Journal of the Egyptian Nat. Cancer Inst., Vol. 17, No. 2, June: 85-92, 2005

A Randomized Study of Accelerated Fractionation Radiotherapy with and Without Mitomycin C in the Treatment of Locally Advanced Head and Neck Cancer

MOHAMAD EZZAT, M.D.*; TAREK SHOUMAN, M.D.*; KHALED ZAZA, M.D.*; AKMAL SAFWAT, M.D.*; AHMAD EL-KHOUDARY, M.D.**; MOHAMAD EL-SENOSI, C.E.S.* and IBRAHIM EZZAT, C.E.S., F.A.C.R.*

The Departments of Radiation Oncology and Medical Oncology**, National Cancer institute, Cairo University.*

ABSTRACT

Objectives: This single-institution study evaluates the feasibility of accelerated fractionation radiotherapy (AF) with and without mitomycin C (MMC) in the treatment of locally advanced head and neck cancer.

Patients and Methods: Between May 1998 and October 2001, sixty patients with locally advanced stage III and IV of head and neck cancer were randomized into three treatment arms: (1) conventional fractionation radiotherapy (CF) (5 fractions per week); (2) accelerated fractionation radiotherapy (AF) (6 fractions per week); and (3) AF plus Mitomycin C (MMC).

Results: The 2-year overall survival (OS) of the whole group was 21%. The OS according to treatment arm was 23%, 20%, and 28% in CF, AF, and AF+MMC arms respectively (p<0.19). The 2-year loco-regional control (LC) rate was 22% for the whole group of patients. The LC was 10%, 25%, and 30% for the CF, AF, and AF+MMC respectively (p=0.27). The only significant parameters for OS and LC were performance status and pre-treatment hemoglobin level. Mucositis grades 3 & 4 occurred in 70% and 90% of the patients in the AF and AF+MMC arm respectively compared to 55% of patients in the CF arm (p=0.04). However the addition of MMC did not significantly increase the incidence or severity of mucositis between AF and AF+MMC (p=0.13). Hematological toxicity grades 3 & 4 were significantly higher after MMC (occurred in 40% of patients versus 10% and 5% in CF and AF arms respectively, p=0.04). There was no statistically significant difference in the incidence of grade 3 dryness of mouth (p=0.06), fibrosis (p=0.6), or lymphoedema (p=0.39) among the three arms.

Conclusion: There was a trend for improvement of LC and OS rates with the use of AF and the addition of MMC to AF compared to CF radiotherapy, although the difference was not statistically significant. The small number of the patients in each treatment arm and the inclusion of multiple tumor sites may contribute to these statistically insignificant results. Accordingly we advise to continue the trial with inclusion of a larger number of patients and restrict tumor sites to one major site.

Key Words: *Head and Neck cancer - Radiotherapy - Altered fractionation - Mitomycin C.*

INTRODUCTION

Squamous cell carcinoma of the head and neck region is a loco-regional disease, whereas distant metastases are infrequently seen at the time of diagnosis. Radiotherapy and surgery are thus the treatment of choice **[1]**. One of the important biological factors related to the outcome of radiotherapy in squamous cell carcinoma is the association of proliferation of tumor cells during treatment period, thus prolongation of the treatment time may reduce the chance for tumor control and in contrast, substantial number of clinical reports indicated that a reduction in the overall treatment time may result in improved local control **[2,3,4]**. Various strategies for reduction of the overall treatment time were investigated including pure treatment acceleration, split course, concomitant boost, and continued hyper fractionated accelerated radiotherapy (CHART) **[5-10]**. These studies showed encouraging results as regards local control rate **[6,7,10]**. However the increased incidence and severity of acute mucosal reactions in these studies were dose limiting factors. The effectiveness of radiation therapy is also limited by the presence of hypoxic cells, which are relatively radio-resistant. Substantial evidence suggested that human tumors especially squamous cell carcinoma of the head and neck contain a large amount of hypoxic tumor cells

[11-14]. To achieve the same proportion of tumor cell killing, about three fold of the radiation dose is required for hypoxic cells compared to that for well-oxygenated cells **[15]**. Methods to overcome hypoxia include blood transfusion, normobaric or hyperbaric oxygen breathing or hypoxic radiosensitizers. In recent years, cytotoxic drugs especially directed against radioresistant hypoxic cells have been tested. Most of these agents are metabolically activated under reductive hypoxic conditions. Theoretically, the concomitant administration of Mitomycin C and radiation therapy should result in an enhanced effect since these agents are directed against different tumor subpopulations **[12,16, 17]**. The analysis of the results of the studies using Mitomycin C and radiotherapy, so far suggests that Mitomycin C improves the radiation induced local tumor control without enhancing the radiation reactions in normal tissues **[18,19]**.

