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Accelerated fractionation radiotherapy in treating patients with locally advanced head and neck squamous cell carcinoma

Abstract

Purpose: Acute toxicity, tumor control and survival outcomes were prospectively evaluated following accelerated fractionation radiotherapy for head and neck squamous cell carcinoma (HNSCC).

Methods: Between 2012-2013, patients with non-metastatic HNSCC (T1-2N1 or T3-4N0-1) were accrued to a phase I/II prospective study. All patients were treated with 70 Gy in 30 fractions over 5weeks (6 fractions/week). Acute toxicity, clinical response, local (LC), regional (RC) and distant control (DC), disease free- (DFS) and overall- survival (OS) were analyzed.

Results: In total, 40 patients were enrolled; median follow-up was 41 months. The majority of patients were clinical stage III (n=37, 92.5%), ≥ 50 year (n=34, 85%), and male gender (n=29, 72.5%). Approximately half of the patients had laryngeal cancer. The overall grade 3 acute toxicity was 62.5%; mainly mucositis (n=23, 57.5%) and dysphagia (n=18, 45%). Overall, 34 patients (85%) showed complete response following radiotherapy. Three-year LC, RC, DC, OS and DFS were 81.6%, 85.3%, 90.3%, 64.4% and 58.7%, respectively.

Conclusion: Our proposed accelerated fractionation radiotherapy regimen appears feasible and safe. Future research is required to investigate the longer term outcomes including late toxicity with comparison to the standard treatment (i.e. concurrent chemo-radiotherapy).

Keywords: head and neck, squamous cell carcinoma, radiotherapy, accelerated fractionation, outcomes

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Ali Hosni, Mohamed Alawady, Abdolmonem Nooreldeen, Hanem Sakr
Department of Clinical Oncology and Nuclear Medicine, Mansoura University, Egypt

Correspondence: Hanem Sakr, Department of Clinical Oncology and Nuclear Medicine, Mansoura University, Manoura, Egypt, Email alihosniali@gmail.com

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Introduction

The incidence of squamous cell carcinoma of the head and neck (HNSCC) is increasing, and it was estimated to be the seventh most common malignant disease worldwide. There are more than annual 680,000 new cases and 375,000 deaths due to HNSCC.[1]

Prospective trials in HNSCC have proven that improvement in the loco-regional control has led to better overall survival. Strategies to improve the loco-regional control in HNSCC include combining radiation therapy (RT) with sensitizing chemotherapy or radiation dose escalation using altered fractionation. The latter approach has been tested with hyper-fractionation and accelerated fractionation schedules.[2-8]

Treatment with any cytotoxic agent, including radiation, can trigger the tumor stem cells to divide more rapidly than before, this is known as "accelerated repopulation".[9] A shorter overall treatment time (i.e. accelerated fractionation) aiming to overcome the accelerated repopulation in order to improve the loco-regional control could be obtained by: 1) applying higher dose per fraction (such using simultaneous integrated boost to the gross tumor target with a fraction size ranges from 2.2 to 2.46 Gy) or 2) increasing the number of weekly radiation fractions (such using 6 or 7 fractions per week). These both approaches of accelerated RT have independently improved the tumor control. However, employing both approaches together could be associated with higher rates of acute toxicity which could potentially lead to treatment interruption and prolongation of overall treatment time with subsequent decline of the loco-regional control.[9-11]

This prospective study aimed to assess the feasibility of acceleration of RT in the management of HNSCC through applying higher dose per fraction using simultaneous integrated boost, and at the same time increasing the number of weekly fractions using 6 fractions per week, without decreasing the total radiation dose or exceeding the tolerance limit of acute toxicity effects.

Methods

Study design and participant

This is a prospective phase I/II single arm study that included patients (≥18years old) with ECOG performance status ≤2 who had squamous cell carcinomas of oral cavity, oropharynx, hypoharynx or larynx (T1-2 N1 or T3-4a N0-1) presented to our institution from January 2012 till September 2013. Patients with N2-3 or M1 disease or those who had prior treatment with radiotherapy to head and neck area were excluded.

