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Randomized controlled study comparing simultaneous modulated accelerated radiotherapy *versus* simultaneous integrated boost intensity modulated radiotherapy in the treatment of locally advanced head and neck cancer

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ABSTRACT

Objectives: Comparison of two fractionation schedules of intensity modulated radiotherapy (IMRT) for locally advanced head and neck cancer – simultaneous integrated boost (SIB-IMRT) and simultaneous modulated accelerated radiotherapy (SMART) boost in terms of toxicity and survival end-point measures.
Patients and methods: Sixty patients with locally advanced head and neck cancer were randomized in two treatment arms (SIB-IMRT [control arm] and SMART boost arm [study arm]). In the control arm, patients received 70, 63 and 56 Gy in 35 fractions to clinical target volumes (CTV) 1, 2 and 3, respectively. In the study arm, patients received 60 and 50 Gy to CTV 1 and CTV 3, respectively. Toxicities, progression free survival (PFS) and overall survival (OS) were compared between both arms.
Results: Baseline patient-related characteristics were comparable between the arms except for primary site of tumour. No significant differences were noted in acute toxicities between the arms except for fatigue which was statistically higher for control arm. No significant differences in 2-year late toxicities were observed. The median follow-up duration was 25.5 (range, 1.8–39.9) months. The 2-year PFS was 53.3% and 80.0% ($p = 0.028$) for control and study arm, respectively. The 2-year OS was 60.0% and 86.7% ($p = 0.020$) in control and study arms, respectively. Multivariate analysis showed clinical stage and site to be significant predictors for OS and PFS, respectively.
Conclusions: The SMART boost technique can be a feasible alternative fractionation schedule that reduces the overall treatment time, maintaining comparable toxicity and survival compared with SIB-IMRT.

Introduction

Head and neck cancers (HNC) have a low global incidence, accounting for 1.6–2.7% of cancer cases worldwide. However, this epidemiological statistic changes dramatically for less developed nations, especially in the World Health Organization's South East Asian region, where HNC represents the third most common cancer, accounting for 3.8–8.7% of cases [1].

The majority of patients (especially those of Asian origin) present with locally advanced HNC (LAHNC). Achieving good locoregional control (LRC) is an important parameter that is associated with increased overall survival (OS). However, despite the best locoregional treatment, LAHNC is generally associated with a poor outcome, with 3-year OS rates of 40–50% [2–4]. Radiotherapy has undergone rapid advancements since its inception in the early twentieth century. Since the breakthrough discovery of fractionated radiotherapy by Thor Stenbeck in Stockholm, intense research has focused on the optimal fractionation schedule that will ensure maximum therapeutic gain. With better understanding of the 4 R's of radiobiology (repopulation, redistribution, repair, and reoxygenation), a fraction size of 1.8–2.0 Gy was found to achieve good local control rates with acceptable normal tissue side effects.

Tumor clonogen repopulation or "accelerated repopulation" is a phenomenon that causes accelerated regrowth of monoclonal

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tumor cells, which has been the subject of intense research. The concept was first studied by Withers et al. [5], who concluded that accelerated repopulation can initiate at any time, although data from the literature suggests that it usually occurs within 3–5 weeks of commencing radiotherapy. Therefore, it was hypothesized that if treatment extends beyond 4 weeks, then there is a need to increase the total dose (0.6 Gy/day) to effectively counteract the effects of tumor clonogen repopulation. Accelerated fractionation was thus conceptualized to counteract accelerated repopulation, mainly by reducing the overall treatment time (OTT). However, few studies have explored alternative fractionation schedules in conjunction with intensity modulated radiotherapy (IMRT) and concurrent chemotherapy.

The use of IMRT and dose painting by simultaneous integrated boost (SIB), as outlined by Mohan et al. [6], has enabled dose escalation to the gross tumor volume (GTV), while maintaining relatively low doses to intermediate and low risk volumes, without compromising the OTT. In HNCs, as in other carcinomas, the OTT is a well-established prognostic marker for OS [7]. The use of concurrent chemotherapy with conventionally fractionated radiotherapy has become a standard of care in the management of LAHNC, however the use of chemotherapy with altered fractionated in yet to standardised [8].

SMART boost is an IMRT fractionation schedule first introduced by Butler et al. [9]. This study [9] primarily included LAHNC and were treated with SMART boost without concurrent chemotherapy. The dose prescribed to the primary and secondary targets (draining lymphatics and elective volumes) was 60 Gy/25# and 50 Gy/25# respectively. The use of accelerated radiotherapy in this fractionation schedule enabled the authors to achieve high complete response rate of 95% with only 5% local recurrence at a follow-up of 15 months. However, SMART boost fractionation schedule was not widely accepted in comparison to the contemporary fractionation schedules because of smaller sample size, larger fraction size and lack of use of concurrent chemotherapy. In the era of high precision delivery and image guided radiotherapy, it would only be a logical step to increase dose per fraction to the gross tumour simultaneously maintaining constraints to normal tissues thus yielding a high therapeutic ratio.

