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Salvage surgery following irradiation with different fractionation regimes in the treatment of carcinoma of the laryngo pharynx: experience gained from a British Institute of Radiology Study

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Abstract
The 10-year follow-up of patients in a clinical trial involving the comparison of treatment by three fractions per week *versus* five fractions per week in radiotherapy of squamous carcinoma of the larynx and hypopharynx has now been completed. The trial involved an intake of 734 patients between 1966 and 1975. No statistically significant differences have been found between the two trial arms in terms of overall survival, age corrected survival, local recurrence, laryngectomy-free rates or effects on the normal tissues. Local recurrence was found in 320 of the 713 evaluable patients (45 per cent). Salvage laryngectomy was performed in 151 of the 320 patients with recurrence (47 per cent). Survival at 10 years for all node negative patients was 50 per cent in those patients without primary recurrence, compared with 40 per cent in those undergoing salvage laryngectomy.

Introduction

The majority of head and neck Surgical Oncologists in the United Kingdom and world wide accept the proposition that radiotherapy is the treatment of choice for 'Early' (T_1 and most T_2) laryngeal cancer (Groves and Gray, 1985; Southam and Tobias, 1986). Many would also support the use of radiotherapy for T_3 carcinoma, especially for glottic tumours, reserving 'salvage' surgery for irradiation failures (Dobbs and Barrett, 1985; Robin and Olofsson, 1987).

The management of T_4 laryngeal cancer and tumours of the hypopharynx is more controversial, but it is possible to defend a practice of primary irradiation, again with salvage surgery where appropriate, particularly in elderly patients and in those with co-existing medical problems (Henk and Whittam, 1982; Million *et al.*, 1982).

In general, the surgeon may take only a passing interest in the technique and treatment schedule of his radiotherapy colleague. However, with a policy of primary irradiation and salvage surgery, he may show a greater interest in the morbidity caused by radiotherapy, particularly if a fundamental change is made to the radiotherapy schedule. Just such a change was proposed in 1962–63 by Dr Frank Ellis, during his year as President of the British Institute of Radiology. He proposed a trial to test the 'Null hypothesis', that with certain provisos, patients with cancers of the larynx and hypopharynx could be treated equally effectively with a three fraction per week schedule as with a five fraction per week schedule (Preliminary report of the Working Party of the British Institute of Radiology on the Effects of Dose Fractionation in Radiotherapy, 1963).

The multi-centre trial commenced recruiting in 1966, and entry closed in 1975. Follow-up information was collected for each patient until 10 years had elapsed from the start of treatment or earlier death. The final results of this trial have been published in a comprehensive paper (British Institute of Radiology Working Party, 1990).

The purpose of this report is to explore aspects of the trial that have a direct bearing on the practice of the Head and Neck Surgical Oncologist, namely, overall survival between the two treatment arms (3 fraction/week *versus* 5 fraction/week); the morbidity of therapy; any variations in the frequency of recurrence and hence need for salvage laryngectomy; survival post-laryngectomy in the two groups; and any correlation between late radiation damage and morbidity following salvage surgery.

Materials and methods

In the 10 years between 1966–1975, 734 patients were entered into the trial, from 17 United Kingdom Radiotherapy Centres. Twenty-one patients have been omitted from the final analysis for reasons given in the final report, leaving 713 patients for the main analysis.

For each patient entered into the trial, clinical infor-

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mation was collected with the aid of a diagram (Fig. 1). It may be seen from this diagram that patients with squamous and anaplastic carcinomas of the larynx and hypopharynx were considered suitable for entry into the trial. On the basis of this, patients were categorized by primary tumour extent (T) and nodal status (N). They were also allocated a stage group (S) which is a composite of T, N, and M status. (All the patients in this trial were classified M_0). One of the problems in reporting this trial more than 20 years after first entry of patients, is that there have been four editions of the U.I.C.C. staging handbook in the interim. For the purpose of this report, 'T-stage' is as classified in the U.I.C.C. 1987 edition. Unfortunately, nodal staging in the 1987 edition depends on lymph node dimensions, information that was not recorded on the original registration diagram (Fig. 1). We have therefore had to fall back on the U.I.C.C. 1978 edition for N status. This edition, as previous editions categorizes lymph node status by virtue of site (homolateral, contralateral, or bilateral) and fixity. As a result, stage grouping (S) is a composite of 'T' stage from the 1987 U.I.C.C. version and 'N' stage from the 1978 version of U.I.C.C. handbook.

