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## Management of Breast Cancer in the Elderly

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The management of breast cancer in elderly women was analysed by a retrospective study of 150 women over 70 years old referred to our department between 1984 and 1988. 80 were T1-T2, 33 were T3 and 34 were T4. 107 were N0 and 43 were N1-N2. 16 women (11%) were in poor health, preventing conventional treatment. Treatment choice varied with age: 60% of the women aged 70–79 (group 1) and 23% of the oldest women (group 2) were treated conventionally. The use of surgery decreased with age and surgical procedures were conventional in only 85% of the group 1 women and in 56% of the group 2 women. Definitive radiation therapy was used more frequently in the oldest women, as was primary hormone therapy. Quality of follow-up also varied with age. Five-year survival rates were still high in both groups while relapses were frequent. Breast cancer was consequently a frequent cause of death. The increase in the proportion of elderly people with breast cancers over the next few years will require validated guidelines. Specific protocols and specific rules of management must be drawn up.

**Key words:** breast cancer, elderly, surgery, radiotherapy, hormone therapy

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### INTRODUCTION

AGE IS one of the principal risk factors for breast cancer. The incidence of breast carcinoma increases with age to over 300 per 100 000 woman-years in women over 70 years old [1]. Thirty per cent of the new cases diagnosed in France are aged over 70 [2]. In western countries, this proportion is increasing as life expectancy grows. The percentage of elderly women treated for breast cancer was greater between 1968–1978 than between 1958–1968 [3]. Breast carcinoma is a major health problem in the elderly but retrospective studies have shown that treatment varies according to the patient's age and is often less intensive in old patients [4–7]. This may be because breast carcinoma is often accompanied by other medical problems that may contraindicate aggressive treatment, such as surgery or radiotherapy. Nevertheless, there may be other subjective reasons. Breast adenocarcin-

oma is thought to be a slow growing cancer in elderly patients, with no imperative need for conventional treatment. It has also been said that these patients do not accept aggressive treatment, that they are often indifferent to cancer and not concerned with breast preservation. This could lead to sub-optimal treatment. Breast carcinoma is a major problem, and even early breast carcinoma is a major cause of death in women aged over 65 [3, 8, 9]. A 70-year-old woman has a life expectancy of 16 years in western countries, and an 85-year-old woman can expect to live 7 years [9]. Since 95% of tumour relapses occur in the first 4 years after treatment, local-regional control must be a major concern for physicians, even in the oldest patients [10]. While there is evidence that local regional control of breast cancer is needed in both elderly and younger women, the general frailty of the elderly plus the health of each individual must be taken into account. This may require a wide range of treatments, some of them unconventional. The validity of some of these unusual therapeutics has not been demonstrated, and physicians lack guidelines because few data are available. Clinical trials targeting this population are rare [11]. Most trials exclude older women and specific data mainly come from retrospective studies of selected elderly populations. Moreover, comparison between treatments in terms of overall survival and disease-free survival

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may be inappropriate because patients have a much shorter life expectancy [3, 6, 8, 12].

Attempts have been made to compare different treatments, but they have always been made on selected populations. This study examines the management of a non-selected elderly population with breast carcinoma. All the patients aged 70 years or older treated in our institution for breast cancer were examined for the influence of age on treatment choice, quality of the follow-up and outcome. This retrospective study will enable us to identify specific trends in the elderly and hence to prepare guidelines for treating this growing population.

## PATIENTS AND METHODS

### Patients

A total of 166 patients, aged 70 years or older were treated in the Oncology Department at the Henri Mondor Hospital between 1984 and 1988. Those patients treated for breast cancer relapse were excluded from the study if the primary tumour occurred before the patient was aged 70, or if she had been treated in another institution. 10 patients were excluded because histology or surgery reports were not available, and 6 were excluded because the patients did not return after the first visit. Hence, 150 patients took part in the study.

