Eur J Cancer, Vol. 29A, No. 12, pp. 1658–1663, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

Papers

Prospective Randomised Trial Comparing Fluorouracil Versus Doxifluridine for the Treatment of Advanced Colorectal Cancer

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Doxifluridine (dFUR) is a fluoropyrimidine derivative that has shown activity on a variety of solid tumours. The purpose of this study was to compare its therapeutic effect with a standard fluorouracil (FU) regimen in patients with locally advanced or metastatic colorectal cancer. 222 previously untreated patients were randomised to receive dFUR (4000 mg/m²) or FU (500 mg/m²) daily for 5 days every 28 days. The primary tumour originated in the colon in two-thirds of the cases in both groups; approximately 90% of patients had metastatic extension, and liver involvement was present in 69% of the patients in the dFUR and FU groups. A good performance status (ECOG 0–1) was recorded in 90% of cases in both arms. A median of five cycles was administered to the patients (range 1–12). Only one partial response among 110 patients in the FU arm and one complete response and five partial responses out of 112 evaluable patients in the dFUR group were observed. Time to progression was significantly longer in the dFUR group ($P = 0.02$); overall survival, while longer in the dFUR arm (48 weeks vs. 39 weeks), was not significantly so ($P = 0.08$). Toxicity was acceptable in both arms, although grade 3–4 neurological side-effects and leukopenia were more common after dFUR infusion. Despite the low response rate, our results indicate that dFUR may be a superior alternative to FU. The possibility of enhancing significantly the activity of dFUR with biochemical modulators should be further investigated.
Eur J Cancer, Vol. 29A, No. 12, pp. 1658–1663, 1993.

INTRODUCTION

DESPITE THE large number of drugs available, only a few single agents or combinations have been proved to be active in locally advanced or metastatic colorectal cancer [1]. The reference drug remains fluorouracil (FU), with a widely accepted response rate that ranges between 10 and 20% [2, 3]. More recent randomised trials using strict response criteria established a response rate of 5–15% for FU alone, whereas studies combining FU with biochemical or biological modulators, either leucovorin or interferon, improved the response rate to 20–40% [4–6].

Nevertheless, the median survival time of these patients does not exceed 12 months, and the percentage of patients who really benefit from these treatments cannot be considered satisfactory. Much effort has thus been made to develop new fluoropyrimidine analogs with a better therapeutic index than FU.

Doxifluridine (5'-deoxy-5-fluorouridine, dFUR) is a 5-deoxynucleoside fluoropyrimidine derivative synthesised in 1976 by Cook *et al.* [7]. The chemical structure consists of an FU molecule attached to a pseudopentose. Its antineoplastic activity is due to a selective conversion to FU by pyrimidine phosphorylases. In animal models, the level of the enzyme is higher in malignant than normal tissues, leading to a preferential release of FU within tumour cells [8, 9]. In many *in vivo* experimental tumour models [10, 11], dFUR showed a therapeutic index 10–15 times higher than FU or other fluoropyrimidines. Phase I–II studies have reported 5 g/m² per day in a 5-day schedule as the maximal tolerated dose of dFUR, with granulocytopenia and stomatitis as dose-limiting toxicity [12, 13].

Other phase II studies have shown that infusion time may have a central role in determining the type of toxicity. Bolus injection shows essentially gastrointestinal side-effects and possibly cardiac toxicity; the 6-h infusion of 12.5 g/m²/week gives

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Revised 15 Mar. 1993; accepted 28 Apr. 1993.

neurological symptoms as dose-limiting toxicity, and a 24-h infusion produces mainly a hand-foot syndrome [13–16]. The 1-h infusion schedule, for 5 days every 28 days, appeared to be the most suitable regimen. A previous study with this schedule showed a good tolerability and a better activity of dFUR than FU against colorectal cancer [17].

The aims of this randomised trial were to compare the antitumour activity and toxicity of dFUR and FU administered in a 1-h infusion in patients with advanced colorectal cancer.

PATIENTS AND METHODS

Eligibility

Patients were required to have histologically confirmed colorectal carcinoma, advanced, metastatic or recurrent, not suitable for curative surgery and not previously treated with chemotherapy. The presence of measurable or evaluable lesions was mandatory to monitor the response. Patients with one lesion < 3 cm in diameter on the liver, ascites, pleural effusion or bone metastases as the unique lesion were considered ineligible. Other exclusion criteria were: active CNS disorder or known cerebral metastases, uncontrolled infections or metabolic disease, age ≥ 75 or ≤ 18 years, ECOG performance status > 2, WBC count $< 4000/mm^3$, platelet count $< 100\ 000/mm^3$, abnormal renal function and total bilirubin > 3 mg/dl. Eligible patients gave informed consent according to the guidelines of the study protocol.

