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TREATMENT RESULTS IN MAMMARY CARCINOMA STAGES I-IV

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Surgery is the most common primary treatment of breast carcinoma, but opinions differ about the type of operation to be preferred. Radical surgery includes radical, modified radical and extended radical mastectomies (HANDLEY & THACKRAY 1969, HAAGENSEN 1974, URBAN 1976). After radical surgical treatment, postoperative irradiation has been given selectively or not at all (HAAGENSEN) and its value has been disputed (STJERNSWÄRD 1974, LEVITT et coll. 1977). The most frequent conservative treatments are simple mastectomy (MCWHIRTER 1955), and local excision of the tumour (MUSTAKALLIO 1972, PETERS 1977), both methods being combined with postoperative irradiation. To date, prophylactic hormonal therapy has played no role at the time of primary treatment (KENNEDY 1974). In 1978 NISSEN-MEYER et coll. published results according to which short-term adjuvant cytostatic therapy prolongs survival. Combined adjuvant chemotherapy is at present the most common adjuvant treatment, but long term results are still lacking (BONADONNA et coll. 1976, B. FISHER et coll. 1977, WEISS & DEVITA 1979, BONADONNA 1980).

The purpose of this retrospective review is to set out the results of the treatment in different clinical stages including adjuvant single cyclophosphamide treatment and prophylactic castration, to assess the influence of various prognostic factors on the survival, to investigate the part played by the differentiation grade of an infiltrating ductogenic carcinoma on the prognosis, and to explain the complications of primary treatment. The prognostic factors analysed

were duration of symptoms before diagnosis, type of biopsy, location of the tumour, status of axillary nodes, and age.

Material and Methods

During the years 1961 to 1970 a total of 644 cases of primary breast carcinoma in women were diagnosed and treated in the city of Turku. Of all the cases, 590 could be evaluated (Table 1) and in all cases the diagnosis had been confirmed by biopsy. Clinical staging was carried out according to the TNM classification (UICC 1974; Table 2). The same pathologist (S. T.) reviewed all the biopsy samples again and classified them according to the WHO classification (SCARFF & TORLONI 1968; Table 3). Based on the degree of tubule formation, the frequency of hyperchromatic and mitotic figures, and nuclear pleomorphism, the infiltrating ductogenic carcinoma was divided into three malignancy grades or degrees of differentiation: grade I or low malignancy, grade II or intermediate, and grade III or high (SCARFF & TORLONI). Axillary biopsy was done from 1 to 3 axillary nodes; in 123 cases (21%) no biopsy was taken.

The age distribution of all patients is presented in Table 4, the mean age being 58 years (range 24-95). The mean age in clinical stage I was 55, in stage II 58, in stage III 63 and in stage IV 61 years. The age grouping under 50 years (160 patients), 50 to 64 (235

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patients) and 65 and over (195 patients) was used. Carcinoma in the right breast occurred in 271 patients and in the left breast in 319. In 342 cases the duration of symptoms before diagnosis had been 0 to 3 months, in 107 cases 3 to 6 months and in 141 cases over 6 months. In 525 cases (89%) the primary symptom was a palpable tumour either alone or in conjunction with other symptoms.

Treatment methods in stages I–III (569 patients). The diagnosis was confirmed by preoperative biopsy in 251 cases and by frozen section biopsy in 318 cases. In the former group the operation was carried out within two weeks of biopsy. Radical mastectomy was performed in 456 patients (80.1%), simple mastectomy in 92 (16.2%), local excision in 15 (2.6%), and in 6 patients (1.1%) only a biopsy was taken. Radical mastectomy consisted of en bloc removal of the breast, pectoral muscles and axillary lymph nodes, the clavicular portion of the pectoralis major was usually preserved. The radical mastectomy group consists of 21 mastectomies which involved removal of the breast with axillary dissection. Simple mastectomy with or without axillary biopsy was chosen in operable cases in the initial years of the period and otherwise only with the aged.

