Benefits of Accelerated Hyperfractionation for Head and Neck Cancer

Bernard J. Cummings

From the Department of Radiation Oncology, The Princess Margaret Hospital/University of Toronto, Toronto, Ontario, Canada

Correspondence to: Dr Bernard J. Cummings, Department of Radiation Oncology, Princess Margaret Hospital, 610 University Avenue, Room 4-819, Toronto, Ontario, Canada M5G 2M9. Tel: + 1 416 946 21 29. Fax: + 1 416 946 20 38.

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Accelerated hyperfractionation is a strategy intended to improve the likelihood of cancer control by delivery of a higher total dose of radiation without an offsetting increase in severe late normal tissue complications. The early results of a recently completed randomized trial of a 4-week hyperfractionated radiation schedule, and of two other regimens of accelerated hyperfractionation, confirm to some degree the biological hypotheses on which this strategy is based. The clinical benefits seen so far are limited, but are sufficient to support further refinement of the strategy and additional clinical trials.

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Alterations to conventional once-daily, five fractions a week, radiation schedules play a major part in current clinical research into the treatment of squamous cell cancers of the head and neck. The rationale for modifying fractionation continues to evolve, and has been revised many times as new information becomes available (1, 2). The premises underlying studies now being implemented were not all known when the clinical trials discussed in this presentation were designed. However, it is by our present understanding of radiobiology that the outcomes of these trials must be interpreted. Accelerated fractionation may be defined as a radiation schedule in which the overall treatment time is reduced, relative to the schedule with which it is compared. The standard of comparison is variously, and arbitrarily, taken to be either the schedule used in the center conducting the study, or the schedule 'commonly' used in some reference community. Hyperfractionation describes an increase in the number of fractions delivered in the same overall treatment time as the comparative standard. Some suggest that each hyperfraction should be less than 1.8 Gy, the lowest conventional once per day dose fraction in common use. Although a hyperfractionated schedule may be defined narrowly as delivering the same radiation dose as the conventional standard, there is little agreement on whether this should be the 'same dose' in total Gray or measured by some clinical endpoint such as the level of morbidity or tumor control. Hybrids of acceleration and hyperfractionation are common and generally result in complex alterations of conventional radiation schedules.

The current biological bases for accelerating and/or hyperfractionating radiation may be summarized broadly as follows (adapted from (1)): (a) Tissues differ in their response to radiation, both in the mechanisms by which they are damaged and in their ability to repair. Slowly proliferating tissues (for example, the spinal cord) are generally better able to repair sublethal damage than are acutely responding tissues (for example, the mucosa of the upper air and food passages) and, probably, most epithelial cancers of the head and neck. An important effect of radiation injury on acutely responding tissues is to trigger accelerated repopulation by the surviving cells. Epithelial cancers also demonstrate accelerated repopulation although this phenomenon appears to start somewhat later than repopulation in normal tissues. The longer the overall treatment time, the more likely is significant repopulation of a cancer by surviving cells. The delay to the onset of repopulation in normal tissues and tumors may be shortened if the initial rate of damage is more than usually severe. In more rapidly proliferating normal tissues and tumors, cell cycle redistribution leads to some degree of sensitization relative to the absence of such redistribution in non- or very slowly proliferating tissues. Whilst tissue hypoxia affects response to radiation, the time-course of reoxygenation as a tumor shrinks is difficult to determine, but is probably not affected adversely by shortening radia-

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tion schedules within the limits so far tested in clinical trials. (b) The response to radiation in 'early' and 'late' responding tissues can be manipulated by altering the dose of each fractional increment. By delivering smaller than conventional fractional doses (considered to approximate the range 1.8 Gy to 3 Gy), and allowing sufficient time between fractions for substantial repair of sublethal damage (currently considered to be ≥ 6 h), it is theoretically possible to give a higher total radiation dose without a corresponding increase in late sequelae. Acute reacting normal tissues are not protected to the same extent by such reductions in the fractional dose. The greater total radiation dose delivered by the hyperfractionated schedule should result in an increased likelihood of controlling the cancer. There is some offsetting increased intensity of reaction in acutely responding normal tissues, which can be managed in a variety of ways. However, increases in long-lasting serious late morbidity are lessened by the use of the smaller 'hyperfractionated' dose increments, leading to a net benefit.

