Original article

5 year follow up study of bulky cervical cancer patients treated with chemoradiation with concomitant boost followed by radical hysterectomy

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ABSTRACT

AIM**:** To report the final outcome and complications at the end of 5 years in bulky cervical cancer patients treated with chemoradiation with concomitant boost followed by radical hysterectomy.

MATERIALS AND METHODS: 30 bulky (Stage IB2, IIA2 and IIB) cervical cancer patients were treated with concomitant boost irradiation to a total dose of 50.4Gy (180cGy/22# to whole pelvis and 90cGy thrice weekly boost to primary) along with concomitant weekly cisplatin 40mg/m^2 followed by radical hysterectomy between January and October 2012. Patients were followed up to assess the final outcome and complications.

RESULTS: 73.3% of patients attained a complete pathologic response. The median follow up is 33 months [range: 3-64months]. 20 out of 30 patients are alive and disease free. 5 patients lost for follow up. 2 patients developed local recurrence and 3 patients developed distant metastases. No major long term morbidity was seen in any patients.

CONCLUSION: Different treatment modalities were combined diligently in this study and we were able to achieve a better outcome with acceptable toxicity rates. In a resource constrained situation with limited access to brachytherapy resources, it becomes imperative to frame alternative newer treatment modalities which have the potential to save lives. Though the 5 year outcome data is encouraging, the number of patients included in our study is very small to arrive at any definitive conclusions and the results need to be tested in a larger cohort.

INTRODUCTION:

Concurrent chemoradiation followed by brachytherapy is the standard of care for bulky locally advanced cervical cancers. Despite significant advancements in the management of cervical cancers, the ultimate outcome is not optimal. Locally advanced cervical cancers especially those with tumor diameter more than 4cm are prone for loco regional recurrence. With conventional treatments, the overall 5 year survival for advanced cervical cancers is around 40% [1 – 4]. Several alternative combination modalities like neoadjuvant chemotherapy followed by radical hysterectomy, preoperative chemoradiation followed by radical hysterectomy have been tried to achieve better results.

Pathologic response rate can be assessed with surgical evaluation. A pathologic response rate ranging from 39% to 67.5% has been reported in several studies [5 – 7]. There are also studies which have shown a correlation between pathologic response rates and overall survival [8 – 10]. The advantage of adding surgery after chemoradiation includes removal of treatment resistant tumor foci. The therapeutic outcome of such alternative combination modalities has shown results at least comparable to exclusive chemoradiation. But any multimodal approach has got the potential risk of increased short term and long term toxicity profile.

In the present study we tried to evaluate the 5 year treatment results and toxicity profile of bulky cervical cancer patients treated with chemoradiation with concomitant boost followed by radical hysterectomy.

MATERIALS AND METHODS:

Between January 2012 and October 2012, 30 patients with histologically proven carcinoma of cervix stage IB2 to IIB with ECOG performance status 0-1 were treated using the concomitant boost regimen of radiotherapy with weekly chemotherapy followed by radical hysterectomy. A written informed consent and an institutional ethical committee approval were obtained prior to the study.All patients underwent examination under anaesthesia and a contrast enhanced computed tomography of abdomen and pelvis was obtained. Proctosigmoidoscopy and cystoscopy was done in patients with suspicious bladder and rectal involvement on CT scan. A complete blood profile was taken for all patients and a cardiopulmonary assessment was done before treatment.

RADIOTHERAPY

A concomitant boost irradiation of 180cgy/#/22# to whole pelvis (39.6Gy) was delivered by four field box technique and 90cgy thrice weekly boost to primary (10.8gy) was delivered by AP/PA portal to a total dose of 50.4gy. The concomitant boost dose was delivered on Monday, Wednesday and Friday of every week. All patients received weekly cisplatin dose of 40mg/m^2 along with radiation.

Weekly assessment of haematological parameters was done and RTOG acute radiation morbidity scoring criteria was used to assess the acute toxicity profile.

