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EN-BLOC IRRADIATION OF TUMOURS OF THE HEAD AND NECK AND THEIR LYMPHATICS

II. Early results and side effects

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A technique for en-bloc irradiation of tumours of the head and neck and their lymphatics using ^{60}Co and 8 MV roentgen rays has recently been described (LANDBERG & SVAHN-TAPPER 1976). This technique is a multi-field treatment, allowing for a high radiation absorbed dose in both the primary tumour and its regional lymph nodes in the neck, without exceeding the tolerance dose of organs at risk such as the spinal cord. The report included a description of patient immobilization, dose planning, simulation, and surveyance of treatment. The dose distributions for the first 68 patients who received a full treatment were analyzed.

The early treatment results and the side effects are now reported in the 68 patients who concluded the radiation and in 6 who discontinued the treatment.

Material and Methods

The material included 74 patients with primary malignant tumours of the head and neck region, who were treated with the new technique during the years 1971 to 1975.

The site of the primary tumour was the nasopharynx in 10 patients, the hypo-

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pharynx in 19, the larynx in 10, the thyroid gland in 18; 17 patients had miscellaneous tumours mainly of the oral cavity.

The lesions had been classified according to the TNM system of UICC (1974). No patient had distant metastases at the time of treatment.

The radiation therapy was combined with major surgical procedures in totally 23 patients. The irradiation was given before surgery in 3 patients, following surgery in 18, and 2 patients received irradiation both before and after the operation.

In 22 patients chemotherapy was given, and then mainly for relapsing disease.

The patients were followed regularly. The follow-up was concluded on 1 January 1976, and had then ranged from 1 to 5 years.

Radiation side effects were divided into early effects and late effects. The early side effects were recorded as mucositis, dryness of the mouth, skin reactions (e.g. erythema or moist epidermitis), impaired food intake, and 'others'. Late side effects were divided into dryness of the mouth, dental decay, osteonecrosis induced by radiation, fibrosis of normal connective tissue, skin reactions (e.g. cutaneous atrophy or ulceration), and 'others'. For both early and late reactions a 4-grade scale was used, where 0 = no detectable reaction, + = normal radiation side effect, + + = more marked but during the follow-up clinically reversible side effect, and + + + = marked and irreversible side effect (e.g. necrosis).

For each patient the minimum radiation absorbed dose in demonstrated tumour had been calculated as well as the maximum target absorbed dose. For each patient the cumulative radiation effect (CRE) was calculated for these 2 absorbed dose values. Most treatments had been given in 2 series, with two thirds of the total absorbed dose in the first series and an interval of 4 to 5 weeks between the two series. When calculating the CRE, gap correction according to KIRK et coll. (1975) was used.

Conclusions about the results of treatment could only be drawn regarding tumours of the nasopharynx and tumours of the hypopharynx. In other sites the results did not at the time of follow-up lend themselves to a meaningful analysis for several reasons, such as heterogeneity of the patient material or of types of combinations of different treatment modalities, or due to too short follow-up. All 74 patients were suitable for the analysis of the radiation side effects.

Clinical data for all patients are given in Table 1.

Tumours of the nasopharynx. Ten patients had a nasopharyngeal tumour, 5 males and 5 females; the ages ranged between 26 and 72 years, with a mean of 55.

Seven patients had anaplastic carcinoma, and 3 poorly differentiated squamous cell carcinoma.

Five of the tumours were classified as T1, and 5 as T2, and the nodal status was N0 for 2 patients, N1 for 2, N2 for 3 and N3 for 3 patients.

Tumours of the hypopharynx occurred in 19 patients, 17 males and 2 females; their ages ranged between 54 and 83 years, with a mean of 66.

