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NEOADJUVANT CHEMOTHERAPY AND HYPOFRACTIONATED IRRADIATION IN THE TREATMENT OF HEAD AND NECK CANCERS

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Abstract

NEOADJUVANT CHEMOTHERAPY AND HYPOFRACTIONATED IRRADIATION IN THE TREATMENT OF HEAD AND NECK CANCERS.

A study has been initiated to assess the feasibility and efficacy of combining chemotherapy with irradiation in head and neck cancers. A total of 151 consecutive patients were enrolled, all recently diagnosed and previously untreated. There were 118 males and 33 females, ranging in age from 27 to 91 years. The predominant sites were: oropharynx (58), oral cavity (31), larynx (29) and hypopharynx (18). Most tumours were locally advanced (21 T_1, 40 T_2, 54 T_3, 34 T_4) with frequent lymph node involvement (77 N_0, 23 N_1, 5 N_2, 44 N_3). Squamous cell carcinoma was present in 144 cases. The chemotherapy consisted of a low dose combination of bleomycin (10 mg), etoposide (100 mg) and cis-platinum (15 mg) given on days 1, 3, 5 and 15, 17, 19. A major response rate of 70% was obtained (11% complete response +59% partial response). Primary tumours regressed in 86% of cases and nodes in 58%. The response rates differed according to tumour site, tonsil and floor of the mouth showing maximum sensitivity. Side effects were minimal: 85% nausea, 50% vomiting, 10% mild haematologic depression, 20% alopecia. Ancillary support consisted of anti-emetics but no hyperhydration programme or mannitol diuresis was used. This chemotherapy was carried out on an out-patient basis. A total of 122 cases received exclusive radiotherapy. The treatment was initiated with a mean interval of 14 days. A split-course modality was used, consisting of two treatment periods separated by a 15 day rest interval; each irradiation sequence comprised 6 fractions over 2 weeks. The tumour dose per fraction amounts to 4 Gy, the total dose being 48 Gy with a TDF of 103. Eighty-eight per cent of primary tumours and 54% of lymph nodes had completely regressed at the end of irradiation. Acute side effects remained acceptable and patient compliance amounted to 100%. Late complications were infrequent and no cumulative toxic effect was observed. Two year survival rates for 36 stage III and 64 stage IV patients are 57 and 50%, respectively. Results at 3 years indicate 48 and 31% survival. Preliminary comparison with historical controls only shows trends in favour of neoadjuvant chemotherapy. The combination of chemotherapy with a hypofractionated split irradiation also possesses economic advantages and social benefits: lower staff occupation, better output of treatment machines, reduction of patients' travel and hospital stay.

1. INTRODUCTION

A study has been initiated to evaluate the effects of chemotherapy given before radical treatment in head and neck cancers with bad prognosis. The planned treatment consisted of exclusive radiotherapy or surgery followed by irradiation. We used a course of hypofractionated radiotherapy which has previously proved to be quite effective with minimal acute and late side effects.

The feasibility and efficacy of the neoadjuvant chemotherapy were assessed and a possible benefit on the patients' early survival was tested.

Effectiveness and harmlessness constitute the requirements of neoadjuvant chemotherapy. The main purpose is to obtain a significant reduction of the tumour volume in order to increase radiosensitivity, especially in hypoxic areas, and to ensure a better and easier surgical resection. A lethal effect on occult metastases already present at the time of diagnosis is also anticipated. Side effects should be minimal with good patient compliance. Pre-treatment with chemotherapy must not unduly delay the planned radical treatment nor add peculiar complications to irradiation or surgery.

2. TREATMENT POLICY

All stages of oropharynx, hypopharynx and nasopharynx cancers are treated with chemotherapy before radiotherapy. T_3N_3 and T_4 larynx cases receive the same treatment modality. Most tumours of the oral cavity, whatever the stage, and salivary gland localizations are treated with chemotherapy, surgery and post-operative irradiation.

