Acta Oncologica Vol. 32, No. 6, pp. 637–640, 1993

A FEASIBILITY STUDY OF CONCOMITANT BOOST RADIOTHERAPY FOR PATIENTS WITH CANCER OF THE SUPRAGLOTTIC LARYNX

KRZYSZTOF BUJKO, JERZY Z. SKOCZYLAS, SØREN M. BENTZEN, ANDRZEJ HLINIAK, MICHAL WASILEWSKI, ZBIGNIEW J. SZUTKOWSKI and ANTONI OSMÓLSKI

Between February 1988 and December 1989, 65 patients with supraglottic cancer completed a course of concomitant boost radiotherapy. Cases with N3 disease, a Karnovsky performance score less than 70, age above 70 years, or a second primary cancer were not eligible for the study. Distribution of the patients was: Stage T1–T2 30%, T3–T4 70%, N0 68%, N+ 32%. The total dose ranged from 60 Gy to 76 Gy (median 66 Gy); overall treatment time ranged from 36 to 56 days with a median of 42 days. The daily dose during the first 4 weeks was 1.8 Gy, and during the last 2 weeks it was 1.6 Gy b.i.d. with a 4- or (after September 1988) 6-h interval. The clinical impression was that the early mucosal reactions were acceptable but more severe than after conventional treatment, with confluent membranous mucosal reaction being observed in 54% of the patients. Also, this reaction was significantly more frequent in patients treated with a 4-h interval (68%) than with a 6-h interval (41%) between the daily fractions. To relieve severe dysphagia, narcotics were required in 22% of the patients. The follow-up time ranged from 22 to 50 months, median 34 months. Treatment-requiring late complications were observed in 8 patients, and the 3-year actuarial risk was 17% with 95% confidence limits (6%, 27%). Two of these patients had severe complications: one of them required a temporary tracheostomy due to arytenoid edema and the other developed a laryngo-cutaneous fistula which healed after pharmacological treatment. Actuarial 3-year local-regional control was 59% (46%, 71%) and 3-year actuarial crude survival 55% (42%, 67%). There was no significant difference in the incidence of late complications or tumor control between the two groups of patients treated with a 4- or 6-h interval between the daily fractions. This study shows that the concomitant boost regimen tried here is feasible, but also stresses that the interval between dose fractions should be 6 h or more.

One of the current approaches to improving radiation therapy in patients with squamous cell carcinoma of the head and neck is to shorten overall treatment time, with the so-called accelerated fractionation regimen. The radiobiological rationale is to reduce the detrimental effect of tumor clonogen proliferation during treatment. If overall treatment time is shortened without increasing the dose per fraction, the current expectation is that late complications will be unaffected by this strategy, provided that the interfraction interval is sufficient to allow complete repair of sublethal damage in the late-responding normal tissue cells. In contrast, early reactions are expected to worsen as less time is available for regeneration in the early-responding tissues.

Several strategies have been devised to accelerate treatment (1). One of these is the concomitant boost regimen, in which the boost field is treated as a second daily fraction

Received 28 December 1992.
Accepted 19 August 1993.
From Danish Cancer Society, Dept. of Experimental Clinical Oncology, Aarhus, Denmark (S. M. Bentzen, J. Z. Skoczylas), the ENT Department of the Postgraduate Teaching Medical Center, Warsaw (A. Osmólski), and Dept. of Radiotherapy II, Center of Oncology-Institute, Warsaw, Poland (K. Bujko, A. Hliniak, M. Wasilewski, Z. J. Szutkowski).
Correspondence to: Dr. K. Bujko, Department of Radiotherapy II, Center of Oncology-Institute, Findera 101, PL-02-781 Warsaw, Poland.

during the treatment of the wide fields. This modification of the shrinking field technique was originally proposed by Fletcher (2). The concomitant boost regimen is expected to be relatively well tolerated, and makes it possible to give the whole treatment without break. This is because only in the second part of the treatment is the irradiation administered at a high dose. Moreover, the volume of tissues treated with the second daily fraction (boost) is small.

This paper reports the results of a feasibility study of a concomitant boost regimen used in the Department of Radiotherapy in Warsaw.

Patients and treatment technique

Between February 1988 and December 1989, 89 patients with supraglottic cancer received radiotherapy in the Department of Radiotherapy II, Center of Oncology-Institute in Warsaw; 71 of them met the eligibility criteria for concomitant boost radiotherapy. Eighteen patients were excluded for the following reasons: age over 70 years (n = 3), second primary cancer (n = 1), Karnovsky performance score less than 70 (n = 4), N3 stage (n = 4), and both N3 stage and Karnovsky less than 70 (n = 6). Patients with N3 stage were excluded from the study because it was presumed that the boost field would be too large and that tolerance of the treatment, therefore, might not be acceptable. Among the elgible patients 6 were excluded for other reasons: palliative irradiation due to massive tumor (n = 1), incomplete radiotherapy due to cardiac infarct (n = 1), planned preoperative radiotherapy (n = 1), major protocol violations (n = 2), no consent to concomitant boost technique (n = 1).

