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Papers

Randomised EORTC Head and Neck Cooperative Group Trial of Preoperative Intra-arterial Chemotherapy in Oral Cavity and Oropharynx Carcinoma

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Between February 1978 and January 1984, 222 eligible patients were randomised in a multicentre trial of preoperative intra-arterial chemotherapy in the treatment of oral cavity and oropharynx carcinoma. Patients were randomised between either surgery or preoperative chemotherapy. This latter group received vincristine and bleomycin for 12 days. Patients were stratified according to the primary site: floor of the mouth (FM) versus posterior oral cavity or oropharynx (POC) and institution. The FM group received postoperative radiotherapy depending upon quality of the margins and lymph-node pathological involvement, when it was systematically applied in the POC group. Tumour regression after chemotherapy either complete (CR) or partial (PR > 50%) was observed in 48% in the FM group and 41% in the POC group, and lymph-node regression (CR + PR) was respectively 15% and 23%. Some discrepancies appeared between clinical regression and pathological response, and the number of cases without histological response was clearly higher than the number of cases without clinical response. The overall survival showed a statistically significant difference ($P = 0.048$) between FM and POC groups. In the FM group, median survival in the chemotherapy arm was estimated at 7 years compared with 3 years in the surgery arm. In the POC group, median survival was estimated at 3 years in both treatment arms. Chemotherapy lowered the uncontrolled disease and local recurrence in the FM group. These differences do not exist in the POC group, which may be due to the systematically postoperative radiotherapy.
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INTRODUCTION

SNOW AND SINDRAM [1] have shown the advantage in tumour regression of intra-arterial chemotherapy (IAC) compared with intravenous administration in experiments on rats. From a clinical point of view, the first trial comparing IAC prior to radiotherapy was conducted at the Institut Gustave-Roussy in patients with T4 tumours of the oral cavity in 1965 [2]. This trial showed that this treatment resulted in a higher tumour regression rate and a prolonged survival of about 3 months.

A second clinical trial conducted within the Head and Neck Group of the EORTC comparing methotrexate and bleomycin administered intra-arterially showed tumour regression greater than 50% of the initial volume in about 60% of patients with tumours of the oral cavity. It also indicated a clear advantage for bleomycin as far as toxicity and tumour regression were concerned [3].

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Richard and Sancho [4] demonstrated that tumour regression obtained by neoadjuvant chemotherapy was able to predict survival. At the time the present study was initiated, some clinical trials had evaluated the role of chemotherapy as an adjuvant treatment while others had evaluated the association of chemotherapy with radiotherapy. No other study had yet been designed to evaluate the role of intra-arterial chemotherapy given prior to surgery in tumour sites, taking survival as the major end point. The aim of this randomised trial was to evaluate the role of preoperative intra-arterial chemotherapy on survival of patients with tumours of the oral cavity and oropharynx.

PATIENTS AND METHODS

Patients with a biopsy-confirmed squamous cell carcinoma of various sites of the oral cavity or of the oropharynx and considered for surgical treatment were included in the study. The tumour sites included the floor of the mouth (FM), the retromolar trigone, the glossotonsilar sulcus and the anterior faucial pillar. Patients with either a T1 staged tumour (UICC 79), with local extension or nodal involvement contraindicating surgery (i.e. bilateral N3 or jugular N2b) or a previously treated lesion, and those for whom surgery or chemotherapy was considered a contraindication were not considered eligible for this trial. Other

patients deemed ineligible were those with metastasis or a second primary and those who could not be followed up.

Patients were randomised by sealed envelopes to one of the two treatment arms. The procedure used was permuted blocks for each of the two following strata: primary sites (FM versus posterior oral cavity or oropharynx [POC]). These two strata were used because of important differences in prognosis for regression and survival. As is usually done, hospital was used as a secondary stratification variable; this was necessary because five centres accepted to include patients in the FM group and only three in the POC group.

Patients were randomised between either surgery or preoperative chemotherapy. This latter group received vincristine and bleomycin over 12 days. Vincristine was delivered at a dose of 1 mg on days 1, 5 and 9 and bleomycin was delivered at a dose of 15 mg/day, 8 h a day, for 12 days and starting 6 h after vincristine on days 1, 5 and 9.

