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Rapidly Alternating Combination of Cisplatin-based Chemotherapy and Hyperfractionated Accelerated Radiotherapy in Split Course for Stage IIIA and Stage IIIB Non-small Cell Lung Cancer: Results of a Phase I–II Study by the GOTHA Group*

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The prognosis of stage III non-small cell lung cancer (NSCLC) can be improved by a combination of radiotherapy (RT) and chemotherapy (CT). In this study, the GOTHA group evaluated the feasibility, tolerance, tumour response, pattern of failure and effect on survival of a combination alternating accelerated hyperfractionated (AH) RT and CT in patients with tumour stage III NSCLC. 65 patients received 3 cycles of cisplatin 60 mg/m² and mitomycin C 8 mg/m² on day 1, and vindesin 3 mg/m² on days 1 and 8 in weeks 1–2, 5–6 and 9–10, alternating with AHRT, 2 daily 1.5 Gy fractions, 5 days/week, in weeks 2–3 (30 Gy) and weeks 6–7 (33 Gy). The dose actually delivered was >98% for RT, and 85–100% for CT. Mean duration before last CT cycle was 9.5 weeks. Toxic effects were leucopenia, nausea and vomiting, mucositis, diarrhoea, alopecia and peripheral neuropathy. 1 patient died of bronchial haemorrhage at the end of RT. 1 of 5 patients, who underwent secondary pulmonary resections, died of acute respiratory distress syndrome. Evaluation of tumour response was hampered by lung condensations in radiation fields. Some long-term survivors had an initial tumour response assessed as partial response or no change. First failures were more frequent outside (34) than within (21) radiation fields. The median survival was 15.7 months and the 5 year survival rate was 15% (95% CI = 6–26%). 1 patient died of bladder cancer and another of myocardial infarction. Alternating CT and AHRT, as used in this study, were well tolerated and allowed full dose delivery within less than 12 weeks. Initial response was not predictive of survival. The survival curve is encouraging and the 5 year survival is superior to the 5% generally observed with conventionally fractionated radiotherapy.

Key words: Phase I–II study, alternating radiotherapy–chemotherapy, hyperfractionated accelerated radiotherapy, non-small cell lung cancer
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INTRODUCTION

CONVENTIONALLY, FRACTIONATED, high dose (55–65 Gy) radiotherapy (RT) is the most common curative aimed treatment for stage III non-small cell lung cancer (NSCLC). With this treatment, the median survival in most published series is 1 year or less, and 5 year survival is around 5% [1–4]. Failures are due to recurrence within radiation fields or to metastatic extension. No major improvement has resulted yet from the use of hyperfractionated RT. In a study by the Radiation Therapy Oncology Group [5], the median survival of NSCLC patients after hyperfractionated irradiation was 6.3–14.1 months in subgroups selected by radiation dose and disease stage. Continuous accelerated RT (CHART) with three fractions per day [6] and hyperfractionated accelerated RT [7] are presently under investigation in NSCLC.

Various cisplatin-based combination chemotherapy (CT) regimens are active in NSCLC. In a study by the Swiss Group SAKK in 183 patients with advanced stage NSCLC [8], an overall response rate of 41%, and a median survival time of 8 months, were obtained with a combination of mitomycin C, vindesin and cisplatin. Other results have suggested that cisplatin-based chemotherapy could improve the survival of NSCLC patients [9].

Several clinical studies have compared a combination of CT and RT with RT alone in locally advanced NSCLC, of which only three showed an advantage of combined treatment, either in a sequential [10–12] or concomitant scheme [13]. The benefit of combined treatments may be explained by various factors. Due to local synergy of RT and CT in the irradiated volume, a decrease in intratumoral interstitial pressure, resulting from the

tumour response, may be achieved more rapidly, improving the drug delivery and the oxygen-dependent radiosensitivity [14]. In addition, the systemic adjuvant effect of CT may prevent extrathoracic failures, and, according to the model proposed by Goldie and associates [15], a rapid alternation of RT and CT could delay the occurrence of double resistance. A double resistance to radiation treatment and chemotherapeutic agents in patients with NSCLC is speculative, but a low sensitivity to X-irradiation after exposure to CT has been observed [16]. In human tumour cell lines, cross resistance as well as collateral sensitivity to CT have been observed after exposure to X-irradiation [17, 18].

