RANDOMIZED CONTROLLED TRIAL ACCELERATED HYPERFRACTIONATION RADIOTHERAPY CONCURRENT WITH CISPLATINUM VERSUS CONVENTIONAL RADIOTHERAPY FOR TREATING LOCALLY ADVANCED NASOPHARYNGEAL UNDIFFERENTIATED CARCINOMA

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ABSTRACT

Background : Nasopharyngeal carcinoma (NPC) is the most frequent head and neck cancer, and a serious health problem in most radiotherapy centers in Indonesia. Patients usually come when they are in locally advanced stage, with poor prognosis.

Problem encountered in the bulky primary tumor and lymph node metastasis in the neck of the locally advanced stage III and IV, non distant metastasis, which is the majority of cases particularly in the hospitals in Indonesia. The result of the treatment with radiotherapy is unsatisfactory. For this reason, attention is being paid to the combined use of modified radiation therapy and chemotherapy for solving this problem. Chemotherapy would probably increase the chances of local tumor control, either by : (1) reducing cell burden in tumors undergoing radiotherapy, (2) rendering tumor cells more suspectible to radiation damage, or (3) spatially cooperating radiotherapy through its systemic action on micro metastastic disease.

Objective : To investigate the efficacy of concurrent therapy Cisplatinum + accelerated hyperfractionation radiotherapy (C+AHR) for treatment of un differentiated type (WHO type III) carcinoma of the nasopharynx in locally advanced stage, compared to the treatment of conventional radiotherapy (CRT).

Material and method : Randomized control trial is designed in two arms,: investigated arms consist of 55 cases of Nasopahryngeal carcinoma stage III and IV without distance metastasis, undifferentiated carcinoma histology, treated concurrently with Cisplatinum + accelerated hyperfractionation,, radiotherapy (C+AHR), a two fraction dose per day, and the dose per fraction is 125 cGy, with the interval between fraction 4-6 hours to total dose equal with 70 Gy. Control arm consists of 55 cases NPC, treated with only conventional radiotherapy (CRT) of 70 Gy. Observation after treatment includes (1) Response of the primary tumor, (2) response of the lymph node metastasis in the neck, (3) relapse of the primary tumor and lymph node metastasis, (4) Duration of free disease interval.

Result : (1) Response of the primary tumor : in the arm treated with Cisplatinum

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+radiotherapy accelerated hyperfractionation , complete response in the primary tumor is 52/55 (94.5%), compared to conventional Radiotherapy, wich is only 33/55 (58. 9 %). The differences of statistical analysis are significant ($p < 0.001$). (2) Response of the Lymph node metastasis : C + AHR : 47/55 (8.5%), CRT: 39/55 (69.6%) $p = 0.131$ (3) Relapse rate of the primary tumor : C+AHR : 10/55 (18.2%), CRT : 27/55 (48.2%) $p = 0.007$. (4) Relapse rate of lymph node metastasis in the neck : C+AHR : 13 / 55 (23. 6%), CRT 16 / 55 (28. 6%) $p = 0.554$ (5) Duration of relapse : C+ AHR : mean duration of local free relapse 17 .2 months, and CRT : 9.11 months. F probability 0.003. This mean C+ AHR is able to inhibit the development of local relapse.

Conclusion : Radiotherapy accelerated hyperfractionation, conncurrent with Cisplatinum for treament of local advanced Undifferentiated Carcinoma of the nasopharynx produce better result compared to the conventional fractionation of external radiotherapy, in terms of local response, relapse rate and disease free interval.