Recent review of all the raw data has confirmed that 520 patients with carcinoma of the larynx were entered into the trial. An additional 49 patients were classified as carcinoma of the hypopharynx, and 144 patients had tumours involving both larynx and hypopharynx, and therefore have been classified as 'dual' tumours (Table I). Randomization resulted in 351 patients being treated three times a week, and 362 patients five times per week. The prognostic factors, T, N, stage and site were reasonably evenly distributed between the two arms of the trial (Table I). However, there was a slightly higher proportion of S_1 and larynx patients in the three fractions per week group. Histological review has confirmed an even distribution of poor and well differentiated tumours in the two treatment groups. The statistical methods are fully detailed elsewhere (British Institute of Radiology Working Party, 1990).

With regard to the irradiation schedules, the same overall treatment time was used in each centre for both arms of the trial, but this varied from centre to centre, depending on the local standard practice. A reduction in total radiation dose was employed for treatment with three fractions per week compared with five fractions per week. This reduction was from 13 to 11 per cent for overall treatment times of three to six weeks respectively. The reduction was aimed at achieving a similar acute normal tissue radiation reaction.

Patients who had persistent or recurrent tumour at the primary site following irradiation were assessed for surgery. Recurrent disease within the primary irradiation volume was treated, when appropriate, by total laryngectomy.

Results

Observed survival rates

The percentage observed survival rates for patients treated with three fractions per week and five fractions week are shown in Figure 2a. There is no statistically significant difference between the two groups; at five years ($\chi^2 = 0.61$; $p = 0.43$), and at 10 years ($\chi^2 = 0.57$; $p = 0.44$). The error bars shown at the time points represent the 95 per cent confidence limits for the probability of survival. The χ^2 values and the related P-values were obtained from comparison of survival data using the method of Mantel (1966). When survival was corrected for age, as shown in Figure 2b, again there is no significant difference between the two groups. A sub-group analysis of the 336 patients in the S_1 stage group (T_1N_0) has shown that there is no statistically significant difference between the two treatment groups. Similarly, analysis of S_2, S_3 and S_4 patients shows no statistically significant difference between the two trial arms. A multi-variate analysis, including age, sex, site, stage, T, N and treatment has shown that only age, stage and site were significant, independent, prognostic factors. Mortality was higher in older patients, more advanced stages, and patients with hypopharynx or 'dual' tumours. With these three factors included, the relative risk for the treatment effect (*i.e.* ratio of mortality rate in the three fraction per week arm to that in the five fraction per week arm) was 1.05, with a 95 per cent confidence interval of 0.87–1.27.

Recurrence

The incidence of recurrence at the primary site during the 10 years from the start of treatment was 159 (45 per cent) patients in the three fraction per week arm, and 161 (45 per cent) patients in the five fraction week arm. In the analysis, patients were assigned 'tumour-free' if there was no evidence at clinical follow-up of persistent or recurrent tumour at the primary site. Deaths without local recurrence were counted as withdrawals at the time of death. The tumour-free rates for the trial population are shown in Figure 3a, where there is no statistically significant difference between the two arms.

One large subgroup—S_1 stage glottic tumours (known in previous interim reports as 'cords mobile' group) accounts for 283/713 (40 per cent) of the patients. Tumour-free rates for this population are shown in Figure 3b.

Laryngectomy

In the 320 patients with disease recurrence, 151 laryngectomies were performed (47 per cent). This represents 21 per cent of the total patient population entered into the trial.

In the three fraction per week arm, 79/159 (50 per cent) of patients with recurrence underwent laryngectomy, while in the five fractions per week arm, 72/161 (45 per cent) of patients underwent laryngectomy for locally recurrent carcinoma. The reasons for not proceeding to laryngectomy include locally advanced and inoperable disease, synchronous or prior development of distant metastases; poor medical conditions, or refusal of surgery.

