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SIB-IMRT radiotherapy concomitant with cisplatin in locally advanced hypopharyngeal cancer: safety, feasibility

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SUMMARY

Introduction: Radiotherapy is the main line of treatment of head and neck cancer including hypopharyngeal cancer either adjuvant/neoadjuvant radiotherapy or neoadjuvant/adjuvant concurrent chemoradiotherapy. The aim of radiotherapy is to provide maximum safe dose to organ at risk (healthy normal tissues). Studies had shown that the need to increase dose to the tumour was associated with great hazard to healthy normal tissues with induction of acute and late toxicity. The acute toxicity will result in treatment breaks and decreased local control due to repopulation of the tumour cells especially in head and neck cancer.

Aim of the study: It was to reduce the radiation dose received by critical normal organs to allowed tolerance.

Materials and methods: Twenty-two hypopharyngeal cancer patients either receiving radiotherapy as definitive therapy with concurrent cisplatin in dose of 40 mgm/m^2 (group A) or adjuvant radiotherapy concurrent with same dose of cisplatin (group B). The closest critical organs of interest were the eye lens, parotid gland, submandibular salivary gland, oral mucosa, and thyroid gland. The patients were treated with Simultaneous Integrated Boost (SIB) (2 Gy to 2.21 Gy) Intensity Modulated Radiation Therapy (IMRT) with total dose of 66 -70 Gy, 5 fractions per week.

Results: Response after definitive treatment with concurrent simultaneous boost were 5 out of elven cases 45.5% achieved pathological complete response. Median overall survival is 33 months with range from 14 month-36 month for the whole group, with 2-year overall survival 63.3% and 81.8% in definitive and adjuvant group respectively which was statistically insignificant (p=0.457). Two-year local control 90.9% versus 63.6% in adjuvant versus definitive treatment which was statistical significance (p=0.034). Two-year larynx preservation survival was 63.3%. As regard the homogeneity index and confirmatory index, they were per guidelines to decrease the dose to organ at risk. No more than grade 2 xerostomia was reported in both treatment arms.

Conclusion: These results showed high local control with simultaneous integrated boost IMRT with reduced dose to organ at risk and it was complementary to other studies regarding the new era of modern radiation therapy techniques.

Key words: IMRT, OAR, hypopharynx, simultaneous integrated boost

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INTRODUCTION

When human cells are subjected to ionizing radiation, it leads to deleterious effects on DNA. Among DNA damage, double strand DNA breaks are the most deleterious event for the side effects of radiotherapy [1-2].

The prognosis of hypopharyngeal cancer is poor and its treatment depends on stage. In early stage, radiotherapy and surgery give equivocal results while in advanced stage but operable disease, adjuvant radiotherapy or concurrent chemo radiotherapy increased tumour control but at the expense of side effects [3]. While inoperable cases, radical concurrent chemo radiotherapy is the main line of treatment but at the expenses of increased acute and late toxicities [4-5].

Intensity Modulated Radiation Therapy (IMRT) has been emerged as modern technique that increased local tumour control with reduced dose to organ at risk especially the salivary glands with decreased xerostomia risk [6-9].

Escalation of radiation dose had been used to improve the treatment outcome [10,11]. One the dose escalation technique is simultaneous integrated boost, which associated with increased local treatment control due to reduced repopulation [12-14].

So, the aim of our study was to evaluate simultaneous integrated boost IMRT/with without chemotherapy in locally advanced hypopharyngeal cancer as regard locoregional control, dosimetric study and toxicity in our institution.

MATERIALS AND METHODS

Patients

This study was carried out at the oncology department; Tanta University in the period from January 2017 to December 2020, following written consent was taken from twenty-two locally advanced hypo pharyngeal cancer stage III and stage IVA patients according to TNM 8th edition [15-17]. The protocol was approved by the ethical committee.

Following panendosopy and biopsy of suspected lesion in the ENT department, Tanta university, patients were evaluated with thorough history taking, physical examination complete laboratory evaluation with special attention to complete blood picture, renal function, creatinine clearance and electrolytes,

and radiological evaluation computed tomography of neck, MRI neck with contrast and PET- CT if indicated.

Treatment

For postoperative radiotherapy: Primary tumour and macroscopic suspicious lymph nodes diagnosed clinically and by imaging studies are delineated as the Gross Target Volume (GTV). High risk CTV1 was defined as tumour bed +0.5-1 cm and extracapsular nodal extension +0.5-1 cm, CTV2 was produced by GTV primary and nodal. Elective CTV3 is produced by elective nodal and adjacent tumour bed [18, 19]. To account for patient and treatment setup errors margin of 5 mm was added to each CTV to obtain planned target volume.

