Radiotherapy Alone Versus Combined-Modality Therapy for Initial Treatment of Early Stage Hodgkin's Lymphoma

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Abstract: Purpose: Retrospective analysis and comparison of the efficacy, feasibility and long term side effects, of combined-modality therapy (CMT) versus radiotherapy alone as front-line therapy in early stage Hodgkin's lymphoma (HL). **Patients and Methods:** Between January 1998 and January 2008, 115 patients with early stage IA and IIA Hodgkin's lymphoma were allocated to receive either radiotherapy alone (n= 43), with a mean dose, of 40 Gy, or radiochemotherapy (n = 72) with low dose involved field radiotherapy (LDIFRT), with a mean dose, of LDIFRT of 30 Gy. The primary endpoint of this study was overall and disease -free survival time at 5 and 10 years in both treatment arms. Secondary endpoints included treatment response, tolerability and late treatment related events of each schedule. Kaplan-Meier method estimated overall survival (OS) and disease -free survival (DFS). Log rank test compared survival curves with p value ≤ 0.05 considered significant. **Results:** A total of 115 eligible patients were analyzed. Adverse prognostic factors were almost higher in the CMT group. Both treatment protocols could be delivered in an optimal dose and without significant delay. After 10 years of follow-up CMT produced significantly less nausea and vomiting ($p = 0.023$), as well as less incidence of second malignancy ($p = 0.001$), also less pulmonary toxicity ($p = 0.11$), Hyporthyroidism ($p = 0.07$), cardiac complications ($p = 0.38$), and Hyperthyroidism ($p = 0.19$) but without statistical significance. For CMT arm, the 10-years DFS and OS were 87% and 83%, respectively, compared with 75% and 71%, respectively, for the radiotherapy alone arm. Elevated ESR > 50 ($p = <0.001$), stage IIA disease ($p = 0.01$), and involvement of > 3 lymph node sites ($p = 0.003$) had statistically significant adverse effect on the OAS. However age, sex, pathological subtype, and bulky mediastinum had no statistically significant effect on the OAS (all p = NS). Univariate analysis of factors that might affect DFS showed that patients with involvement of < 3 lymph node sites ($p = 0.007$), ESR < 50 ($p = 0.001$) and stage IA disease ($p = 0.01$), had statistically significant longer DFS. Conclusion: In patients with early stage HL, a CMT results in less incidence of late treatment related events, and has a trend toward better DFS and OS, when compared with radiotherapy alone, however a larger number of patients and longer follow-up is required for a definitive statement on survival.

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Key words: early stage IA and IIA Hodgkin's lymphoma, combined-modality therapy, radiotherapy alone, prognostic factors, toxicity.

1. Introduction

Hodgkin's lymphoma (HL) is one of the most common malignancies in young adults[1,2]. It has become a highly curable cancer[3,4]. Patients have a relatively long survival, although a few studies have concluded that the death rate of patients with HL still is greater than that of the general population[5,6]. This may relate to various complications, such as second malignancies[7-11], cardiac toxicity[12-14], and infections[6]. Twenty years after their treatment, more patients have died from other causes than from HL[6,15]. Given an overall 5-year relative survival rate of 85% for patients with HL[16], and the fact that the highest incidence rates occur between ages 20 and 34 years, large numbers of patients remain at lifelong risk for the late effects of treatment. Because treatment efficiency has improved dramatically, one way to improve long-term survival is to reduce mortality from causes other than HL.

In limited-stage disease (stages I and II), HL can be cured in the majority of patients by a variety of treatments used on their own or in combination. Combined chemotherapy and radiation is the most effective treatment approach for early stage Hodgkin lymphoma. Chemotherapy with involved field radiation therapy (IFRT) is shown to be superior to radiation therapy alone in a large EORTC clinical trial[17]. Most trials have shown that two to six cycles of chemotherapy with IFRT is adequate treatment for early stage HL[17-22], as regard, cure and in minimizing toxicity, especially late toxicity that has an impact on future quality of life and survival[23].

We now present our experience with the combined-modality therapy versus radiotherapy alone schedule at our Clinical Oncology Department, Tanta University Hospital in 115 patients with limited-stage HL and report on efficacy and late treatment related events of each schedule.

2. Patients and Methods

Patients

Between January 1998 and January 2008, 115 eligible patients had histologically verified HL based on the World Health Organization (WHO) histologic classification, stages IA and IIA according to the American Joint Committee on Cancer (AJCC), Seventh Edition, 2010 for HL. The medical records of all patients at our Clinical Oncology Department, Tanta University Hospital were properly revised, organized, and analyzed to achieve the goal of our work.