Postoperative irradiation was given to 517 patients, 52 patients received no irradiation. During the years 1961 to 1966 the postoperative irradiation was given using conventional roentgen therapy to 303 patients at 180 to 250 kV, 15 to 20 mA, HVL 0.5 mm Cu, FSD 40 to 50 cm. The field dose in the supraclavicular and parasternal area was 21 to 28 Gy, in the chest wall and in the axilla 21 to 31 Gy given over 21 to 28 days. Each of 4 fields was irradiated separately by daily fractionation 6 days a week, the single dose being usually 3 Gy. During the years 1967 to 1970 the treatment was given to 214 patients with megavoltage therapy using ^{60}Co to the supraclavicular and parasternal area and posteriorly to the axilla with a field dose of 40 Gy over 12 days. The megavoltage therapy was administered by daily fractionation 5 days a week, the single dose being 4 Gy. The fields of the supraclavicular and parasternal area were irradiated simultaneously. The chest wall was irradiated with 8 MeV electron to 30 Gy or with roentgen therapy as mentioned. Both irradiation series were begun about 3 weeks after operation.

Prophylactic castration was carried out without randomization on 68 patients, on 39 with surgery and on 29 with irradiation. The castration dose to

Table 1

Total admissions for first treatment of women with breast carcinoma, 1961 to 1970

Patients admitted	644
Excluded	
Benign tumour upon re-examination	3
Cystosarcoma phylloides	1
Bilateral carcinoma at time of diagnosis	1
Cytologic diagnosis	1
Clinical diagnosis without biopsy	20
Inadequate clinical data for TNM	28
Total exclusions	54 (8.4%)
Included in the present review	590

Table 2

TNM classification of entire material (UICC 1974)

Stage I	113
T1a N0 or N1a	94
T1b N0 or N1a	19
Stage II	352
T0 N1b	11
T1a T1b N1b	12
T2a T2b N0 or N1a	263
T2a T2b N1b	66
Stage III	104
Any T3 with any N	33
Any T4 with any N	55
Any T with N2 or N3	16
Stage IV	21
Any T any N with M1	

Table 3

Typing of entire material after WHO classification

	No. of cases
Intraductal or intralobular non infiltrating carcinoma	8
Infiltrating ductogenic carcinoma (not otherwise specified)	520
Special types of carcinoma	62
Medullary carcinoma	15
Papillary carcinoma	16
Cribriform carcinoma	8
Mucous carcinoma	9
Lobular carcinoma	9
Paget's disease	5

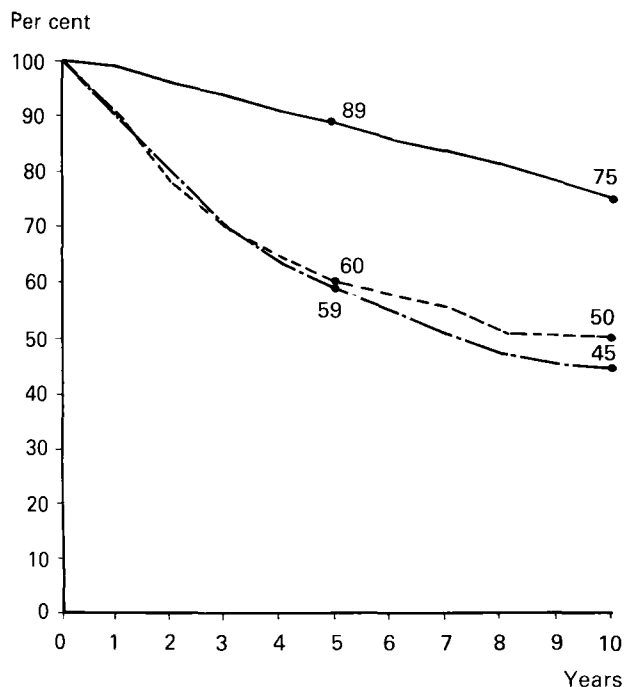


Fig. 1. Crude (—) and corrected (---) survival curves (in per cent) for all patients with breast carcinoma (n=590) and the expected curve (· · ·).

