Hyperfractionated Radiation Therapy and Concurrent Chemotherapy for Advanced Head and Neck Cancers

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Purpose
To investigate the feasibility of combining hyperfractionated radiotherapy regimen with concomitant chemotherapy and to assess its toxicity in patients with advanced head and neck carcinoma (HNC). Progression free survival (PFS) and overall survival (OS) were set as secondary end points.

Patients and Methods
Between November 2003 and November 2007, 48 patients with stage III and IV HNC who met the eligibility criteria were enrolled in the study. Hyperfractionated Radiation consisted of 120 Gys twice daily, 6 hours apart, for a total of 69.6 Gys in 58 fractions over 6 weeks and boost of 6 Gys in 3 fractions in case of residual disease. Three cycles of concurrent chemotherapy in the form of Cisplatin 75 mg/m² on day 1 and Fluorouracil 750 mg/m² 24 hour infusion on day 1-4 during weeks 1, 4 and 6 of irradiation.

Results
48 patients have completed the treatment to date. The median radiation dose was 72 Gys including the boost to residual lymph node or primary site. The treatment was delivered in a median overall period of 54 days, with a recorded median delay of 7 days. Grade 4 skin toxicity was experienced by 4.1% of patients only. Therapy was well tolerated (grade 3 mucositis in 21%, grade 4 in 26%, grade 3 leukopenia in 10%). Weight loss of more than 10 kg was reported in 10 (16.7%) of the cases. The most common late toxicity was mild to moderate xerostomia which was encountered in 34 (70.8%) cases and improved thereafter. Hypothyroidism was encountered in 7 (14.6%) of the cases.

Complete response (CR) was observed in 40 patients (83.3%). Partial response (PR) was achieved in the remaining 8 patients (16.7%). Disease relapse occurred in 9 patients (18.8%) after complete response and 2 patients developed progressive disease after partial response. 3 patients relapsed locally, 5 patients developed distant metastasis and 1 patient developed both local and distant metastasis. 2 patients (4.1%) died of treatment complications, 8 patients (16.7%) died with progressive locoregional, and metastatic disease. The 2-year disease free survival was 77% and the 2-year overall survival was 79%.

Conclusion
Hyperfractionated radiotherapy and concurrent chemotherapy is tolerable. Results regarding LC and OS are encouraging as compared to conventional radiotherapy and concurrent chemotherapy.

Keywords
Locally advanced H&N cancer, Hyperfractionated radiotherapy, concurrent chemotherapy.

Introduction
Primary head and neck cancers are the major public health problem in both developed and developing countries. Each year more than 40,000 people are diagnosed with squamous cell carcinoma of head and neck region.
Approximately 16,000 deaths occur every year due to this dreadful disease. Kuwait falls into the group of countries with intermediate risk population. Head and neck cancer account for 12.75% of all cancer cases diagnosed in Kuwait Cancer Control Center from 1993-1999. The annual age standardized incidence ranges from 3-6 per 100,000 population.

Treatment of locoregionally advanced head and neck cancer had undergone many changes to improve local control and overall survival\(^{(1)}\). An aggressive treatment approach is necessary to achieve a cure in such cases. There has been extensive clinical research aimed at improving locoregional tumor control as well as functional and cosmetic outcome of those patients using modifications of radiation fractionation regimen and combination with chemotherapy\(^{(2,3)}\). One of these methods is the application of hyperfractionation or accelerated fractionation radiotherapy schedules, which has been shown to be superior to standard fractionation in terms of locoregional control and disease-free survival. However, the existence of a real benefit has been challenged and neither hyperfractionation nor acceleration alone has been widely accepted as standard of care\(^{(4,5,6)}\). Hyperfractionation stemmed from the observation of preferential sparing of late responding tissues relative to epithelial tissues and some tumors as a result of decreasing the size of radiation dose per fraction\(^{(7,8,9)}\) and accelerated fractionation regimens emerged through the recognition of the magnitude and hazard of tumor clonogen proliferation during the course of radiotherapy\(^{(10,11,12)}\). Results of large randomized trials addressing the optimization of radiation fractionation regimen collectively show that a number of biologic-based modifications of fractionation schedules have improved the locoregional control rate in the order of 10% to 15% but only had a modest impact on the overall survival rate\(^{(13,14)}\). Although several altered fractionation regimens consistently induce more severe acute mucositis, the general observation is that the late toxicity is not appreciably increased\(^{(15)}\).