The vincristine and bleomycin association was chosen after the results from a preceeding EORTC Cooperative trial showed a greater treatment efficacy with bleomycin than with methotrexate [3]. Also, Pouillart and Schwarzenberg showed the advantages of synchronisation by vincristine [5].

Intra-arterial catheter placement was performed after local anaesthetic and vertical preauricular skin incisions. The catheter was then advanced retrograde into the external carotid artery until the catheter tip was in the external carotid artery and below the origin of the appropriate branch. This was confirmed by the injection of 1–5 ml of patent blue. In the setting where tumour extended across the midline or was located astride the midline, the opposite external carotid was canulated and the drug dose was divided equally between the two sides.

In the FM group postoperative radiotherapy was delivered depending upon the lymph-node pathological involvement and the completeness of the tumour resection. Irradiation was systematically applied in the POC group.

In case of technical problems preventing IAC, vincristine was to be injected intravenously at the same doses and on the same days for a total of 12 days. Bleomycin was to be injected intramuscularly while respecting the same 6 h delay after vincristine on days 1, 5 and 9. Injection of intra-arterial or intramuscular polaramine was advised to be done for each bleomycin course.

Tumour regression was evaluated 10–15 days after the end of chemotherapy. Tumour size was measured as the product of the two largest perpendicular diameters.

The distribution of patients' characteristics by treatment was analysed, using the Pearson χ^2 test. The comparison of survival curves was done using the logrank test in the univariate case and the Cox regression model in the multivariate case. All survival curves are Kaplan–Meier plots.

The decomposition of the disease-free survival curves was used to estimate the cumulative incidence rate (CIR) for each type of first event as a function of time.

RESULTS

Administrative information

This study was activated in February 1978 and closed to patient accrual in January 1984. A total of 225 patients were entered on study; 128 to the FM group, and 97 to the POC group. 3 cases were considered ineligible after randomisation: 1 patient presented a T1 type tumour (FM, chemotherapy arm) and 2 patients refused treatment (POC, surgery arm). Most of the patients (91%) came from three institutions. The accrual rate was about 21 patients per year in the FM group and 16 patients per year in the POC group. Patient accrual was constant over time.

Table 1. Patients' characteristics

	FM		POC	
	Surgery	Chemotherapy plus surgery	Surgery	Chemotherapy plus surgery
Cases	63	64	47	48
Age (mean)	52.9	53.3	53.0	53.0
Sex (females)	3%	0	6%	8%
T2	47%	41%	51%	36%
T3	48%	42%	47%	60%
T4	6%	17%	2%	4%
N0–N1a	67%	58%	66%	54%
N1b–N2ab	25%	36%	23%	35%
N3	8%	6%	11%	10%
T2 (N0–N1a)	41%	28%	34%	23%
Treatments administered				
Surgical resection, free margins	79%	89%	77%	79%
Radiotherapy on primary	68%	55%	83%	90%
Mean duration (days)	41	42	39	41
Mean dose (Gy)	54.8	55.9	52.7	54.3
Radiotherapy on nodes	68%	58%	83%	90%
Mean dose (Gy)*	55.3	57.8	55.3	56.1
Pathological node status				
Involvement N+	55%	58%	68%	65%
Extra-capsular rupture R+	30%	36%	34%	42%
Embols	3%	8%	15%	17%

*Maximal dose calculated on the cervical area.
FM = floor of mouth, POC = posterior oral cavity or oropharynx.

Patients' characteristics

The patients' characteristics for the FM group and the POC group are presented in Table 1. The mean age was 53 years overall and the sex (M/F) ratio was 32 in the FM group and 12 in the POC group. In the FM group, 6% of patients had a T4 tumour in the surgery arm versus 17% in the chemotherapy arm. There also seemed to be slightly more clinical lymph-node involvement in the chemotherapy arm: 42% versus 33% in the FM group and 46% versus 34% in the POC group. Although these difference are not statistically significant, both prognostic factors were taken into account in the survival analysis. No other differences are observed between the treatment arms.

Treatment administration

In the FM group, 3 patients were not operated on (2 in the surgery arm and 1 in the chemotherapy arm) because of rapid tumour progression. In the POC group, 2 patients did not have surgery (1 in each arm). One patient experienced rapid tumour progression and another experienced a lethal toxicity related to a protocol violation.