Evaluation

Initial pretreatment evaluation included comprehensive head and neck examination, fiberoptic examination with laryngopharyngoscopy, head and neck MRI and/or CT and chest CT. All patients underwent an educational session to review the rationale, expected outcomes, early and late toxicity of RT.

Patients were assessed weekly during treatment. Assessment of response to treatment was performed 10-12weeks following the end of RT by head and neck physical and endoscopic examination as well as head and neck MRI and/or CT. Clinical response was assessed

according to revised RECIST guideline (version 1.1) as follows: complete response (CR, disappearance of all known lesions, partial response (PR, ≥ 30% decrease from baseline), progressive disease (PD, ≥ 20% increase over smallest sum observed or appearance of new lesions), and stable disease (SD, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD).[12]. Patients were assessed clinically every 3months for 2years, every 4months in the third year, and then every 6 months. Imaging was performed as clinically indicated.

Radiation treatment

Determination of target volume

The extent of gross tumor volume (GTV) including the primary tumor and involved lymph nodes was primarily determined by clinical examination, diagnostic MRI and/or CT images and endoscopic findings. Imaging finding indicating involved lymph node included: focal necrosis, extrandoal extension or ≥1.0 cm lymph node in shortest axial diameter. All radiological images were reviewed with radiologists before target delineation.

The clinical target volume (CTV) included: 1) high-risk CTV (CTV1, created by expanding the GTV with 3–5 mm margins); 2) intermediate-risk CTV (CTV2, generated by adding 1 cm margin around the GTV tailored by potential microscopic extension of the tumor and barriers of tumor spread); and 3) standard-risk CTV (CTV3, included cervical nodal levels with lower risk of microscopic involvement which depends on location and extent of primary tumor, nodal category and location of nodal disease). The guidelines for selections of nodal regions to receive elective irradiation are summarized in Table 1. The CTV1, CTV2, and CTV3 were expanded 5-8 mm to generate the corresponding planning target volumes (PTV1, PTV2, PTV3, respectively).

Determination of organs-at-risk (OAR)

The parotid glands, submandibular glands, spinal cord, oral cavity, mandible and un-involved larynx were contoured as OAR. Brachial plexus was contoured if nearby involved lymph node. Planning at-risk volume (PRV) was generated around the spinal cord by 5 mm circumferential expansion.

Table 1 Guidelines for selection of elective nodal target volume

	Oral cavity cancer	Oro-, hypo-haryngeal or laryngeal cancer
NO	Levels I-III	Levels II-IV
N I	As NO+ If nodal disease at level II, includes: reiropharyngeal nodal region. If nodal disease at level III, includes: level 4 and 5.	As NO+ If nodal disease at level II, includes: level IB and retrophatyngeal nodal region. If nodal disease at level III or IV, includes: level 5 If the primary tumor involves or extends to the posterior pharyngeal wall, includes reiropharyngeal nodal region.

Dose and fractionation

Patients were treated with 30 fractions using a dose-painting approach, where different simultaneous daily doses were delivered to different target structures (simultaneous integrated boost). The dose prescription was 70 Gy (2.33 Gy per fraction) to the PTV 1, 60 Gy (2 Gy per fraction) to the PTV 2, and 54 Gy (1.8 Gy per fraction) to the PTV3. The prescribed doses were designed to cover at least 95% of the target volumes and no more than 20% of PTVs receive more than 110% of their prescribed doses. For normal tissue constraints, we followed those specified in QUANTEC review.[13]. Patients were planned to receive totally 30 fractions, six fractions per week over 5 week (1 fraction/day; and the sixth fraction was received on separate day).

Technique and Delivery

High conformal radiotherapy was delivered using forward treatment multi-segment planning technique. A standardized 13-field conformal plan was used (Table 2), to achieve the pre-defined target objectives and OAR constrains.

