INT. J. HYPERTHERMIA, 1990, VOL. 6, NO. 3, 479–486

Head and neck cancers: results of thermoradiotherapy versus radiotherapy

N. R. DATTA, A. K. BOSE*, H. K. KAPOOR* and S. GUPTA*

Department of Radiotherapy, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India
*Department of Radiotherapy, Maulana Azad Medical College and associated Lok Nayak Jai Prakash Narain and G. B. Pant Hospital, New Delhi, India

(*Received 2 November 1988; accepted 27 April 1989*)

Sixty-five patients were included in a randomized clinical study to evaluate the efficacy of local hyperthermia as a concomitant agent to radiotherapy in the treatment of carcinoma of the head and neck region. Local hyperthermia at 42–43 °C was generated by a 27·12 MHz radiofrequency diathermy unit and was used before radiotherapy in 33 patients; the remaining 32 patients were subjected to radiotherapy alone. The response in patients with early lesions (Stage I and II) was similar for both the groups, while in patients with advanced disease (Stage III and IV) a significantly better tumour control was obtained by the use of the combined treatment.

Key words: Hyperthermia, head and neck carcinoma, radiotherapy, randomized trial.

Int J Hyperthermia Downloaded from informahealthcare.com by dr Gianfranco baronzio on 03/15/12
For personal use only.

1. Introduction

The factors limiting the efficacy of radiotherapy in the locoregional control of cancerous lesions are well known. These include primarily the presence of hypoxic cells in the tumour mass, cells in the radioresistant phase of the cell cycle, i.e. S and G_1, and the potentially radioresistant type of cancer cells.

Results from various *in vitro* and *in vivo* studies have indicated that hyperthermia at 42–45 °C is lethal to the radioresistant hypoxic cells, cells at low pH and the radioresistant S-phase cells (Field 1987, Hall and Roizin-Towle 1984, Overgaard and Bichel 1977). Based on these *in vitro* studies, subjecting malignant lesions at supranormal temperature to irradiation has been shown to produce a higher response in patients with different malignancies (Manning *et al.* 1982, Perez *el al.*, 1983, Perez and Emami 1985). We report herein the use of local hyperthermia as a concomitant agent to radiotherapy in the treatment of various head and neck malignancies.

2. Materials and methods

Sixty-five patients with histopathologically confirmed and previously untreated squamous cell carcinoma of the head and neck were included in this prospective study. The cases were divided into two groups – Group A (control group) and Group B (study group) – by a formal random allocation. All the patients had disease limited to a locoregional area. Patients with distant metastasis were excluded from the study. The lesions were easily approachable for temperature measurement. The control group consisted of 32 patients treated with irradiation alone, while 33 patients in the study group were subjected twice-weekly to local hyperthermia before radiotherapy. Prior written consent was obtained from all patients included in this trial. Analysis of the patients according to the primary site of malignancy is shown in table 1.

Address correspondence to: Dr N. R. Datta, Assistant Professor, Department of Radiotherapy, Sanjay Gandhi Post Graduate Institute of Medical Sciences, P.B. No. 375, Lucknow 226001, India.

0256-6736/90 $3.00 ©1990 Taylor & Francis Ltd.

RIGHTSLINK

Table 1. Profile of the patients according to their diagnosis

Diagnosis	Control group	Study group
Carcinoma of the cheek	10	14
Carcinoma of the tongue (anterior two-thirds)	6	4
Carcinoma of the hard palate	3	3
Carcinoma of the tonsil	3	4
Carcinoma of the alveolus	4	2
Carcinoma of the floor of the mouth	2	3
Secondary neck tumour, primary unknown	4	3
Total	32	33

Clinical staging was undertaken according to the American Joint Committee (AJC) staging system (AJC 1983). The distribution of the patients according to the stage is depicted in Table 2. The size of the primary tumour as well as the lymph nodes were recorded and sub-classified (Table 3). In cases of two or more lymph nodes, these tumours were recorded separately and grouped according to their individual sizes. Of the total 65 patients, 19 had no significant lymph nodes at the time of presentation and seven patients were labelled as occult primary with secondary neck nodes.

