HOW MUCH RADIATION IS THE CHEMOTHERAPY WORTH IN ADVANCED HEAD AND NECK CANCER?

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Purpose: To estimate the radiotherapeutic dose equivalence of chemoradiotherapy in head and neck cancer.

Methods: The biologic equivalent dose (BED) of radiotherapy in nine trials of standard and five trials of modified fractionated radiotherapy with or without chemotherapy was calculated using the linear-quadratic formulation. Data from Radiation Therapy Oncology Group (RTOG) study 90-03 were used to calculate the relationship (S) between increase in locoregional control (LRC) and increase in BED with modified vs. standard fractionated radiotherapy. The increase in LRC with chemoradiotherapy vs. radiotherapy alone, the BED of the radiotherapy-alone arms, and the “S” value were used to calculate the BED contribution from chemotherapy and the total BED of chemoradiotherapy from each study.

Results: From RTOG 90-03, a 1% increase in BED yields a 1.1% increase in LRC. The mean BED of standard fractioned radiotherapy was 60.2 Gy\textsubscript{10} and 66 Gy\textsubscript{10} for modified fractionation. The mean BED of standard fractionated chemoradiotherapy was 71 Gy\textsubscript{10} (10.8 Gy\textsubscript{10} contributed by chemotherapy). The mean BED of modified fractionated chemoradiotherapy was 76 Gy\textsubscript{10} (10.4 Gy\textsubscript{10} contributed by chemotherapy).

Conclusions: Chemotherapy increases BED by approximately 10 Gy\textsubscript{10} in standard and modified fractionated radiotherapy, equivalent to a dose escalation of 12 Gy in 2 Gy daily or 1.2 Gy twice daily. Such an escalation could not be safely achieved by increasing radiation dose alone.

INTRODUCTION

Prospective studies show that biologic dose escalation with modified fractionation (hyperfractionation or accelerated fractionation with concomitant boost) improves locoregional control (LRC) compared with standard fractionation in patients with advanced head and neck cancer (1, 2). In a recent meta-analysis, enhanced LRC with modified fractionation translated into a 3.4% improvement in overall survival (OS) at 5 years (3).

Prospective trials have also shown that chemotherapy given concurrently with radiotherapy (RT) enhances LRC and OS compared with RT alone (4–9). Similarly, concurrent radiation and cetuximab, a monoclonal antibody against the epidermal growth factor receptor, has recently been shown to improve LRC and OS compared with radiation alone in locally advanced head and neck cancer (10). Chemotherapy or targeted-therapy-induced radiosensitization can therefore be considered a method of biologic dose escalation. No method exists to quantify the radiotherapeutic dose equivalent of this treatment intensification.

Whereas the biologic equivalent dose (BED) of a given RT-only regimen can be calculated and compared with other RT-only regimens, there is no method to determine the biologic contribution to BED made by concurrent chemotherapy.

A rational approach to this problem begins by relating the improvement in LRC achieved by biologic dose escalation with modified vs. standard fractionated RT. Using this relationship, along with known improvements in LRC from adding chemoradiotherapy vs. radiation alone, one can calculate the increase in biologic dose due to chemotherapy. This report estimates the radiotherapeutic dose equivalent of concurrent chemotherapy (or cetuximab) when combined with either standard or modified fractionated RT in locally advanced head and neck cancer.

Conflict of interest: none.

Received Feb 8, 2007, and in revised form Feb 28, 2007. Accepted for publication March 13, 2007.
METHODS AND MATERIALS

The BED, which is derived from in vitro cell survival data and measures of tumor repopulation, can be used to compare different radiation fractionation schedules (11, 12). The BED delivered by a particular RT fractionation scheme can be calculated by using the equation:

\[
BED = D \times \left[ 1 + \frac{d}{(\alpha/\beta)} \right] - \left( \frac{0.693}{\alpha} \right) \left( \frac{t}{T_{pot}} \right) \quad (1)
\]

where D is total dose (Gy), d is dose per fraction (Gy), \( \alpha \) (Gy\(^{-1}\)) and \( \beta \) (Gy\(^{-2}\)) are the linear and quadratic constants, respectively, in the linear-quadratic cell-survival equation, t is the total treatment time (days), and \( T_{pot} \) is the potential doubling time (days) (11, 12).

The assumptions made to calculate BED from Eq. 1 for modified and standard fractionated RT are \( \alpha/\beta = 10 \) Gy, \( \alpha = 0.3 \) Gy\(^{-1}\) and \( T_{pot} = 5 \) days. All BED values are reported in Gy\(^{10}\).

Radiation Therapy Oncology Group (RTOG) trial 90-03 (2) compared hyperfractionated RT with 81.6 Gy over 46 days in 68 fractions (BED = 70 Gy\(^{10}\)) with 70 Gy delivered with standard fractionation over 47 days in 35 fractions (BED = 62 Gy\(^{10}\)). The 12% increase in biologic dose achieved with hyperfractionation resulted in an 8% absolute improvement in LRC compared with the standard arm. In addition, RTOG 90-03 (2) compared standard fractionation with accelerated fractionation using a concomitant boost to 72 Gy in 18 daily fractions of 1.8 Gy followed by 1.8 Gy and 1.5 Gy delivered with a 6-h interval over 40 days in 42 total fractions (BED = 65.9 Gy\(^{10}\)). The 6% increase in biologic dose achieved by accelerated fractionation with concomitant boost also resulted in an 8% absolute improvement in LRC over the standard arm.