'Laryngectomy-free rates' have been quoted both in the interim reports and the final report, and are included for completeness. The results for the entire study population are shown in Figure 4, where no statistically significant diference is seen between the two arms of the trial—either for the whole group (Figure 4a) or the S_1 sub-group (Figure 4b).

The survival for the different sub-groups of N_0 (lymph node negative) patients is given in Table II. There is no statistically significant difference in survival betwen the

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British Institute of Radiology Fractionation Survey 65/2

LARYNGO-PHARYNX

Please put information in boxes. ALL boxes after question 5 MUST HAVE A NUMBER inserted
Please send to 32 Welbeck Street, London W.1, as soon after prescribing treatment as possible

No. of F per week

1. FULL NAME (block letters) surname / given names *
2. PATIENT'S HOSPITAL No.
3. RADIOTHERAPY CENTRE *
4. DATE RADIATION TRT. STARTED / /19

* leave blank

5. DIAGNOSIS—PRIMARY
N.B.—In this block, put 1 where present in each box. Blank boxes will automatically have 0 filled in

	Rt.	Central	Lt.
Epiglottis			
Aryepiglottic fold			
Arytenoids			
Pyriform sinus			
Supraglottic			
Ventricle			
Cord mobile			
Cord fixed			
Subglottic			
Post cricoid			
Pharyngeal Wall—Lat			
Pharyngeal Wall—Post			

6. OEDEMA No 0 Yes 1
PAIN No 0 Yes 1
'SPHAGIA 0 1
PERICHONDRITIS No 0 Yes 1

NODES None 0 Mobile 1 Fixed 2 (Insert in each box)

Rt.	C	Lt.

7. HISTOLOGY IF CANCER
Non malignant 0
Squamous 1 other 2
Indeterminate as to malignant 3
Well differentiated 1
Anaplastic 2

RADIATION TREATMENT INTENDED

8. RADIATION Accelerator 1 Cobalt 2 Caesium 3 Electrons 4
If accelerator or electrons insert energy.....(MV or MeV)

9. TECHNIQUE
Unilateral 1 Bilateral 2
Fixed field 1 Rotation 2

10. FIELDS Number of fields
Size of each × × ×
(cm x cm) × × ×
Direct field 0 Wedge 1
Compensator 1 Contact Bolus 2 Neither 0

11. TOTAL PLANNED TUMOUR DOSE
Per cent Dose
..... Modal rads
..... Maximum rads
..... Minimum rads

12. PLANNED HIGH DOSES IN NON-TUMOUR TISSUES
Subcutaneous (½—1 cm) rads
Other positions of interest (state where):
Per cent Dose
..... Spinal cord rads
..... Cartilage rads
..... rads

13. No. OF TREATMENT SESSIONS PLANNED

OVERALL TREATMENT TIME PLANNED
(First day—day no. 0) days

SPACING No. of sessions/week

IS GAP IN TRT. EXCEEDING 5 DAYS PLANNED?
If yes, give details No 0 Yes 1

Signature
Date

FIG. 1
British Institute of Radiology laryngo-pharynx trial data form.

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TABLE I

DISTRIBUTION OF PATIENTS IN THE TWO ARMS OF THE FRACTIONATION TRIAL (3 FRACTIONS PER WEEK AND 5 FRACTIONS PER WEEK) GROUPED ACCORDING TO THE TNM CLASSIFICATION AND ANATOMICAL SITE

TNM classification	T_1		$T_2+T_3+T_4$		N_0		$N_1+N_2+N_3$		S_1		$S_2+S_3+S_4$		Total no.
Fractions per week	3	5	3	5	3	5	3	5	3	5	3	5	
Larynx	175	148	93	104	258	243	10	9	171	143	97	109	520
Pharynx	12	21	6	10	9	16	9	15	5	10	13	21	49
Dual tumours	2	5	63	74	38	47	27	32	2	5	63	74	144
Total number	189	174	162	188	305	306	46	56	178	158	173	204	713

whole group of patients (611), those who underwent laryngectomy, and those who remained laryngectomy free. This has been calculated both from the time of initial treatment, and from the time of laryngectomy. A careful analysis was also made, comparing survival of laryngectomy and laryngectomy-free patients with regard to a number of other variables, *i.e.* larynx only (excluding pharynx), different T stages (T_{1-4}) and with regard to 3 three fractions a week *versus* five fraction week. No statistically significant difference could be found in any of the sub-group analyses when comparing laryngectomy patients *versus* laryngectomy-free patients. It should be pointed out that the vast majority of laryngectomy patients underwent surgery because of recurrent disease. The 'laryngectomy-free' group comprised some patients who remained tumour-free and therefore required no further treatment, and also some patients who had recurrent disease but were not fit enough to undergo laryngectomy.

