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Accelerated Fractionation Radiotherapy and Chemotherapy Might Improve Loco-Regional Control of Head and Neck Squamous Cell Carcinoma

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ABSTRACT

Background: Managing advanced head and neck squamous cell carcinoma is challenging with a limited outcome, especially in stage IVA disease. However, altered fractionation proved to be a promising alternative to standard radiotherapy.

Objectives: This study aimed to explore the effect of concomitant chemotherapy with accelerated fractionation on the disease outcomes.

Material and methods: Forty-seven patients were enrolled in this trial. A phase 2 trial with two arms was conducted between Jan 2018 and March 2021. The experimental arm used accelerated fractionation 70 Gy given on 35, six fractions per week. The control arm used a standard fractionation protocol of 70 Gy on 35 fractions, five fractions per week. Chemotherapy using platinum salts was given in both arms.

Results: At the end of this study, 44.7% of patients had local-regional relapses, with a one-year loco-regional failure of 40.9%. There was a near significant difference in the one-year loco-regional failure rate between the accelerated and standard fractionation arms (25% versus 54.2%, respectively, p = 0.069). The same near-significant difference was also seen in the cumulative probability of loco-regional failure (28.6% versus 57.7%, respectively, P= 0.076). The rates of grade 3 and 4 acute and late toxicities were comparable in both arms.

Conclusion: Accelerated fractionation with concomitant chemotherapy did not improve loco-regional control. However, there was a trend toward improvement. Further evaluation by a large phase 3 trial is mandatory to confirm the results.

Keywords: Accelerated fractionation, HNSCC, Radiotherapy, Radiation therapy, Altered fractionation, Cancer.

INTRODUCTION

One million individual suffers from head and neck cancer each year. Roughly 50% of them will die from this disease. Head and neck cancer is more pronounced in gentlemen, especially in the Middle East [(1)]. Tobacco smoking is associated with increased head and neck squamous cell carcinoma (HNSCC). The risk was reported as high as 8.5 times the risk of non-smokers [(2)]. The presence of nitrosamines and polycyclic aromatic hydrocarbons in inhaled smoke negatively affects cell proliferation and apoptosis pathways [(3)]. Consumption of alcohol over 50 grams/day was linked to increased risk of developing HNSCC by 5-6 times [(4)]. There is a strong link between oropharyngeal cancer and human papillomavirus (HPV) infection [(5)]. However, the prevalence of HPV related-oropharyngeal cancer was low in Egypt. It was reported as low as 3 per cent [(6)].

The initial diagnosis of HNSCC depends on tissue biopsy [(7)]. HNSCC usually express cytokeratin as a pan-marker. In addition, there was some specialised marker for the specific subsite, such as p16, which is seen with HPV-positive oropharyngeal cancer [(8)]. Radiation therapy represents an acceptable alternative to surgery in selected head and neck subsites. The RTOG 7303 proved that definitive radiotherapy had a comparable outcome to surgical resection in selected HNSCC [(9)]. The commonly used fractionation schedule is 70 Gy in 35 fractions, 2 Gy per fraction and five fractions per week [(10)]. Several trials found that hyperfractionation (1.2 Gray per fraction, twice daily) and accelerated fractionation increased disease-free survival and loco-regional control [(11)]. However, as shown by the MARCH meta-analysis, the improved outcome comes at the expense of higher acute toxicity and treatment complexity [(12)].

Two trials explored using concomitant chemotherapy with accelerated fractionation, the RTOG 0129 and the GORTEC 99-02 [(13)]. They failed to show any benefit in terms of overall and distant metastasis-free survival. However, they showed modest improvement in the loco-regional control [(13, 14)]. In this study, we explored the effect of concomitant chemotherapy with accelerated fractionation on the disease outcomes.

