RESEARCH ARTICLE

Long-term Efficacy of Microwave Hyperthermia Combined with Chemoradiotherapy in Treatment of Nasopharyngeal Carcinoma with Cervical Lymph Node Metastases

Min Kang, Wen-Qi Liu, Yu-Tao Qin, Zhu-Xin Wei, Ren-Sheng Wang*

Abstract

Objective: The long-term efficacy of microwave hyperthermia combined with chemoradiotherapy in treating nasopharyngeal carcinoma (NPC) with metastatic foci in cervical lymph nodes was evaluated. Methods: A total of 154 cases of N2 or N3 stage NPC were randomized into two groups: hyperthermia group (76 cases) and control group (78 cases). Both received cisplatin chemotherapy and radiotherapy. In addition, the hyperthermia group further received microwave hyperthermia to the metastatic cervical nodes with different patterns (before or after radiotherapy), heating temperatures (T90 < 43°C and T90 ≥ 43°C) and hyperthermia episodes (< 4 times, 4-10 times and > 10 times). Results: The 3-month and 5-year complete response (CR) rates of cervical lymph nodes in the hyperthermia group were significantly higher than those in the control group. The 5-year disease-free survival (DFS) rate and the 3-year / 5-year overall survival rate in the hyperthermia group were also significantly higher. There was no significant difference in 5-year metastatic rates. In the hyperthermia group, the 3-month and 5-year CR rates of T90 < 43°C treatment were significantly lower than with T90 ≥ 43°C treatment. The CR rate was highest when the hyperthermia was performed 4-10 times. There were no significant differences in 3-month and 5-year CR rates between hyperthermia before or after radiotherapy treatment. Conclusion: Microwave hyperthermia combined with chemoradiotherapy can increase local control, DFS and 3, 5-year overall survival rates of patients with N2 ~ N3 stage NPC. The heating temperature should be over 43°C with hyperthermia repeated 4-10 times.

Keywords: Nasopharyngeal carcinoma - metastatic node - chemoradiotherapy - hyperthermia - efficacy

Asian Pac J Cancer Prev, **14 (12)**, 7395-7400

Introduction

Nasopharyngeal carcinoma (NPC) is a unique type of head and neck cancer in terms of epidemiology, method of treatment and prognosis, and is particularly prevalent in Southeast Asia (Roychowdhury et al., 1996; Erkal et al., 2001; Liu et al., 2003). The incidence of cervical lymph node metastasis in nasopharyngeal cancer (NPC) is high. About 70% ~ 80% of newly diagnosed NPC patients have enlarged cervical lymph nodes (Yin et al., 2008). After radiotherapy and chemotherapy, some enlarged cervical lymph nodes still exist in NPC patients. Increased local radiation dose is likely to lead to severe radiotherapy complications, such as skin ulcers, neck fibrosis and cranial nerve damage (Tate et al., 1999; Teo et al., 2000; Lee et al., 2001; Wolden et al., 2001; Jen et al., 2002; Levendag et al., 2002; Lu and Yao, 2008). However, without increased radiation, local recurrence and distant metastasis rate will certainly increase. Microwave hyperthermia combined with radiotherapy and chemotherapy has been used widely and successfully in clinic.

The effects of microwave hyperthermia on tumor cells are as follows. Firstly, hyperthermia has cytotoxic effects on tumor cells. The thermo sensitivity of tumor cells is higher than normal cells. Tumor cells would be killed after treatment at 42°C for 2 h. Due to their high thermo sensitivity, the temperature of tumor cells is 3°C-7°C higher than that of surrounding normal tissues when heating. Therefore, appropriate hyperthermia will directly kill tumor cells without injuring surrounding normal tissues. Secondly, radiation-insensitive tumor cells are mainly S phase cells and hypoxic cells, which are highly sensitive to hyperthermia. Thirdly, hyperthermia can inhibit the damage repair of tumor cells after radiotherapy (Zastrow et al., 2010; Ghahremani et al., 2011; Colombo and Moschini, 2013). Fourthly, because of the sufficient blood supply in tumor surrounding tissues, the cytotoxicity of hyperthermia on surrounding tissues is much less severe than that on tumor center. The hyperthermia treatment failure is mainly due to the peripheral tumor recurrence while radiotherapy failure is mainly due to local recurrence in the tumor center. Therefore, combination of hyperthermia and radiotherapy can have a synergistic sensitizing effect (Perez and Brady,