Table 2 Planning parameters for forward multi-segment planning technique

Beam number	Beam direction	Gantry angleb	Couch angle	Energy (Mev)
Beam 1	Antero-posterior	0	0	6
Beam 2	Left anterior oblique	60	0	6
Beam 3	Left anterior oblique	60	0	15
Beam 4	Left Laterala	90	0	15
Beam 5	Left posterior oblique	150	0	6
Beam 6	Left posterior oblique	150	0	15
Beam 7	Postero-anterior	180	0	15
Beam 8	Right posterior oblique	210	0	6
Beam 9	Right posterior oblique	210	0	15
Beam 10	Right laterala	270	0	15
Beam 11	Right anterior oblique	300	0	6
Beam 12	Right anterior oblique	300	0	15
Beam 13	Right/left anterior obliquea	300/60	0	15

[a]Beams 3 (left lateral), 10 (right lateral) and 13 (right/left anterior oblique) were designed to boost PTVI (corresponding to GTV) only, and the direction of beam 13 (right versus left) is based on the side of the tumor.

[b]Proper weighting of each beam with adequate choice of wedging and minor modification of gantry angels were allowed to ensure adequate PTV coverage and respecting organs-at-risk constraints.

Data collection and statistical considerations

Acute toxicity data were collected within 3 months from the start of radiotherapy and were graded according to the RTOG acute radiation morbidity score. Tumor control and survival outcome were determined at each follow-up visit.

The primary end points (i.e. acute toxicity and clinical repose rates) were estimated using proportion. The secondary end points included local, regional and distant control rates (which were estimated using competing risk method), disease-free and overall survival (which were analyzed using Kaplan-Meier method). Outcomes were calculated from the first day of RT. All reported p-values were 2-sided, with a statistical significance level of $p < 0.05$. Statistical analyses were performed using SPSS statistical package version 16 (SPSS, Inc., Chicago, IL, USA) and R software (http://CRAN.R-project.org, R Foundation, Vienna, Austria).

Results

Patient and tumor characteristics

Between January 2012 and September 2013, 40 patients with HNSCC were enrolled in this study. The median follow-up for alive patients was 41 months (range, 6-54), and for all patients was 31 months (range, 5-54). The majority of patients were clinical stage III (n=37, 92.5%), ≥ 50 year (n=34, 85%), and male gender (n=29,

72.5%). Approximately half of the patients had laryngeal cancer. Patient and tumor characteristics are summarized in Table 3.

Table 3 Patient and tumor characteristics

Characteristics	Value
Age at the Time of Diagnosis	
Median (range), year	59 (44-69)
Gender	
Male	29 (72.5%)
Female	11 (27.5%)
ECOG Performance Status	
0	13 (32.5%)
1	26(65%)
2	1 (2.5)
Smoking History at the Time of Diagnosis	
Current smoker	12 (30%)
Ex-smoker	5 (12.5%)
Non-smoker	23 (57.5%)
Smoking Pack-Year Index *	
Median (range)	38 (20-60)
Alcohol consumption	
Yes	0
No	40 (100%)
Primary Tumor Site	
Oral cavity	4 (10%)
Floor of mouth	4 (10%)
Oropharynx	6 (15%)
Tonsil	3 (7.5%)
Base of tongue	3 (7.5%)
Hypo pharynx	12 (30%)
Post-cricoid	9 (22.5%)
Purl form fossa	1 (2.5%)
Posterior pharyngeal wall	2 (5%)
Larynx	18 (45%)
Supraglottic	15 (37.5)
Glonie	2 (5%)
Subglottic	1 (15%)
Histological Grade	
Low grade	13 (32.5%)
Intermediate grade	17 (42.5%)
High grade	10 (25%)
cT-Category	
T1	1 (2.5)
T2	4 (10%)
T3	32 (80%)
T4a	3 (7.5)
cN-Category	
NO	26 (65%)
N1	14 (35%)
AJCC/UICC 7th Edition TNM Stage Grouping	
III	37 (92_5%)
IVA	3 (7.5%)

*Among patients who are current or ex-smoker.

Treatment characteristics

The median total delivered radiation dose was 70 Gy (range, 46.7–70). Thirty-nine patients (97.5%) completed the planned total radiation dose, while only one patient opted to discontinue radiation treatment after 20 fractions in view of acute toxicity. The median overall treatment time was 33 days (range, 17-39). Only 4 patients required an overall treatment time of more than 33 days with interruptions due to acute toxicity.

Clinical response

All patients were assessed by CT and or MRI, and all except oral cavity cancer patients were evaluated by laryngopharyngoscopy. Two patients (5%) had SD, of whom one patient didn't complete the planned radiation course. Four patients (10%) had PR (all had radiotherapy interruption). The remaining 34 patients (85%) showed CR following radiotherapy.