MATERIAL AND METHODS

This phase two study investigated two different radiotherapy schedules in advanced (stage III-IV based on TNM 8th edition) HNSCC (oral cavity, oropharynx, hypopharynx or larynx). The standard arm used a standard fractionation protocol of 70 Gy given on 35 fractions, five fractions per week. The experimental arm was 70 Gy given on 35, six fractions per week (accelerated RT protocol). Chemotherapy with platinum salts was given in both arms. The choice between cisplatin and carboplatin was based on the physician's evaluation of the patient's eligibility for cisplatin. Eligibility to cisplatin was defined as (age less than 65 years, ECOG PS 0-1, eGFR ≥ 50 mL/min, no G2 or worse neuropathy, normal hearing function).

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Patients' assessment: A complete history and careful examination were proposed for all participants. Baseline haemopoietic function, CT scan for the brain, neck and chest, MRI scan for the neck, and skilful endoscopic evaluation and biopsy under anaesthesia should be done for all patients. After reception of the primary radiotherapy, follow-up imaging by CT scan at three months interval were proposed. In addition, a PETCT scan at twelve weeks from the last RT fraction was allowed. Patients randomly allocated to the conventional arm received 70 Gy in seven weeks, five fractions of 2 Gy per week with concomitant chemotherapy either (cisplatin 100 mg/m^2 or carboplatin AUC 5 on days 1, 22 and 43). Patients allocated to the accelerated radiotherapy arm received 70 Gy in six weeks, six fractions of 2 Gy per week with concomitant chemotherapy (cisplatin 100 mg/m^2 or carboplatin AUC 5 on days 1 and 22).

Radiotherapy techniques:

Patients were immobilised in a supine position by a head and shoulder thermoplastic immobilisation system (Klarity©, R461ST White S-Type, 42% perforation, 3.2 mm). Patients were scanned without contrast by a CT simulator for 2-3 mm slice thickness. The scan range was from the vertex to the level of the carina. The scan level extended to the diaphragm level for subglottic disease and hypopharynx. Varian © ARIA 13.6 version was used for target contouring and treatment planning. Volumes were defined according to the recommended ESRTO/DAHANCA/RTOG consensus[17]. The 70 Gy (high-risk) volume included the gross tumour (primary and nodes) and 5-10 mm margin. The 59.4 – 63 Gy (intermediate-risk) volume harboured the high-risk anatomical areas such as the entire laryngopharynx complex for laryngeal and hypopharyngeal sites or oral tongue for tongue cancer. The intermediate-risk volume included the high-risk nodal groups, such as level II-IV for laryngeal disease. The 56 Gy (low-risk group) included the nodal groups with a low but significant risk of having micrometastasis, such as level V for positive neck or superior mediastinum for subglottic disease [(17)].

Rapid arc plans were calculated using two 360 degrees arcs, a single isocenter, and energy of 6 MeV. One-plan VMAT (dose-painting) was adapted to deliver the prescribed doses to the gross disease, intermediate and low-risk volumes. Digital reconstructed radiographs were calculated using the following parameter (HU -16.0 – 126.0, weight 2.0 and HU 10.0 – 1000, weight 10.0). This allowed bone visualisation on a background of soft tissue. All plans were verified by OCTAVIUS® 4D phantom and underwent 3D gamma volume analysis before the approval of starting radiotherapy.

Image-guided radiotherapy:

The setup verification protocol depended on obtaining MV portal images for the initial two fractions, then twice weekly for every patient. The images were taken only after correctly positioning the patients and aligning the in-room lasers on the marks drawn on the thermoplastic meshes. Afterwards, the verification was initiated by capturing two images for every setup event, taken at 0^o and 270^o. Setup corrections were made before treatment if the error was more significant than 2 mm.

Measure outcomes: The measured outcomes were loco-regional control, progression-free survival, overall survival, acute and later toxicities, nutritional needs, weight changes and risk of geometrical miss.

Ethical consent: The Academic and Ethical Committee, Sohag University approved the study. Every patient signed an informed written consent for acceptance of the treatment. This work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The primary endpoint was PFS, defined as the time between randomisation and the first of the following events: loco-regional progression or relapse, distant relapse, or death from the disease. Secondary endpoints were loco-regional progression (disease progression or relapse above the clavicles), distant metastases, overall survival, acute and late toxicity, nutritional needs, weight changes and risk of geometrical miss. The Chi-square test was used to analyse categorical data, while Kaplan-Meier and log-rank tests evaluated patients' survival data. The commercially available statistical software IBM-SPSS (version 23 for Windows; IBM Inc.) was used for data analysis. An alpha level of 5% was used for all tests to consider the statistical significance.