Hyperfractionated, accelerated RT, in addition to its radiobiological rationale, may easily by alternated with monthly cycles of CT when given in split course. Looney and colleagues [19] have recently reviewed the potential advantages of alternating treatments. We present here the results, with a follow-up time of 41 to 84 months, of a Phase I–II study evaluating the feasibility, tolerance and therapeutic effect, in terms of tumour response, pattern of failure and survival, of a combination of chemotherapy and radiation in which the cisplatin-based CT described by SAKK [8] was alternated with a hyperfractionated accelerated RT in split course in patients with stage III NSCLC.

PATIENTS AND METHODS

Eligibility, study parameters

Patients with a pathologically documented squamous-cell carcinoma, adenocarcinoma, large cell/undifferentiated carcinoma or cytologically documented non-small cell lung cancer in stage IIIA or stage IIIB [20] were eligible, with the exception of those with pleural or pericardial effusions. In addition, the protocol specified that patients who had undergone full surgical resection of a single brain metastasis followed by cranial irradiation could be considered eligible if they had no residual CNS symptoms, no other M1 lesions and if they fulfilled all other requirements. The upper age limit was 69 years and the World Health Organisation (WHO) performance status was to be 0 or 1 [21]. 7 patients with a WHO performance status 2 who were erroneously entered were kept in the study for this analysis. Patients with tumour resection, radiotherapy or chemotherapy were not eligible. Other requirements for eligibility were a forced expiratory volume of 1.5 l or more, a normal blood count, normal heart, liver and kidney function, and no history of other malignant diseases, with the exception of cutaneous basal cell carcinoma and cone resected cervix carcinoma. The pretreatment evaluation included AP and lateral chest films, computer axial tomography (CAT) of the thorax, CAT or ultrasonography of the abdomen, CAT of the brain and bone scintigram. Informed consent was obtained according to the regulations in the participating institutions.

Treatment

The treatment regimen included three cycles of CT alternating with two courses of RT, as shown in Figure 1. The CT cycles were started on weeks 1, 5 and 9, or were delayed for 1 or 2 weeks, if necessary, due to WHO grade 3–4 toxicity [21]. Patients were hyperhydrated during the day of the 1 h cisplatin infusion. The choice of antiemetic treatment was left to the local investigators. Cisplatin was to be discontinued in case of WHO grade 2–4 renal toxicity. Mitomycin C and vindesin were administered by rapid intravenous injection. The second vindesin dose in cycle 1 and cycle 2 was given on the day radiotherapy was started, or was omitted in case of granulopenia, if judged necessary by the local investigators. No other dose modifications on the basis of toxicity were permitted.

RT was given with an accelerated and hyperfractionated regime, consisting of 2 courses of 30 and 33 Gy, each delivered in 2–2.5 weeks, on weeks 2, 3 and 6, 7 (or delayed when required). Thus, the total dose was 63 Gy. This was given at 1.5 Gy per fraction, twice a day, with a minimum interval of 6 h between fractions. The first target volume comprised the primary tumour, draining ipsilateral hilar lymph nodes, the mediastinum, thoracic inlet and the supraclavicular fossae. Up to 42 Gy, this volume was treated with antero-posterior parallel-opposed fields without cord shielding. The second target volume included only the primary tumour and grossly involved lymph nodes. This was treated to a total dose of 63 Gy, generally with oblique, parallel-opposed, off-the-cord reduced fields. Megavoltage (=6 MV) photons, isocentric techniques and cerrobend blocking were required. No corrections for lung heterogeneity were made.

Evaluation of response and toxicity, patients follow-up

The assessment of tumour response was based on the comparison of the initial tumour measurements with the tumour status 4–6 weeks after completion of the treatment. The WHO guidelines [21] were used for the assessment of response and toxicity. Blood counts were checked weekly. Chest roentgenograms and blood chemistries were repeated before cycles 2 and 3, and after completion of the treatment. The non-haematological toxicity was reported at the end of each course of RT and before each cycle of CT. Surgery was not part of the initial management and was not foreseen in this protocol. However, for various individual reasons, 6 patients underwent thoracotomy after completion of the study treatment (see Results). All patients were to be followed for the whole duration of their life, monthly during the first year, every 3 months in the second year and yearly afterwards, and the date of the site of first tumour relapse was registered. In case of failure, the choice of eventual treatment was left to local investigators.

Week	1	2	3	4(-6)1	2	3	4(-6)1	2
Mitomycin C, 8mg/m²	X				X			X
Vindesin, 3mg/m²	X	X			X	X		X X
Cisplatin, 60mg/m²	X				X			X
Radiotherapy 2x1.5 Gy, 5 days/week		■		(30Gy)		■	(33Gy)	

Figure 1. Treatment schedule.

