Original Article

Hyperthermia with radiation in the treatment of locally advanced head and neck cancer: A report of randomized trial

ABSTRACT

Background: Head and neck cancer is the leading cause of male mortality due to cancer in India. Surgery, radiation alone or in combination has been the backbone of treatment strategies. Chemo-radiation has emerged as the standard of care in most types of head and neck cancer. This strategy has the advantage of maintaining both structure and functions, albeit with increased acute and delayed side effects. Radiation with hyperthermia can achieve the same objective without additional toxicities.

Materials and Methods: A total of 56 patients were randomized to radiation therapy (RT) alone or RT–hyperthermia (RT–HT) arm. Twenty-six patients were included in RT alone arm and 28 patients in the RT–HT arm. Both groups were evenly matched for age, sex, and stage. Patients in both the arms received radiation to a dose of 66–70 Gy in 6.5–7 weeks. Patients in the study group received weekly HT. HT was started after impedance matching to last for 30 minutes.

Results: Complete response was seen in 42.4% of RT alone group compare to 78.6% in the HT group. The difference was statistically significant (< 0.05). Kaplan–Meir analysis of survival also showed a significant improvement in favor of RT–HT. No dose limiting thermal burns and excessive mucosal or thermal toxicity were recorded.

Conclusion: Radiofrequency (RF) based heating and radical radiation of head and neck cancers is better than in RT alone group. HT should be considered as a valid option wherever the facility for HT is available. This report should infuse greater confidence in radiation Oncologists to practice HT as an adjuvant treatment modality.

KEY WORDS: Chemoradiation, head and neck cancer, hyperthermia, radiofrequency

Nagraj G. Huilgol, Sapna Gupta, Sridhar C. R.

Department of Radiation Oncology, Dr. Balabhai Nanavati Hospital, Mumbai, India

For correspondence: Dr. Nagraj G. Huilgol, Department of Radiation Oncology, Dr. Balabhai Nanavati Hospital, S.V. Road, Vile Parle (W), Mumbai - 400 056, India. E-mail: nagrajhuilgol@gmail.com

INTRODUCTION

Head and neck cancer in men is the leading cause of morbidity and mortality in the Indian subcontinent. Locoregionally, advanced cancer of head and neck still poses a therapeutic challenge. Conventional strategies like radical surgery and radiation have reached the zenith of effectiveness. Chemo-radiation has emerged as a new standard of care in head and neck cancers. The meta-analysis of chemotherapy and radiation reported by Pignon[1] confirmed the benefit of concomitant chemotherapy with radiation to be around 4–6%. However, this modest benefit is achieved with considerable morbidity. Innovations in the treatment of recalcitrant head and neck cancers are urgently needed, as improvement in survival over last two decades has been marginal.

Hyperthermia (HT) is an ancient therapeutic approach for treating various ailments, including cancer. A renaissance of HT seen in the mid-seventies ushered in a new hope. It was followed by disappointment and hence desertion of HT for lack of evidence. Now, there is a level one evidence to prove the effectiveness of HT delivered with radiation in the treatment of various malignancies. Van-der-Zee published a randomized trial to demonstrate the effectiveness of HT and radiation in pelvic tumors.[2] Similarly, Valdagni has shown a significant superiority of combined modality of HT and radiation over radiation alone, in head and neck cancer.[3] There are more than 15 positive randomized trials demonstrating the survival benefits due to HT and radiation. There has been a clamor for more evidence for the effectiveness of HT and radiation. Hence, the following randomized trial was initiated.

The present prospective randomized study was designed to assess the effects of adding HT to radical radiation in the treatment of locally advanced head and neck cancers.

MATERIALS AND METHODS

The trial was initiated in the year 2005 following institutional ethics committee clearance and

Access this article online
Website: www.cancerjournal.net
DOI: 10.4103/0973-1482.77101
Quick Response Code:

concluded in 2009. Patients were recruited for the study following histological confirmation of epithelial cancer. Endoscopy, complete blood chemistry and X-ray chest were obtained for staging of disease. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans were considered in special situations only. Patients were staged according to Tumor Node Metastasis (TNM) staging. Patients with metastatic disease, short and fat neck and Karnofsky's index of less than 70 were excluded from treatment. Block randomization was done after obtaining the informed consent from each patient. Randomization was done by a person not directly involved in the study and the patients were allocated to control or experimental arm. Radical radiation with HT was delivered in the experimental arm and radiation alone in control arm.