Exclusion criteria included the following: KPS scale < 70, age greater than 75 years or less than 18 years, previous treatment with chemo- immuno-, or radiotherapy for HL, inadequate bone marrow function (WBC count < 3.0 x 10^9/L or platelet count < 100 x 10^9/L), inadequate renal function (serum creatinine of no more than 1.25 x upper normal limit or creatinine clearance < 60 mL/min/1.73 m^2), and inadequate liver function (serum bilirubin of more than 1.25 x upper normal limit). Also patients were excluded if they had a history of ventricular arrhythmia, congestive heart failure, or documented myocardial infarction. Pregnant and lactating patients were also excluded, as were patients with inadequacy of follow-up.

Investigations

The following parameters were assessed at baseline: KPS, weight, nodal examination, computed tomography (CT) scan of the neck, chest, abdomen and pelvis, ECG, echocardiography, ESR, LDH, blood counts (hemoglobin, granulocytes, and platelets), and blood chemistry (renal and liver function tests). All baseline parameters, except the CT scan of the neck, chest, abdomen and pelvis, and ECG, were performed before each cycle.

Blood counts were performed weekly during treatment. Assessment of nodal areas, 1 month after the patient stopped therapy and then every 3 months together with assessments of ESR, LDH, blood counts, chemistry, weight, performance status, toxicity, and general examination. Scans were performed at the time when progressive disease was suspected on clinical examination or every follow-up visit. Follow-up visits were scheduled every 3 months in the first 2 years after cessation of treatment and every 6 months thereafter, for a median follow-up time of 132 months (mean; 113.4 months, range; 1 - 137 months).

Treatment

Patients were allocated to receive either radiotherapy alone (n= 43), or radiochemotherapy (n= 72) with low dose involved field radiotherapy (LDIFRT). The mean dose of radiotherapy in the radiotherapy alone arm was 40 Gy (range, 35 to 45 Gy). Standard radiotherapy treatment was 30 Gy to the primary wide field, with a smaller field boosted to a total dose of 40 Gy. In the radiochemotherapy arm (n= 72) the mean dose, of LDIFRT was 30 Gy (range, 20 to 36 Gy). The chemotherapy regimen in patients who were to receive the combined-modality therapy (CMT), was administered in the form of ABVD (Adriamycin "doxorubicin", bleomycin, vinblastine, dacarbazine). The schedule was repeated for 4- 6 cycles followed by LDIFRT. Before every cycle of chemotherapy, standard premedication was administered with dexamethasone 20 mg intravenously (IV), diphenhydramine 50 mg IV, and cimetidine 300 mg IV (or ranitidine 50 mg IV) were administered 30 minutes before chemotherapy. Antiemetics were administered at the oncologist's discretion.

In the CMT arm dose reductions were performed according to nadir and nadir duration. Most of the patients received at least 4 cycles of protocol treatment unless they developed progressive disease or unacceptable toxicity. In patients with assessable disease and no change in disease status after six cycles, treatment was continued by 2nd line therapy, but subsequent treatment protocol in these patients was left to the discretion of the oncologist and not reported in our study.

Toxicity and Response Criteria

Late complications were scored according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring schema[24]. No special investigations were required. Tumor response was evaluated according to modified WHO criteria. Complete response was considered to be the disappearance of all known disease, together with a return to within-normal values of relevant blood chemistries, including ESR and LDH, for at least 4 weeks. Partial response was considered to be a ≥50% decrease in tumor area (calculated by multiplying the longest diameter by the greatest perpendicular diameter) or, in the case of multiple lesions, a ≥ 50% decrease in the sum of the products of the perpendicular diameters of the multiple lesions. Progressive disease was defined as a greater than 25% increase in the size of the target lesion or, in the case of several target lesions, a greater than 25% increase in the sum of the products of the perpendicular diameters of these lesions or the appearance of any new lesion. An increase in ESR and/or LDH levels not associated with radiologic or clinical evidence of tumor progression was not used as the sole indicator of progressive disease. Stable disease was defined as a bidimensionally measurable decrease of less than 50% or increase of less than 25% in the sum of the products of the largest perpendicular diameters of all measurable lesions for at least 6 months.