Table 1

Distribution of sex, age, and TNM-stage in 74 patients. All patients were in M 0 stage

Site	No. of cases	Males	Females	Age (range and mean)	TNM								
					T0	T1	T2	T3	T4	N0	N1	N2	N3
Nasopharynx	10	5	5	26–72 (55)	—	5	5	—	—	2	2	3	3
Hypapharynx	19	17	2	54–83 (66)	—	3	7	5	4	12	2	4	1
Larynx	10	9	1	47–73 (60)	—	—	4	3	3	5	4	1	—
Thyroid	18	10	8	16–80 (58)	—	—	6	5	7	9	4	5	—
Miscellaneous tumours of the oral cavity	17	13	4	25–76 (68)	2	3	1	5	6	9	3	1	4

One patient had an anaplastic carcinoma, and 17 squamous cell carcinoma, which was poorly differentiated in 3 and moderately or well differentiated in 14. In one patient only cytologic examination of a lymph node metastasis was performed which revealed necrotic carcinoma.

Three of the tumours were classified as T1, 7 as T2, 5 as T3 and 4 as T4. The nodal status was N0 for 12 patients, N1 for 2, N2 for 4, and N3 for 1 patient.

Tumours of other sites. Ten patients had carcinoma of the larynx, 18 carcinoma of the thyroid, and 17 miscellaneous tumours of mainly the oral cavity. For all these 45 patients the tumours were classified as T0 in 2 instances, as T1 in 3, as T2 in 11, as T3 in 13, and as T4 in 16, and the nodal status was N0 for 23 patients, N1 for 11, N2 for 7 and N3 for 4 patients. Thus, these patients generally had advanced tumours.

Results and Discussion

Early treatment results

Tumours of the nasopharynx. The radiation therapy was concluded in all 10 patients. The minimum radiation absorbed dose in demonstrated tumour was 61 Gy given in 36 fractions during 90 days split-course, all mean values.

In all 10 patients a complete regression of the nasopharyngeal tumour was obtained. In 7 of the 8 patients with palpable neck metastases a total regression of the neck masses occurred, whereas in 1 the enlarged nodes persisted. A neck dissection was performed in this patient.

Four patients are alive with no evidence of disease at 24, 26, 27 and 29 months, respectively, after treatment. Four have died after 13, 13, 22 and 44 months, respectively, with distant metastases but no local recurrence, and 2 patients have died after 14 and 19 months, respectively, with distant metastases and local recurrence.

In 5 of the patients distant metastases were the first new indication of disease and

were diagnosed 9 to 40 (mean 17) months after the beginning of the treatment. In one patient a local recurrence was the first new sign of disease, being diagnosed after 6 months.

Three of the 4 patients alive without evidence of disease had initially lymph node metastases. In 2 of them the nodal status was classified as N1, and in the third as N2. The follow-up for these 3 patients is 24, 26 and 29 months, respectively.

Six of the 10 patients have had distant metastases, which were diagnosed after 8 to 40 (mean 17) months.

Radiation therapy is considered to be the method of choice in the treatment of malignant tumours of the nasopharynx. Recently, 3 large patient series have been reported (WANG & MEYER 1971, LEDERMAN 1975, HOPPE et coll. 1976). WANG & MEYER found that patients without regional metastases had an overall 5-year survival rate of 54 per cent, whereas patients with unilateral lymphadenopathy had a survival rate of only 38 per cent. In the series of LEDERMAN, the corresponding values were 46 and 18 per cent, respectively. Thus the occurrence of regional lymph node metastases has a significant influence on the survival, and it would seem to be preferable to treat the lymph nodes in the neck before metastases are detectable, an opinion which is supported by the report of HOPPE et coll. They found prophylactic irradiation of the neck always to be successful if the primary site was controlled. The anatomic distribution of these regional lymph nodes has been explored by LINDBERG (1972). He found that the upper parts of both the deep and the posterior cervical lymph nodes had the highest incidence of metastases. These nodes as well as practically all other lymph nodes in the neck and the supraclavicular fossae are included in the target volume with the technique used in the present series.

Of the present 10 patients, 8 were locally symptom-free in the nasopharynx and the cervical lymph nodes, but 6 relapsed at distant sites. Distant failure also dominated in the series of HOPPE et coll., but their patients also had a high frequency (21 %) of local failure.