RESULTS

Forty-seven patients were enrolled between Jan 2018 and March 2021. Table (1) showed the baseline characteristics of the patients. Most of the patients were male and had stage IV disease (n 39, 83%). Median FU was 15 (range, 3 – 52.0) months. Heavy Smokers represented 31.9% of the patient population. The primary pathology was squamous cell carcinoma in 45 (95.7%) patients, and the remaining was undifferentiated carcinoma. Grade one, two and three diseases were seen in 6 (12.8%), 33 (70.2%), and 8 (17%) histological samples, respectively. Eleven (23.4%) patients had a tracheostomy. ECOG performance statuses were 22 (46.8%) and 25 (53.2%) for ECOG 1 and 2 performance status, respectively. The median overall radiotherapy doses for the high, intermediate and low-risk CTV were 70, 60 and 54 Gy for both the standard and the accelerated arms.

Table (1): Patients characteristics

		Standard fractionation n (%)	Accelerated fractionation n (%)
Age (mean) in years		61.4 (57.1 – 65.73)	57.3 (53.0 – 61.6)
Sex (male)		17 (65.5%)	17 (81.0%)
Primary site	*Larynx*	12 (46.2%)	3 (61.9%)
	Hypopharynx	10 (38.5%)	5 (23.8%)
	Oral Cavity	3 (11.5%)	2 (9.5%)
	Oropharynx	1 (3.8%)	1 (4.8%)
T stage	*T2*	4 (15.4%)	3 (14.3%)
	T3	9 (34.6%)	13 (61.9%)
	T4	13 (50%)	5 (23.8%)
N stage	*N0*	9 (34.6%)	6 (28.6%)
	N1	2 (7.7%)	0 (0%)
	N2	12 (46.2%)	15 (71.4%)
	N3	3 (11.5%)	0 (0%)

Efficacy

By the time of the analysis, 19 patients died (95% were due to disease progression). One patient died due to COVID-19-related respiratory failure. One-year and the two-year mortality rate was 29.8% and 50%, retrospectively. In 21 (44.7%) patients, local-regional relapses were seen, while distant disease progression occurred in 9 (19.1%) patients. One-year loco-regional failure and distant-relapse rates were 40.9% and 19.4%, respectively.

Chi-square tests identified a near significant difference in the one-year loco-regional failure rate between the accelerated and standard fractionation arms (25% versus 54.2%, respectively, p = 0.069). The same near-significant difference was also seen in the cumulative probability of loco-regional failure (28.6% versus 57.7%, respectively, P= 0.076) as shown in Table (2).

TABLE (2): Treatment outcomes

		Standard Fractionation n (%)	Accelerated fractionation n n (%)	p
LOCAL CONTROL	Loco-regional failure	15 (57.7%)	6 (28.6%)	0.076
	One-year LRF	13 (54.2%)	5 (25%)	0.069
	The median loco-regional relapse-free survival	10 months	18 months	P = 0.039 Kaplan Meier

Safety

Grade three and four acute toxicities happened in 48.9% of the patients. The rate of acute toxicities did not differ between the standard and accelerated fractionation arm (chi-square 0.55). Grade three and four late toxicities occurred in 19.1% of the patients. The rate of late toxicities did not differ between standard and accelerated fractionation arms (chi-square 0.359). Treatment-related toxicities were summarised in Table (3) and (

Table (4).