Radiotherapy

All patients underwent radiation on a telecobalt machine (Theratron 780C, Atomic energy of Canada limited, Ontario, Canada) with parallel opposed compensated beams or multiple beams, as per the clinical requirements. A dose of 70 Gray Gy in 7 weeks with conventional fractionation was planned for all patients. Patients were treated 5 days a week from Monday to Friday. Fields were modified at 50 Gy to spare the spinal cord. All the patients underwent weekly evaluation to assess acute toxicities due to radiation or HT included daily fluoride application before radiation, as part of the protocol.

Hyperthermia

HT was delivered on modified Thermatron, a radiofrequency (RF) machine operating at 8.2 MHz. Patients underwent pre-cooling before starting HT. A pair of antennae was placed across the neck, guided by visible tumor or anatomical landmarks. The power input was started after impedance matching input varied from 400 to 1000 kW. Power was gradually escalated till the patients complained of unbearable pain, stress or discomfort. Power was then reduced and maintained till completion of the treatment. Invasive thermometry with a thermistor probe was performed when feasible. Patients received HT for 30 minutes after pre-cooling for 10 minutes. HT was delivered on the same day of the week, every week after radiation. Five to seven weekly sessions of HT were planned along with conventional radiation for each patient. Figure 1 shows the block diagram of the HT procedure.

HT was stopped if patients developed grade II or higher thermal burns. Patients were assessed for response on completion of the treatment.

RESULTS

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 groups. The mean age of patients in the control group was

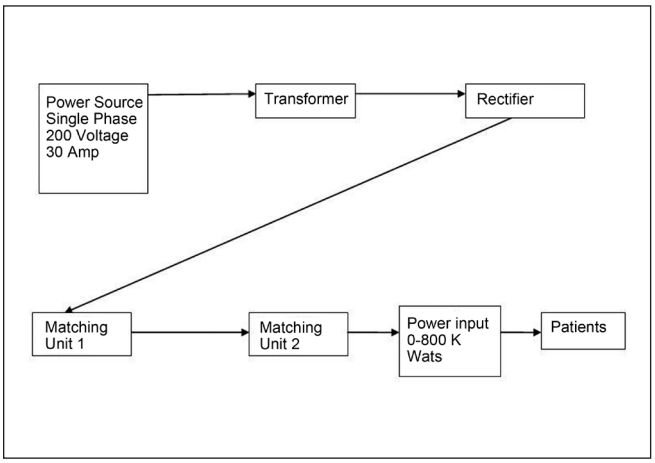

Figure 1: Flow chart of HT treatment on RF 8

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, with 24 males in the control and 22 males in the trial group. Both the groups were evenly matched with no statistical difference. Table 2 shows anatomical subsites of affliction in both the groups. There was a non-significant preponderance of oropharyngeal cancers in the control group, while oropharyngeal and hypopharyngeal cancers were slightly more in the trial group. Patients were staged 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

Table 1: Demographic data

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	40–76 years	31–78 years
Sex#		
Male	24 (92.3%)	22 (78.6%)
Female	02 (07.7%)	06 (21.4%)

$P < 0.05$ significant

Table 2: Anatomical sites of head and neck cancer in control and trial groups

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

By Chi-square test, $P < 0.05$ significant

Table 3: Staging status in trial and control 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
T3N2	04	15.4	04	14.3
T3N3	06	23.1	02	07.1
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

By Chi-square test, $P < 0.05$ significant

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.

Table 3 shows the stratification according to TNM staging. Most of the patients were of T3–T4 and N1–N3, except one patient of T2N0 in both groups.

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 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 patients in RT + HT group and one patient in RT alone group had progressive disease. This difference was not statistically significant. There were three deaths 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].

Kaplan–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 be rounded off to 203 days, 145-261 In the trial group, median survival time was 241 days and mean survival time was (95% CI) 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 much better. Consequently, the hazard plot also indicates that 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.