All the patients had histologically or cytologically proven cancer (cytology, drill biopsy or lumpectomy). The Scarff and Bloom grading [13], and oestrogen and progesterone receptor levels were obtained from biopsies or lumpectomies. The tumour margins, the number of explored nodes and the number of positive nodes were also given for lumpectomies and axillary dissections. All patients underwent a complete physical examination before treatment and their clinical stage was established using the UICC staging system [14].

### Treatment

Breast carcinoma was treated as previously described, by surgery or surgery plus radiotherapy [15, 16]. According to the protocol used during the period 1984–1988, the women underwent radical mastectomy or lumpectomy with axillary dissection. Excisional biopsy and no axillary dissection were considered unconventional treatments. A few patients were treated under local anesthesia and were also considered out of conventional protocol. Though the indications for lumpectomy or mastectomy depended on the extent of the tumours, both were considered conventional treatments when they were performed in the elderly.

Several radiotherapy procedures were used. The conventional treatment first delivered 45 Gy ( $5 \times 1.8$  Gy per week); the target volumes and irradiation fields have been described previously [15, 16]. Tumour bed boosting was performed with external beams or interstitial implants. Unconventional procedures of radiotherapy were accelerated therapy (30 Gy in 10 fractions over 12 days), or "flash irradiation" (23 Gy in four fractions over 23 days). The combined surgery and radiotherapy procedures have been described elsewhere [15, 16]. Treatment that did not follow these procedures was considered unconventional, such as lumpectomy without irradiation and definitive radiotherapy.

Hormone therapy as primary treatment (tamoxifen 20–40 mg per day) was regularly checked by the patient's general practitioner. The patient came back for a clinical reassessment after 3 months. Surgery or radiotherapy was then performed if the tumour response was unsatisfactory. Hormone therapy was considered conventional when it was given for an extended carcinoma (T4).

### Follow-up

The disease status (disease-free, local regional relapse, metastatic disease) was determined at the end of each follow-up year from the medical notes. Patients were classified as not followed up when no data were available from regular observations for at least 6 months (undocumented patients). Other patients or patients who had died from known causes were identified as documented. Enquiries were made at the Registry Office about all the patients 5 years after the beginning of the therapy to determine whether they had died or not and if so, the dates of their deaths. Deaths were considered to be related to breast carcinoma when patients were not disease-free at the time of death. Deaths were considered undocumented when no data on the status of the disease were available for the 6 months before death and when the patients were disease-free at the last medical examination.

## RESULTS

### Population

The average age of the population was 77.2 years (range 70–94), with 34% of the patients aged 70 to 74 years, 28% aged 75 to 79 years, 20% aged 80 to 84 years and 18% aged over 85 years. Pertinent medical histories and physical examinations were available for only 95 patients. The circumstances of breast cancer diagnosis varied according to the patient's age. It was discovered after self examination by 51% of the 70–74-year-old patients but only by 31% of the 75–79-year-olds, 30% of the 80–84-year-olds and 6% in the patients aged over 85. Most of the patients older than 85 years were diagnosed by a clinician during hospitalisation for causes unrelated to cancer (66%); this also occurred for 30% of the patients aged 80–84 and for 20% of the younger patients. The tumour was discovered by a general practitioner during a visit in 40% of the 70–79-year-old patients and in 20% of the oldest women. Diagnosis was made because of signs of metastasis in 5 patients.

150 patients included: 3 T0 (2%), 18 T1 (12%), 62 T2 (41%), 33 T3 (22%) and 34 T4 (23%) according to the TNM classification. 107 patients were NO, and 43 were N1–N2. As shown in Figure 1, the younger population (70–80 years) had a higher percentage of small tumours (T1–T2) than the elderly patients. Nevertheless, the difference was not statistically significant. The percentage of T4 tumours grew slowly with age, but no inflammatory breast carcinoma was noted in women older than 79 years. There was no correlation between lymph node