The aim of this study was to evaluate the therapeutic gain of using accelerated fractionation radiotherapy with or without Mitomycin C in the treatment of locally advanced head and neck cancer.

MATERIAL AND METHODS

Between May 1998 and October 2001, sixty patients with locally advanced stage III and IV squamous cell carcinoma of the head and neck were enrolled in this study. They were treated at the radiation oncology department of the National Cancer Institute (NCI), Cairo University. Eligibility criteria included tumors classified as stage III-IV according to TNM classification (UICC 1987) located in the oropharynx, hypopharynx, larynx, and oral cavity with histopathological diagnosis of squamous cell carcinoma. Patients were ≥18 up to 70 years of age, had performance status of 0-2 according to WHO criteria and had no prior chemotherapy, radiotherapy or surgery except for biopsy. Patients with proven distant metastasis or synchronous multiple malignancies were excluded.

All patients underwent uniform staging procedures including: Physical examination, routine laboratory tests (complete blood count, hepatic and renal function), and imaging studies including computerized tomographic (CT) scan of primary site and draining lymph nodes, chest radiograph, and abdominal ultrasound. Bone scan was optional when there was suspicion for bone metastasis. Fiber-optic endoscopy of upper aero-digestive tract was routinely done.

Randomization: Patients were randomized to either conventional (CF) or accelerated fractionation (AF) radiotherapy with or without Mitomycin C. The overall study design is shown in Fig. (1).

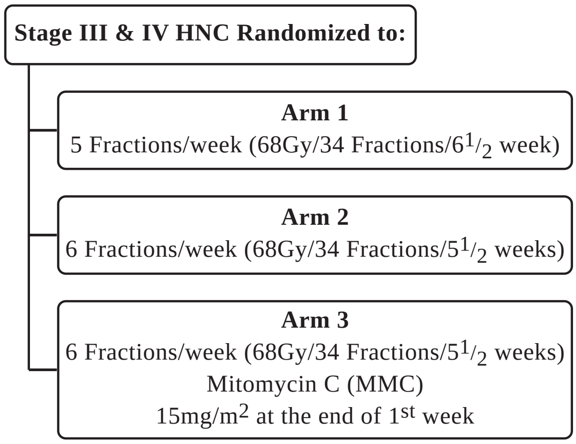

Fig. (1): Randomization scheme.

Radiation treatment: Prior to treatment, dental care was done for all patients. Patients were immobilized with individually made plastic casts. All patients were treated in the supine position. Simulation was carried out for all patients in the treatment position. The treatment portals were tailored according to site of primary tumor and draining lymph nodes. All patients were treated by 6MV photon beam and electron beam of appropriate energy. The total dose for the three arms was 68GY and the dose per fraction was 200cGy. The clinical target volume (CTV) received a dose of 50Gy and the gross target volume (GTV) including the primary tumor and gross palpable lymph node was treated to 68Gy. The spinal cord should not receive more than 45Gy.

Chemotherapy: Mitomycin C was given in one arm only with AF radiotherapy. It was given with a dose of 15mg/m^2 as an IV infusion over 15 minutes. The drug was given once at the end of the first week of radiotherapy after complete hematological assessment. On the day of drug treatment, radiation was given first followed by the drug 2 hours later.

Follow up: During treatment, patients were examined weekly. The treatment toxicity was reported according to the RTOG/EORTC scoring of acute and late radiation reactions. Patients were assessed for treatment response 2 months after end of radiation treatment. Treatment evaluation included computerized tomographic (CT) scan and fiber-optic examination. Patients were followed up every 2 months for the first year and every 3 months for the second year and semiannually thereafter.

