Journal of Radiotherapy in Practice

Journal of Radiotherapy in Practice (2008)
7, 31–38

doi: 10.1017/S1460396907006231

Original Article

Gap compensation during accelerated hypofractionated radiotherapy in head and neck cancer

Paul Sanghera[1], John Arnfield[1], Chris McConkey[2], Andrew Hartley[1]

[1]*Cancer Centre, Queen Elizabeth Hospital, Birmingham, UK,* [2]*Clinical Trials Unit, University of Warwick, UK*

Abstract

Introduction: In squamous-cell carcinoma (SCC) of the head and neck, unplanned gaps risk prolongation of the overall treatment time (OTT) and reduction in tumour control. This audit determines whether further acceleration can safely be employed to compensate for missed treatments during accelerated hypofractionated radiotherapy.

Methods: Patients receiving accelerated hypofractionated radiotherapy for SCC of the head and neck were prospectively audited. Outcome measures were OTT, degree of compensation and acute toxicity determined by incidence of grade 3 mucositis, prolonged grade 3 mucositis, grade 3 dysphagia and pain.

Results: In the 87 patients identified, the dose administered was 55 Gy in 20 fractions (81 patients), 50 Gy in 20 fractions (1 patient) and 50 Gy in 16 fractions (5 patients). Of those patients receiving 20 fractions, 94% completed within 28 days. Grade 3 mucositis was seen in 56 patients (64%). Compensating for unplanned gaps did not result in any significant increase in toxicity. Administering 6 fractions/week, as compensation, was associated with a lower pain score ($p = 0.003$) as was receiving 2 fractions on the same day ($p = 0.0004$).

Conclusions: Accelerated hypofractionation is tolerable with most patients completing treatment within the planned OTT. When unplanned gaps occur, then compensation by further acceleration is possible.

Keywords

Acceleration; head and neck cancer; hypofractionation; Radiotherapy; squamous-cell carcinoma

INTRODUCTION

Overall treatment time (OTT) is an important factor in successful tumour control for squamous-cell carcinomas (SCCs) of the head and neck. Accelerated repopulation, predicted to occur 3–4 weeks from the start of radiotherapy, becomes a significant factor in prolonged treatment schedules.[1] Such tumour-cell repopulation could compromise the local control particularly if the OTT goes beyond the intended duration.[2,3] Accelerated fractionation has been shown to improve tumour control.[4,5]

In the United Kingdom, there are a variety of radical radiotherapy schedules in use including the accelerated hypofractionation schedule,

Correspondence to: Andrew Hartley, Cancer Centre at Queen Elizabeth Hospital, Birmingham B15 2TH, UK. Email: Andrew.Hartley@uhb.nhs.uk

55 Gy in 20 fractions for 4 weeks, which aims to complete treatment before accelerated radiotherapy becoming a significant factor. The reduction in the number of fractions spares resources and this may help to reduce waiting times, another factor in local tumour control.

Predictable gaps in treatment may occur owing to bank holidays and machine service days. In addition, there may be less predictable gaps owing to patient illness and machine breakdown. The Royal College of Radiologists, United Kingdom, issued guidelines for dealing with such gaps[6] and each department should have a local policy to follow in such situations. Ideally, compensation of some description should be planned at the outset for predictable gaps. A recent survey confirmed that most departments in the United Kingdom have a policy in place to handle such interruptions.[7] A common practice is to compensate gaps with either two treatments in the same day or, assuming treatment is confined to 5 days/week, an extra treatment at the weekend. If this is not practical, then radiobiological modelling should be used to prevent prolongation of schedules.[8]

When a gap occurs during a hypofractionated schedule, the safety of further acceleration to maintain the OTT is unknown. The use of large doses per fraction when administering more than 5 fractions in 1 week and, in particular, 2 fractions in the same day raises the concern of acute and late toxicity.

The aim of this study was to assess whether safe compensation is possible for patients experiencing a gap during hypofractionated radiotherapy for head and neck cancer. In this article, the term ''gap'' will encompass both predictable breaks in treatment, such as bank holidays, and non-predictable breaks, such as those arising through patient toxicity.