The addition of chemotherapy to radiotherapy was analyzed in the MACH-NC meta-analysis and showed a significant survival advantage in favour of chemotherapy (4% at 5 years), which was higher (8% at 5 years, hazard ratio (HR) 0.81) in case of concurrent chemoradiotherapy compared to sequential or adjuvant chemotherapy\(^{(16,17)}\).

This study is a Phase II prospective study which started in November 2003 to investigate the feasibility of combining hyperfractionated radiotherapy regimen with concomitant chemotherapy, and to assess its toxicity in patients with advanced head and neck carcinoma (HNC). Progression free survival (PFS), and overall survival (OS), were set as secondary end points.

We plan to compare the results of this study with historical randomized controlled studies of advanced head and neck cancers done previously using conventional chemoradiotherapy. At KCCC, there are only about 20 patients with advanced head and neck cancer cases per year and not all of them meet the eligibility criteria. This is the reason why we do not have enough numbers for a randomized controlled trial in a 4 year period.

**Patients and Methods**

Between November 2003 and November 2007, 48 patients with stage III - IV\(^{(18)}\) head and neck cancers who met the eligibility criteria were enrolled in the study. All of these patients were analyzable.

**Eligibility/inclusion criteria**

- Patients with histologically- proven disease
- Patients with H & N cancer at stage III-IVA (AJCC 6th ed.)
- Patients with irresectable disease greater than or equal to 18 years and less than 65 years old
- Performance status (ECOG) of 0-2
- No previous history of other primary malignancy or treatment by chemotherapy
- Life expectancy > 2 years.
- Laboratory values performed within 14 days prior to concurrent chemotherapy:
  - Absolute neutrophil count (ANC) ≥ 2000/mm.
  - Platelet count ≥ 100,000/mm.
  - Hemoglobin ≥ 10g/dl or 100g/L.
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- Urea and serum creatinine < 1.25 times upper limit of laboratory normal range.
- Creatinine clearance ≥ 1.25 times lower limit of laboratory normal.
- SGOT and SGPT < 1.25 times upper limit of laboratory normal.

**Pre-treatment evaluation (baseline)**

All pre-treatment evaluations were performed within 14 days before starting treatment, includes:
- Complete medical history
- Vital signs including weight and height were recorded
- Complete physical and systemic examination
- Assessment of performance status
- E.N.T examination
- E.U.A and biopsy of primary lesion for histopathological confirmation of disease
- C.B.C and oncology profile includes renal function, liver function and serum electrolytes
- 24-hr urinary creatinine clearance
- CXR PA and lateral view
- C.T scans of primary site of disease and regional lymph node drainage area
- Bone scan
- Audiogram
- Pre-treatment dental evaluation and prophylaxis
- Nutritional assessment

To be eligible for enrolment, the patient must meet all inclusion criteria. Following above investigations, patients will be staged according to TNM staging (AJCC 6th Ed.)

The characteristics of these patients are listed in (Table 1). There were 40 males and 8 females. The median age was 47 years (range 19 - 65 years). The majority of cases were males 83.3%. Poorly differentiated carcinoma represented 35.5% and undifferentiated carcinoma 37.5%. Performance status 1-2 (WHO). Nasopharynx was the commonest site of primary disease in 28 patients (58.3%), T3-4 were encountered in 25 patients (52.1%), N2-3 in 32 patients (66.6%) (see Table 1). The staging was 16 patients in Stage III and 32 patients in Stage IVA.

