Head and Neck Cancer: Altered Fractionation Schedules

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Abstract
Local control is paramount in the treatment of localized advanced head and neck cancer. Standard radiotherapy cures a high percentage of early tumors—more than 80% of the early laryngeal tumors—but fewer of the advanced tumors. Attempts have therefore been made to improve the therapeutic ratio by: A) hyperfractionation: reducing the dose per fraction to reduce late morbidity; the total dose is then elevated in an attempt to improve local tumor control with equal morbidity, and B) acceleration: reducing the overall treatment time to overcome repopulation during a protracted course of radiotherapy. The total dose and dose per fraction have been reduced in the accelerated arm in some trials, while in others the total dose has been maintained. Both these strategies have been tested in multicenter randomized controlled trials, but neither have become part of routine clinical practice. The biological parameters determining local tumor control and normal tissue effects are being studied at Mount Vernon by an analysis of selected randomized controlled trials, with the aim of designing new schedules of radiotherapy for future studies. The Oncologist 1999;4:11-16

Introduction
Over 5,000 patients are diagnosed each year as having cancer of the head and neck, and this accounts for about 2% of all cancer registrations. It occurs predominantly in an older population, occurring in males more than in females at all sites. The most common histological type is that of squamous cell carcinoma and is associated with tobacco and tobacco products; 70%-80% of all cancers in the oral cavity, oropharynx, and larynx in India may be due to smoking or chewing tobacco. The other major etiological factor is alcohol, and if adjustment is made for smoking habits, alcohol remains an independent risk factor, particularly for pharyngeal tumors. A genetic basis for the development of head and neck cancer is currently being sought, as there is a younger population who neither smoke nor drink but develop head and neck cancer. If underlying genetic factors can be discovered, then patients who are more likely to develop head and neck cancer can be warned at an early stage in their life and the major etiological risk factors avoided.

In this paper, squamous cell carcinoma of the oral cavity, oropharynx, pharynx, and larynx will be discussed. The uncommon histologies such as non-Hodgkin’s lymphoma, adenocarcinoma, and neuroblastoma are not addressed.

Unlike tumors at other sites, head and neck cancer tends to present with locoregional disease, and only 18%-20% develop distant metastases. Control of the primary site and nodal metastases is paramount, therefore, and will impact overall survival.

Biological Basis of Altered Fractionation Schemes
Conventional radiotherapy in head and neck cancer involves daily treatments, Monday to Friday, over three to seven weeks depending upon the cancer center in which the patient is treated. In the south of England, 66 Gy to 70 Gy over six and one-half to seven weeks would be considered conventional treatment, compared with 50 Gy to 55 Gy over four weeks in the north of England, and 52 Gy over three weeks in Manchester. These different fractionation schedules have arisen from clinical experience extending over the past 60 years, and balance dose per fraction, overall time, and total dose together with the volume of tissue irradiated give a high chance of locoregional tumor control with acceptable morbidity. There has never been any randomized controlled trial comparing the different conventional fractionation schedules used in head and neck cancer in the...
United Kingdom. In the United States and Europe, daily fractionation from 66 Gy to 72 Gy would be considered conventional radiotherapy, but in Canada the shorter overall times of four weeks are more traditional.

If these well-tried fractionation schedules are to be modified, then there must be a good scientific basis for so doing. In head and neck cancer, there were two main research initiatives which led to novel fractionation schemes, aimed at an improvement in the therapeutic benefit, namely, an increase in tumor cell kill without an increase in morbidity. Table 1 illustrates the fractionation studies discussed below.

HYPERFRACTIONATION

In the early 1980s a review of the time fractionation schedules in the normal tissues of rodents led to the hypothesis that a low dose per fraction could give reduced morbidity in the late-reacting normal tissues—spinal cord, bone, subcutaneous tissue, and lung [1]. This led to clinical work in which a low dose per fraction was given in the same overall time as routine treatment by giving treatment twice per day and achieving a higher dose in an attempt to increase local tumor control with equal late morbidity. The European Organisation for Research on the Treatment of Cancer (EORTC) carried out a randomized controlled trial in oropharyngeal cancer in which 1.15 Gy was given twice per day to a total dose of 80.5 Gy and compared with 2 Gy per fraction to 70 Gy in the same overall time.