The assessment of benefits of a medical treatment should properly include formal cost-expense and cost-benefit analyses. Whilst it is basically easy to say that, for example, a treatment schedule which delivers twice the number of fractions in half the overall time will 'cost' the same as the conventional standard, this is true only with respect to the number of treatment fractions actually delivered by a machine. The interests of patients, physicians, administrators and the public will not be congruent in the assessment of the benefits of accelerated hyperfractionation, as they are not for nearly every medical treatment.

In this presentation, the results of a randomized trial of hyperfractionated radiation, in a schedule also considered accelerated by some commentators, conducted at the Princess Margaret Hospital, Toronto (PMH), will be compared descriptively with other regimens also categorized as accelerated and hyperfractionated. Benefits and disadvantages will be considered by clinical outcomes rather than monetary costs.

THE PRINCESS MARGARET HOSPITAL TRIAL

The general philosophy of management of head and neck cancer followed for many years at PMH is primary radiation therapy, with surgery reserved for the treatment of residual or recurrent cancer (3). This philosophy is based on the desire to preserve normal anatomy and function to the greatest extent possible. Careful follow-up and use of salvage surgery have resulted, in general, in survival rates comparable with those of other philosophies of management of head and neck cancer. The radiation dose used at PMH has been generally somewhat less than that in many centers because the philosophy included the intent to minimize the risks of salvage surgery that might be required at varying intervals after radiation. The dose is, however, greater than that usually adopted in protocols of planned combined preoperative radiation and surgery. The basis of radiation treatment practice at PMH between about 1970 and 1990 was a standard prescription of 50 Gy in 20 fractions, each of 2.5 Gy, delivered at the rate of 5 fractions per week, Monday to Friday, one fraction per day, over a total elapsed time of 4 weeks (equivalent to 51 Gy TAD prescribed according to the ICRU 29 convention (4) adopted at PMH in 1988). The dose prescribed was the same for both large and small tumors, and whether or not there were regional node metastases. The total and fractional doses and the number of fractions were not changed to compensate for unscheduled interruptions.

During the 1980s, the results of this philosophy were reviewed closely and compared with those published by other centers. One such review was a formal evaluation of the outcome of different total dose and conventional once daily fractionation schedules for squamous cell cancer of the tonsil (5). In this analysis, the PMH schedule of 51 Gy in 20 fractions over 4 weeks was found to result in local control rates (with radiation only, excluding the effects of salvage surgery) comparable to those of higher total doses and more prolonged overall treatment schemes for primary tumors up to 4 cm in size (UICC category T1 and T2, (6)). However, the PMH schedule was less effective for larger tumors (category T3) (JM Taylor, pers. comm. 1995).

The philosophy of management at PMH was also influenced by other developments. Starting about 1980, the potential biologic advantages of accelerated treatment and hyperfractionation were discussed extensively (7, 8). Early in the decade the preliminary results of a randomized trial of hyperfractionated radiation for squamous cell cancers of the oropharynx conducted by the EORTC were presented (9). Several non-randomized clinical studies of hyperfractionation, with or without acceleration, for a variety of head and neck cancers were also reported (10, 11). These results supported the use of higher total radiation doses, delivered by more than one treatment fraction per day, without extension of the overall time taken to administer conventional standard radiation treatment.

In 1987, the Head and Neck Group at PMH designed a trial in which hyperfractionated radiation would be compared with once daily treatment, within the framework of the 4-week schedule with which we were familiar (12). The strategy adopted was to deliver a higher total dose of radiation in 4 weeks, but to reduce the risk of increased late sequelae by hyperfractionation. Although we at PMH considered this principally a trial of hyperfractionation, with escalation of total dose within the same 4-week overall treatment time as our standard schedule, some commentators regard the 4-week overall time favored at PMH as accelerated in comparison with the 6- to 8-week schedules common in many other centers. Hence, the PMH trial may contribute information relevant to future studies of both accelerated and hyperfractionated radiation schedules.