*The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China *For correspondence: km10192013@126.com*

Table 1. Clinical Data of NPC Patients Used in This Study

Clinical features		Hyperthermia group	Control group	X^2	*P*
Cases		76	78		
Gender	Male	54	62		
	Female	22	16	3.178	0.078
Age (year)	Range	18 ~ 65	19 ~ 68		
	Median	47	48	1.41	0.532
Pathologic type	WHO II	6	7	1.402	0.442
	WHO III	70	71		
N staging	N2	41	40	0.533	0.363
	N3	35	38		
Clinical staging	III	33	34		
	IV	43	44	0.042	0.736
KPS scoring	90	19	22		
	80	43	35	1.104	0.563
	70	14	21		

KPS, Karnofsky performance status

1987; Li et al., 2004; Nikfarjam et al., 2005). Fifthly, hyperthermia can upregulate expression of pro-apoptotic genes while downregulate expression of apoptosis suppressor genes (Li et al., 2004). Sixthly, hyperthermia enhances cytotoxicity of some chemotherapy drugs, such as cisplatin. In vitro experiments (Zheng et al., 2006) showed that the anti-cancer effect of chemotherapy drugs can be enhanced 10 to 100 times after heating at 42°C for 2 h. Combination of heating and chemotherapy drug can increase the drug concentration within the tumor and increase its anticancer effect. And the toxicity of chemotherapy drugs on unheated normal tissues can be reduced, which will help prevent or delay the drug resistance. Therefore, it is shown by a number of clinical trials that the efficacy of combined treatment including hyperthermia, radiotherapy and chemotherapy were better than the efficacy of each therapy alone (Song et al., 2006; Chen et al., 2009).

Currently, the specific details of hyperthermia treatment such as timing, treatment times and temperature are still controversial. In this study, the long-term effect of hyperthermia in combination with radiotherapy and chemotherapy on NPC patients with cervical lymph node metastasis was investigated. A total of 154 cases of NPC patients at stage N2 ~ N3 were enrolled in this study. The complete response rate, the disease-free-survival rate and the survival rate were analyzed. The number, temperature and timing of hyperthermia were compared.

Materials and Methods

Patient Selection

Patients who fulfilled all of the following criteria were enrolled in this study: (1) NPC confirmed by biopsy and histology; (2) no evidence of distant metastasis; (3) no previous treatment for NPC; (4) T1-4N2-3M0 disease according to the staging system of the 2002 American Joint Committee on Cancer (AJCC) / International Union Against Cancer (UICC) (Fleming et al., 1997); (5) adequate liver function; (6) adequate renal function; (7) adequate bone marrow function; and (8) Karnofsky performance status (KPS) ≥80. The exclusion criteria were as follows: (1) presence of distant metastases; (2) pregnancy or lactation; (3) previous malignancy or other concomitant malignant disease; and (4) without previous radiotherapy, chemotherapy or immunotherapy.

Pretreatment Evaluation

Pretreatment evaluation included a complete history and physical examination with nasopharyngoscopy, chest radiography, ultrasonography of the abdominal region, and hematologic and biochemical profiles. Additional investigations were performed if indicated. Magnetic resonance imaging (MRI) and Contrast-enhanced computed tomography (CT) of the nasopharyngeal region and neck were performed to determine stage. The disease was staged according to the 2002 AJCC/UICC staging classifications.

