Altered Fractionation for Head and Neck Cancer

A conventional course of radiation for squamous cell carcinoma in the United States is generally 70 Gy in 7 weeks, with a once-daily dose of 1.8 to 2 Gy. This schedule has a modest success rate in curing head and neck cancer. The delivery of therapeutic radiation in multiple sessions, or fractions, has been practiced since the discovery of radiation’s potential to cure malignancies. Initially, this was done out of practical necessity: Radiation was delivered at a low dose rate, and the treatment sessions had to be repeated to obtain the desired effect. Technologic improvements eventually allowed for treatments in one session, but clinical observations of improved outcomes with multiple fractions were noted in the 1920s, and the concept of fractionated radiation took hold.

A second clinical observation was also made during this era. When the testes of animals were irradiated in a single fraction, the overlying scrotal tissue broke down as a result of the effects of the higher dose of radiation necessary to achieve sterilization. However, when multiple smaller fractions were delivered, sterilization was accomplished without severe damage to the scrotal skin. Making the analogy that the testes were akin to tumors, whereas the scrotum represented normal tissues, investigators formulated the concept of fractionating radiation to treat malignancies. The practice gained credibility, and spreading a course of radiation over many days is now considered to be the most efficacious method of delivering therapeutic radiation.

While fractionated radiation is recognized as an improved method of delivering radiation, the optimal fractionation schedule remains unknown. Over the decades, clinical practice has led to the development of standard, or conventional, schedules. In the United States, a conventional course of treatment for squamous cell carcinoma entails the use of 1.8 to 2 Gy per fraction, delivered once daily, 5 days a week. In the treatment of advanced head and neck cancers, a total dose of 70 Gy is administered to gross disease. At the dose rates described, a standard course of radiation takes 7 weeks to deliver.

These doses and schedules have evolved from clinical observations. Such observations reflect not only the probability of curing a disease, but also of obtaining these cures with acceptable morbidity. Greater understanding of the radiobiology of both tumor and normal tissues and attempts to increase the therapeutic gain of radiation have led to the development of fractionation schemes that deviate from the conventional.

Two separate concepts of altering the fractionation schedule—hyperfractionation and accelerated fractionation—have been studied. The rationale and clinical results of each concept will be described below. Although the rationales differ for each approach, most clinical trials have used schedules that are hybrids of the two concepts.

Hyperfractionation

Rationale

Theoretically, the greater the total dose, the greater the probability of cure. Yet with conventional fractionation, total doses of radiotherapy for head and neck cancer are limited by normal tissue tolerance. The rationale for hyperfractionation is its potential to increase the total dose—translating into a higher probability of cure without an increase in late toxicity.

The two types of reactions of normal tissues to radiation are acute (or early) and chronic (or late). The acute type is primarily seen in tissues such as skin or mucosa. These reactions typically manifest as radiation dermatitis and mucositis, develop during a course of fractionated radiation, and resolve over a period of weeks after completion of radiation. Late-responding tissues include fibroblasts, bone, and neural tissues. It can take months, or even years, before the effects of radiation are seen in these tissues.

Normal tissue reactions are dependent on both the dose per fraction and the total dose. Modifying the dose per fraction has more effect on late-responding tissues, and, with lower doses, there is
greater repair of these tissues than with the tissues involved in acute reactions. Hyperfractionation attempts to take advantage of these differing normal tissue responses. Compared with a conventional fractionation schedule, hyperfractionation increases the total dose and decreases the dose per fraction. The increase in total dose is to the level at which the same degree of late effects seen with the conventional schedule also occurs with hyperfractionation. Multiple fractions are delivered on each treatment day, and the overall treatment time is therefore unchanged. Head and neck cancers are believed to have a rapidly proliferating clonogenic population. Their behavior would most likely mimic the acute-responding tissues. Therefore, these tumors would be less likely to be affected by the decrease in dose per fraction. An increase in total dose would enhance the tumor kill, but would also affect normal acute-responding tissues and possibly increase the incidence and/or severity of radiation dermatitis and mucositis.

