Hyperthermia Combined with Radiation Therapy and Chemotherapy for Locally Advanced Head and Neck Cancer

Pramook Phromratanapongse M.D.

Abstract

From July 1993 to October 1996, 18 patients with locally advanced head and neck cancers were treated with hyperthermia, radiation therapy, and chemotherapy. Primary tumors were located in nasopharynx (10), base of tongue (4), pyriform sinus (2), and larynx (2). All patients were in stage III or IV (5T1, 3T2, 5T3, 5T4/2N2, 16N3). Microwave hyperthermia, administering twice weekly, was given to enlarged neck nodes and aimed at 42.5-43°C for 60 minutes during each session. Radical dose of irradiation was delivered to primary tumor and regional neck nodes. Concomitant chemotherapy (cisplatin/5FU; carboplatin/UFT) of 2 courses was given during radiation therapy with additional 2-4 courses as an adjuvant treatment. At one month after completion of treatment, 6 patients (33%) achieved CR and 12 patients (67%) had PR. Subsequently, 6 patients had surgical salvage of their neck nodes. Thus, at 3 months follow up, 13 patients (72%) demonstrated local regional control. (One patient who initially had PR turned into CR without surgical intervention). Relapse rate of 30% (4 out of 13) was noted. Significant toxicity included mucositis (28% gr. 3), neutropenia (6% gr. 3) and anemia (6% gr. 3). The 12 and 18-month actuarial survival were 93% and 81% respectively. In conclusion, the trimodality approach of hyperthermia, radiation therapy and chemotherapy proved feasible, effective and safe. Further studies to maximize the effects of this multidisciplinary approach are necessary, preferably in a prospective randomized trial.

Introduction

More than two-thirds of head and neck cancer patients present with stage III and IV. Despite aggressive local therapy, 50-60% of these patients would ultimately develop local recurrence. The survival rate is 40% for patients whose tumors are completely resected and only 20% for those with unresectable tumors treated with radiotherapy alone[1,2,3]. Concomitant chemoradiotherapy has resulted in increased disease-free survival and overall survival in several randomized studies[4,5,6]. However, patients with large and fixed node (diameter > 5 cm.) remain a difficult problem with regard to local control[7,8]. Neck recurrence of 45% has been reported in patients with advanced stage and extracapsular spread[9]. More than 60% of these patients would die as a result of local disease progression. Factors limiting the efficacy of radiation therapy in controlling neck node disease include the presence of hypoxia and cells in the radioresistant phase of the cell cycle i.e. S and G1. However, high thermo sensitivity of cells in the S and G2 phases has been observed by many investigators[10,11]. Both in vitro and in vivo studies have demonstrated that when one combined hyperthermia

Division of Radiation Oncology, Department of Radiology, Pramongkutklao Hospital,
315 Rajavithi road, Bangkok 10400, Thailand

with radiation therapy, more cell kill would be expected as compared to radiation alone. Heat enhances cell-killing effect of irradiation by inhibiting repair of sublethal and potentially lethal radiation damage[12]. Heat also selectively kills hypoxic cells that are normally resistant to irradiation[13]. In addition, radioresistant S-phase cells are more sensitive to heat. Hyperthermia also enhances the cytotoxicity of many chemotherapeutic agents[14]. The activity of cisplatin is potentiated linearly at temperature above 38°C[15,16]. For 5-fluorouracil (5FU), some investigators reported a positive interaction with hyperthermia[17,18]. 5FU is also a radiosensitizing agent. Its activity in combination with radiation has been clearly demonstrated in head and neck cancer[19,20]. UFT is a combined drug of tegafur and uracil. The antineoplastic effect of UFT is due to 5FU which is gradually converted from tegafur. Uracil inhibits the degradation of 5FU, permitting the maintenance of 5FU. With the convenience of oral administration, more studies on UFT have been performed with promising results[21,22]. By combining hyperthermia and radiation therapy,[23] we initiated a pilot study of thermoradiochemotherapy (trimodality approach) in locally advanced head and neck cancer patients to evaluate the efficacy and toxicity of this regimen.

Materials and Methods

From July 1993 to October 1996, 18 patients with locally advanced head and neck cancers were accrued in this study. Eligibility criteria included biopsy proven squamous cell carcinoma, N2/N3neck nodes, ECOG performance 0-2, adequate bone marrow function (WBC > 3.5x10 /L, platelet count >100x10 / L), adequate liver function (serum bilirubin <1.5 mg/dl, normal SGOT,SGPT, alkaline phosphatase), adequate renal function (serum creatinine <1.5 mg/dl, BUN <25 mg/dl), no previous radiation therapy or chemotherapy, and no evidence of distant metastases.

