BIOLOGY CONTRIBUTION

RADIOBIOLOGICAL CONSIDERATIONS IN THE DESIGN OF FRACTIONATION STRATEGIES FOR INTENSITY-MODULATED RADIATION THERAPY OF HEAD AND NECK CANCERS

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Purpose: The dose distributions of intensity-modulated radiotherapy (IMRT) treatment plans can be shown to be significantly superior in terms of higher conformality if designed to simultaneously deliver high dose to the primary disease and lower dose to the subclinical disease or electively treated regions. We use the term “simultaneous integrated boost” (SIB) to define such a treatment. The purpose of this paper is to develop suitable fractionation strategies based on radiobiological principles for clinical trials and routine use of IMRT of head and neck (HN) cancers. The fractionation strategies are intended to allow escalation of tumor dose while adequately sparing normal tissues outside the target volume and considering the tolerances of normal tissues embedded within the primary target volume.

Methods and Materials: IMRT fractionation regimens are specified in terms of “normalized total dose” (NTD), i.e., the biologically equivalent dose given in 2 Gy/fx. A linear-quadratic isoeffect formula is applied to convert NTDs into “nominal” prescription doses. Nominal prescription doses for a high dose to the primary disease, an intermediate dose to regional microscopic disease, and lower dose to electively treated nodes are used for optimizing IMRT plans. The resulting nominal dose distributions are converted back into NTD distributions for the evaluation of treatment plans. Similar calculations for critical normal tissues are also performed. Methods developed were applied for the intercomparison of several HN treatment regimens, including conventional regimens used currently and in the past, as well as SIB strategies. This was accomplished by comparing the biologically equivalent NTD values for the gross tumor and regional disease, and bone, muscle, and mucosa embedded in the gross tumor volume.

Results: (1) A schematic HN example was used to demonstrate that dose distributions for SIB IMRT are more conformal compared to dose distributions when IMRT is divided into a large-field phase and a boost phase. Both were shown to be significantly superior compared to dose distributions obtained using conventional beams for the large-field phase followed by IMRT for the boost phase. (2) The relationship between NTD and nominal dose for HN tumors was found to be quite sensitive to the choice of tumor clonogen doubling time but relatively insensitive to other parameters. (3) For late effect normal tissues embedded in the tumor volume and assumed to receive the same dose as the tumor, the biologically equivalent NTD for the SIB IMRT may be significantly higher. (4) Normal tissues outside the target volume receive lower dose due to the higher conformality of the IMRT plans. The biologically equivalent NTDs are even lower due to the lower dose per fraction in the SIB strategy.

Conclusions: IMRT dose distributions are most conformal when designed to be delivered as SIB. Using isoeffect radiobiological relationships and published HN data, fractionation strategies can be designed in which the nominal dose levels to the primary, regional disease and electively treated volumes are appropriately adjusted, each receiving different dose/fx. Normal tissues outside the treated volumes are at reduced risk in such strategies since they receive lower total dose as well as lower dose/fx. However, the late effect toxicities of tissues embedded within the primary target volume and assumed to receive the same dose as the primary may pose a problem. The efficacy and safety of the proposed fractionation strategies will need to be evaluated with careful clinical trials.

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IMRT, Fractionation, Conformal radiotherapy.

INTRODUCTION

This paper describes an analysis of fractionation options for clinical protocols employing intensity-modulated radiotherapy (IMRT) for the management of head and neck (HN) carcinomas. IMRT has the unique ability to produce significantly superior dose distributions when designed to simultaneously deliver large and boost fields. However, conven-
tional fractionation strategies are not applicable to such treatments and new regimens must be designed.

Standard HN radiotherapy often delivers doses equal to or greater than 70 Gy to gross tumor, intermediate doses of between 70 and 50 Gy to tissues surrounding the gross tumor, and approximately 50 Gy to electively irradiated tissues, such as lymph node–bearing tissues at risk for subclinical or microscopic disease. The success of curative HN radiotherapy depends on the principle that the entire HN region must be irradiated with a dose sufficient to control subclinical disease with a likelihood of greater than 90%. This is normally accomplished in the first phase of a traditional radiotherapy course, during which fraction sizes of 1.8–2.0 Gy are used for the treatment of the tumor as well as the electively irradiated tissues. In the second phase, an additional dose is delivered, also at 1.8–2 Gy/fx, to tissues at a greater risk for a larger tumor burden, typically tissues involved with or immediately surrounding the gross tumor. The treatment course frequently requires treatment times of up to 7 weeks or more. Tissues irradiated during the large-field phase of radiotherapy receive substantial unwanted additional dose during the boost phase from beams attempting to gain access to the gross tumor. Despite this clearly recognized disadvantage, there have been few practical alternatives until now.

