Acta Oncologica 26 (1987) Fasc. 6

FROM THE HEAD AND NECK ONCOLOGY UNIT, GENERAL AND UNIVERSITY HOSPITALS, NOTTINGHAM, ENGLAND.

EARLY RESULTS OF RADIOTHERAPY FOR ADVANCED LARYNGEAL CANCER USING THREE SMALL FRACTIONS PER DAY

D. A. L. MORGAN, P. J. BRADLEY and K. A. MACLENNAN

Abstract

Fifteen patients with stage III or IV squamous cell carcinoma of the larynx were treated by primary radiotherapy using a schedule of 3 small (1.1–1.5 Gy) fractions per day, an interval between fractions of 3–4 h, and a total dose of approximately 60 Gy. Primary tumour control was achieved in 13 cases, but in one of these neck node metastases were not controlled. Acute mucosal reactions were brisk, but tolerable; late complications were severe in 3 patients. Early, encouraging results in terms of tumour response must be tempered by caution over the late damage: a number of factors probably contribute to this, especially interval between fractions and total dose. From a practical viewpoint, the latter may be easier to influence, if 3 small fractions per day are to continue to be used.

Key words: Therapeutic radiology; laryngeal cancer, multiple daily fractions, early results, complications.

Current radiobiological theory suggests that the use of smaller doses per fraction should result in less late damage to normal tissues than conventional radiotherapy schedules of equivalent tumoricidal effect, or even that more effective treatments could be given without increased damage, particularly if the overall treatment time can be shortened (6). In order to realise these benefits, much interest has developed in schedules that employ irradiation by multiple fractions per day (MFD).

Such treatments have been used by us since 1983 in the treatment of advanced head and neck cancer. The series of patients is small, and follow-up on many is still short, so we make no attempt to draw any firm lessons about tumour control at present, but our early clinico-pathological experience does lead us to sound a cautionary note about the late damage to normal tissues associated with the schedules employed. As these problems were unexpected we report the individual cases involved in some detail, and discuss factors that may have contributed to them and ways in which they might perhaps be avoided.

Material and Methods

Between June 1983 and August 1986, 15 patients with stage III and IV squamous cell carcinoma of the larynx were treated by MFD. Details of the patients and their treatments are shown in the Table.

In all cases, the volume irradiated included the primary tumour, and clinically-involved nodes; prophylactic nodal irradiation was not employed in clinically node-negative patients, so as to minimise the area of irradiated mucosa. All patients were treated using 3 fractions per day, given during the normal working hours of the Department (0830–1700 h), and so the interval between fractions each day could not exceed 4 h; a minimum of 3 h was stipulated. The dose per fraction was either 1.1 Gy or 1.5 Gy. The intention was always to deliver 45 Gy without interruption. This was followed, in the early part of the study (4 patients) by a 'rest' of 4 to 5 weeks to allow early reactions to subside, with a subsequent boost to at least 60 Gy, also using MFD. Fractions of 1.5 Gy were used for 3 of these patients, and 1.1 Gy for the fourth.

For the latter part of the study (11 patients), continuous treatments were attempted, with the intention of delivering approximately 60 Gy in 4 weeks. One of these patients (No. 7 in the Table) had treatment interrupted because of the development of stridor at 47 Gy, described in more detail below. Another (No. 13) had treatment discontinued at 31.7 Gy since he was unable to cope psychologically, and defaulted from follow-up.

Results

The patient who defaulted in mid-treatment eventually died of uncontrolled local disease. Another (No. 11) died

Accepted for publication 26 May 1987.