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Histological and cytological diagnosis

The patient accrual was based on the diagnosis made by the histo- and cytopathologists of participating institutions. For the preparation of this final report, a central review was done retrospectively by one of the authors on the histological material, available for 58 patients only. The cytological material was not centrally reviewed. The diagnosis of NSCLC was confirmed in 57 cases. 1 patient with a reviewed diagnosis of small cell carcinoma was retrospectively withdrawn as ineligible.

Statistical methods

The survival was measured from day 1 of treatment to death (from any cause) or to the date of last contact. All censored data were for patients alive on 1 March 1993. The probability of survival was calculated according to the method of Kaplan–Meier [22]. The confidence interval (CI) for the probability of survival at a given time was calculated according to Dorey and Korn [23], with Rothman–Wilson upper limit [24] and Simon–Lee lower limit [25]. Reflected confidence interval of the median survival was calculated [26]. The survival curves were compared by the log-rank test of Mantel–Cox [27].

RESULTS

Patients

67 patients were accrued by the member institutions of the GOTHA group in Geneva (30 patients), Lausanne (20 patients) and Grenoble (17 patients) from February 1986 to September 1989. 2 ineligible patients were withdrawn: 1 unduly entered with skeletal and renal metastases, and 1 with a reviewed diagnosis of small cell carcinoma. Table 1 summarises the characteristics of the 65 eligible patients. The sex ratio and predominance of squamous cell type are in keeping with the regional epidemiology of lung cancer in the area of the participating institutions at that time. Stage IIIA and stage IIIB were equally represented. There were 25 T4, 16 T3 and 24 T1–2 patients. 9 patients had N0 tumours (5 T3 and 4 T4). 1 patient had a previously treated single brain metastasis. In 6 patients, the study treatment was preceded by an unsuccessful attempt of tumour resection or by a laser desobstruction.

Feasibility, dose intensity

All patients underwent the first cycle of CT and the first course of RT, during which one patient died of tumour progression. The third cycle could not be given to 4 patients: 1 died as a consequence of massive bronchial bleeding, 1 developed a tumour cavitation with sepsis, 1 had a prolonged thrombocytopenia and 1 refused further treatment. 2 patients received a modified CT regimen fractionated over 5 consecutive days with cisplatin 20 mg/m^2/day and vinblastin 2 mg/m^2/day. As shown in Table 2, the mean percentage dose was superior to 97% for all components of the combined treatment, with the exception of vindesin in cycles 2 and 3, principally because the dose on day 8 was omitted in 8 and 13 patients, respectively. The duration of RT courses was slightly longer than the scheduled 14 days, with mean values of 15.6 and 18.5 days. Also, the duration of cycles 1 and 2 was longer than the scheduled 28 days, with mean values of 32.1 and 34.7 days.

Response, pattern of failure, survival

The assessment of tumour response was hampered by the early appearance of lung condensations in radiation fields. Taking this limitation into account, 13 responses were evaluated as complete responses and 35 as partial responses, representing 20 and 54%, or an overall rate of 74%. 3 patients only had a progressive tumour by the time of the first assessment at the end of treatment. The sites of first treatment failure are indicated in Table 3. 21 patients had a first relapse within the chest irradiation fields, either with or without simultaneous metastatic extension. From the 13 tumours with locoregional recurrence only, 12 were of squamous cell type. 34 patients had first failures outside the radiation fields. From 11 intracranial lesions, 6 occurred in epidermoid tumours. In 7 patients, the site of first failure could not be defined by the time of their death which was, nevertheless, considered to be tumour-related.

The survival of eligible patients is shown in Figure 2. The overall median survival was 15.7 months, with a 95% confidence interval of 10.7–20.1 months. The 2, 3, 4 and 5 year survival rates (with 95% confidence interval) were 28% (18–40%), 18% (11–30%), 17% (9–28%) and 15% (6–26%). No significant survival differences occurred with respect to histology, institution or sex. The 2 year survival rate (with 95% confidence interval) was 50% (24–76%) for 10 patients with T3/T4–N0 tumour stage (5 T3 and 5 T4), and 24% (14–36%) for tumour stage N1–N3 (55 patients). The survival curves of patients with stage IIIA and stage IIIB tumours were almost identical (not shown). In many patients with peripheral tumours, lung condensations of increasing density in radiation fields made the detection of local recurrence impossible. For this reason, the time to disease progression could not be adequately defined. 12 patients had a survival time superior to 3 years at the time of the present analysis. 9 of them are alive and free of recurrence 43–84 months