Clinical data

From January 2007 to September 2008, 154 cases of nasopharyngeal patients at stage N2 ~ N3 were treated in the First Affiliated Hospital of Guangxi Medical University (Table 1), including 116 males and 38 females and with male to female ratio of 3.1:1. They were aging from 18 to 68 years old, with median age of 47 years. All cases were confirmed by histopathological examination. Of them, 13 cases were World Health Organization (WHO) subtype II (8.4%), and 141 cases were WHO subtype III (91.6%). Patients were randomly divided into control group (78 cases, radiotherapy + chemotherapy) and hyperthermia group (76 cases, radiotherapy + chemotherapy + hyperthermia). Of the 78 cases in the control group, 34 cases were in clinical stage III (2002 UICC staging system), and 44 cases were in stage IV. Of the 76 cases in hyperthermia group, 33 cases were in stage III, and 43 cases were in stage IV. Cervical lymph node metastasis (2002 UICC staging system) were all in stage N2 ~ N3. There was no significant difference in KPS score, histological type, clinical stage and N stage between two groups ($P > 0.05$).

Prior written and informed consent was obtained from every patient and the study was approved by the ethics review board of Guangxi Medical University.

Treatment method

(1) Control group: Control group received radiotherapy combined with chemotherapy. Radiotherapy was performed by weekly exposure of 2Gy per day for 5 days. The primary foci firstly received X ray of 6 MV on face and neck with a dose of DT36Gy. Afterwards, fields before ear of both sides received radiation of DT34 ~ 40 Gy. The total radiation for nasopharynx was DT70 ~ 78Gy, 35 to 39 times and 47 to 51 d in total. After the 6 MV perpendicular X ray radiation dose on cervical lymph node metastasis site reached 50Gy, 9 to 12 MeV electron beam radiation was used as supplement with total vertical radiation amount of DT68 ~ 72 Gy for 34 ~ 36 times in total of 46 ~ 50 d on the neck and with prophylactic dose of DT50 ~ 54 Gy.

Concurrent chemotherapy was performed during radiotherapy, which consisted of cisplatin alone (80 mg/

Table 2. Lymph Node Regression Rate and Survival Rate Analysis (n (%))

	Hyperthermia group (n = 76)	Control group (n = 78)	X^2	*P*
The lymph node regression rate at 3 months				
CR rate (%)	62 (81.6)	49 (62.8)	5.537	0.014
PR rate (%)	14 (18.4)	27 (34.6)	4.378	0.038
SD rate (%)	0 (0)	2 (2.6)	1.674	0.287
Efficacy (%)	100	97.4	2.976	0.078
Survival rate				
1-year survival rate	74 (97.4)	73 (93.6)	0.546	0.46
3-year survival rate	65 (85.5)	48 (61.5)	3.87	0.049
5-year survival rate	52 (68.4)	39 (50.0)	11.338	0.001
5-year local control rate	73 (96.1)	60 (76.9)	11.961	0.001
5-year distant metastasis rate	28 (36.8)	34 (43.6)	0.729	0.393
5-year DFS rate	39 (51.3)	16 (20.5)	15.908	0.001

m2/d, intravenous infusion over 2 hours on Days 1 and 22).

(2) Hyperthermia group: Radiotherapy and chemotherapy in hyperthermia group was the same as the control group. Pingliang 778WR-L-4 microwave hyperthermia machine (Sunostick Medical Technology Co., Ltd, London, UK), with frequency of 915 MHz and external heating diameter of 80 mm or 150 mm, was used for hyperthermia. Different types of radiators were used according to different tumor sizes and the radiator was 2 to 4 cm above the surface. The hyperthermia site was cooled with water bags. SYI thermal system (Sunostick Medical Technology Co.,Ltd, London, UK) was used to measure temperature of tumor center and surrounding area. And the surface temperature was maintained at 41.5°C to 42°C. Temperature measurement was performed 1 h before and after radiotherapy, and heating time was recorded every time. The duration of effective heating was 45 min, 2 times per week and 3 to 14 times in total.

For comparison of effect of hyperthermia pattern on regression, 36 patients received hyperthermia before radiotherapy and 40 patients received hyperthermia after radiotherapy. For comparison of effect of heating temperature on regression, 70 patients with well temperature curve were further divided into patients with T90 < 43°C treatment (28 cases) and patients with T90 ≥ 43°C treatment (42 cases). And to compare effect of heating time on regression, 15 cases received heating of < 4 times, 38 cases were treated with heating of 4-10 times and 23 cases received heating of > 10 times.