The same disadvantage exists in the accelerated radiotherapy schedules reported in the literature. These schedules were developed with the recognition that overall treatment time is critically linked to tumor control probability (TCP) (1–3). Such schedules commonly use twice-daily superfractionation to deliver similar or higher doses in shorter overall treatment times. Examples of accelerated superfractionation schedules include the concomitant boost used at M. D. Anderson, a modified one used at Medical College of Virginia, and the twice-daily split-course (4–7). Superfractionation approaches have demonstrated improved tumor control without significant increases in late normal tissue morbidity at pioneering institutions.

In principle, fractionation strategies similar to the conventional or accelerated ones can be used to design IMRT plans as well. For example, in a strategy similar to the conventional 1.8–2 Gy/fx schedule, a major portion of the dose could be delivered in the initial phase using uniform fields designed with standard 3D conformal methods followed by an IMRT boost. Alternatively, separate IMRT plans could be designed for both the initial large-field treatment and the boost treatment. We refer to such strategies as “IMRT-boost” strategies. It may be intuitively obvious that, if a large portion of the dose has already been delivered using large fields, it may be very difficult to achieve a high level of dose conformation with the remaining fractions in the IMRT-boost phase.

Thus, the dose distributions of IMRT treatment plans can be expected to be significantly superior in terms of higher conformation if designed to simultaneously deliver different dose levels to different tissues of the HN region in a single treatment session. This permits graded dose levels to tumor-bearing tissues and tissues at risk for subclinical tumor spread, such as tissues surrounding gross tumor and lymph node–bearing areas, and spares normal tissues to the greatest extent possible. We use the term “simultaneous integrated boost” (SIB) to define such a treatment. The SIB-IMRT strategy not only produces superior dose distributions, but is also an easier, more efficient, and perhaps a less error-prone way of planning and delivering IMRT since it involves the use of the same plan for the entire course of treatment. Furthermore, there is no need for electron fields and the supraclavicular nodes can be included in the IMRT fields, thus avoiding the perennial problem of field matching and junctioning. Assuming that the IMRT is delivered from a set of fixed gantry positions with a dynamic multileaf collimator (MLC), a single sweep of MLC leaves across the gross disease, regional disease, and electively treated volumes is used to deliver each of the intensity-modulated fields in such treatments.

Since each of the target regions receives different doses per fraction in the SIB-IMRT strategy, prescribed nominal (physical) dose and dose per fraction must be appropriately adjusted. The adjusted nominal dose and fraction size for each region depends upon the number of IMRT fractions chosen. At the same time, the effect of the modified fractionation on acute and late toxicity of normal tissues both outside as well as within the volumes to be treated must be considered.

One can select the conventional 2 Gy per fraction for the gross disease for an SIB strategy, but that might lead to a significantly lower dose per fraction to volumes of microscopic disease and electively treated nodes. On the other hand, one can choose to deliver 2 Gy per fraction to the lower and intermediate dose volumes, but this would require a high dose per fraction, as much as 2.5 Gy or more per fraction, to the gross disease. The latter scheme may have the advantage of shortening the treatment duration and a potential for improvement in local control but at an increased risk of injury to the embedded normal tissues. The choice of SIB fractionation strategy must take into account the clinical outcome data available from extensive experience in HN radiotherapy. It has been established that gross carcinoma has to be treated to doses between 65 and 75 Gy for acceptable control rates. Further, the elective irradiation of subclinical disease in lymph nodes to 45–54 Gy results in greater than 90% control rates. In addition, tissues within 1–2 cm around the gross tumor, frequently referred to as the margin, require an intermediate dose for optimal control of subclinical extension.

To evaluate various IMRT fractionation strategies, we used an isoeffect relationship based on the linear-quadratic (LQ) model and the published results of analysis of HN carcinomas. Most pertinent to the present task are the publications of Ang et al. (7), and Withers et al. (1, 2, 8, 9). In two of these papers, Withers et al. (2, 8) analyzed the patterns of radiotherapy fractionation data from nine institutions for carcinoma of the tonsil, whereas Ang et al. summarized the results of a wide range of fractionation schemes for various tumors and normal tissues. The follow-
ing conclusions, drawn from these publications, are relevant to the present work:

1. Due to accelerated repopulation of tumors during the course of treatment, each extra day of treatment requires a compensatory increase in dose of 0.5–0.7 Gy in total dose. This roughly corresponds to a tumor clonogen doubling time of 3 to 5 days. The accelerated tumor growth was found to be similar for all HN tumor sites and stages (9). Values of 14 days (9) to 30 days (2) have been suggested for the lag time before the onset of accelerated tumor growth after the initiation of radiotherapy. We should indicate that our results and conclusions drawn therefrom should not be affected by the variability reported in lag time as long as the overall treatment duration is longer than the lag time, which is usually the case.

2. Fraction size in the range of 1.6 Gy to 3.0 Gy was not an important factor in determining the tumor response, meaning that the \(\alpha/\beta\) is high. Maciejewski et al. (9) have suggested an \(\alpha/\beta\) value of at least 15 Gy.

3. Analysis of complication data showed that the total dose was a factor for Grade 3 and 4 late complications of the bone, muscle, and mucosa of the oral cavity.

