.54% for stage III patients who were treated with total radiotherapy dose of more than 85Gy to point A. This was found to be equivalent to a loss of 0.6-0.7Gy per day (Fyles et al., 1992; Perez et al., 1995; Petereit et al., 1995). The effect of prolonged and interrupted treatment on patients survival was recently published based on experience from Srinagarind Hospital in Thailand which further supports the reduced survivals. A recent publication based on an treatment experienced from Srinagarind Hospital in Thailand further supports the effect of prolonged and interrupted treatment which results in reduced survival of patients as evidenced by more superior 3-year OS of 63.29% in the uninterrupted group compared to the interrupted group which showed a drop to 55% (Krusun et al., 2014). Unfortunately, this aim was often not met in daily clinical practice as demonstrated by our study. Only 71.7% of the patients managed to complete treatment within 56 days with HR 0.91 (95% CI, 0.41-2.04) of obtaining a significant survival advantage over patients who exceeded 56 days. The HR although not significant but it has shown the pattern towards supporting the better survival in the patients who completed RT within 56 days based on log-rank test.

The regimen was well tolerated and there was no treatment-related death. The meta-analysis by Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration (2010) reported that 16 trials that did report on the acute toxicity were analysed. Based on the data available, the most common acute toxicity was hematologic toxicity including white blood cells (WBC), platelets, and hemoglobin toxicities as well as genitourinary toxicities and skin toxicities. Based on the meta-analysis the serious hematologic toxicity increased by two to 10-fold depend on the individual trials. The hematologic toxicity was also more prominent in the combination regimen especially in a combination involving hydroxyurea (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2010). The main acute haematological toxicity in our centre was anaemia, but mostly low grade and only 3.3% of patients developed serious hematologic events and needed hospitalization. The most common acute gastrointestinal and genitourinary toxicity in our patient cohort was diarrhea and acute cystitis respectively. The patients with grade 3 toxicities had to be admitted to ward to receive appropriate treatment.

The most common late toxicities were cystitis (13.3%) and proctitis (8.3%). There were two patients who developed recto-vaginal fistulas and one patient developed vesico-vaginal fistula. This is certainly higher than the recommended TD5/5 (severe 5% complication rate in 5-years after completion of RT) by The Radiotherapy Oncology group (RTOG). The dose to point A received by all these patients with grade 3-4 toxicities were between 75-95Gy which may have contributed to the developments of grade 3-4 late radiation effects on the bladder and rectum. Reports on late toxicities are scarce. The meta-analysis by Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (2010) suggested a fairly low incidence of severe late toxicities, affecting a mere 1-3 % of all cases. Shingo et al. (2013) reported the cumulative rates of grade ≥2 complications in their study namely for rectum was 20.2% (95% CI 10.0-30.4%), bladder was 11.7% (95% CI 4.3-19.1%) and for small bowels of 6.2% (95% CI 0.3%-12.1%) and two patient developed rectovaginal fistulas (grade 4). In their study, there was no bladder complications documented.

In conclusion, our study obtained inferior survival outcome as compared to established studies of concurrent chemoradiotherapy in patients with locally advanced cervical cancer. A better public awareness on the importance of early detection of cervical cancer as well as the implementation of image guided 3-D brachytherapy that allows better and higher dose delivery to the tumour will hopefully increase the survival of patients with cervical cancer in our centre and Malaysia in general.

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