Patient evaluation and follow-up

All patients were evaluated at least once a week during the radiotherapy. The first assessment of tumor response was performed 1 month after the completion of radiotherapy by physical examination and flexible nasopharyngoscopy. This was followed by contrast-enhanced CT of the head and neck 3 months after radiotherapy. Then patients were followed up every 3 months from 3 months through 3 years, and every 1 year thereafter for 5 years. During every follow-up visit, disease status and treatment toxicity were assessed. Complete physical and fiberoptic nasopharyngoscopy or indirect nasopharyngeal speculum examinations were performed. The assessments included blood tests, biochemistry profiles, chest radiography, abdominal ultrasonography, and CT of the nasopharynx and cervical region. Further investigations were arranged as indicated. Management of residual disease and tumor relapse, if detected, was determined on a case-by-case basis. Nasopharynx MRI should be performed every six months. Local or cervical lymph node recurrence was examined by pathologic diagnosis. Suspicious metastasis was analyzed by thoracic and abdominal CT and bone scintigraphy. Acute and late adverse reaction was evaluated by standards of USA Radiation Therapy Oncology Group or European Organization for Research and Treatment of Cancer (Cox et al., 1995). Efficacy evaluation was in accordance with WHO Response Evaluation Criteria in Solid Tumors and classified as complete response (CR), partial response (PR), incomplete response/stable disease (SD) and progressive disease (PD). Neck mass was assessed by CT results. Regression of cervical lymph nodes was assessed 3 months after treatment. Complete regression was recorded as CR, and tumor size regression ≥ 50% was PR.

Statistical analysis

SPSS 17.0 software was used for statistical analysis. The Kaplan-Meier (Kaplan and Meier, 1958) method was used to compare the overall survival rate. Pearson Chi-Square test was used for the analysis of distant metastasis rate, disease-free survival rate (DFS) and local control rate. $P < 0.05$ was considered statistically significant.

Results

Regression rate of cervical lymph nodes in hyperthermia group is higher at 3 months after treatment

At 3 months after treatment, regression rate of cervical lymph nodes was evaluated. As shown in Table 2, the CR rate in hyperthermia treatment group and control group was 81.6% and 62.8%, respectively. And the difference between these two groups was significantly different ($P < 0.05$). Thus hyperthermia group had higher regression rate of cervical lymph nodes.

The 3-year and 5-year survival rates in hyperthermia group are higher

The follow-up was ended in May 2012, or 5 years after treatment or patient death, with a median follow-up time of 58 months. The follow-up was performed by telephone or letters and with successful rate of 96.1% (148/154). The 1-year, 3-year and 5-year survival rates were calculated. The results were shown in Table 2. The 1-year survival rate in hyperthermia group and control group was 97.4% and 93.6%, respectively. The 3-year survival rate in hyperthermia group and control group was 85.5% and 61.5%, and the 5-year survival rate was 68.4% and 50.0%, respectively. Statistically, there were significant differences in the 3-year and 5-year survival rate ($P < 0.05$), but not the 1-year survival rate ($P > 0.05$), between the hyperthermia group and control group. Therefore, hyperthermia group had higher 3-year and 5-year survival rates.

Table 3. The Lymph Node Regression in Hyperthermia Group Treated with Different Hyperthermia Pattern at 3-month and 5-year after Treatment (n (%))

Hyperthermia pattern	n	3-month		5-year	
		CR rate (%)	PR rate (%)	CR rate (%)	PR rate (%)
Hyperthermia before radiotherapy treatment	36	28 (77.8)	8 (22.2)	33 (91.7)	3 (8.3)
Hyperthermia after radiotherapy treatment	40	33 (82.5)	7 (17.5)	38 (95.0)	2 (5.0)
X^2		0.267	0.267	0.015	0.015
P		0.606	0.606	0.903	0.903

CR, complete response; PR, partial response

Table 4. The Lymph Node Regression in Hyperthermia Group Treated with Different Temperature at 3-month and 5-year after Treatment (n (%))