The technique used in the present series resulted in a good cure-rate in the nasopharynx and cervical lymph nodes. The main obstacle for cure was distant metastases, which occurred within 2 years. This length of interval was considered by LEDERMAN to be critical for the evaluation of treatment of tumours of the nasopharynx, and thus, though the follow-up averaged only 17 months in the present series, it may be concluded that the irradiation used is sufficient for achieving acceptable local cure. However, there may be a need for systemic treatment of occult distant metastases.

Tumours of the hypopharynx. The radiation therapy was concluded in 17 patients, but discontinued in 2 because of poor general condition. Patients who concluded treatment received a minimum radiation absorbed dose in demonstrated tumour of mean 60 Gy, given in mean 34 fractions over mean 82 days split-course.

Nine patients had a total regression of all demonstrated disease. Three had T1 tumours, 4 had T2, 1 had T3 and 1 had T4; and the nodal status was N0 for 8

Table 2

Number of patients with early and with late radiation side effects of marked character

		Marked late radiation side effects	
		Yes	No
Marked early radiation side effects			
Yes	40	13	27
No	34	1	33
Total		14	60

patients. Two of the 9 patients with complete remission are alive without evidence of disease at 42 and 45 months, respectively, after treatment, and one is alive with a local recurrence (follow-up 22 months), whereas 6 have died after mean 24 months, all 6 with a local recurrence and 2 of them also with distant metastases.

Ten patients had only a partial remission; all 10 have died after mean 9 months, one of them also having distant metastases.

Distant metastases thus occurred in 3 of the 19 patients, and they were diagnosed after 10, 11 and 14 months, respectively.

A neck dissection was performed in one patient; otherwise surgery was not applied.

In the present series, irradiation was used as the treatment of tumours of the hypopharynx. Most tumours were of moderate or advanced size at diagnosis. On the other hand a relatively low frequency of regional lymph node metastases was encountered. Further, distant metastases occurred in only a few cases.

The early results indicate a fair local response initially after radiation therapy, since all tumours showed a regression of varying degree. However, most patients died within 2 years, and then above all because of a local recurrence at the site of the primary tumour or in the cervical lymph nodes.

Since failures occur early in carcinoma of the hypopharynx, a relatively short follow-up may be adequate for evaluation of the treatment results.

Figures for results of therapy in carcinoma of the hypopharynx vary widely in the literature, and it is difficult to get a representative impression of the value of different therapeutic modalities. Most reports are not based on prospective controlled series, and a breakdown into subgroups of stage and type of therapy usually gives such small materials that general conclusions are not warranted. However, it is apparent that radiation therapy alone usually only offers a short-lasting remission, and cures are usually reported to be unusual. Thus, CARPENTER et coll. (1976) reported a 5-year survival rate of only 4 per cent after radiation therapy alone.

Apparently a more aggressive therapeutic approach is needed in order to improve the results. FLETCHER & JESSE (1977) found a reduction in local recurrence rate from

Table 3

Radiation absorbed dose, number of fractions and number of days for patients with and without early and late radiation side effects

	Early radiation side effects		Late radiation side effects	
	Normal	Marked	Normal	Marked
Absorbed dose (Gy)				
Maximum target absorbed dose				
Range	29–76	30–81	29–81	53–77
Mean	64	66	65	65
SD	9	8	9	6
Minimum absorbed dose in demonstrated tumour				
Range	23–64	26–68	23–69	46–65
Mean	55	56	56	56
SD	9	9	9	7
Number of fractions				
Range	12–41	15–43	12–41	27–43
Mean	32	33	32	34
SD	6	5	5	5
Number of days				
Range	17–153	21–126	21–153	61–126
Mean	80	81	79	88
SD	24	18	21	18

35 per cent for radiation therapy alone to 11 per cent with a combination of surgery and irradiation. They recommended a relatively restricted surgery followed by radical irradiation.