![Table 1: Patients Characteristics](image)

All patients were planned for hyperfractionated radiotherapy with 1.2 Gy/fraction twice daily with 6 hours interval for a total dose of 69.6 Gy and 6 Gy more were added as a boost in case of residual disease, with 3 cycles of concurrent chemotherapy in the form of Cisplatin 75mg/m² D1 and 5-Flurouracil 750 mg/m² D1-4 every 21 days with daily subcutaneous Amifostine 250
mg 15-20 minutes before each radiotherapy fraction.

**Radiotherapy planning**

Immobilization of the head was accomplished by individually mounted thermoplastic cast and rigid pillows to support their neck and head position. Contiguous CT-slices (Somatom CT, Siemens, Medical Systems) of 5 mm thickness covering the primary and the neck were taken for the patients in supine position without gap and were transferred to Helax-TMS planning station. Intravenous contrast medium was given to better visualize tumor extension and relation to blood vessels. Contours were delineated on all CT cross sections containing relevant information. The treatment plans of three-dimensional conformal radiotherapy (3D CRT) were based on these images. One iso-center and same positioning setup was used for all treatment fields in order to minimize junction errors between them.

**Target volumes definition:**

Target volumes were delineated according to ICRU recommendations. The gross target volume (GTV1) was defined as the volume of gross primary tumor. The GTV2 was defined as the volume of grossly visible metastatic lymph nodes. The clinical target volume (CTV1) was defined as the volume including GTV 1 and the volume at risk of local extension according to the primary site. CTV2 was defined to include GTV 2 and all lymphatic drainage up to level III bilaterally. The lymphatic region below level III to the bilateral clavicle bone was irradiated with separate anterior lower neck field. To all these CTV’s, a margin of 5 mm (automatic 3D expansion) was added for inaccuracies in patient setup and beam placements to create the different PTV’s. Organs at risk including both parotids, the brain stem, the spinal cord, and both eyes were outlined on the CT-images. The spinal cord was defined as the structure within the bony edges of the vertebra.

Patients were treated in an immobilization device using linear accelerators with appropriate photon (4- and 10-MV photons) and electron (6- and 15-MeV) energies at a source-to-axis distance of 100 cm (Primus, Siemens, Medical solution, Germany). Beam verification films were obtained for each field and repeated whenever any field adjustments were made.

**Dose and Dosemetric evaluation:**

Phase one was treated using 3D-CRT using multiple (5-7) beam portals. Fields were wedged and deferentially weighted according to the situation. Multi-leaf collimator was used for field shaping. At 39.6 Gys two lateral fields 6-MV were used for phase two, after shielding the spinal cord up to 69.6 Gys. A boost of 6 Gyrs/5 fr was added to primary site and residual bulky nodes. Posterior electron fields were used to reach a total dose of 60 Gys in posterior neck. Lower neck nodes were treated to 50 Gys.

It was aimed to keep the mean total dose to at least one parotid gland at ≤34 Gys. The parotid gland selected for protection was usually the one opposite the high dose volume. Thus a shallower dose gradient between low dose PTV and the parotid gland was easier to realize and the risk of under dosage at the high dose volume was minimized. Maximum dose of 45Gys was allowed to the spine. The maximum allowed dose to the brain stem was 50 Gys.

**RT modification due to blood picture:**

If the ANC < 750 or platelets < 75,000, and there is uncontrolled infection, radiotherapy was interrupted. Radiotherapy was not restarted until blood counts were above these levels. The hemoglobin should be maintained at >10 g/dl.

**RT modification due to mucositis/oesophagitis:**

If the patients become symptomatic from oesophagitis/mucositis or if mucositis becomes confluent in the absence of symptoms, radiation was interrupted until recovery of mucositis and subsidence of symptoms.

**Supportive Care during Radiation**

Aggressive prevention and treatment of radiation mucositis was implemented according to current measures adopted for all head and neck cancer patients in the Department of Radiation Oncology. It includes routine mouth washes with salt and baking soda solutions, antibiotic and antifungal preparations, and pain medication.
when necessary. Patients who have difficulties in eating solid food were provided with supplemental liquid food. The patient's weight was monitored once a week. Patients who are undernourished before starting radiation, or patients who lose 10% or more of their weight during radiation, chemotherapy dose-modified because of severe myelosuppression.