Randomisation

Patients were randomised to the dFUR or FU arm by a central randomisation office. Randomisation lists were stratified by centre, using randomly permuted blocks of varying sizes.

Treatment

Both dFUR and FU were administered as a 1-h intravenous infusion daily for 5 consecutive days every 28 days. The daily dose for dFUR and FU was 4000 and 500 mg/m^2, respectively. Antiemetic prophylaxis was given on a regular basis. Treatment was planned for a maximum of 12 cycles.

Dose reduction or treatment delay was calculated according to toxicity or myelosuppression recorded at the time of recycling (day 28). The dose was reduced by 50% if WBC was < 3000 but $> 2000/mm^3$ or platelets $< 75\ 000$ but $> 50\ 000/mm^3$. For WBC < 2000 or platelets $> 50\ 000$, the treatment was delayed by 1 week or until haematological recovery. dFUR was supplied by Roche as a 2.5% infusion solution in bottles of 6.25 g (= 250 ml) or 1.25 g (= 50 ml). Patients with progressive disease, or patients with stable disease after 12 months, suitable for a second-line therapy, were candidates for a treatment with FU (600 mg/m^2) + folinic acid (500 mg/m^2) once weekly for 6 consecutive weeks every 8 weeks [4].

Evaluation of response and toxicity

The evaluation of response was performed every two cycles according to WHO criteria: complete response (CR) was considered as complete disappearance of all evident tumour determined by two observations not less than 4 weeks apart. Partial response (PR) was a $> 50\%$ decrease in the cross sectional areas of the measurable lesions in the absence of progression in other sites or appearance of new lesions. Stable disease was a change in size of the measurable disease by $< 25\%$ with no appearance of new lesions. Progressive disease was an increase of $> 25\%$ of any pretreatment area of measurable disease or the appearance of new lesions. Objective responses were reviewed by independent clinicians not involved in the study. Side-effects from treatment were graded according to the WHO scale and evaluated at the time of recycle.

Assessment

Eligible patients were informed of the overall study requirements. A complete medical history, clinical and physical examinations, and laboratory tests were done. Laboratory and instrumental tests included: WBC (total and differential); RBC; platelet count; blood urea nitrogen (BUN); creatinine; creatinine clearance; prothrombin time; bilirubin, total and indirect; total protein; albumin; aspartate aminotransferase; alanine aminotransferase; lactate dehydrogenase; alkaline phosphatase; gamma-glutamyltranspeptidase; carcinoembryonic antigen; electrocardiogram; chest X-ray; computed tomography scan or ultrasound (abdomen, liver). A subgroup of 35 patients underwent Holter monitoring at baseline and during the first and fourth cycle. Every 4 weeks, all patients had a physical examination, together with haematology and blood chemistry. Every 8 weeks, the assessment of evaluable lesions was performed together with a determination of blood chemistry, haematology and chest X-ray. When the patient went off treatment owing to treatment failure, toxicity or other reasons, a full assessment was performed.

Statistics

The number of patients to be enrolled in the study, 220, was estimated on the basis of an expected response rate of 10% in the FU arm, fixing the α error at 0.05 (two-sided) and the β error at 0.2 for an increase in response rate of 15%. Comparison between response rates in the two arms using standard χ^2 techniques, as originally planned, was not possible due to the paucity of responses. Therefore, the two-sided Fisher's exact test was used. The comparisons included all randomised patients according to the intention-to-treat principle, and every patient not classifiable as a responder was included in the no response category. However, analyses limited to patients completing two or more cycles of therapy provided similar results. Overall survival and progression-free survival (PFS) curves were estimated according to Kaplan and Meier and compared by means of the log-rank test. Again, all randomised patients were included in these analyses. In overall survival, deaths for any cause were considered events. In PFS, deaths for any cause and disease progressions at any site (including the appearance of new lesions) were considered as events.

RESULTS

Patients' characteristics

Between February 1990 and January 1991, 222 patients entered the prospective randomised trial from 11 Italian institutions. The characteristics of the patients were well balanced in both arms (Table 1). All patients had a performance status ≤ 2, and the median age was 65 years in the dFUR arm and 60 years in the FU arm.

