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A Novel Fractionation for Head and Neck Tumors: SWITCH-02

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Abstract

The management of head and neck carcinomas represents a challenge for multidisciplinary teams. Radiation therapy is one of the pillars of treatment, the modulation of fractionation being one of the most widely used strategies to improve local control. The present article describes a new radiation therapy schedule based on solid radiobiologic concepts and the novel use of bayesian algorithms for the computation of probabilities in decision making.

Keywords: Radiotherapy; Chemotherapy; Hyperfractionation; Head and neck carcinoma; Radiobiology

Introduction

Squamous cell carcinomas of the head and neck (SCCHN) rank sixth in both incidence and mortality in malignancies in men across the globe. It is estimated that 931931 cancers of the head and neck were diagnosed, and 467125 deaths were caused by them in the year 2020 [1]. Progress in radiation therapy techniques has contributed to better disease control, developing altered fractionation schedules aimed to improve local control, sometimes also adding radio modifiers to the radiotherapy course. Data from the MACH-NC meta-analysis [2] and its update [3] showed that the addition of concurrent chemotherapy to radiotherapy improves overall survival, progression free survival, as well as locoregional control, and it decreases cancer-specific deaths.

The pivotal study RTOG 9003 [4] and the meta-analysis MARCH [5] showed that exclusive hyperfractionation (HF) together with normal fractionated chemoradiotherapy are the therapeutic strategies that offer the greatest local control for advanced head and neck tumors. A comparison remained to be done between hyper fractionated treatment with chemotherapy and normal fractionated chemotherapy, which was recently addressed by Petit et al. [6], concluding in a network meta-analysis from individual patient data that hyperfracionatied chemoradiotherapy (HFCRT) took the first place in overall survival, event-free survival, locoregional control and cancer-specific survival, providing solid results after sensitivity analysis.

Why is then HFCRT not a standard in the treatment of head and neck malignancies? If the present evidence proves it is the most effective approach, acute adverse effects must have prevented this strategy to be the gold standard. In the present article we present a novel fractionation model to be applied to the treatment of head

and neck carcinomas, aimed at the optimal selection of candidates for an intensified treatment.

Discussion

General description

There is only one published clinical trial that combined both normal fractionated and hyper fractionated radiation treatment schedules for head and neck cancers, comparing two arms with or without the addition of chemotherapy [7]. This trial showed that the concurrent use of chemotherapy was superior in terms of local control but contrasted two similar treatment strategies without a dynamic approach to patient selection. SWITCH 02 is designed for the treatment of patients with head and neck carcinomas with a curative intent using sequential intensity-modulated radiation therapy (IMRT), with tumors classified as stage II-IVB located in oropharynx, hypopharynx, larynx (not glottic stage II), or oral cavity, in patients with a Karnofsky score of 70 to 100, within an age range of 18 to 70 years, who are adequate candidates to receive platinum-based chemotherapy and who do not have another concomitant malignancy.

Patients would begin standard normal fractionated chemoradiotherapy treatment with a target dose of 4000 cGy in 20 fractions of 200 cGy, one fraction per day, five times a week. At this point a data-based decision-making system would be used prior to continuation and in the case of a favorable result the patient will continue to the hyperfractionated arm with weekly chemotherapy in order to receive an additional dose of 3600 cGy in 30 fractions of 120 cGy given twice daily (BID) Mondays through Fridays separated by at least eight hours between fractions (Figure 1). In the case that the algorithm score does not reach the cutting point, the patient would continue with standard normal fractionated treatment with chemotherapy. It should be noted that both treatment schedules have a total duration of seven weeks.