Sixty-five patients (53 men and 12 women) ranging in age from 31 to 69 years (median of 55 years) were studied. Stage of disease is shown in Table 1. Most of the patients (70%) had locally advanced primary tumor (T3–T4). The follow-up time of living patients without recurrence ranged from 22 to 50 months (median 34 months).

Treatment was given 5 days a week. The elective dose to the wide fields was delivered as 1.8 Gy per fraction during the first 19 treatment days. Thereafter the dose per fraction for the wide field was reduced to 1.6 Gy and the boost field was treated as a second daily fraction, also with a fraction size of 1.6 Gy. This was continued for another 10 treatment days. This technique delivered a total dose of 66.2 Gy to the gross disease, the elective dose being 50.2 Gy and the boost dose 16 Gy. When two treatments per day were given, the interval between the two daily fractions was at least 4 h (31 patients), and after September 1988, at least 6 h (34 patients). The planned overall treatment time was 39–41 days. Minor deviations from this basic schedule were allowed: in some patients the dose was modified due to a large tumor volume, and in some patients treatment time was prolonged due to public holidays.

All patients were irradiated on a ^{60}Co machine with a source-skin distance of 80 cm, in two parallel opposing fields. The patient's head was immobilized with a strip of adhesive tape. Doses were prescribed in the midplane of the patient at the central axis of the beams. A wedge filter was used to compensate for the neck contour in order to keep the dose variation in the treatment volume within $\pm 5\%$ of the midline value. In patients with ipsilateral lymph node metastases and with the primary tumor limited to one side of the larynx, the doses to the two fields were weighted at 2:1. All patients received elective irradiation of the upper and midjugular lymph nodes. Field sizes ranged from 7 cm × 10 cm to 10 cm × 12 cm, and were tailored to the shape of the neck and the extent of neck disease. In patients with positive neck disease, the posterior cervical lymph nodes and the low jugular and supraclavicular lymph nodes were also irradiated additionally, the latter through an abutted anterior field. The boost was limited to the primary tumor an positive neck nodes with a narrow margin—the field size was usually 6 cm × 6 cm for N0 patients and 1–2 cm longer in some N+ patients. The total dose in the spinal cord was kept below 45 Gy. The dose to the posterior neck nodes was usually supplemented by using 10 MeV electrons. For single anterior photon and electron fields the doses were prescribed as maximum absorbed doses.

The actual total dose ranged from 60 Gy to 76 Gy (median 66 Gy). It was intented not to exceed 70 Gy, but

Table 1

Distribution by T and N categories according to UICC (1987) criteria

	N					
T	0	1	2a	2b	2c	Total
1	5	—	—	—	—	5 (8%)
2	11	2	—	—	1	14 (22%)
3	23	9	—	1	3	36 (55%)
4	5	1	1	2	1	10 (15%)
Total	44 (68%)	12 (18%)	1 (1.5%)	3 (5%)	5 (8%)	65 (100%)

two patients received higher doses due to errors in the dose calculation. The boost dose was adjusted to the T category, and ranged from 10 to 16 Gy for T1–T2, and from 16 to 20 Gy for T3–T4 tumors. The actual overall treatment time ranged from 36 to 56 days (median 42 days).

Statistical evaluation. Three-year actuarial loco-regional control, actuarial incidence of late complications, and survival rates were estimated using the Kaplan–Meier method (3); 95% confidence limits of the estimate are shown in parentheses.

Results

Early reactions are given in Tables 2–5. The clinical impression was that the mucosal reaction was more severe than after conventional treatment, after a median total dose of 68 Gy during a median overall treatment time of 54 days with 1.8 or 2.0 Gy per fraction. The most intense reactions were usually observed during the first week after the end of treatment, and in most cases subsided within the following week. Confluent membranous mucosal reaction was observed in 54% of the patients and lasted for more than 3 weeks in 2 (3%) patients. To relieve severe dysphagia, narcotics were necessary in 22% of the patients. However, there was no need to feed the patients by nasogastric tube or to hospitalize them because of severe early effects. Nevertheless, many patients experienced considerable weight loss which, unfortunately, was not well documented in the patients records. In 2 patients treatment was interrupted due to dysphagia (for 6 and 7 days).

Table 2

Maximum early mucosal reaction

	Number of patients
Moderate erythema	4 (6%)
Marked erythema	6 (9%)
Patchy membranous reaction	20 (31%)
Confluent membranous reaction	35 (54%)

Table 3

Confluent membranous reaction and the interval between fractions

Interfraction interval	No. of patients	No. of patients with confluent membraneous reaction
4 h	31	21 (68%)
6 h	34	14 (41%)

Table 4

*Maximum degree of dysphagia**

	Number of patients
Some discomfort swallowing, no change in diet	11 (17%)
Difficulty swallowing, soft diet	21 (33%)
Considerable difficulty swallowing, fluids only	19 (30%)
Severe difficulty swallowing fluids	13 (20%)

* 64 patients (1 patient excluded due to insufficient observations).