Outcome Measures

The primary endpoint of this study was overall and disease -free survival time at 5 and 10 years in both treatment arms. Secondary endpoints included treatment response, tolerability and late treatment related events of each schedule.

Statistical Methods

The date of final analysis was November 2011. Patients' first relapse (as measured by physical examination and ultrasound or CT scan) served as the end point for DFS. If clinical detection of disease was preceded by an elevation in ESR and/or LDH levels, the date that the ESR and/or LDH levels were first above normal was recorded.

Disease free survival was measured from the day of starting treatment until the date of documented disease relapse or to last follow-up. Overall survival (OS) time was calculated from the time of diagnosis until death from any cause or to the date of last follow-up. SPSS version 17.0 was used for data management. Kaplan Meier method[25] estimated OS and DFS. Log rank test compared survival curves with p value ≤ 0.05 considered significant.

3. Results

Between January 1998 and January 2008, the total number of patients eligible for this study was 115. Patient and tumor characteristics are listed in table 1. Adverse prognostic factors were almost significantly higher in the CMT group. The mean age in both treatment arms was identical: 30 years.

Treatment Compliance

Most patients (97.6% in the radiotherapy alone arm and 90.3% in the CMT arm) received the full dose of the planned treatment protocols. Treatment delays of 7 days or more occurred more frequently in the CMT arm than in the radiotherapy alone arm (9.3% versus 11.1%, respectively) but without statistically significant difference ($p = 0.94$), (Table 2).

Dose reductions were performed infrequently. Overall, only 8 patients (6.9%, 8/115) received at least one dose reduction (Table 2). There was no statistically significant difference between the treatment arms in the percentage of patients with dose reductions (2.4% in the radiotherapy alone arm versus 9.7% in the CMT arm; $p = 0.98$). The mean radiotherapy doses for all patients in the radiotherapy alone and CMT arms were 40 Gy and 30 Gy, respectively.

Response to Treatment and Survival

Although not statistically significant the CMT protocol was associated with more clinically complete response (Table 2) than the radiotherapy alone protocol (98.6% versus 95.3%, respectively, $p= 0.11$). The higher response rates following treatment with the CMT protocol did not result in a significant superior DFS ($p=0.12$), or a significant better OS ($p=0.17$) (Figs. 1, 2).

Patients were followed for a median of 132 months, range; 1 – 137 months (mean±SD = 130 ± 36.6 month). With respect to the primary endpoint, the difference in the DFS at 5 and 10 years was not statistically significant different between the 2 treatment arms (85% and 75%, respectively for the radiotherapy alone arm versus 90% and 87%, respectively for the CMT arm).

Univariate analysis of factors that might affect DFS showed that patients with a number of lymph node sites of less than 3 before start of treatment ($p = 0.01$), ESR < 50 ($p = 0.001$), and stage I disease ($p = 0.01$), had statistically significant longer DFS while age ($p = 0.12$), sex ($p = 0.11$), and pathological subtype ($p = 0.59$), had no significant impact on DFS (Table 3).

Elevated level of ESR > 50 ($p = < 0.0001$), stage II ($p = 0.01$) and number of lymph node sites > 3 ($p = 0.003$) had statistically significant adverse effect on the OS. However, age ($p = 0.19$), sex ($p = 0.15$), pathological subtype ($p = 0.66$), and presence of bulky mediastinum ($p = 0.26$) had no statistically significant impact on the OS (Table 4).

Late events after therapy

Late events after therapy were evaluated and summarized in table 5. After about 10 years of follow-up CMT produced significantly less nausea and vomiting ($p = 0.02$), as well as less incidence of second malignancy ($p = 0.001$). Other late events including pulmonary toxicity ($p = 0.11$), Hypothyroidism ($p = 0.07$), cardiac complications ($p = 0.38$), and Hyperthyroidism ($p = 0.19$) were more frequent in the radiotherapy alone arm than in the CMT arm but this difference was not statistically significant (all p = NS) (Table 5).