4. Dose per fraction was a significant factor for bone and muscle complications with estimated \(\alpha/\beta\) values of 0.85 and 3.1 respectively. Mucosal late effect complications were not affected by fraction size in the range of 1 to 3.5 Gy.

5. The overall treatment duration was not a factor for bone and muscle. In contrast, it was a significant factor in mucosal breakdown.

6. Data analyzed by Withers et al. (8) suggested that mucosal late effects might be a consequence of the severity of acute mucosal injury. Mucosal late complications were characterized by a high \(\alpha/\beta\) ratio.

Unfortunately, there is little or no data on the effect of various fractionation strategies on early mucosal injury. However, Ang et al. indicated that the intensity of acute reactions depends primarily on the rate of dose accumulation (i.e., weekly dose rate).

It is recognized that there is considerable uncertainty in the available data and numerous assumptions in the LQ model and isoeffect formalism, the validity of which has not been fully established. Therefore, the application of these models and data to estimate the dependence of response of tumors and normal tissues on fractionation regimens may be questioned and should temper the enthusiasm with which the results and conclusions of this paper may be accepted. As emphasized by Ang et al. (7), “no isoeffect formula is sufficiently reliable to preempt clinical judgment, and that in the final analysis, each new fractionation schedule must be tested clinically to establish its safety.” The main purpose of this work is to design fractionation strategies for such clinical tests. We propose to adjust the model parameters so that they produce results consistent with existing knowledge and current strategies before designing new fractionation strategies for clinical tests.

METHODS AND MATERIALS

Superiority of SIB dose distributions

To illustrate the superiority of SIB dose distributions, we used a phantom schematically depicting a patient with HN carcinoma (Fig. 1). One conventional and three IMRT plans were developed. The aim of the treatment plans was to deliver 70 Gy to the gross disease (gross tumor volume [GTV]) and 50 Gy to the nodes while limiting the cord dose to 45 Gy with no more than 50% of the parotid volume receiving higher than 32 Gy. Two of the IMRT plans were two-phase plans with IMRT employed only in the boost phase. In the first one, the first phase of the treatment was intended to be delivered using conventional beams; whereas in the second one both phases were designed with IMRT. The third IMRT plan was a single-phase SIB plan.

In the conventional plan, 40 Gy was to be delivered in 20 fractions to the tumor and nodes with a large-field parallel-opposed wedged pair, followed by a 30 Gy boost in 15 fractions with an “off-cord” parallel-opposed pair. The first five of the boost fractions were combined with electron fields delivering 2 Gy/fx to the nodes only.

In the plan that combined the conventional first-phase treatment with IMRT boost, the off-cord photon boost of the conventional phase was limited to five 2 Gy fractions. The IMRT phase involved nine coplanar, equispaced beams, and was designed to deliver 20 Gy in 2 Gy fractions to the primary and no more than 5 Gy to the cord.

In the two-phase IMRT plan the primary and the nodes were prescribed to receive 50 Gy in 25 fractions in the first phase. In the second (boost) phase, only the GTV was to receive another 20 Gy in 10 fractions. The dose limits to critical structures were divided proportionately into two phases. That is, in the first phase, the cord dose was limited to 32.1 Gy and no more than 50% of the parotid volume was limited to 22.9 Gy. In the second phase the corresponding limits were 12.9 and 9.1 Gy respectively. (We should point out that the volumes constrained to the proportionally divided dose may, in general, be different in the two-phase plan and the summed plan may not obey the desired constraint. Fortunately, this was not a factor in the particular example we chose. This is due in part to the beam configurations, which were the same for the two phases, and in part to the similarity of the anatomic geometry of the two phases. The only difference between the two phases was that nodes were excluded from the second phase. As we shall see, the two-phase and SIB dose distributions [Figs. 1c and 1d] indicate almost identical parotid sparing. A more complex, but general solution is to first optimize phase 1 and then optimize the overall plan using the phase 1 dose distributions as input.)

The SIB IMRT plan also employed 9 coplanar, equispaced beams. In this plan, the required prescription doses were to be delivered to the gross disease and nodes using the same dose distribution for the entire course. Since the purpose of creating this plan was to illustrate the higher conformity achievable with the SIB strategy, the effect of
different fraction sizes for the GTV and nodes was ignored. (If we had chosen, for example, 30 fractions to deliver the SIB plan, the dosimetric advantage should be greater. As shown later in this paper, the 70 Gy and 50 Gy NTDs are roughly equivalent to 66 Gy and 54 Gy in 30 fractions respectively. The reduced gradient between the two desired dose levels should make it easier for the optimization process to produce the desired dose distribution.)