CHEMOTHERAPY:

All patients received weekly cisplatin dose of 40mg/m^2 along with radiation. Appropriate antiemetic regimens were prescribed for all patients. All patients attended weekly clinics and for patients with grade3/4 adverse events, cisplatin dose was reduced by 20% in subsequent cycles.

SURGERY:

A radical wertheim's hysterectomy was done in all patients 5 to 6 weeks after completion of chemoradiation. A thorough pathological analysis of surgical specimen was done to assess the extent of residual disease. The pathologic response rate was documented in all patients.

FOLLOW UP:

All patients were followed up every 3 months in the first two years with a thorough history and clinical examination. Between 3 to 5 years, patients were followed up every 6 months. RTOG late radiation morbidity scoring criteria was used to assess late toxicity. The time interval between the completion of surgery and the date of last follow up was used to assess the survival rates. Overall survival and progression free survival rates were computed using Kaplan- Meier method.

RESULTS:

30 patients with bulky cervical cancer underwent chemoradiation with concomitant boost followed by radical hysterectomy between January and October 2012. Patients were followed up subsequently. The median follow up is 33 months [range: 3 to 64 months].

PATIENT CHARACTERISTICS:

The median age of patients enrolled in the study was 46 years [range: 35 – 64years]. 63% of patients had stage IIB, 30% had stage IB2 and 7% had stage IIA2 disease. 50% of patients had tumor size between 4 – 6cm and 50% had tumor size between 6 -8cm. The estimation of tumor size was by clinical and radiological examination.

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Vaginal involvement was seen in 40% of patients. 33% of patients had bilateral parametrial involvement. Around 86% of cases were squamous cell carcinomas. There were 2 cases of adenocarcinoma and 2 cases of adenosquamous carcinoma. About 63% of patients had poorly differentiated cancers. Patient characteristics are tabulated in Table1.

S.NO	PATIENT CHARACTERISTICS	NO. OF PATIENTS	%
1	AGE: 35 – 44 years	14	46.7%
	45 – 54 years	12	40%
	55 – 64 years	4	13.3%
2	FIGO IB2	9	30%
	IIA2	2	7%
	IIB	19	63%
3	Size of the tumor		
	4 – 6cm	15	50%
	6 – 8 cm	15	50%
4	Parametrial involvement		
	Nil	11	37%
	Unilateral	9	30%
	Bilateral	10	33%
5	Vaginal involvement		
	Nil	18	60%
	Upper 2cm	12	40%
6	Histology		
	Squamous	26	86%
	Adenocarcinoma	2	7%
	Adenosquamous	2	7%
7	Grade		
	I	8	27%
	II	3	10%
	III	19	63%

TREATMENT:

A majority of 76.6% of patients completed treatment within the time frame of 4.2weeks and received 5 cycles of weekly cisplatin. A clinical and radiologic examination was done at the end of 4 weeks of chemoradiation to assess the response. All 30 patients were subjected to Wertheim's hysterectomy 4 to 6 weeks after the completion of chemoradiation. The median number of lymph nodes dissected was 7 [range: 7 – 17]

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PATHOLOGIC RESPONSE RATES:

Totally 22 out of 30 patients attained complete pathologic response (73.3%). This included 13 out of 19 patients with stage IIB disease. Gross residual disease was seen in 6 patients. One lymph node was found to be positive in 2 patients (microscopic partial response).

ACUTE TOXICITY

Gastrointestinal toxicity was the most common toxicity observed. Majority of patients experienced some form of gastrointestinal toxicity. Toxicity was graded as per RTOG acute radiation morbidity scoring criteria. The median operating time was 2 hours 15 minutes. Median blood loss was 350ml. 4 patients had significant post void residual urine. Incisional hernia was seen in 1 patient.

FACTORS ASSOCIATED WITH MORE FAVOURABLE PATHOLOGIC RESPONSE:

Patients with unilateral/nil parametrial involvement, patients with poorly differentiated cancers, patients with tumor size between 4 to 6cm, patients with normal haemoglobin during treatment had higher complete response rates.

LATE TOXICITY:

One patient had grade 1 lymphedema of lower extremity and one patient had grade 2 lymphedema of lower extremity. Other commonly encountered complications of multimodality treatment like intestinal obstruction, fistula, vaginal necrosis were not seen in any patients. 6 patients complained of mild dyspareunia.