All patients were treated with radical intent in a beam-directional shell using either conventional or CT planning. Two lateral fields were used to treat the upper neck with a matched anterior field where appropriate. Electrons were used to treat the posterior neck after the first 12 fractions. The intended radiotherapy dose to the primary tumour and involved nodes was 55 Gy in 20 fractions; 50 Gy in 20 fractions to the neck after preoperative neck dissection; 41.25 Gy in 15 fractions as a prophylactic dose to clinically negative nodal areas. During the study period, patients with locally advanced disease were considered for chemotherapy concurrently with radiotherapy. Earlier, patients were treated with methotrexate in which two doses of methotrexate 100 mg/m^2 were planned for day 1 and day 14 of radiotherapy. Later, patients were treated with two doses of carboplatin, given on day 1 and day 21.[1]

METHODS

Data collection

All patients under the care of a single consultant (AH) receiving accelerated hypofractionated radiotherapy for SCC of the head and neck, between November 2002 and January 2005, were identified. The tumour sites included were oral cavity, oropharynx, larynx and hypopharynx. Oral cavity and oropharynx were grouped together as were hypopharynx and larynx. Acute-toxicity data were collected prospectively.

The main outcome measures were acute toxicity, OTT and degree of compensation. Toxicity was evaluated according to the National Cancer Institute common toxicity criteria.[9] Acute toxicity was determined by the incidence of grade 3 mucositis, prolonged grade 3 mucositis, grade 3 dysphagia and pain. Patients were reviewed weekly and prolonged grade 3 mucositis was defined as lasting for 4 weeks or longer. Mucositis grade was confirmed using weekly naso-endoscopic examination in the case of laryngeal and hypopharyngeal tumours. Pain was scored by use of analgesia (see Table 1). Other data collected included age, site of primary tumour, length of field and use of concurrent chemotherapy.

https://doi.org/10.1017/S1460396907006231 Published online by Cambridge University Press

Table 1. Pain scoring system used based on analgesic use

Analgesia	Score
Mouthwash*	1
Cocodomol	2
Tramadol	3
Oramorph	4
Fentanyl 25	5
Fentanyl 50	6
Fentanyl 75	7
Fentanyl 100	8

*Aspirin, glycerine and sucrulfate mouthwash.

Table 2. Patient characteristics

Characteristic	
Gender	
Male	70
Female	17
Age	
Median	58 years
Range	31–80 years
UICC stage [No. of patients (%)]	
1	11 (13%)
2	23 (26%)
3	17 (20%)
4	36 (41%)
Site	
Oral/Oropharynx	37
Larynx/Hypopharynx	50

Table 3. Treatment time for patients receiving 20 fractions

Overall treatment time (days)	Number of patients
Patients receiving 20 fractions	
25	61
26	1
27	4
28	11
30	2
31	3
Patients receiving 16 fractions	
21	3
22	1
23	1

Analysis

Each of the above end points was assessed independently against OTT, field length, total dose, concurrent chemotherapy and site of primary tumour: oral versus laryngeal. Associations were assessed by Pearson's χ^2 test and the Wilcoxon test. Linear regression was used to identify factors affecting the pain score and logistic regression to analyse the presence of grade 3 toxicity.

RESULTS

Patients

Table 2 shows the patient characteristics. Eighty-seven patients meeting the above criteria were identified and analysed. The median age of patients was 58 years (range 31–80 years). The distribution of primary disease was as follows: oral/oropharynx, 37 patients and larynx/hypopharynx, 50 patients. Concurrent chemotherapy was administered in 35 patients.

The stage distribution, according to the sixth edition of UICC TNM classification of malignant tumours, is also given in Table 2 and was as follows: stage I, 11 patients; stage II, 23 patients; stage III, 17 patients and stage IV, 36 patients.

Radiotherapy dose, treatment time and field length

The total dose administered was as follows: 55 Gy in 20 fractions in 81 patients, 50 Gy in 16 fractions in 5 patients and 50 Gy in 20 fractions in 1 patient. The median field length was 9.7 cm (5.9–15.5 cm) and this remained unchanged when excluding patients receiving 50 Gy in 16 fractions. The median time taken to complete treatment was 25 days (20–29 days). Of the 82 patients receiving 20 fractions, 77 (94%) completed treatment within 28 days and 61 (74%) within 25 days. The median time for those receiving 16 fractions was 21 days (range 21–23 days). The details of the time taken to complete treatment are given in Table 3.

Interruptions to radiotherapy and compensation

Fifty-three patients completed treatment without any gap occurring while a total of 62 gaps occurred in the remaining 34 patients (see Table 4). In those patients experiencing a gap,

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the distribution was as follows: single gap, 17 patients; 2 gaps, 8 patients; 3 gaps, 7 patients; and 4 gaps, 2 patients. No patient had more than 4 gaps. Compensation, in the form of an extra fraction of the same dose to prevent prolongation of the OTT, was performed in 25 of the 34 patients experiencing a gap. Thirty-five such fractions were delivered to compensate for the 62 gaps occurring and thus 56% were compensated for overall. Details of compensation are given in Table 5. No patient received any further altered fractionation as a method of compensating for a gap.

