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LOW DOSE IRRADIATION IN ADVANCED TUMOURS OF HEAD AND NECK

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The increasing interest in continuous low dose rate irradiation seems to justify a report on the results of a second series of patients treated between December 1971 and August 1973 at this hospital. In the first series, 6 cases with head and neck neoplasms were treated at L'Institut Gustave Roussy between January and December 1970 (PIERQUIN & BAILLET 1971) and the results were sufficiently encouraging for a second series to be begun. Only the 19 cases with more than 9 months follow-up are reported here; an account of the results of the entire series is in preparation.

No definite conclusions can yet be drawn regarding the place of low dose rate irradiation in the management of advanced head and neck tumours, but certain trends seem clear, as well as certain effects associated with this technique alone.

The clinical staging used is that described by PIERQUIN et coll. (1970); this TNM classification is based essentially on the apparent dimensions of the tumour: T1: 1 cm; T2: 1 to 2 cm; T3a: 3 to 4 cm; T3b: 4 to 5 cm; T4a: 5 to 7 cm; T4b: more than 7 cm. The staging is also influenced by the type of the tumour growth, i.e. exophytic, infiltrative or ulcerative.

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Table 1

The material of 19 patients with tumours of the mouth and pharynx

Case No.	Age	Sex	Tumour Site	Extension	Stage
1	57	M	Tonsil	Palate, tongue	T4a N3
2	78	M	Vallecula	Posterior 2/3 tongue	T3b N3
3	60	M	Base of tongue	Complete fixation	T4b N1
4	67	M	Base of tongue	Mid 1/3 tongue and floor	T4a N0
5	48	F	Mobile tongue	Tonsil and post. 1/3	T4a N3
6	51	M	Laryngo-pharynx	Tongue	T4b N0
7	60	M	Soft palate	Uvula, tonsil	T3a N3
8	85	M	Base of tongue	Pyriform sinus	T3b N0
9	50	M	Tonsil	Tongue	T4a N2
10	47	M	Floor of mouth	Gingiva, tongue	T4a N3
11	62	M	Base of tongue	Fauces, floor of mouth	T4a N0
12	51	M	Tonsil	Post. 2/3 of tongue	T4a N0
13	44	M	Tonsil and tongue*	Post. 1/3 of tongue	T4b N3
14	46	M	Epiglottis	Pharyngal walls	T3b N0
15	48	M	Base of tongue	Tonsil, mid 1/3	T4a N0
16	49	M	Mobile tongue	Post. 1/3	T4a N3
17	77	M	Base of tongue	Post. 1/3	T3b N3
18	60	M	Hypopharynx	Vallecula, larynx	T4b N1
19	66	M	Tonsil and tongue	Vallecula, larynx	T3b N3

* This patient had two tumours on opposite sides.

Material and Methods. On admission all 19 patients had advanced tumours of the upper respiratory and alimentary tracts, which would have had a grave prognosis if treated by conventional radiation therapy (CHASSAGNE 1958, PIERQUIN et coll. 1966). The site of origin of the tumours and their clinical extension and staging are given in Table 1, as well as the age and sex of the patients. With few, if any, exceptions the major aetiologic factor was alcohol, closely followed by tobacco (WYNDER et coll. 1957), and the general condition of most patients was poor.

All patients were treated by a Theratron junior, whose source had been replaced by a small industrial source with a cross-sectional area of 0.78 cm^2, and at installation in December 1971 had an activity of 45 Ci.

The patients were treated lying down with the head held gently by calipers or sandbags. In the first series it was found that rigid immobilisation was neither tolerable nor necessary.

Irradiation was given by two direct, parallel opposed, horizontal beams of equal size for 7 to 8 hours per day. At a source to skin distance of 55 cm, this gave a daily tumour fraction of 800 to 1 000 rad (range of output, 103 to 139 rad/h). A minimum

Table 2

Treatment and results

Case No.	Dose (rad)	Treatment		Survival (months)	Recurrence	Necrosis	Condition in March 1974
		Time (days)	No. of fractions				
1	7 000	10	8	6.5	Probable	No	Dead, following tracheostomy
2	7 000	10	8	6	No	No	Dead, of bronchial carcinoma
3	7 000	10	8	25	No	Large	Alive
4	7 000	9	7	18	No	Small	Dead, of prostatic carcinoma
5	7 000	13	11	24	No	Large	Alive
6	7 000	10	8	8	Not known	Large	Dead, following gastrostomy
7	7 000	13	11	23	No	No	Well
8	7 000	10	8	21	No	No	Well
9	7 000	10	8	8	Yes	No	Dead, of recurrence at site of treated area
10	7 000	16	12	19	Yes	Yes	Alive
11	6 500	13	11	10	Yes	No	Dead, of persistent disease
12	3 500 + 3 500	35	5 + 5	14	No	Yes	Dead, of gastro-intestinal haemorrhage
13	3 500 + 3 500	47	5 + 5	13	Yes	No	Dead, of primary tumour
14	4 500 + 2 500	45	6 + 4	15	No	No	Well
15	4 500 + 2 500	48	7 + 4	14	No	No	Well
16	4 500 + 2 500	51	6 + 4	8.5	Yes	No	Dead, of primary tumour outside treated area
17	4 500 + 2 500	67	6 + 5	12	No	No	Well
18	7 000	18	14	11	Possible	Yes	Alive
19	4 500 + 2 500	44	5 + 4	11	No	No	Well