Statistical analysis:

Survival is defined as the time from registration to death regardless of the cause. Survival and local control curves were constructed by the method of Kaplan-Meier **[20]**. Statistical comparisons were conducted by the log rank test **[21]**. Descriptive statistics were presented as means ± standard deviation and number and percentage (frequency distribution). Analytical tests included unpaired student *t* test (two sided) for comparing two groups.

RESULTS

This study included 60 patients, 20 patients in each arm. All patients completed their treatment. The period of follow-up ranged from 6 to 42 months with a median of 10.5 months. Table (1) shows the patients characteristics and their distributions according to treatment arm. There was no significant difference in the distribution between the three arms.

The pre-radiotherapy Hb level for the whole group of patients ranged from 8 to 15.7g/dl with a median value of 12g/dl with comparable results between the three arms. The Hb level at the end of treatment (week 7) ranged from 6 to 13.6g/dl, with a mean value of 10.7g/dl. The post treatment means Hb values were 10.8g/dl, 11.4g/dl and 9.9g/dl for CF, AF, and AF + MMC arms respectively.

Forty two patients (70%) required intravenous fluid (IV) or tube feeding during their treatments (55% in CF arm, 75% in AF arm, and 80% patients in AF + MMC arm).

For the whole group of patients the overall treatment time (OTT) ranged from 38 to 66 days with a median value of 48 days. The median value of OTT was 55, 43, and 42 days for CF, AF, and AF + MCC arms respectively. Seven, 8 and 8 patients in CF, AF, and AF + MMC, respectively, completed their treatment in the planned OTT (38% compliance rate).

Treatment response: Twenty patients achieved CR (25%) (4 in CF arm, 9 in AF arm, and 7 in AF + MMC arm). The remaining 40 patients showed partial regression or disease progression. The duration of CR ranged from 3 to 42 months with a median value of 7 months. Ten patients sustained CR (2 in CF, 3 in AF, and 5 in AF + MMC arm), while the other 10 patients failed. The cause of failure was tumor recurrence in 6 patients, 2 of them associated with nodal failure. Distant metastases occurred in 4 of these 10 patients (3 patients in the AF arm, and one patient in AF + MMC arm). All patients failed within a period of 3-7 months with a median value of 5 months.

Distant metastasis: It occurred in 6/60 patients (10%); one patient in the CF arm, 3 in the AF arm and 2 patients in AF+ MMC arm (p=0.2). The site of the primary tumor was hypopharynx in 2 patients, oropharynx in 3 patients and laryngeal in one patient. In 3 patients, the distant metastases were the only site of failure, in the other 3 patients the distant metastases were associated with loco-regional failure.

Overall survival: The 2-year overall survival (OS) for the whole group of patients was 21% (Fig. 2). In a univariate analysis, we studied the influence of age, sex, performance status (PS), histopathological grade, primary site, pre-radiotherapy hemoglobin level and treatment arm. The only prognostic factors were PS and pre treatment hemoglobin level. The OS for patients with PS0 was 40% compared to 21% for patients with PS1-2 (p<0.005). The OS was significantly better for patients with Hb >12g/dl than for patients with Hb ≤12 (40% Vs 16%, p<0.04). According to treatment arm, the OS of patients treated in AF + MMC arm was 28% compared to 23% in the CF arm and 20% in the AF arm (Fig. 3), but the difference was not statistically significant (p<0.19).

Local control: The 2-year loco-regional control rate (LC) for the whole group of patients was 22%. In a univariate analysis, we studied the influence of age, sex, performance status (PS), histopathological grade, primary site, pre-radiotherapy hemoglobin level and treatment arm. As in OS estimation, the only prognostic factors were PS and pre treatment hemoglobin level. Patients with PS0 were associated with significant better loco-regional control rate

(39%) compared to patients with PS1-2 (13%) (p<0.026). Also patients with the pre treatment Hb level >12g/dl had better LC rate (31%) than for patients with Hb ≤12 (13%) (p<0.05). The treatment arm had no significant impact over LC rate, whereas AF + MMC arm showed LC rate of 30% compared to 25% and 10% for AF and CF arms (p<0.27) (Fig. 4).