Other Possible Mechanisms

While the primary rationale for hyperfractionation is to escalate total dose in light of the differences in repair between acute- and late-responding tissues, this approach may also be effective because the malignant clonogens have the opportunity to redistribute more frequently to sensitive portions of the cell cycle. One reason for the incomplete eradication of tumor cells during a fraction of radiation is that some cells are in a portion of the cycle that confers resistance. As these cells are rapidly proliferating, it is probable that between fractions surviving cells will redistribute to a sensitive phase of the cycle, resulting in a greater probability of tumor kill. Radiation resistance also increases with tumor hypoxia. At lower doses per fraction, tumor sensitivity to radiation is less dependent on the presence of oxygen. Thus, hyperfractionation may circumvent the protection that hypoxia provides to tumor cells.

Clinical Results of Hyperfractionation

Retrospective Trials

In the United States, the largest reported experiences using hyperfractionation as therapy for head and neck cancers have been retrospective. At the University of Florida, hyperfractionation regimens using 1.2 Gy twice a day to total doses of 74.4 to 81.6 Gy have been used to treat over 350 patients with carcinomas of the oropharynx, hypopharynx, and larynx.[1,2] An improvement in local control was seen in cases of intermediate-stage tumors of the larynx and hypopharynx treated with hyperfractionation, compared with historical controls treated with conventional radiation.

At The University of Texas M. D. Anderson Cancer Center, we reported our experience treating more than 200 patients with carcinomas of the supraglottic larynx and hypopharynx with hyperfractionation.[3] Subsite analysis suggested an improvement in local control, particularly for patients with T2 hypopharyngeal carcinoma.[4,5] Clinicians were cautioned against overinterpreting the role of hyperfractionation in these retrospective results, however, because coinciding technologic advances in treatment and diagnostic imaging may have contributed to the improvements.

Prior to a randomized trial of various altered fractionation studies (discussed below), the Radiation Therapy Oncology Group (RTOG) conducted a study comparing a conventional radiation schedule ranging from 66 to 73.8 Gy with hyperfractionation to 60 Gy at 1.2 Gy twice daily.[6] Despite a lower dose in the hyperfractionation arm, locoregional control at 2 years was equivalent in both arms. This study, as well as the retrospective experiences described above, showed that hyperfractionation results in greater acute reactions than conventional therapy. These studies also demonstrated the critical importance of the interfraction interval: Both acute and late reactions were fewest when the interfraction interval was at least 6 hours.

Randomized Trials

Several international randomized trials of hyperfractionation have also been reported. Pinto and associates at the National Cancer Institute of Brazil randomized 112 patients with stage III/IV squamous cell carcinoma of the oropharynx to either 66 Gy in 33 fractions or 70.4 Gy in 64 fractions twice daily. There were significant improvements in both local control and survival in the patients treated with hyperfractionation.[7]

In Spain, Sanchiz and colleagues performed a randomized trial comparing the same hyperfractionation regimen used in Brazil with 60 Gy in 30 fractions. They enrolled 859 patients with stage T3/T4 head and neck cancer. The authors described an improvement in median duration of response and overall survival for patients treated with hyperfractionation.[8] Disease control rates were not reported, although for the stages of disease treated, the expected control rates with only 60 Gy in 30 fractions would be poor. This was one of the first randomized trials evaluating the role of concurrent chemotherapy as well, with a third arm receiving 60 Gy combined with fluorouracil (5-FU). The chemotherapy arm demonstrated improved results similar to those seen in the hyperfractionation arm.

The European Organization for Research and Treatment of Cancer (EORTC) randomly assigned 356 patients to conventional radiation, 70 Gy in 35 fractions, or to hyperfractionation, 80.5 Gy in 70
fractions at 1.15 Gy twice daily. The study (EORTC 22791) was restricted to patients with T2/T3, N0/N1 squamous cell carcinomas of the oropharynx (excluding base-of-tongue tumors). The patient population was selected to eliminate patients with a low probability of surviving 2 years. Patients treated with hyperfractionation had a 5-year local control rate of 59%, compared with 40% for patients treated with conventional treatment ($P = .02$). Analysis by stage suggested these differences were due to improvements in control in patients with T3 disease. An improvement in 5-year overall survival was also reported for patients treated with hyperfractionation ($P = .08$).[9] Table 1 summarizes the randomized hyperfractionation trials.[6-11]

### Accelerated Fractionation Radiation

#### Rationale

Accelerating the radiation schedule involves shortening the overall duration of therapy to less than the 7 weeks used in a conventional schedule. Both the dose per fraction and the total dose are either the same or slightly lower than the doses used in standard fractionation. The key element is the reduction in the overall time.