Initial feasibility studies established that a dose of 58 Gy TAD, as 40 fractions, each of 1.45 Gy, delivered at the

rate of two fractions a day separated by 6 h or more, 5 days a week, over a total time of 4 weeks, was tolerable, although fairly intensive supportive care in the form of analgesics and feeding gastrostomy was often necessary. The volume of mucosa treated was typically large since all of the jugular lymph node chains were included. Those eligible for the trial had biopsy proven squamous cell cancer arising in the larynx, hypopharynx or oropharynx; UICC 1987 primary tumor categories T3 or T4 without regional node metastases, or any T category with clinical regional lymph node metastases; no distant metastases; age not less than 18 or more than 75; and gave informed consent to participation in the study. Patients were randomized either to conventionally fractionated radiation (CF) (51 Gy TAD/20 fractions of 2.55 Gy, one per day, 5 days per week/4 weeks), or hyperfractionated radiation (HF) (58 Gy TAD/40 fractions of 1.45 Gy, 2 fractions per day separated by 6 hours, 5 days per week/4 weeks). The spinal cord was shielded from the direct beam (Cobalt 60 or 6 MV photons) after 34.8 Gy in the hyperfractionated schedule and 35.7 Gy in the conventional prescription.

The primary endpoints of the trial were the locoregional control rate at 5 years and the late toxicity rate. The study was designed to identify an improvement in locoregional control from 35% (the level previously observed at PMH with radiation alone in this group of patients) to 50%, at conventional levels of statistical significance. The target accrual was met and 336 patients were randomized between 1988 and 1995. An interim analysis, based on intention to treat, with a median follow-up of 3 years, showed an absolute improvement of 5% in locoregional control rates with HF (a relative improvement of 12.5%), which was not statistically significant. A secondary analysis indicated that the improvement seen was in the control rate for the primary tumors rather than the regional node metastases. Acute mucosal toxicity, RTOG Grade 3 or 4, occurred in 63% of those who received HF versus 40% with CF. The time course of the development and regression of mucositis was similar with both fractionations. Other measures of acute toxicity such as skin reactions, and the ability to maintain adequate nutrition without intravenous or gastrostomy supplementation, were similar with both schedules. The actuarial 3-year rate of late toxicity (RTOG Grade 3 or 4) was not increased in the HF group (6% versus 11%, $p = 0.18$). The risk of post-surgical morbidity in those patients who underwent salvage surgery was comparable in each group (13). Unexpectedly, there was a significant advantage for HF over CF in the 3-year overall survival rate (53% versus 38%, $p = 0.02$). However, the improvement in cause-specific survival rates was less marked (59% versus 51%, $p = 0.10$). The difference in overall survival rates appeared to be due in large part to a preponderance of deaths from unrelated causes (other cancers, cardiovascular disease, etc.) in those who received CF. We concluded from this interim analysis that the HF schedule used was tolerable, and resulted in some improvement in the probability of control of the primary cancer and in cause-specific survival.

THE UNITED KINGDOM AND EUROPEAN TRIALS

Two other randomized trials have addressed the merits of accelerated hyperfractionation. In one, a very short overall treatment time of 12 days was adopted, about one-third to one-half of the time it would have taken to deliver the total dose of 54 Gy by conventional fractionation (14). Because of the increase in acute normal tissue reactions produced by this degree of acceleration, the total dose was less than that used in the conventionally fractionated control arm in this study. In the other trial, overall time was shortened by 14 days, from 7 weeks to 5 weeks (15). The increased severity of acute mucositis was managed by introducing a 12-day interruption in treatment. The reports from these trials present contrasting results.

The trial conducted on behalf of the United Kingdom Medical Research Council on continuous hyperfractionated accelerated radiation therapy (CHART) called for the delivery of 54 Gy total dose with 3 fractions each day of 1.5 Gy, at intervals of 6 h, over a total elapsed time of 12 days, without interruption for weekends (14). This was compared with a conventional schedule of 66 Gy, at the rate of a single fraction of 2 Gy per day, 5 days per week, over 45 days. Nine hundred and eighteen patients with squamous cell cancers from all head and neck sites were entered. Only patients with category T1 N0 tumors were excluded. There were no differences in local or regional control rates, or in overall survival rates, at 5 years. Acute morbidity, particularly mucositis, was increased with the CHART prescription, but was considered tolerable. The risk of late morbidity observed in various tissues was less or similar to that of conventional fractionation.