All patients were assessed by complete medical history, physical and ENT examination, complete blood count, biochemical profile, chest x-ray, computed tomography or magnetic resonance imaging of the head and neck. Informed consent was obtained from all patients before entering the study. Summary of patients' characteristics was shown in Table 1.

Treatment

Radiation Therapy

All patients received radiation therapy from megavoltage equipment (Cobalt-60 or Linear accelerator). The treatment volume encompassed the primary site and the regional neck nodes. Normally, parallel opposed technique was used for upper neck field and single anterior field was used for lower neck field. The dose to the spinal cord was limited to 44 Gy. Electron of appropriate energy was used to bring the dose of the posterior neck under the spinal cord block to 50 Gy. Enlarged neck nodes were boosted up to 60-70 Gy. The average dose to the primary tumor and neck node were 6710 cGy and 6697 cGy, respectively (range 6580-7000 cGy/6400-7600 cGy).

Hyperthermia

Local hyperthermia was performed with microwave system using waveguide applicator operating at a frequency of 915 MHz. The applicator is a rectangular waveguide and is excited symmetrically by a cylindrical brass probe antenna. Air-cooling system is equipped with each applicator. The intratumoral catheter implantation for thermometry was done before the start of the treatment. Normally, 1-2 catheters were inserted in the cervical node

under local anesthesia. This was done to obtain temperature measurement which would represent both central and peripheral region of the tumor. Thermocouple thermometer (multisensor probe with accuracy of ±0.05°C), completely immune from external microwave interference, was used. Hyperthermia was administered twice per week, 72 hours apart, to avoid thermotolerance. Each heat session was applied within 10-20 minutes of radiation. The external applicator was placed over enlarged neck node. The goal was to reach minimal tumor temperature of 42.5-43°C for 60 minutes during each session. Monitoring of surface temperature was also conducted to avoid excessive heating of skin. Temperature parameters that were measured during each session for final analysis included minimal temperature ($\overline{T}$min), average minimum temperature ($\overline{T}$min), maximum temperature ($\overline{T}$max), average maximum temperature ($\overline{T}$max), minimum and maximum thermal dose in equivalent minutes at 43°C. Pain medication or sedation was not given routinely except in patients who experienced difficulty in keeping a stable rest position during heat treatment.

Chemotherapy

Chemotherapy was given concurrently with radiation therapy. Two regimens of chemotherapy were used. The first one (16 patients) consisted of cisplatin and 5FU. Cisplatin was administered at a dose of 100 mg/m^2 intravenously on day 1, 28 and 5FU 800 mg/m^2/day as a continuous infusion for 96 hours on day [1-14, 28-31]. The second regimen (2 patients) consisted of carboplatin and UFT. Carboplatin was administered at a dose of 300 mg/m^2 intravenously on day 1, 28 and UFT 300 mg/m^2 orally on day 1-21. Adjuvant chemotherapy of 2-4 courses was started 4-6 weeks after completion of radiation. The same dose of cisplatin/5FU or carboplatin/UFT was used and the cycle was repeated every 28 days.

Evaluation

Tumor response was determined by using WHO criteria. Complete response (CR) was defined as the disappearance of all known lesions; partial response (PR) as a 50% or more reduction of all measured lesions, and no change (NR) as a reduction of less than 50% of lesions. Response evaluation was done at one and three months after completion of therapy. Nodal dimensions were measured in two orthogonal directions and nodal volume was calculated with the following formula:

$$V\ (cc) = 4/3 \times \pi \times a \times b^2$$

where a is the maximum nodal radius and b is its orthogonal radius. Toxicity of radiation treatment was recorded by using the RTOG/EORTC criteria. Chemotherapy related toxicity was evaluated by WHO criteria.

Results

The major end points of our study are 1) local control of neck node, as well as primary site and 2) acute side effect of hyperthermia combined with chemoradiotherapy. At one month after completion of treatment, 6 patients (33%) achieved CR and 12 patients (67%) had PR. Subsequently, 6 patients who had residual neck node but complete regression of their tumors at primary site underwent neck dissection. Pathological specimen in 5 out of 6 patients revealed only area of necrosis in the nodes recovered. Only one patient had positive malignant cell in one node that was removed. Ultimately, at 3 months of follow up, 13 patients (72%) achieved local regional control (one patient who had PR initially turned into a CR without surgical intervention).