Acute reactions were slightly more troublesome, but in the hyperfractionated group there was an increase in local tumor control—56% versus 38% at five years—with equal morbidity. In the latest review of the data, there was a suggestion of improvement in overall survival ($p = 0.05$) [2, 3].

In the United States, nonrandomized studies using similar techniques have shown advantages over retrospectively compared groups at all sites within the head and neck region. In a phase I/II trial by the Radiation Therapy Oncology Group (RTOG), fractions of 1.2 Gy were given twice a day for five days a week, and patients were assigned to receive total doses of 67.2 Gy, 72 Gy, 76.8 Gy, and, later, 81.6 Gy. The highest dose of 81.6 Gy was given over a period of just under seven weeks; it was found to give an incidence of late effects no greater than that with the other arms and similar to that expected using conventional radiotherapy [4]. This regimen has been chosen for one of the four arms of an RTOG trial of fractionation in head and neck cancer which has recruited over 1,000 patients but in which no interim report has been published to date.

Pure hyperfractionation has therefore been shown to be an advantage in clinical radiotherapy. However, there is a considerable economic and social problem in doubling the number of treatments and requiring patients to wait 6 h within a department in order to complete their treatment on each day on a course lasting up to a total of seven weeks.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose per fraction</th>
<th>$n$ of fractions</th>
<th>Total dose (Gy)</th>
<th>Overall time (days)</th>
<th>Interfraction interval (hrs)</th>
<th>Interfraction interval (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperfractionation [2]</td>
<td>1.15</td>
<td>70</td>
<td>80.5</td>
<td>47</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Acceleration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Pure [10]</td>
<td>2</td>
<td>24-27</td>
<td>48-54</td>
<td>9-11</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Acceleration with a split [18, 19]</td>
<td>1.6</td>
<td>40</td>
<td>64</td>
<td>40</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>EORTC [3]</td>
<td>1.6</td>
<td>45</td>
<td>72</td>
<td>33</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Concomitant boost [22]</td>
<td>1.8</td>
<td>30</td>
<td>69</td>
<td>40</td>
<td>3-6</td>
<td>3-6</td>
</tr>
<tr>
<td>CHART [23]</td>
<td>1.5</td>
<td>36</td>
<td>54</td>
<td>12</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>
Thus, except in certain centers in the United States, hyperfractionation is not part of routine practice in the treatment of head and neck cancer.

**Accelerated Treatment**

When untreated human tumors are observed, their volumes increase relatively slowly, and volume doubling times can range from 25 to 100 days. Such findings led clinicians to the view that cell proliferation during a conventional course of radiotherapy was not of importance in determining outcome. In the 1980s, however, a study of the cellular proliferation of human tumors using bromodeoxyuridine, showed that the potential doubling times of the tumors were much more rapid, with a median time in head and neck cancer of 5.1 days [5, 6]. The difference between the volume doubling time and potential doubling time is accounted for by cell loss in the unperturbed tumor, but when an effective treatment is given, the cell loss may diminish and the potential doubling time realized, causing repopulation during treatment.

Clinically, this hypothesis was supported by the work of Maciejewski [7, 8] and Withers, who showed that with increasing overall time the total dose to cure a tumor of the head and neck area had to be raised; this was attributed to repopulation, which may not be important until the third week of a course of treatment. Following this work, many other reviews of retrospective studies have shown a reduction in tumor control with increasing overall time, which has been estimated to be as much as 14% per week [9]. Accelerated regimens with shortened overall duration of treatment were therefore investigated with the aim of reducing the time in which cellular repopulation could occur.

**Acceleration**

There are four major strategies for accelerating radiotherapy:

- **Pure acceleration** using a dose per fraction of 1.8 Gy to 2 Gy.
  - Using more than one treatment per day.
  - Treating once per day on six to seven days of the week.
- **Acceleration using a split-course treatment.**
- **The concomitant boost.**
- **Accelerated hyperfractionated radiotherapy.**

**Pure Acceleration**

To achieve accelerated radiotherapy, Peracchia and Salti and, subsequently, Olmi, treated a group of patients with 2 Gy three times per day to a total dose of 54 Gy to 56 Gy within two working weeks [10, 11]. Despite the reduction in total dose, acute reactions were severe and in a number failed to heal, leading to consequential necrosis. There was no improvement in overall survival with a high incidence of late morbidity, which led to the conclusion that the dose intensity was too great if the dose per fraction was not reduced below 2 Gy when multiple treatments were given per day.