The European Organization for the Research and Treatment of Cancer (EORTC) reported the results of a trial of split-course hyperfractionated accelerated radiation (SCHAR) (EORTC 22851) (15). Patients received a total of 72 Gy at the rate of 1.6 Gy, 3 times a day at intervals of not less than 4 h, 5 days a week, over a total time of 35 days. The split-course design was based on observations of the severity of acute mucositis produced by accelerated hyperfractionation in a previous EORTC study (16). In the first part of the trial of SCHAR, patients received 28.8 Gy in 18 fractions over 8 days (15). Following a recovery period of 12 to 14 days, the balance of the treatment was delivered—43.2 Gy in 27 fractions in 17 days. This schedule was compared with a CF of 70 Gy as 35 fractions each of 2 Gy, 1 fraction per day, 5 days a week, over 49 days. Five hundred and twelve patients with squamous cell cancer of the head and neck, excluding those whose primary tumor arose in the hypopharynx or nasopharynx, were randomized. In contrast to the UK experience, the

locoregional control rate at 5 years was improved by the SCHAR schedule (59% versus 46%, $p = 0.02$). Benefit was seen principally in improved control of the primary cancers rather than of regional node metastases (J. C. Horiot, pers. comm. 1997). There was no difference in overall survival rates, but cause-specific survival marginally favored accelerated hyperfractionation ($p = 0.06$). Acute morbidity, particularly mucositis, was increased by the experimental schedule but was tolerable with the 2-week interruption in radiation after 8 days. However, this schedule was not considered suitable for further study because of the unanticipated finding of a greatly increased risk of EORTC Grade 3 or 4 late morbidity, particularly fibrosis and/or neuropathy and/or mucosal necrosis or edema. The actuarial incidence of severe late morbidity in those treated by SCHAR was 50% at 5 years.

DISCUSSION

These three randomized trials examined markedly different radiation schedules (Table 1). There were numerous other differences also, including accession criteria. A qualitative descriptive comparison indicates that it is possible to deliver potentially curative doses of radiation by accelerated hyperfractionated schedules over total times ranging from 2 to 5 weeks. The principal acute toxicity reported in all three trials was mucositis with its secondary effect on nutrition, and active supportive care was often required. In each study, 85% or more of the patients completed the experimental protocol as prescribed. This is not surprising in that all three experimental schedules were designed on the basis of prior pilot or randomized studies. However, when late sequelae are considered, the findings in one study were unexpected. The EORTC investigators found an unacceptable risk of clinically significant late morbidity, whereas in both the PMH and CHART studies the risk of late morbidity was not increased by the accelerated hyperfractionated schedules used, and may even have been reduced (as would be predicted by theory, provided the total dose was not excessive). It has been suggested that the interval of only 4 h required between fractions in the EORTC trial, compared with 6 h in the other studies, may not have allowed adequate repair of sublethal damage between fractions, thereby increasing the severity of acute morbidity and leading to residual damage which was scored as late toxicity (17). However, variations in all radiation prescription factors between the trials are such that at present the causes of the differences in late toxicity observed are speculative.

Although only the EORTC investigators reported an improvement in locoregional control rates that reached conventional levels of statistical significance, relative differences at 3 years ranging between about 10% to 25% favored accelerated hyperfractionation for control of the primary tumor in all three trials. The reasons why the experimental schedules appear to have influenced the eradication of the primary cancer and not of lymph node metastases are not known and require further investigation. Two of the studies suggested improved local control was more likely to be seen in larger tumors (14, 15), whereas the reverse was seen in a sub-analysis of the PMH study (12). There was a relative advantage for the experimental protocol with respect to cause-specific survival rates in the two studies for which this parameter was reported (12, 15). An overall survival advantage for accelerated hyperfractionation was seen in the PMH study, probably not related to the experimental radiation schedule, but was not observed in either of the other trials.