Carcinoma of the hypopharynx is a deleterious disease, and today no apparent way to improve the results is visible.

Radiation side effects

Early radiation side effects of marked degree (grades + + or + + +) were observed in 40 of the 74 patients (Table 2), the remaining 34 having no or only slight (grades 0 or +) side effects. Twenty-three of the 40 had more than one reaction. Marked mucositis occurred in 14 patients, a very dry mouth in 5, moist skin reaction in 5, and impaired food intake in 22.

In 6 patients the treatment had to be discontinued, most often due to early side effects in old and debilitated patients.

Late radiation side effects of marked degree (grades + + or + + +) occurred in 14 patients. Ten experienced a very dry mouth, 2 had abnormal dental decay, and 4 had soft tissue fibrosis. No instance of skin ulceration and no case of radiation myelopathy occurred.

Table 4

CRE-values for patients with and without early and late radiation side effects

	Early radiation side effects		Late radiation side effects	
	Normal	Marked	Normal	Marked
Number of patients	34	40	60	14
CRE-value of				
Maximum target absorbed dose				
Range	1 170–1 990	1 120–2 130	1 120–2 130	1 460–1 960
Mean	1 700	1 750	1 750	1 700
SD	250	176	174	135
Minimum absorbed dose in demonstrated tumour				
Range	930–1 700	970–1 880	930–1 880	1 080–1 800
Mean	1 500	1 550	1 550	1 500
SD	169	174	172	180

When treating a nasopharyngeal tumour, care has to be taken to avoid radiation effects in the eyes, optic fascicles (DESCHRYVER et coll. 1971), brain stem and pituitary gland. Such radiation side effects did not occur in the present series.

The correlation between the occurrence and non-occurrence of early and late radiation side effects, respectively, appears in Table 2. Of the 40 patients with marked early reactions, 13 also had marked late reactions. Of the 34 without marked early reactions, 1 later had a marked late reaction (dental decay due to xerostomia).

An analysis was carried out to see if there were any particular characteristics about the patients who developed marked early or late radiation side effects.

In an area like the head-and-neck, it may often be difficult to establish precisely if a reaction is a pure radiation reaction of normal tissue. Radiation reactions of the tumour, infection, and poor food intake may also play a role. Further, the premorbid condition of the mucosal lining and the connective tissue also play a role, a factor which has long since been established. The age of the patient may also be assumed to play a role due to less perfect regenerative capacity in high age and a more strained circulation.

The relation between side effects and absorbed dose, number of fractions, and number of treatment days was analyzed (Table 3). The maximum target absorbed dose and the minimum absorbed dose in demonstrated tumour were chosen for this analysis, since their distribution corresponds well with the region of radiation reactions. The largest absorbed dose value was taken as the maximum provided its isodose included an area of at least 2 cm^2 in a section. The minimum value represents an absolute minimum in demonstrated tumour. The size of the target volume only varied little in the present series and all patients were treated with the method described. From Table 3 it appears that no separation between the occurrence and the

Table 5

Age of patients with and without marked early and late radiation side effects

	Marked early radiation side effects		Marked late radiation side effects	
	Yes	No	Yes	No
Range	26–83	16–80	47–76	16–83
Mean	63	61	69	60
SD	12	13	7	13

non-occurrence of side effects could be demonstrated only on the basis of absorbed dose and fractionation. However, the analysis includes 6 patients in whom treatment was discontinued, mainly due to side effects. These patients only received low absorbed doses, and thus to some extent bias the analysis.

For each patient a calculation of the CRE-value for the absorbed dose levels given in Table 3 was performed. The CRE-values for groups with and without early and late radiation reactions, respectively, appear in Table 4. No correlation between CRE-values and radiation reactions was found.