Table 5

Early treatment-related morbidity

	No. of patients
Hemoptysis	17 (26%)
Stridor	1 (2%)
Moist desquamation of skin	6 (9%)
Narcotics necessary	14 (22%)
Confluent mucositis > 10 days after treatment	2 (3%)

A confluent membranous mucosal reaction was seen more frequently in patients with a 4-h interval between the two fractions per day (68%) than in patients with a 6-h interval (41%). This difference was statistically significant ($p = 0.036$, Fisher's test).

Treatment-requiring late complications were observed in 8 patients. Six patients presented with arytenoid edema and/or chondritis. All were successfully treated with steroids and antibiotics. The remaining two had severe damage; one required a transitory tracheostomy due to severe arytenoid edema, and one developed a laryngocutaneous fistula which healed after pharmacological treatment. The 3-year actuarial risk of late complications was 17% (6%, 27%). There was no significant difference between patients with a 4- and 6-h interval between fractions. However, the total number of events was low.

Twenty-eight local-regional failures were observed. Of these, two patients, classified T3N0 and T4N0, had in-field control but experienced a regional recurrence outside the irradiation field in the supraclavicular region. This observation has led to a change in the strategy of elective irradiation in concomitant boost patients. Currently, in patients with T3–T4 tumors of the supraglottic larynx, not only the upper and midjugular neck nodes but also the lower neck and the supraclavicular area are electively irradiated.

Actuarial 3-year local-regional control with the concomitant boost technique (patients cured with salvage surgery were scored as failures) for all stages of disease was 59% (46%, 71%); the actuarial 3-year survival was 55% (42%, 67%). The results for T1–T2 and T3–T4 tumors separately are presented in Table 6. A 4-h interfraction interval appeared to yield a better local tumor control than a 6-h interval (72% [63, 81%] versus 47% [39%, 55%], $p = 0.02$). However, when we used Cox's proportional hazards model, the beneficial effect of a short interfraction interval vanished after correction for N-stage of the patients.

Table 6

Treatment results 3 years after concomitant boost radiotherapy

	Crude survival	Loco-regional control*
T1–2	78% (59%, 97%)	68% (48%, 89%)
T3–4	44% (27%, 61%)	56% (41%, 71%)
all	55% (42%, 67%)	59% (46%, 71%)

* In-field control rates. For T3–4 tumors the overall loco-regional control rate was 54% (40%, 69%). In T1–2 tumors all recurrences occurred within the field.

Discussion and conclusion

The concomitant boost regimen used in this study was found to be a safe and feasible procedure. In general, there was no need to interrupt treatment. However, it should be noted that early reactions were more severe in comparison to conventional treatment; in many patients strong analgesics had to be administered to relieve dysphagia. The late complication rate was acceptable, but admittedly the number of observations was small.

The present study, together with the recent reports by Knee et al. (4), Ang et al. (5), Johnson et al. (6), and Kaanders et al. (7), demonstrates that concomitant boost schedules are feasible, and although the early reactions are more pronounced than after conventional fractionation, they are still acceptable. Preliminary observations suggest that late toxicity after concomitant boost radiotherapy is comparable to what is seen with conventional radiotherapy. Finally, tumor control appears to be at least as good as that seen after conventional fractionation. The incidence of severe mucositis was higher in patients treated with a 4-h than with a 6-h interval between the wide and the boost field. On the basis of this finding we suggest that when treatment is given in multiple fractions per day, the interval between the fractions should be kept as long as possible, i.e., at least 6 h or even longer.

REFERENCES

1. Peters LJ, Ang KK, Thames HD. Accelerated fractionation in the radiation of head and neck cancer. Acta Oncol 1988; 27: 185–94.
2. Fletcher GH. Basic principles of radiotherapy. In: Fletcher GH, ed. Textbook of radiotherapy, 2nd Edition, Philadelphia: Lea and Febiger, 1973: p. 140.
3. Kaplan EL, Meier P. Non-parametric estimation for incomplete observations. J Am Statist Soc C 1958; 53: 457–81.
4. Knee R, Fields RS, Peters LJ. Concomitant boost radiotherapy of the head and neck. Radiother Oncol 1985; 4: 1–7.
5. Ang KK, Peters LJ, Weber RS, et al. Concomitant boost radiotherapy schedules in the treatment of carcinoma of the oropharynx and nasopharynx. Int J Radiat Oncol Biol Phys 1990; 19: 1339–45.
6 Johnson CR, Schmidt-Ullrich RK, Wazer DE. Concomitant boost technique using accelerated superfractionated radiation therapy for advanced squamous cell carcinoma of the head and neck. Cancer 1992; 69: 2749–54.
7. Kaanders JH, van Daal WA, Hoogenraad WJ, van der Kogel AJ. Accelerated fractionation radiotherapy for laryngeal cancer: acute and late toxicity. Int J Radiat Oncol Biol Phys 1992; 24: 497–503.