Figure 2 Shows Kaplan- Meir survival curve for radiation

Table 4: Profile of radiation dose in both the groups

Response (Gy)	RT group (*n* = 26)		RT + HT group (*n* = 28)	
	No.	%	No.	%
≤50	04	15.4	04	14.3
>70	01	03.8	01	03.6
50–60	–	–	01	03.6
60–70	21	80.8	22	78.5

By Chi-square test, $P < 0.05$ significant

Table 5: Comparison to HT treatment

No. of HT treatment	No. of patients
0–1	3
2–4	2
5–7	23

Table 6: Comparison of response between two treatment 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

By Chi-square test, $P < 0.05$ significant

Table 7: Profile of follow-up period

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

By Chi-square test, $P < 0.05$ significant

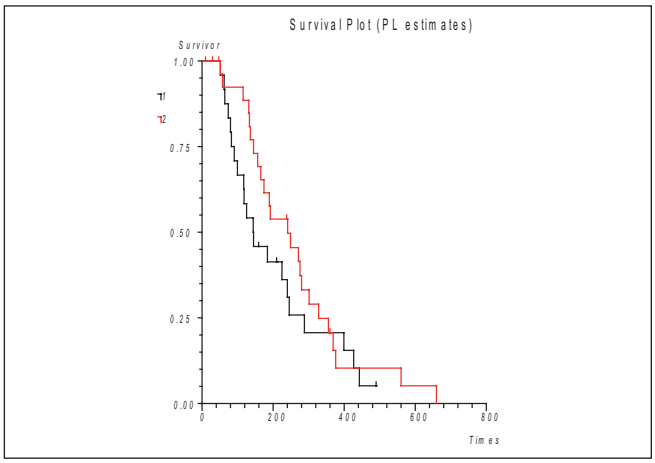

Figure 2: Survival plot

with hyperthermia in red. Radiotherapy alone in black. The maximum temperature never exceeded 44°C in any of the patients. The average temperature was 42.3°C. Acute and late toxicities were comparable in both treatment arms except for an overall increase of thermal burns in the HT group.

DISCUSSION

Improvement in survival, locoregional control, better cosmesis and improved function are the objectives to be fully achieved in the management of head and neck cancer. Radiation therapy as a single modality has failed to achieve the above objectives. Globally, chemo-radiation has emerged as the standard of care in locally advanced oral and hypopharyngeal cancers. The benefits of chemo-radiation come at the cost of increased acute and late toxicities. Perhaps radiation with HT is an alternative approach in the treatment of head and neck cancer with lesser toxicity. The present randomized study has demonstrated an improved initial response and survival in the study group as compared to the control group. Patients in the present study were treated with weekly HT and radical radiation and compared to those treated with radiation alone. Improvement due to the addition of HT to RT is statistically significant. The current study reconfirms the findings of Valdagni.[4] HT is a clinical treatment for malignant diseases, in which tumor tissue is heated to a minimum of 40–41°C for 30–60 minutes. HT can be categorized as thermoablation where temperatures are above 50°C, classical HT where the temperature varies from 41 to 45°C, and moderate HT when temperature varies from 40 to 43°C. The heating is achieved generally by electromagnetic radiation.[5] The biological rationale for adding HT to radiation or chemotherapy is well known. Raaphorst has demonstrated protein to be a unique target for inflicting injury when the temperature is raised beyond 41°C.[6] HT in the range of 40–45°C acts by affecting various cellular targets like cell membrane, cytoskeleton of cells and enzymes in the respiratory chain.[7-9] HT alone has been shown to be effective in inducing response in 10–15% of patients. HT is also a potent radiation sensitizer.[10] Cellular hypoxia induces resistance to radiation. Moderate HT leads to increased vascular permeability and increase in oxygen pressure levels in the tumors. This altered microenvironment due to HT enhances the radiosensitivity of the tumor. Thermal radiation sensitization may also be due to DNA inhibition of repair and alteration in nuclear protein aggregation and higher order chromatin organization.[9]

There is an increasing belief that HT may influence DNA double-strand breaks.[11] Indirect biochemical evidence suggests that heat may exert its major effects on radiosensitivity by inhibiting the repolymerization step in the repair of radiation-induced base damage, resulting in the formation of secondary toxic DNA double-stand breaks.