According to a previous protocol, patients are then eligible for long term maintenance chemotherapy.

3. PATIENT MATERIAL

A total of 151 consecutive patients were enrolled without case selection, all recently diagnosed and previously untreated. There were 118 males and 33 females (sex ratio = 3.58) ranging in age from 27 to 91 years (mean age = 58). The Karnofsky index was higher than 70 in most cases. The minimum follow-up period amounted to 6 months.

The predominant sites of the disease were the oropharynx (mainly tonsil), oral cavity (mainly floor of the mouth and tongue); larynx cancers were all supraglottic and other tumour localizations were involved to a lesser extent (Table I).

TABLE I. TUMOUR SITES

Oropharynx		
Tonsil	46	58
Base of tongue	11	
Soft palate	1	
Oral cavity		
Floor of mouth	12	31
Tongue	12	
Gingiva	4	
Cheek mucosa	2	
Hard palate	1	
Larynx		29
Hypopharynx		18
Nasopharynx		4
Nasal cavities		3
Salivary glands		3

TABLE II. UICC TNM CLASSIFICATION AND AJC GROUPING

	N_0	N_1	N_2	N_3	Total		
T_1	15	2	0	4	21	I	15
T_2	22	6	1	11	40	II	18
T_3	21	7	2	24	54	III	41
T_4	19	8	2	5	34	IV	73
Total	77	23	5	44			

TABLE III. HISTOLOGY

Squamous cell carcinomas		144
Well differentiated	67	
Moderately differentiated	26	
Poorly differentiated	25	
Undifferentiated	3	
Not otherwise specified	23	
Adenocarcinomas		6
Synoviosarcoma		1

Staging refers to the UICC TNM classification and AJC grouping. Most tumours were locally advanced: T_3 and T_4 with frequent lymph node involvement. About 50% of cases belonged to AJC group IV. No metastatic patient was included (Table II).

As regards histology there were essentially squamous cell carcinomas of various degrees of differentiation (Table III).

4. CHEMOTHERAPY PROTOCOL

A single course chemotherapy regimen combines bleomycin (10 mg), etoposide (100 mg) and cis-platinum (15 mg) in a 3 h IV[1] perfusion of 1 L normal saline. This chemotherapy is given 6 times over a 3 week period, on days 1, 3, 5 and 15, 17, 19. Total doses are low – 60 mg for bleomycin, 600 mg for etoposide and 90 mg for cis-platinum.

Ancillary support consists of anti-emetics given as required (domperidone, metoclopramide, alizapride). No hyperhydration programme or mannitol diuresis was used. This treatment is carried out on an out-patient basis.

TABLE IV. RESPONSE RATES ACCORDING TO SITE

	T[a]	N[a]	Global
Tonsil	98	70	78
Larynx	66	54	62
Hypopharynx	76	50	61
Floor of mouth	100	40	75
Tongue	92	25	75
Base of tongue	64	33	50

[a] Per cent of major response rates (CR + PR).

TABLE V. RESPONSE RATES ACCORDING TO VOLUME

	T_1	T_2	T_3	T_4	N_1	N_3
% CR	26	14	19	3	5	0
% PR	53	69	72	69	53	58
% CR + PR	79	83	91	72	58	58

[1] IV = intravenous.

TABLE VI. RESPONSE RATES ACCORDING TO HISTOLOGY

	T[a]	N[a]
Well differentiated	82	56
Moderately differentiated	83	47
Poorly differentiated	92	59

[a] Per cent of major response rates (CR + PR).

5. CHEMOTHERAPY RESPONSE

The results are clinically assessed 8 days after the last injection. The response criteria are those in standard use: complete response (CR) in cases of tumour disappearance, partial response (PR) when the product of two diameters is reduced by more than 50%, minor response (MR) when the reduction is less than 50%, no response (NR) in cases of stable disease or even tumour progression.