BACKGROUND

The failure of treating local advanced Nasopharyngeal carcinoma with conventional radiation therapy is widely published. The efficacy of radiotherapy as a single modality treatment in patients with local or regional advanced cancers is limited by a number of factors : (1) High number of clonogenic cells, (2) Intrinsic cellular radioresistance, (3) Repair proficiency from radiation damage, (4) Hypoxia, and (5) accelerated cell proliferation. Tumor cells may resist undergoing cell death after radiation, efficiently repair DNA damage, may be able to resume or even accelerate proliferation in the period between radiation fractions, or posses radioresistence associated with hypoxia within the tumor mass. In addition, occult tumor cells may exist outside the irradiated field and thus lead to distant metastasis. For this reason , increased attention is being paid to the combined use of radiotherapy and chemotherapy. Chemotherapeutic agent increases the chances of local tumor control, either by : (1) Reducing cell burden in tumors undergoing radiotherapy or by (2) Rendering tumor cells more suspectible to radiation damage. (3) They may also spatially cooperate with radiotherapy through their systemic action on micro metastasic disease.[1]

Several approaches have been used in combining radiotherapy and chemotherapy. They include alternating chemotherapy and radiotherapy, which is given before radiation (neo adjuvant chemotherapy) or after radiation adjuvant chemotherapy), administration of drug during the course of radiation (Concurrent or simultaneous chemotherapy)

The rationale of accelerated hyperfractionation is based on the fact that malignant cells after single hit of one radiation fraction of 2 Gy, small part of cell going to cell death because of severe double strand break damage of DNA, but another surviving fraction still becomes sub lethal because of the moderate damage of DNA, such as single strand break DNA, base damage, sugar damage, DNA-DNA Cross link or DNA Protein cross link. These sub lethal cells, within 4 to 6 hours, are going to repair from sublethal damage, and after 6 hours, complete repair has been done, and the cells become potent malignant cells. These lead to repopulation after the completion of radiotherapy and residual disease after radiotherapy.[2] The second fraction of radiation therapy is given within 4 to 6 hours after the first fraction, the process of repairing DNA will be inhibited, and

lead to cell death. This procedure of radiotherapy is called accelerated hyperfrac-tionation.[4]

The administration of cisplatinum which also inhibits and destroys DNA by 4 types of cross links, will enchance cell killing of malignant cells in accelerated hyperfractionation combined simultaneously with cisplatinum.

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MATERIAL AND METHOD

All cases were nasopharyngeal carcinoma Stage III and IV without distant metastasis (T3 N0-3 M0, T4, N0-M0), Undifferentiated carcinoma histology, admitted to DR. Sardjito Hospital during 1993-1998, which were selected using exclusion and inclusion criteria One hundred and eleven cases were collected, and randomized, into two groups. The first group consisted of 55 cases treated with radiotherapy accelerated hyperfractionation simultaneously with cisplatinum, and the second group consisted of 56 cases treated with conventional radiotherapy.

INCLUSION CRITERIA

(1) Minimum age was 10 years old and maximum 80 years old. and average was 45. (2) Perfomance status measured uses Karnofski Index, minimum 70 (3) Normal haemopoetic system (normal WBC, haemoglobin and platelet count) (4) TNM stage III (T3N0M0, T1-2-3 N1M0) and stage IV without distant metastasis (T4N0M0, T1-2-3N2-3M0, T1-2-3N1-2-3 M0). (5) Undifferentiated carcinoma is the histology of the nasophrayngeal cancer. This histologic type is the most frequent (95%) of all Nasopahryngeal cases admitted to RSUP. DR. Sardjito Hospital in Yogyakarta (6) Normal function of the visceral organs, normal liver function test, normal kidney function and normal heart detected by electrocardiograph.

EXCLUSION CRITERIA

(1) Distant metastasis including lung metastasis was detected by chest x ray, and liver metastasis was detected by abdominal ultrasonography and laboratory test. Bone metastasis was detected by bone scintigraphy. Brain metastasis was detected by head CT Scan (2) Having previous radiotherapy or chemotherapy, or locoregional recurrences after previous treatment (3) Diabetes mellitus (4) Heart diseases including coronary heart disease, malignant hypertension, defect of valve caused by reheumatic heart disease, congenital heart diseases.