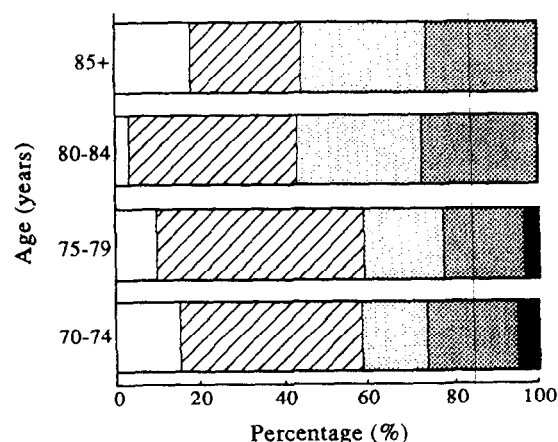


Figure 1. Tumour extent distribution related to patient's age. T1 □; T2 ▨; T3 ▩; T4 ■.

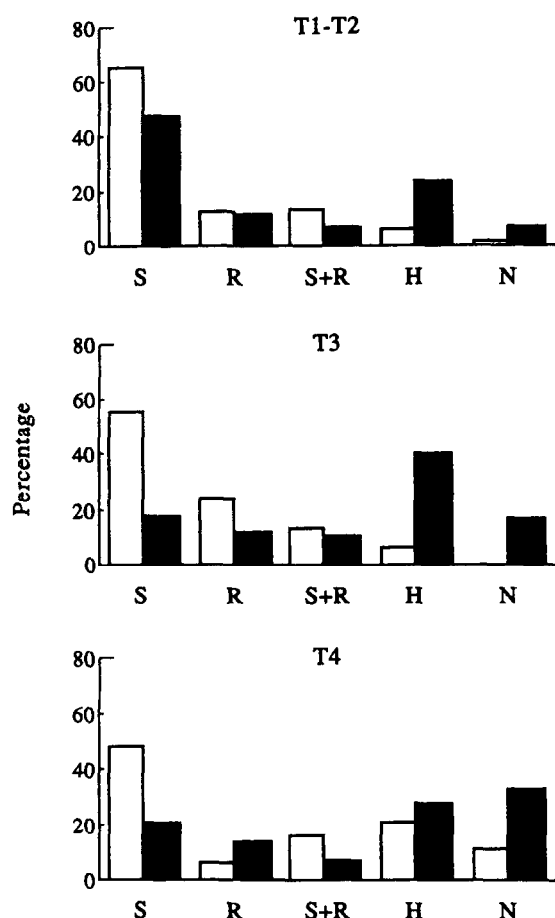


Figure 2. Treatment used related to patients' age and to tumour extent. White bars, 70-79 years old; black bars, 80 and over years old. S, surgery; R, radiotherapy; H, hormone therapy; N, no treatment.

invasion and age. Among the 14 patients (9%) who had metastases, 6 patients were 70-79 years old and 8 were older. Histological material from a biopsy or surgical specimen was available for 101 cases. 93 patients had invasive ductal carcinomas, 4 had intraductal carcinomas and 4 had invasive lobular carcinomas. There were 20 grade I, 43 grade II and 38 grade III patients by the criteria of Scarff, Bloom and Richardson. Among the 57 patients without palpable axillary nodes, 31 had histologically positive axillary nodes. Oestrogen receptors were found in 82 patients (81%) and progesterone receptors were found in 42 patients (42%).

#### Therapy (Figure 2)

After the first physical examination, 16 patients were not given conventional treatment because of their poor physical condition (4 patients) or dementia (12 patients). 3 patients refused surgery and 1 patient refused to be treated. Surgery and radiation therapy were less common as the patient's age increased. Figure 2 shows the treatment procedures used according to age and extent of the cancer. Almost all (91%) the younger women (group 1: < 80 years) with early breast cancer (T1-T2) were treated by surgery and/or radiation. Patients with larger tumours tended to be given less aggressive treatment. Most of the other patients had hormone therapy. 5 patients, all under 75 years, underwent chemotherapy; 2 patients had metastatic diseases, 1 had a locally advanced tumour and 2 had chemotherapy as an adjuvant therapy.