2.1. *Radiotherapy*

All the patients were treated with telecobalt therapy and an attempt was made to deliver a tumour dose of 50 Gy in 5 weeks by using two parallel, opposed fields encompassing the primary and the regional lymphatics. A further dose of 10–15 Gy in 5–10 days was given to the site of the gross disease. The daily tumour dose delivered was 2 Gy. All the fields were treated daily. No brachytherapy was used.

2.2. *Local hyperthermia and thermometry*

Local hyperthermia was carried out with radiofrequency waves at 27·12 MHz using a Siemens Ultraterm 607E diathermia machine. Two rubber pad electrodes were placed on either side of the tumour with a felt pad placed between skin and electrode to act as a coupling medium. Thermometry was measured with a copper eureka thermocouple. Prior to treatment the thermocouple was placed in the centre of the tumour after infiltration of the subcutaneous tissue with 2% xylocaine. Temperature readings were performed at 15 min intervals while switching off the diathermia apparatus. The treatment was continued until a temperature of $42 \cdot 5 \pm 0 \cdot 5$°C was achieved. Once this tumour temperature was obtained, the output of the diathermia unit was adjusted so as to maintain the temperature for at least 20 min. The details of thermotherapy and thermometry were as described previously (Datta *et al.* 1986). Immediately following hyperthermic treatment the tumour was irradiated. The local hyperthermic treatment was carried out only twice a week with a period of 72 h between the two sessions to prevent thermotolerance; irradiation was carried out 5 days a week.

2.3. *Response criteria*

The patients were monitored closely during treatment and at monthly intervals following the completion of their treatment. At 8 weeks following the completion of treatment the response of the patients was classified as complete response (CR) if there was complete disappearance of the demonstrable disease, partial response (PR) if there was more than

Int J Hyperthermia Downloaded from informahealthcare.com by dr Gianfranco baronzio on 03/15/12
For personal use only.

RIGHTSLINK

Int J Hyperthermia Downloaded from informahealthcare.com by dr Gianfranco baronzio on 03/15/12
For personal use only.

Table 2. Response after 8 weeks of completion of treatment

Stage	Complete response (CR)		Partial response (PR)		Total response (CR+PR)	
	Control group	Study group	Control group	Study group	Control group	Study group
I	3/3 (100%)	2/2 (100%)	0/3 (0%)	0/2 (0%)	3/3 (100%)	2/2 (100%)
II	4/5 (80%)	3/3 (100%)	1/5 (20%)	0/3 (0%)	5/5 (100%)	3/3 (100%)
III	2/10 (20%)	7/12 (58%)	4/10 (40%)	3/12 (25%)	6/10 (60%)	10/12 (83%)
IV	1/14 (7%)	6/16 (37%)	4/14 (29%)	4/16 (25%)	5/14 (36%)	10/16 (63%)
Total	10/32 (31%)	18/33 (55%)	9/32 (28%)	7/33 (21%)	19/32 (59%)	25/33 (76%)

RIGHTSLINK

Table 3. Complete response according to the size of the primary tumour and the lymph node (at 1 month following completion of therapy)

	Primary tumour		Lymph node	
Size (cm^2)	Control group	Study group	Control group	Study group
≤10	3/4 (75%)	6/6 (100%)	6/9 (67%)	8/8 (100%)
11–20	5/10 (50%)	6/7 (86%)	5/7 (71%)	5/7 (71%)
21–30	4/11 (36%)	8/12 (67%)	1/2 (50%)	2/3 (67%)
>30	0/3 (0%)	2/5 (40%)	0/2 (0%)	0/1 (0%)

50% reduction in the measurable disease and no response (NR) if there was less than 50% reduction.

3. Results

All 65 patients in this trial were able to undergo the treatment fairly well and were followed-up for a median period of 21 months (range 18–28 months). Most of the patients had advanced disease (Stages III and IV) at the time of presentation (75% in control group, 85% in study group).