Table 2. Type and grade of toxicity

	FM (n = 64)				POC (n = 48)		
Toxicity*	Mild	Moderate	Severe	Total	Mild	Severe	Total
Neurological	6(3 MIX)	1	–	7	1(MIX)	–	1
Cutaneous	1	–	1(SYS)	2	–	–	–
Mucous	–	–	–	–	4	–	4
Asthenia	3	1	–	4	4	–	4
Alopecia	2	–	–	2	–	–	–
Fever	2(1SYS)		1(SYS)	3	–	–	–
Haematological	–	–	–	–	–	2	2
Headache	–	–	–	–	1	–	1
Total reactions	14	2	2	18	10	2	12
(patients)	(14)	(2)	(2)	(18)	(7)	(2)	(9)

*Mild = without treatment modification, moderate = with treatment modification, severe = with treatment interruption.
SYS = systemic intravenous chemotherapy, MIX = change during treatment from intra-arterial to systemic chemotherapy.

In the chemotherapy arm, 17 patients (27%) in the FM group and 11 (23%) in the POC group did not receive the treatment intra-arterially according to the treatment schedule. Among the 17 patients in the FM group, 11 received systemic intravenous chemotherapy (SYS) and 6 shifted from intra-arterial to systemic route during treatment (MIX). In the POC group, the corresponding numbers were 7 SYS and 4 MIX patients, respectively. In almost all cases, this was because of technical difficulties related to the catheter placement or maintenance.

Of the 47 patients receiving IAC in the FM group, 14 (30%) were infused bilaterally. All 37 IAC patients in the POC group received IAC unilaterally.

2 patients in the FM group and 1 patient in the POC group received less than the 3 mg of vincristine required in the protocol. 5 patients in the FM group and 2 patients in the POC group received less than 180 mg of bleomycin.

In the FM group, postoperative radiotherapy was delivered on the tumour bed and on the neck nodes to 68% of patients in the surgical arm. In the chemotherapy arm the tumour bed was irradiated in 55% of patients and the neck nodes in 58% of them.

As the pathological involvement of the nodes is equivalent in the two compared groups, the difference in the postoperative radiotherapy rate of the FM groups may be explained by the increased number of patients with free margins after surgical resection in the chemotherapy arm (89% versus 79%). In the POC group no notable difference was observed in postoperative radiotherapy as a consequence of the systematic attitude.

Toxicity

The chemotherapy toxicity encountered in the FM and POC groups is presented in Table 2. All the side-effects are in the IAC patients unless otherwise indicated.

A total of 18 patients (28%) in the FM group (12 IAC, 3 SYS and 3 MIX) and 9 patients (19%) in the POC group (8 IAC and 1 MIX) presented some type of toxicity. As previously mentioned, 1 patient died because of methotrexate haematological toxicity in the POC group. 2 patients in the FM group had to interrupt the chemotherapy because of toxicity and 1 in the POC while receiving IA systematic chemotherapy.

In 3 patients (2 FM, 1 POC), the initial doses of bleomycin and vincristine were decreased after toxic reactions occurred.

Table 3. Tumour regression by chemotherapy modalities

	FM				POC			
	IAC	SYS	MIX	Total	IAC	SYS	MIX	Total
Patients	47	11	6	%	37	7	4	%
CR	4	0	0	6	2	0	1	6
PR ≤ 50%	22	2	3	42	14	1	2	35
PR ≤ 50%	13	2	1	25	15	2	1	38
No regression	8	5	2	23	4	3	0	15
Progression		2		4	2	1		6

22% and 15% of the FM and POC groups, respectively, experienced a mild toxicity which did not alter the chemotherapy schedule.

Tumour regression

Tumour regression after chemotherapy either complete (CR) or partial (PR ≥ 50%) was observed in 48% (95% confidence interval [CI]: 36–61%) of patients in the FM group and in 41% (28–57%) of patients in the POC group. Tumour regression by group and by treatment modalities are presented in Table 3. 2 out of the 4 women in the POC group experienced a complete response.

Lymph-node regression (CR + PR ≥ 50%) among the patients with initial clinical node involvement was observed in 15% of cases in the FM group and in 23% of cases in the POC group.