T90	n	3-month		5-year	
(°C)		CR rate (%)	PR rate (%)	CR rate (%)	PR rate (%)
< 43	28	18 (64.3)	10 (35.7)	24 (85.7)	4 (14.3)
≥ 43	42	36 (85.7)	6 (14.3)	41 (97.6)	1 (2.4)
X^2		4.375	4.375	8.491	8.491
P		0.036	0.036	0.004	0.004

CR, complete response; PR, partial response

Table 5. The Lymph Node Regression in Hyperthermia Group with Different Hyperthermia Treatment Times at 3-month and 5-year after Treatment (n (%))

Times of	n	3-month		5-year	
hyperthermia		CR rate (%)	PR rate (%)	CR rate (%)	PR rate (%)
< 4	15	10 (66.7)	5 (33.3)	11 (73.3)	4 (26.7)
4-10	38	31 (81.6)	7 (18.4)	37 (97.4)	1 (2.6)
> 10	23	16 (69.6)	7 (30.4)	19 (82.6)	4 (17.4)
X^2		3.906	0.035	7.272	0.47
P		0.046*	0.851	0.007*	0.493

Compared with hyperthermia times of 4-10 times, $*P < 0.05$. CR, complete response. PR, partial response

Hyperthermia group has higher local control rate and DFS rate

At 5 years after treatment, the local control rate, the distant metastasis rate and DFS rate were analyzed. As shown in Table 2, there was significant difference in local control rate (96.1% vs. 76.9%) and 5-year DFS rate (51.3% vs. 20.5%) between hyperthermia group and control group ($P < 0.01$). While the 5-year distant metastasis rate (36.8% vs. 43.6%) was not statistically significant ($P > 0.05$).

Comparison of adverse reactions

Two patients in control group and four patients in hyperthermia group presented skin moist dermatitis on the neck when the radiation dose was 45 to 55 Gy. After short suspension of radiotherapy and corresponding treatment for skin moist dermatitis, the skin healed and the treatment for NPC was continued. The moist dermatitis incidence was 5.7% (4/76) in hyperthermia group, and 2.6% in control group (2/78). The skin reaction was severe in hyperthermia group but without statistically significant difference ($P > 0.05$). No severe sequela or complication was observed in all patients during the five years follow-up. Data are not shown.

In hyperthermia group, 15 patients died of distant metastasis, including 3 cases of widespread metastases, 4 cases of liver metastases, 5 cases of lung metastases, and 3 cases of bone metastases. In control group, 17 patients died of distant metastasis, including 4 cases of widespread metastases, 5 cases of liver metastases, 4 cases of lung metastases, and 4 cases of bone metastases. In hyperthermia group, 6 patients died of recurrent NPC and nasopharyngeal bleeding, without cervical lymph node recurrence. While in control group, 6 patients died of recurrent NPC, 10 cases died of cervical and nasopharynx lymph node recurrence, including 3 cases of nasopharyngeal bleeding. Eight patients remained relapsed after second radiation. Data are not shown.

Hyperthermia pattern dose not affect regression of cervical lymph nodes

In order to evaluate the effect of hyperthermia pattern on regression of cervical lymph nodes, 76 patients in hyperthermia group were treated differently, with 36 patients received hyperthermia before radiotherapy and 40 patients received hyperthermia after radiotherapy. There was no significant difference in gender, age, KPS score, histological type, clinical stage and N stage between these of patients with different hyperthermia pattern ($P > 0.05$). The regression of cervical lymph nodes at 3 months and 5 years after treatment were evaluated, as shown in Table 3. The differences between hyperthermia before radiotherapy treatment and hyperthermia after radiotherapy treatment in CR rate were not significant (77.8% vs. 82.5%, 91.7% vs. 95.0%) ($P > 0.05$).