For definitive radiotherapy: CTV high disease GTV primary+5mm, GTV nodal +10mm; CTV high risk: tumour high risk areas and borderline lymph node and CTV low risk area adjacent to tumour and elective lymph node areas.

Patients are classified into two groups:

Group A: Concurrent chemo radiotherapy as primary treatment it was given in SIB IMRT dose of 7095 Gy/33 fxs, 2.15cGy/fx to PTV high disease (CTV high disease +5mm), 62.7Gy/33 fxs, 1.9Gy/fx for PTV high risk (CTV high risk+5mm) and 56.7Gy/33fx 1.7Gu/fx to PTV low risk (CTV low risk+5mm).

Group B: in postoperative group adjuvant concurrent chemo radiotherapy. the prescribed SIB IMRT was formed of 65Gy/30 fxs; 2.17/fx for PTV1 is formed by adding 5 mm to CTV1; for PTV3 formed by adding 5mm to CTV3 and the dose is 54Gy /30 fxs; 1.8 Gy/fx.

In both groups, patients received cisplatin in dose of 40 mgm/m^2 weekly during radiotherapy with proper hydration. The energy used for treatment was 6MV photons using LINAC Linear accelerator, with multileaf collimators (UNIQUE) with dynamic multileaf collimator.

If patients lost weight more than 15%, nasogastric tube or per cutaneous gastrectomy were done.

Target (SIB and PTV) should be covered by 95% of prescribed dose. We evaluated the homogeneity index for both SIB and PTV as HI=(D1%-D99%) /D50%. Also, we record the conformity index for both SIB and PTV as CI=V95%^{2}/(TV · PIV).

Dose volume histogram was used to evaluate organ at risk (parotid glands, spinal cord, brain stem, oral cavity) which are routinely contoured.

Follow up

Treatment follow up was done weekly during radiotherapy and month after end of treatment. In the first 2 years was done every month and every 6 months thereafter. Radiation therapy oncology group/European organization for treatment cancers defined acute toxicity as toxicity that occurred during radiotherapy or within 90 days after [20].

Statistical analysis

We used descriptive statistical using median, frequency. Locoregional control, overall survival and larynx preservation free survival was analysed using Kaplan-miere IBM statistics 21 and this was considered primary endpoints [21]. p value less than 0.05 was considered statistically significant. While the secondary endpoints were toxicity and adverse effects according to RTOG toxicity criteria [22].

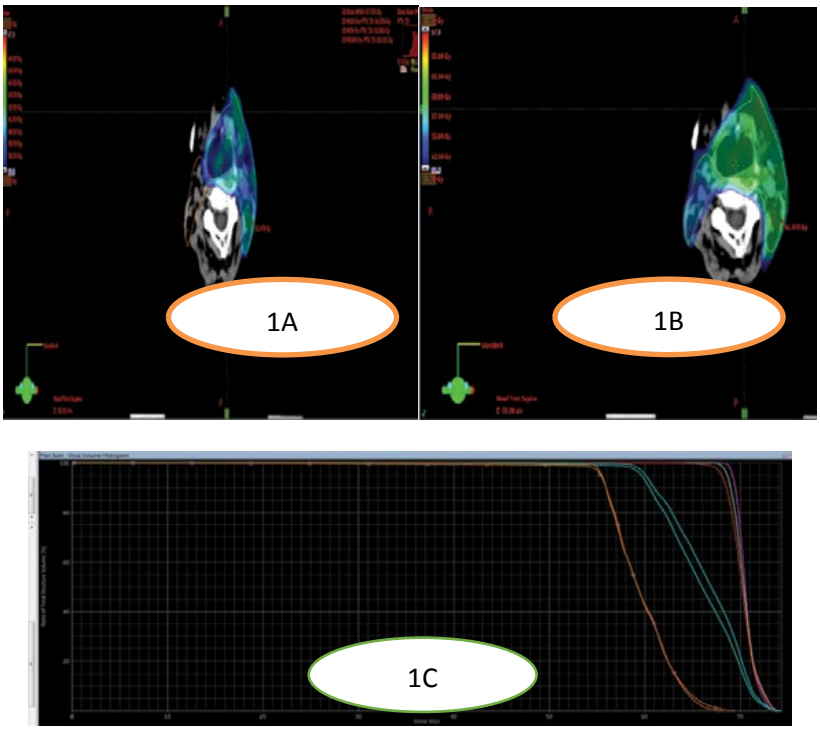

Fig.1. Case (1): Left pyriform fossa T3N1 received IMRT-SIB; (1A): showed the dose distribution of PTV-high disease; (1B): PTV -low risk; (1C): isodose distribution.