The current study aimed at comparing two fractionation schedules, SIB-IMRT and SMART boost, in terms of toxicities and survival outcomes.

Patients and methods

Patient selection

This prospective, non-blinded randomized study was approved by the Institutional Review Board and the Scientific Committee. The inclusion criteria were as follows: Stage III or non-metastatic Stage IV LAHNC, adults aged 18–65 years, no prior history of cancer or radiation to the head and neck region, squamous cell carcinoma (at the primary site or through cervical lymphadenopathy), an Eastern Cooperative Oncology Group performance status of $\leq$2, and signed study-specific informed consent prior to registration.

Sixty patients with HNC who were treated at our institution between June 2014 and March 2016 and met the inclusion criteria were recruited and randomised into a control arm and a study arm using chit method. Patients in the control arm received radiotherapy using the standard SIB-IMRT fractionation technique, while those in the study arm received radiotherapy using the simultaneous modulated accelerated radiotherapy (SMART) boost technique. Patients in both arms received weekly cisplatin-based concurrent chemotherapy at 40 mg/m^2.

Pretreatment evaluation included clinical, endoscopic, and radiological examinations. Staging was performed according to the American Joint Committee on Cancer (AJCC) Tumor Node Metastasis Staging System (seventh edition). Magnetic resonance imaging, or 18F-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT), and endoscopy were done to assess the extent of the disease. Metastatic work-up in patients without PET-CT included a chest X-ray and an upper abdominal ultrasound. Human Papillomavirus (HPV) status testing was not done.

Target volume delineation

For the control arm, clinical target volume (CTV) 1 included the GTV based on clinical and radiological information, including the primary tumor and involved lymph nodes, plus a 5 mm margin in three dimensions. CTV2 included the high-risk areas harboring microscopic disease. CTV2 was created individually for the primary target and secondary lymphatics. A 1.5- to 2.0-cm margin was taken from CTV1 and was manipulated to exclude uninvolved bone and air on radiological imaging. CTV3 included the elective nodal regions. Model dose prescriptions of 70, 63, and 56 Gy in 35 fractions were assigned to 95% of CTV1, CTV2, and CTV3, respectively.

For the study arm, CTV1 included similar delineation parameters as those of the control arm. A dose of 60 Gy in 25 fractions (2.4 Gy per fraction per day, 5 days a week) was prescribed to 95% of CTV1. CTV3 included the region encompassing CTV1, regions adjacent to it deemed at harboring subclinical disease, but without direct tumor involvement based on clinical and imaging information, and the elective nodal regions. A dose of 50 Gy was prescribed to 95% of CTV 3. There was no CTV2 for the study arm.

Patients were treated using the TrueBeam™ system (version 1.6; Varian Medical Systems Inc., Palo Alto, CA, USA) equipped with high-definition 120 multileaf collimators. Plans were generated by Varian Eclipse software (version 11; Varian Medical Systems Inc., Palo Alto, CA, USA) using 7–9 coplanar static fields with a collimator angle of 0°. The IMRT plans were optimized using the dose volume optimizer and the final dose calculation was made with the anisotropic analytical algorithm (Fig. 1).

Radiobiological rationale

The linear quadratic model is a popular radiobiological model that helps to quantify the biological effect in terms of cell kill with respect to dose (Gy). Comparisons of the radiotherapy schedules pertaining to the two arms in this study revealed an apparent large difference in the BED (84 Gy_{10} *vs.* 74.4 Gy_{10} for the control and study arms, respectively). Based on this model alone, treatment schedules assigned to the study arm could be considered biologically ineffective due to low doses to the GTV.

However, when the reduced tumor proliferation and lower OTT for the study arm were considered, the difference in the BED was dramatically reduced. After compensating for time, as suggested by Fowler et al. [10], a range of BEDs were calculated for each arm, according to the time of initiation of accelerated repopulation (referred to as the "Kick-off" time). The range of BEDs were 65.9–76.2 Gy_{10} and 66.1–73 Gy_{10} for the control and study arms, respectively. For the study arm, the equivalent dose at 2.0 Gy per fraction was calculated to be 62 Gy.

Nutritional and dental intervention

Assisted feeding in the form of a nasogastric tube (preferred) or percutaneous endoscopic gastrostomy was performed as required. Dental prophylaxis, oral care, nutritional supplementation, and adequate hydration were encouraged for patients in each arm.

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