Acute toxicity

No grade 4 or 5 acute toxicity was reported. The most common grade 3 acute toxicity was mucositis (n=23, 57.5%) and dysphagia (n=18, 45%). The overall grade 3 acute toxicity was 62.5%. Table 4 shows the worst acute toxicity proportions among the whole cohort.

Table 4 Worst acute toxicity

Worst Toxicity	Whole Cohort (n=40)
Skin (Dermatitis)	
Grade 1	21 (52.5%)
Grade 2	17 (42.5%)
Grade 3	2 (5%)
Mucous Membrane (Mucositis)	
Grade 1	9 (22.5%)
Grade 2	8 (20%)
Grade 3	23 (57.5)
Salivary Gland (Xerostornia)	
Grade 1	21 (52.5%)
Grade 2	19 (47.5%)
Pharynx (Dysphagia)	
Grade 1	3 (75%)
Grade 2	19 (47.5%)
Grade 3	18 (45%)
Larynx	
Grade 1	31 (77.5)
Grade 2	8 (20%)
Grade 3	1 (2.5)
Overall	
Grade 2	15 (37.5%)
Grade 3	25 (62.5%)

Local control

The estimated 3-year local control rate was 81.6% (Figure 1). Seven patients (3 floor of mouth, 2 supraglottic and 1 posterior pharyngeal wall cancer) had local failure at median (range) time of 0 (0-23) months. Local failure developed in patients with T3 (n=5) and T4a (n=2) disease. All local failures except one were reported in patients who had PR (n=4) or SD (n=2) following radiation treatment. Salvage surgical resection was performed in 28.6% (2 out of 7) of patients who had local failure, while other patients didn't undergo salvage surgery in view of locally unresectable disease (n=2) or patients declined surgery (n=3). On univariable analysis, oral cavity cancer was associated with local failure, $p<0.001$ (Table 5).

Regional control

The 3-year regional control was 85.3% (Figure 1). Five patients developed regional failure in N0 (n=1) and N1 (n=4), at median 10 months (range, 0-25). Two patients had salvage neck dissection, while one patient refused the surgery and 2 had distant metastases.

All patients who had radiotherapy interruption (n=4) or did not complete the full-course of radiation due to acute toxicity developed locoregional failure. On univariable analysis, both oral cavity cancer (p = 0.03) and N1-category (p = 0.008) were associated with regional failure (Table 5).

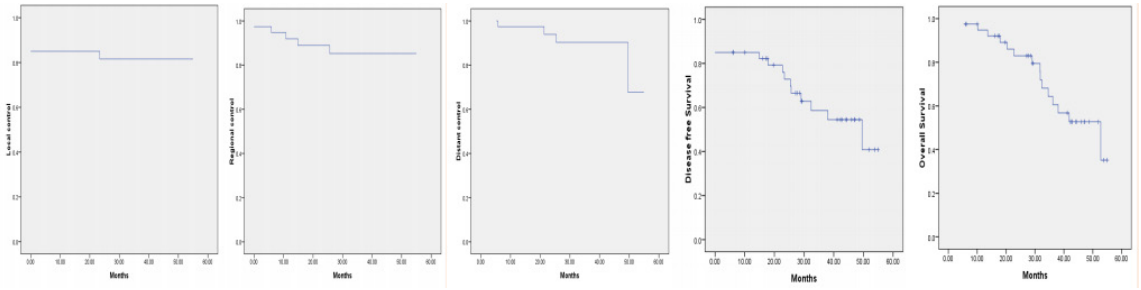

Figure 1 Treatment outcomes for the whole cohort.