Early normal tissue reactions:

Mucositis: All patients experienced mucositis grade 1-2, while grades 3 & 4 occurred in only 70% (43/60 patients). The incidence of high grade mucositis (Gr 3 & 4) was significantly higher in AF + MMC arm (18/20 patients; 90%) compared to 11/20 patients (55%) in CF arm and 14/20 patients (70%) in AF arm (p<0.04).

Skin reaction: There was no significant difference in the incidence of grade 3 & 4 skin reaction between the three treatment arms.

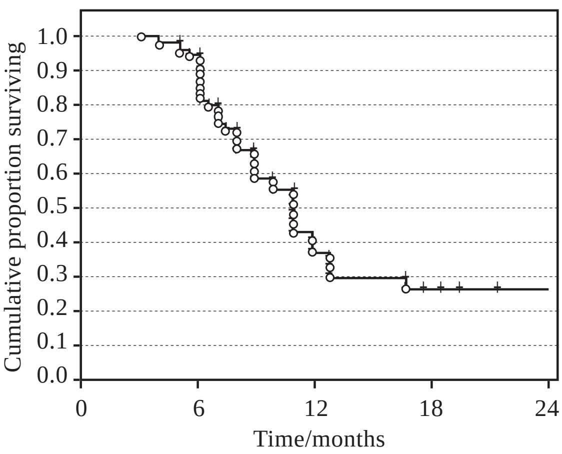

Fig. (2): Overall survival for the whole group of patients.

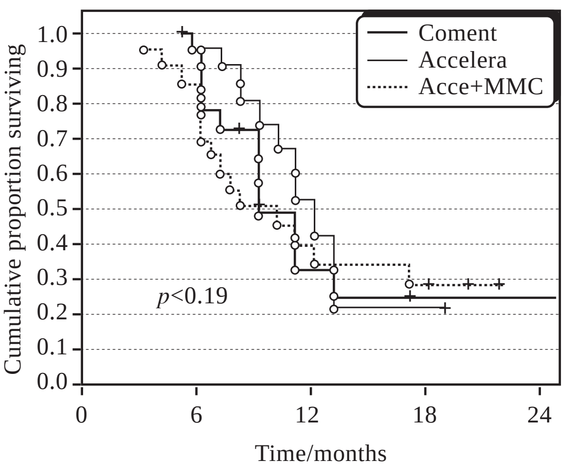

Fig. (3): Overall survival according to treatment arm.

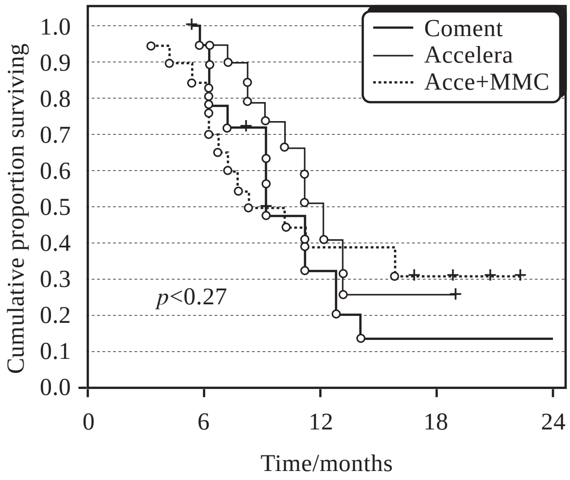

Fig. (4): Local control rate according to treatment arm.

Table (1): Distribution of patients' characteristics according to treatment arm.