The isoeffect formalism used to design SIB fractionation strategies is described in the Appendix. Following Withers et al. (1), we define the term normalized total dose (NTD) as the biologically equivalent total dose, normalized to 2 Gy per fraction. We also use the term “nominal dose” to denote the actual physical dose. The parameters of the formalism are $d_{\text{ref}}$, the reference fraction size, which we select to be 2 Gy/fx; $SF_{d_{\text{ref}}}$, the surviving fraction for the reference dose; the accelerated tumor clonogen doubling time, $T_{d,a}$; and $\alpha/\beta$. Based on these isoeffect formulae, we have written software to convert nominal dose to NTD, and vice versa. Starting with commonly used values of various parameters $d_{\text{ref}}$ and $SF_{d_{\text{ref}}}$ and $\alpha/\beta$ and accelerated clonogen doubling time parameters suggested by the analysis of Withers et al., we investigated the effect of variation in these parameters upon the relationship between NTD and nominal dose values. Table 1 contains the values of the isoeffect formalism parameters used in our work.

Table 1. The values of the tumor isoeffect formalism parameters for the treatment of HN carcinomas

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha/\beta$</td>
<td>20 Gy</td>
</tr>
<tr>
<td>$T_{d,a}$</td>
<td>4 days</td>
</tr>
<tr>
<td>$d_{\text{ref}}$</td>
<td>2.0 Gy</td>
</tr>
<tr>
<td>$SF_{d_{\text{ref}}}$</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Fig. 1. Treatment plans of a schematic HN carcinoma case illustrating the superiority of SIB dose distributions. Isodose distributions are in terms of nominal dose.
have ignored these effects. As an alternative, we have assumed that embedded mucosa responds in the same manner as the tumor, and we have used the biologically equivalent tumor dose to estimate the changes in the intensity of acute reactions. Regardless of the approach taken, any of the proposed IMRT schedules will have to be tested clinically for tumor control as well as for normal tissue sequelae.

With these assumptions, we studied the variation in biologically equivalent dose for normal tissues as a function of $\alpha/\beta$ values. In general, tissues immediately adjacent to the high-dose regions of the disease receive lower dose in IMRT plans than in a conventional three-dimensional conformal radiotherapy (3DCRT) plan. In addition, if the number of SIB-IMRT fractions chosen is larger than the number of fractions for the large-field portion of the conventional treatment, the dose per fraction would also be lower. Consequently, the risk of injury should be reduced further.

We applied the isoeffect models described in the Appendix to design SIB-IMRT strategies for HN carcinomas for 25, 30, and 35 fractions for prescribed NTD levels of 70, 80, and 90 Gy to the gross disease, 60 Gy to the microscopic extensions (margins), and 50 Gy to the electively treated regions. Typically, these values are converted into the corresponding nominal dose values, which are then used to design IMRT plans. Normal tissue constraints are also specified in terms of nominal dose. Details of our methods for IMRT planning are described elsewhere (10, 11). We typically use 9 coplanar 6 MV beams placed at equi-angular spacing for HN cases. The optimization criteria are based on dose–volume constraints.

To analyze the resulting dose distributions, we transform the dose–volume histograms for the target regions into equivalent uniform dose (EUD) (12). EUD is defined as the dose, which, if given uniformly to the tumor volume, is expected to lead to the same cell kill as the actual nonuniform dose distribution. EUD can easily be calculated using $\alpha/\beta$ models. EUD is relatively insensitive to the choice of parameters. For each target region, EUD is converted back to biologically equivalent normalized total equivalent uniform dose (NTEUD) and compared with the original prescribed NTD.

For normal tissues, the dose–volume histograms are converted into normal tissue NTD–volume histograms. Table 2 shows the $\alpha/\beta$ values we used for the estimation of the effect for many of the normal tissues involved in the treatment of HN carcinomas.

RESULTS AND DISCUSSION

Figures 1a–1d illustrate the dosimetric advantage of simultaneously delivering high and lower doses to the appli-
cable target volumes in a schematic HN phantom. Dose distributions shown are in terms of nominal doses. As mentioned in “Methods and Materials,” the aim of the treatment plans was to deliver 70 Gy to the gross disease (GTV) and 50 Gy to the nodes while limiting the cord dose to 45 Gy with no more than 50% of the parotid volume receiving higher than 32 Gy. Dose distributions in all plans involving IMRT were superior compared to the conventional plan (Fig. 1a) in terms of lower dose to normal tissues outside the target volume, especially parotids. In the plan that combined the conventional first-phase treatment with IMRT boost (“Conventional + IMRT Boost,” Fig. 1b), the objective of maintaining the cord dose to below 45 Gy could not be met, and the nodes received additional dose over and above the intended 50 Gy from IMRT beams. Although dose to parotid glands was lower than for the conventional plan, the specified tolerance limits were exceeded.