Perhaps a more interesting analysis is comparing survival of laryngectomy patients with those who remained 'laryngectomy-free' *and* 'tumour-free' (Table III). Included in this table are the survival data for a third group of patients, namely recurrent disease who did not undergo laryngectomy. There is a statistically highly significant difference in five and 10 year survival between the three groups analysed (χ^2 for trend = 66.4; $p<0.0001$).

We have also looked at survival of all node negative patients with carcinoma of the larynx who either remained free of recurrence at the primary site (314 patients) or relapsed at the primary site and required laryngectomy (99 patients). No statistically significant difference between three fractions per week and five fractions per week was found for survival in each of these two groups (Table IV).

Laryngectomy pathology

Laryngectomy specimens were examined histologically. In a small number of patients histological review of the laryngectomy specimen revealed no obvious viable tumour. The number of these patients was distributed as follows: 12 patients were found to have no evidence of tumour in the main pathological specimen, 4 in the three fraction per week group and 8 in the five fraction per week group.

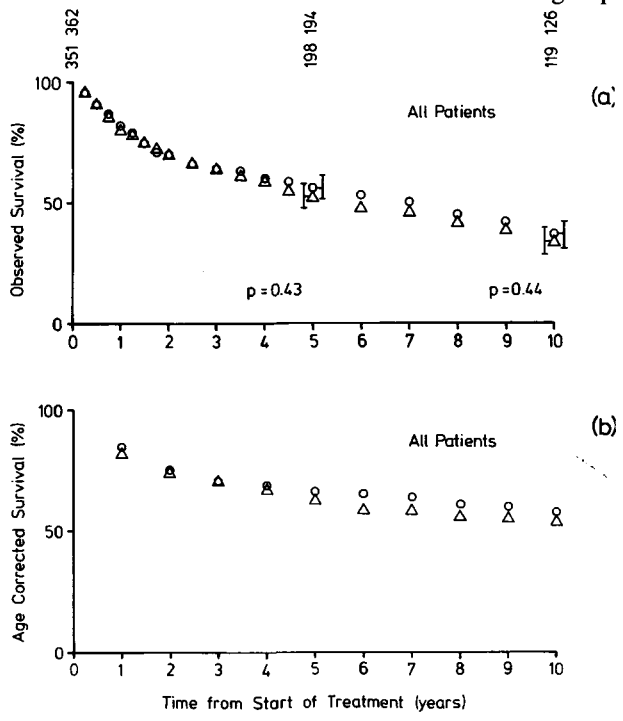

FIG. 2

(a) Observed, (actuarial) survival rates of all patients entered into the trial, with the exception of the 21 excluded patients, *versus* time from start of radiation treatment. No correction for age of the patients or mortality of patients without cancer is made.

(b) Similar data to that shown in (a), but after 'age-correction'. Symbols ○ 3F/week. △ 5F/week. Patients numbers at 0, 5 and 10 years are shown at the top of each panel.