One problem with a fractionated course of radiation is that tumor regeneration can occur during a course of treatment, reducing the probability of cure. Keane and colleagues calculated that a 2.7% reduction in local control for patients with tonsillar carcinoma would be seen with each day of treatment prolongation.[12] In an attempt to reduce acute effects, it had been common practice to interrupt a course of radiation and give patients a 2- to 3-week rest to allow their radiation-induced injuries to heal. These split courses would continue after the break without a compensation for the delay. This also allowed for tumors to “heal,” hence yielding the inferior results. Indeed, Million and Zimmerman reported inferior results with split-course schedules compared with continuous-course treatments.[13] It was postulated that if prolongation of therapy adversely affects outcome, accelerating the treatment might improve the results of radiation.

#### Development of Accelerated Fractionation Strategies

Several studies have attempted to determine the dose of radiation necessary to overcome the effects of tumor regeneration. Budhina et al[14] and Overgaard et al[15] determined that approximately 0.5 Gy/d is required to compensate for a 3-week break in treatment. Withers et al analyzed the dose equivalent of regeneration during therapy. They suggested that tumor clonogens undergo an accelerated repopulation after a certain period of time, and that an additional 0.6 Gy is required for each day of therapy beyond the time when repopulation sets in.[16] It was estimated that this phenomenon of accelerated repopulation begins in the fourth week of a conventionally fractionated schedule, based on a retrospective analysis of local control rates in tonsillar carcinomas achieved at different international centers using a variety of fractionation schedules.[17]

Unfortunately, simply adding this supplementary dose to overcome repopulation could potentially increase late effects on normal tissue. An alternative method was to shorten the time of therapy to prohibit accelerated repopulation from occurring. This could be accomplished by delivery of more than five fractions per week, either by treating 6 or 7 days a week or delivering multiple fractions per day. It was anticipated that an increase in late sequelae would not be seen, provided that the dose per fraction remained at 2 Gy or less and that there was sufficient time between fractions to allow repair of normal tissues. Nevertheless, an increase in acute mucositis was expected.

Another way of reducing the overall treatment time is to increase the dose per fraction and deliver the total dose over a shorter period of time. In some parts of the United Kingdom and Canada, these hypofractionated schedules[17] which deliver 51 to 55 Gy in 16 to 20 fractions over 3.5 to 4 weeks are the conventional fractionated regimens.[17] These schedules are not believed to be superior to conventional US schedules, and are not commonly used in the United States because of concerns for potential late effects with the large fields used to treat advanced head and neck cancers.

Ideally, multiple fractions per day might not be required if one could deliver larger doses per fraction to the tumor only, while maintaining lower doses per fraction to subclinical disease and normal tissues. This may be feasible with intensity-modulated radiation therapy, which can achieve higher total doses in tumors while sparing more normal tissue. Butler and colleagues have described an initial experience with this approach, with encouraging results that warrant further study.[18]

#### Clinical Results of Acceleration Strategies

Many schedules have been tested to improve the results of radiation by shortening the overall treatment time for patients with head and neck cancer. The simplest approach is to increase the number of fractions per week while maintaining total dose and dose per fraction.

Two randomized trials, in Denmark[19] and Poland,[20] evaluated conventional therapy with five
fractions per week, compared to accelerated regimens using six to seven fractions per week. Total dose and fraction size remained the same, resulting in a shortening of treatment time by 1 or 2 weeks. Both studies demonstrated significant improvements in locoregional control, and maintaining the weekly dose below 13 Gy resulted in acceptable sequelae.