Tab. 1. Patients' Demographic Information

Parameter	Group A Definitive group	Group B Adjuvant group	Total	p value
Age				
Range ± SD	40-70 ± 12.15	42-80 ± 13.39	40-80 ± 12.54	
Median	50	49	49	
Sex				
Male	10 (90.9%)	9 (81.8%)	19 (86.4%)	0.543
Female	1 (9.1%)	2 (18.2%)	3 (13.6%)	
Cigarette smoking				
Cigarette smoking	10 (90.9%)	9 (81.8%)	19 (86.4%)	0.543
Non-smoker	1 (9.1%)	2 (18.2%)	3 (13.6%)	
Performance status				
0-1	9 (81.8%)	9 (81.8%)	18 (81.8%)	1
2	2 (18.2%)	2 (18.2%)	4 (18.2%)	
Stage				
III	2 (18.2%)	10 (90.9%)	12 (54.5%)	0.001
IVA	9 (81.8%)	1 (9.1%)	10 (45.5%)	
Site				
Pyriform	8 (72.7%)	8 (72.7%)	16 (72.7%)	1
Postcircoid	3 (37.3%)	3 (37.3%)	6 (37.3%)	

RESULTS

Patients

Demographic data of 22 patients with locally advanced hypopharyngeal carcinoma stage III and IV A and divided in two groups: group A formed of elven cases received definitive concurrent chemo radiotherapy IMRT with simultaneous integrated boost while group B consisted of elven cases which received adjuvant chemo radiotherapy IMRT with SIB , and were summarized in table 1. No statistical difference as regard sex performance status, site either pyriform or postcorcoid squamous cell carcinoma in both treatment groups. But nine (81.8%) cases in definitive group (group A) were stage IVA while ten (90.9%) cases in adjuvant group (group B) were stage III which was statistically significant (0.01).

Response after definitive treatment with concurrent simultaneous integrated boost were 5 out of elven cases 45.5% achieved pathological complete response Table 2.

Six patients underwent salvage surgery two needed neck dissection and four needed both laryngectomy and neck dissection. Two patients needed tracheostomy during follow up period. Two-year larynx preservation survival was 63.3% Figure 2.

Median overall survival is 33 months with range from 14-36 month for the whole group, with 2-year overall survival 63.3% and 81.8% in definitive and adjuvant group respectively which was statistically insignificant (p=0.457) Figure 3. Univariate analysis showed no statistical significance except for pyriform fossa tumour which was associated with higher 2-year overall survival 87.5% versus 50% in PCC not statistically difference (P value was 0.21).

Tab. 2. Response after definitive treatment with concurrent chemoradiotherapy arm (SIB-IMRT)

		Number	Percent
Response	CR	5	45.5
	PR	4	36.4
	SD	1	9.1
	PD	1	9.1
	Total	11	100

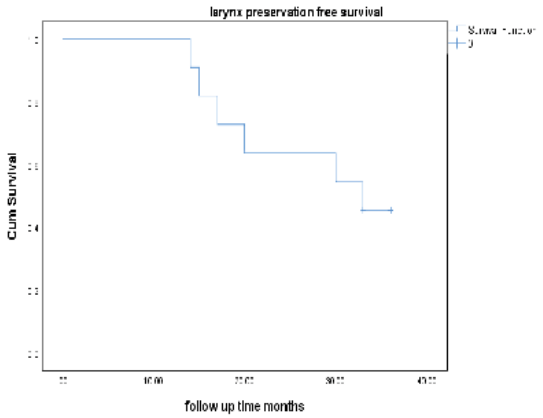

Fig. 2. Larynx preservation free survival in relation to definitive group

Two-year local control 90.9% versus 63.6% in adjuvant versus definitive treatment which was statistical significance figure (p=0.034) (Figure 4). Multivariate analysis showed no statistical significance of all prognostic factors (Table 3).