Table

Details of patients and treatments

Patient No.	Tumour site	TNM stage	Fraction size Gy	Split-course or continuous	Total dose Gy	Overall time Weeks	Follow-up
1	Supraglottic	T2N1	1.5	Split-course	64.5	8	Alive NED, 42 months, radiation myelitis
2	Glottic	T4N0	1.5	Split-course	64.5	8	Died, 18 months, brain metastases
3	Supraglottic	T4N3	1.5	Split-course	72	8	Died, 4 months, failed surgical salvage
4	Supraglottic	T2N1	1.1	Split-course	67.1	9	Alive NED, 24 months
5	Supraglottic	T3N0	1.5	Continuous	60.5	4	Alive NED, 22 months
6	Glottic	T3N0	1.1	Continuous	58.3	4	Alive NED, 21 months
7	Glottic	T3N0	1.1	See text	70.4	7	Died, 18 months, relapsed in larynx
8	Supraglottic	T4N0	1.1	Continuous	66	5	Died, 4 months, laryngectomy (necrosis)
9	Glottic	T3N0	1.1	Continuous	62.7	4	Alive NED, 18 months
10	Glottic	T3N0	1.1	Continuous	64.9	5	Alive NED, 18 months
11	Supraglottic	T3N0	1.1	Continuous	63.8	4	Died NED, 9 months
12	Supraglottic	T2N1	1.1	Continuous	63.8	4	Alive NED, 12 months
13	Supraglottic	T4N0	1.1	Continuous	31.7	2	Died, 6 months, defaulted treatment
14	Glottic	T3N0	1.1	Continuous	63.8	4	Alive NED, 8 months
15	Glottic	T3N0	1.1	Continuous	62.7	4	Alive NED, 7 months

of intercurrent disease (small bowel infarction) 9 months after treatment; her larynx and neck were clinically tumour-free.

The patient whose treatment was temporarily interrupted (No. 7) recovered from his stridulous episode with conservative treatment, and resumed MFD irradiation for his T3N0 glottic carcinoma. He received a total of 70 Gy in an overall time of 7 weeks. Despite early signs of response (direct laryngoscopy at 3 months revealed no definite tumour), at 6 months from the end of treatment there was recurrence at the primary site, and he underwent total laryngectomy. Post-operatively he developed a pharyngeal fistula which failed to heal despite several further interventions; he died of distant metastases (neck clear) 8 months post-operatively. Histologically, the operative specimen showed completely-excised recurrent tumour. The normal tissues showed severe radiation damage: there was focal mucosal ulceration, the submucosa was fibrotic with a perivascular chronic inflammatory cell infiltrate, and the vessel walls were thickened and hyalinized with focal vacuolation in the subintimal region; most striking changes were seen in skeletal muscle, which showed severe atrophy, and in hyaline cartilage, where there were tinctorial changes (uniform eosinophilic staining) and focal loss of chondrocyte nuclei—indicative of radionecrosis. Small foci of chronic inflammatory cells and macrophages were seen deep to the perichondrium, associated with resorption of necrotic hyaline cartilage.

In the other 12 cases there have been, to date, no laryngeal recurrences, but 2 have subsequently needed laryngectomy. The first (No. 3) presented with a T4N3 carcinoma of the epiglottis, with extension into the base of the tongue and bilateral, fixed, cervical lymph node metastases. She was treated by fractions of 1.5 Gy, 3 times per day, to a dose of 45 Gy, and then had a 5-week rest before receiving a further 27 Gy, using the same fractionation. Towards the end of the first phase of irradiation, she experienced increasing difficulty in swallowing, and a nasogastric feeding tube was passed. Although the laryngeal tumour subsequently showed good clinical evidence of regression she continued to need the tube because of laryngeal incompetence and aspiration, and the cervical lymphadenopathy persisted. Laryngectomy and bilateral radical neck dissection was therefore performed, 6 weeks after completion of her radiotherapy. The specimen showed no evidence of residual tumour in the larynx, but evidence of severe radiation damage, as already described; the cervical nodes still contained apparently-viable squamous cell carcinoma. Her post-operative course was stormy, with skin necrosis, pharyngeal fistula and eventual carotid haemorrhage, resulting in death 10 days post-operatively.

The third patient who underwent laryngectomy (No. 8) also had the operation performed because of persistent inability to swallow, 3 months after completing irradiation for a T4N0 supraglottic carcinoma. She had been treated with fractions of 1.1 Gy continuously for nearly 5 weeks, to a total of 66 Gy. Again, the operative specimen showed marked histological evidence of radiation damage. Post-operatively, she developed a pharyngeal fistula which

failed to heal, and she succumbed to a stroke 6 weeks after her operation.

A fourth larynx from this series of patients was available for histological examination, in this case having been examined post-mortem. The patient (No. 2) had been treated by a 'split-course' schedule using fractions of 1.5 Gy, for a T4N0 glottic carcinoma. A total of 64.5 Gy in an overall 8 weeks had been given, and the tumour had shown complete regression. This was maintained for 18 months, and the patient then died of cerebral metastases, confirmed at post-mortem. In this case, although pronounced, the degree of radiation damage did not amount histologically to radionecrosis.