The CRE-concept (KIRK et coll. 1971) is based on the NSD-concept (ELLIS 1969). The derivation of the NSD-concept allows for its use for comparison between different fractionation schedules and different absorbed dose levels with respect to one radiation reaction, namely late necrosis of normal connective tissue. KIRK et coll. stated that the CRE-concept could also be used for comparison of different levels of normal radiation effects on connective tissue up to and including necrosis. In the present series no case of late necrosis of normal connective tissue was found, and thus the use of the NSD-concept (and CRE-concept) according to the original definitions laid down by ELLIS is not warranted. Nor could a separation on the basis of CRE-values be found when considering late reactions other than necrosis, or when considering early reactions.

The age of the patient may be considered to be of importance. Patients with late reactions were somewhat older than those without (Table 5), but for early radiation reactions, no age difference could be demonstrated.

The site of the tumour seems to be of importance for the occurrence of reactions (Table 6). Early reactions were particularly common in patients in which the tumour was located to the food passages (oral cavity and hypopharynx). Late reactions did not show any clear trend.

Surgery did not seem to be an important factor for the development of marked radiation side effects since of 40 patients with early such effects, in only 8 had major surgery been performed, and of 14 with late such effects, only 2 had been operated upon.

Table 6

Frequency of marked early and late radiation side effects for different tumour sites. Each number denotes number of patients

Tumour localization	No. of patients	Marked early radiation side effects		Marked late radiation side effects	
		Yes	No	Yes	No
Nasopharynx	10	5	5	3	7
Hypopharynx	19	14	5	5	14
Larynx	10	3	7	0	10
Thyroid	18	6	12	3	15
Oral cavity	17	12	5	3	14
Total	74	40	34	14	60

Early and late reactions after radiation therapy of tumours of the head and neck often represent complex effects. It is usually not a simple task to sort out what quality or quantity of reactions that depend only on the ionizing radiation, and which role other factors such as tumour reaction, effects of surgery, and infection may play. In the present series, reactions of clinical importance were particularly frequent in patients who had tumours of the oral cavity and the hypopharynx. The size of the total absorbed dose in the range used probably also plays a role, even though this could not be demonstrated in the present series, which only had a limited range of this parameter. Also, the CRE values did not give a separation between patients with and without reactions.

The present series illustrates a common difficulty in the evaluation of tissue tolerance, since patient series, when other parameters are comparable, usually differ only little as regards radiation absorbed dose and fractionation.

SUMMARY

The results and side effects of en-bloc irradiation of ear, nose and throat tumours and their lymphatics showed that the technique had been successful in nasopharyngeal carcinoma, but poor in carcinoma of the hypopharynx. Marked early and late radiation side effects were relatively common in high age and with certain tumour sites, whereas no correlation could be demonstrated with total absorbed dose, fractionation, cumulative radiation effect or major surgery.

ZUSAMMENFASSUNG

Die Ergebnisse und Nebeneffekte einer en-bloc-Bestrahlung von Ohren-Nasen-Hals-Tumoren und deren Lymphgefässe zeigte, dass die Technik erfolgreich beim Nasopharynx-Karzinom ist, jedoch wenig erfolgreich beim Karzinom des Hypopharynx. Ausgeprägte frühzeitige und späte Strahlennebeneffekte waren relativ gewöhnlich bei hohem Alter und bei gewisser Tumorgrösse, während keine Korrelation zur gesamtabsorbierten Dosis, der Fraktionierung, dem kumulativen Strahleneffekt oder umfassender Chirurgie gefunden werden konnte.

RÉSUMÉ

Les résultats et les effets secondaires de l'irradiation en bloc de tumeurs oto-rhino-laryngologiques et de leurs lymphatiques ont montré que cette technique a été efficace dans le carcinome naso-pharyngien mais a donné de mauvais résultats dans le carcinome de l'hypopharynx. Les effets secondaires précoces et retardés des radiations ont été relativement fréquents chez les sujets d'âge élevé et dans certains sièges de tumeurs alors qu'on ne peut pas mettre en évidence de corrélation avec la dose absorbée totale, le fractionnement, l'effet cumulatif de l'irradiation ou une chirurgie majeure.

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