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Original Article

Retrospective Analysis to Assess the Effect of Hyperthermia along with Radiotherapy on the Outcomes of Treatment in Locally Advanced Carcinoma Cervix

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Abstract

Aims: The present study was aimed to assess the impact of Hyperthermia along with Radiotherapy on the outcomes of treatment in locally advanced carcinoma cervix. **Materials and Methods:** Present study is a retrospective analysis of cancer cervix patients treated with radiotherapy and hyperthermia+/- chemotherapy from Jan 2012 to Jan 2018. Total twenty patients were included in this study. Among Twenty patients 12 patients received (HT+RT) while 8 patients received chemotherapy along with hyperthermia and Radiotherapy, (HT+RT+CT). All patients received EBRTdose 50 Gy in 25 fractions and 5 weeks. All patients were prescribed once a week or twice a week hypertermia for 5 weeks along with radiotherapy. Boost was given to primary disease either via brachytherapy or EBRT. **Results:** Complete response observed 75% of patients in RT+HT group. Similarly in RT+HT+CT group also 75% patients had complete response. Mean overall survival of 46.98 months with a median follow up time of 22 months. On univariate analysis significant impact of Hyperthermia fractions with (Hazard Ratio = 6.426 (95% CI 1.06 – 38.80), *P* value = 0.021) and radiation boost with (Hazard Ratio = 4.32 (95% CI 0.86 – 21.48), *P* value = 0.049) observed. On multivariate near about significance for Hyperthermia Fractions once a week as compared to twice a week (Hazard Ratio = 20.08 (95% CI 1.33 – 303.74), (*P* value = 0.030). Four patients developed pelvic recurrence. Mean recurrence free survival was 41.17 months. Kaplan Meier survival analysis was used as univariate analysis. *P*-value < 0.05 considered statistical significant. **Conclusion:** Combination of hyperthermia and radiotherapy shows better over all survival and hyperthermia is good option in patients with locally advanced carcinoma cervix who are not eligible for chemotherapy.

Keywords: *Hyperthermia, Kaplan Meier, radiotherapy*

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Introduction

Loco-regional therapy is a crucial cog in the multidisciplinary management of cervical cancer of all stages. There has been a substantial improvement in outcomes. However, loco-regional failure rate of 41%–72% in locally advanced stage of carcinoma cervix with radiotherapy (RT) alone to achieve high local control is the primary requirement.[1,2] Once local control achieved, survival benefit expected to increase to be 50-60%.[3,4] Cisplatin-based chemoradiation has improved the survival around 23%, with a median survival of 6–8 months, and is considered a standard of care.[5,6] Similar advantages have been reported when hyperthermia (HT) is combined with RT.[7] HT has the potential to be cytotoxic and/or to sensitize cells to radiation and chemotherapy (CT). Hypoxic cells are particularly sensitive to heat.[8] Hypoxic cells are steeped in an environment of low pH, besides being nutritionally deprived. These cells which are generally resistant to

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radiation are sensitive to HT. HT sensitizes the effects of radiation by interfering with repair of DNA damage.[9] Mild HT may also increase perfusion and oxygenation which may, in turn, lead to increased sensitivity to radiation therapy.[10] The therapeutic benefit observed with the addition of HT was at a cost of limited HT-induced toxicity, whereas radiation-induced toxicity remains unaffected. Combining HT with RT has shown improved response rate and tumor control in many randomized trials.[11-14]

Materials and Methods

Patients

Files of patients with confirmed diagnosis of carcinoma cervix with histology of squamous cell carcinoma were opened. A total of 20 patients who received RT and HT with or without CT with stages the International Federation of Gynaecology and Obstetrics from I to IVA were included in this study. Patients with metastasis were excluded from study. All patients had given the consent before starting the treatment.

Radiotherapy

All patients received external beam radiotherapy (EBRT) dose 48–50 Gy in 24–25 fractions using technique three-dimensional conformal radiotherapy (3DCRT, 4-field box technique) or intensity-modulated radiotherapy (IMRT) with 6–15 MV photons. Treatment was given by linear accelerator Elekta Precise Digital Sr. no. 4512, and planning was done on Monaco Version 5.1.2 Planning System. After completion of external RT, boost was given to primary disease at cervix via brachytherapy (high dose rate [HDR] and low dose rate [LDR]) and in few patients via EBRT. Brachytherapy machine used was GammaMed Plus iX Varian Made for HDR and Cs 137 source was used for LDR brachytherapy. Total brachytherapy boost dose was given 20–25 Gy in 2–3 fractions for HDR or via single application for LDR. For EBRT, boost dose of 18–20 Gy was given only to primary disease at cervix via small conformal field or via IMRT technique. Dose specification and target volume definition were according to the International Commission on Radiation Units and Measurements report 50 and 62.