Table 1. Characteristics of patients

Number of patients entered	67
Number of ineligible patients	2
Number of evaluable patients	65
Number of males/females	55/10
Median age (range) in years	55 (32–69)
Median weight (range) in kg	69 (46–106)
Cell types	
Epidermoid carcinoma	42
Adenocarcinoma	18
Large cell carcinoma	4
NSC, unspecified (cytology)	1
Stage IIIA/IIIB	32/32
Stage IV (see text)	1
Blank thoracotomy/laser desobstruction	4/2

Table 2. Dose intensity

	Mean % of due dose	Mean duration in days
First cycle		32.1
Mitomycin C	99.8	
Vindesin	98.9	
Cisplatin	99.0	
Radiotherapy, first course	99.6	15.6
Second cycle		34.7
Mitomycin C	99.3	
Vindesin	92.0	
Cisplatin	99.7	
Radiotherapy, second course	98.8	18.5
Third cycle		
Mitomycin C	97.2	
Vindesin	85.4	
Cisplatin	98.8	

Table 3. Sites of first failure

	All	Epidermoid	Other
Alive, free of event	9*	5*	4
Dead without NSCLC relapse	3	2	1
Local–regional recurrence only	13	12	1
Local–regional + extrathoracic	8	3	5
Extrathoracic extension only	26*	16*	10
CNS metastasis	11*	6*	5
Dead, first site of failure unknown	7	5	2

* Including 1 patient free of disease 6 years after surgery and radiotherapy of single brain metastasis.

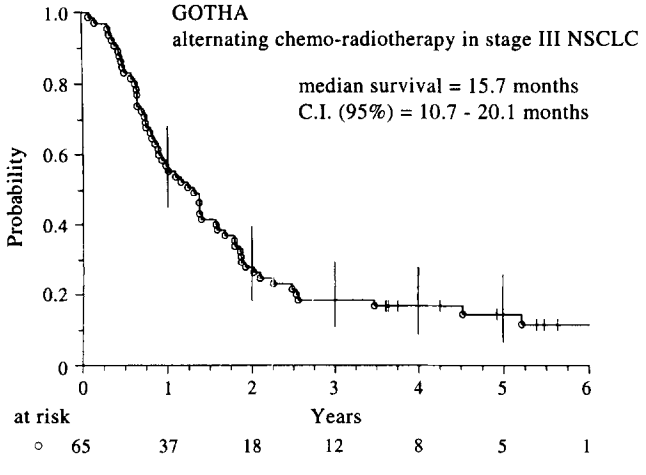

Figure 2. Survival curve with 95% confidence intervals (CI) at 1, 2, 3, 4 and 5 years.

from day 1 of study treatment. 2 died from tumour progression and 1 from an unknown cause.

Toxicity

Moderate cough, nausea, dysphagia, hair loss, and skin reaction in radiation fields were observed in all patients. Most of these minor symptoms, at the level of WHO Grade 1, were not registered in the patient record forms. The overall non-haematological toxicity, as reported in the study documentation, is shown in Table 4. As mentioned before, 1 patient died shortly after completion of the second course of radiotherapy as a consequence of a massive haemoptysis that could have been related to the effects of the combined treatment. WHO grade 3–4 nausea–vomiting and oesophageal mucositis were observed in 11 and 9% of patients, respectively. Peripheral neuropathy was frequent but rarely severe (2%). An increase of serum creatinine concentration above normal values was observed in 4 patients. Table 5 summarises the haematological toxicity. The more pronounced toxicity observed during the second cycle reflects probably an additive effect of CT and RT. Nadir leucocyte counts below 1.000/ml were more frequent after the second cycle (33%) than after the first (18%) or the third (17%). A severe and transient leucopenia occurred frequently in the middle of radiation courses that were, in general, not interrupted. Anaemia was frequently cumulative and long lasting. Thrombocytopenia was less frequent and generally mild. Late respiratory complications, occurring more than 90 days after initiation of therapy, were seen in 8 patients. They were described as a prolonged invalidating respiratory insufficiency in 1 patient, as respiratory symptoms reported as dyspnoea with or without cough in 2 patients, and as minor symptoms in 5 patients. No leukaemia or myelodysplastic syndrome was recorded. 1 patient died of transitional cell cancer of the urinary bladder 30 months after day 1 of treatment, without recurrence