Fewer of the older patients (group 2: > 79 years) underwent surgery and/or radiation therapy. The difference between the two groups increased with increasing tumour size. The proportion of untreated women increased with the tumour stage, whereas the proportion of women given hormonal therapy was not correlated with the extent of the cancer. Hormone therapy was frequently prescribed with high frequency for the entire subgroup. No patient had chemotherapy in this group. None of the 150 women was included in the prospective trial.

#### Surgery (Table 1)

The number of unconventional surgical treatments increased with the patient's age. Most (85%) of the surgical procedures used for group 1 patients were conventional, while only 56% of patients from group 2 were treated this way. The use of surgery decreased as the patients became older, and the procedures used also differed. Lumpectomy and axillary node dissection were less frequent in older women. There was a trend towards performing mastectomy rather than lumpectomy in older women even for small tumours.

#### Radiation

93 women (62%) had radiation therapy: either alone or following surgery. Radiation therapy was more frequently used in younger patients than in older ones. Radiation procedures also varied with age. Conventional procedures were used in most patients younger than 84 years whereas non-conventional therapy was almost always used for patients older than 85 years. The primary tumour areas were given an interstitial implant performed in 24 cases.

#### Hormone therapy

26 patients were given hormonal therapy as primary treatment (Figure 2). Among them, 18 had early operable tumours and 8 had inoperable extended tumours. Hormone therapy was chosen for the early tumour cases because of their general clinical status. There was generally no real pre-anaesthetic examination. The receptors levels for 23 of these 26 women were known (20 RO +, 12 RP +). The response to hormone therapy during the first year was assessed in only 15 patients (Table 2). There were three complete remissions (CR), 4 partial responses (PR), 6 stable diseases and 2 progressions. The outcome of these women is shown in Table 2. Radiotherapy was combined with hormone therapy for 5 patients whose responses to tamoxifen were considered insufficient. The survival of these few women was

Table 1. Surgical procedures used according to patient age

Age (years)	Conventional		Unconventional		
	Mamm. with axill.	Lumpec. with axill.	Surgery without axill.	Excisional surgery	No surgery
70-74	13	22	5	4	7
75-79	18	11	1	1	11
80-84	6	7	4	1	12
85 and +	2	0	1	6	18
Total	39	40	11	12	48

Mamm., modified radical mastectomy; lumpec., lumpectomy; axill., axillary dissection.

Table 2. Hormone therapy in documented patients

Patient no.	Age (years)	TNM status	Hormone receptor status	Response	Time to relapse or progression (months)	Second therapy	Survival (months)
1	81	T2 N0	ER+ PR-	CR	32	R	>60
2	84	T3 N1	ER+ PR+	CR	34	S	>60
3	75	T3 N0	ER+ PR-	CR	*	—	18
4	78	T1 N1	ER+ PR-	PR	10	S	13
5	73	T4 N1	ER+ PR+	PR	15	S	>60
6	85	T4 N2	ER+ PR-	PR	*	—	19
7	88	T2 N2	ER+ PR+	PR	23	—	33
8	82	T2 N1	PR- ER-	St	8	R	51
9	77	T3 N0	ER- PR-	St	14	R	>60
10	80	T2 N0	ER+ PR+	St	18	R	>60
11	79	T2 N1	ER+ PR-	St	18	S	>60
12	83	T4 N1	ER- PR-	St	20	—	24
13	82	T2 N0	ER+ PR+	St	*	—	35
14	74	T2 N1	ER- PR-	Prog	—	R	7
15	81	T1 N0	ER+ PR+	Prog	—	R	18

ER, oestrogen receptor; PR, progesterone receptor; CR, complete response; PR, partial response; St, stable disease; Prog, progressive disease; S, surgery; R, radiotherapy. \* Deceased with no evidence of disease.

comparable to that of patients who underwent surgery plus hormone therapy.