Characters	CF	AF	AF+ MMC	Total No. (%)
Age (mean)	53	54	49	
Sex:				
Male	6	5	9	20 (25)
Female	14	15	11	40 (75)
Performance status:				
P0	8	10	5	23 (38)
P1	8	8	14	30 (50)
P2	4	2	1	7 (12)
Site:				
Oral cavity	4	5	6	15 (25)
Oropharynx	5	5	4	14 (23)
Hypopharynx	6	5	3	14 (23)
Larynx	5	5	7	17 (29)
Stage:				
III	7	10	7	24 (40)
IV	13	10	13	36 (60)
T-stage:				
T2	1	4	1	6 (10)
T3	10	10	8	28 (47)
T4	9	6	11	26 (43)
N-stage:				
N0	5	7	5	17 (28)
N1	8	7	6	21 (35)
N2	6	5	5	16 (27)
N3	1	1	4	6 (10)
Histopathological Gr.:				
G1	5	2	4	11 (18)
G2	11	10	12	33 (55)
G3	4	8	4	16 (27)
Pre treatment Hb % (mean)	12	12.5	11.5	

Hematological toxicity: There was a high incidence of grade 3 and 4 hematological toxicity in the AF + MMC arm, 8 patients (40%), with only 2 patients in CF arm and one patient in AF arm. This difference was statistically significant (*p*=0.04).

Late normal tissue reactions:

There was no significant difference in grade 3 dryness of the mouth, subcutaneous fibrosis, trismus and lymphoedema between the three arms. Severe post radiation laryngeal edema occurred in two patients with cancer larynx (one in the AF arm, and the other one was in the AF + MMC arm), which necessitated tracheostomy done for them. Three patients (one in each arm) developed malignant fistulae 2-3 months after the end of treatment due to disease progression.

DISCUSSION

Squamous cell carcinoma of head and neck is predominantly a loco-regional disease, and the primary treatment methods are radiotherapy and surgery **[22]**. Head and neck cancer can be cured by radiation, but tumors might be heterogeneous for intrinsic radiosensitivity. The heterogeneity results in variation in the total dose needed to control the tumor, the presence of tumor hypoxia with the consequential hypoxic radioresistance, and tumor cell proliferation during treatment **[2,13,22,23]**.

A cause of treatment resistance could be radiation induced accelerated proliferation of colonogenic tumor cells. A reduction of chance of tumor control through the lengthening of radiation treatment time has been proved clinically and biologically **[2,5]**. Furthermore, in several clinical studies, reduction in the total treatment time has improved tumor control **[1,24]**. Various AF schedules have been proposed with efficacy confirmed by randomized trials **[5-9]**. The DAHANCA-7 schedule **[10]** was an attractive one to be investigated in our patients as there was lower risk of excessive late toxicity and the number of fractions remained the same, so that no extra hours of machine utilization per patient are required.

We chose to add Mitomycin C to AF arm as MMC targets, predominately the hypoxic cells, which are less radiosensitive, and therefore it might improve the therapeutic outcome **[12,16,18]**.

In the present study there was relatively more laryngeal tumors (29%) followed by oral cavity tumors (25%), then oropharyngeal and hypopharyngeal tumors (23% of patients in each of them). This was comparable to other Egyptian studies **[25,26]** but was different from those reported in some western literatures, where there were more oropharyngeal and oral cavity tumors, and less laryngeal tumors and hypopharyngeal tumors **[6,13,18,19]**.

The pre-radiotherapy Hb level for our group of patients ranged from 8 to15.7g/dl with a median value of 12g/dl. these values of Hb level were similar to those reported in other Egyptian series **[25,26]** but were less than those reported in western studies (the upper range of normal level) **[9,11,22,27]**.

Forty two patients (70%) required intravenous fluid (IV) or tube feeding during their treatments (55% in CF arm, 75% in AF arm, and 80% patients in AF + MMC arm). Similarly, in the study of Lee et al. **[28]** they reported that a high proportion of patients in the AF arm (6 fractions per week) compared to CF arm required nasogastric tube feeding (*p*<0.01).