Hyperthermia

Along with EBRT, all patients were prescribed once a week or twice a week HT for 5 weeks. For HT, the treatment time was 40 min and intratumor temperature was above 42°C. Intrapelvic temperature was kept high and homogenous as per patients' tolerance limit. Once patient complained about uncomfortable feelings, treatment settings such as phase, amplitude, frequency, and power were adjusted accordingly. Pulse and blood pressure were measured before and every 5 min during treatment. HT machine used was YAMAMOTO Model: T-RF8.

Study design

The present study is a retrospective analysis of cancer cervix patients treated with RT and HT with or without CT. The study period was from January 2012 to January 2018. The study area was Advanced Centre of Radiation Oncology Department in Nanavati Super Speciality Hospital, Vile Parle, Mumbai. During this period, 20 patients received RT along with HT. Primary endpoint of the study was complete response and overall survival. A complete response was defined as disappearance of all tumors in the irradiated volume; this was established 3 months after treatment. Response was assessed by physical examination, and if indicated, supplemental investigations were done. Overall survival was defined as the time between randomization and death or last follow-up. Secondary endpoint was recurrence-free survival (RFS) and defined as length of time after primary treatment for cancer end that the patient survive without any signs and symptoms of that cancer.

Statistical methods

Data were presented as mean ± standard deviation, median (range), and frequency (percentage). Kaplan–Meier survival analysis was used as univariate analysis. For univariate analysis, variables such as age, stage, technique, CT, response, boost required, and HT fraction were compared with Kaplan–Meier method and compared using log rank test. Factors associated with the

Table 1: Demographics and treatment technique characteristic of patients

	No. of patients	Percentage
Age		
<50 years	9	45%
>50 years	11	55%
Stage		
I	3	15%
II	4	20%
III	9	45%
IV	4	20%
Technique of Radiation		
Coventional/Conformal	13	65%
IMRT	7	35%
Hyperthermia Schedule		
Once a week (0-5 weeks)	14	70%
Twice a week (5-10 weeks)	6	30%
Treatment Received		
RT + HT	12	60%
RT + HT + CT	8	40%
Radiation boost technique		
BT	13	65%
EBRT	4	20%
Boost not received	3	15%

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presence of problems which are significant ($P < 0.05$) on univariate analysis were included in the multivariate model using Cox regression. $P < 0.05$ was considered statistically significant. IBM SPSS 24.0 (Armonk, NY, USA) was used for analysis.

Results

HT introduced in our department from 2000. Patients with proved cases of carcinoma cervix received RT, HT, and CT were analyzed. Cases studied from 2012 to 2018 were included. The total number of patients was 20. Among 20 patients, 12 (60%) received HT + RT while eight patients received CT along with HT + RT + CT. On demographic analysis, the mean age was 54 years (minimum 30 years to maximum 80 years). Stage III (45%) was predominant among all 20 patients. Fifteen percent of patients were of Stage I and 20% each of Stage II and IV [Table 1].

RT techniques were used 3DCRT and IMRT. Maximum number of patients received 3DCRT (13, 65%) while IMRT in 7 (35%) [Table 1]. RT boosts were given by brachytherapy in 13 (65%) patients. EBRT boost received by 4 (20%) patients as cervical os was not negotiable in two patients and two patients refused for brachytherapy boost; three patients (15%) did not report for boost [Table 1]. All patients received HT from 0 to 5 weeks; 16 patients (80%) were once a week and 4 (20%) patients were on twice a week HT schedule [Table 1].

Table 2: Survival status and treatment response

Survival Status		No of patients		
Dead		7		
Alive		4		
Recurrence*		4		
Metastasis		0		
Not available		9		
Response				
CR		15		75%
PR		3		15%
Stable disease		2		10%
Technique vs. Response				
		CR	PR	NR
RT + HT	N=12	9 (75%)	1 (8.3%)	2 (16.7%)
RT + HT + CT	N=8	6 (75%)	2 (25%)	0 (0%)
Stage vs. Response				
Stage		CR	PR	NR
I	N=3	3 (100%)	-	-
II	N=4	3 (75%)	1 (25%)	-
III	N=9	6 (66.67%)	1 (11.1%)	2 (22.2%)
IV	N=4	3 (75%)	1 (25%)	-

*Among 4 patients who had recurrence, 2 patients died and 2 lost follow up after few months. N=No. Of patients. CR- Complete response. PR- Partial response. NR- No response

Pelvic tumor response

Complete response observed 75% of patients (9/12) in RT + HT group. Similarly, in RT + HT + CT group also, 75% of patients (6/8) had complete response. Of 12 patients, 2 (10%) had no response in RT + HT group. In Stage III, complete response was observed in 66.67% of patients (6/9) [Table 2].