In Vancouver, Canada, Jackson and associates attempted a greater reduction in overall treatment time, delivering 66 Gy in 33 fractions in either 45 to 48 days or 22 to 25 days.[21] These schedules resulted in similar tumor control, but the shorter treatment time led to increased toxicity and necessitated early closure of the Canadian trial.

In the United States, two separate approaches have been undertaken to accelerate radiation for patients with head and neck cancer. Both involve reducing the treatment time by 1 week. This is accomplished by using doses slightly lower than 1.8 Gy for all or part of the therapy. Although the critical element is the decreased treatment time, the use of smaller fractions introduces an element of hyperfractionation into these schedules as well.

**Split-Course Regimen** At the Massachusetts General Hospital, Wang and colleagues pioneered the split-course accelerated schedule. Treatment is administered at 1.6-Gy fractions twice per day. After 38.4 Gy is delivered, the patient is given a break. Treatment resumes at week 5 and continues with the same fractionation, to complete therapy to a dose of 67.2 Gy in 6 weeks.[22] Compared with historical controls treated with once-daily fractions, local control rates were significantly higher in patients treated with this accelerated schedule.[23,24] Wang et al reported that minimizing the time of the "gap," or break, resulted in the most effective control.[25]

**Concomitant Boost** At M. D. Anderson Cancer Center, we have used a schedule referred to as concomitant boost. Radiation for head and neck cancers involves delivery of both a planned dose to the gross tumor and a lesser dose to sites of microscopic or subclinical disease. Conventional radiation delivers 50 to 54 Gy to these subclinical sites, and then the radiation portals are reduced in size to deliver the "boost" to the gross disease.

Concomitant-boost therapy delivers this boost on the same days that the therapy to subclinical disease is given. As the boost is given on the same day as a second daily fraction, the dose per fraction is lowered. Thus, large fields treating gross and subclinical disease are delivered at a dose of 54 Gy in 30 fractions over 6 weeks. In addition, an 18-Gy boost is delivered over 12 fractions as a second daily dose. The total dose is 72 Gy delivered in 42 fractions over 6 weeks.[26] The timing of the boost was determined from a three-arm randomized trial. The boost was either delivered during the first or last 12 days of treatment, or equally divided throughout the 6 weeks in two fractions per week. Administering the boost during the last 2.5 weeks of treatment proved most efficacious.[27] This was consistent with the concept of accelerated repopulation of tumor clonogens and the strategy of overcoming this phenomenon by an additional dose beginning in the fourth week of radiation.

We have used concomitant-boost therapy in over 200 patients with oropharyngeal carcinoma. The majority of patients have stage T2/T3 disease. Subsite analysis revealed local control rates > 90% for patients with stage T2 squamous carcinomas of the base of the tongue and tonsillar fossa.[28,29] Selected patients with stage T3 disease at these sites have control rates > 75% when treated by accelerated fractionation with concomitant boost.

**CHART Trial** Several regimens of more aggressive acceleration of therapy have been studied in Europe. Continuous hyperaccelerated radiation therapy (CHART) was tested in a randomized trial of over 900 patients in the United Kingdom. CHART treats patients in 12 consecutive days; doses of 1.5 Gy are delivered 3 times a day. Due to the significant shortening of time, the total dose is lowered to 54 Gy. CHART was compared with 66 Gy delivered in 33 fractions. Acute mucositis was more severe with CHART, but nearly all cases healed within 8 weeks posttherapy. There was no observable difference in cancer control or survival rates.[30,31]

**EORTC 22851** The EORTC tested 72 Gy in 45 fractions over 5 weeks in EORTC 22851. The investigational regimen was a split-course schedule. Fractions of 1.6 Gy were delivered three times a day. An approximate 2-week break was administered after 28 Gy. Continuing with the same dose per fraction, the remaining 44-Gy dose was delivered during the last 17 days.[32] A total of 512 patients were enrolled in the study. Patients treated with the accelerated schedule had significantly better locoregional control, with a 13% gain over conventional fractionation. There was also a trend toward improved survival for patients on the experimental arm. Improvement in disease control was balanced by a significant increase in severe late toxicity seen in patients treated with accelerated therapy. The authors concluded that despite the improvements in local control, a less aggressive regimen should be tested. **Table 2** summarizes the randomized accelerated fractionation trials.[11,20,21,31,32]
RTOG Four-Arm Randomized Trial