Clinical regression was compared to pathological regression, when possible, and some discrepancies appeared (Table 4). From the pathological point of view, 16% (9/57) of FM cases and 20% (8/40) of POC cases had a CR; 23% (13/57) FM and 15% (6/40) POC had a PR. In total, the number of cases without histological modification was clearly higher than the number of cases without clinical response [61% (35/57) versus 17% (14/57) in the FM, 65% (26/40) versus 23% (7/40) in the POC].

The histological node involvement was also compared within the two treatment arms (with or without chemotherapy). The false negative rates (no modification of tumour cells, with histological confirmed involvement) were, respectively, 41% and 40% in both arms, but the false positive rates (palpable nodes without histological node involvement) were 8% in the arm without chemotherapy and 21% ($P<0.10$) in the arm with chemotherapy. This observation may imply that chemotherapy is able to clean the nodes from tumour cells.

Table 4. Comparison between clinical and histological regression after chemotherapy

	FM (n = 57)				POC (n = 40)			
Clinical	CR	PR ≥ 50%	PR < 50%	None	CR	PR ≥ 50%	PR < 50%	None
Pathological*								
CR	2	6	–	1	2	4	1	1
PR	1	12	–	–	–	4	1	1
NO	1	7	14	13	–	7	14	5

*CR = disappearance of living tumour cells, PR = persistance of islets of living tumour cells, NO = no modification of tumour cells.

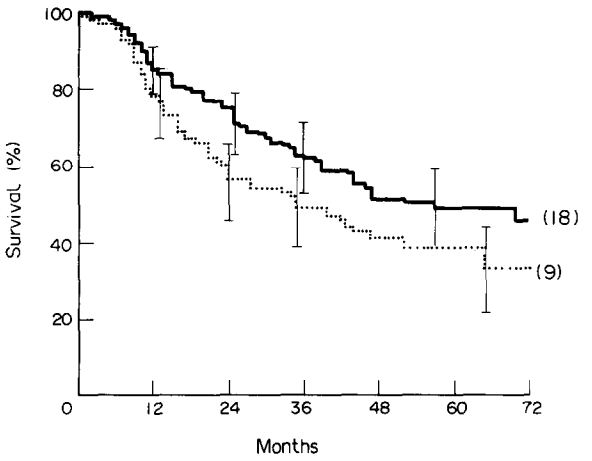

Fig. 1. Overall survival. —— FM (n = 127), ····· POC (n = 95).

Overall survival

Overall survival was calculated as the time from the date of randomisation to either the date of death of patients or to the date of last follow-up. Median duration of follow-up was 5 years and ranged from 1 to 9 years. At the time of analysis, ($4\frac{1}{2}$ years after the accrual of the last patient) 118 deaths were reported (62 out of 127 in the FM group and 56 out of 95 in the POC group).

The overall survival curves of the FM and POC groups, respectively, are shown in Fig. 1. The difference between the survival curves is statistically significant at the $P = 0.048$ level. Tumour stage (T-UICC) and clinical lymph-node involvement (N) are both prognostic factors, significant at the $P = 0.035$ (T2 versus T3 or T4) and the $P = 0.0003$, (no involvement versus involvement) levels, respectively.

Patients in the chemotherapy plus surgery arm had significantly better survival ($P = 0.044$) than those of the surgery arm when adjusted for the main effects of T and N using a Cox proportional hazards regression model stratified by site (FM or POC). The T × N interaction term was not significant, implying that results are not different for particular combination of T and N. In the FM group, median survival in the chemotherapy arm is estimated at 7 years compared to 3 years in the surgery arm (Fig. 2). In the POC group, median survival is estimated at 3 years in both treatment arms (Fig. 3).

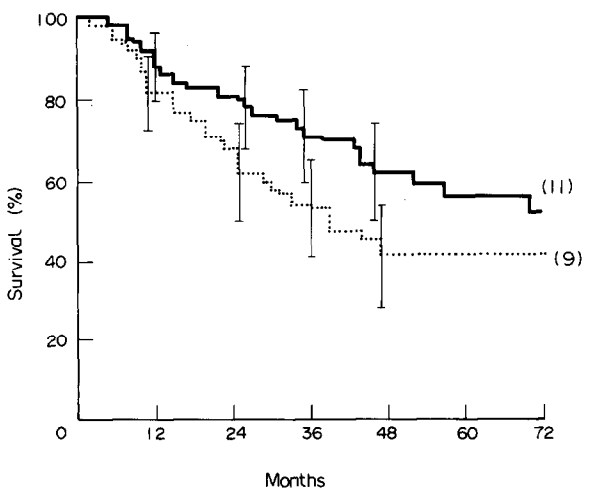

Fig. 2. Overall survival for FM group. —— Chemotherapy plus surgery (n = 64), ····· surgery (n = 63).

