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Hyperthermia in the management of head and neck cancer – A single institution study from India

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Abstract

The addition of hyperthermia to chemo radiation or radiation can enhance the efficacy and increase disease free and overall survival. The review is the documentation of single institution study to assess the effects of hyperthermia in conjuction with radiation alone and chemo-radiation. This data has been published earlier. The retrospective analysis of patients receiving either paclitaxel or cisplatinum along with radical radiation and weekly hyperthermia did yield spectacular survival in advanced head and neck cancer. Similarly a randomized trial to assess the role of HT with radiation therapy has shown a statistically significant improvement.

Introduction

Head & neck cancers constitute a major burden of all cancers in men from India. There has been a trend towards a decline in oral cancer in a few major cities following a sustained campaign against tobacco consumption. Radiation and surgery alone have been supplanted by chemo-radiation laying an emphasis on organ preservation. Cyto toxic drugs and targeted therapies like cetuximab and nimatuzumab have been tried with success 43. Chemo-radiation or radiation with targeted therapies have come with a set of enhanced toxicities. But further improvement in survival with similar strategies in not very likely. Unfortunately addition of hyperthermia to radiation or chemo-radiation has not been pursued vigorously despite three randomized trials albeit sample size being small in these trials. S. Dutta, J. Valdagn, G. Huilgol. The present review documents data emanating from a single institution from India.

Material and methods

Hyperthermia facility was made available since 2003. A modified Thermatron was installed. It is a RF based machine which operates at 8.2 MH, the energy input varies from 0-1000 HW with impedance matching pre cooling and thermistors for online thermometry. A servo ensures an automatic shutdown if the temperature exceeds 50 °C. Three sets of antennae of different size ensure steezing of heat deposition. These is a dedicated head and neck antennae with a bolons for circulating cold water the temperature of which can be varied from 5° Celsius unless the tumor is just below the skin or skin is involved. Hyperthermia session lasts for 30-40 minutes. Thermometry is not done routinely but the energy inputs and values for impedance matching are recorded. Hyperthermia sessions are delivered on any of the days of radiation or on a weekend along with weekly chemotherapy. Patient also have been treated twice a week with adequate internal to account for thermal tolerance. Patients who were on chemo radiation besides hyperthermia receive either Cisplat or Paclitaxel, Cetuximab has been added to the armamentoteriom since last 4 years.

Patients with locally advanced head & neck cancers are routinely treated in our centre with both triple and dual modalities of CT+HT+RT, besides chemo radiation which is deemed a standard of care. An informed consent is a pre-requisite before starting any treatment. Patients who were recruited for the randomized trial, which was conducted from 2005 to 2009, were informed of the protocol before obtaining the informed consent.

Radiotherapy was delivered on a tele cobalt machine in the randomized trial. (Theratron 780C.). Patients treated after 2008 were treated on a linear accelerator with 6MV photons. Appropriate technique was adopted. Very few patients have been treated with intensity modulated radiation. Patients received 66-70 Gy in 6 to 7 weeks.

Hyperthermia was delivered on modified Thermatrom, a radiofrequency based machine which operates at 8.2 MHz. All patients underwent pre-cooling before starting chemotherapy only a few underwent invasive thermometry. The power input varied from 400 to 1000 k/w pain was the limiting factor for escalation of achieved to the extent possible.

Result

Patients were randomized to receive radiation therapy (RT) alone (control) or radiation with HT (trial). Twenty-six patients in the control group and 28 patients in the trial group were accrued. Table 1. shows demographic profile of both the group. The mean age of patients in the control group was 58.42 years (45-76 years) and in the trial group was 57.71 years (31-78 years). There was a male preponderance in both the groups. Both the groups were evenly matched with no statistical difference. Table 2. shows anatomical sub sites of affliction in both the groups. There was a non-significant preponderance of orpharyngeal cancers in the control group, while oropharyngeal and hypo pharyngeal cancers were slightly more in the trial group. Patients were saged according to Tumor Node Metastasis (TNM) system of stratification 1978 (UICC). Stage wise distribution is shown in Table 3. There is no significant difference in clinical parameters between both groups (Chi-square test, $p<0.05$=statistically significant). Patients in both the groups received radiation to total dose of 70 Gy in 7 weeks with conventional fractionation of 5 days a week with no treatment on weekends. Patients in the trial group received RF-based weekly HT in addition to RT. Twenty-one patients in the control group and 22 patients in the experimental arm received more than 60 Gy [Table 4]. Not all patients completed the planned number of sessions of HT. Twenty-three patients could finish more than five sessions [Table 5]. Those who dropped early were the ones who could not bear pain or the systemic stress.