From 1991 to 1997, the RTOG conducted a randomized four-arm trial (RTOG 9003) comparing three experimental schedules with standard fractionation of 70 Gy in 7 weeks (35 fractions). The three schedules tested were (1) hyperfractionation, consisting of an 81.6-Gy total dose delivered in 70 fractions (two fractions per day) over 7 weeks; (2) split-course accelerated fractionation, delivering 67.2 Gy in 42 fractions over 6 weeks; and (3) accelerated fractionation with concomitant boost, delivering 72 Gy in 42 fractions over 6 weeks.

The first analysis of this trial was recently reported.[11] Eligibility was moderately heterogeneous with respect to sites of disease and stages, and 1,073 patients were analyzable. The median follow-up for surviving patients was greater than 3 years. Patients with stage III/IV squamous cell carcinoma of the oral cavity, oropharynx, and supraglottic larynx were entered in the study. Patients with stage II-IV squamous cell carcinoma of the base of the tongue and hypopharynx were also eligible. The most common primary site was the oropharynx, accounting for 60% of patients, with the remaining patients roughly equally distributed among the other sites.

The 2-year primary site failure rates were 43.7%, 37.8%, 43%, and 36.9% for standard fractionation, hyperfractionation, accelerated fractionation with split course, and accelerated fractionation with concomitant boost, respectively. The three experimental arms were compared individually with the control (standard fractionation) arm. Hyperfractionation and concomitant boost local control rates were significantly improved ($P = .045$ and $P = .05$, respectively); there was no statistical difference between standard fractionation and split-course accelerated fractionation.

Three-quarters of patients entered in the study were node-positive. There were no differences seen in regional failure rates among the control and investigational arms. Similarly, the incidence of distant metastases was similar among all arms. There was a trend toward improved disease-free survival for hyperfractionation ($P = .067$) and concomitant-boost fractionation ($P = .054$), but no differences were seen in overall survival.

All three experimental arms had a significant increase in acute reactions, primarily mucositis. The incidence of grade 3 or greater acute reactions was 35% with standard fractionation, and ranged from 50% to 59% with the investigational treatments. The incidence of grade 3 or greater late effects with standard fractionation was 27%. Only concomitant-boost fractionation had a significantly higher (37%) rate of late effects. Late toxicity was mostly attributed to effects seen 3 to 6 months posttherapy as a result of prolonged acute effects. There was no significant difference in the incidence of persistent late toxicity (more than 6 months after therapy) between any of the treatment arms.

Summary

Hyperfractionation has been studied in numerous randomized trials, and its role in the control of head and neck cancer has been controversial. Although two separate meta-analyses came to differing conclusions regarding the role of hyperfractionation,[33,34] the results of the randomized EORTC 22791 and RTOG 9003 trials together provide compelling evidence of the efficacy of hyperfractionation compared with standard fractionation.

Both trials used accepted doses in the control arm and had excellent compliance. To answer the question in the most scientific manner, the EORTC studied the fractionation question in a homogeneous population. In contrast, the RTOG studied a broader selection of patients with head and neck cancer. This may be the reason the differences in outcome were smaller in the RTOG trial than in the EORTC trial, but the differences were statistically significant in both studies.

Studies of acceleration strategies have been more varied because there are numerous ways to accelerate treatment. Since accelerated fractionation increases acute toxicity, a conclusion from the different studies is that only a modest decrease in overall treatment time is feasible without a decrease in total dose or, perhaps, the use of novel normal tissue radioprotectors.[35] The CHART trial showed that greater time reductions must be accompanied by a sacrifice in total dose, and this strategy did not improve disease control for head and neck cancer. Thus, an overall time reduction of 1 week, as tested in the United States, appears to be the most practical strategy. The results of the RTOG 9003 trial suggest that differing strategies to alter radiation schedules—both by hyperfractionation and accelerated fractionation with concomitant boost—can improve the therapeutic gains achievable with radiation. The study validates decades of clinical observations and laboratory studies regarding fractionation sensitivity of normal tissues and tumors. It also supports the concern that tumors undergo accelerated repopulation when injured by radiation.
Without a single strategy showing an advantage, the optimal choice of a new standard for fractionation remains unclear. In the RTOG trial, two schedules showed improvement in local control. It has been argued that the results of accelerated fractionation with a split course also could have been improved, either by further limiting the duration of the split or adding additional fractions to deliver 70 to 72 Gy. Thus, the choice of fractionation may hinge on nonmedical considerations, since all of these schedules involve more treatments and greater time commitments from patients. The acute effects of these schedules are also greater, and patients treated with altered fractionation need enhanced pain management and nutritional support.