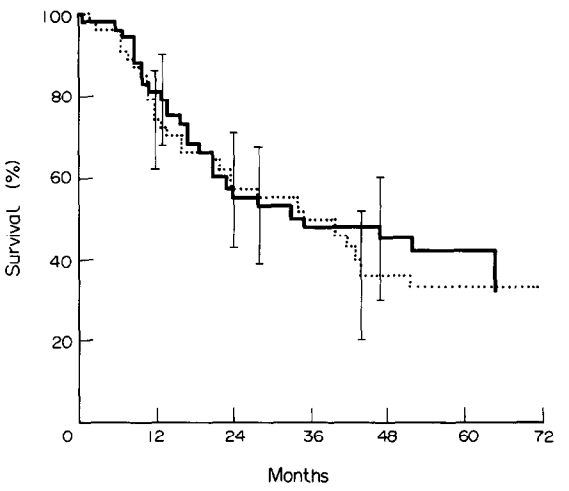

Fig. 3. Overall survival for POC group. —— Chemotherapy plus surgery (n = 48), ····· surgery (n = 47).

Disease-free survival

Disease-free survival was calculated as the time from the date of randomisation either to the date of first relapse (local or lymphatic recurrence, metastase), to the date of second primary (if no relapse was observed before), to the date of death (if no relapse nor second primary was reported) or to the date of last follow-up (if neither death nor relapse nor second primary was observed). Table 5 shows the number of patients by type of first relapse (alone or associated) and treatment in both the FM and POC groups.

Disease-free survival for both treatment arms is shown in

Table 5. Patients by type of first relapse treatment and group

	FM		POC	
	Surgery	Chemotherapy plus surgery	Surgery	Chemotherapy plus surgery
First relapse				
Alone or associated				
Recurrence	22	20	10	14
Local	18	10	8	7
Nodal	3	9	2	3
Local + nodal	1	1	–	4
Metastase	7	6	8	6
Second primary	14	14	5	6
Alone				
Recurrence	20	16	10	13
Metastase	5	2	7	5
Second primary	10	12	4	6
Associated				
Recurrence + metastase	–	3	–	1
Recurrence + second primary	2	1	–	–
Metastase + second primary	2	1	1	–
Deaths (uncontrolled)	3	4	10	7
Alive without relapse	21	25	15	16

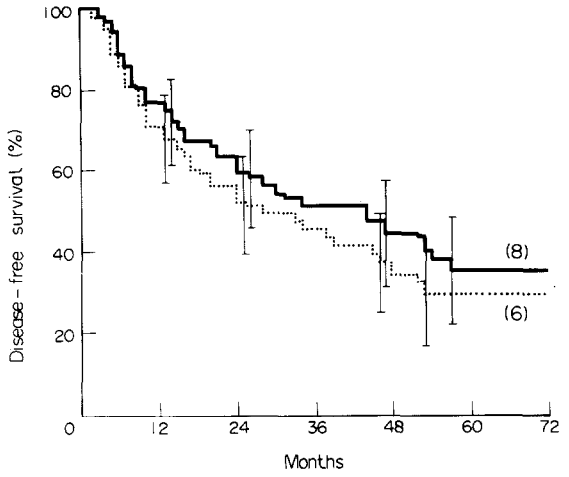

Fig. 4. Disease-free survival for FM group. —— Chemotherapy plus surgery (n = 64), ····· surgery (n = 63).

Fig. 4 for the FM group and Fig. 5 for the POC group. The difference in disease-free survival between surgery and chemotherapy plus surgery is not significant when adjusted for the main effect of T and N and stratified by site (P = 0.22).

When "disease-free" was limited to events representing uncontrolled disease after treatment (local or nodal recurrences, metastases or deaths as first events), the estimated cumulative incidence rates by treatment group and by type of first relapse in the FM and POC groups are shown in Figs 6–9.