Overall survival

The mean overall survival was 46.98 (32.60–61.36) months, with a median follow-up time of 22 months ranging 6–72 months. The 1 year, 2 years, and 3 years and above yearly estimates are 89.7%, 65.9%, and 54.9%, respectively [Figure 1]. On univariate analysis, we have significant impact HT fractions with hazard ratio (HR) = 6.426 (95% confidence interval [CI] 1.06–38.80), $P = 0.021$ and radiation boost with HR = 4.32 (95% CI 0.86–21.48), $P = 0.049$. On multivariate analysis, we had near about significance for HT fractions once a week as compared to twice a week (HR = 20.08 [95% CI 1.33–303.74], $P = 0.030$) [Figure 2].

Recurrence-free survival

Twenty percent of patients (4/20) developed pelvic recurrence. The mean RFS was 41.17 (26.60–55.74) months. The estimated 1 year, 2 years, and 3 years and above yearly RFS estimates are 68.8%, 57.4%, and 47.8%, respectively [Figure 3]. For univariate analysis, variables such as age, stage, techniques, CT response, boost techniques, and HT fraction were compared with Kaplan–Meir method and compared log rank test. For RFS, none factor was significant.

Discussion

HT with RT has been explored in cancer cervix. HT at 39–43°C is a potent radio- and chemo-sensitizer.[7,8,10] This

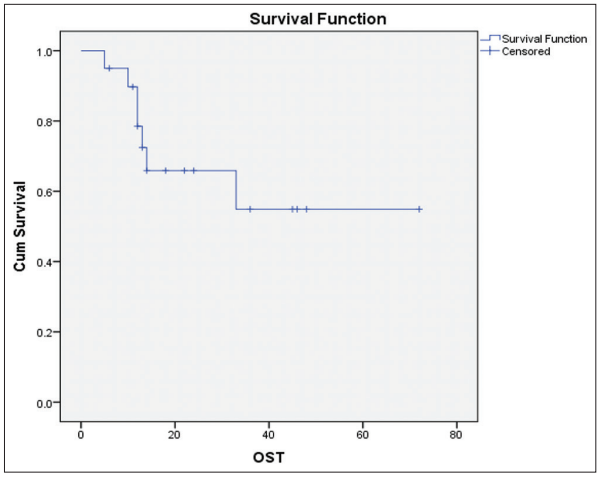

Figure 1: Kaplan–Meier survival curve for all patients received hyperthermia for locally advanced carcinoma cervix. OST: Overall survival time in months

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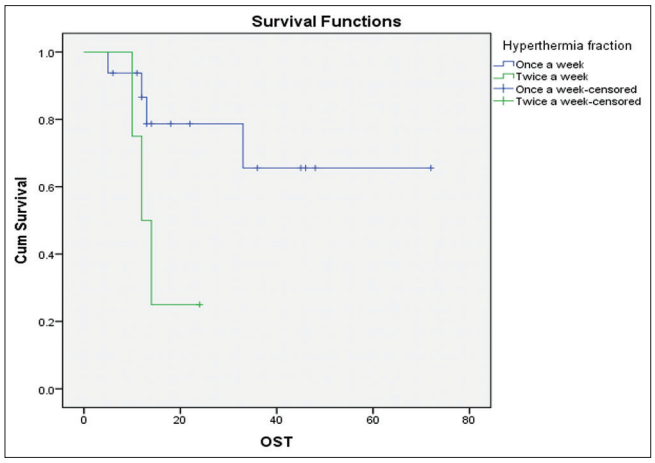

Figure 2: Kaplan–Meier survival curve for hyperthernia fractionation schedule in locally advanced carcinoma cervix patents. OST: Overall survival time in months

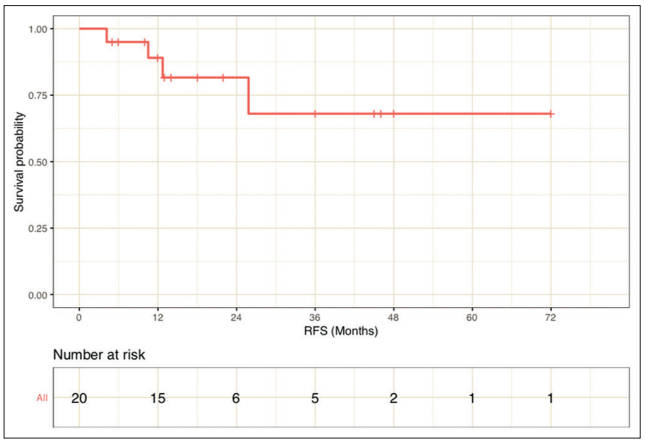

Figure 3: Kaplan–Meier survival curve for recurrence-free survival in all patients received hyperthermia for locally advanced carcinoma cervix. RFS: Recurrence-free survival

is may be particularly relevant in locally advanced cancer cervix cases which are known to harbor a significant population of radioresistent hypoxic cells.[9] Recently, a number of studies adding CT to RT and HT have been published, and some of these trials compared RT + CT + HT outcomes with RT + CT which is preferred therapeutic option for locally advanced carcinoma cervix. The present study is a retrospective analysis of carcinoma cervix patients treated with either RT + HT or RT + HT + CT.