Table (3): Acute toxicity

		Standard Fractionation (%)	**Accelerated fractionation (%)**
Mucositis p = 0.153	Grade 0-1	0 (0%)	0 (0%)
	Grade 2	13 (50%)	6 (28.6%)
	Grade 3	10 (38.5%)	14 (66.6%)
	Grade 4	3 (11.5%)	1 (4.8%)
Skin toxicity p = 0.043	Grade 0-1	2 (7.7%)	0 (0%)
	Grade 2	17 (65.4%)	20 (95.2%)
	Grade 3	7 (26.9%)	1 (4.8%)
	Grade 4	0 (0%)	0 (0%)
Vomiting p = 0.520	Grade 0	7 (26.9%)	3 (14.3%)
	Grade 1	13 (50%)	11 (52.3%)
	Grade 2	6 (23.1%)	6 (28.6%)
	Grade 3	0 (0%)	1 (4.8%)
Fatigue p = 0.476	Grade 0-1	4 (15.4%)	1 (4.8%)
	Grade 2	11 (42.3%)	9 (42.8%)
	Grade 3	11 (42.3%)	11 (52.4%)
	Grade 4	0 (0%)	0 (0%)
Pain p = 0.095	Grade 0-1	6 (23.1%)	1 (4.8%)
	Grade 2	9 (34.6%)	13 (61.9%)
	Grade 3	11 (42.3%)	7 (33.3%)
	Grade 4	0 (0%)	0 (0%)
Dysphagia p = 0.730	Grade 0-1	6 (23.1%)	6 (28.6%)
	Grade 2	13 (50%)	10 (47.6%)
	Grade 3	7 (26.9%)	5 (23.8%)
	Grade 4	0 (0%)	0 (0%)

Table (4): Late toxicity

		Standard Fractionation (%)	Accelerated fractionation (%)
Dysphagia p = 0.520	Grade 0-1	5 (20.8%)	2 (10%)
	Grade 2	12 (50%)	13(65%)
	Grade 3	7 (29.2%)	5 (25%)
	Grade 4	0 (0%)	0 (0%)
Skin toxicity p = 0.031	Grade 0-1	6 (25%)	12 (60%)
	Grade 2	18 (75%)	8 (40%)
	Grade 3	0 (0%)	0 (0%)
	Grade 4	0 (0%)	0 (0%)
Xerostomia p = 0.365	Grade 0-1	8 (33.3%)	9 (45%)
	Grade 2	16 (66.7%)	10 (50%)
	Grade 3	0 (0%)	0 (0%)
	Grade 4	0 (0%)	1 (5%)
Taste alteration p = 0.648	Grade 0	7 (29.2%)	3 (15%)
	Grade 1	7 (29.2%)	8 (40%)
	Grade 2	8 (33.3%)	8 (40%)
	Grade 3	2 (8.3%)	1 (5%)

DISCUSSION

The management of HNSCC is a challenge that mandates skilful evaluation by various specialities within the scope of MDT [15]. Several risk factors were linked to an increased risk of suffering from HNSCC. The most crucial factors were tobacco smoking, alcohol consumption and HPV infection [6, 16].