Rectal cancer was more frequent in the dFUR group (33 vs. 25%). The primary cancer was present in 24 (21%) patients treated with dFUR (3 patients with locally advanced and 21 patients with metastatic disease) and in 35 (31%) patients treated with FU (2 with locally advanced and 33 with metastatic disease). A slightly higher incidence of peritoneal carcinosis was observed in the FU arm (14 vs. 8%).

Five hundred and eleven courses of dFUR and 469 courses of FU were delivered, with a median number per patient of five

Table 1. Major characteristics of patients

	dFUR	FU
Eligible patients	112*	110
Male/female	57/55	66/44
Median age (range)	65 (30–74)	60 (26–75)
ECOG performance status		
0	50 (45)	45 (41)
1	53 (47)	53 (48)
2	9 (8)	12 (11)
Site of primary		
Colon-sigmoid	62 (55)	70 (64)
Sigmoid-rectum	13 (12)	12 (11)
Rectum	37 (33)	28 (25)
Locally advanced or recurrent	10 (9)	7 (6)
Metastatic	102 (91)	103 (94)
Site of metastasis		
Liver	54 (48)	37 (34)
Lung	14 (13)	13 (12)
Liver + others	23 (21)	38 (35)
Others	11 (10)	15 (14)

*Number of cases. Percentage values in parentheses.

cycles in both groups. In the dFUR arm, approximately 17% of the cycles were delayed by 1 week compared to 11% of the FU arm. Of 980 cycles delivered, only 89 were reduced by 10% or more of the planned dose. Dose reduction was well balanced in both arms (9.2% for dFUR and 8.9% for FU).

Response

Table 2 shows the objective responses achieved: 6/112 patients treated with dFUR were responsive (1 CR and 5 PR; 5%; 95% confidence interval 2–11%), whereas 1 patient treated with FU achieved a PR (1%; 95% confidence interval 0–5%). The difference was not statistically significant ($P = 0.12$). The median duration of response was similar in the two treatment arms: 26 weeks (range 12–42) for patients receiving dFUR, whereas the only response in the FU arm had a duration of 27 weeks. Stable disease was seen in, respectively, 53 and 48% of patients in the dFUR and FU groups. The median duration of stable disease was 45 weeks in the dFUR arm and 43 weeks in the FU arm (difference not significant). The median time to progression was 18 weeks in the dFUR group and 13 weeks

Table 2. Objective response

	dFUR	FU
Eligible patients	112*	110
Total number of cycles	511	469
Median number of cycles (range)	5.3 (1–12)	5 (1–12)
Response to treatment		
PD	47 (42)	56 (51)
SD	59 (53)	53 (48)
PR	5 (4)	1 (1)
CR	1 (1)	—
CR + PR	6 (5)	1 (1)

*Number of cases. Percentage values in parentheses. PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

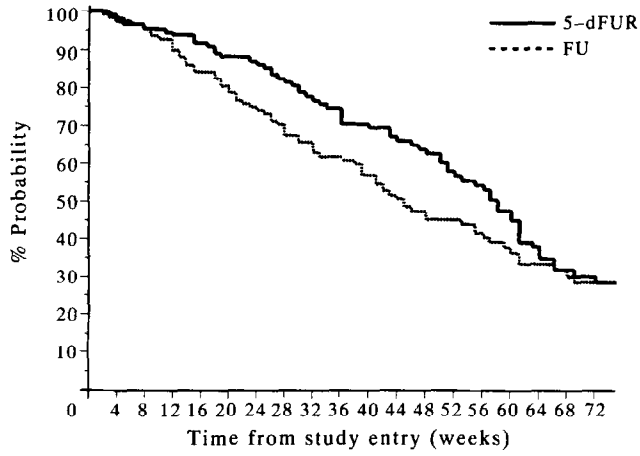

Fig. 1. Progression-free survival of eligible patients.

in the FU group: this difference was statistically significant ($P = 0.02$, log-rank test) (Fig. 1).

Survival

At the time of the last follow-up, 153 patients had expired: 73 out of 112 in the dFUR arm and 80 out of 110 in the FU arm. 34 patients in the dFUR group and 28 in the FU group were alive and in progression.