CRITERIA OF RESPONSE

The criteria of response include : (1) local response (2) regional response (3) Local relapse (4) regional relapse (5) duration of relapse

The determination of Local response of the primary tumor by clinical examination, rhinoscopy anterior / posterior, done by two ENT surgeons, and the disagreement were measured by Kappa index. Head CT scan with axial and coronal plane, observed by two radiologists. The disagreement was measured by Kappa Index.

Determination of regional remission was done by properly palpating and measuring the size of lymph node metastasis of the neck by two Radiation Oncologists. The disagreement was measured by Kappa index.

The disappearance of primary tumor after treatment had to be proven histologically. A re-biopsy of the primary tumor was done 3 months after the completion of treatment. The specimen of biopsy was then scored into 7 categories: Score 1: Malignant cell intact, no change at all. Score 2: There was a change of the differentiation of malignant cells. Score 3 : There were changes from undifferentiated into moderate differentiation. Score 4 ; There were changes from undifferentiated into good differentiation. Score 5: Malignant cells underwent subtotal necrosis with differentiation. Score 6 : Malignant cells underwent total necrosis. Score 7 : Malignant cells completely dissappeared

RESEARCH DESIGN

Research design was a randomized control trial with two arms. One arm was the investigated arm, treated with radiotherapy accelerated hyperfractionation combined simultaneously with Cisplatinum. The other arm was the control arm, treated with conventional radiotherapy. Statistical analyses of Chi square Pearson method were used to analyse the significance, multi variate analysis was used to investigate the variables, the distribution of which was not homogeneous. The research design as seen in figure I

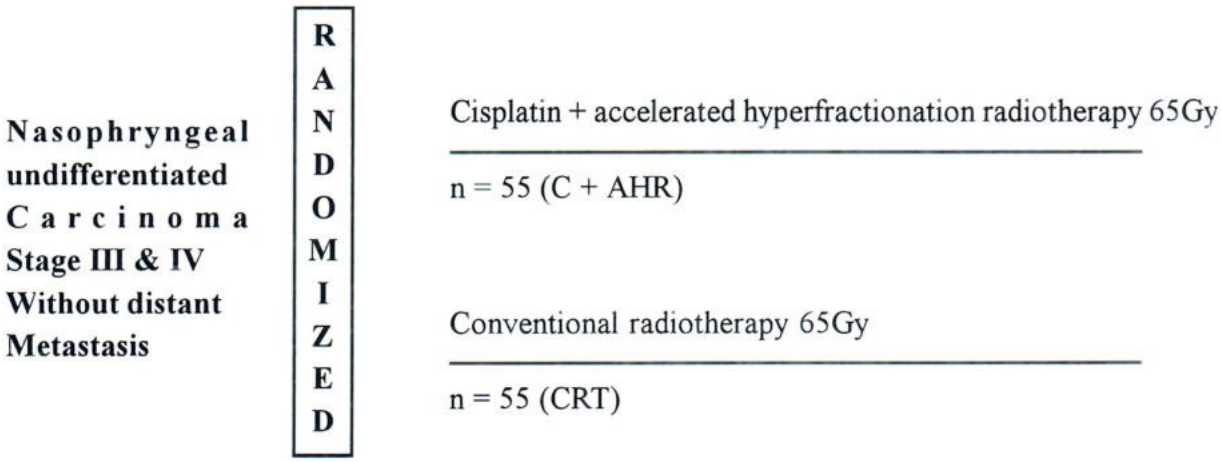


Fig. 1. A schematic diagram of a randomized control trial. First arm consisted of 55 cases, treated with Cisplatin 100 mg + Radiotherapy accelerated hyperfractionation which equal to 65 Gy. Control or second arm consisted of 55 cases, treated with conventional radiotherapy 65 Gy.