An overall response rate of 92% was obtained with a rate of major response amounting to 70% (11% CR + 59% PR). Primary lesions proved sensitive in 86% (14% CR + 72% PR) and nodes in 58% (6% CR + 52% PR). Multiple nodes in the same patient are considered as a unique target.

The response rates differed according to site, primary tumours of the floor of the mouth and tonsil as well as node satellites of tonsillar cancers showing the maximum sensitivity (Table IV).

The major response rates are little dependent on tumour volume but a complete response is more likely to occur when the lesion is of limited extent (Table V).

Histological differentiation seems to exert no influence (Table VI).

6. SIDE EFFECTS

The side effects remained acceptable without any life threatening complications. Eighty-five per cent of the patients experienced nausea (mild to severe) and 50% had vomiting. Digestive intolerance was maximal on days 1 and 15. A mild haematological depression – leukopenia and thrombopenia – usually occurred. The treatment had to be protracted in 5 cases by doubling the time interval; the etoposide dose was reduced by half in 10 cases and bleomycin withdrawn in another. No renal dysfunction was observed as measured by rise of serum levels of creatinine. No pulmonary side effects were encountered but

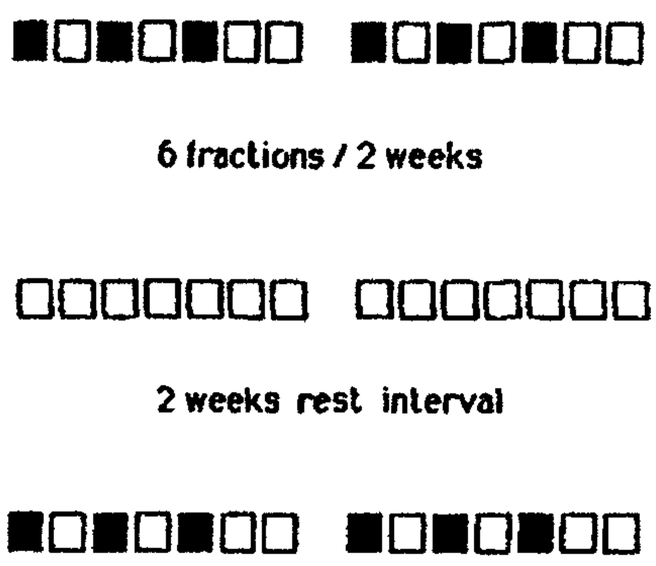

FIG. 1. Irradiation modality.

2 transient bronchospasms occurred at the time of injection. Alopecia has been noted in 20% of cases, more frequently among women. Two patients experienced mild cutaneous effects from bleomycin.

7. RADICAL TREATMENT

The planned radical treatment consisted of exclusive radiotherapy (122 cases) or surgical resection followed by irradiation (18 cases). Eleven non-respects of planning included patients who refused treatment and cases where clinical deterioration prevented further treatment.

The radical treatment was always initiated without undue delay (mean interval of 15 days for radiotherapy and 18 days for surgery).

Seventy-four patients were eligible for further chemotherapy with monthly courses of high dose methotrexate (3 g) and leucovorin rescue.

8. IRRADIATION MODALITY

For the last 12 years we have been routinely using an original irradiation modality in the radiotherapy of head and neck cancers. The course consists of 2 treatment periods separated by a rest interval of 2 weeks. Each sequence comprises 6 fractions distributed over 15 days. The tumour dose per fraction amounts to 4 Gy and the TDF[2] is 103. The biological equivalent dose in conventional fractionation would be 63 Gy in 30 fractions over 6 weeks (Fig. 1).

The treatment parameters such as radiation quality, portals, loading, target volumes were those in current use.

Combining hypofractionation with a split course allows to benefit by the effectiveness of large doses per fraction without undergoing their poor tolerance.

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[2] TDF = Time–dose fractionation.