In our study, the mean age was 54 years; similarly, in Dutch deep HT, the trial mean age was 50 years.[15-17] Approximately 65% patients were from Stage III and IV. In a meta-analysis of RT + HT versus RT, Datta *et al*. observed maximum number of patients had locally advanced Stage III and IV.[18] Similarly, in Cochrane review, Lutgens *et al*. reported that higher number of patients were of locally advanced stage of cancer cervix.[19] In a meta-analysis reported by Yan *et al*., they also noticed that Stage III and IV were predominant.[20] In the present study, the technique included were both 3DRT and IMRT. 65% patients were treated with 3DRT and 35% patients received IMRT. In recent few years, IMRT has gain popularity because of sparing of organ at risk and precise dose to target approach.

After completion of EBRT, 65% patients received boost via brachytherapy and 20% with EBRT in the present study. 15% patients did not report for boost of primary disease at cervix. In a study, Franckena *et al*. also observed that 87% patients were treated via brachytherapy boost and 13% patients did not receive brachytherapy boost.[17]

In response assessment, this retrospective study shows that 75% patients had complete response. Datta *et al*. also showed similar 74% complete response in locally advanced cancer cervix patients treated with RT and HT.[21] Similarly, Franckena *et al*. in a study observed that 83% of patients in the RT + HT group (48/58) achieved a complete response and 57% (32/56) in the RT group (P = 0.03). At follow-up, the difference in pelvic tumor control was sustained with 5-year pelvic tumor control rates of 61% in the RT + HT group and 37% in the RT group. At 12 years, the pelvic tumor control rate was 56% in the RT + HT group and remained 37% in the RT-group.[17] This difference was significant (P = 0.01). Chen *et al*. and Harima *et al*. also observed 72% and 80% complete response in their studies, respectively.[22,23] Pelvic tumor control with RT and HT was 70% in a study by Sharma *et al*.[24] Similarly, Vasantha *et al*. also observed that pelvic tumor control at 3 years in locally advanced cancer cervix was 70% patients treated with RT and HT.[25]

Three randomized trials also show improved overall survival with RT and HT compared to RT alone. Datta *et al*. observed that 2-year overall survival was 81% with RT + HT while 73% with RT only.[21] Harima *et al*. and Vasantha *et al*. also noticed that 3-year overall survival was 58% and 73%, respectively, when HT added to RT.[23,25] In an update of Dutch deep HT trial, Franckena *et al*. studied long-term outcomes after RT and HT in locally advanced carcinoma cervix. They described overall survival at 12 years was 37% in RT + HT group and 20% in RT-alone group (P = 0.03). The median overall survival was 2.64 years in the RT + HT group and 1.78 years in the RT group. In a multivariate analysis, the treatment arm remained an independent prognostic factor with a significant advantage in overall survival after RT + HT (P = 0.03, HR 0.60, 95% CI 0.38–0.95).[17]

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Similar to these studies in our retrospective analysis, the mean overall survival was 46.98 (32.60–61.36) months, with a median follow-up time of 22 months (6–72 months). The estimated 1 year, 2 years, 3 years and above yearly estimates were 89.7%, 65.9%, and 54.9%, respectively. On univariate analysis, we have significant impact of HT fractions with (HR = 4.32 [95% CI 0.86–21.48], $P = 0.049$). On multivariate analysis, we had near about significance for HT fractions on overall survival.

In Dutch deep HT update, Franckena *et al*. observed 25% pelvic recurrences in RT + HT group while it was 31% in RT-alone group.[17] This difference was not significant. Similar to this in our study, pelvic recurrence was 20% (4/20) while RFS was 41.7 months. The estimated 1 year, 2 years, and 3 years and above yearly RFS estimates are 68.8%, 57.4%, and 47.8%, respectively. For RFS, none factor was significant. Similar to above-mentioned all trials, our retrospective study also shows improved local response and overall survival when HT added to locally advanced carcinoma cervix patients.

Conclusion

Combination of HT and RT shows better overall survival in patients of carcinoma cervix. HT is a good option in patients with locally advanced carcinoma cervix who are not eligible for CT. However, further studies are required to establish the role of HT in other patients of locally advanced carcinoma cervix.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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