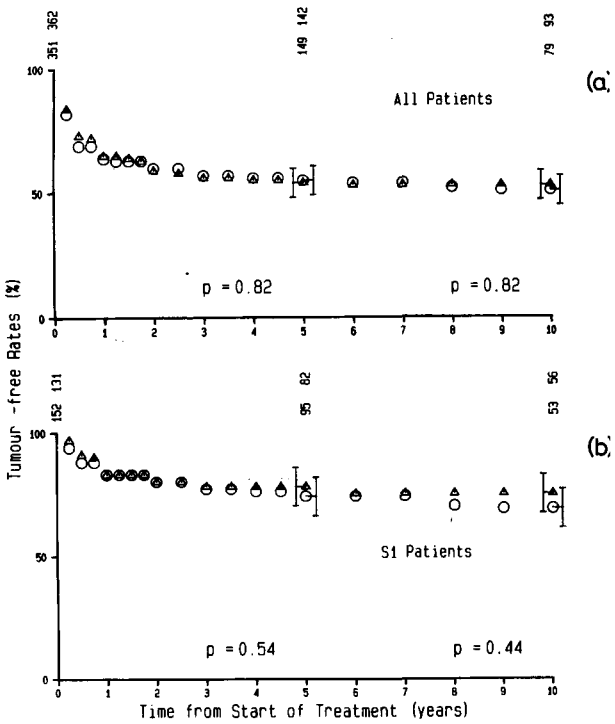

FIG. 3

Tumour free rates. (a) Percentage of all patients, except 21 exclusions, without persistent or recurrent tumour versus time from start of radiation treatment.

(b) Confined to patients in the glottic subsite, S_1 stage grouping (cords mobile). Symbols as in Fig. 2. Patients numbers at 0, 5 and 10 years are shown at the top of each panel.

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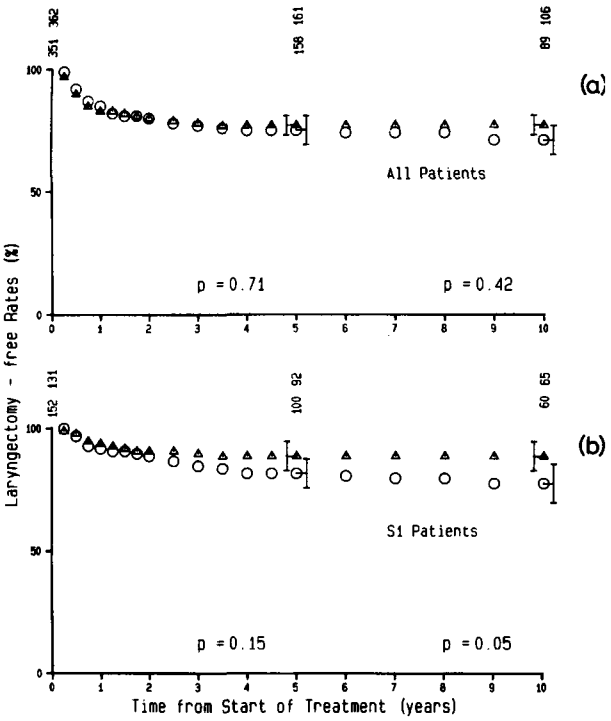

FIG. 4

Laryngectomy-free rates. (a) Percentage of all patients, except 21 exclusions, surviving without having had a laryngectomy versus time from start of radiation treatment.
(b) Confined to patients in the glottic subsite, S_1 stage grouping (cords mobile). Symbols as in Fig. 2. Patients numbers at 0, 5, and 10 years are shown at the top of each panel.

Acute and late effects of radiation therapy

The detailed information relating to acute and late normal tissue reactions is reviewed both in the final report, and in a separate paper devoted to normal tissue responses (Rezvani *et al.*, 1989). The majority of patients were noted to have an acute mucous membrane reaction—94 per cent of patients treated with three fractions per week and 96 per cent of those treated with five fractions per week. The incidence of severe acute reaction as denoted by perichondritis was low, and six per cent in each treatment group.

Late reactions, such as telangiectasis, fibrosis, atrophy, oedema and dyspigmentation of the skin were scored for all patients, and were noted in 59 per cent of patients with three fractions per week and 62 per cent of patients treated with five fractions per week. This difference was not statistically significant (p = 0.62).

TABLE II

ACTUARIAL SURVIVAL OF NODE NEGATIVE PATIENTS GROUPED BY PRESENCE OR ABSENCE OF LARYNGECTOMY. TIMES FROM BEGINNING OF RADIATION TREATMENTS EXCEPT WHERE INDICATED OTHERWISE

	Number of patients	Percentage survival 5 years	10 years
All patients	611	61	39
Laryngectomy-free	479	62	39
Laryngectomy (survival from start of radiation treatment)	132	55	39
Laryngectomy (survival from time of operation)	132	52	39

Discussion

The details of the radiotherapy schedules used in the treatment of carcinoma of larynx and hypopharynx may not be of major interest to the Head and Neck Surgical Oncologist. Nonetheless, changes in the schedule which might result in a reduced cure rate, particularly in the eminently curable early glottic lesions, will concern the surgeon. A proportion of patients managed radiotherapeutically will at a later date require salvage surgery, and the surgeon will be anxious lest the radiotherapy schedule used, increases the hazards associated with major surgery.