Of the 61 patients receiving 20 fractions and completing within 25 days, 47 did not have a gap while 14 required compensation to complete on time. Twenty-one patients having an interruption to their therapy did not complete on the time.

The reasons for gaps are detailed in Table 6. The most common reason for a gap was a bank holiday occurring during treatment. Therapy was interrupted in only 8 patients owing to illness or toxicity.

Table 4. *Overall number and distribution of gaps during radiotherapy*

Number of gaps	Number of patients	Total number of gaps
0	53	NA
1	17	17
2	8	16
3	7	21
4	2	8

Toxicity

Acute-toxicity data are available for all patients and is given in Table 7. There were no treatment-related deaths.

The median pain score was 3 (range 1–8). There was no significant difference in analgesia requirement between patients with oropharyngeal tumours and those with laryngeal tumours, mean pain scores were 3.73 and 3.06, respectively. The addition of chemotherapy was significantly associated with an increase in pain score ($p = 0.008$). OTT was associated with an increase in pain score of 0.21 for each extra day ($p = 0.03$).

Grade 3 mucositis was seen in 56 patients (64%). It was more frequent in patients having chemotherapy (89% versus 48%), giving an odds ratio of 11.1. As expected, a higher incidence of grade 3 mucositis was seen with a higher radiotherapy dose ($p = 0.02$). No significant associations were seen between the incidence of grade 3 mucositis and administering 2 fractions in 1 day, 6 fractions in 1 week or OTT. Prolonged grade 3 mucositis was seen in 10 patients (11%). None of the patients having prolonged mucositis received >5 fractions in 1 week/1 fraction in a day. Grade 3 dysphagia was seen in 34 patients (39%) with no statistical difference between different groups.

Compensatory acceleration and toxicity

Receiving 6 fractions in 1 week, to compensate for a gap, was associated with a lower pain score ($p = 0.003$). In line with this, administration of >1 fraction in a single day was associated with a lower pain score ($p = 0.0004$). There were no

Table 5. *Details of compensatory fractions* administered to prevent prolongation of overall treatment time*

	Nil compensation	1 gap compensated	2 gaps compensated	3 gaps compensated	4 gaps compensated
1 gap	8	9	NA	NA	NA
2 gaps	1	4	3	NA	NA
3 gaps	0	2	3	2	NA
4 gaps	0	2	0	0	0

*Compensatory fractions were all delivered at the same dose per fraction as the original prescription.

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associations between compensation and dysphagia or mucositis.

DISCUSSION

This audit confirms that accelerated hypofractionated radiotherapy is tolerable and a high proportion of patients can complete this schedule on time. When interruptions occur, further acceleration to avoid prolongation of OTT in selected patients is possible. A negative association of pain with compensation for a gap suggests that physician selection for compensation was appropriate.

Reduced OTT has been shown to increase local control[4,10] and local control may be increased when delays are reduced, both before starting and during radiotherapy.[11,12] The schedule described earlier employs a reduced OTT and completes therapy before accelerated repopulation becoming a significant factor. In this study, 94% of patients were able to complete radiotherapy within 28 days achieving this goal in practice. The ability of this shorter schedule to deliver most of the therapy before toxicity becoming a significant problem may be one reason why such a high proportion of patients complete treatment within 1 month. Efficacy data from such an accelerated hypofractionated regimen have recently been published in locally advanced head and neck tumours but is yet to be subjected to prospective randomised comparison.[13,14]

Prolongation of OTT by 5 days or more occurs in up to one in four patients within randomised clinical trials.[15] Consideration of the proportion of patients able to complete a schedule is seldom discussed but is an important issue. There is no currently described model to radiobiologically compare different schedules which takes into account the proportion of patients actually completing treatment on time within a given schedule. Having a high compliance rate within a schedule could increase the overall rates of local control.

Acceleration has shown to be limited by toxicity so care must be taken when adopting shorter schedules. Within the CAIR study, a reduction in dose per fraction was required to render the schedule tolerable when reducing OTT from 7 to 5 weeks.[16] The hypofractionated schedule studied here has an acceptable acute-toxicity profile with incidences of grade 3 toxicity consistent with other published data. When considering trials not using concurrent chemotherapy, the reported incidence of minimum grade 3 mucositis ranges from 25 to 96%;[4,5,16–19] details are given in Table 8. When considering only patients receiving altered fractionation and excluding the CAIR study, which had an unacceptable level of acute toxicity before a reduction in the dose per fraction, this range is 41–73%. The incidence of