Heating temperature of T90 ≥ 43°C has higher cervical lymph node regression rate

Seventy cases of patients from hyperthermia group with well temperature curve were further analyzed for heat dosage. They were divided into patients with T90 < 43°C treatment (28 cases) and patients with T90 ≥ 43°C treatment (42 cases). There was no significant difference in gender, age, KPS score, histological type, clinical stage and N stage between these patients with different heating temperature ($P > 0.05$). At 3 months after treatment, the CR rate in patients with T90 < 43°C treatment and T90 ≥ 43°C treatment were 64.3% and 85.7% while the PR rate were 35.7% and 14.3%, respectively. And at 5 years after treatment, the CR rate in patients with T90 < 43°C treatment and T90 ≥ 43°C treatment were 85.7% and 97.6%, respectively. Statistically, the differences between T90 < 43°C treatment and T90 ≥ 43°C treatment were significant ($P < 0.05$). Therefore, the efficacy of cervical

lymph node regression in patients with T90 ≥ 43°C treatment was significantly higher than that in patients with T90 < 43°C treatment, as shown in Table 4.

Hyperthermia treatment times of 4-10 times have higher cervical lymph node regression rate

Patients in hyperthermia group received different amount of hyperthermia and the efficacy of different times of hyperthermia was compared at 3 months and 5 years after treatment (Table 5). There was no significant difference in gender, age, KPS score, histological type, clinical stage and N stage among these patients ($P > 0.05$). The CR rate was highest when the hyperthermia was 4-10 times at 3 months and 5 years after treatment (81.6% and 97.4%). Meanwhile, the PR rate was the lowest when the hyperthermia was 4-10 times (18.4% and 2.6%). And compared with patients with hyperthermia times of < 4 times and > 10 times, patients with hyperthermia times of 4-10 times had significantly higher regression rate ($P < 0.05$).

Discussion

In this study, complete lymph node regression rate in hyperthermia group and control group was 81.6% and 62.8% at 3 months after treatment ($P < 0.05$), and local control rate of cervical lymph node was significantly higher in hyperthermia group than that in control group at 5 years after treatment ($P < 0.01$). The 3-year and 5-year survival rate was statistically significant ($P < 0.05$). The 5-year DFS rate was statistically significant ($P < 0.01$). The 5-year distant metastasis rate was 36.8% and 43.6% respectively in hyperthermia group and control group, without significant difference ($P > 0.05$). Our results showed that local control rate of cervical lymph nodes, 3-year and 5-year survival rate and 5-year DFS rate was significantly higher in hyperthermia group, indicating that local hyperthermia can increase local control rate of cervical lymph nodes. In this study, there was no significant difference in the efficacy of distant metastasis control between the two groups. This might be associated with inadequate number of cases, or with the status of nasopharyngeal lesions, which needs to be further improved. Moreover, we observed some late toxicities (data not shown). The most common late toxicities were of grades 1 and 2 among patients with 5 years of follow-up. The skin reaction was severe in hyperthermia group but without statistically significant difference ($P > 0.05$). No severe sequela, or complication was observed in all patients during the five years follow-up. There was no significant difference of adverse reactions between the hyperthermia group and the control group. Deng et al. (2002) found that hyperthermia combined with radiotherapy and chemotherapy treatment could significantly improve the local control rate for patients with NPC staging in III and IVa without increasing toxicity, which was in accordance with this study.

Although hyperthermia with radiotherapy has been used for many years, the implement of hyperthermia such as its timing, treatment times and temperature is still controversial. Liu et al. (2005) showed that there was no significant difference in different procedure (hyperthermia before radiotherapy or radiotherapy after hyperthermia) on the inhibition rate of HeLa cells ($P > 0.05$). With same procedure but different time intervals (30 min, 2 h, 24 h), there was also no significant difference of inhibition rate on HeLa cells ($P > 0.05$). In this study, the cervical lymph nodes regression rate in patients with hyperthermia before radiotherapy treatment and those with hyperthermia after radiotherapy treatment was not statistically significant ($P > 0.05$). This data suggest that there was no significant difference in lymph node metastasis regression between hyperthermia before radiotherapy treatment and hyperthermia after radiotherapy treatment. And this data was consistent with findings of He et al. (2002) in esophageal cancer.