Of 13 patients rendered disease free after completion of treatment, 4 patients (30%) subsequently developed recurrence at 4,5,15 and 32 months of follow up. Two patients recurred at their primary site. One relapsed at both primary site and distant site (bone metastasis). One relapsed at distant site only (liver). No patient relapsed at nodal site. Two patients who experienced distant metastases died one month after a relapse was established. Two patients who had primary site recurrence were salvaged by re-irradiation and chemotherapy. Both of them were still alive at 3 and 12 months of follow up.

As of July 1997, the median time to follow up for all patients was 13 months (range 1-40). Two patients died from disease progression. By using Kaplan-Meier method, the 12 and 18-month actuarial survival were 93% and 81% respectively.

Toxicity

Local toxicity

Acute cutaneous side effect occurred in all patients. Grade 2 skin toxicity occurred in 16 patients (89%) and grade 3 in 2 patients (11%). No thermal blister has been observed. Severe pain developed in two patients during heat session which required major adjustment of power deposition and applicator set up. Pain medication was also given. Eight patients (44%) experienced grade 2 mucositis and 7 patients (39%) had grade 3 mucositis. Seven patients (39%) developed grade 3 pharyngitis/esophagtis requiring NG tube feeding. Radiation interruption of more than 2 weeks was necessary in 4 patients due to mucositis and/or neutropenia.

Systemic toxicity

Eight patients (44%) developed grade 2 neutropenia and only one patient (6%) had grade 3 neutropenia. Grade 2 and 3 anemia developed in 5 (28%) and 1 patient (6%) respectively. Gastrointestinal toxicity seemed to be mild and only one patient experienced grade 2 toxicity (transient vomiting). Delay in administration of second cycle of chemotherapy occurred in 6 patients due to bone marrow suppression and/or mucositis. Summary of treatment related toxicity was shown in Table 2.

Hyperthermia Data

A total of 174 heating sessions were performed on 18 patients. The average number of hyperthermia treatment was 10 for each patient (range 2-14). Only one patient had premature discontinuation of hyperthermia after 2 sessions due to pain, discomfort and difficulty in breathing during supine position. Thermal parameters were recorded and shown in Table 3. No significant correlation has been observed between thermal parameters and clinical response.

Discussion

There is convincing evidence that tumor response to ionizing radiation is improved by temporary exposure to elevated temperature. When heat and radiation are performed simultaneously, more than additive effects on cell killing are observed. Hyperthermic radiosensitization is usually expressed in terms of thermal enhancement ratio (TER) and is generally considered to result from inhibition of the repair of radiation-induced damage, particularly on DNA strand break rejoining[24,25]. Jorritsma and Konings demonstrated that the rate of repair of DNA strand breaks diminished progressively after exposure to a temperature of 42°C or higher [26].

Both in vivo and in vitro studies have demonstrated that the efficacy of many chemotherapeutic agents were potentiated by hyper-

thermia. Drugs that have been studied extensively and revealed promising results when given concurrently with hyperthermia are cisplatin, carboplatin, alkylating agents, and nitrosoureas[27]. Several investigators have clearly demonstrated that hyperthermia significantly enhanced cisplatin cytotoxicity. Cohen and Robins studied on carboplatin and showed thermal enhancement above 40°C with maximal thermal enhancement at 42°C[28]. This finding was similar to that reported by Lindegaard for cisplatin[29].

Patients who presented with enlarged neck node (>6 cm) or fixed nodes remained a difficult situation to achieve long term control even after radical dose of irradiation. Only 40-60% of N2-N3 neck nodes experienced durable local control. Two randomized studies have shown beneficial effects in terms of local control and survival when hyperthermia was added to radiation therapy in treating locally advanced head and neck cancer. The first one reported by Datta demonstrated a 37% CR for combined hyperthermia and radiation therapy in stange IV head and neck cancer patients as opposed to only 7% CR for radiation alone[30]. In addition, the 18-month disease-free survival was significantly better for the combined arm (25% vs 8%). The second one reported by Valdagni demonstrated significant improvement in early response (82% CR vs 36% CR) favoring the combined arm for stage IV head and neck cancer patients. More importantly, the initial response also translated into a superiority in overall survival. The 5-year survival was 53.3% for combined hyperthermia and radiation which was significantly better than 0% in the radiation alone arm[31]. Of particular note was that both studies did not reveal any significant increase in acute toxicity when hyperthermia was added to radiation therapy.