The overall treatment time for all our patients ranged from 38 to 66 days with a median value of 48 days. The median value of OTT was 55 days, 43 days and 42 days for CF, AF, AF + MMC arms, respectively. Seven, 8 and 8 patients in CF, AF, and AF + MMC, respectively completed their treatment in the planned OTT (38% compliance rate). The prolongation of OTT is against the aim of using AF and this may contribute to the insignificant results of AF vs CF in our series. On the other hand, Overgaard et al. **[13]** reported that the median overall radiotherapy times were 46 and 39 days for the five and six fractions per week arms, respectively, and 96% of patients received the planned total dose. Similarly, Lee et al. **[28]** reported that the median OTT was 46 (range 44-51) days in CF and 39 (range 37-46) days in the AF (6 fractions per week), and despite the significantly higher incidence of grade 3-4 toxicities in AF arm, the mean number of days in excess of the scheduled treatment time was 2.2 days in both groups (*p*=0.89). There are many causes of OTT prolongation in our study. The OTT was prolonged in 20 patients due to patient non-compliance, in 33 patients the cause of the prolongation was due to acute radiation reactions, in 20 patients the machines were out of function, and in 16 patients it was due to public holidays. In some patients there was more than one cause.

The 2-year loco-regional control rate in the present study was 22%. This figure is lower than that reported in similar studies **[6,8,9,10]** as our study was restricted to stages III & IV, while the other studies included in addition stage II and some stage I **[13]**. As regards the treatment arm, the loco-regional control rates were 10%, 25%, and 30% for the CF, AF, and AF + MMC respectively and the difference was statistically insignificant (p=0.27) which may be explained by the small number of patients and the low compliance rate for the overall treatment time. On the other hand, Overgaard et al. **[10]** reported that the 5-year loco-regional control rate was significantly better in the AF arm (6 fractions per week) (67%) vs. the CF arm (58%) (p<0.006). Similarly Skaldowski et al. **[9]** reported a significant improvement in the 3-year local control rate in patients treated by 7-day-continuous accelerated irradiation (CAIR) (82 %) versus patients treated by CF (37%, p=<0.0001). The results of addition of mitomycin C to radiotherapy in HNC are controversial. Haffty et al. **[18]** reported that with addition of MMC to radiation, the loco-regional control was improved from 54% to 76% (p<0.002). The median follow up was 138 months. Similar results were reported by Dobrowsky and Naude **[19]**. On the other hand, Grau et al. **[17]** found that CF radiotherapy alone (66-70Gy/33-35 fractions) was associated with 4-year LC rate of 18% versus 14% with the addition of MMC to CF. The difference was not statistically significant.

The 2-year overall survival rate in our series was 21%. According to treatment arms, it was 23%, 20%, 28% in the CF, AF, and AF + MMC arms, respectively. Shortening the OTT from $6^1/_2$ weeks to $5^1/_2$, the survival did not improve survival. Similarly Horiot et al. **[6]** reported that the AF did not improve the overall survival (p=0.99). However Overgaard et al. **[13]** reported that the accelerated arm yielded a significantly higher tumor control and a trend towards improved survival (95% confidence interval for odds ratio ranged from 0.9 to 1.8). This may be due to inclusion of T1 lesions in this study that accounted for dilution of the overall benefit of survival. Skladowski et al. **[9]** reported that with AF (CAIR), the overall survival was improved from 32% to 78% (p=0.0001).

In our series, the addition of MMC to the AF arm improved the OS from 20% to 28%, however it did not reach statistical significance. Similarly Haffty et al. **[18]** reported that there was no statistically significant difference in the overall survival with addition of MMC to radiation (48% in the MMC + RT vs 42% in the RT alone group). Similar results were reported by Grau et al. **[17]**. However, Dobrowsky and Naude **[19]** reported that the overall crude survival was 24% after CF, 31% following AF and 41% after AF + MMC (p=<0.05).

In the present series, performance status (PS) emerged as a significant prognostic factor as regards LC and OS (p<0.026 and p<0.005 respectively). Similar results were reported by many series **[6,29]**, where PS >0 indicated a poor survival in their patients. However, Dische et al. **[7]** found that the PS was not a significant factor as regards loco-regional control rate (p<0.419).

In the present series, the median value of the pre treatment Hb level was 12g/dl. Patients with pretreatment Hb>12g/dl, had better LC and OS rates (p<0.05, p<0.04 respectively) compared to patients with Hb level ≤12g/dl. The results reported in other Egyptian series **[25,26]** did not show significant influence of Hb level on both the loco-regional control and survival. Bentzen et al. **[11]** reported that, in oropharyngeal tumors, patients with Hb level in the upper normal range had a significantly higher tumor control probability. Similarly, Lee et al. **[30]** reported that patients with normal Hb level (>14.5g/dl for men and, >13g/dl for women) was associated with better survival rate than anemic patients (35.7% vs. 21.7%). The estimated loco-regional failure rate was 51.6% in patients with normal Hb level vs. 67.8% in anemic patients. This was in agreement with other reported series **[27,31]**.