#### Tolerance

One patient died in the month following surgery. Surgical complications were rare and did not depend on the procedure used. Two thrombo-embolic accidents occurred; they were resolute without aftermath. Healing was delayed in 4 women. The mean hospitalisation time was 12 days (range 9–22), and the mean time between surgery and the first day of radiotherapy was 24 days (range 17–38). These data were similar to those for younger women treated in our institution. Radiation therapy was interrupted in 2 patients because of severe acute reactions. Mild to moderate arm oedema occurred in 5 patients and persisted for over a year after completion of the treatment for 3 of them. Other reported complications included breast oedema (3 patients) and symptomatic radiation pneumonitis (3 patients). They were all resolved.

#### Follow-up

Follow-up was greatly influenced by age and treatment in this elderly population. Patients who had had conventional treatment were regularly examined by the oncologist, whereas the patients given hormone therapy or flash radiotherapy were not often monitored by the hospital (Table 3). Only 16% of the patients given conventional therapy were undocumented 5 years later. The cause of death for older patients given unconventional therapies was seldom known (Table 3). Overall, the death rate increased with age (Table 4). Nevertheless, about 50% of the women aged 80 years and older were still alive 5 years after diagnosis (Table 4). Specific survival rate would be the best criterion to assess the impact of breast carcinomas, but there were so many undocumented deaths that it biased results. The rates of deaths and relapses in the population followed show that many deaths were due to breast carcinomas (Table 4). The relapse rates were also high.

Table 3. Follow-up correlated with patient age and treatment

	n	Percentage of documented patients			Deaths (%)	Documented deaths (%)
		1 year	3 years	5 years		
70–79 years						
Conv. treatment	56	89	89	86	26	88
No conv. treatment	47	74	72	64	34	68
80 years or more						
Conv. treatment	13	92	92	77	23	66
No conv. treatment	34	41	41	36	36	14

Conv., conventional; n, number of patients; documented, knowledge of the disease status of the patient. Deaths are the proportion of deaths as assessed from the civil registry. Documented deaths are the proportion of deaths from known cause.

Table 4. Survival, relapse rates and cause of deaths in the documented population after 5 years of follow up

	n	Alive (%)	Local regional relapse (%)	Metastasis relapse (%)	Proportion of deaths due to breast carcinoma
70–79 years					
Conv. treatment	48	79	25	25	2/10
No conv. treatment	30	50	33	20	5/15
80 years and more					
Conv. treatment	10	80	20	30	1/2
No conv. treatment	16	50	75	25	4/8

Conv, conventional.

## DISCUSSION

The distribution of TNM stages according to age in these patients is consistent with those found in other studies [3, 4, 7, 17, 18]. As age increases, the percentage of early stage cancers decreases slightly. Inflammatory breast carcinoma is rare in elderly patients, whereas the incidence of locally advanced tumours with skin or parietal extension increases with age. This suggests that the development of breast carcinoma can change depending on the age of the subject. As shown in other studies, nodal and metastatic status conditions do not vary with age [4, 19]. The histological type did not differ in our population [19], but positive oestrogen receptors response was higher [20, 21].

A recent study has shown that elderly women are less frequently given mammographies than younger women, whereas the incidence of breast carcinoma increases with age [22]. This seems to be due to both patient's and physician's attitudes. Our study supports this: diagnosis was more often than not made during hospitalisation for other reasons. The rate of histological axillary node invasion in patients without clinically palpable nodes was also higher in this elderly population than in a younger population. Complete histological data were available for 101 patients, and follow-up was poor, especially in the older women.