Table 6. *List of reasons for gaps in treatment*

Reason for gap	Number of gaps
Bank holiday	41
Machine breakdown	1
Machine service	5
Patient toxicity	8
Lymph node irradiation started late	3
Repeating planning required	2
Not started on a Monday	1
Unknown	1

Table 7. *Details of acute toxicity*

	Grade 3 mucositis (%)	Grade 3 dysphagia (%)	Prolonged mucositis (%)	Mean pain score
Overall $N = 87$	56 (64)	34 (39)	10 (11)	3.34
Larynx/hypopharynx $N = 50$	24 (8)	15 (30)	2 (4)	3.06
Oral/oropharynx $N = 37$	32 (8)	19 (51)	8 (21)	3.73
Radiotherapy alone $N = 52$	25 (48)	17 (33)	7 (13)	2.90
Concurrent chemotherapy $N = 35$	31 (89)	17 (59)	3 (9)	4.00

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Table 8. *Incidence of minimum grade 3 acute mucosal reaction in published studies using radiotherapy alone**

Author	Radiotherapy dose/fractionation	Overall Time	Number of patients	Incidence G3/4 mucositis (%)
Dische (CHART)	54/34	12 days	552	73
	66/33	6.5 weeks	366	43
Fu (RTOG 9003)	70/35	7 weeks	268	25
	81.6/68	7 weeks	263	42
	67.2/42	6 weeks	274	41
	72/42	6 weeks	268	47
Horiot 1997 (EORTC22851)	70/35	7 weeks	253	50
	70/35	7 weeks	253	50
	72/45	5 weeks	247	67
Horiot 1992	70/35	7 weeks	158	49
	80.5/70	7 weeks	162	66.5
Overgaard DAHANCA6&7†	66–68/33–34	7 weeks	726	33
	66–68/33–34	6 weeks	750	53
Skladowski CAIR study‡	66–72/33–36	7 weeks	49	71
	66–72/33–36	5 weeks	49	96

*Different studies may use different grading systems.
†Concurrent Nimorazole administered.
‡Fraction size altered part way through trial from 2 Gy to 1.8 Gy due to a high incidence of grade 4 reaction in accelerated arm.

interruption due to toxicity was also very low supporting the tolerability of the schedule.

This study shows that should unplanned interruptions occur then compensation is tolerable without prolongation of the OTT. This is important information for clinicians faced with the difficult decision of how to manage patients who have an unexpected interruption in therapy. Being able to compensate for missed therapy during treatment, and before accelerated repopulation, means the total dose can remain the same, which is the preferred method of compensation.[8] If however the treatment time is extended beyond the prescribed overall time, and is also beyond the point of accelerated repopulation, then the iso-effect dose has to be increased to compensate for the repopulation. Such a dose increase risks increased normal-tissue toxicity.

Late toxicity reactions are a particular concern with high doses per fraction. When employing radiobiological modelling based on the linear quadratic model, the estimated late biological effective dose (BED) of 55 Gy/20 in 25 days is only 105.4 Gy, well below the accepted 117 Gy calculated when using 70 Gy in 35 fractions (BED for late effects calculated using an $\alpha/\beta = 3$).[20] There is also evidence to suggest that late mucosal and skin damage occurs as a consequence of acute loss of squamous epithelium.[21–24] The rate of prolonged grade 3 mucositis (a surrogate marker for consequential damage) within this study is acceptable at 11%. Although more detailed late toxicity data are desirable, no unexpected late toxicity was seen within this group of patients.

The repair of sub-lethal DNA damage is likely to be slower in some normal tissues and caution needs to be employed when using multiple daily fractions for compensation. An adequate time interval has to be allowed to minimise the incidence of late toxicity and this may be particularly important when using large doses per fraction. Where required, the administration of an extra fraction for compensation should be done with a minimum gap of 6 hours and ideally, if resources permit, on a Saturday/Sunday. Demonstrating such benefits in a clinical study may prove difficult and in the absence of such data we have to rely on the radiobiological modelling.

The hypofractionated schedule discussed offers many practical benefits in terms of admin-

https://doi.org/10.1017/S1460396907006231 Published online by Cambridge University Press

istration and resource utilisation. This study has demonstrated that when using this schedule a high proportion of patients complete treatment on time, compensation is safely possible for selected patients and there is an acceptable acute reaction rate.

CONFLICT OF INTEREST

No sources of funding or conflicts of interest to declare.