Figure 1c shows the two-phase IMRT plan in which both the large-field and the small-field phases were designed with IMRT. Figure 1d shows the SIB IMRT plan. It is evident that both the two-phase IMRT plan and the SIB IMRT plan are considerably superior to either of the two plans involving conventional beams. The former pair of plans provides a significantly improved sparing of parotids and higher conformality. Comparing the two-phase IMRT plan with the SIB IMRT plan, we find that, while both provide the requisite coverage for the gross disease and equivalent sparing of the cord and parotids, the dose distribution for the SIB plan is more conformal. Dose to normal tissues outside the tumor volume is lower for the SIB plan than for the two-phase IMRT plan. Table 3 shows the normal tissue volume outside the target (tumor and nodes) regions exposed to specified or higher dose (in terms of nominal dose) for all four plans. The last column shows the percentage by which the exposed normal tissue volume in the two-phase IMRT plan is greater than in the SIB-IMRT plan, clearly demonstrating the higher conformality achievable by the latter. In addition, the nodes receive extra dose in the second phase of the two-phase IMRT plan. The mean dose to the nodes for the two-phase plan was found to be approximately 8 Gy higher than the mean dose for the SIB plan. (We note, however, that the volume of generic normal tissue below about 3500 cGy is greater for IMRT plans, the clinical consequences of which are not clear.)

We next show the results of calculations to assess the sensitivity of the relationship between NTD and nominal dose, and vice versa, to the choice of parameters of the isoeffect model. Figure 2a shows the variation in biologically equivalent nominal dose given in 28 fractions as a function of $SF_{d_{ref}}$ for the prescribed NTDs of 70 Gy. Figures 2b and 2c show similar data as a function of $\alpha/\beta$ values and the accelerated tumor clonogen doubling time parameter $T_{d,a}$ respectively. It is apparent that the biologically equivalent nominal dose is not very sensitive to the values of $SF_{d_{ref}}$ and $\alpha/\beta$ within normally accepted ranges but is quite sensitive to $T_{d,a}$ in the neighborhood of values recommended for HN carcinomas. For slowly growing tumors, the effect should be much smaller. We should note that there is a range of values of each parameter that can produce results consistent with clinical experience. Modest changes in one parameter may be compensated by changes in other param-

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$\alpha/\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosa</td>
<td>10</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>2.5</td>
</tr>
<tr>
<td>Brainstem</td>
<td>2.5</td>
</tr>
<tr>
<td>Bone</td>
<td>0.85</td>
</tr>
<tr>
<td>Muscle</td>
<td>3.1</td>
</tr>
<tr>
<td>Parotids</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 3. Data comparing the nontarget volume exposed to high levels of dose (specified in terms of nominal dose) for the conventional 3DCRT plan with different IMRT plans for the schematic HN case shown in Fig. 1.*

<table>
<thead>
<tr>
<th>Dose level (cGy)</th>
<th>Conventional</th>
<th>Conventional with IMRT boost</th>
<th>Two-phase IMRT</th>
<th>Simultaneous integrated boost IMRT</th>
<th>% Difference between SIB IMRT and 2-phase IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000</td>
<td>1,640</td>
<td>1,895</td>
<td>2,183</td>
<td>2,169</td>
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<td>1,355</td>
<td>1,557</td>
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<td>1,016</td>
<td>7.9</td>
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<tr>
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<td>1,016</td>
<td>1,141</td>
<td>897</td>
<td>797</td>
<td>12.5</td>
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<td>5,000</td>
<td>762</td>
<td>977</td>
<td>732</td>
<td>604</td>
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<tr>
<td>5,500</td>
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<td>810</td>
<td>567</td>
<td>407</td>
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<td>61.5</td>
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<td>409</td>
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<td>83</td>
<td>62</td>
<td>33.9</td>
</tr>
</tbody>
</table>

* Both plans that employ IMRT only are considerably more conformal than those that use conventional beams for all or a part of the treatment. Furthermore, the SIB plan is more conformal than the two-phase IMRT plan.
eters. More clinical and biological data are needed to determine a unique set of parameters. However, in the meantime we propose to use the currently available data to design treatment regimens as has been done by others (4–6, 13).

Figure 3 shows nominal dose, delivered in 25, 30, and 35 daily fractions, as a function of NTD. The parameters used for these calculations were $d_{ref} = 2$ Gy, $SF_{dref} = 0.5$, $\alpha/\beta = 20$ Gy, and accelerated proliferation doubling time $T_{d,\alpha} = 4$ days. The discontinuities at 50, 60, 70, and 80 Gy NTD values are due to weekends. The figure shows that 60 Gy NTD is equivalent to 60 Gy nominal dose in 30 fractions, and 70 Gy NTD is equivalent to 70 Gy nominal dose in 35 fractions, and so on, indicating that the method is self-consistent. The data also show that 50 Gy NTD is equivalent to 54 Gy nominal dose in 30 fractions of 1.8 Gy. This is consistent with current practice and indicates that the choice of parameters is clinically relevant. Examination of the same data in a tabular form (Table 4) is useful in providing guidance with regard to the choice of the (nominal) prescription doses for SIB-IMRT. For instance, if our intention

Fig. 2. Dependence of the variation of nominal dose as a function of NTD on radiobiological parameters. The data shown were calculated for nominal dose given in 28 fractions for the biologically equivalent NTD of 70 Gy as a function of (a) $SF_{dref}$ ($\alpha/\beta = 20$ Gy, doubling time = 4 days), (b) doubling time ($SF_{dref} = 0.5$, $\alpha/\beta = 20$ Gy), and (c) $\alpha/\beta$ ($SF_{dref} = 0.5$, doubling time = 4 days).
is to prescribe 80 Gy NTD to the primary disease, 60 Gy NTD to the regional disease, and 50 Gy NTD to the electively treated nodes, and if we choose to deliver the treatment in 30 fractions, the corresponding equivalent nominal doses would be 71.7 Gy (2.39 Gy/fx), 60 Gy (2 Gy/fx), and 54 Gy (1.8 Gy/fx).