The median follow-up in the two groups was, respectively, 56 and 67 weeks. Survival curves for the study are shown in Fig. 2. Survival in the group of patients receiving dFUR was longer (median 48 weeks, standard error 0.0481; 95% confidence limit ± 0.09; upper quartile 90 weeks), than in those treated with FU (median 39 weeks; standard error 0.0482; 95% confidence limit ± 0.009; upper quartile 78 weeks). However, this difference was not statistically significant ($P = 0.08$, log-rank test). Similar results were recorded in the patients who received a minimum of two treatment cycles (evaluable for objective response), the median survival being 48 weeks in the dFUR group and 41 weeks in the FU group ($P = 0.12$, log-rank test).

Side-effects

The side-effects of treatment are summarised in Tables 3 and 4. Toxicity was more frequent in the dFUR arm but it was milder than that described in previous phase II studies [12, 16]. Moreover, the incidence of severe or life-threatening side-

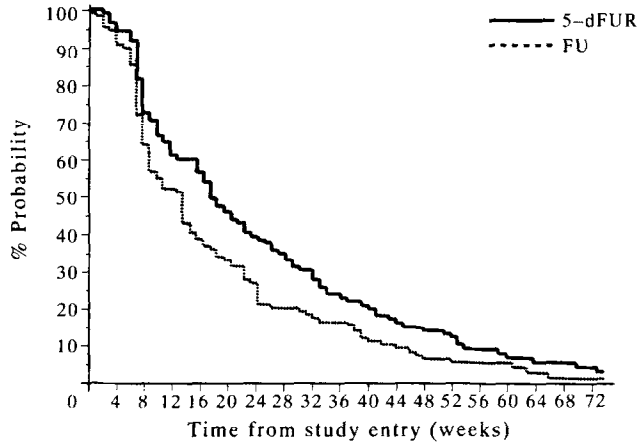

Fig. 2. Overall survival of eligible patients.

Table 3. Side-effects in eligible patients on dFUR arm

Side-effects	WHO grade 1	2	3	4
Nausea/vomiting	27 (24)*	6 (5)	4 (4)	—
Diarrhoea	10 (9)	14 (13)	6 (5)	—
Stomatitis	18 (16)	11 (10)	3 (3)	—
Leukopenia	10 (9)	9 (8)	2 (2)	2 (2)
Alopecia	4 (4)	3 (3)	2 (2)	—
Cardiac	—	—	1 (1)	1 (1)
Neurological	14 (13)	4 (4)	6 (5)	1 (1)
Other	9 (8)	10 (9)	4 (4)	—

*Number of cases. Percentage values in parentheses.

Table 4. Side-effects in eligible patients on FU arm

Side-effects	WHO grade 1	2	3	4
Nausea/vomiting	2 (18)*	9 (8)	1 (1)	—
Diarrhoea	9 (8)	15 (14)	4 (4)	—
Stomatitis	12 (11)	10 (9)	4 (4)	—
Leukopenia	7 (6)	3 (3)	1 (1)	1 (1)
Alopecia	3 (3)	—	—	—
Cardiac	—	—	1 (1)	—
Neurological	1 (1)	—	—	—
Other	6 (5)	16 (15)	1 (1)	—

*Number of cases. Percentage values in parentheses.

effects was very limited. Haematological toxicity was primarily leukopenia, whereas thrombocytopenia was minimal. The incidence of grade 3–4 leukopenia was 4% in the dFUR group and 2% in the FU group. Patients in the dFUR group experienced more prominent neurological toxicity than those in the FU group. It consisted mostly of dizziness, lethargy, transient disorientation and paresthesia, which were always reversible when treatment was discontinued. 1 patient in the dFUR group had signs of cerebellovestibular syndrome. As regards gastrointestinal side-effects, patients treated with dFUR experienced more grade 3 nausea/vomiting and diarrhoea than those in the FU group. Cardiotoxicity was observed in 2 patients treated with dFUR and in 1 patient treated with FU. All but 1 of these patients went off treatment. The episodes of grade III were asymptomatic and registered during Holter monitoring. They consisted of multiple premature ventricular contractions. During the following months, cardiac function was regularly checked by ECG monitoring and remained normal. The episode of grade IV cardiotoxicity was observed in a patient treated with dFUR with no history of previous cardiac disease. Symptomatic transient ventricular tachycardia was registered during Holter monitoring on the fourth day of the first cycle. It spontaneously abated after 50 s. In this patient the treatment was completed (12 cycles) without any further cardiological problem observed during further Holter monitoring.