In the FM group, uncontrolled disease after treatment, especially local recurrences, seems to be lowered by chemotherapy, whereas nodal recurrences and metastases do not seem to be improved. These differences are not seen in the POC group, even though nodal recurrences are slightly more frequent in the chemotherapy arm, where metastases appear later and the cumulative event rate after 5 years is lower.

When analysing the survival after local recurrences as the first event, we observed that in the FM surgery group, 3/22 patients had a prolonged (18–70 months) survival time versus 6/18 in the chemotherapy group.

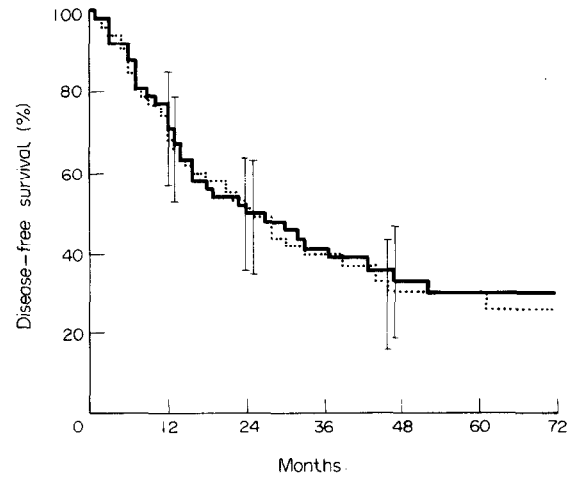

Fig. 5. Disease-free survival POC group. —— Chemotherapy plus surgery (n = 48), ····· surgery (n = 47).

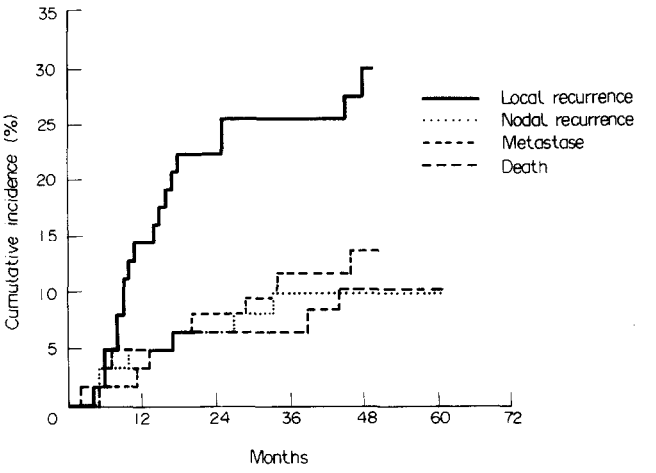

Fig. 6. Cumulative incidence of first relapse FM group, surgery arm.

DISCUSSION

This trial, although it uses a schema of chemotherapy which has been shown less efficient than current polychemotherapies, seems to indicate that chemotherapy prior to surgery can improve the survival of patients with carcinoma of the floor of the mouth (FM group).

Analysing the causes of failure, it appears that this improvement is essentially due to a decrease in local recurrences and to a better control of these recurrences through a secondary treatment. Although chemotherapy led to some node regressions, it did not reduce the number of node recurrences; on the contrary, they were slightly more numerous in the chemotherapy group. In fact, out of the 9 cases of node recurrences in this group, 3 did not show histological node involvement in the initial neck dissection specimen. These nodes may have been sterilised by chemotherapy at least up to the subdigastric node level while other involved nodes persisted in the lower part of the chain, left in place by the partial neck dissection technique.

In the posterior oral cavity, on the other hand, chemotherapy provoked less modification for all parameters. Chemotherapy-induced regressions were less numerous than in the FM group (56% versus 43%) but not significantly different; no difference as to histological regression was observed and there was no difference in survival in either group, with or without chemotherapy.