**Future Research Directions: Chemoradiation Trials**

Although the controversy regarding the ideal radiation fractionation schedule has not been fully resolved, the RTOG fractionation trial will probably be the last large-scale trial to specifically address fractionation. Meanwhile, other investigators have been studying the use of radiation and concurrent chemotherapy. Numerous randomized trials addressing chemoradiation have been conducted, and although markedly heterogeneous in design, several meta-analyses have suggested that the use of radiation and concurrent chemotherapy improves survival compared with radiation alone.[36] This benefit was not clearly demonstrated by the fractionation trials. As with aggressive fractionation, however, normal tissue tolerance also limits radiation and concurrent chemotherapy. The prospective systemic agents to be used concurrently with radiation, the dosing of these agents (ie, daily, weekly, or “cycled”), and the differing potential radiation schedules create numerous permutations for the treatment of head and neck cancer. The role of an altered radiation schedule to be used concurrently with chemotherapy must be defined, but the biological rationale for these schedules when combined with systemic agents is ambiguous. Both Adelstein et al and Calais et al performed randomized trials demonstrating improvements in outcome when chemotherapy was added to conventionally fractionated radiation.[37,38] Would the same results have been obtained if the control arm had used an altered fractionation schedule? Or would the differential gains be greater if a variant schedule had been combined with concurrent chemotherapy?

When chemotherapy is added, is it also important to escalate the radiation dose via hyperfractionation? Based on the general concepts of multiagent therapy, addition of a therapy with differing toxicities and either an independent or synergistic mechanism of action would support a dose decrement rather than an increase. Brizel and colleagues combined hyperfractionated radiation with cisplatin (Platinol) and 5-FU. The radiation-only arm received 75 Gy, while patients in the combination arm received 70 Gy. In both arms, the fractionation was 1.25 Gy twice daily. Despite the lower total radiation dose, concurrent chemotherapy and radiation improved locoregional control.[39] It is unclear whether giving a higher radiation dose would have further improved outcome, enhanced toxicity, or both. It is also uncertain whether twice-daily radiation was necessary. Is acceleration of therapy required when systemic therapy is added? Again, the data are unclear. At the University of Chicago, phase II trials using hydroxyurea (Hydrea), 5-FU, and radiation have enrolled patients with both advanced and/or recurrent squamous cell cancers of the head and neck. The investigators used a schedule in which therapy is given for 1 week and then withheld for a week. Treatment to a total dose of 70 Gy at 2 Gy per fraction requires 13 weeks. In a time-dose analysis of their results, the authors argued that the radiation protraction's possible detriment is countered by the addition of chemotherapy.[40]

Recently, these investigators have accelerated their therapy by continuing the alternating-week strategy but curtailting the overall treatment by delivering 15 Gy per week at a rate of 1.5 Gy twice daily; thus, overall treatment time is approximately 9 weeks.[41] Randomized data for this strategy are unavailable. The investigators have tested other systemic therapies in combination with this novel radiation schedule, and its importance as an independent factor remains unclear, but in certain combinations, it may be too toxic.

The RTOG recently tested the feasibility of concomitant boost fractionation with cisplatin in a phase II trial. Results are pending.

**Conclusions**

In conclusion, large randomized trials of radiation fractionation in the treatment of head and neck cancer have been completed. They suggest that altered schedules can result in improved therapeutic outcome, and have answered many questions regarding radiation and tumor biology. The optimal radiation schedule and the importance of radiation schedules when combined with systemic therapies are factors that remain to be studied.
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