Plan evaluation

We aimed at coverage of the planned target volume and

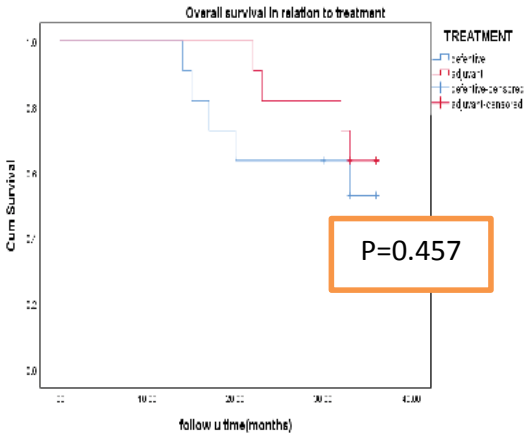

Fig. 3. Overall survival in relation to treatment

simultaneous integrated boost with 95% of prescribed dose in both treatment arms. Table 4 showed the homogeneity index for PTV and SIB, it showed no statistical difference. It is defined

(D1%-D99%) /D50%was calculated for SIB and PTV minus SIB. Confirmatory index was calculated by V95% ^{2}/(treatment volume · planned integrated volume) and it was not statistically significant difference as regard both treatment groups. As regard organ at risk no statistically significant difference as regard mean dose to parotid D60% to oral cavity, spinal cord d 1c and brain stem D1cm as shown in Table 4.

Toxicity

Mucositis grade 2 and grade 3 were observed in 12 cases (54.5%), 3 cases (13.6%) respectively. Ten cases (45.4%) developed xerostomia, of them grade 2 and grade 3 were observed in 2 cases (9.1%), and four cases (18.2) respectively. Grade 2 mucositis in

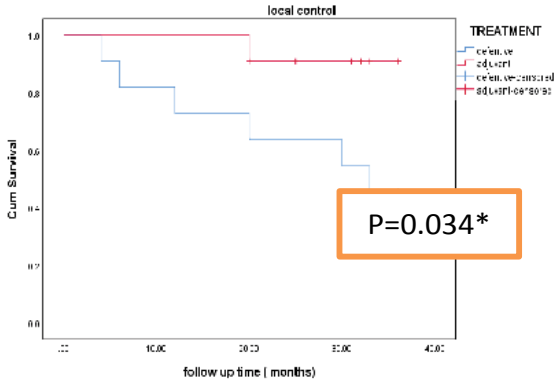

Fig. 4. Two-year local control in relation to treatment

Tab. 3. Multivariate analysis of local control

Parameter	Sig.	Exp(B)	95.0% CI for Exp (B) Lower	Upper
Treatment definitive versus adjuvant	0.115	0.101	0.006	1.745
Sex male versus female	0.337	7.356	0.125	432.817
Ps0-1 versus 2	0.118	14.05	0.51	387.022
Stage III VERSUS IVA	0.922	1.135	0.092	14.053
Site pyriform versus PCC	0.919	0.911	0.152	5.477

Tab. 4. Plan evaluation

	Group A (Definitive group)	Group B (Adjuvant group)	p value
PTV HI	0.17 ± 0.045	0.18 ± 0.05	0.849
PTV-SIB HI	0.045 ± 0.036	0.038 ± 0.025	0.766
PTV CI	0.75 ± 0.373	0.82 ± 0.322	0.521
SIB CI	0.93 ± 0.21	0.93 ± 0.21	0.95
Spinal cord D1cm	36.07 ± 5.24	35.3 ±5.2	0.849
Brain stem D 1cm	43.6 ± 10.43	10.43 ± 43.10	0.783
Parotid gland (left)	23.29 ± 1.25	23.80 ±1.37	0.783
Parotid gland (right)	23.54 ± 1.61	23.29 ±1.25	0.893
Oral cavity V60%	31.45 ± 4.3	31 ± 4.39	0.958

PTV HI: Planned Target Volume Homogeneity Index, PTV-SIB: Planned Target Volume Simultaneous Integrated Boost, CI: Confirmatory Index

Tab. 5. Toxicity of both treatment groups

Parameter	Group A	Group B	p value
Mucositis grade 2	9 (89.3%)	3 (27.3%)	0.01
Mucositis grade 3	2 (18.2%)	1 (9.1%)	0.534
Xerostomia grade 2	1 (9.1%)	1 (9.1%)	1
Xerostomia grade 3	2 (18.2%)	2 (18.2%)	1

the definitive group was higher than adjuvant group which was statistically significant (0.01) Table 5 No grade 3 late toxicity was observed. Only late grade 1 xerostomia was reported in 4 cases (18.2%) and grade 3 was reported in 2 cases (9.1%).