Other toxicities were mild with the exception of grade 3 alopecia, which was encountered in 2% of the cases in the dFUR arm.

DISCUSSION

Fluorouracil has long been considered the only marginally active drug against colorectal cancer [18]. Despite the optimistic response rate of 20% reported by Moertel [3], few studies have reported a survival advantage for patients treated with FU compared to untreated control groups and the real efficacy of the drug is still under discussion [19]. Among the many different FU dosages and schedules tested, the standard regimen in colorectal cancer is controversial, but short-term daily infusion for 5 days every 4 to 5 weeks is one of the most common schedules utilised [1].

Nevertheless, the importance of fluorinated pyrimidines in colorectal cancer has been recently emphasised by their combining with biochemical or biological modulators [5, 6, 20] and their administration by very long infusions [21]. These regimens have improved the objective response rate and, sometimes, the quality of life and survival of these patients, but more effective agents are clearly needed.

The results of this randomised multicentre trial produced three major conclusions. First, FU alone has limited activity in colorectal cancer at the dose of 500 mg/m^2/day for 5 days every 28 days. The objective response rate of 1% observed in this study is very low but consistant with at least three recent randomised studies evaluating the efficacy of FU in advanced colorectal cancer, which reported a response rate of 3 to 7% [22–24]. In our study, all objective responses were reviewed by independent clinicians not involved in the study; this, as well as the intention-to-treat design of the study, contributed towards lowering the response rate.

A dose–response relationship has been suggested in metastatic colorectal cancer [25]. Although the dose intensity of FU used in our study was in accordance with that reported by phase III trials comparing FU alone with FU + folinic acid or FU + methotrexate (Table 5), it is noteworthy that, with the exception of one study, a dose intensity that does not exceed 625 mg/m^2 does not give a response rate above 10%. A second major point is that dFUR has a good tolerability profile at this dosage and schedule, with no toxic deaths encountered. Other reports have cited important side-effects with dFUR administered as a bolus injection or as a 1-h infusion. Side-effects seem to be dependent on the schedule of administration, with dose-limiting neurotoxicity mainly after brief infusion and cardiac toxicity after bolus injection [12, 14]. In our study we observed only 1.6% cardiotoxicity out of 112 patients and 511 cycles, whereas neurotoxicity was recorded in about 20% of the cases, 6% of which were grade 3–4 (WHO). The low toxicity encountered in both arms can

Table 5. Dose-intensity in mg/m^2/week of FU in phase III studies during the first 8 weeks of treatment

Authors	No. of patients	Dose intensity	Response rate (%)
Martoni *et al.* [24]	30	450	3
Petrelli *et al.* [23]	22	450	5
Erlichman *et al.* [22]	61	480	7
Labianca *et al.* [20]	90	500	10
NGTATG [28]	125	600	3
Nobile *et al.* [27]	39	600	5
Present study	110	625	1
Petrelli *et al.* [4]	107	640	12
Poon *et al.* [26]	70	650	10
Di Costanzo *et al.* [31]	78	680	18
Valone *et al.* [30]	55	740	16.9
Herrmann *et al.* [29]	74	840	17.6

partially be explained considering that in about 30% of patients only two cycles were administered. In addition to neurotoxicity, the only side-effect that was more prominent with dFUR than with FU was leukopenia (21 vs. 11%). These facts are probably related to the well-known presence of dFUR after a brief infusion in preferential sites such as bone marrow and the central nervous system [11].

The third point of this study is the observation that PFS was significantly longer in the dFUR arm and that survival time, although not significant, was different for the two groups (48 vs. 39 weeks). The two treatment groups were well balanced in terms of clinical characteristics, which indicates that confounding of the outcome by other determinants is unlikely to have influenced the differences between the two arms (Table 1). In analysing our data, it is noteworthy that 65 patients in the dFUR arm did not experience disease progression during the first 4 months, compared with only 54 in the FU arm. Although no determination of the quality of life of the patients was undertaken, it is well known that patients with objective response or stable disease for a long time experience better symptomatic control than patients with progressive disease who usually became subjectively worse [20, 22, 26]. This objective takes priority in symptomatic patients when no possibility of definitive cure is available.