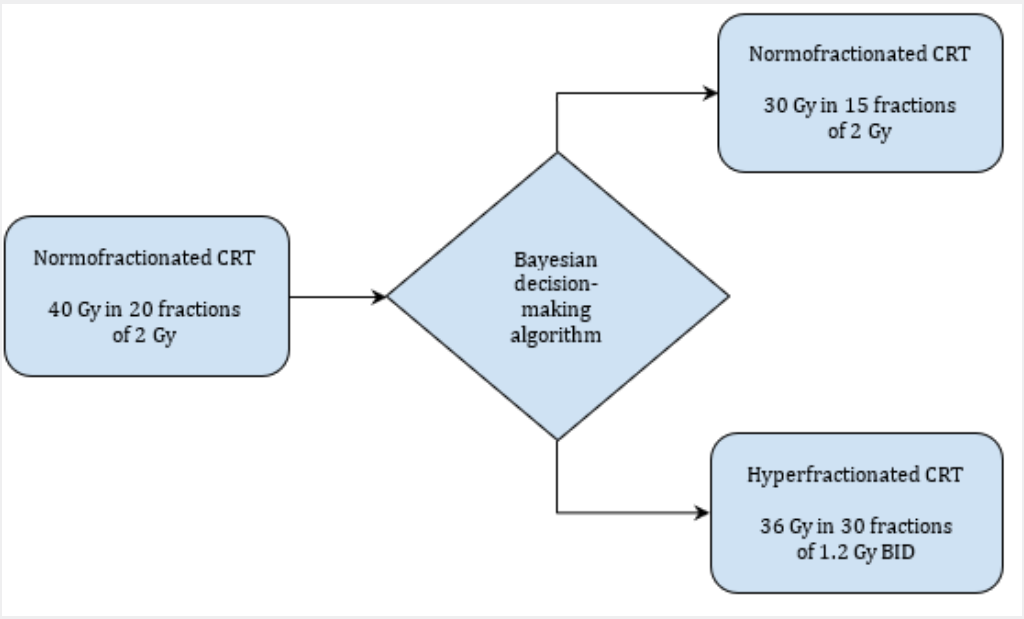

Figure 1: SWITCH-02 treatment schedule.
CRT: chemoradiotherapy

Advantages

Oncology often applies an "all or nothing" treatment paradigm. This is to say, after implementing a treatment strategy with satisfactory results, or a partial response, it is seldom modified to a more aggressive technique assuming a greater commitment towards the probability of tumor control. This conception is applied in all oncologic areas. SWITCH 02 involves an ad-hoc selection perspective for patients who would be candidates for treatment escalation, based on a predetermined Bayesian algorithm.

It is in this aspect that SWITCH 02 offers a solution based on four main advantages. Firstly, there is an in-situ patient pre-selection; patients who would inadequately tolerate escalation are dropped from entering the arm with higher tumor control probability and thus continue standard treatment. Secondly, patients who show good tolerance and are candidates to the switch arm would go on to receive only fifteen days of hyper fractionated treatment with reduced treatment volumes, after having completed irradiation to low-risk volumes. Thirdly, biologically effective dose is superior in the switch arm compared to standard treatment, which would

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result in a higher probability of locoregional control. Lastly, treatment escalation would begin at a key point of tumor control, namely the start of accelerated repopulation in tumor cells [8].

Chemotherapy

Cisplatin is the mainstay of radiosensitizers in head and neck tumors, and the most widely used and studied, with a proven impact in a meta-analysis encompassing over 17 thousand patients, although the optimal treatment scheme is debated, whether a dose of 100 mg/m^2 every 21 days on a weekly dose of 35-40 mg/m2 [9]. Attempts to administer hypofractionated radiotherapy combined with Cisplatin used the weekly schedule [10], which is the reason behind using this weekly plan at a dose of 40 mg/m2, on condition that normal liver and kidney function are present. Impaired liver function is defined as elevation of liver enzymes representing 2.5 times or more relative to the upper limit of the normal reference value for the local institution; impaired kidney function is considered as serum creatinine 1.5 times or greater than the upper limit of the normal reference value for the institution, or a creatinine clearance less than 50 mL/min.

Radiobiologic Justification

For both treatment arms of the SWITCH 02 schedule, the linear-quadratic model was used to calculate effective doses [11]. Biologically effective dose is defined as:

$$BED = nd\left[1+\frac{d}{\alpha/\beta}\right] \quad (1)$$

Where n is the number of fractions, d is the dose per fraction and y α/β is the fractionation quotient for the radiobiological parameters of the model.

To model for BED delivered to squamous cell tumors in standard radiation treatment it is necessary to account for accelerated repopulation, thus modifying the previous equation to:

$$BED = nd\left[1+\frac{d}{\alpha/\beta}\right]-\frac{In(2)}{\alpha T_D}(T-T_k) \quad (2)$$

Where TD is the mean cell doubling time, T is the total treatment time and Tk is the time at the onset of accelerated repopulation. To model for BED in tumor cells in the hyper fractionation arm in SWITCH 02 we accounted for both accelerated repopulation and sublethal damage repair, thus rendering the equation:

$$BED = nd\left[1+(1+h_m)\frac{d}{\alpha/\beta}\right]\frac{In(2)}{\alpha T_D}(T-T_k) \quad (3)$$

Where m is the number of daily fractions and hm is the fraction of tumor cells that are unable to repair sublethal damage:

$$h_m = \frac{2\theta}{m(1-\theta)}\left(m-\frac{1-\theta^m}{1-\theta}\right) \quad (4)$$

$$\theta = e\left(-\frac{In_{(2)}\Delta t}{T_{1/2}}\right) \quad (5)$$

In the previous equations, T1/2 is the mean time needed for sublethal damage repair and Δt is the time in between daily fractions.