The clinical benefits and disadvantages of the three accelerated hyperfractionation schedules studied are those outlined above. Much more detailed analyses would be required to produce a reliable cost-benefit analysis. The financial costs to the treatment center of CHART have been studied (18). The costs of medical care in the first 3 months of those treated by the CHART regimen were

Table 1

Summary of three randomized trials of accelerated hyperfractionation for head and neck cancer

	EORTC 22851 (15)	CHART (14)	PMH (12)
AHF	72 Gy/1.6 × 3@4 h/5 w 5 d/w, split course	54 Gy/1.5 × 3@6 h/12 d continuous	58 Gy/1.45 × 2@6 h/4 w 5 d/w
Conventional RT	70 Gy/2.0 × 1/7 w	66 Gy/2.0 × 1/6.5 w	51 Gy/2.55 × 1/4 w
Total patients	512	918	336
Locoregional control	AHF 59% vs 46%, $p = 0.02$	~45%, no difference	AHF 45% vs 40%, $p = 0.14$
Overall survival	~25%, no difference	~42%, no difference	AHF 53% vs 38%, $p = 0.02$
Cause-specific survival	AHF 45% vs 32%, $p = 0.06$	Not stated	AHF 59% vs 51%, $p = 0.10$
Acute toxicity (mucositis)	AHF increased	AHF increased	AHF increased
Late sequelae	AHF 50% vs 15%, $p < 0.001$	AHF reduced or same	AHF 6% vs 11%, $p = 0.18$

EORTC and CHART = 5-year results; PMH = 3-year results.
AHF = accelerated hyperfractionation; RT = radiation therapy.

Table 2

Overview of randomized hyperfractionation trials for head and neck cancer

Study	HF schedule (all 2×/day)			Deaths in HF Odds ratio	Locoregional failures in HF Odds ratio
	Total Gy	Fraction Gy	Time		
Sanchiz et al. (20)	70.4	1.1	6 w	0.35*	0.27*
EORTC 22791 (21)	80.5	1.15	7 w	0.77	0.47*
Datta et al. (22)	79.2	1.2	6.5 w	n.a.	0.30*
Pinto et al. (23)	70.4	1.1	6.5 w	0.61	0.62*
Pooled				0.48* 95% CI (0.40–0.58) $p<0.0001$	0.35* (0.28–0.45) $p<0.0001$
PMH	58	1.45	4 w	0.71*	0.77

Abstracted from Stuschke & Thames (19).
HF = hyperfractionated radiation; * $p<0.05$; n.a. = not available.

£1 100 greater than the costs of conventional fractionation. The investigators considered this increase modest and potentially reducible. While the outcomes of the trials described suggest that there is merit in further studies of the accelerated hyperfractionation strategy, they do not provide sufficient evidence to conclude that such schedules are to be preferred at this time to conventional fractionation, nor is it apparent which of the very different approaches to scheduling radiation is likely to be the most useful.

At PMH, we have for many years considered treatment over 4-weeks as 'standard' for advanced head and neck cancer. Accordingly, we would classify the trial we conducted as a study of hyperfractionation rather than of accelerated hyperfractionation. It is only when the PMH radiation schedules are compared with certain external standards that they are considered accelerated (and comparison with a 3-week conventional schedule would lead to the PMH 4-week schedule being labeled 'protracted'!). The authors of a recent overview of trials of hyperfractionation concluded that there are significant advantages to hyperfractionation without significant acceleration in reduction of either the odds of death or locoregional failure (19). A summary of that analysis is presented in Table 2, to which have been added the data from the PMH trial, analyzed in the same way. Other reviewers who expressed a contrary view considered that the evidence to support the use of hyperfractionation was inconsistent and that increases in late toxicity may offset any improvement in tumor control (24). We are of the opinion that there is merit to hyperfractionation.

The principal objectives of our next study at PMH are to increase the likelihood of primary tumor control, particularly as it affects preservation of the larynx, and to maintain or improve cure rates. These outcomes will be sought through an increase in the total radiation dose. In order to ensure that the level of acute mucositis is tolerable, and the risk of late residual toxicity minimized, smaller areas of oral and pharyngeal mucosa will be exposed to the higher doses than in the PMH trial described earlier. Smaller treatment volumes focused on the primary tumor will be used. This, together with the failure of trials of altered fractionation to demonstrate improved control of regional lymph node metastases, has led us to decide to make much greater use of planned surgery for management of the regional lymph nodes. We intend to continue to study relatively short overall treatment times of the order of 4 weeks because of the theoretical biologic advantages and the preference of patients for shorter overall treatment times.

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