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 (T1-2N0-1) were accrued to a phase I/II prospective study. All patients were treated with 70 Gy in 30 fractions over 5 weeks (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

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 (≥18 years old) with ECOG performance status ≤2 who had squamous cell carcinomas of oral cavity, oropharynx, hypopharynx 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 10-12 weeks 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 3 months for 2 years, every 4 months 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, extranodal 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.

| Number | Beam Direction | Gantry Angle° | 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 Lateral | 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          |

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 weeks (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 constraints.

Table 2: Planning parameters for forward multi-segment planning technique.

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| Beam 3      | Left anterior oblique | 60           | 0           | 15          |
| Beam 4      | Left Lateral  | 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 lateral | 270 | 0 | 15
Beam 11 | Right anterior oblique | 300 | 0 | 6
Beam 12 | Right anterior oblique | 300 | 0 | 15
Beam 13 | Right/left anterior oblique | 300/60 | 0 | 15

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

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%)   |

| Smoking History at the Time of Diagnosis     |       |
| Current smoker                               | 12 (30%)  |
| Ex-smoker                                    | 5 (1.25%) |
| Non-smoker                                   | 23 (5.75%) |

| 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%)   |
| Hypopharynx                                  | 12 (30%)  |
| Post-cricoid                                 | 9 (22.5%)  |
| Purliform 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%)             |
| Salivary Gland (Xerostomia)    |                     |
| Grade 1                        | 21 (52.5%)          |
| Grade 2                        | 19 (47.5%)          |
| Grade 3                        | 18 (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)

Figure 1: Treatment outcomes for the whole cohort.

Citation: Hosni A, Alawady M, Nooreldeen A, Sikr H (2017) Accelerated Fractionation Radiotherapy in Treating Patients with Locally Advanced Head and Neck Squamous Cell Carcinoma. J Cancer Prev Curr Res 8(3): 00277. DOI: 10.15406/jcpcr.2017.08.00277
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%       | 0.5     | 81.80%    | 0.6     | 80%       | 0.3     | 50%        | 0.3     | 66.70%    | 0.6     |
| Ex-smoker         | 100%      |         | 100%      |         | 100%      |         | 100%       |         | 100%      |         |
| Non-smoker        | 82.60%    |         | 82%       |         | 95.70%    |         | 56.50%     |         | 58.80%    |         |
| **Primary Site**  |           |         |           |         |           |         |            |         |           |         |
| Oral cavity       |           | <0.001  | 50%       | 0.03    | 75%       | 0.3     | 0%         | <0.001  | 0%        | 0.003   |
| Oropharynx        |           |         |           |         |           |         |            |         |           |         |
| Hypo pharynx      |           | 83.30%  |           | 0.03    | 83.30%    | 0.3     | 66.70%     | <0.001  | 83.30%    |         |
| Larynx            |           | 87.20%  |           |         | 94.40%    | 0.3     | 58.30%     |         | 62.70%    |         |
| **Histological Grade** |       | 0.08    |           | 0.09    | 91.70%    | 0.9     | 42%        | 0.7     | 65.40%    | 0.6     |
| Low               |           |         |           |         |           |         |            |         |           |         |
| Intermediate      | 94.10%    |         | 100%      |         | 91.70%    |         | 65.40%     |         | 69.20%    |         |
| High              | 9.56%     |         | 77.10%    |         | 90%       |         | 59.20%     |         | 75.50%    |         |
| **cT-Category**   |           |         |           |         |           |         |            |         |           |         |
| T1                | 100%      | 0.06    | 100%      | 0.1     | 100%      | 0.9     | 100%       | 0.003   | 100%      | <0.001  |
| T2                | 100%      |         | 100%      |         | 100%      |         | 100%       |         | 100%      |         |
| 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%    |         | 91.80%    |         | 62.50%     |         | 63.50%    |         |

**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).

**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).

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 Gy[10]. 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 Gy[10] & amBED by 8 Gy[10]. 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 RT with concurrent chemotherapy.

| Conventional RT | Concurrent Chemo-Radiotherapy | Accelerated Radiotherapy without Chemotherapy |
|-----------------|------------------------------|---------------------------------------------|
| Total RT dose (Gy) | 70                           | 70                                         |
| RT dose/fraction (Gy) | 2                            | 2.33                                        |

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
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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 5 weeks 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 2 weeks 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].

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 |
|-----------------------------|-------------------|-------------|-----------------|---------------------|-----------------------|------------|----------------|-----------------|----------|----------|---------------------------|------------------------|------------------------|------------------------|
| CHART 18                   | 54                | 36          | 1.5             | TID                 | 7                     | 1.7        | 552            | 7               | 54%      | 19%      | 73%                       | 50%                    | 66%                    | 42%                    |
| VIENNA 19                  | 55.3              | 33          | 1.65#           | BID                 | 7                     | 2.5        | 78             | 5.6             | 86%      | 60%      | 90%                       | 32%                    | 52%                    | 46%                    |
| 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       | 1.8             | BID                 | 3                     | 3          | 137            | 4.8             | 100%     | 67%      | 75%                       | 42%                    | 21%                    |                       |
| EORTC 2285122             | 72                | 45          | 1.6             | TID                 | 5                     | 5*         | 257            | 4.8             | 64%      | 29%      | 67%                       | 59%                    | 27%                    |                       |
| RTOG 9003 B23             | 72                | 42          | 1.8             | TID                 | 5                     | 6          | 268            | 14              | 67%      | 59%      | 47%                       | 2-year: 54%            | 2-year: 51%            |                       |
| RTOG 9003 S23             | 67.2              | 42          | 1.6             | BID in last 12 days | 5                     | 6          | 268            | 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%            |                       |
| CAIR 27                   | 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 P07928                | 66                | 33          | 2               | BID once weekly     | 5                     | 5.5        | 196            | 4.1             | 9%       | 0%       | 3%                        | 3-year: 81%            | 3-year: 85%            |                       |
| EORTC 2279129             | 80.5              | 70          | 1.15            | BID                 | 5                     | 7          | 166            | 10.3            | 35%      | 0%       | 67%                       | 59%                    | 91%                    | 39%                    |
| RIO 30                    | 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%            |                       |
| PMH-Toronto 31            | 58                | 40          | 1.45            | BID                 | 5                     | 4          | 169            | 7.4             | 70%      | 42%      | 62%                       | 59%                    | 67%                    | 40%                    |

Citation: Hosni A, Alawady M, Nooreldeen A, Sikir H (2017) Accelerated Fractionation Radiotherapy in Treating Patients with Locally Advanced Head and Neck Squamous Cell Carcinoma. J Cancer Prev Curr Res 8(3): 00277. DOI: 10.15406/jcpcr.2017.08.00277
Our Proposed Schedule: Accelerated Simultaneous Integrated Boost with 6 Weekly Treatment

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| MUH-Mansoura | 70 | 30 | 2.33 | 0D | 6 | 5 | 40 | 3.4 | 87.50% | 0% | 57.50% | 3-year: | 81.6% | 3-year: | 85.3% | 3-year: | 64.4% |
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*2 weeks split course

RT: Radiation Therapy; Fe: 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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