Table 5 Univariable analysis for factors associated with tumor control and survival

Variable	3-Year LC	p-Value	3-Year RC	p-Value	3-Year DM	p-Value	3-Year DFS	p-Value	3-Year OS	p-Value
Smoking History										
Current smoker	75%		81.80%		80%		50%		66.70%	
Ex-smoker	100%	0.5	100%	0.6	100%	0.3	100%	0.3	100%	0.6
Non-smoker	82.60%		82%		95.70%		56.50%		58.80%	
Primary Site										
Oral cavity	0%		50%		75%		0%		0%	
Oropharynx	100%	<0.001	83.30%	0.03	83.30%	0.3	66.70%	<0.001	83.30%	0.003
Hypo pharynx	91.70%		83.30%		100%		68.80%		80.20%	
Larynx	87.20%		94.40%		92.30%		58.30%		62.70%	
Histological Grade										
Low	84.60%		69.30%		88.90%		42%	0.7	50%	
Intermediate	94.10%	0.08	100%	0.09	91.70%	0.9	65.40%		69.20%	0.6
High	56%		77.10%		90%		59.20%		75.50%	
cT-Category										
T1	100%		100%		100%		100%		100%	
T2	100%	0.06	100%	0.1	100%	0.9	100%	0.003	100%	<0.001
T3	83.50%		86%		88.80%		59.70%		67.70%	
T4a	33.50%		50%		100%		0%		0%	
cN-Category										
N0	87.20%	0.17	94.70%	0.008	94.70%	0.5	57.70%	0.97	64.50%	0.9
N1	71.40%		64.50%		81.20%		62.50%		63.50%	

Distant control

The estimated 3-year distant control was 90.3% (Figure 1). Four patients had distant metastases at median (range) of 21 (5-49) months, all of them with lung metastases. Chemotherapy was attempted in 2 patients with distant metastases who deemed to be candidate to tolerate chemotherapy. The distribution and patterns of failure are presented in Figure 2. On univariable analysis, no specific clinic-pathologic features were associated with development of distant metastases (Table 5).

Survival analysis

A total of 15 patients died. Causes of death included head and neck cancer (n=9), lung cancer (n=1), cardiac event (n=1), and patients died of unknown cause (n=4). The actuarial 5-year OS and DFS were 64.4% and 58.7%, respectively (Figure 1). Both oral cavity cancer and T-category significantly associated with poor disease free- and overall survival (Table 5).

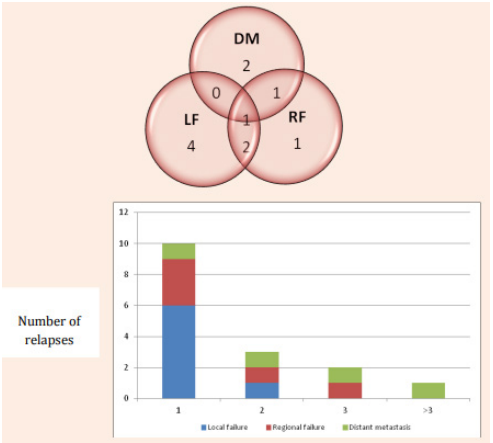

Figure 2 Distribution and pattern of failure.

LF: Local Failure; RF: Regional Failure; DM: Distant Metastases

Citation: Hosni A, Alawady M, Nooreldeen A, et al. Accelerated fractionation radiotherapy in treating patients with locally advanced head and neck squamous cell carcinoma. *J Cancer Prev Curr Res.* 2017;8(3):260–266. DOI: 10.15406/jcpcr.2017.08.00277

Discussion

Strategies of RT intensification aim to increase the tumor biologically effective dose (tBED) without exceeding the tolerance limit of acute mucosal biologically effective dose (amBED) which had been estimated to be 63 Gy10. Acute mucosal toxicity represents the main dose-limiting toxicity for definitive radiation for the treatment of HNSCC. It also limits the radiation efficacy by producing treatment interruptions, which decrease the tBED by prolonging overall treatment time. In addition, severe mucositis may lead to consequential long-term dysphagia and aspiration.[14]

The first strategy of treatment intensification is radio-sensitization by chemotherapy or targeted therapy. Meta-analysis has shown that chemotherapy given concurrently with RT improves the loco-regional control and subsequently overall survival compared with RT alone.[15] Similarly, concurrent radiation and cetuximab has shown to improve the loco-regional control and overall survival compared with radiation alone in locally advanced HNSCC6. Chemotherapy or targeted therapy-induced radio-sensitization can therefore be considered a method of biologic dose escalation.[16]