Concomitant use of local hyperthermia with radiotherapy did not seem to alter the response in patients with early disease (Stage I and II). In fact, 8 weeks after completion of treatment all the patients demonstrated a complete response except one control group patient with carcinoma of the tongue. He had 85% regression of the tumour. By contrast the complete response as observed in Stage III disease was found to be 20% for patients in the control group and 58% in the study group. Likewise, Stage IV patients also demonstrated a better complete response rate when treated with combined therapy compared with radiotherapy alone, it being 38% for the study group and only 7% for the control group (table 2).

The response of the primary tumour and the lymph nodes was also found to be dependent on the initial dimension of the lesions (table 3). For smaller lesions, i.e. <10 cm^2, slight improvement was achieved by the use of hyperthermia, the total response of the primary and the lymph nodes of the control group being 75% and 67%, respectively, while the patients subjected to combined treatment had a 100% response in terms of both their primary and lymph nodes lesions. In lesions having larger dimensions, the regression rates were better when hyperthermia was used along with radiotherapy (table 3).

The most common symptom with which a patient presents for treatment was pain, especially in the advanced stage of the disease. Seventy-nine per cent (26/33) patients undergoing combined treatment had almost complete alleviation of pain, while only 50% had pain relief in the control group ($p<0\cdot02$).

3.1. *Complications*

Both methods of treatment were fairly well tolerated by the majority of the patients. The complications, especially skin and mucosal reactions, of both groups were almost identical in type and magnitude, except one patient who developed moist desquamation: Local erythema and facial oedema were seen in three out of the 33 patients in the study group.

3.2. *Short-term survival rate*

The median duration of follow-up was 21 months (18–28 months). At the end of the study, three patients, each belonging to the study and control group, were lost to follow-up and were recorded as 'dead' for the purpose of computing the results. Five patients

Int J Hyperthermia Downloaded from informahealthcare.com by dr Gianfranco baronzio on 03/15/12
For personal use only.

RIGHTSLINK

treated with radiotherapy alone died (four due to the disease process and one in a roadside accident). Four of the six Group B patients had evidence of disease at the time of death while two died of unknown cause. Nineteen per cent of the control group patients were surviving free of disease as compared with 33% in the study group at 18 months after completion of treatment (table 4). The overall disease-free survival is shown in figure 1, demonstrating a significantly improved effect of thermoradiotherapy on advanced tumours.

4. Discussion

The curative role of radiotherapy in head and neck carcinoma is mainly limited to the early tumours, i.e. those having T_1 and T_2 lesions (Brady and Davis 1988). Advanced lesions (T_3 and T_4) frequently fail to respond to conventional radiotherapy alone and therefore the current practice of pre- or post-operative radiotherapy together with surgical resection is the treatment of choice. However, *in vitro* and *in vivo* studies clearly outline the property of hyperthermia as an hypoxic cell sensitizer along with its selective cytotoxic action on the radioresistant neoplastic cell (Field 1987, Hall and Roizin-Towle 1984, Overgaard and Bichel 1977). Thus radiotherapy and hyperthermia may be expected to complement the action of each other, leading to an improved tumour control. The majority of the patients had advanced disease (Stages III and IV). The response recorded at 8 weeks after completion of treatment showed a better regression rate in the study group patients compared with the control group patients who received radiotherapy alone (table 2). The effect was particularly significant in patients with advanced disease (60% versus 83% in Stage III, 36% versus 63% in Stage IV, $p<0{\cdot}05$).

As might be expected, patients with advanced malignancies have a relatively larger tumour mass. These tumours are likely to possess a large proportion of hypoxic cells and cells at low pH, which are not susceptible to radiotherapy alone. Since hyperthermia at 42°C and above is lethal to these cells the combined administration of hyperthermia and radiotherapy may lead to better regression rates. The results of this trial are in accordance with the above statement. The cure rates were observed to be dependent on the size of the lesions, the larger lesions responding more favourably to the combined use of hyperthermia and irradiation while the smaller lesions (<10 cm^2) were controlled effectively by radiotherapy alone (table 3).