TABLE VII. EVALUATION OF TOLERANCE

Compliance	**Late complications**
Respect of prescribed dose	Laryngeal oedema
Extension of rest interval	Muscle fibrosis
Acute side effects	Cutaneous sequelae
Mucosal congestion	Mucosa/bone/cartilage necrosis
Transient oedema	Asialia and dysgeusia
Degree of skin reaction	Delay in wound healing

TABLE VIII. SOCIAL AND ECONOMIC ADVANTAGES

	12 X 4 Gy	30 X 2.1 Gy	
Patient's travel	12 times	30 times	−60%
Hospital stay	4 weeks	6 weeks	−33%
Staff occupation	3 days/week	5 days/week	−40%
Therapy courses	390/year	312/year	+25%

TABLE IX. TUMOUR CONTROL AFTER IRRADIATION

	All cases (%)	Good responders (%)	Poor responders (%)
Primary tumour			
Complete regression	88	95	67
Partial regression	12	5	33
Stable disease	0	0	0
Nodes			
Complete regression	54	60	33
Partial regression	40	40	54
Stable disease	6	0	13

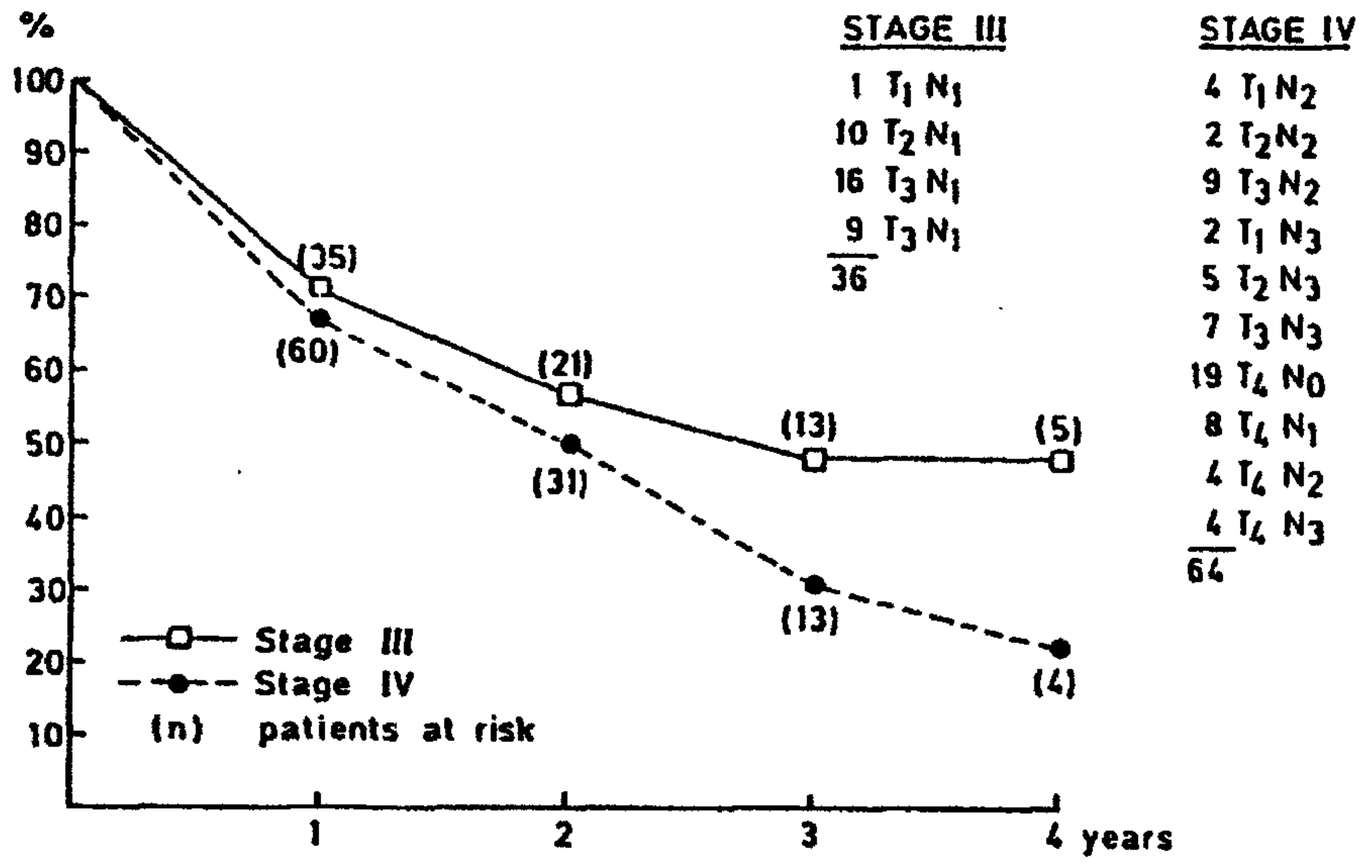

FIG. 2. Actuarial survival.

As part of a study on quality of life, tolerance is at present under investigation (Table VII).

Compliance amounted to 100%; acute and late side effects remained within the normal range. A preliminary comparison seems to indicate that neoadjuvant chemotherapy at low doses does not change local tolerance and has no cumulative toxic effect on normal tissues.

Owing to the low number of fractions, this modality of irradiation presents several social and economic advantages: reduction of patients' travel and hospital stay; the work load for the staff is reduced and the annual output of the treatment machines increases (Table VIII).

9. TUMOUR CONTROL

Immediate assessment indicates that high rates of tumour control were achieved after exclusive radiotherapy. At the very end of irradiation 88% of primary tumours had totally regressed and the complete regression rate of lymph nodes amounted to 54% (multiple nodes in the same patient being considered as a unique target) (Table IX).

Good responders to chemotherapy presented more complete regressions of their primary tumour and satellite nodes.

10. SURVIVAL