Figure 4 shows similar data for 30 fractions for normal tissues for $a/b$ values of 0, 2, 12, and 20. The functional relationship between nominal dose and NTD for differing number of fractions is very similar. In these calculations we assumed that there is no regeneration of tissues and no change in sensitivity as a result of treatment. As one would expect, for large $a/b$ values, nominal dose and NTD are similar and do not depend significantly on the number of fractions. However, for small $a/b$ values, the smaller number of fractions lead to a higher biologically equivalent dose. For instance, for $a/b = 2$ Gy, the nominal dose of 70 Gy given in 30 fractions is equivalent to an NTD of 76 Gy.

Using the tumor parameters given in Table 1 and normal tissue $a/b$ values given in Table 2, we applied the isoeffect formulae to estimate the biologically equivalent NTDs for the HN fractionation strategies listed below. Table 5 summarizes the biologically equivalent NTDs for each fractionation strategy for the primary tumors, regional disease, and normal tissues embedded within the primary tumor volume and assumed to receive the same nominal dose as the primary. We assumed that similar calculations for normal tissues outside the primary target volume were unnecessary considering that the dose to such tissues is substantially reduced due to the higher conformality of IMRT and higher gradients outside the volumes to be treated.

**Conventional sequential boost:** The regional disease volume and the tumor receive 50 Gy in the first 25 daily fractions over 5 weeks, and the primary tumor receives an
additional boost of 20 Gy in 10 fractions over another 2 weeks. NTDs are the same as nominal doses for tumors and all normal tissues.

*M. D. Anderson BID concomitant boost:* Large fields are used to treat the regional disease with 54 Gy in 30 fractions of 1.8 Gy each over 40 days. For the last 12 fractions, a concomitant boost with reduced fields is given with 1.5 Gy/fx. This leads to a total of 72 Gy to the primary disease and 54 Gy to the regional disease over 40 days. According to the isoeffect formulae, the primary tumor dose is equivalent to an NTD of 78 Gy and the large-field dose is equivalent to an NTD of 50 Gy.

*MCV BID concomitant boost:* In this strategy, the first 24 Gy is given with large fields in 12 daily fractions of 2 Gy each, followed by 15 more daily fractions of 1.8 Gy each, also with large fields. Concomitantly, with every Monday, Wednesday, and Friday of the last 15 fractions, a reduced field fraction of 1.6 Gy is delivered for a total of 9 fractions. In addition, on each of the last two treatment days, two reduced field fractions of 1.8 and 1.6 Gy are delivered concomitantly. This results in a total nominal dose to the primary of 72.2 Gy in 39 days and 51 Gy to the regional disease in 37 days, biologically equivalent to NTDs of 78 Gy and 48 Gy respectively.

*MCV TID concomitant boost:* The first 25.2 Gy are given in daily large-field fractions of 1.8 Gy each, followed by 11 large-field daily fractions of 1.5 Gy each. Concomitantly with the last 11 fractions, a reduced field fraction of 1.5 Gy each is given. Each of the last 11 fractions is accompanied concomitantly with a third fraction of 1.5 Gy, which is delivered using small and large fields on alternate days (large fields on Monday, Wednesday, and Friday, except for the first fraction). In this manner, a nominal dose of 74.7 Gy is delivered to the primary over 33 days in 37 fractions, and 50.7 Gy to the regional disease in 31 fractions over 33 days. The two are equivalent to NTDs of 86 Gy and 50 Gy respectively.

*SIB-IMRT strategy 1:* Nominal doses of 65.9 and 54 Gy are delivered simultaneously to the primary and regional diseases in 30 fractions of 2.2 and 1.8 Gy each over 40 days. They are equivalent to NTDs of 70 and 50 Gy respectively.

*SIB-IMRT strategy 2:* Same as SIB-IMRT strategy 1 except that the nominal primary dose is escalated to 71.7, equivalent to an NTD of 80 Gy.

*SIB-IMRT strategy 3:* Same as SIB strategies 1 and 2 except for the nominal primary dose of 77.5, equivalent to an NTD of 90 Gy.

*SIB-IMRT strategy 4:* Nominal doses of 70 Gy to the primary and 58.1 Gy to the regional disease delivered simultaneously in 35 fractions of 2 Gy and 1.66 Gy over 47 days, equivalent to NTDs of 70 Gy and 50 Gy.