TREATMENT PROCEDURE

ACCELERATED HYPERFRACTIONATION RADIOTHERAPY

The external radiation therapy using two fractions a day with fraction size 1,25 Gy. The interval between fraction minimal 4 hours and maximal 6 hours. The total dose would be equal to 65 Gy. After 40 Gy, shielding to spinal cord was done. After 50 Gy, a rest of a week was given to relief severe mucositis

CISPLATINUM

Cisplatinum were given prior to accelerated hyperfractionation radiotherapy. A total dose of 100 mg Cisplatinum were given in divided doses, 20 mg per day for 5 days in 500 cc Dextrose. Prior the administration of cisplatinum, a hydration with Dextrose 5% 1500cc and diuresis with mannitol 20 % 500cc were given, in order to eliminate the nephrotoxicity of cisplatium. For anti-vomiting, ondansetron 8 mg were given prior the administration of Cisplatinum, oral or intravenous.

CONVENTIONAL RADIOTERAPY

The conventional radiotherapy using single fraction a day, with fraction size 2 Gy per fraction. Total dose 65 Gy. after 40 Gy a shield of spinal cord were done. After 50 Gy, a rest of one week were given to relief mucositis.

RESULT

RESPONSE OF PRIMARY TUMOR

The response of the primary tumor in the group treated with combination of Cisplatinum and radiotherapy accelerated hyperfractionation seemed to be much more superior than the result of conventional radiotherapy. In the group treated with Combination of Cisplatinum + Radiotherapy accelerated hyperfractionation complete remission was achieved in 52 cases (94,5 %), only 3 cases had partial remission (5,5 %) and no one had no change (nc) or progressive diseases (pd). In the control arm, of conventional radiotherapy complete remission occurred in only 33 cases (58,9%), 22 cases had partial remission (39,5 %) and 1 case (1,8 %) did not change (nc). The statistical differences were very significant ($p < 0,001$) as shown in table 1.

Stastical analyses of Chi square table Pearson Method revealed a very significant difference in the result of this two types of treatment. The treatment with cipslatin + radiotherapy accelerated hyperfractionation was more superior than the conventional radiotherapy, with $p < 0,001$ (table 1)

Table 1. Response of the Primary tumor of the nasopharyngeal carcinoma undifferentiated type, fisrt arm consists of 55 cases treated with 100 mg cisplatinum + accelerated hyperfractionation radiotherapy (CISPL + AHR). And second arm consist of 56 cases treated with Conventional radiotherapy (CRT)

Type of treatment	Complete Remission (CR)		Partial Remission (PR)		No Change (NC)		Progressive Disease (PD)		Total	
	N	%	n	%	n	%	n	%	n	%
CISPL + RAH	52	94.5	3	5.5	0	0	0	0	55	49.5
Conventional Radiotherapy	33	58.9	22	39.5	1	1.8	0	0	56	50.5
	85	76.6	25	22.5	1	0.9	0	0	111	100
										P < 0. 001

RESPONSE OF LYMPH NODE METASTASIS

The reponse in the lymph node metastastic tumor in the neck region was not as good as the result of the primary tumor. This was probably influenced by many factors: (1) The difference in the nature of the tumor, (2) the environment where the tumor grows, (3) the vascularization systems of the lymph node influencing the distribution of chemotherapy cisplatinum, and (4) the hypoxic cells inside the tumor.

Even there were differences between the results of the two treatments, the results of concurrent chemo radiation cisplatin + radiotherapy accelerated hyperfractionation were better than conventional radiotherapy, but the statistical analyses with Chi square Pearson method was p = 0, 131 , or the difference was not significant (table 2).