The relationship between increase in biologic dose and improvement in LRC is given by the “S” value, which can be calculated using data from the hyperfractionated (BED = 70 Gy\(^{10}\)) and standard fractionation arms (BED = 62 Gy\(^{10}\)) in RTOG 90-03:

\[
S = \frac{\left( \frac{\% \text{ difference in LRC}}{\% \text{ increase in BED with hyperfractionation}} \right)}{\frac{70 \text{ Gy}^{10} - 62 \text{ Gy}^{10}}{62 \text{ Gy}^{10}}} = \frac{8\%}{12\%} = 0.7 \text{ (rounded)} \quad (2)
\]

A similar calculation for accelerated fractionation with concomitant boost yields an S value of 1.5. The average S value obtained from the hyperfractionated and accelerated fractionation arms of RTOG 90-03 is 1.1. Therefore, a 1.1% absolute improvement in LRC is achieved with a 1% relative increase in biologic dose. This S value is used for all calculations in this report.

The increase in LRC from RT and chemotherapy is achieved with a 1% relative increase in biologic dose. Therefore, the difference in total BED between the RT-alone and the chemotherapy arms is 14.8 Gy\(^{10}\) (80.7 Gy\(^{10}\) = 65.9 Gy\(^{10}\)). Matching this escalation in biologic dose with radiation alone requires 16 Gy in 2 Gy per daily fraction delivered over 10 days (BED = 14.6 Gy\(^{10}\)) or 15 Gy in 1.25 Gy per fraction delivered twice daily over 5 days (BED = 14.6 Gy\(^{10}\)).

RESULTS

The total radiation doses, dose per fraction, duration of therapy, chemotherapy regimens, and outcomes from 14 prospective randomized trials comparing chemoradiotherapy with standard or modified fractionated RT alone are provided in Table 1. The BED of chemoradiotherapy with standard or modified fractionated RT was calculated for each trial (Table 2).

The mean BED of chemoradiotherapy was 71.4 ± 6 Gy\(^{10}\) for standard fractionation and 76.4 ± 7.2 Gy\(^{10}\) for modified fractionation. The mean additional BED from chemotherapy...
was 10.8 ± 4 Gy$_{10}$ for studies with standard fractionation and 10.4 ± 5.5 Gy$_{10}$ for studies with modified fractionation. The additional mean biologic dose of 10.4–10.8 Gy$_{10}$ from chemotherapy in these 14 studies corresponds to an additional 12 Gy in 2 Gy per fraction daily over 8 days (BED = 10.7 Gy$_{10}$) or 1.2 Gy twice daily over 5 days (BED = 11.1 Gy$_{10}$).

**DISCUSSION**

Prospective trials in head-and-neck cancer (4–10, 13) and other disease sites (14–17) have proven that improvements in LRC lead to better OS. Strategies to improve LRC in head-and-neck cancer include radiation dose escalation using modified fractionation or combining radiation with sensitizing chemotherapy or biologic therapy.
Bourhis et al. (3) performed a meta-analysis of 16 trials with 6515 patients, comparing modified fractionation with standard fractionation in locally advanced head-and-neck cancer. Modified fractionation regimens were divided into three groups: hyperfractionated (4 studies, 680 patients), accelerated fractionation without a decrease in overall dose (7 studies, 1923 patients), or accelerated fractionation with a decrease in overall dose (5 studies, 1047 patients). The absolute benefit in OS with modified fractionation was 3.4% at 5 years compared with standard fractionated RT. Among the three groups, studies using hyperfractionation achieved the greatest improvement in OS compared with standard fractionated RT (8% at 5 years).

Pignon et al. (18) performed a meta-analysis of studies comparing outcome with locoregional treatment alone or locoregional treatment with chemotherapy in head-and-neck cancer. Combination treatment was divided into trials using adjuvant chemotherapy (8 trials, 1854 patients), neoadjuvant chemotherapy (30 trials, 5269 patients), and concurrent chemotherapy (26 trials, 3727 patients). A significant benefit in OS was seen only with concurrent chemotherapy and was similar to the benefit seen with hyperfractionation vs. standard fractionation in the Bourhis meta-analysis (8% at 5 years).

Although both hyperfractionated RT and chemoradiotherapy improve OS in head-and-neck cancer, direct comparisons between hyperfractionated RT with and without chemotherapy have demonstrated significantly better LRC and OS with combined-modality therapy (Table 1). In fact, in two of these trials, the chemoradiotherapy arm achieved better LRC and OS despite using a lower biologic dose of RT than the hyperfractionated arm (5, 9).

In this report, we found that chemotherapy, added to either standard or modified fractionated RT, adds approximately 10 Gy10. A dose of 80 Gy delivered at 2 Gy per fraction daily over 54 days (BED = 71.1 Gy10) or 84 Gy at 1.2 Gy twice daily over 47 days (BED = 72.4 Gy10) is required to match the total biologic dose of chemotherapy plus standard fractionated RT. A dose of 91.2 Gy in 1.2 Gy per fraction twice daily over 52 days (BED = 78.1 Gy10) with RT alone would be required to equal the total biologic dose of chemotherapy plus modified fractionated RT.

 Delivering 80 Gy or more with standard fractionated RT or 90 Gy or more with modified fractionated RT alone would place patients at unacceptably high risk of both severe acute and late toxicity. Furthermore, our model probably underestimates the true LRC benefit of concurrent chemoradiotherapy because it does not account for the independent cytotoxicity of the drugs themselves.

Thus, combined-modality therapy should be the preferred method to enhance LRC and OS in locally advanced head-and-neck cancer. Efforts should be made to investigate the mechanisms underlying the unique biologic benefit achieved with chemotherapy or targeted therapy in combination with RT.

REFERENCES