SURVIVAL ANALYSIS:

The median duration of follow up was 33 months [range: 3 – 64months]. Local recurrence was seen in 2 patients. One patient had a local recurrence at the end of 8 months after completion of surgery and other patient had a local recurrence at the end of 2.4 years after completion of treatment. But intriguingly, both the patients had a pathologic complete response. 3 other patients developed distant metastases within a period of 3months, 7months and 3 years respectively to the bone, lungs and paraaortic nodes/lung sites and were given palliative chemotherapy but they eventually succumbed to the disease. Two of the above patients had a complete pathologic response and one patient had a partial pathologic response. 20 of the 30 patients are alive and disease free at the end of 5 years. 5 patients lost for follow up [median follow up – 5 months]. Kaplan Meier survival analysis shows a median survival time of 54 months [95%CI: 46months to 61.9months]. Kaplan Meier survival curve is depicted in Figure1.

PROGNOSTIC FACTORS FOR LOCAL RECURRENCE / DISTANT METASTASES:

Out of 5 patients who progressed and died, 4 patients had tumor size between 6 – 8cm. All patients had bilateral parametrial involvement. 2 patients had well differentiated cancer, one patient had moderately differentiated cancer and 2 other patients had poorly differentiated cancer. 4 patients had a pathologic complete response and one patient had a partial pathologic response. The pathologic response rate did not show any significant influence on the local recurrence or distant failure.

DISCUSSION:

Generally, optimising primary treatment could be more rewarding than a deliberate post treatment surveillance or aggressive salvage therapy. Bulky cervical cancers are prone for local recurrence. The risk for central disease recurrence is dependent on the tumor size [11, 12] and the risk continues to remain greater for patients with

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bulky tumors even beyond 3 years. Hence, newer treatment strategies need to be assayed to improve the therapeutic outcome of these patients.

Several studies have evaluated the role of adjuvant hysterectomy after either radiation or chemoradiation with or without brachytherapy. The largest single institution series from Italy [13] reported a five year DFS of 83% and overall survival of 90% in locally advanced cervical cancers treated with trimodality treatment. A 5 year overall survival of 78% was observed in 100 locally advanced cervical cancer patients treated with preop chemo radiation followed by radical surgery at the catholic university of Rome[14].

Trimodality treatment for cervical cancer is criticized for the morbidity associated with surgery. Cyril Touboul et al [15] reported increased morbidity in patients undergoing hysterectomy after neoadjuvant chemoradiation in stage IB2 – IVA cancers. The dose of external beam radiotherapy used was 45Gy with parametrial boost of 10-15Gy followed by brachytherapy. A surgical morbidity rate of 14% was reported by Rouzier et al [16] in patients treated with radical surgery after radical radiotherapy and chemoradiation.

The morbidity associated with adjuvant hysterectomy is determined by the extent of residual disease, the dose of preoperative radiotherapy, addition of brachytherapy, combination with chemotherapy and radicality of surgery. None of our patients had major surgical morbidity like fistula, hydronephrosis or intestinal obstruction. Different treatment modalities were combined diligently in this study and we were able to achieve a better outcome with acceptable toxicity rates. In a resource constrained situation with limited access to brachytherapy resources, it becomes imperative to frame alternative newer treatment modalities which have the potential to save lives. These modalities should be atleast comparable to the standard treatment in terms of outcome or morbidity, if not superior and should be acceptable by the patient population. Though the 5 year outcome data is encouraging, the number of patients included in our study is very small to arrive at any definitive conclusions and the results need to be tested in a larger cohort.

CONCLUSION:

Improving the therapeutic outcome of bulky cervical cancers is a big challenge. Delivering high dose to the tumor using image guided brachytherapy, incorporation of newer chemotherapeutic agents and molecular targeted therapies and addition of adjuvant hysterectomy are being tried to improve the final outcome. In future, a better understanding of the epigenetics of cervical cancer may help individualize the treatment and enhance cure rates.

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