Balanced against these factors must be the impact on the patient of the frequency of attendance for radiotherapy and willingness on the part of often elderly patients to attend at all. Economic factors are bound to play a part in management decisions, particularly at this time of diminishing budgets, and clearly a schedule that treats with three fractions per week is likely to be more economical to a department than a five fraction per week programme, if overall treatment duration is the same.

This prospective randomized trial has demonstrated no statistically significant difference between a three fractions per week and five fractions per week schedule of radiotherapy in terms of observed survival, age corrected survival, local recurrence, laryngectomy-free survival, and damage to normal tissues. With regard to laryngectomy-free rates, there was a difference which approached statistical significance in the large group of stage I glottic cancers (Fig. 4b). The incidence of laryngectomy is of less value than the incidence of local recurrence in judging the efficacy of the two radiotherapy schedules, since only 47 per cent of all patients with a local recurrence underwent laryngectomy, and to be laryngectomy-free does not necessarily mean to be recurrence-free. The concurrent development of distant metastases and medical fitness to undergo major surgery will be factors affecting the decision to operate for local recurrence. In the stage I glottic sub-group, 15 per cent of the patients in the five fractions per week arm went on to laryngectomy for local recurrence, compared with 21 per cent of the patients in the three fractions per week arm. The fact that a greater proportion of patients in the three fractions per week arm who recurred locally went on to laryngectomy could well have been to those patient's advantage. The laryngectomy rate for tumour recurrence is not necessarily a reflection of the efficacy of the initial radiation treatment. The very similar tumour-free curves for each of the arms in stage I glottic patients (Fig. 3b) are a much more satisfactory

TABLE III

ACTUARIAL SURVIVAL OF PATIENTS WHO WERE NODE NEGATIVE AT ENTRY TO TRIAL ACCORDING TO RECURRENCE AND LARYNGECTOMY

	Number of patients	Percentage survival at 5 years	10 years
(1) No recurrence/no laryngectomy	351	73	50
(2) Recurrence/laryngectomy	120*	52	40
(3) Recurrence/no laryngectomy	128	32	22

*Excludes 12 patients undergoing laryngectomy with no recorded recurrence.
Footnote of statistics:
Statistical comparison between groups 1 and 2 $\chi^2 = 7.99$; p = 0.005.
Statistical comparison between groups 2 and 3 $\chi^2 = 16.7$; p = less than 0.001.

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TABLE IV

COMPARISON OF ACTUARIAL SURVIVAL OF PATIENTS WITH CARCINOMA OF THE LARYNX WHO WERE NODE NEGATIVE AT ENTRY TO TRIAL (GROUP A), WHO UNDERWENT SALVAGE LARYNGECTOMY FOR RECURRENCE, AND PATIENTS WHO DID NOT SUFFER FROM PERSISTENT OR RECURRENT TUMOUR (GROUP B)

		Group A % survival at			Group B % survival at		
T category	Treatment regime	Number patients	5 years	10 years	Number of patients	5 years	10 years
T_1	3F/W	32	81	70*	121	78	55
	5F/W	18	61	39*	102	77	58
	Total	50	74	59	223	78	56
T_2	3F/W	17	31	21	20	75	37
	5F/W	4	50	50	31	76	56
	Total	21	35	26	51	76	49
T_3	3F/W	13	46	29	16	63	25
	5F/W	15	40	27	24	54	38
	Total	28	43	28	40	58	32

*3F/W and 5F/W over 0–10 years: $\chi^2 = 4.92$; $p = 0.027$; p 0.05 would normally indicate a statistically significant difference when all data are included in the analysis, but for subgroups $p = 0.025$ may not even be safely assumed to be statistically significant.

method of comparing the tumour control achieved by the two radiotherapy fractionation schedules.