### Therapy

The results show that surgery and/or radiation therapy were still the main treatments given to patients until they were 80 years of age in our institution, but that only half of the older patients were treated in this way. The other half were given less aggressive treatments such as hormone therapy or no treatment at all. This trend has been observed by other authors [4–7, 17]. The patients' medical condition could determine this approach. Other diseases are often associated with cancer, but our retrospective study emphasises that unconventional therapy has been used without any clear objective reason. One of the most important problems encountered in treating the elderly is their tolerance of treatment. We found that none of the conventional surgery procedures led to more complications or sequelae than they did in the younger women. There were few cases of arm oedema. Radiation therapy was also well tolerated with no more complications than in the younger women. Surgery of breast carcinoma does not lead to more complications in elderly patients than in the overall population of patients with the same anaesthetic risk factors [23]. Hence, a correct evaluation of the physiological and pathological status of the patients is needed. We also need to know whether these complications are more

disabling for elderly patients than for a younger population. None of our patients that had complications was hospitalised. Nevertheless, the potential of a therapy to alter a patient's quality of life must be kept in mind when treatment is planned.

The use of less intensive therapy would avoid subjecting frail patients to surgery and/or prolonged radiation. In fact, unconventional procedures of surgery and/or irradiation were also frequently used for healthy women. The present study indicates that three major therapeutic deviations from conventional combinations of surgery and radiation therapy were used. Patients with large tumours underwent lumpectomies or mastectomies without removal of axillary lymph nodes. There is evidence that local regional control of T1 N0 tumours is not affected by omitting axillary dissection provided that the axilla has been irradiated, although axillary dissection provided better local control of locally advanced tumours [24, 25]. The lack of axillary dissection in the elderly was not satisfactory and was not logical, since lumpectomy and mastectomy were used. When it was performed, axillary dissection was very well tolerated by our oldest patients without any more frequent complications than in younger women [25]. The respective proportion of lumpectomies and mastectomies performed also varied with the patient's age. Lumpectomy was preferred to mastectomy in patients younger than 75 years. All patients older than 84 years who were treated surgically had mastectomies. This therapeutic approach was not correlated with TNM staging, as in younger patients. Mastectomy was often preferred to lumpectomy in order to avoid breast radiotherapy, which lengthens treatment. Lastly, some women underwent lumpectomy without radiotherapy. Published data have shown that breast radiotherapy after lumpectomy increases the local regional control in elderly people, as it does in younger patients [8, 26]. Another study has shown that postoperative radiotherapy does not increase local control over that obtained by lumpectomy alone in patients with a tumour smaller than 1 cm or in patients older than 70 years [27]. But there were only 31 of these older patients, and the follow-up period was short. Other data from studies using lumpectomy alone in the elderly gave local regional relapse rates as high as 38% [28]. The combination of lumpectomy and radiation therapy should be the rule for early breast carcinoma. Unconventional procedures of radiotherapy can be used when shorter treatments are needed.

Hormone therapy is commonly used as primary treatment because its efficacy largely outweighs its toxic effects. Hormone therapy was used as the primary treatment for patients older

than 80 years and also for younger patients (70 to 79 years) who were inoperable in our population. The department's policy was to use radiation therapy as secondary treatment when hormone therapy was insufficient. Nevertheless, many patients had no follow-up. Hence, primary hormone therapy may be considered by some as a lack of therapy.