Amifostine (Ethyol) has been used during the course of radiation therapy to reduce xerostomia. A flat dose of Amifostine 250 mg diluted in 2.5 ml of normal saline is administered subcutaneously in the sitting position 20 minutes before each radiotherapy fraction.

**Follow-Up and Data Analysis**

Patients underwent weekly examination during treatment. Patients were observed by all members of the multidisciplinary team after completion of therapy. Careful clinical examination was performed and any suspected local, regional, or distant recurrence was biopsied for confirmation. First follow-up evaluation occurred around 4 weeks after completion of therapy. Subsequently, patients were assessed every two months for the first two years, every 3 and 4 months in years 3 to 5, and 6 monthly thereafter. In addition to tumor and clinical status, acute and late (occurring > 90 days from start of treatment) normal tissue effects were graded. Systemic and acute radiation effects were scored using the National Cancer Institute Common Toxicity Criteria version 2.0, whereas late radiation effects were scored according to the RTOG/European Organization for Research and Treatment of Cancer criteria 19.

A complete response required the disappearance of all clinical, radiographic, and, if applicable, pathologic evidence of disease. Neck dissection was performed if clinical evidence of residual neck node disease was present after completion of treatment.

The primary end point of the study was the feasibility and toxicity of treatment protocol. Additional end points included overall survival, disease-free survival and the incidence of distant metastases. All time-to-failure end points were calculated from the date of registration to the study. Survival analysis was done using Kaplan-Meyer, and comparisons between survival curves was done using Log-rank test. Differences were considered significant when \( p \leq 0.05 \) and highly significant when \( p \leq 0.01 \).

The follow-up interval was defined as the period from the end of the radiotherapy to

**Fig. 1a : Dose distribution of 3D conformal planning for nasopharyngeal carcinoma phase one.**

**Fig. 1b : Composite DVH.**

**Chemotherapy**

Cisplatin was administered in a dose of 75 mg/m\(^2\) intravenously on days 1 and 5; Fluourouracil 750 mg/m\(^2\) on days1-4; continuous infusion with Intravenous Ondansetron 8 mg and Dexamethason premedication and vigorous hydration and diuresis. Guidelines for dose modification because of cytopenia, neurotoxicity, or nephrotoxicity were specified in the protocol. Use of G-CSF was limited to those patients with documented need for amelioration of hematopoietic toxicity. It was prescribed for patients who should otherwise be
September 2008; it ranged from 19 to 60 months (mean 39.5 months).

**Statistical methods**

Statistical Package for Social Sciences (SPSS) version 16 was used to analyze the data. Quantitative variables were summarized using mean and SD, median, minimum and maximum values. Qualitative data was summarized using frequencies and percentage. Survival analysis was done using Kaplan-Meier. Differences were considered significant when \( p \leq 0.05 \) and highly significant when \( p \leq 0.01 \).

**Results**

All patients received both radiation and chemotherapy as per protocol or with minor variations. The median radiation dose was 72.5 Gys including the boost to residual lymph node or primary site. The treatment was delivered in a median overall period of 54 days, with a recorded median delay of 7 days. Most of the patients 40/48 (83.3%) received three cycles of chemotherapy and boost of 6 Gys to residual lymph node or primary tumor. 8 patients (16.7%) received only two courses due to prolonged grade 4 haematological toxicity and mucositis. Although about 25% of the patients have a stormy time and necessitated treatment interruption, most of them managed to complete the treatment within a satisfactory overall time using vigorous nutritional support. Hematological growth factor i.e. G-CSF (Fulgristim) was used wherever necessary. Assessment of toxicity was done according to the NCI-CTC V2. The incidence of grade 3 and 4 acute toxicities is listed in Table 2. Grade 4 skin toxicity was experienced by 4.1% of patients only. Therapy was well tolerated (grade 3 mucositis in 21%, grade 4 mucositis in 26%, grade 3 leukopenia in 10%). The amount of weight loss was maximum during treatment and at three months after irradiation then recovered slowly thereafter. Weight loss during and immediately after treatment was due to acute mucosal reaction whereas at three to six months later, it was due to xerostomia and its sequelae. Weight loss of more than 10 kg was reported in 10 cases (16.7%). The most common late toxicity was mild to moderate xerostomia which was encountered in 34 cases (70.8%) and improved thereafter. Hypothyroidism was encountered in 5 cases (10.4%).