For the comprehensive treatment of superficial tumor with hyperthermia and radiotherapy, different hyperthermia times (such as 3-14 times) had different efficacies (Li and Hu, 1995; Liu et al., 1997). It is indicated that the number of hyperthermia is associated with clinical efficacy. In this study, we showed that CR rate were 66.7% (3-month CR rate) and 73.3% (5-year CR rate) in patients treated with hyperthermia < 4 times, 81.6% (3-month CR rate) and 97.4% (5-year CR rate) in patients treated with hyperthermia 4 - 10 times, and 69.6% (3-month CR rate) and 82.6% (5-year CR rate) in patients with hyperthermia > 10 times. Thus this result indicates that less than 4 times or more than 10 times of hyperthermia could not increase CR rate in tumor of relatively larger volume. Increasing the number of hyperthermia will not only increase the financial burden on patients, but also increase the incidence of heat injury.

It is reported that cell damage from temperature below 43°C is different from that over 43°C. The cytotoxicity target is different with temperature above 43°C and below 42.5°C. Thermal resistance can be changed in the heating process with temperature below 43°C. However, when temperature is above 43°C, thermal resistance cannot be further developed. Kapp and Cox (Kapp and Cox, 1995) analyzed the efficacy of 332 times of hyperthermia combined with radiotherapy in 83 cases of recurrent or metastatic breast cancer patients using the "heat map" or multi-point temperature measurement technology. They found that cumulative Eq min T90 at 43°C was significantly related with CR rate ($P < 0.01$) and with local control rate ($P < 0.01$). In this study, we showed that at 3 months after treatment, regression rate of cervical lymph node was 85.7% and 64.3% in patients with T90 ≥ 43°C treatment and those with T90 < 43°C treatment, and 97.6% and 85.7% at 5 years after treatment. The difference between patients with T90 ≥ 43°C treatment and those with T90 < 43°C treatment was statistically significant ($P < 0.05$).

In conclusion, microwave hyperthermia is easy to implement without significant side effects. For example, radiation skin reactions will not be increased by hyperthermia with carefully operating. Therefore, combination of hyperthermia with radiotherapy and chemotherapy for the treatment of cervical lymph node metastasis of NPC is an effective therapy that worth further study.

Acknowledgements

This work is supported by Key Research Projects of Guangxi Health Department (Grant No. 200626). The author(s) declare that they have no competing interests.

References

Chen J, Liu GG, Luo X (2009). Efficacy of radiotherapy plus microwave hyperthermia treatment for the neck fixed metastatic carcinoma. *J Prac Oncol*, **24**, 487-9.

Colombo R, Moschini M (2013). Role of the combined regimen with local chemotherapy and Mw-induced hyperthermia for non-muscle invasive bladder cancer management. A systematic review]. *Urologia*, **80**, 112-9.

Cox JD, Stetz J, Pajak TF (1995). Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys*, **13**, 1341-6.

Erkal HS, Serin M, Cakmak A (2001). Nasopharyngeal carcinomas: analysis of patient, tumor and treatment characteristics determining outcome. *Radiother Oncol*, **61**, 247-56.

Fleming ID, Cooper JS, Henson DE, et al (1997). AJCC Cancer Staging Manual. 5th ed. Philadelphia, PA: Lippincott-Raven.

Ghahremani FH, Sazgarnia A, Bahreyni-Toosi MH, Rajabi O, Aledavood A (2011). Efficacy of microwave hyperthermia and chemotherapy in the presence of gold nanoparticles: an in vitro study on osteosarcoma. *Int J Hyperthermia*, **27**, 625-36.

Hei BW, Zhao YT, Zhang GF, et al (2002). An evaluation of short-term clinical effectiveness in the treatment of advanced esophageal carcinoma with radiotherapy, radio-frequency hyperthermia and immunotherapy. *J South Yangtze Univ*, **1**, 425-8.

Jen YM, Lin YS, Su WF, et al (2002). Dose escalation using twice-daily radiotherapy for nasopharyngeal carcinoma: does heavier dosing result in a happier ending? *Int J Radiat Oncol Biol Phys*, **54**, 14-22.

Kaplan EL, Meier P (1958). Nonparametric estimation from incomplete observation. *J Am Stat Assoc*, **53**, 457-81.

Kapp DS, Cox RS (1995).Thermal treatment parameters are most predictive of outcome in patients with single tumor nodules per treatment field in recurrent adenocarcinoma of the breast. *Int J Radiat Oncol Biol Phys*, **33**, 887-99.