Several studies within the radiobiology field showed that accelerated repopulation occurs following exposure to squamous cell carcinoma. Reflexively to cell death of nearby cells, the surviving SCC cell enters through an accelerated phase of replication and division in a phenomenon known as tumour repopulation. Studies estimated that SCC tumours enter this accelerated repopulation phase after three weeks of exposure to radiotherapy. Therefore, treatment gaps after the third week of the start date of radiotherapy are linked to a severe decline of the tumour control probability. The accelerated repopulation has become the solid ground for accelerated fractionation in head and neck squamous cell carcinoma. The idea is to provide the total radiotherapy dose within a short duration of time. The accelerated course would reduce the impact of tumour repopulation extensively [17]. In practice, multiple trials and meta-analyses asserted the clinical benefit of accelerated radiation. The MARCH meta-analysis showed that accelerated fractionation was linked to improved overall survival by two per cent in five years as long as no dose reduction was done [12]. Another approach to improve the outcome of radiotherapy was the use of chemotherapy. Several trials tried to examine the best time and agent used with radiation. These trials found that platinum salts, especially cisplatin, used concomitantly with radiotherapy, were linked to the best outcome. The explanatory base behind this discovery was probably related to the inherited nature of cisplatin as a chemotherapeutic agent. Cisplatin induces damage to DNA by adding DNA adducts. This produces DNA twisting and unrepairable DNA double-strand breaks. Theoretically, cisplatin induces damage, augmenting radiation's effect by increasing the magnitude of the unrepairable DNA damage [17]. The MACH-NE meta-analysis stated that concomitant use of chemotherapy was linked to the improvement of overall survival by 6.5% in 5 years. The benefit was even more remarkable, approaching 15% if cisplatin was used. Numerically, the benefit of using concomitant cisplatin appears to be far greater than accelerated fractionation [18]. Joining altered fractionation, hyperfractionation and accelerated fraction with concomitant chemotherapy was reconnoitred by GORTEC 99-02 and RTOG 0129 [13, 14]. Both of the trials were negative in terms of overall survival. Specifically, the GORTEC 99-02 trial had a much accelerated arm of radiotherapy alone. This arm showed that much accelerated radiotherapy harbour inferior outcomes compared to conventional and accelerated radiotherapy concomitant to chemotherapy. These trials confirmed the previous beliefs that adding chemotherapy is more effective than altering fractionation in controlling the disease [13, 14]. Detailed inspection of GORTEC 99-02 would provide a possible explanation for the similar EFS outcome for standard and accelerated chemotherapy when chemotherapy was used with them [14]. The protocol used was carboplatin 70 mg/m^2 and 5 FU 600 mg/m^2 daily for five days. In the conventional radiotherapy arm, three cycles of carboplatin/5 FU were used, while only two cycles were used in the accelerated arm. The reduced total cumulative chemotherapy dose in the accelerated arm was probably the hidden confounding factor. Interestingly, the impact of total cumulative chemotherapy dose per radiotherapy course was well established in another study [14]. Weekly cisplatin at a dose of 30 mg/m^2 for seven weeks was inferior in terms of PFS compared to high dose cisplatin of 100 mg/m^2 for three cycles. The total cumulative dose in the weekly arm was 210 mg/m^2, while every three weeks arm was 300 mg/m^2 [19].

We aimed throughout this study primarily to show the feasibility of implementing new state-of-the-art technology within a minimal healthcare system. The second objective was to examine the effect of combined accelerated fractionation with concomitant chemotherapy against the standard of care and the concomitant chemotherapy with standard fractionation. The study recruitment process started in January 2018 and ended in March 2021. The study included 47 patients of different

subsites of HNSCC. Most of the patients were laryngeal disease and stage IV disease. In addition, 65.5% were males. The mortality rates were 29.8% and 50% at one and two years, which is comparable to the result seen in the GORTEC 99-02 trial. In GORTEC, the one- and two-year mortality rates were around 30% and 55%. Similar to GORTEC 99-02 and RTOG 0129, our trial did not show benefit in overall survival, with median overall survival of 15 and 18 months for standard and accelerated fractionation (p = 0.157) [13, 14].

In our study, the one-year loco-regional failure was 25% and 54.2% for the accelerated fractionation and standard fractionation arms. However, the Chi-square test showed a near-significant difference in LRF (P = 0.069). Probably, the small sample size explains the lack of significance. What probably confirms this claim is the presence of a significant difference in the Kaplan Meier survival functions (p=0.039). Similarly, the GORTEC 99-02 found a significant benefit of accelerated fractionation in loco-regional failure [13, 14].

Acute and late toxicities were comparable between the arms. There was no increase in grade 3 and 4 toxicity with accelerated fractionation. The similarities between both arms keep with the toxicities prevalence of the GORTEC 99-02 [13, 14].

CONCLUSION

Accelerated fractionation with concomitant chemotherapy was a safe alternative to standard fractionation with increased loco-regional control probability. However, a further significant phase 3 trial is mandatory to confirm the results.

Limitation: The sample size of this trial was small to draw definitive conclusions.**Role of funding:** The study was fully funded by the Sohag university hospital and the Sohag faculty of medicine.