Table 1. Patient and tumor characteristics in patients with early stage HL by treatment arm

	Radiotherapy alone arm		Combined-modality therapy arm		*P* value
	No.	%	No.	%	
No. of patients	43		72		
Age					
≥50 years	19	44.2	28	38.9	0.57
< 50 years	24	55.8	44	61.1	
Stage					
I	18	41.9	7	9.7	<0.001
II	25	58.1	65	90.3	
Pathological type					
Nodular sclerosis (NS)	27	62.8	53	73.6	0.51
Mixed cellularity (MC)	10	23.3	9	12.5	
Lymphocyte depletion (LD)	1	2.3	2	2.8	
Lymphocyte predominance (LP)	5	11.6	8	11.1	
Lymph node sites					
≥3	6	13.9	21	29.2	0.06
<3	37	86.1	51	70.8	
Karnofsky performance status					
≥90%	31	72.1	44	61.1	0.52
<90%	12	27.9	28	38.9	
Bulky mediastinum					
Yes	1	2.3	20	27.8	0.001
No	42	97.7	52	72.2	
Sex					
Male	21	48.8	39	54.2	0.58
Female	22	51.2	33	45.8	
ESR					
High	4	9.3	17	23.6	0.05
Normal	39	90.7	55	76.4	

Table 2. Therapy and efficacy parameters in patients with early stage Hodgkin's disease by treatment arm

Parameters	Radiotherapy alone arm		Combined-modality therapy arm		*P* value
	No.	%	No.	%	
Dose reduction for any reason					
No	42	97.6	65	90.3	0.98
Yes	1	2.4	7	9.7	
Treatment delay, days					
0	33	76.7	53	73.6	0.94
1 – 6	6	14	11	15.3	
≥ 7	4	9.3	8	11.1	
Clinical response					
Complete	41	95.3	71	98.6	
Stable disease	1	2.4	0	0.0	0.12
Progressive disease	1	2.4	1	1.4	
Relapse of disease at 10 years					
No	33	76.7	64	88.9	0.11
Yes	10	23.3	8	11.1	

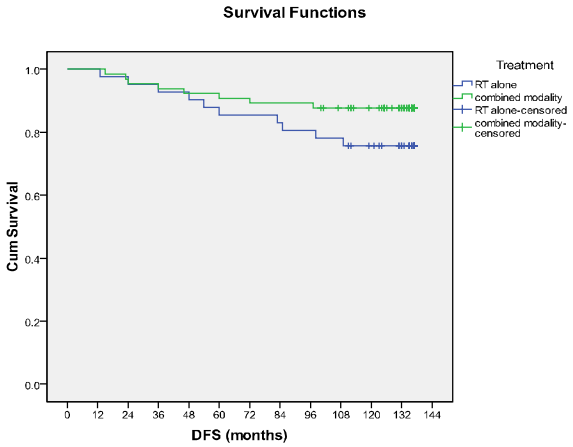

Figure 1. Kaplan–Meier Curves for Disease-Free Survival Time in Patients with Early Stage Hodgkin's Disease by Treatment Arm. Patients were assigned to receive either combined-modality therapy or radiotherapy alone. There was no statistically significant difference between the two treatment arms (p= 0.12).

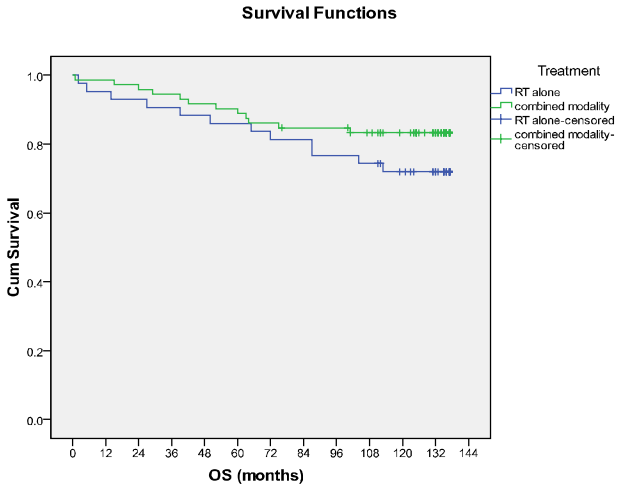

Figure 2. Kaplan–Meier Curves for Overall Survival Time in Patients with Early Stage Hodgkin's Disease by Treatment Arm. Patients were assigned to receive either combined-modality therapy or radiotherapy alone. There was no statistically significant difference between the two treatment arms (p= 0.17).