The main theoretical benefit of combined modality therapy is that there may be an improvement in the therapeutic index compared with using a single modality (radiation alone). However, an agent does rarely improve the tumor control without any increase in toxicity, and in general, concurrent chemotherapy is associated with increased rates of mucositis.[14] Notably, adding chemotherapy to RT increases the risk of mucositis (up to 100% in randomized clinical trials treated HNSCC patients with intensive chemo-radiation).[10]

It had been estimated that addition of concurrent chemotherapy to radiation therapy for HNSCC increases the tBED by 8.8 Gy10 & amBED by 8 Gy10. This may lead to narrow therapeutic gain especially when the compromised effects of systemic chemotherapy are added. In addition the financial aspect of biologic therapy may form an obstacle.[14] Table 6 shows a comparison of our proposed accelerated radiation schedule and conventional RT with concurrent chemotherapy.

Table 6 Radiobiological comparison of our proposed accelerated radiation schedule and conventional concurrent chemo-radiotherapy

	Conventional Concurrent Chemo-Radiotherapy	Accelerated Radiotherapy without Chemotherapy
Total RT dose (Gy)	70	70
RT dose/fraction (Gy)	2	2.33
Number of RT fractions/ week	5	6
Total number of RT fractions	35	30
Overall treatment time (days)	46	33
Calculation of tBED Assuming that Onset for Accelerated Repopulation (Tk)=21 day		
tBED for RT	64.75	77.1
tBED for chemotherapy	8.8	-
tBED (RT+chemotherapy)	73.55	77.1(Better)

Table continued...

	Conventional Concurrent Chemo-Radiotherapy	Accelerated Radiotherapy without Chemotherapy
Calculation of tBED Assuming that Onset for Accelerated Repopulation (Tk)=32 day		
tBED for RT	73.22	85.56
tBED for chemotherapy	8.8	-
tBED (RT+chemotherapy)	82.02	85.5(Better)
Calculation of amBED		
amBED for RT	48	62.3
amBED for chemotherapy	8	-
amBED (RT+chemotherapy)	56	62.3(within tolerance)

RT, radiation therapy; tBED, tumor biologically effective dose; amBED, acute mucosal biologically effective dose The calculations of tBED & amBED are based on the following equation:

$$BED = D \times \left[1 + d / \left(\alpha / \beta\right)\right] - \left[\left(0.693 / \alpha\right) \times \left(T - Tk\right) / Tp\right]$$

D, total radiation dose; d: radiation dose per fraction; α/β, 10 gy for tumors and acute mucosal reaction; α, 0.3 G-1; T, overall treatment time (1st treatment is on day 0 when calculating overall treatment time); Tk, onset time for accelerated repopulation (21 to 32 day for tBED & 7 day for amBED); Tp, average doubling time during Accelerated Repopulation (3 for tBED & 2.5 for amBED); tBED for concurrent chemotherapy, 8.8 Gy10; amBED for concurrent chemotherapy: 8 Gy10; Tolerance limit for amBED: 63 Gy10.

The second strategy of treatment intensification is the use of altered fractionation, including hyper-fractionation and accelerated fractionation. In hyper-fractionation, the total radiation dose is increased, the dose per fraction is reduced and the number of fractions is increased, while the overall treatment time is relatively unchanged. In accelerated fractionation, the overall treatment time is reduced and the number of fractions, total radiation dose and the dose per fraction are either unchanged in "pure accelerated fractionation" or somewhat changed in "hybrid accelerated fractionation".[17]

Evaluation of altered RT fractionation schedules in randomized controlled trials is confounded by differences in proportion of T-category and N-category within the trials, the use and timing of chemotherapy, different overall RT dose, RT technique (2-dimensional versus 3-dimensional), quality assurance measures and protocol violation and inadequate information on pattern of failure. Table 7 describes the different RT fractionation schedules used in clinical trials and their associated outcome.