*SIB-IMRT BID strategy 5:* In this strategy, there are 40

### Table 5. Relationship between nominal doses and normalized total doses for various fractionation strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>GTV</th>
<th>Regional disease and electively treated volumes</th>
<th>NTD for normal tissues embedded in GTV*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nominal dose (Gy)</td>
<td>Fractions and elapsed time</td>
<td>NTD (Gy)</td>
</tr>
<tr>
<td>Conventional</td>
<td>70.0</td>
<td>35 fractions in 47 days</td>
<td>70</td>
</tr>
<tr>
<td>BID (MDA)</td>
<td>72.0</td>
<td>42 fx in 40 days</td>
<td>77.6 (1.99)</td>
</tr>
<tr>
<td>BID (MCV)</td>
<td>72.2</td>
<td>40 fx in 39 days</td>
<td>78.1 (2.00)</td>
</tr>
<tr>
<td>TID (MCV)</td>
<td>74.7</td>
<td>37 fx in 33 days</td>
<td>86.35 (2.01)</td>
</tr>
<tr>
<td>SIB-IMRT 1</td>
<td>65.9</td>
<td>30 fx (2.20 Gy) in 40 days</td>
<td>70</td>
</tr>
<tr>
<td>SIB-IMRT 2</td>
<td>71.7</td>
<td>30 fx (2.39 Gy) in 40 days</td>
<td>80</td>
</tr>
<tr>
<td>SIB-IMRT 3</td>
<td>77.5</td>
<td>30 fx (2.58 Gy) in 40 days</td>
<td>90</td>
</tr>
<tr>
<td>SIB-IMRT 4</td>
<td>70.0</td>
<td>35 fx (2.0 Gy) in 47 days</td>
<td>70</td>
</tr>
<tr>
<td>SIB-IMRT 5 (BID)</td>
<td>73.6</td>
<td>40 fx (1.84 Gy) in 40 days</td>
<td>80</td>
</tr>
</tbody>
</table>

*The values in parentheses are doses per fraction for NTD and indicate that the conversion from a given nominal dose to NTD does not, in general, produce a value divisible exactly by 2.*
fractions of 1.84 Gy/fx to the primary and 1.38 Gy/fx to the regional disease delivered in 40 days. The first 20 are once a day and the last 20 are 2 concomitant fractions per day. These yield biologically equivalent NTDs of 80 and 50 respectively.

The data in Table 5 indicate that with respect to tumor and regional disease, SIB-IMRT strategies 1, 2, and 3 should be suitable since they allow the dose/fx to the regional disease to remain at a value consistent with conventional experience (1.8 Gy/fx). Examination of NTDs of embedded bone, muscle, and mucosa data, however, indicates that one may need to be concerned about late complications if the number of fractions is reduced to as few as 30 and the dose is escalated. On the other hand, considering that the volume of tissues exposed to high doses is reduced with IMRT, there is a possibility that the probability of such complications would also be reduced. An alternative dose escalation strategy might be of the type SIB-IMRT strategy 5 in which part or the entire IMRT course is delivered BID using the same plan for both daily fractions. Such a strategy assumes that dose per fraction as low as 1.4 Gy to the regional disease and as high as 1.8 Gy twice daily to the primary would be acceptable. Only careful clinical trials can resolve these issues.

As an illustration, we show the use of the methodology described here to design an IMRT treatment plan and to evaluate the results. We used SIB-IMRT strategies 1, 2, and 3. Table 6 shows prescribed doses in terms of NTD and biologically equivalent nominal doses. The nominal doses were used as input to the IMRT optimization system. The resulting nominal dose distributions in treatment volumes were used to compute nominal EUDs. Using isoeffect formulae, these were then converted back to equivalent uniform NTDs. Corresponding calculations for normal tissues are illustrated in Fig. 5, which shows the nominal dose–volume histograms and biologically equivalent NTD–volume histograms for spinal cord and parotid glands. The data indicate that, because of the lower dose per fraction, the biologically effective doses to both the cord and parotids are generally lower. An exception is a small volume (~5%) of parotids with dose above 60 Gy. Parotids are generally known to have a large volume effect. Based on clinical experience, it is assumed that about 50% of the volume can tolerate high doses provided the remainder is maintained below a threshold of about 30 Gy. Therefore, the fact that the NTD above 60 Gy is higher than the nominal dose above 60 Gy has no impact on parotid toxicity.