This trial confirmed that salvage surgery is possible for recurrent disease, and if all node negative cases are considered (T_{1-4}, N_0), observed survival at five years in those having laryngectomy was 55 per cent, and a respectable 39 per cent at 10 years. However, survival in the group with recurrence is significantly worse than that in patients without recurrent disease. It is difficult to judge the effect of the two treatment schedules in terms of potential morbidity following laryngectomy, particularly when it is remembered that the trial covered a 20 year period, with 17 centres involved, and numerous Head and Neck Surgical Oncologists. Using death within three months of a laryngectomy as a parameter of surgical morbidity, there is no significant difference between the two arms.

Careful recording of early normal tissue radiation reactions revealed an equal effect in both arms. Similarly, the late radiation reactions were comparable at 59 per cent in the three fractions per week and 62 per cent in the five fractions per week groups. In terms of severe damage that might have had an influence on surgical management, there was no difference between the two groups and, in the event, this was low, and similar in the two arms, as shown by the perichondritis rate of 6 per cent.

Conclusion

The two radiotherapy fractionation schedules chosen for comparison (three fractions per week *versus* five fractions per week), with appropriate dose modification, have been found to give comparable results in terms of survival, tumour control and normal tissue damage. The curtailed schedule (three fractions per week) may offer social advantages for patients, with the additional benefit of being more economical. Neither fractionation schedule demonstrates a clear-cut advantage with respect to later surgery. The trial has demonstrated that salvage surgery is possible with a respectable overall survival rate. The trial provides valuable evidence on which the Head and Neck Oncologist may base his choice for further treatment policies.

Acknowledgements

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References

British Institute of Radiology Working Party (1990) Final report of the general clinical results of the British Institute of Radiology Fractionation Study of 3f/week versus 5f/week. *Radiotherapy of the Laryngo-pharynx*, **63:** 169–180.

Dobbs, J., Barrett, A. (1985) Larynx. In *Practical Radiotherapy Planning*. Edward Arnold (Publishers) Ltd.: London. p. 21.

Groves, J., Gray, R. F. (1985). In *A Synopsis of Otolaryngology*. Wright: Bristol. p. 399.

Henk, J. M., Whittam, D. E. (1982) Ear, Nose and Throat. In *Treatment of Cancer*. Chapman & Hall Ltd.: London. p. 236.

Mantel, N. (1966) Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports*, **5:** 163–170.

Million, R. R., Cassisi, N. J., Wittes, R. E. (1982) Cancer in the Head and Neck. In *Cancer Principles and Practice of Oncology*. J. P. Lippincott Company, Philadelphia, Toronto. p. 361.

Preliminary Report of the Working Party of the British Institute of Radiology on the Effects of Dose Fractionation in Radiotherapy (1963) *British Journal of Radiology*, **36:** 382–383.

Rezvani, M., Alcock, C. J., Fowler, J. B., Haybittle, J. L., Hopewell, J. W., Wiernik, G. (1989) A comparison of the normal tissue reactions in patients treated with either 3F/week or 5F/week in the BIR Trial of Radiotherapy for Carcinoma of the Laryngopharynx. *International Journal of Radiation Biology*, **56:** 717–720.

Robin, P. E., Olofsson, J. (1987) Chapter title, In *Scott-Brown's Oto-*

laryngology, Fifth Edition, Vol. 5, *Laryngology* (Stell, P. M. and Kerr, A. G., eds.) Butterworths: London, Boston.
Souhami, R. L., Tobias, J. S. (1986) Cancer of the Head and Neck. In Cancer and its Management. Blackwell Scientific Publications: Oxford. p. 156.
U.I.C.C. (1968) *TNM Classification of malignant tumours*. First edition. (International Union Against Cancer, Geneva).
U.I.C.C. (1974) *TNM Classification of Malignant Tumours*, Second edn., (International Union Against Cancer, Geneva).
U.I.C.C. (1978) *TNM Classification of Malignant Tumours*, Third edn., (International Union Against Cancer, Geneva).
U.I.C.C. (1987) *TNM Classification of Malignant Tumours*, Fourth edn., International Union Against Cancer (Springer-Verlag, London).

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