Lamb et al. reduced the dose per fraction to 1.8 Gy and treated three times per day to a total dose of 58 Gy in 3.5 weeks with increased acute morbidity but no report of severe late morbidity so far [12].

An alternative strategy is to achieve a modest acceleration by treating daily on more than five days of the week. A study by the Danish Head and Neck Study Group has given six treatments of radiotherapy per week. In some centers this has been achieved by treating on Saturdays and in others, twice on another day. This strategy leads to a modest decrease in overall time, and 66 Gy has been achieved in five and one-half weeks. In this study, there have been no problems with acute or late morbidity, and local tumor control appears improved [13].

In contrast, Maciejewski in Poland treated seven days of the week including weekends, giving 70 Gy in five weeks. This resulted in an unacceptable level of acute morbidity and has not only failed to effect healing but has gone on to consequential late morbidity [14]. A modification of this trial has been made, and the dose per fraction has been reduced to 1.8 Gy with a lessening of the morbidity; the trial currently continues [15].

**Acceleration Using a Split**

The difficulties in obtaining a satisfactory total dose when using a dose per fraction between 1.8 Gy and 2 Gy led to the use of a lower dose per fraction combined with a rest period during treatment to allow the normal tissues to recover (split-course). van der Schueren and his group observed the reactions to be seen in patients with head and neck cancer given accelerated radiotherapy and established a regimen in which 1.6 Gy was given three times daily for two working weeks to a total dose of 48 Gy. This was followed by a gap of four weeks during which reactions settled, followed by a boost dose to a total dose of 67 Gy to 72 Gy in an overall time of 47 days [16]. A large randomized controlled trial was carried out by the EORTC comparing the split-course treatment with 72 Gy in seven weeks and failed to show any advantage to the accelerated arm [17]. It should be noted, however, that the overall duration of treatment was similar in both groups, and repopulation in tumors as well as normal tissues during the four-week gap may well have resulted in such a tumor burden that the final dose was inadequate to eradicate residual tumor cells.

Other workers are, however, using similar regimens: Wang et al. gives a dose of 1.6 Gy twice daily to 38.4 Gy, with a short rest period during the third and fourth week to be followed...
with a boost dose to 64 Gy [18, 19]. This accelerated radiotherapy schedule with a split forms one of the arms of the Radiation Therapy Oncology Group (RTOG) randomized controlled trial.

In an effort to overcome the deleterious effect of a long split in the middle of treatment, the EORTC devised a new accelerated fractionation schedule which was designed with a short split after the first week of treatment and achieved 70 Gy over five weeks. This was tested in a randomized controlled trial compared with 70 Gy in 35 fractions over seven weeks in patients with T2, T3, and T4 head and neck tumors (excluding hypopharynx) who had a performance status of 0, 1, or 2. The results of this trial were published by Horiot in 1997 and reported a significant improvement in locoregional control to the accelerated arm. At five years, the locoregional control gained was 13%, representing a 24% reduction in the risk of local failure. Acute morbidity was acceptable, but there was a surprising increase in severe late morbidity which occurred in 14% of the accelerated arm compared with 4% of patients in the conventional arm. Time to severe late toxicity was also significantly shorter on the accelerated arm, and this increase in morbidity has offset any improvement in locoregional control [20]. From this study, it can be concluded that even with a reduced dose per fraction, a total dose of 70 Gy cannot be achieved in five weeks without unacceptable morbidity.

CONCOMITANT BOOST

Generally in radiotherapy, and particularly in the management of head and neck tumors, a reducing field technique is employed during radiotherapy. During the first phase, the tumor and areas at risk of microscopic involvement are irradiated; following this, a smaller volume is irradiated to include the areas of known tumor with a margin. In this way, the smallest possible volume is given the highest dose, minimizing problems that may occur due to late radiation morbidity.

At the MD Anderson Cancer Center in Houston, Texas, the overall duration of treatment has been reduced from seven and one-half to six weeks by giving the boost as a second treatment of the day during the main course of treatment [21]. Following pilot studies in which the boost was given during various phases of the main, it was found that the best results were achieved by boosting during the last two weeks. A pilot study in oropharyngeal carcinoma has yielded promising results, and this regimen is now also incorporated in the RTOG fractionation trial in head and neck cancer [22].