#### Benefits from therapy

Most elderly patients can be treated in the same way as younger women. Nevertheless, it is hard to assess treatments in this population because life expectancy is shorter. Local regional control should be the main goal for elderly patients suffering from early disease or locally advanced carcinoma. In young women, a combination of surgery and radiotherapy has been extensively studied, and is the reference treatment. Hormone therapy is often suggested as the first line treatment of non-metastatic diseases in the elderly because it is well tolerated and effective (45–75% of partial responses), even in patients with small breast tumours [28–32]. Our patients were given hormone therapy for early extended tumours when the patient's clinical and/or physical status was poor. Complete remission was achieved in only 3 of the 15 patients evaluated. The 12 other women continued to live with the tumour in place until surgery, radiotherapy or death. These latter women should undergo important medical management that does not favour comfort of life. Two randomised prospective trials have compared the efficacy of hormone therapy and mastectomy [33] or lumpectomy alone [28]. The first study showed no difference in terms of 5-year overall survival rate, but local regional control rate was better among patients who had had a mastectomy (65%) than for those given hormone therapy (30%) [33]. The second study comparing hormone therapy to lumpectomy found that local regional control was better among patients given hormone therapy, but lumpectomy alone was not appropriate for local control [28]. As we noted in our study, patients with early breast cancer treated with tamoxifen should be carefully followed up because the median time to progression was 32–35 months [31, 34]. Hence, these patients should be examined at least four times a year. At the end, many of the women who suffer relapses will undergo salvage surgery (33–55%) [28, 35]. Hence, hormone therapy does not remove cancers, does not avoid surgery and needs intensive follow-up. It should be reserved for inoperable patients. One procedure used for these patients was the combination of radiotherapy plus hormone therapy. In our study, 12 patients underwent such treatment. A response occurred in only 5 patients, but the survival data indicate that some women can live for a long time after this combination as they can after limited surgery plus hormonal therapy and/or radiotherapy. One of the future goals of our department is to carry out such a controlled study for inoperable patients.

#### CONCLUSION

This retrospective study has shown that many types of treatment are used for elderly patients because of the lack of specific data. Clinicians can choose a conventional treatment that combines surgery with radiotherapy, or a minimal treatment with hormone therapy. Nevertheless, a modified conventional therapy is often used. This type of therapy has not, however, been validated. Conventional treatments are well tolerated. There are few absolute contraindications, and the elderly should be treated in the same way as young patients whenever possible. Hormone therapy and/or radiotherapy should be reserved as primary treatment for inoperable patients. Many data on the

outcome and follow-up of this population were missing, which prevented any decisions as to the best management of breast carcinomas. As the proportion of elderly people with breast cancers will grow in the years to come, validated guidelines are needed; specific protocols as well as specific rules of management must be drawn up.

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# Etoposide, Doxorubicin and Cisplatin (EAP) Treatment in Advanced Gastric Carcinoma: a Multicentre Study of the Italian Trials in Medical Oncology (I.T.M.O.) Group

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Various reports have documented the efficacy of the combination of etoposide, doxorubicin and cisplatin (EAP) in the treatment of advanced gastric cancer, although other studies have not confirmed such results. This multicentre phase II study was designed to try to define the efficacy and tolerability of the original EAP regimen. From January 1990 to May 1992, 96 patients with locally advanced or metastatic gastric cancer were treated every 3 weeks with etoposide (120 mg/m<sup>2</sup>) on days 4, 5 and 6, doxorubicin (20 mg/m<sup>2</sup>) on days 1 and 7, and cisplatin (40 mg/m<sup>2</sup>) on days 2 and 8. All of the patients had measurable lesions, and were to receive a maximum of six cycles. A total of 416 courses was given (median four/patient), 27% with a delay of  $\geq 2$  weeks. Objective responses were achieved in 34 of the 91 evaluable patients (37%: confidence interval 27-47%), with complete response (CR) in 11 (12%) and partial response (PR) in 23 (25%). The median duration of response was 6 months (range 1-19), and the median survival of the 96 eligible patients was 9 months. Side-effects (WHO grade 3-4) were leucopenia (30%), thrombocytopenia (9%) and mucositis (10%). We conclude that the EAP regimen is active in inducing major objective responses (12% of CR), and that treatment is feasible in patients with good performance status.

**Key words:** gastric cancer, etoposide, doxorubicin, cisplatin combination, chemotherapy  
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## INTRODUCTION

SURGICAL RESECTION remains the usual approach for patients affected by gastric cancer. However, among the cases who undergo a potentially curative resection, relapse is common and the 5-year survival rate is unsatisfactory [1]. Greater emphasis

has, therefore, been placed on the development of better systemic chemotherapy for patients who cannot be cured with surgery.

The most investigated drugs are fluorouracil (FU), mitomycin C, doxorubicin (ADM) and cisplatin. As single agents, these