References

1. Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988; 27:131–146.
2. Hendry JH, Bentzen SM, Dale RG, Fowler JF, Wheldon TE, Jones B, Munro AJ, Slevin NJ, Robertson AG. A modelled comparison of the effects of using different ways to compensate for missed treatment days in radiotherapy. Clin Oncol 1996; 8:297–307.
3. Slevin NJ, Hendry JH, Roberts SA, Agren-Cronqvist A. The effect of increasing the treatment time beyond three weeks on the control of T2 and T3 laryngeal cancer using radiotherapy. Radiother Oncol 1992; 24:215–220.
4. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised control trial. Lancet 2003; 362:933–940.
5. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, Garden AS, Ridge JA, Cooper JS, Ang KK. A Radiation therapy oncology group (RTOG) phase III randomised study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000; 48:7–16.
6. Guidelines for the management of the unscheduled interruption or prolongation of a radical course of radiotherapy, 2nd edition., London: The Royal College of Radiologists, 2002.
7. Dale RG, Jones B, Sinclair JA, Comins C, Antoniou E. Results of a UK survey on methods for compensating for unscheduled treatment interruptions and errors in treatment delivery. Br J Radiol 2007; 80:367–370.
8. Dale RG, Hendry JH, Jones B, Robertson AG, Deehan C, Sinclair JA. Practical methods for compensating for missed treatment days in radiotherapy, with particular reference to head and neck schedules. Clin Oncol 2002; 14:382–393.
9. Trotti A, Byhardt R, Stetz J, et al. Common toxicity criteria: version 2.0. An improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys 2000; 47:13–47.
10. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006; 368:843–854.
11. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol 2003; 21:555–563.
12. Robertson C, Robertson AG, Hendry JH, Roberts SA, Slevin NJ, Duncan WB, MacDougall RH, Kerr GR, O'Sullivan B, Keane TJ. Similar decreases in local tumor control are calculated for treatment protraction and for interruptions in the radiotherapy of carcinoma of the larynx in four centers. Int J Radiat Oncol Biol Phys 1998; 40:319–329.
13. Sanghera P, McConkey C, Ho KF, Glaholm J, Hartley A. Hypofractionated accelerated radiotherapy with concurrent chemotherapy for locally advanced squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2007; 67:1342–1351.
14. Sykes AJ, Slevin NJ, MacDougall RH, Ironside JA, Mais KL. Results of a phase I study to determine the maximum tolerated dose of capecitabine when given concurrently with radical radiotherapy in the treatment of squamous cell carcinoma of the head and neck. Radiother Oncol 2004; 71:81–84.
15. Khalil AA, Bentzen SM, Bernier J, Saunders MI, Horiot JC, Van Den Bogaert W, Cummings BJ, Dische S. Compliance to the prescribed dose and overall treatment time in five randomized clinical trials of altered fractionation in radiotherapy for head-and-neck carcinomas. Int J Radiat Oncol Biol Phys 2003; 55:568–575.
16. Skladowski K, Law MG, Maciejewski B, Steel GG. Planned and unplanned gaps in radiotherapy: the importance of gap position and gap duration. Radiother Oncol 1994; 30:109–120.
17. Dische S, Saunders M, Barrett A, Harvey A, Gibson D, Parmar M. A randomised multicentre trial of CHART versus conventional radiotherapy in head and neck cancer. Radiother Oncol 1997; 44:123–136.
18. 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.
19. Horiot JC, Le Fur R, N'Guyen T, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol 1992; 25:231–141.
20. Fowler JF. Is there an optimum overall time for head and neck radiotherapy? A review, with new modelling. Clin Oncol 2007; 19:8–22.

21. Bentzen SM, Overgaard M. Relationship between early and late normal-tissue injury after postmastectomy radiotherapy. Radiother Oncol 1991; 20:159–165.

22. Maciejewski B, Skladowski K, Pilecki B, Taylor JM, Withers RH, Miszczyk L, Zajusz A, Suwinski R. Randomized clinical trial on accelerated 7 days per week fractionation in radiotherapy for head and neck cancer. Preliminary report on acute toxicity. Radiother Oncol 1996; 40:137–145.

23. Wang CJ, Leung SW, Chen HC, Sun LM, Fang FM, Huang EY, Hsiung CY, Changchien CC. The correlation of acute toxicity and late rectal injury in radiotherapy for cervical carcinoma: evidence suggestive of consequential late effect (CQLE). Int J Radiat Oncol Biol Phys 1998; 40:85–91.

24. Withers HR, Peters LJ, Taylor JM, Owen JB, Morrison WH, Schultheiss TE, Keane T, O'Sullivan B, van Dyk J, Gupta N. Late normal tissue sequelae from radiation therapy for carcinoma of the tonsil: patterns of fractionation study of radiobiology. Int J Radiat Oncol Biol Phys 1995; 33:563–568.

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