Follow-up had been less than adequate in both the groups. The difference of follow-up pattern was not significant. Patients were assessed for any local recurrence, distant metastasis or development of new co-morbid illness not related to the original cancer at treatment. Both the groups were evenly matched for gender, stage, anatomical sites, treatment received and follow-up pattern. Initial response was assessed within 7-10 days of completion of treatment. The assessment of response was based on clinical assessment. Complete response was based on clinical assessment. Complete response was scored when total regression of the disease was seen, and partial response was scored when regression was more than 50% but not complete. Progressive disease was any increment in size of the tumor.
A complete response was observed in 11 of 26 (42.4%)
Patients in the radiation alone arm, while 22 of 28 (78.6%) patients had complete response in HT+RT group [Table 6]. Improvement in complete response due to addition of HT to radical radiation was statically significant (Chi-square test, $p< 0.05$). Three patient in RT+HT group and one patient in RT alone group had progressive disease. This difference was not statically significant. There were three details in the control group and five deaths in the trial group. Deaths were unrelated to treatment.

In RT+HT group, 3/28 (10.7%) showed progressive disease which was more than that in the RT alone group (1/26, 3.8%) but the difference was not statistically significant. Also, 17.9% subjects in RT+HT group were followed up for more than 12 months, which was more than (7.7%) that in the RT group, but was not statistically significant [Table 7]

Kalpan-Meir survival curve analysis showed a statistical benefit in those treated with RT+HT. The median survival of control arm was 145 days and mean survival time should median be rounded off to 203 days, 14-261. In trial group, median survival time was 241 days and mean survival time was (95% Cl) 260.471893 days (199.27426-321.669527 days). Median survival time is a better statistical tool to compare the treatment effectiveness.

The difference between the median times of survival between RT+HT and RT groups was almost 100 days. The survival function shows that the probability of survival was significantly different between the two groups. Except for a few days around 400, the survival function of RT+HT was the probability of death at any time was higher for patients treated with just RT. Cutaneous and mucosal toxicity in both the groups was comparable.

Parameters	**RT group**	**RT + HT group**
No. of cases	26	28
Age		
Mean	58.42 Years	57.71 Years
SD	11.39	12.93
Range		
Sex #		
Male	24 (92.3%)	22 (78.6%)
Female	02 (07.7%)	06 (21.4%)

P<0.05 significant

Table 1. Demographic data

Site	RT group (n=26)		RT+HT group (n=28)	
	No.	%	No.	%
Oropharynx	17	65.4	10	35.7
Hypopharynz	05	19.2	12	42.9
Oral cavity	04	15.4	06	21.4

By Chi-square test, P<0.05 significant

Table 2. Anatomical sites of head and neck cancer 1 control and trail groups

Response	RT group (n=26)		RT+HT group (n=28)	
	No.	%	No.	%
T2N0	01	03.8	01	03.6
T2N1	01	03.8	01	03.6
T2N3	02	07.7	02	07.1
T3N1	02	07.7	03	10.7
T3N3	04	15.4	04	14.3
T3N0	06	23.1	02	07.1

Table 3. Staging status in trial and control groups

T3N0	04	15.4	07	25.0
T4N0	-	-	03	10.7
T4N1	-	-	02	07.1
T4N2	02	07.7	02	07.1
T4N3	04	15.4	01	03.6

Table 4.

No of HT Treatment	No. of patients
2-4	2
5-7	23

Table 5. Profile of radiation dose 1 both the groups

Response	RT group (n=26)		RT+HT group (n=28)	
	No.	%	No.	%
Complete response	11	42.4	22	78.6
Partial response	13	50.0	03	10.7
No response	01	03.8	-	-
Progressive disease	01	03.8	03	10.7

Table 6. Comparison of response between two treatment groups

Duration (Months)	RT group (n=26)		RT+HT group (n=28)	
	No.	%	No.	%
<6	16	61.5	11	39.3
6-12	08	30.8	12	42.8
>12	02	07.7	05	17.9

Table 7. Profile of follow-up period

Discussion

There has been a considerable progress in the treatment of head and neck cancer. Chemo radiation as a standard of care has led to increase in organ sparing and maintaining functional integrity. This has come with on increased morbidity. Hyperthermia is a modality has been under utilized in the west as well as emerging countries including China and India. Hyperthermia that is raising the temperature to 41 °to 45° Celsius has unique mechanism of actions which is distinct from ionizing radiation and cytotoxic drugs. The biological rationale for the use of hyperthermia alone or as an adjuvant to radiation and chemotherapy are well known. Heat in the range 41 °to 45° Celsius affect various cellular targets like cell membrane Cyto Skelton and enzymes in respiratory chain.

Hyperthermia is very potent hypoxic cell senstiser. Thus hyperthermia in conjunction with radiation is an ideal combination to pursue. The present randomized study supported by Indian Council of Medical Research has shown a survival benefit for adding hyperthermia to radical radiation therapy. The median survival benefit of radiation therapy alone was 145 days as compared to 241 days in the HT+RT group.
A similar survival benefit was earlier demonstrated by Valdagin: (Similarly addition of hyperthermia to chemo radiation has shown excellent results. The morbidity due to addition hyperthermia was not significant in any of the patients. In conclusion both the randomized trial and the analysis of retrospective data demonstrate a significant improvement in survival due to the addition of hyperthermia.