One other possible case of late radiation damage to normal tissues was also seen. Patient No. 1 presented with a T2N1 carcinoma of the right ary-epiglottic fold, and he too was treated by a 'split-course', 1.5 Gy per fraction, schedule, receiving a total of 64.5 Gy in 8 weeks. As the lymph node involvement, although unilateral, was quite extensive, the spinal cord was included in the treatment volume for the first 45 Gy. Loco-regional control was achieved and maintained (3 years at the time of writing), but 2 years after treatment he developed signs of a mild spastic paraparesis. Investigations have failed to detect any alternative explanation, so radiation myelitis is suspected.

Discussion

The purpose of this report is not to announce an apparently good response rate—it is much too early to claim this—but to draw attention to, and to discuss, the late damage that has occurred in the normal tissues of some patients.

Many factors may contribute to such a damage. These include total dose, volume irradiated, overall time, dose per fraction, interval between fractions, or a combination thereof. With this heterogeneous group of patients and treatment schedules, it is not possible to be sure which are most important although a number of obvious features warrant some discussion.

The 3 patients (Nos 3, 7 and 8) who had severe soft-tissue and laryngeal damage were all given over 65 Gy. Disregarding the patient who did not complete treatment, there are 11 who, as yet, have no signs of such problems (and whose primary tumours have been controlled). Only one of these received over 65 Gy. This does suggest that, for this schedule, 65 Gy represents an upper limit to the dose that can be safely used.

Another possible explanation is that the severity of the late damage correlates with that of early damage, and that the late effects are a manifestation of unhealed severe early reactions. We feel that the evidence points away from this, for the following reasons. Two of the 3 laryngectomies were performed upon patients who had received 'split-course' treatments, one intentionally, and one because of onset of stridor. In each case, the interruption occurred just as the mucosal reaction was reaching a peak; it had healed clinically before irradiation was resumed, and the acute reaction to the lower dose employed during the second phase of irradiation was not severe. (A similar split-course regimen—although using fractions of 1.6 Gy—has been reported by the EORTC group, in a large study, with no suggestion that the early reactions were unacceptably severe (7).) The patients treated by continuous schedules all developed intense early mucosal reactions, but only one has, as yet, suffered severe late damage—and this patient was given a total dose of 66 Gy. For doses below this, a dissociation between acute and late damage does seem to have been achieved, as the early reactions of the other continuous-schedule patients have all healed satisfactorily.

Again, it may be that the 3–4-h interval employed here is too short to allow adequate repair of normal, late responding tissues between fractions. Such a conclusion was indeed drawn from a series treated by 3 fractions of 2 Gy per day at 4-h intervals in a short overall time (3), and is in accordance with experimental data (2, 5). Perhaps a longer interval between fractions would allow higher doses to be given safely, but our findings do suggest that the 3–4-h interval allows an adequate degree of recovery from small fractions, as long as the total dose is kept below 65 Gy.

The one case of possible radiation myelitis should be considered separately from the 3 cases of severe laryngeal late damage. From such a single case, no firm conclusions can be drawn, although it is of interest that experimental data for rat spinal cord does suggest that the use of doses below 2 Gy confers no extra protection from late damage (1). It would seem wise in future to keep the cord dose lower than the 45 Gy received in this case when accelerated fractionation is employed.

Although late damage has been the subject of this report, we have been encouraged by the tumour response rates achieved so far, and as the acute reactions have been acceptable, it is our intention to pursue further the study of continuous treatments employing 3 fractions of 1.1 Gy per day, but to keep the total dose below 65 Gy, hoping, in this way, to prevent late problems, as explained above. To use longer intervals between fractions in the hope of being able to give higher doses would make it impossible to continue to give 3 fractions daily within the normal working hours of the Department (4). To change to a twice-a-day schedule would necessitate either using larger fractions, or lengthening overall treatment times; both of these options are theoretically undesirable.

ACKNOWLEDGEMENT

We thank Professor Jack Fowler for his encouragement and help in presenting and interpreting these findings. He is, of course, in no way responsible for any erroneous conclusions that may have been drawn.

Request for reprints: Dr D. A. L. Morgan, Hogarth Centre of Radiotherapy and Oncology, General Hospital, Nottingham NG1 6HA, England.

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