In the present study two daily fractions separated by at least eight hours would be used in the hyper fractionation arm, so that:

$$h_2 = e\left(-\frac{In_{(2)}\Delta t}{T_{1/2}}\right) \quad (6)$$

To model for tumor cells, it was assumed that α/β = 10 Gy; T1/2 = 1h; ln(2)/αTD = 0.65 cGy/día; Tk = 28 days; Δt = 8h. It should be noted that a T1/2 of one hour was chosen, this being the least favorable scenario for the calculation. To model for late effects in normal tissues skin reaction was used as a reference, assuming α/β = 2.8 Gy and T1/2 = 3.8h for telangiectasia, α/β = 1.7 Gy and T1/2 = 4.4h for fibrosis [12,13].

BED calculations for tumor cells and for late effects in the skin are presented for both treatment fractionation schedules in table 1. Therefore, an increase of 6 % in BED is achieved for tumor cells, which results in an improvement of tumor control probability (TCP). However, the hyper fractionation arm entails an increase of about 2-3% in BED for late skin reactions, with a consequently discrete increase in normal tissue complication probability (NTCP).

Table 1: Tumor and normal tissue biologically effective dose.

	Tumor	Skin / telangiectasia	Skin / fibrosis
BED for NF CRT arm (Gy)	72.30	120.00	152.35
BED for switch arm (Gy)	76.64	123.59	155.68
Difference (%)	6.00 %	2.99 %	2.18 %

BED: Biologically effective dose

NF-CRT: Normofractionated chemoradiotherapy

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Algorithm Parameters

The proposed algorithm, which is the essence of SWITCH 02, is based on predetermined evaluation parameters using initial weighing established for the creation of a score to guide the decision-making process. The strength of this algorithm lies in its use of a bayesian prediction model [14] to modify weighing in line with acquired clinical experience. Data input for the algorithm has two instances, pre-treatment to evaluate intrinsic patient and disease features, and after completing the 40Gy stage to include data related to tolerance, response and treatment adherence (Figure 2). In cases where the total obtained score as a sum of both data input instances is higher than the predefined threshold, patients would enter the hyper fractionation switch arm with concurrent chemotherapy. Otherwise, patients would continue with the standard chemoradiotherapy schedule.

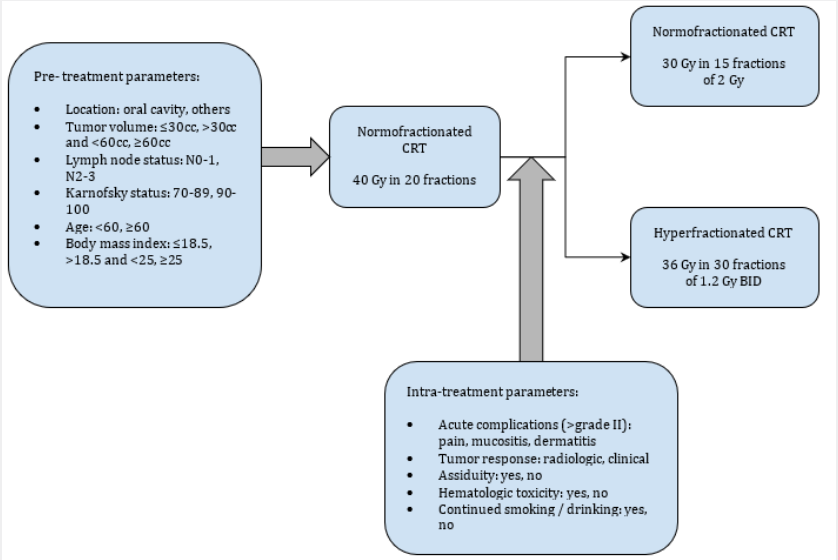

Figure 2: SWITCH-02 algorithm parameters.

Conclusion

We propose a novel and dynamic schedule for radiation treatment of head and neck carcinoma, which contemplates an ad-hoc selection that escalates treatment in fitting candidates. SWITCH 02 schedule is solid in its radiobiological foundation, offering a greater tumor control probability for patients that reach the minimum suitability score in the evaluation algorithm. Phase I - II studies will be necessary in the future to assess tolerance, as well as validate the algorithm.

Conflict of Interest

Authors declare no conflict of interest.

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