AF is commonly associated with a high incidence of acute toxicities **[8,9,19,28]**. In the present study, the incidence of grades 3 & 4 mucositis occurred in 70% and 90% of patients in AF and AF + MMC, relative to 55% in the CF arm. There was a statistically significant difference between CF and AF arms (p<0.04). This is consistent with the result of the DAH-

ANCA 7 trial **[10]**, where the incidence of acute mucositis was higher in patients receiving 6 fractions per week ($p<0.001$). Several reports showed that MMC did not influence mucosal reaction and overall duration of mucositis **[18,19]**. In the present study the incidence of grade 3 & 4 hematological toxicity was 40% in AF + MMC arm, 10% and 5% in CF and AF arms ($p=0.04$). Dobrowsky and Naude **[19]** reported that grade 3-4 hematological toxicity was seen after MMC administration in 18% of patients. Similar result was reported by Haffty et al. **[18]**.

As regards late toxicity, the current study showed that neither AF nor the addition of MMC did significantly increase late toxicities. This was in agreement with other reported series **[10,18,28]**.

Conclusion:

Conventional fractionation radiotherapy alone is not sufficient for controlling locally advanced cancer of the head and neck. This warranted the use of innovative treatment modifications such as altered fractionation schedules and combination with chemotherapy. The shortening of overall treatment time by increase of weekly number of fractions was associated with improvement in the loco-regional control rate and further improvement was achieved with the addition of the Mitomycin C to accelerated fractionation. However, this improvement was not statistically significant due to the small number of the patients in each treatment arm, low compliance rate for overall treatment time and the inclusion of different tumor sites. Accordingly we advise to continue the trial with inclusion of a larger number of patients and restrict tumor sites to one major site.

REFERENCES

1- Nguyen LN, Ang KK. Radiotherapy for cancer of the head and neck: altered fractionation regimens. Lancet Oncol. 2002; 3: 693-701.

2- Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol. 1988, 27: 131-46.

3- Fowler JF, Lindstrom MJ. Loss of local control with prolongation in radiotherapy. Int J Radiat Oncol Phys Biol. 1992, 23: 457-67.

4- Overgaard J, Alsner J, Horsman MR, Grau C. Importance of overall treatment time for the response to radiotherapy in patients with squamous cell carcinoma of the head and neck. Rays. 2000, 25: 313-19.

5- Overgaard J, Vendelbo Johansen L, Hjelm-Hansen M, Andersen AP. Comparison of conventional and split-course radiotherapy as primary treatment in carcinoma of the larynx. Acta Oncol. 1988, 27: 147-52.

6- Horiot JC, Bontemps P, Van den Bogaert W, et al. accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: Results of EORTC 22851 randomized trial. Radioth Oncol. 1997, 44: 111-21.

7- Dische S, Saunders M, Barrett A, Harvey A, Gibson D, Parmer M. A randomized multicentre trial of CHART versus conventional radiotherapy in head and neck cancer. Radioth Oncol. 1997, 44: 123-36.

8- Fu KK, Pajak TF, Trotti A, et al. Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. Int J Radiat Oncol Phys Biol. 2000, 48: 7-16.

9- Skladowski K, Maciejewwski B, Golen M, Pilecki B, Przeorek W, Trnawski R. Randomized clinical trial on 7-day-continuous accelerated irradiation (CAIR) of head and neck cancer: Report on 3-year tumor control and normal tissue toxicity. Radioth Oncol. 2000, 55: 101-10.

10- Overgaard J, Sand Hansen H, Specht L, Overgaard M, Grau C, Andersen E, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 & 7 randomized controlled trial. The Lancet. 2003, 362: 933-40.

11- Bentzen SM, Thames HD. Clinical evidence for tumor clonogen regeneration: Interpretation of the data. Radioth Oncol. 1991, 22: 161-67.