Table 3. Factors affecting disease-free survival in patients with early stage HL by treatment

Patient characteristics	Radiotherapy alone arm		Combined-modality therapy arm		*P* value
	5y DFS	10y DFS	5y DFS	10y DFS	
Age					
≥50	82	76	91	87	0.12
<50	83	75	90	88	
Sex					
Male	80	65	87	81	0.11
Female	90	85	93	93	
Pathological type					
NS	100	92	96	96	
MC	40	20	33	0.0	0.59
LD	0	0	0	0	
LP	100	100	100	100	
ESR					
>50	0.00	0.00	54	45	0.001
<50	89	79	98	96	
Stage					
I	100	94	100	100	0.01
II	73	60	89	86	
LN sites					
>3	4	0	60	46	0.01
<3	91	86	100	100	

Table 4. Factors affecting overall survival in patients with early stage HL by treatment arm

Patient characteristics	Radiotherapy alone arm		Combined-modality therapy arm		*P* value
	5y OS	10y OS	5y OS	10y OS	
Age					
>50	91	74	90	88	0.19
<50	78	68	85	75	
Sex					
Male	85	61	84	74	0.15
Female	86	81	93	93	
Pathological type					
NS	96	88	94	94	
MC	60	20	55	16	0.66
LD	0	0	50	0	
LP	100	100	100	100	
ESR					
>50	0	0	58	32	<0.001
<50	94	79	98	98	
Stage					
I	100	94	100	100	0.01
II	76	56	87	81	
LN sites					
>3	50	0	66	47	0.003
<3	91	83	98	98	
Bulky mediastinum					
YES	0	0	90	90	0.26
NO	88	73	88	80	

Table 5. Late events after therapy

Event	Number of Events After Therapy				*P*- value
	Radiotherapy alone arm		Combined-modality therapy arm		
	No.	%	No.	%	
Number of all Events	**38**		**25**		**0.18**
Second malignancy	6	14	0	0	0.001
Cardiac	5	11.6	5	6.9	0.38
Pulmonary Grade < 3 Grade > 3	 0 3	 0 7	 1 0	 1.4 0	0.11
Hypothyroidism	17	39.5	17	23.6	0.07
Hyperthyroidism	1	2.3	0	0	0.19
GIT	3	7	0	0	0.02
Other	3	7	2	2.8	0.28

4. Discussion

This study was designed to test the hypothesis that the tolerability advantage that CMT has over radiotherapy alone is maintained without affecting efficacy. To our knowledge, this is the first study at our Clinical Oncology Department, Tanta University Hospital focusing on patients with early stage Hodgkin's lymphoma that compares radiotherapy alone with CMT consisting of chemotherapy plus additional LDIFRT.

The primary endpoint of this study was to compare the efficacy of CMT with radiotherapy alone arms. The results of the CMT regimen were not statistically significantly different from those of the radiotherapy alone schedule in terms of DFS (p =0.113), or OS (p =0.173). The EORTC H7F trial compared radiotherapy alone schedule to CMT consisting of 6 cycles chemotherapy and involved-field radiotherapy [(26)]. Similarly, ten-year OS was not different in the 2 groups[(26)]. This notion was supported by a clinical trial comparing CMT with radiotherapy alone in which no significant survival disadvantage was observed in patients receiving CMT[(27)]. In this trial, 5-year DFS and OS was better but without statistical significant difference in the group receiving CMT[(27)].

In our study, the 5-year DFS rate was 85% and 90% for patients in the radiotherapy alone arm and CMT arm respectively, while the 5-year OS rate was 86% and 88% for patients in the radiotherapy alone arm and CMT arm respectively. This is comparable to that observed in other three published trials[(28-30)].

In this study elevated level of ESR > 50, stage II and number of lymph node sites > 3 had statistically significant adverse impact on the OS. Univariate analysis of our data revealed the well-known prognostic factors of number of lymph node sites of less than 3, ESR < 50, and stage I disease, to be statistically significant predictors for longer DFS. Similarly, early on the EORTC identified features at presentation that allow patients to be stratified into more favorable or less favorable prognostic groups. The unfavorable group comprised patients aged >50 years with clinical stage II and 2 to 5 involved nodal areas, if no B symptoms ESR >50 or with B symptoms ESR >30[(31)].