The trimodality approach of hyperthermia, radiation therapy, and chemotherapy has been tested more extensively during the past few years. Herman treated locally advanced malignancies with radiation therapy, microwave hyperthermia and 20, 30, or 40 mg/m^2 of cisplatin. This protocol was proved to be feasible and effective with 50% CR[32]. Side effects included second and third degree burn (50% and 25% respectively) and bone marrow suppression (21%). Amichetti treated 18 locally advanced head and neck cancer patients with hyperthermia, weekly cisplatin (20 mg/m^2) and radiation therapy and demonstrated 66.6% CR and 22.2% PR[33]. Three-year actuarial nodal control was 53.5% and 3-year actuarial survival was 50%. Local toxicity was mild but systemic toxicity was moderate with 3 patients experiencing grade 3 anemia. The only randomized study was conducted by Krishnamurthi[34]. In that report., 69% CR was obtained with the three modalities combined; 61% CR with pleomycin and radiation and 32% CR with radiation alone. However, the trimodality approach did not convey a statistically significant benefit over radio-chemotherapy. It should be aware that in that study the thermometry was not performed in the later stages of therapy and the desired temperature of 42°C in the tumor core might be suboptimal.

Our results of 33% CR obtained initially and 72% CR after surgical salvage are comparable to other reports in the literature. Significant mucositis was observed which was attributable to the addition of 5FU/UFT. This necessitated aggressive supportive care to improve nutritional status of patients to carry on the planned treatment.

In conclusion, the trimodality approach of chemotherapy (cisplatin/carboplatin; 5 FU/UFT), radiation therapy, and hyperthermia proved feasible, effective and safe. Further adjustment of dose and schedule of this

multidisciplinary approach is still needed. Whether this high initial complete response rate would turn into an improved overall survival remains to be proved in prospective randomized trial.

Table 1. Patient Characteristics

Total number of patients	18
Sex; Male : Female	13 : 5
Age; range/mean (yr.)	17-77/48
ECOG performance status; range/median	0-2/1
Primary site of tumor	
Nasopharynx	10
Base of tongue	4
Pyriform sinus	2
Larynx	2
T category	$5T_1$, $3T_2$, $5T_3$, $5T_4$
N category	$2N_2$, $16N_3$
Nodal volume; range/mean (cm^3)	34 - 1505/273

Table 2 Summary of toxicity

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	-	-	16 (89%)	2 (11%)	-
Mucous membrane	-	3 (17%)	8 (44%)	7 (39%)	-
Pharynx & esophagus	-	3 (17%)	8 (44%)	7 (39%)	-
Neutropenia	9 (50%)	-	8 (44%)	1 (6%)	-
Anemia	12 (66%)	-	5 (28%)	1 (6%)	-

Table 3 Thermal Parameters

Parameter	Average	Range	
		Minimum	Maximum
T-max (°C)	42.21	40.16	44.40
T-min (°C)	40.24	39.25	41.32
T-avg (°C)	41.24	39.76	42.91
Max. Thermal dose Eq 43°C	544.60	11.80	2026.50
Min. Thermal dose Eq 43°C	63.61	0.80	150.60

References

1. Hong WK, Dimery IW. Overview of combined modality therapies for head and neck cancer. J Natl Cancer Inst 1993; 85:95-111
2. Jacobs C. Adjuvant and neoadjuvant treatment of head and neck cancer. Semin Oncol 1991; 18:504-14
3. Forastiere AA. Randomized trials of induction chemotherapy. A critical review. Hematol Oncol Clin North Am 1991; 5:725-37
4. A randomized trial of combined multidrug chemotherapy and radiotherapy in advanced squamous cell carcinoma of the head and neck : an interim report from the SECOG participants. Eur J Surg Oncol 1986; 12:289-95
5. Adelstein DJ, Sharan VM, Earle AS, et al. Simultaneous versus sequential combined technique therapy for squamous cell head and neck cancer 1990; 65:1685-91
6. Merlano M, Corvo R, Margarino G, et al. Combined chemotherapy and radiation therapy in advanced inoperable squamous cell carcinoma of the head and neck. The final report of a randomized trial cancer 1991; 67:915-21
7. Mendenhall WM, Million RR, Bova FJ. Analysis of time-dose factors in clinically positive neck nodes treated with irradiation alone in squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1984; 10: 639-43
8. Goffinet DR, Fee WE, Goode RL. Combined surgery and postoperative irradiations in the treatment of cervical lymph modes. Arch Otolaryngol 1984; 110:736-8
9. Johnson JT, Myersen EN, Bedetti CD, Barnes EL, Schramm VL, Thearle PB. Cervical lymph node metastases: incidence and implications of extracapsular carcinoma. Arch Otolaryngol 1985; 111:534-7
10. Schlag H, Lllcke-Huhle C. Cytokinetic studies on the effect of hyperthermaia on Chinese hamster lung cells. Eur J Cancer 1976; 12:827-31
11. Kim SH, Kim JH, Hahn EW. The enhanced killing of irradiated He La cells in synchronous culture by hyperthermia. Radiat Res 1976; 66:337-45
12. Overgaard J. The current and potential role of hyperthermia in radiotherapy. Int J Radiat Oncol Biol Phys 1989; 16:535-45
13. Moulder JE, rockwell S. Hypoxic fractions of solid tumors. Int J Radiat Oncol Biol Phys 1984; 10:695-712
14. Dahl O. Interaction of hyperthermia and chemotherapy. Recent Results Cancer Res 1988; 107:157-169
15. Fisher GA, Hahn GM. Enhancement of cisplatinum (II) diaminedi chloride cytotoxicity by hyperthermia. Natt Cancer Inst Monogr 1982; 61:255-7
16. Los G, Sminia P, Wondergem J. et al. Optimisation of intraperitoneal cisplatin therapy with regional hyperthermia in rats. Eur J Cancer 1991; 27:472-7
17. Shiu MH, Cahan A, Fogh J, Fortner JG. Sensitivity of xenografts of human panereatic adenocarcinomas in nude mice to heat and heat combined with chemotherapy Cancer Res 1983; 43:4014-8
18. Sutton CH. Tumour hyperthermia in the treatment of malignant gliomas of the brain. Trans Am Neurol Assoc 1971; 96 :195-9
19. Al-Sarraf. Head and neck cancer : chemotherapy concepts. Semin Oncol