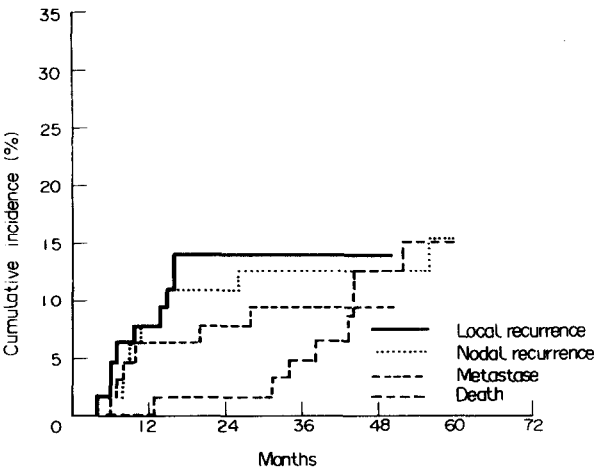

Fig. 7. Cumulative incidence of first relapse FM group, chemotherapy plus surgery arm.

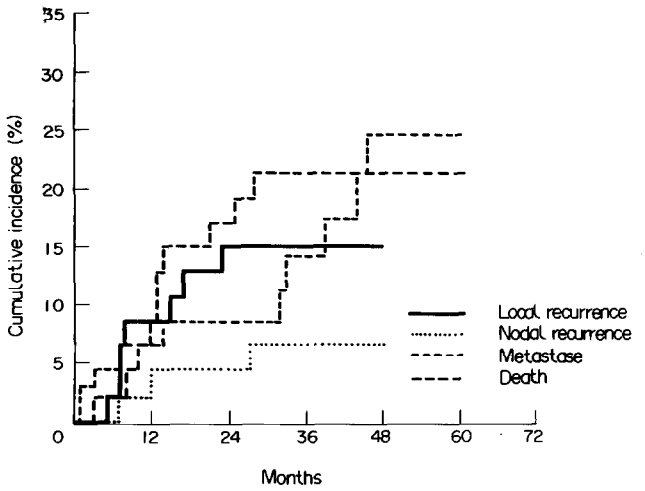

Fig. 8. Cumulative incidence of first relapse POC group, surgery arm.

The results could be explained by a less satisfactory tumour perfusion through drugs, due to vascularisation problems or the poorer prognosis of tumours arising in these sites as illustrated by the high level of node invasion (Table 1), such as in oropharynx carcinomas.

As far as randomised trials are concerned, no other preoperative intra-arterial chemotherapy randomised trial has yet been published, and we only can rely on outdated published trials to get a view of the situation for analysis. These trials used systemic chemotherapies with a poor activity index which do not allow to prejudge current polychemotherapy results.

Among the most important trials, the Head and Neck Contracts Programme [6] has not shown, out of 411 relevant cases, any benefit in survival due to induction systemic chemotherapy associating cisplatin and bleomycin on a single 7 day cycle.

The Southwest Oncology Group trial [7] reported by Schuller included 46 stage III or IV patients treated by induction chemotherapy with 3 cycles of cisplatin, bleomycin, methotrexate and vincristine every 3 weeks. The average therapy included surgery followed by postoperative irradiation (50 Gy). After chemotherapy 45% partial regressions and 25% complete regressions were shown. There was no difference in survival between both groups. But, as already demonstrated by us in this study, there is a discrepancy between clinical and histological regression; and histological regression is the more important prognostic factor. These two trials mixed numerous primary tumour sites with different prognostic issues and consequently confused positive effects eventually induced by chemotherapy on specific sites.

In a trial including 63 stage III and IV patients, Toohill [8] compared a standard therapy (preoperative 50 Gy irradiation) with an induction chemotherapy followed by the same treatment. Chemotherapy associated cisplatin on day 1 with 5-fluorouracil (5-FU) on days 1–5 using 12-hour perfusion schedules for 3 cycles at 3 week intervals. After a period of 24–44 months, there was a significant survival difference against the chemotherapy group. However, this chemotherapy used small doses of 5-FU (500 mg) and 12-hour instead of 24-hour perfusions. The importance of continuous perfusions was related by Al Sarraf and colleagues [9] and we have noted ourselves the importance of the 5-FU dosage [10]. Moreover, this chemotherapy was followed by preoperative irradiation which is well known to increase the postoperative complications and deaths.

Another study reported by Ervin [11] comprised a systematic induction chemotherapy followed by standard therapy. The patients were randomised at the end of therapy for maintenance versus no treatment chemotherapy in case they had experienced an initial massive chemotherapy-induced regression. Maintenance chemotherapy was shown to be effective, particularly for the group having a partial regression after induction chemotherapy.