There has been considerable debate on the best sequence of RT + HT. It is suggested that HT + RT should be delivered sequentially but not simultaneously. Thermal enhancement ratio is the highest when HT + RT are administered sequentially as in this study. The general acceptance of the strategy to integrate HT with RT has not been popular despite favorable outcomes reported in randomized trials. It has been shown in many tumor types that the addition of heating once or twice a week with conventional radiation can improve outcomes of many clinical end points like initial response, local control, and overall survival. The meta-analysis of five reported trials of HT and RT in primary and recurrent breast cancer suggested that there was an improvement in local control but not survival benefit. No long-term toxicity was reported in this analysis.[12] A Cochrane review of RT + HT of rectal cancer revealed a survival benefit in HT + RT arm as compared with RT alone. After 2 years, the difference in overall survival between the two arms disappeared.[13] The present study has also shown an improved response rate and overall survival with RT + HT. Valdagni's study published in 1988 also has shown a similar benefit.[4] Our study as well as that of Valdagni's cohort suffer from small number of patients in both the arms. The technique of HT has evolved over the years. The technical innovations have resulted in improved heating of both superficial and deep-seated tumors. Pre-treatment planning with CT and or MRI has improved the quality of heating. Online MRI-based thermometry with a facility to steer energy also has improved heat delivery. It is possible that improved heating technology will translate into better outcome.

Patients in the present study were treated on Radio Frequency (RF) based heating system. RF based systems have shown clinical utility in heating deep-seated tumors. Lack of flexibility in antennae was a major limitation in our study. Yet, we have demonstrated a clear benefit in response rate and survival due to HT in the treatment of locally advanced head and neck cancer. HT with radiation is not only a feasible option but also an option which can enhance response rates and survival.

CONCLUSION

RF based heating of head and neck cancer is feasible. The

current randomized study has shown a survival advantage and better response rate when HT is added to radical RT. RT with HT should be considered as one of the valid options for the treatment of locally advanced head and neck cancers.

ACKNOWLEDGMENTS

The trial was supported by Indian council of medical research. Grant no-5/13/44/2002-NCD-III.

REFERENCES

1. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949-55.
2. Pignon JP, le Maître A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14.
3. Van der Zee J, González González D, van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: A prospective, randomised, multicentre trial. Dutch Deep Hyperthermia Group. Lancet 2000;355:1119-25.
4. Valdagni R, Amichetti M, Pani G. Radical radiation alone versus radical radiation plus microwave hyperthermia for N3 (TNM-UICC) neck nodes: A prospective randomized clinical trial. Int J Radiat Oncol Biol Phys 1988;15:13-24.
5. Issels RD. HT adds to chemotherapy. Eur J cancer 2008; 44(17): 2546-54.
6. Raaphorst G. Fundamental aspects of HT biology. In: Fields HJ, editor. An introduction to the practical aspects of clinical HT. London: Taylor and Francis; 1990. p. 10-54.
7. Roti Roti JL. Heat-induced alterations of nuclear protein associations and their effects on DNA repair and replication. Int J Hyperthermia 2007;23:3.
8. Lepock JR. Role of nuclear protein denaturation and aggregation in thermal radiosensitization. Int J Hyperthermia 2004;20:115.
9. Vidair CA, Dewey WC. Division-associated and division-independent hyperthermic cell death: Comparison with other cytotoxic agents. Int J Hyperthermia 1991;7:51-60.
10. Ressel A, Weiss C, Feyerabend T. Tumor oxygenation after radiotherapy, chemotherapy, and/or hyperthermia predicts tumor free survival. Int J Radiat Oncol Biol Phys 2001;49:1119-25.
11. Iliakis G, Wu W, Wang M. DNA double strand break repair inhibition as a cause of heat radiosensitization: Re-evaluation considering backup pathways of NHEJ. Int J Hyperthermia 2008;24:17.
12. Gainal US. OH OJ, Issels RD, Wesslowski R. Clinical Results of quality assured HT, 48-57 in HT in oncology principles and theraupeutic outlook. Uni – Med, 2010.
13. De Hass- Kock DF, Buijsen J, Pijls- Johannesma M. Concomitant HT and radiation therapy for treating locally advanced rectal cancer. Cochrane Data base syst Rev 2009;CD006269.

Source of Support: Indian council of medical research. Grant no-5/13/44/2002-NCD-III, **Conflict of Interest:** None declared.