Secondary endpoints of our study included treatment response, tolerability and late treatment related events of each schedule. The CMT regimen was associated with a higher complete response rate than the radiotherapy alone schedule but without statistical significance. However, the results for the response analysis should not be over-interpreted because the minority of patients (9.7%) in the CMT arm had stage I compared to 41.9% of the patients in the radiotherapy alone arm (p = < 0.001). Moreover, the study population was not stratified with respect to presence or absence of bulky mediastinum (27.8% of cases in the CMT arm versus 2.3% in the radiotherapy alone arm { p = 0.001} had bulky mediastinum) or number of lymph node sites (29.2% of cases in the CMT arm versus 13.9% in the radiotherapy alone arm { p = 0.06} had > 3 lymph node sites), thus adverse prognostic factors were almost significantly higher in the CMT group which may have resulted in imbalances within this subset of patients. In their HD7 trial[(18)] the German Hodgkin Study Group (GHSG) showed in 650 patients that 2 cycles of ABVD followed by extended-field radiotherapy (EFRT) was superior to EFRT alone in clinical stages I-IIB. However, in the HD8 trial[(20)] 1204 patients with stages I and II, apart from more acute hematological, gastrointestinal and mucosal toxicity after extended-field radiotherapy, there was no difference between the trial arms in terms of complete response rates, freedom-from-treatment failure and overall survival, leading to the conclusion that when combined with effective chemotherapy a reduction in field size from extended to involved is entirely appropriate[(20)].

In this study, the radiotherapy in the CMT arm was able to be delivered in an adequate dose. The dose

of radiotherapy used in our study is accepted by many as the optimal dose for radiotherapy in a combination regimen, and proof is lacking that a higher dose is more efficacious[32,33]. Results in these trials suggested no relevant radiotherapy dose effect exists in the range of 20 to 40 Gy following 4 cycles of modern chemotherapy, indicating that doses of more than 30 Gy were no longer appropriate[32,33]. Thus devotees of the "more is better" school of oncology must face the uncomfortable truth that many trials have failed to show survival benefit associated with an increase in the total dose or dose-intensity of radiotherapy[32,33].

In 2005, the Institute of Medicine and the National Research Council of the National Academies issued the report *From Cancer Patient to Cancer Survivor: Lost in Transition*[34]. Recommendations in this report included the conduct of additional studies to measure the prevalence and risk of late effects. Thus, it becomes increasingly important for health-care providers to evaluate the risk of late sequelae, and to be able to critically evaluate research results. The need is especially important for clinicians who take care of patients with HL, in view of the escalating number of reports which document late effects[35].

Given in our study, that 5-year DFS rate was 85% and 90% for patients in the radiotherapy alone arm and CMT arm respectively, while the 5-year OS rate was 86% and 88% for patients in the radiotherapy alone arm and CMT arm respectively, and the fact that the highest incidence rates occur between ages 20 and 35 years, thus, large numbers of patients remain at lifelong risk for the late effects of treatment.

With respect to late events after therapy we found that after a median follow-up of 132 months, CMT produced significantly less nausea and vomiting, as well as less incidence of second malignancy. Other late events including pulmonary toxicity, Hypothyroidism, cardiac complications, and Hyperthyroidism were more frequent in the radiotherapy alone arm than in the CMT arm but this difference was not statistically significant (all p = NS). The results of our study were supported by the findings of other clinical trials, Hoppe[36] and Aleman et al[6] found that second primary cancers are the leading cause of death in patients with HD[6,36]. Another study demonstrated that survivors are also at elevated risks for cardiac disease, pulmonary disorders, endocrine dysfunction, and other sequelae[35]. For patients with early stage disease, the 20-year cumulative secondary malignancy rate is estimated between 4% and 20%[37,38]. Risk factors for secondary malignancies and cardiac disease are the choice and dose of chemotherapy and radiotherapy[5,6,37-42]. Koontz *et al.*[27] demonstrated that CMT resulted in statistically significant less incidence of Hypothyroidism (p = 0.0027), as well as less incidence of second malignancy (p = 0.023) than in the radiotherapy alone arm[27]. Our data confirmed this finding and this reduced late treatment related toxicities in the CMT arm was accompanied by an improvement in quality-of-life.

In summary, the results of our study showed that the CMT regimen used is safe and easy to administer in our patients. The regimen is overall less toxic than the wide field high dose radiotherapy alone schedule. Because the treatment related late events of the CMT regimen was lower than that of the radiotherapy alone regimen with comparable OS and DFS, the substitution of CMT for wide field high dose radiotherapy alone schedule is not only feasible, but may be in the patients' best interest. The regimen was so well associated with less treatment related late events that its widespread use at this point in time is recommended by several authorities in the field[17-23,27].

We recommend evidence-based treatment for early stage HL which will require large prospective randomized trials comparing efficacy, toxicity, and quality of life. Because of the complex relationship between treatment efficacy and toxicity and the diverse assumptions and expectations for treatment held by patients with cancer, the comprehensive measurement of health status should become an important and appropriate component of many clinical trials.

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