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REFERENCES

1. **Lambert R, Sauvaget C, De Camargo C *et al*. (2011):** *Epidemiology of cancer from the oral cavity and oropharynx*. Eur J Gastroenterol Hepatol., 23 (8): 633-641.
2. **Wyss A, Hashibe M, Chuang S *et al.* (2013):** *Cigarette, cigar, and pipe smoking and the risk of head and neck cancers: Pooled analysis in the international head and neck cancer epidemiology consortium*. Oxford University Press. https://pennstate.pure.elsevier.com/en/publications/cigarette-cigar...
3. **Jethwa, A and Khariwala S (2017):** *Tobacco-related carcinogenesis in head and neck cancer.* Cancer and Metastasis Reviews, 36 (3): 411-423.
4. **De Stefani E, Boffetta P,vOreggia F *et al*. (1998):** *Hard liquor drinking is associated with higher risk of cancer of the oral cavity and pharynx than wine drinking. A case-control study in Uruguay.* Oral Oncology, 34 (2): 99-104.
5. **Woods R, O'Regan E, Kennedy S *et al.* (2014):** *Role of human papillomavirus in oropharyngeal squamous cell carcinoma: A review.* World Journal of Clinical Cases, 2 (6): 172-172.
6. **Salem A, Rouby M (2020):** *Prevalence of HPV Infection in Head and Neck Cancer Patients in Egypt : National Cancer Institute Experience*. https://assets.researchsquare.com/files/rs-49031/v1/19b73532-da18-4676-a1c9-7990 fd54a175.pdf?c=1631847958: 1-13.
7. **Devaney K, Ferlito A, Rinaldo A (2004):** *The language of surgical pathology - A precis for the head and neck surgeon*. Oral Oncology, 40 (3): 233-235.
8. **Economopoulou P, de Bree R, Kotsantis I *et al*. (2019):** *Diagnostic tumor markers in head and neck squamous cell carcinoma (HNSCC) in the clinical setting*. Frontiers Media S.A., 9 (1): 827-827.
9. **Kramer S, Gelber R, Snow J *et al*. (1987):** *Combined radiation therapy and surgery in the management of advanced head and neck cancer: Final report of study 73–03 of the radiation therapy oncology group.* Head & Neck Surgery, 10 (1): 19-30.
10. **The Royal College of RCR (2006):** *Radiotherapy Dose - Fractionation.* Royal College of Radiologists, https://www.rcr.ac.uk/publication/radiotherapy-dose-fractionation-third-edition.
11. **Fu K,Pajak T, Trotti A *et al.* (2000):** *A 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.* International Journal of Radiation Oncology Biology Physics, 48 (1): 7-16.
12. **Lacas B, Bourhis J, Overgaard J *et al.* (2017):** *Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis.* The Lancet Oncology, 18 (9): 1221-1237.
13. **Nguyen-Tan P, Zhang Q, Ang K *et al.* (2014):** *Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the radiation therapy oncology group 0129 trial: Long-term report of efficacy and toxicity.* Journal of Clinical Oncology, 32 (34): 3858-3867.
14. **Bourhis J,. Sire C, Graff P *et al*. (2012):** *Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): An open-label phase 3 randomised trial.* The Lancet Oncology, 13 (2): 145-153.
15. **Machiels J, René Leemans J, Golusinski W *et al.* (2021):** *Reprint of "Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up".* Oral Oncology, 113 (11): 105042-105053.
16. **D'Souza G, McNeel T, Fakhry C (2017):** *Understanding personal risk of oropharyngeal cancer: Risk-groups for oncogenic oral HPV infection and oropharyngeal cancer.* Annals of Oncology, 28 (12): 3065-3069.
17. **Hall E (1988):** *Radiobiology for the Radiologist*. https://openlibrary.org/books/OL2375485M/Radiobiology_for_the_radiologist 18.
18. **Pignon J, Maître A, Maillard E *et al.* (2009):** *Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients.* Radiotherapy and Oncology, 92 (1): 4-14.
19. **Noronha V, Joshi A, Patil V *et al.* (2018):** *Once-a-week versus once-every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a phase III randomized noninferiority trial.* Journal of Clinical Oncology, 36 (11): 1064-1072.