DISCUSSION

The standard therapy for locally advanced head and neck cancer particularly hypopharynx is standard fractionation radiotherapy concurrent with cisplatin chemotherapy either single agent or combined with 5 fluorouracil or taxene chemotherapy [23-25]. This was associated with increased toxicity.

The introduction of new modalities of treatment such as IMRT and arc therapy lessen the toxicity associated with concurrent chemoradiotherapy especially salivary gland affection had to been introduced [3, 26-29].

In our study twenty-two patients with locally advanced hypopharyngeal cancer received concurrent cisplatin with intensity modulated radiotherapy with simultaneous. 11 patients in group A received treatment as definitive treatment, while elven patients received treatment as adjuvant treatment after surgery.

No statistical difference in patient demographic data between two groups of treatment like other [30-31]. Complete response in our series in patients received definitive IMRT-SIB with cisplatin was 45.5% and this was in accordance with huang et al. who reported complete response rate of 48% in which patients with locally advanced hypopharyngeal cancer received concurrent IMRT-SIB with cisplatin [30].

This in contrast to that reported in the study done by Franchin et al. in which patients with laryngeal cancer T3N0-1 or hypopharynx T2-4 N2-3 stage received induction chemotherapy followed by concurrent IMRT-SIB with cisplatin-5 fluorouracil, the complete response was 88.3% higher than reported by us due to addition of cancer larynx, induction chemotherapy and different concurrent chemoradiotherapy in that study [31]. Our complete response was also different from that reported by Liu et al being higher than that reported by us 82.5% because in that study patient with locally advanced hypopharyngeal cancer received IMRT-SIB concomitant with cisplatin and 5 fluorouracil [32].

In our study, two-year larynx preservation survival was 63.3% coincident with other authors [31-32], different from Huang et al., who reported that two laryngeal preservation rates of 50% that is lower than that reported by us and this may be due to 6% of cases in that trial was posterior hypopharyngeal wall but no cases in our trial [30].

In our study, two-year overall survival 63.3% and 81.8% in definitive and adjuvant group respectively which was statistically insignificant (p=0.457), this was similar to that reported by Harris et al. who reported that two-year overall survival was 66% and 77% in CRT and surgery plus radiotherapy and without chemotherapy non-significant [33]. And this was different from that reported by Huang et al. was reported higher two year overall survival in the CCRT group (55%) than that reported by adjuvant group (50%) which was statistically in significant(p=0.788) and this may be due to not all patients in the comparative study of adjuvant group received chemotherapy 50% only [30]. Univariate analysis of different prognostic factors with overall survival was statistically insignificant and this was similar to that reported by many other authors [30-33].

In our study, two-year local control 90.9% versus 63.6% in adjuvant versus definitive treatment which was statistical significance figure (p=0.034), and this was different from that reported by Huang et al higher 2-year locoregional group in the definitive group and statistically insignificant and may be due to only 50% of cases of adjuvant group received concomitant chemoradiotherapy [30].

Multivariate analysis of locoregional control in our study showed no statistically significant of age, sex, cigarette smokers, performance status, site of tumor, stage and treatment lines similar to other authors [30-33].

Our study showed that SIB-IMRT had produced accepted treatment plan for both lines of treatment either adjuvant or definitive line of treatment with acceptable dose to organ at risk as mentioned in results and this in line with that reported by many authors [10-14].

Conventional 3D conformal radiotherapy is associated with increased xerostomia; several studies had showed that IMRT has been used to reduce the dose to the salivary glands and resultant xerostomia [25, 33-34].

As our study compromised hypopharyngeal carcinoma, it was associated higher incidence of xerostomia due irradiation of submandibular lymph nodes with subsequent submandibular and minor salivary glands beside parotid glands. Grade 2 mucositis in the definitive group was higher than adjuvant group which was statistically significant (0.01) and no late grade 3 xerostomia was reported, only grade 1 xerostomia was reported in 4 cases (18.2%) and grade 3 was reported in 2 cases (9.1%). similar to that reported by other authors [35-36].

So, our study revealed that IMRT-SIB was associated improved 2 year overall survival, loco regional control which was higher in adjuvant group and improved larynx preservation free survival in the definitive group with reduced incidence of early late toxicity.

STUDY LIMITATIONS

The limitation of our study is the small sample size; more cases are needed to document the results and longer duration of follow up.

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