12- Rockwell S. Use of of hypoxia-directed drugs in the therapy of solid tumors. Semin Oncol. 1992, 19: 29-40.

13- Overgaard J, Horsman MR. Modification of hypoxia-induced radioresistance in tumors by the use of oxygen and sensitizers. Semin Radiat Oncol. 1996, 6: 10-21.

14- Brizel DM, Prosnitz LR, Sibley GS, Scher RL, Rosner GL, Dewhirst MW. Tumor hypoxia adversely affects the prognosis of squamous cell carcinoma of the head and neck. J Radiat Oncol Phys Biol. 1997, 14: 831-38.

15- Awwad HK. In: Radiation Oncolgy: Radiobiological and Physiological Perspectives. Kluwer Acadamic Publishers, Dordecht, Boston and London, Chapter IV 6 and IIV 5. 1990.

16- Rauth A, Mohindra JK, Tannock IF. Activity of mitomycin C for aerobic and hypoxic cells in vitro and in vivo. Cancer Res. 1983, 43: 4145-58.

17- Grau C, Overgaard J. Radiosensitizers and cytotoxic prosperities of mitomycin C in a C3H mouse mammary carcinoma in vivo. Int J Radiat Oncol Phys Biol. 1991, 22: 265-69.

18- Haffty BG, Son YH, Papac R, Sasaki CT, Weissberg B, Fischer D, et al. Chemotherapy as an adjunct to radiation in the treatment of squamous cell carcinoma of the head and neck: results of the Yale mitomycin randomized trials. J Clin Oncol. 1997, 15: 268-76.

19- Dobrowsky W, Naude J. Continuous hyperfractionated accelerated radiotherapy with/without mitomycin C in head and neck cancers. Radioth Oncol. 2000, 57: 119-24.

20- Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958, 53: 457-81.

21- Peto R, Pike MC, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Analysis and examples. Br J Cancer. 1977, 35-39.

22- Overgaard J, Hansen SH, Jorgensen K, Hjelm Hansen M. Primary radiotherapy of larynx and pharynx carcinoma: an analysis of factors influencing local control and survival. Int J Radiat Oncol Phys Biol. 1986, 12: 515-21.

23- Peters L, Ang K. The role of altered fractionation in head and neck cancers. Semin Radiat Oncol. 1992, 2: 180-94.

24- Bernier J, Bentzen SM. Altered fractionation and combined radio-chemotherapy approaches: Pioneering new opportunities in head and neck oncology. Eur J Cancer. 2003, 39: 560-71.

25- Shouman TH. Clinically relevant predictors of radiation response of epidermoid cancer of head and neck. National Cancer Institute, Cairo University 1994.

26- Lotayef M. A comparative study of the methodology of tumor growth measurement As a guide for choice of the optimum radiotherapy fractionation scheme in some head and neck cancers. National Cancer Institute, Cairo University 1999.

27- Van Acht MJ, Hermans J, Boks D, Leer JW. The prognostic value of hemoglobin and a decrease in hemoglobin during radiotherapy in laryngeal carcinoma. Radioth Oncol. 1992, 23: 229-35.

28- Lee A, Man Sze W, Kok Yau T, Yeung R, Chappel R, Fowler J. 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-years tumor control and normal toxicity. Radioth Oncol. 2001, 58: 121-30.

29- Van den Bogaret W, van der Schueren E, Horiot JC, De Vilhena M, Cchraub S, Svoboda V, et al. The EORTC randomized trial on three fractions per day and misonidazole in advanced head and neck cancer: prognostic factors. Radioth Oncol. 1995, 35: 100-6.

30- Lee WR, Berkery B, Marcial V, Fu K, Cooper J, Vikram B, et al. Anemia is associated with decreased survival and increased loco-regional failure in patients with locally advanced head and neck carcinoma. A secondary analysis of RTOG 85-27. Int J Radiat Oncol Phys Biol. 1998, 42: 1069-75.

31- Lutierbach J, Guttenberger R. Anemia is associated with decreased local control of surgically treated squamous cell carcinoma of glottic larynx. Int J Radiat Oncol Phys Biol. 2000, 48: 1345-50.