Assessment of response was done according to RECIST criteria. 48 of our patients have completed the treatment to date. Complete response (CR) was observed in 40 patients (83.3%). Partial response (PR) was achieved in the remaining 8 patients (16.7%). Disease relapse occurred in 9 patients (18.8%) after complete response. 2 patients have progressive disease after partial response, 3 patients relapsed locally, 5 patients developed distant metastasis, and 1 patient developed both local and distant metastasis. 2 patients (4.1%) died of treatment complications, 8 patients (16.7%) died with progressive locoregional and metastatic disease. The 2-year disease free survival rate was 77% and the 2-year overall survival rate was 79%.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No.</th>
<th>Grade 3-4(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomatitis</td>
<td>48</td>
<td>27 (47.9%)</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>30</td>
<td>17 (35.4%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>10</td>
<td>10 (20.8%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10</td>
<td>7 (14.7%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>4 (8.3%)</td>
</tr>
<tr>
<td>Skin</td>
<td>10</td>
<td>2 (4.1%)</td>
</tr>
</tbody>
</table>

Table 2 : Incidence of acute toxicities

**Fig. 3 : Progression free survival**
Discussion

Head and neck cancers are now receiving special attention all over the world as a result of increasing use of tobacco. In the state of Kuwait, head and neck cancers are also of prime concern due to high consumption of tobacco. It accounts for 9.5% of Kuwaiti and 8.8% of non-Kuwaiti patients seen at KCCC for the year 2005.

Nearly 60% of head and neck cancer patients present with locally advanced disease. Treatment for loco regionally advanced disease remains challenging because of high rate of local recurrence and distant metastasis. Radiotherapy is often the primary treatment for advanced head and neck cancer, but the rates of locoregional recurrence are high and survival is poor (2), several researchers have tried to deliver a higher radiation dose (3) to improve the local control rate and survival probability. One of these methods is the application of a hyperfractionated radiotherapy schedule or accelerated fractionation which has been shown to be superior to standard fractionation in terms of locoregional control and disease-free survival (4). The basic rationale of hyperfractionation is that the use of small dose fractions allows higher total doses to be administered within the tolerance of late-responding normal tissues which translates into a higher biologically effective dose to the tumor. However, the existence of a real benefit has been challenged and neither hyperfractionation nor acceleration alone has been widely accepted as a standard of care (5). The addition of chemotherapy to radiotherapy was analyzed in the MACH-NC meta-analysis and showed a significant survival advantage in favor of chemotherapy (4% at 5 years), which was higher (8% at 5 years, hazard ratio (HR) 0.81) in case of concomitant chemoradiotherapy compared to sequential or adjuvant chemotherapy (21).

From these data, we can say that our study with hyperfractionated radiotherapy and concurrent chemotherapy gives encouraging results regarding LC and OS as compared to conventional radiotherapy and concurrent chemotherapy.

Conclusions and Recommendations

Our experience in the last 4 years with hyperfractionated radiation therapy and concurrent chemotherapy shows that it is a feasible approach, with reasonably tolerable and manageable toxicities and was associated with improved local control and overall survival.

Out of the 48 patients who have completed their treatment, only 11 patients did not survive: 9 of them died with progressive metastatic disease or with treatment related toxicities and 2 patients were lost for follow-up with partial response before completion of two years of follow-up.

In this type of study, 5-year survival is the usual final concluding point. We will therefore, wait for the completion of 5 years of follow-up on these 48 patients before reporting the final result on the 5-year overall survival rate. We are only considering this data of 2-year survival and local control as a preliminary report which needs to be confirmed with proper statistical analysis. After a five year period the overall survival rate will be reported in a final report.

Acknowledgements

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