CONCLUSIONS

IMRT dose distributions are most conformal when designed to be delivered as an SIB. The same IMRT plan can be used for the entire course of treatment. Furthermore, electron beams are not necessary and problems related to field junctioning do not arise. There is no need to change any accessories between fields; thus, there is no need to enter the treatment room between fields. These factors make the planning and delivery of SIB-IMRT more efficient.
Since the large-field and boost doses are delivered in the same number of fractions, one must consider the radiobiological consequences of different fraction sizes for the gross disease, regions of microscopic spread, and electively treated nodes. Due to the improved conformity of IMRT plans, dose to normal tissues outside the target volume is typically lower. In addition, if the number of fractions is greater than the number of fractions used to deliver large fields in conventional therapy, the dose per fraction to normal tissues would be lower as well. Therefore, the biologically effective dose would be lower still. This may allow escalation of biologically equivalent dose to the tumor. However, normal tissues embedded within the target volumes may present an impediment. In the event that they do, SIB-IMRT fractionation regimens with multiple fractions per day may be considered. Another alternative may be to sacrifice some of the conformity of SIB-IMRT and use two-phase IMRT. The latter is inferior compared to the former in terms of dose conformity, but both are considerably better than conventional 3DCRT. Clinical trials are needed to establish the suitability of any of the strategies.

APPENDIX: THE ISOEFFECT FORMALISM AND ITS APPLICATION TO SIB FRACTIONATION STRATEGY

According to the LQ model, the surviving fraction $SF_{n,d}$ of cells after $n_f$ fractions of dose $d_f$ each is

$$SF_{n,d} = e^{-n_f d_f + \beta d_f^2},$$

which leads to

$$SF_{n,d} = SF_{n,d,f}(\frac{n_f d_f}{d_f} + \alpha \beta d_f),$$

where $d_{ref}$ is the reference fraction size, which we select to be 2 Gy/fx. The expression for the surviving fraction, when incorporating tumor repopulation, including accelerated repopulation, becomes

$$SF = 2\left(\frac{T_{ta}}{T_{ta}} T_{is} - T_{ref} T_{ta} = \frac{d_f}{d_{ref}} \times \frac{\alpha \beta + d_f}{\alpha \beta + d_{ref}}\right),$$

where $T_f$ is the total treatment time in days, $T_{lag}$ is the lag time before accelerated repopulation begins, $T_{d,a}$ is the accelerated tumor clonogen doubling time, and $T_{d,ref}$ is the unperturbed doubling time. For a given fractionation strategy in which the same dose per fraction is used for the entire course of treatment, the biologically equivalent normalized total dose, for which the dose per fraction is equal to $d_{ref}$, can be expressed as

$$(SF_{d_{ref}})_{NTD} = 2\left(\frac{T_{ta} - T_{ref}}{T_{ta}}\right) \times (SF_{d_{ref}})\left(\frac{n_f d_f}{d_f} \times \frac{\alpha \beta + d_f}{\alpha \beta + d_{ref}}\right),$$

where $n_f$ is the number of fractions in which the NTD will be delivered in $T_{LND}$ days at a rate of $d_{ref}$/fx. Here we have assumed that the total treatment time in either fractionation strategy is greater than the lag time. Expression (4) may be solved to yield

$$n_{f,NTD} = \frac{T_f - T_{LND}}{T_{d,a}} \times \left[\frac{\ln(2)}{\ln(SF_{d_{ref}})} + \frac{n_f d_f}{d_{ref}} \times \frac{\alpha \beta + d_f}{\alpha \beta + d_{ref}}\right].$$

There are two unknowns in expression (5), $n_{f,NTD}$ and $T_{LND}$. If the treatment is delivered once per day and only on weekdays, the difference between the new and old number of fractions is not equal to the difference in elapsed days. This is due to the fact that a change in the number of fractions may lead to crossing the weekend boundary. We adopted an iterative search scheme to calculate $n_{f,NTD}$. Initially, we assume that $T_{LND} = T_f$ and calculate an approximate value of $n_{f,NTD}$ (i.e., $n'_{f,NTD}$). Assuming further that the treatments begin on Mondays, the corresponding elapsed time is then computed using the following algorithm:

$$T_{LND}' = n'_{f,NTD} + \text{Integerize}\left(\frac{n'_{f,NTD}}{5}\right) \times 2 - 2,$$

if $n'_{f,NTD}$ is evenly divisible by 5, otherwise

$$T_{LND}' = n'_{f,NTD} + \text{Integerize}\left(\frac{n'_{f,NTD}}{5}\right) \times 2.$$

The second term (or the second and the third terms) on the right-hand side is the number of days in all the weekends. $T_{LND}'$ is then increased or decreased by one day at a time and the value of $T_{LND}'$ is recomputed. This process is repeated until the difference between $T_{LND}'$ and $T_{LND}$ is minimum.

Expression (4) above can be generalized for fractionation strategies involving multiple phases and multiple fractions per day. For the general case in which each fraction is of a different size,

$$(SF_{d_{ref}})_{NTD} = 2\left(\frac{T_{ta} - T_{ref}}{T_{ta}}\right) \times (SF_{d_{ref}}) \sum \frac{d_f}{d_{ref}} \times \frac{\alpha \beta + d_f}{\alpha \beta + d_{ref}},$$

The remaining expressions and steps are the same as for the simpler case discussed above.

REFERENCES