The last point concerns the specific contribution of intra-arterial infusion technique. This is important to consider since systemic chemotherapy leads to a good rate of regression. Still, it is difficult to settle the question. From our experience in the Head and Neck EORTC Group, the arterial route seems to be somehow better than the systemic one, as far as the tumours of the buccal cavity are concerned. Besides, the tumour regression induced by intra-arterial chemotherapy is achieved more quickly since the results can be obtained within 15 days of infusion while the systemic route needs a standard treatment schedule over 9 weeks. As Toohill and colleagues have stressed the total duration of therapy largely contributes to its success [9]. In a preliminary study we found that the local regression rate was clearly greater with intra-arterial than with intravenous chemotherapy.

To date, very few chemotherapy trials carried out in the head and neck field have shown any improvement in survival, whether chemotherapy has been delivered as an induction or as a maintenance therapy. It should be pointed out in this trial that the use of an intra-arterial technique could be the reason for prolonged survival in the tumours of the floor of the mouth.

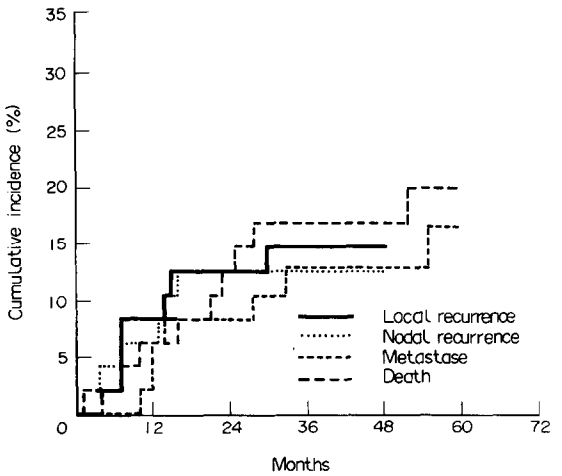

Fig. 9. Cumulative incidence of first relapse POC group, chemotherapy plus surgery arm.

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Development and Validation of an Instrument to Measure Satisfaction of Participants at Breast Screening Programmes

Jill Cockburn, David Hill, Les Irwig, Trudy De Luise, Deborah Turnbull and Penny Schofield

A reliable and valid questionnaire has been developed to measure the satisfaction of participants with service offered at mammography screening programmes. The questionnaire measures five specific aspects: convenience and accessibility, staffs' interpersonal skills, information transfer between staff and client, physical surroundings and perceived technical competence of staff. A general satisfaction dimension was also included. Systematic procedures were followed to ensure that the initial pool of items met the criteria for satisfactory content validity. These procedures included extensive literature review and interviews with participants and service providers. Discriminant validity was assessed by a modified Q-sort procedure, where eight expert judges sorted items into relevant dimensions. The sample for other validity and reliability testing consisted of 584 women who were participants at a breast X-ray programme in Melbourne, Australia. Concurrent validity was demonstrated by considering the correlation of the sum of the subscale scores for each respondent with their score on the general subscale ($r = 0.76$; $P < 0.001$). Multiple regression was used to provide further evidence for the discriminant validity of the proposed subscales and support for the multidimensional conceptualism of satisfaction. Scores on the general satisfaction subscale were used as an outcome variable and other subscale scores were predictor variables. All subscale scores significantly contributed to the prediction of satisfaction, over and above that of other subscales ($R^2 = 0.59$). This indicates that these subscales are measuring distinct dimensions of satisfaction. Cronbach's alpha of each subscale was over 0.50, indicating that the subscales are reliable. The instrument is a potentially useful tool for assessing the quality of care at mammographic screening services and could be used routinely by such services to monitor satisfaction.
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INTRODUCTION

BREAST CANCER is one of the most common causes of death in many western countries [1]. Mass mammography screening has the potential to reduce the death rate from the disease. A reduction in mortality of about one third in populations of women over about 50 offered screening has been demonstrated [2, 3]. The United Kingdom has therefore introduced population screening for women in the appropriate age groups. Among the key elements of the quality assurance goals of the National Health Service breast screening programme is "minimising dissatisfaction and striving to ensure that women find screening a positive and healthy experience" [4].

There are a number of reasons why the measurement of satisfaction is essential. First, ongoing evaluation of health services is necessary to ensure that participants are being offered the best possible service. The degree of satisfaction expressed

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