A direct effect of better time to progression on survival was not observed. However, the fact that a statistically significant difference in survival was not observed may be related to the accrual of patients and median follow-up: given the recruited number of patients, the demonstration of a small survival benefit may have been difficult; moreover, median follow-up was, respectively, 56 and 67 weeks in the dFUR group and in the FU group. It is possible that, as reported by other authors [22], a longer follow-up may be necessary in order to detect a significant difference in slowly growing cancers, such as colon cancer.

Finally, about half of the patients (50 in the dFUR arm and 47 in the FU arm) were given FU plus folinic acid as second-line treatment after the failure of front-line therapy, or when the disease had been stable for 1 year. Although no substantial activity was observed, it is possible that a difference in survival might have been detected if no other treatment had been used.

Therefore, the higher although non-significant median survival, and the increased PFS observed in the dFUR arm, suggest a promising activity of this experimental drug in colorectal cancer. Similar results in terms of better PFS in comparison with FU have been previously reported only with the combination of biochemical modulators and FU [22, 26, 28]. The fact that dFUR alone was able to achieve these results is encouraging, and stimulates the use of the combination of the drug with biochemical modulators. Furthermore, new studies should develop more effective schedules of dFUR administration. Short infusion of the drug over 6 h once a week for 3 weeks [14] was evaluated in a phase II trial, but was characterised by a large incidence of severe non-haematological side-effects due to the very high dose used. A similar schedule, but with a lower monthly dose, could give better results. Continuous infusion over 1 to 5 days is under evaluation in phase II studies after the encouraging results observed in phase I trials [32]. Furthermore, the oral route is an attractive way to administer dFUR. Early studies with dFUR have demonstrated an optimal absorption of the agent, a high percentage of the drug free in the blood during the first 2 h, and lower side-effects than with the intravenous route [33]. Other studies are required to fully define these issues.

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Acknowledgements—The following investigators are co-authors of the study: F. de Braud, M. Di Bartolomeo, Milano; A. Guglielmi, Genova; L. Frassineti, P. Innocenti, Forlì; P. Comella, R. Casaretti, Napoli; D. Turci Ravenna; S. Perrone, Milano; F. Berardi, Bari; M. Barduagni; Roma; A. Pandolfi, Milano.

Eur J Cancer, Vol. 29A, No. 12, pp. 1663–1668, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

How Cost-effective is Breast Cancer Screening in Different EC Countries?

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Should the decision to start breast cancer screening in the Netherlands and in the U.K. be followed by other EC countries? This question has been addressed in an exploratory analysis of the differences in cost-effectiveness of breast cancer screening in Spain, France, the U.K. and the Netherlands. A detailed cost-effectiveness analysis of breast cancer screening in the Netherlands has been used as the starting point. Country specific data on incidence, mortality, demography, screening organisation and price levels in health care have been used to predict the costs and effects of nationwide screening programmes, in which women aged 50–70 are invited for 2-yearly mammographic screening. The relative effect of screening is highest in the U.K. (16.55 life-years gained per 1000 screens) and lowest in Spain (8.23 life-years gained per 1000 screens). The cost per screen is highest in Spain (£38) and lowest in the U.K. (£18). In comparison with the yearly health expenditures per capita, the cost per life-year gained is 2.8 times higher in the Netherlands, 3.1 times higher in the U.K., 6.5 times higher in France and 20.6 times higher in Spain. These marked differences show that no uniform policy recommendations for breast cancer screening can be made for all countries of the EC.
Eur J Cancer, Vol. 29A, No. 12, pp. 1663–1668, 1993.

INTRODUCTION

TRIALS FOR screening on breast cancer, conducted in north–west Europe in the past decade, have shown that early detection will result in a lower mortality from breast cancer [1–6]. Thus far, a positive effect has only been demonstrated in women over the age of 50 [7]. Cost-effectiveness studies performed in the U.K. [8] and in the Netherlands [9] indicate that the costs per life-year gained are relatively low in comparison to many other health care provisions. As a result of these findings, nationwide screening programmes are now being implemented in the U.K., the Netherlands, Finland and Sweden.

An interesting question is whether the conclusions about cost-effectiveness of breast cancer screening may be drawn for other countries in the European Community as well. The effects of a breast screening programme depend on many factors, such as incidence and mortality rates, quality of the screening test, participation rates, and screening policy. The cost-effectiveness is further influenced by the cost of the screening programme and by extra costs or savings in the diagnosis and treatment of breast cancer. Quite large differences regarding these factors exist between countries. For example, the crude mortality rate for

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Received 12 Feb. 1993; accepted 29 Mar. 1993.