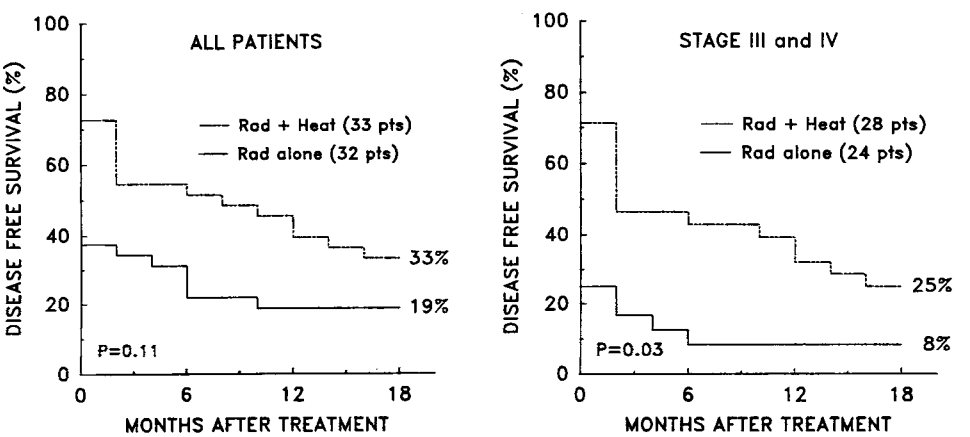

Figure 1. Kaplan-Meier estimate of the probability of disease-free survival as a function of treatment for all patients (left) and patients with advanced (Stage III and IV) disease (right).

Int J Hyperthermia Downloaded from informahealthcare.com by dr Gianfranco baronzio on 03/15/12
For personal use only.

RIGHTSLINK

Int J Hyperthermia Downloaded from informahealthcare.com by dr Gianfranco baronzio on 03/15/12
For personal use only.

Table 4. Patient status at 18 months after completion of treatment

	NED		Alive with disease		Died	
Stage	Control group	Study group	Control group	Study group	Control group	Study group
I	2/3 (67%)	2/2 (100%)	1/3 (33%)	0/2 (0%)	0/3 (0%)	0/2 (0%)
II	3/5 (60%)	2/3 (67%)	2/5 (40%)	1/3 (33%)	0/5 (0%)	0/3 (0%)
III	1/10 (10%)	4/12 (33%)	7/10 (70%)	7/12 (58%)	2/10 (20%)	1/12 (8%)
IV	0/14 (19%)	3/16 (19%)	8/14 (57%)	8/16 (50%)	6/14 (43%)	5/16 (31%)
Total	6/32 (19%)	11/33 (33%)	19/32 (59%)	16/33 (48%)	8/32 (25%)	6/33 (18%)

NED=no evidence of disease.

RIGHTSLINK

Recurrence of the tumour after complete regression is a common observation in head and neck malignancy, especially in advanced tumours. The recurrence may be from the radioresistant cells that may remain in a dormant state soon after the clinically complete disappearance of tumour following radiotherapy alone. Hyperthermia being cytotoxic to radioresistant cells may prevent the existence of such a nidus of radioresistant cells. This may be reflected as an ability to maintain the initial regression and thereby improve the disease-free survival in the patients receiving combined methods of treatment (figure 1).

Complications as a result of hyperthermia are almost negligible. The development of blister, erythema and facial edema in three out of the 33 patients did not significantly hamper the treatment schedule. On the whole, hyperthermia treatment was well tolerated and was almost free of any additional toxicities. Radiotherapy and hyperthermia have been used by many workers in different schedules using different techniques in various tumours. Manning *et al.* (1982) have shown that by the administration of external thermoradiotherapy an 80% response rate could be achieved even in previously treated but failed cases. In an RTOG pilot study, Marcial and his colleagues (1988) subjected 48 head and neck cancer patients to thermoradiotherapy. Twenty-eight patients (58%) showed complete response at 6 months and 43% of these cases with <3 cm diameter lesions and 18% with ≥ 3 cm diameter lesions were alive at 6 months following the completion of therapy. Similar encouraging results were also reported by a randomized study in cervical lymph nodes (Scott *et al.* 1983). Complete regression of cervical nodes was observed in 80% of patients while the total tumour control including the primary site was 75% in patients receiving thermoradiotherapy and 54% in those receiving radiotherapy alone. In our study the total response rate of 76% with the combined methods of treatment and 52% in patients on radiotherapy alone further emphasizes the positive role of hyperthermia as a concomitant agent to radiotherapy in the treatment of malignant tumours, especially advanced malignancies.