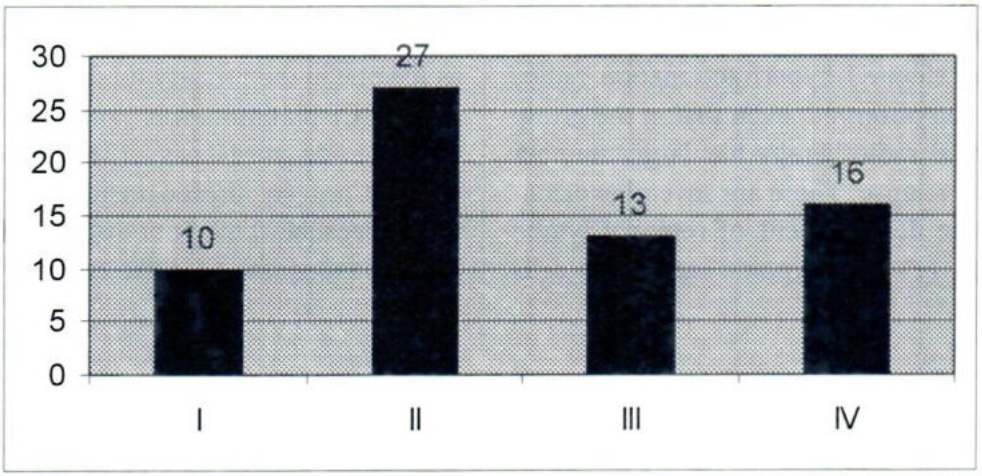
The explanation of this phenomenon could be several points: (1) The differences of vascularization in the lymph node metastasis were not as rich as those of vascularization in the primary tumor of the nasopharynx, this lead to hypoxia of the majority of the malignant cells in the lymph node that made intrinsic cellular resistence within the cells. (2) In the big lymph node metastasis in the neck, (N 3) there was a high number of clonogenic cells (3) The ability of malignant cells to repair proficiency from radiation damage

Table 2. Response of the lymph node metastastis of nasopharyngeal undifferrentiated carcinoma in the neck region. The first arm treated with Concurrent Cisplatin 100 mg in 5 days + accelerated hyperfractionation radiotherapy. The second arm treated with conventional radiotherapy.

Type of treatment	Complete Remission		Partial Remission		No Change		Progressive Disease		Total	
	N	%	n	%	n	%	n	%	n	%
CISPLATIN + RAH	47	85.5	7	12.7	1	1.8	0	0	55	49.5
Conventional Radiotherapy	39	69.6	14	25.0	3	5.4	0	0	56	50.5
	86	77.5	21	18.9	4	3.6	0	0	111	100
	P = 0. 131									

LOCO REGIONAL RELAPSE
LOCAL RELAPSE

After the completion of the treatment in both arms, observation was periodically made every month until 2 years after the treatment, to observe : (1) The locoregional relapse (2) The duration of the development of locoregional relapse. The result of this observation can be seen in figure 2



I : Primary tumor relapse group cisplatinum + AHR
II : Primary tumor relapse conventional radiotherapy
III : Regional lymph node metastasis relapse group cisplatinum + AHR
IV : Regional lymph node relapse conventional radiotherapy

Fig. 2. Local relapse in the primary tumor in group of Cisplatin + AHR (I) compared to Conventional Radiotherapy (II). Regional relapse in the Lymph node in Group of Cisplatin + RTAH (III) compared to Conventional Radiotherapy (IV).

Statistical analysis was done by Chi Square Pearson method resulted in $p = 0.007$ ($p < 0.05$). There is significant difference in local relapse treated by concurrent Cisplatin + Radiotherapy accelerated hyperfractionation with much less relapse compared to conventional Radiotherapy (table 3)

Table 3. Local relapse in the primary tumor of Nasopharyngeal undifferentiated carcinoma local advanced Stage III and IV without distant metastasis treated with concurrent cisplatin + accelerated hyperfractionation radiotherapy compared to conventional Radiotherapy

Type of treatments	Relapse +		Relapse --		
	n	%	n	%	P
Cisplatin + accelerated hyperfractionation radiotherapy	10	18.2	45	81.8	0.007
Conventional Radiotherapy	27	48.2	29	51.8	