The possible long term benefit of a neoadjuvant chemotherapy is still putative in the treatment of head and neck cancers. Actuarial survival curves have been

TABLE X. POSSIBLE LONG TERM BENEFIT

	Study		Controls	
	Survival (%)	No. at risk	Survival (%)	No. at risk
Larynx stage IV				
1 year	73	22	63	36
2 years	47	12	46	22
3 years	33	4	32	16
Tonsil stage III				
1 year	78	9	69	13
2 years	78	6	61	9
3 years	61	5	46	8
Tonsil stage IV				
1 year	67	22	60	20
2 years	54	10	50	11
3 years	27	4	30	10

established for 36 stage III and 64 stage IV patients. Correction was made for duly documented deaths from intercurrent disease in cancer controlled cases, any uncertain fatal issue being considered as a therapeutic failure (Fig. 2).

Results at 2 years seem promising with rates of 57 and 50%, respectively. Owing to the low number of patients at risk, values obtained at 3 years should be taken with caution. Stage III cases then enter a plateau phase with 48% survivors, whereas the survival of stage IV still decreases to 31%.

A comparison of survival rates with historical controls treated in the same way but without neoadjuvant chemotherapy is being made. Preliminary results do not allow any clear cut conclusion up to now. Trends exist for a benefit in advanced carcinomas of the larynx and tonsil. However, more cases and time are needed (Table X).

11. CONCLUSIONS

(1) Neoadjuvant chemotherapy with bleomycin, etoposide and cis-platinum at low doses has shown significant anti-tumour activity and minimal toxicity. This chemotherapy is suitable for out-patient treatment. Irradiation and surgery are possible without undue delay and their tolerance is unchanged. A maintenance chemotherapy is not precluded.

(2) High rates of immediate tumour control are observed after hypo-fractionated split-course radiotherapy. This irradiation modality is well tolerated and, besides, possesses social and economic advantages.

(3) More cases and time are needed to ascertain a possible beneficial effect on the long term prognosis.