of 5 treatments were given per week, but weekends, holidays and staffing arrangements sometimes caused gaps between one or two sessions. Provided that an opportunity for refreshment and to walk about was given every hour or two, the long immobilisation was well tolerated.

Apart from 7 patients who underwent split-course irradiation, the midpoint, axial dose received was 7 000 rad, in 8 to 11 fractions. This represents 6 300 rad to the 90 per cent isodose, which encompassed the tumour volume.

The initial treatment volume included the tumour, a margin of healthy tissue, and the sub-digastric and jugulo-carotid lymph nodes, if clinically involved. This gave a maximum cross section of the irradiated volume of 10 cm by 8 cm, which was reduced if possible when 4 500 rad had been administered.

If the cervical nodes were clinically involved, the lower nodes were treated by standard ^{60}Co irradiation, and a neck dissection was recommended 3 months after the end of irradiation.

The 7 patients who underwent split course irradiation were treated in the same way, except that after 4 500 rad an interval of 3 to 6 weeks was interposed to allow re-oxygenation of the tumour and to lessen the reaction of the normal tissues.

Results

A summary of the results appears in Table 2. Recurrence or necrosis, if any, occurred in less than 9 months. All the survivors without symptoms or signs of tumour have passed this period and may be expected to remain cured. Provisional figures can be given as follows: of the 19 patients treated, 10 are alive, of whom 8 are without signs of malignant disease at the original site, and 9 are dead. Of the latter, 3 tumour free patients died of intercurrent disease (Nos 2, 4, 12) and 5 due to continued growth of the original tumour. There have been 8 definite or probable recurrences, 2 of which were at the margin of the treated volume.

Tumour regression. The rate of regression of these extensive tumours was striking, and the same may be said of the nodal regression; in 15 of the 19 patients there was no evidence of tumour 3 months after treatment and recurrence occurred in 3 cases only, at 4 months, at 9 months (masked by a necrosis), and probably at 6 months, respectively (Nos 10, 7, 18). The mean time for the tumour to disappear clinically was 39 days (14 observations, maximum 60 days, minimum 30 days).

Radical neck dissections were performed after 3 months in 5 patients who, at presentation, had had clinically involved lymph nodes. In only one specimen, an N2 case, was residual tumour tissue found. The negative cases had been N1 in one case and N3 in three.

Skin reactions. (a) Early. Of the 19 patients, 2 developed moist desquamation, and 6 dry desquamation at the height of their reaction. The remainder had only a well demarcated erythema. All these reactions were more intense in the lower (cervical) part of the field than in the upper (facial) part. The skin dose was of the order of 7 000 rad, given in 8 to 11 fractions.

(b) Late. There were practically no late changes in any of the surviving patients. There were no telangiectases and no definite subcutaneous induration. The skin re-

tained its normal thickness and elasticity and could be moved over the underlying tissues without difficulty. Apart from depilation and very slight pigmentation, the skin remained indistinguishable from normal.

Mucosal reactions. (a) Early. Sixteen of the 19 patients developed severe mucosal reactions, with confluent false membrane formation. Two others (in neither of these had the tumours disappeared) had only moderately severe reactions, whilst one patient inexplicably produced only a slight mucositis. The tumour in the latter case did not regress either.

(b) Late. Like the late skin changes, the late mucosal changes were slight. There were some telangiectases but the mucosa retained its normal consistency and suppleness, and induration did not occur.

Complications. The high rate of tumour regression was not obtained without some complications of which necrosis was the most common. Six patients developed large necroses requiring special care and one had a small necrosis causing no inconvenience up to the time of his death from carcinoma of the prostate (No. 4). Of the 7 cases of necrosis, 4 were confined to the tumour bed and of these patients, 3 have died: one (No. 1) of pulmonary complications following a tracheostomy for laryngeal oedema, one (No. 6) of septicaemia following a gastrostomy, and one (No. 12) of haemorrhage from a benign peptic ulcer. The latter patient, together with 2 others (Nos 3, 6) had a gastrostomy to facilitate nutrition following large necroses of the tumour located in the tongue. In 3 patients the necrosis extended outside the tumour site. One was small (No. 4), another patient (No. 5) continued to smoke and drink heavily and refused all dental care, with the result that a massive bilateral necrosis of the mandible with fistulas developed which, however, caused only slight inconvenience. The third patient (No. 10) had necrosis in the remaining tumour. Haemorrhage from these necroses occurred rarely and only once required the ligation of the internal carotid artery (No. 1).