This study should be interpreted within the context of its limitation, mainly the sample size, the non-randomized design and the lack of data regarding the HPV status or its surrogates (e.g. p16 immunohistochemical analysis). However, our proposed RT schedule offers a planned total RT dose of 70 Gy to be delivered within only 5weeks of overall treatment time to reach a higher tBED without exceeding the amBED tolerance (63 Gy10) with better save of resources as there is no need for use of concomitant chemotherapy or target therapy in addition to better use of radiotherapy machines through saving of 2weeks of working for each patient without increasing the daily treatment settings. On the other hand, there is no need to expose the patients to systemic compromised effects of chemotherapy. Future research is required to investigate the longer term outcomes including late toxicity with comparison to the standard treatment (i.e. concurrent chemo-radiotherapy).[18-31]

Citation: Hosni A, Alawady M, Nooreldeen A, et al. Accelerated fractionation radiotherapy in treating patients with locally advanced head and neck squamous cell carcinoma. *J Cancer Prev Curr Res.* 2017;8(3):260–266. DOI: 10.15406/jcpcr.2017.08.00277

Table 7 Radiotherapy fractionation and outcome of different altered fractionation schedules

Altered Fractionation Study	Total RT Dose (Gy)	Total RT fx	Dose Per fx (Gy)	No. of RT fx Per Day	No. of RT Days / Week	OTT (Week)	No. of Patients	Median FU (Year)	T3-4 (%)	N2-3 (%)	Acute Confluent Mucositis	5-Year Local Control	5-Year Regional Control	5-Year Overall Survival
												5-Year LRC		
Accelerated Fractionation with Reduction of the Total Radiation Dose														
CHART 18	54	36	1.5	TID	7	1.7	552	7	54%	19%	73%	50%	66%	42%
VIENNA19	55.3	33	1.65#	BID	7	2.5	78	5.6	86%	60%	90%	32%		31%
TROG 910120	59.4	33	1.8	BID	4	3.5	172	3.9	70%	44%	94%	52%		46%
GORTEC 940221	62-64	31-32	2	BID	5	3	137	4.8	100%	67%	75%	42%		21%
Accelerated Fractionation without Reduction of the Total Radiation Dose														
EORTC 2285122	72	45	1.6	TID	5	5*	257	4.8	64%	29%	67%	59%		27%
RTOG 9003 B23	72	42	1.8	1.5last 12 days BID in	5	6	268	14	67%	59%	47%	2-year: 54%		2-year: 51%
RTOG 9003 S23	67.2	42	1.6	BID	5	6*	247	14	67%	57%	41%	2-year: 48%		2-year: 46%
BCCA 911324	66	33	2	BID	5	3.5	41	7.8	73%	29%	66%	3-year recurrence free survival:49%		3-year: 59%
DAHANCA 6 and 725	66-68	33-34	2	OD	6	6	750	6.8	32%	NA	53%	76%	88%	CSS: 73%
ORO 930126	64-67.2	40-42	1.6	BID	5	6*	65	6.6	82%	43%	40%	2-year relapse free rate: 20%		2-year: 37%
CAIR27	64-72	32-36	1.8-2	OD	7	4.5-5	51	5.7	82%	0%	62%	3-year: 82%	3-year: 100%	3-year: 78%
KPN PO7928	66	33	2	BID once weekly	5	5.5	196	4.1	9%	0%	3%	3-year: 81%		3-year: 85%
Hyper-Fractionation														
EORTC 2279129	80.5	70	1.15	BID	5	7	166	10.3	35%	0%	67%	59%	91%	39%
RIO30	70.4	64	1.1	BID	5	6.5	50	6.7	88%	44%	58%	84%	55%	42 months: 27%
RTOG 9003 HF23	81.6	68	1.2	BID	5	7	263	14	69%	55%	42%	2-year: 53%		2-year: 55%
Accelerated Hyper-Fractionation														
PMH-Toronto31	58	40	1.45	BID	5	4	169	7.4	70%	42%	62%	59%	67%	40%
Our Proposed Schedule: Accelerated Simultaneous Integrated Boost with 6 Weekly Treatment														
MUH-Mansoura	70	30	2.33	OD	6	5	40	3.4	87.50%	0%	57.50%	3-year: 81.6%	3-year: 85.3%	3-year: 64.4%

*2 weeks split course.

#First day: only 1fraction of 2.5 Gy, then BID 1.65 Gy/fraction. RT, radiation therapy; fx, fraction; No., number; OTT: overall treatment time; FU, follow-up; LRC, loco-regional control; TID, three times-daily; BID: bi-daily; OD, once daily; CSS, cancer specific survival.

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None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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