Lee AW, Sze WM, Yau TK, et al (2001). Retrospective analysis on treating nasopharyngeal carcinoma with accelerated fractionation (6 fractions per week) in comparison with conventional fractionation (5 fractions per week): Report on 3-year tumor control and normal tissue toxicity. *Radiother Oncol*, **58**, 121-30.

Levendag PC, Lagerwaard FJ, de Pan C, et al (2002). High-dose, high-precision treatment options for boosting cancer of the nasopharynx. *Radiother Oncol*, **63**, 67-74.

Li DJ, Hu ZX (1995). Hyperthermia science [M]. *Henan Medical University Press*, **8**, 366-9.

Li G, Mitsumori M, Ogura M (2004). Local hyperthermia combined with external irradiation for regional recurrent breast carcinoma. *Int J Clin Oncol*, **9**, 179-83.

Li ZQ, Zhang WM, Li J, et al (2004). Curative effect of radiochemical therapy and hyperthermia therapy for nasopharyngeal carcinoma with cervical lymph node metastasis. *J Prac Med*, **20**, 532-3.

Liu MT, Hsieh CY, Chang TH, Lin JP, Huang CC, Wang AY (2003). Prognostic factors affecting the outcome of nasopharyngeal carcinoma. *Jpn J Clin Oncol*, **33**, 501-8.

Liu SX, Chen DX, Zhang SJ, et al (1997). The treatment of nasopharyngeal carcinoma by using thermoradiotherapy. *J Clin Otorhinolaryngol*, **11**, 150-2.

Liu YS, Niu JW, Zhang WH, et al (2005). The experimental study of the effects of radiotherapy combined with hyperthermia on the HeLa Cells of cervical carcinoma in laboratory. *J Cap Univ Med Sci*, **26**, 593-6.

Lu H, Yao M (2008). The current status of intensity-modulated radiation therapy in the treatment of nasopharyngeal carcinoma. *Cancer Treat Rev*, **34**, 27-36.

Nikfarjam M, Muralidharan V, Malcontenti-Wilson C, Christophi C (2005). The apoptotic response of liver and colorectal liver metastases to focal hyperthermic injury. *Anticancer Res*, **25**, 1413-9.

Perez CA, Brady LW (1987). Hyperthermia Principles and Practice of Radiation oncology. *JB Lippincott Company*, 317-52.

Roychowdhury DF, Tseng AJr, Fu KK, Weinburg V, Weidner N (1996). New prognostic factors in nasopharyngeal carcinoma. Tumor angiogenesis and C-erbB2 expression. *Cancer*, **77**, 1419-26.

Song LQ, Wang XJ, Guan HT, et al (2006). Study of high power microwave hyperthermia combined with chemotherapy in the treatment of patients with advanced cancer. *Shanxi Med J*, **11**, 1437-9.

Tate DJ, Adler JR, Chang SD, et al (1999). Stereotactic radiosurgical boost following radiotherapy in primary nasopharyngeal carcinoma: impact on local control. *Int J Radiat Oncol Biol Phys*, **45**, 915-21.

Teo PM, Leung SF, Chan AT, et al (2000). Final report of a randomized trial on altered-fractionated radiotherapy in nasopharyngeal carcinoma prematurely terminated by significant increase in neurologic complications. *Int J Radiat Oncol Biol Phys*, **48**, 1311-22.

Wolden SL, Zelefsky MJ, Hunt MA, et al (2001). Failure of a 3D conformal boost to improve radiotherapy for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys*, **49**, 1229-34.

Yin WB, Yu ZH, Xu GZ, et al (2008). Radiation oncology [M]. Fourth edition. Beijing: China Union Medical University Press, 451. [in Chinese].

Zastrow E, Hagness SC, Van Veen BD (2010). 3D computational study of non-invasive patient-specific microwave hyperthermia treatment of breast cancer. *Phys Med Biol*, **55**, 3611-29.

Zheng Z, Zhang Y, Pan JJ, et al (2006). Results of hyperthermia for cervical lymph node metastasis in nasopharyngeal carcinoma. *J Fujian Med Univ*, **40**, 629-31.