From the patients' point of view the main purpose of seeking medical aid is relief of symptoms. Any treatment that can meet this need more effectively and for a longer duration without increasing undesirable side-effects is of benefit to the patient. In this study a significantly higher degree of palliation, especially pain, was achieved in patients subjected to thermoradiotherapy compared with those receiving radiotherapy alone. Thus, better response, both subjective and objective, better survival rate and lower frequency of complications of local hyperthermia favour its use with radiotherapy and in future may establish itself in anti-cancer therapy.

Acknowledgment

The authors thank Dr M. M. Saha, Head Thin Film Division, National Physical Laboratory, and Dr A. Wason, Thermometry Division, National Physical Laboratory, for technical assistance.

References

AJC 1983. *American Joint Committee on Cancer: Manual for Staging of Cancer*, edited by O. H. Beahrs and M. H. Myers (Philadelphia: J. B. Lippincott), pp. 27–52.

BRADY, L. W., and DAVIS, L. W., 1988, Treatment of head and neck cancer by radiation therapy. *Seminars in Oncology*, **15**, 29–38.

DATTA, N. R., KAPOOR, H. K., GUPTA, S., and BOSE, A. K., 1986, A method for temperature measurement in clinical hyperthermia. *AMPI Medical Physics Bulletin*, **11**, 106–109.

FIELD, S. B., 1987, Hyperthermia in the treatment of cancer. *Physics in Medicine and Biology*, **32**, 789–811.

HALL, E. J., and ROIZIN-TOWLE, L., 1984, Biological effects of heat. *Cancer Research* (Suppl.) **44**, 4708s–4723s.

Int J Hyperthermia Downloaded from informahealthcare.com by dr Gianfranco baronzio on 03/15/12
For personal use only.

RIGHTSLINK

MANNING, M. R., CETAS, T. C., MULLER, R. C., OLESON, J. R., CONNOR, W. G., and GERNER, E. W., 1982, Clinical hyperthermia: results of a phase I trial employing hyperthermia alone or in combination with external beam or interstitial radiotherapy. *Cancer*, **49**, 205–216.

MARCIAL, V. A., PAJAK, T. F., KRAMER, S. K., DAVIS, L. W., STETZ, J., LAROMORE, G. E., JACOBS, J. R., AL–SARRAF, M., and BRADY, L. W., 1988, Radiation therapy oncology group (RTOG) studies in head and neck cancer. *Seminars in Oncology*, **15**, 39–60.

OVERGAARD, J., and BICHEL, P., 1977, The influence of hypoxia and acidity on the hyperthermia response of malignant cells *in vitro*. *Radiology*, **123**, 511–514.

PEREZ, C. A., and EMAMI, B., 1985, A review of current clinical experience with irradiation and hyperthermia. *Endocurietherapy/Hyperthermia Oncology*, **1**, 265–277.

PEREZ, C. A,, NUSSBAUM, G., EMAMI, B., and VONGERIEHTEND, D., 1983, Clinical results of irradiation combined with local hyperthermia. *Cancer*, **54**, 1597–1603.

SCOTT, R. S., JOHNSON, R. J. R., KOWAL, H., KRISNAMSETTEY, M. S., STORY, K., and CLAY, L., 1983, Hyperthermia in combination with radiotherapy. A review of five years experience in the treatment of superficial tumours. *International Journal of Radiation Oncology, Biology, Physics*, **9**, 1327–1333.

Int J Hyperthermia Downloaded from informahealthcare.com by dr Gianfranco baronzio on 03/15/12
For personal use only.

RIGHTSLINK