1988; 15:70-85
20. Lo TCM, Wiley AL, Ansfield FJ, et al. Combined radiation therapy and 5-fluorouracil for advanced squamous cell carcinoma of the oral cavty and orpharynx: A randomized study. Am J Roentgenol 1976; 126:229-35
21. Inuyama Y, Fujii M, Mashno S. Et al. Clinical effect of UFT for head and neck cancer. Cancer and Chemotherapy 1983; 10:90-6
22. Valverde JJ, Ganzale JI, Neoadjuvant chemotherapy with cisplatin and 5-FU versus cisplatin and UFT in advanced squamous head and neck cancer. Proc. ASCO 1993; 12:281
23. Phromratanapongse P, Sangvirojkul S, Tesavibul C, et al. Hyperthermia and radiation therapy for neck node metastasis from head and neck cancer. Proceeding of the 12th Asia Pacific Cancer Conference, 1995; Singapore p83
24. Konings AWT. Effects of heat and radiation on mammalian cells. Radiat Phys Chem 1987; 30:339-49
25. Frankenberg - Swager M. Review article : review of repair kinetics for DNA damage induced in eukaryotic cells in vitro by ionizing radiation. Radiother Oncol 1989; 14:307-20
26. Jorritsma JBM, Konings AWT Radiosensitization by hyperthermia in thermotolerant cells and its relationship with the repair of DNA strand breaks. Radiat Res 1984; 98:198-208
27. Dahl O. Interactions of heat and drugs in vitro and in vivo. In Seegenschmiedt MH, Fessenden P, Vernon CC (eds) Thermoradiotherapy and thermochemotherapy 1995 Berlin, Springer. pp 103-121
28. Cohen JD, Robins HI. Thermal enhancement of tetraplatin and carboplatin in human leukaemic cells. Int J Hyperthermia 1990; 6:1013-7
29. Lindegaard JC, Radacic M, Khalil AA, Horsman MR, Overgard J. Cisplatin and hyperthermia treatment of a C3H mammary carcinoma in vivo. Acta Oncol 1992; 31:347-51
30. Datta NR, Bose AK, Kapoor HK, Gupta S. Head and neck Cancer; results of thermoradiotherapy versus radiotherapy. Int J Hyperthermia 1990; 6:479-86
31. Valdagni R, Amichetti M. Report of long-term follow-up in a randomized trial comparing radiation therapy and radiation therapy plus hyperthermia to metastatic lymphnodes in stage IV head and neck patients. Int J Radiat Oncol Biol Phys 1994; 28:163-9
32. Herman TS, Jochelson MS, Teicher BA, et al. A phase I-II trial of cisplatin, hyperthermia and radiations in patients with locally advanced malignantes. Int J Radiat Oncol Biol Phys 1989; 17:1273-9
33. Amichetti M, Graiff C. Fellin G, et al. Cisplatin, hyperthermia, and radiation (trimodal therapy) in patients with locally advanced head and neck tumors: a phase I-II study. Int J Radiat Oncol Biol Phys 1993; 26:801-7
34. Krishnamurthi S, Shanta V, Vasanthan A, Balakrishnan IS, Jayaraman R. Radiation, pepleomycin and hyperthermia in the therapy of locally advanced squamous cell carcinomas of the buccal mucosa. Clin Oncol 1990; 68:10-13