REGIONAL RELAPSE

The regional relapse in the lymph node metastasis of undifferentiated nasopharyngeal carcinoma, after the treatment with concurrent cisplatin + accelerated hyperfractionation radiotherapy was still observed, even that in the group of Conventional radiotherapy has larger number of lymph node relapse. There are several explanations about the development of regional lymph node relapse.: (1) The hypoxic malignant cells resistance to radiation, then lead to residual disease and create regional relapse (2) The vascularization in the lymph node tumor was not as good as the one in the primary tumor, then the distribution of Cisplatinum was not optimal inside the Lymph node metastasis . (3) The repair mechanism is not so altered inside the lymph node tumor because of the poor distribution of Cisplatin due to inadequate vascularization

Table 4. Lymph node metastasis tumor relapse after the treatment with Cisplatin + Radiotherapy accelerated hyperfractionation and Conventional Radiotherapy.

Type of treatments	Relapse +		Relapse --		P
	n	%	n	%	
Cisplatinum + radiotherapy accelerated hyperfractionation	13	23.6	42	76.4	0.554
Conventional Radiotherapy	16	28.6	40	71.4	

Statistical analysis reveals p = 0,554 (p< 0,05), the differences in regional lymph node relapse after the treatment are not significant in both treatments.

DURATION OF FREE DISEASE

DURATION OF LOCAL RELAPSE.

Local relapse in the arm consisting of 55 cases treated with Cisplatinum + Radiotherapy accelerated hyperfractionation, was only 10 cases (18.18%), and the mean duration of relapse (disease free) was 17.2 month

Among local relapses in the control arm consisting of 56 cases treated with conventional Radiotherapy, 27 cases have local relapse (48.21%). Mean duration of local relapse (disease free) was 9.11 months. Statistical analyses of F Probability 0,003. This means the addition of Cisplatinum and radiotherapy accelerated hyperfractionation is able to delay the development of local relapse.

DISCUSSION

Undifferentiated carcinoma of the nasopharynx is the most frequent head and neck cancer in Indonesia .Treatment in early stage T1 and T2 with small tumor using conventional radiotherapy, the result is satisfactory. But in locally advanced disease with large tumor in T3 or T4, the result is poor. Innovation in the treatment of this local advanced stage nasopharyngeal undifferentiated carcinoma should be created to obtain better result, by analyzing factors causing the failure of radiotherapy treatments. The factors are : (1) Large tumor have clonogenic cells, (2) Intrinsic cellular resistence (3) Repair proficiency from radiation damage (4) Hypoxia (5) Accelerated cell proliferation (6) Repair mechanism in the malignant cells. These factors are taken into account in designing innovation in radiotherapy. The most suitable method to overcome this problem is Cisplatinum concurrent with accelerated hyperfractionation radiotherapy. To make sure that the result is better, compared to conventional radiotherapy. The result in group treatment of cisplatin + accelerated hyperfractionation radiotherapy is significantly better compared to conventional radiotherapy (p < 0,001). The local relapse rate is significantly better compared to the conventional radiotherapy (p = 0,007)

CONCLUSION

Local advanced stages of nasopharyngeal undifferentiated carcinoma, if treated with concurrent cisplatin + accelerated hyperfractionation radiotherapy, the result of treatment compared to the result of Conventional Radiotherapy alone : The complete response of the primary tumor of the Nasopahrynx are much better than the conventional radiotherapy

The complete response in the lymph node metastastic tumor in the neck are better in the treatment of Cisplatin + accelerated hyperfractionation radiotherapy, compared to the conventional radiotherapy alone, but statistically not significant.

Relapse rate in the primary tumor of nasopharynx is significantly much less in the treatment group of cisplatin + accelerated hyperfractionation radiotherapy compared to the conventional radiotherapy. The relapse rate in the lymph node metastasic tumor of the neck, the differences between the two treatment modalities were not statistically significant

The duration of development of local relapse in the primary tumor of nasopahrynx (disease free survival period) is significantly longer in the group treated with cisplatin + accelerated hyperfractionation radiotherapy compared to the conventional radiotherapy alone.

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