Table 4. Per cent overall (and WHO3–4) non-haematological activity

	Cycle of chemotherapy			Whole treatment
	First	Second	Third	
Nausea, vomiting	46 (5)	43 (7)	35 (6)	61 (11)
Mucositis	41 (5)	36 (9)	19 (2)	52 (9)
Diarrhoea	3 (2)	2 (0)	4 (0)	8 (2)
Skin	7 (3)	5 (4)	2 (0)	8 (5)
Neuropathy	12 (0)	25 (0)	31 (2)	31 (2)
Respiratory (acute)	0 (0)	1* (1)	0 (0)	1 (1)
Alopecia WHO3				12
Serum creatinine†				7 (0)

* Lethal haemoptysis possibly related to treatment (see text).
† WHO1–2 = 125–500 μmol/l; WHO3–4 = >500 μmol/l.

Table 5. Haematological toxicity median nadir counts (range)

	Cycle of chemotherapy		
	First	Second	Third
Haemoglobin (g/dl)	11.3 (8.0–14.3)	10.0 (6.9–14.1)	9.8 (6.6–14.3)
Leucocytes (g/l)	2.2 (0.5–7.0)	1.2 (0.2–7.5)	2.2 (0.0–5.2)
Thrombocytes (g/l)	196 (81–363)	117 (13–330)	130 (33–300)

of the lung tumour. Another patient died of myocardial infarction in the 15th month without evidence of a tumour.

Secondary surgery

6 patients underwent chest surgery 10–99 days after completion of the study treatment. The pulmonary resection was a pneumonectomy in 3 patients, a lobectomy in 1 patient, and a limited resection in 1 patient with a superior sulcus tumour. 1 patient did not have a pulmonary resection. No residual tumour was disclosed by the histological examination of two specimens. Isolated tumour cell clusters were found in 2 cases and overt tumour tissue was still present in 1 case. 1 patient died on the 16th postoperative day with acute respiratory distress syndrome. 2 patients died of tumour progression 13 and 22 months after surgery. 2 patients are free of tumour recurrence 60 and 36 months after day 1 of treatment.

DISCUSSION

The alternating schedule designed for this study delivered, within 10 weeks, 63 Gy in split course on the tumour and the local–regional nodal areas with an accelerated hyperfractionated scheme, and a cumulative dose of cisplatin 180 mg/m^2, vindesin 30 mg/m^2 and mitomycin C 24 mg/m^2. Besides the theoretical considerations based on the Goldie–Coldman model, the alternating schedule was also selected in order to avoid the synchronised additive toxic effects of CT and RT produced by simultaneous application. The tolerance of this treatment programme is indicated by the fact that the overall dose intensity was close to 1. Although nadir leucopenia frequently occurred during RT, the radiation courses were generally not interrupted. Oesophageal mucositis was similar to that which would have been expected with hyperfractionated radiation alone. Late pulmonary complications (8 out of 65 patients) were rare. There were 2 deaths possibly related to the treatment: a massive haemoptysis following radiotherapy, and a postoperative acute respiratory distress syndrome, the genesis of which the combined treatment could have played a role.

Although short-term tumour response was not the primary objective of this study, tumour measurements at start and after completion of treatment were compared. The results show that short-term tumour response cannot be used as a surrogate of survival. Some long-term survivors were evaluated as partial responders or even as non-responders. The fact that non-responders may have had tumours with low proliferative poten-

tial may be an explanation. However, the main problem was that residual lesions within radiation fields could have been, in many cases, due to radiation pneumonitis.

The pattern of first treatment failure shows that extrathoracic extensions were more frequent than local–regional recurrences. This suggests that CT, as given in this study, was not able to prevent or to delay efficiently the metastatic extension, even in stage III tumour patients with subclinical systemic tumour load. Local–regional recurrence was still an important problem, since there were 21 recurrences within radiation fields, including 8 with concurrent metastatic extension. It is likely that these 21 local–regional recurrences are an underestimate of this relapse pattern, since patients with distant disease as the first site of relapse were not systematically checked for local–regional failure. With one exception, all first failures limited to the chest were seen in epidermoid tumours. This finding probably reflects the known higher metastatic potential of adenocarcinomas and large cell carcinomas, and the known high local–regional failure rate of squamous-cell carcinoma. 26 patients relapsed outside the chest without loco-regional recurrence. The most frequent site of extra-thoracic metastasis was the CNS. CNS metastases occurred with or without concurrent local recurrence. An important observation was that of 11, 6 occurred in patients with epidermoid tumours.