HYPERFRACTIONATED ACCELERATED RADIOTHERAPY

The Cancer Treatment Center at Mount Vernon Hospital, in collaboration with colleagues at the Gray Laboratory, introduced a novel scheme of radiotherapy—continuous, hyperfractionated, accelerated radiotherapy (CHART)—aimed at achieving the greatest chance of eradicating tumor with the minimum of late side effects by significantly reducing the dose per fraction to 1.5 Gy and completing the treatment in two weeks, treating three times per day including the weekends, to a total dose of 54 Gy. Initial pilot studies gave promise for improved local tumor control in locally advanced head and neck cancer [23], and randomized controlled trials of CHART versus conventional radiotherapy (66 Gy in six and one-half weeks at 2 Gy per fraction daily, Monday to Friday) were carried out under the auspices of the Medical Research Council between April 1990 and April 1995. Nine hundred and eighteen patients with squamous cell carcinoma of the head and neck were entered by 13 cooperating centers in the United Kingdom and Europe.

There was no overall benefit in terms of locoregional control; a slight, nonsignificant improvement in local tumor control being offset by a reduction in nodal control. In subgroup analyses, however, patients with advanced T3/T4 carcinoma of the larynx and those with well and moderately differentiated tumors had a significant improvement in local tumor control [24].

Acute morbidity in terms of mucositis and dysphagia were acceptable, with no incidence of sequential necrosis. In follow-up, late morbidity was reduced after CHART, particularly in terms of mucosal ulceration, laryngeal edema, and subcutaneous change. Severe late morbidity was low in both arms of the study; osteoradionecrosis was seen in only 0.4% of patients in the CHART arm and 1.4% in the conventional arm. Likewise, the incidence of cartilage necrosis was low and equal in both arms of the study. Nine patients developed Hermitte’s sign, five treated with CHART and four with conventional radiotherapy. In all cases except one, the symptoms have settled and there has been no incidence of radiation myelitis. In head and neck cancer, therefore, continuous, hyperfractionated, accelerated radiotherapy gave local tumor control with a dose of 54 Gy in 12 days equal to that of 66 Gy in 47 days. 12 Gy of radiotherapy is therefore necessary to overcome the repopulation that took place between days 12 and 47 and this amounts to 0.3 Gy per day if repopulation takes place over the whole time; 0.6 Gy per day if it begins in the third week.

In summary, the CHART trials show that repopulation is an important cause of locoregional failure in head and neck cancer, and a higher dose than 54 Gy has to be achieved if there is to be an improvement in locoregional control. The accelerated fractionated study recently completed by the EORTC has, however, shown that 70 Gy cannot be achieved in five weeks without any increase in late morbidity.

CONCLUSIONS

There is now a great body of data related to altered fractionation studies in head and neck cancer. One of the confounding
factors in all these trials is that of the interfraction interval. When we began the CHART trials, recovery of sublethal injury in human tissues was thought to take place with a half-time of one to one and one-half hours as found in rodents [25]. Our work with CHART gave an unexpected incidence of radiation myelitis which further research in spinal cord tolerance has shown to be due at least in part to a slow component of repair of sublethal injury leading to unexpected morbidity [26, 27]. In support of this, N’Guyen had reported unacceptable morbidity with an interfraction interval of 2 h [28]. At Mount Vernon, we are currently reviewing the CHART database and are showing that in human normal tissues, the half-time of repair may be as long as 4 h; this will mean that the interfraction interval is vital for future studies.

The results of the RTOG randomized controlled trial of fractionation in head and neck cancer is awaited. More than 1,000 patients have been randomized to one of four arms—conventional, hyperfractionated, concomitant boost, or acceleration with a split, the results of which will expand the database considerably. At Mount Vernon, we are gathering together the databases from six randomized controlled trials of altered fractionation in head and neck cancer with the aim of unraveling the tumor and normal tissue characteristics in humans which determine the outcome of radiotherapy; we can thus model new schedules which may be brought into clinical practice with the hope of a therapeutic benefit.

20 Horiot JC, Bontemps P, van den Bogaert W et al. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother Oncol 1997;44:111-121.