Discussion

The results of this second series seem to justify the tentative conclusions drawn from the first one. In the previous series the first two pharyngeal tumours were each treated with 3 000 rad. This dose was chosen because normal tissue reaction begins at about this dose in classical fractionated irradiation. In both patients, the tumour volume decreased (approximately 50 %) with only a slight mucositis and without evident skin reaction. This result encouraged us to treat the remaining head and neck tumours with a tumour dose of 7 000 rad.

The conclusions drawn from the first series were threefold: the immediate reactions to 7 000 rad given by continuous low dose rate irradiation were severe, but tolerable; the late effects on the skin and mucosa were slight, but there appeared to

be a risk of necrosis in extensive tumours; and the effect on the tumour was greater than that of conventional fractionated irradiation, with a total regression of tumour in the treated volume within 2 to 3 months.

The present series has confirmed and amplified those conclusions. The technique was entirely feasible. The patient tolerated 7 or 8 hours irradiation per day and the treatment set-up was easily and simply maintained for that period of time without elaborate immobilisation techniques.

The dose, 7 000 rad maximum, seems to have been right. Although the mucosal reactions were severe, they were no more severe than is seen in the short radical course of fractionated irradiation of head and neck tumours, and many patients have maintained their nutrition at home. The skin reaction, however, is markedly less than that encountered following a fractionated course given in a cast or jig.

A dose of 7 000 rad seemed to have an effect on the tumour in nearly all cases. In one patient (No. 11), however, the necrotic tumour did not regress completely, nor did the skin or the mucosa show more than slight signs of having been irradiated. Retrospectively the technical factors were controlled and found satisfactory and the failures to respond remain unexplained.

Of 4 recurrences, 2 occurred outside or at the limit of the treated volume and the remaining 2 followed the split course treatment.

On the other hand it may be that the dose of 7 000 rad is marginally too high. Seven necroses (6 extensive) in 19 patients is a high rate but all of the patients with necrosis had T4 tumours. It must be emphasised that there has been no recurrence and no necrosis in any of the 6 uncomplicated T3 tumours up to the present time (July 1974).

It seems that the RBE of continuous low dose rate external irradiation cannot be the same as that of high rate irradiation since daily doses of 1 000 rad given at the usual rate would undoubtedly be unsupportable for more than a very few treatments. The time relationships of the reactions and the effect on the tumour closely resemble those of implantation which is not merely a reflection of a small volume, but is due also in part to the low rate of irradiation. Furthermore, the remarkable efficacy of the irradiation in treating extensive, ulcerating tumours suggests that it may have a lower oxygen enhancement ratio than conventionally fractionated irradiation.

In a third series, just started, the effectiveness of low-output irradiation will be compared prospectively with conventional cobalt-therapy in a controlled trial of treatment of T3 head and neck tumours. This stage has been chosen since T3 tumours are more narrowly defined than T4 tumours which develop complications that are attributable more to destruction of normal tissue than to the treatment.

A word of caution is necessary, however. Late necrotic complications may develop after the present period of observation and for this reason a split course therapy will be used in the third series (3 500 rad $\times$ 2, with a three week interval) accepting the higher risk of recurrence.

Conclusion

A second series of 19 patients with T3 and T4 tumours of the mouth and pharynx has been treated by fractionated low dose rate irradiation. The results have confirmed the conclusions tentatively drawn from a first series of head and neck tumours, that such treatment is feasible, tolerable and highly effective. Regression occurred in a large proportion of tumours, though at the expense of a rather high necrosis rate: complications, however, were only encountered in the T4 cases. Further improvement in results are expected from a closer selection of patients in a planned comparative trial.

SUMMARY

A material of 19 patients with T3 and T4 tumours of the mouth and pharynx was treated by fractionated low dose rate irradiation. Regression occurred in a large proportion of tumours but at the expense of a high rate of necrosis.

ZUSAMMENFASSUNG

Neunzehn Patienten mit T3 und T4 Tumoren des Mundes und Pharynx wurden mit fraktionierter Bestrahlung mit niedriger Dosis-Leistung behandelt. Eine Regression war bei einem grossen Teil der Tumoren zu verzeichnen, jedoch auf Kosten einer hohen Frequenz von Nekrosen.

RÉSUMÉ

Dix-neuf malades atteints de cancers ORL largement étendues (T3 et T4) ont été irradiés par télécobalthérapie à faible débit. La régression tumorale a été totale dans la grande majorité des cas; les nécroses au sein du volume tumoral ont été relativement fréquentes.

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