The median survival of 15.7 months is suggestive of an improvement by comparison with several studies of radiotherapy alone. This is also reflected by a 5 year survival of 15%, significantly above the value of 5% generally reported when conventionally fractionated irradiations were used. Other recently conducted trials of combined cisplatin-based chemotherapy and radiotherapy in locally advanced NSCLC have obtained similar results. A median survival of 14.2 months was achieved in a study of the Northern California Oncology Group [28] where 22 patients with tumour stage IIIB received an alternation of radiotherapy in split course and cisplatin. The median survival was 26 months in 23 patients with disease stage IIIA or IIIB treated at the Mayo Clinic [29] with concomitant accelerated hyperfractionated irradiation and a combination of cisplatin and etoposide. In a randomised comparative study by the Cancer and Leukaemia Group B [10], the addition of chemotherapy to a conventionally fractionated irradiation was associated with a significant prolongation of survival (13.8 versus 9.7 months). The survival was also improved in a similar study by the Institut Gustave Roussy [12], where the 3-year survival was 4% without and 12% with chemotherapy. Of the 4 recent randomised trials comparing radiotherapy versus concomitant radiotherapy and cisplatin, only one, by EORTC, demonstrated a significant improvement in local control and survival, when daily, low dose cisplatin was added to radiation treatment [13]. In our study, the accelerated hyperfractionation as well as the alternation with chemotherapy may have played a role in the median survival of 15.7 months.

The comparison of survival in stage IIIA and stage IIIB NSCLC is still a controversial issue [4, 30]. The difference observed by Bonomi and associates [30] was mainly the result of a significantly longer survival in patients with T3–N0 tumours, whereas no significant difference was seen between stage IIIA–N2 and stage IIIB. In the present study, the small proportion of tumour stage T3–N0 (5/32 patients with stage IIIA) and the exclusion of stage IIIB patients with pleural or pericardial effusions may explain the lack of survival difference between stage IIIA and stage IIIB.

Secondary surgical treatment was not part of the study protocol, but left to the decision of local investigators. 6 patients underwent a thoracotomy, and a pulmonary resection was performed in only 5. Interestingly, no histologically detectable residual tumour was found in 2 cases. Among them was 1 patient who died of acute respiratory failure shortly after surgery. The role of secondary pulmonary resection after complete response to combined treatment, especially in patients receiving high dose comprehensive thoracic irradiation, remains to be defined, particularly in terms of postsurgical acute and chronic complications, quality of life and long-term survival.

In conclusion, an alternating combination of accelerated hyperfractionated RT and cisplatin-based CT has been well tolerated in 65 patients with locally advanced NSCLC. An encouraging effect on median survival and 5 year survival has been achieved in this study. Both the unconventional irradiation technique and the alternating RT–CT combination could have contributed to this result, in a proportion only assessable in a randomised trial. Such a trial would be unfortunately beyond the patient accrual potential of our study group.

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A Model-based Prediction of the Impact on Reduction in Mortality by a Breast Cancer Screening Programme in the City of Florence, Italy

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The efficacy of breast cancer screening for women older than 50 years has been shown in several studies. Service screening is now ongoing or planned in several countries in Europe. MISCAN, a computer simulation programme, has been used to analyse data from the Florence District Programme (FDP) breast cancer experience. First, the model was fitted to the screening results for the period 1975–1986. A good correspondence between the model outcomes and the FDP results was achieved. It was then used to predict the impact on mortality of the new starting programme of the city of Florence (63 000 women, 50–69 years old). Assuming a 70% attendance rate, then for the city of Florence, 2563 screen-detected breast cancers are predicted for the period 1991–2020 out of the total number of 9095 breast cancers for all ages (28%). A total of 3720 deaths for breast cancer are expected without screening. An absolute reduction of 472 deaths (13%) is predicted for the whole population. The estimated number of years of life gained by screening until 2020 is 4354. Simulation by MISCAN has previously been a useful support tool for decision-making about screening. The present paper is the first based on a southern European experience. The possibility of applying MISCAN to predict the impact of a national programme in Italy is discussed.

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INTRODUCTION

EVIDENCE OF the efficacy of breast cancer screening for women older than 50 years has been provided by several randomised trials and case–control studies [1], and service screening is now ongoing or is planned in several countries in Europe. The question remains as to what the consequences of such programmes are in a population as a whole, in terms of the effectiveness of the programme in reducing mortality for breast cancer. This can be investigated by using simulation models.

In the Netherlands, the MISCAN model was used to make a