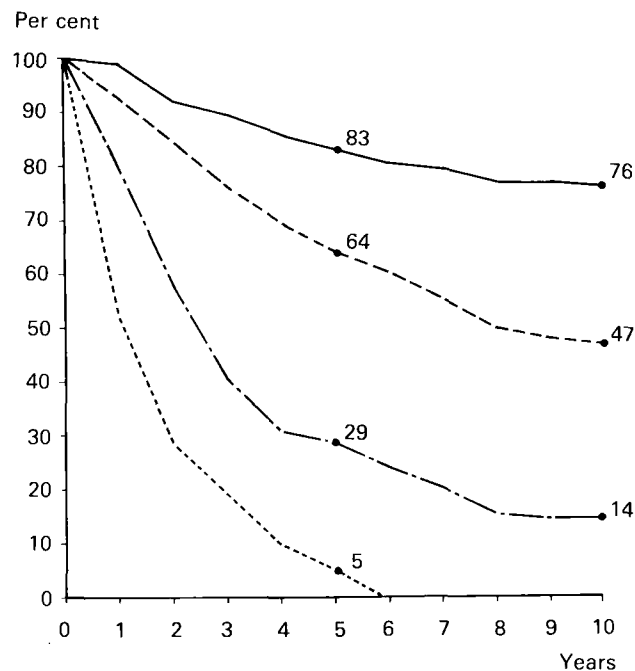


Fig. 2. Crude survival curves of patients with breast carcinoma by stage. Stage I (—). Stage II (---). Stage III (· · ·). Stage IV (- · -).

the ovaries was 6 to 8 Gy over 9 days with roentgen therapy and 10 to 12 Gy over 7 days with megavoltage therapy.

Adjuvant cyclophosphamide treatment was given to 157 patients without randomization. The cytostatic therapy was begun on the day of operation, the daily dose being 100 mg intravenously until 3 to 5 days and thereafter daily 150 mg orally up to a total dose of 2 to 6 gram.

The treatment in clinical stage IV (21 patients) consisted of surgery, irradiation, different combina-

tions of hormones and single cytostatics, treatment being palliative from the beginning.

Follow-up and statistical methods. The follow-up period for all patients varied from 5 to 15 years and ended in June 1976. Complete follow-up was achieved. Survival rates have been calculated from the time of diagnosis according to the life table method (CUTLER & EDERER 1958) and deaths from all causes are included. For all patients corrected survival rates are also given, i.e. crude survival rate corrected for observed deaths from intercurrent diseases. Expected survival was calculated by the method proposed by EDERER et coll. (1961) from mortality and survival tables of Official Finnish Statistics (1974).

Results

Total survival rates in correlation to different types of treatment. The crude, corrected and expected survival curves for all patients are presented in Fig. 1, crude survival curves in different clinical stages in Fig. 2. Corrected 5- and 10-year survival rates in stage I were 87% and 82%, in stage II 66% and 53%, in stage III 29% and 16% and in stage IV 5% and 0%.

Table 4

Age distribution of entire material

Years	No. of cases	Per cent
20-29	2	0.3
30-39	25	4.3
40-49	133	22.6
50-59	160	27.1
60-69	147	24.9
70-79	108	18.3
≥80	15	2.5
Total	590	100.0

No significant correlation between survival and the type of biopsy was found, although the 10-year survival rate in stages II and III was higher in the frozen section than in the preoperative biopsy group. The crude 10-year survival rate in stage I diagnosed with preoperative biopsy was 83% (52 patients) and with frozen section technique 70% (61 patients), in stage II correspondingly 39% (131 patients) and 52% (221 patients) and in stage III correspondingly 9% (68 patients) and 25% (36 patients). In all clinical stages the crude 10-year survival rate was independent of the duration of symptoms before diagnosis. The location of the primary tumour in clinical stages I and II failed to affect the 10-year survival (Table 5).

The 10-year survival rates in stages I to III with different methods of surgery are presented in Table 6. Since operative treatment was selective, the different surgical methods were not fully comparable. In stages I to III the 10-year survival was less favourable when metastatic axillary nodes were present (Table 7).

Postoperative irradiation was given to 91 per cent of patients, stage I–III. During the period the irradiation technique was changed from roentgen therapy (303 patients) to megavoltage therapy (214 patients); in the latter group 8 years was the longest follow-up period. In clinical stage II, the 5- and 8-year survival rates for those treated with radical mastectomy followed by roentgen therapy (158 patients) were 60% and 44% and with the same operation followed by megavoltage therapy (116 patients) 68% and 59%. The difference in survival at 8 years is significant on the level of $p=0.05$. In neither irradiation technique group were significant differences found as to age distribution, axillary node histology and differentiation grade of carcinoma. Eight-year survival rate in patients stage I treated with radical mastectomy and roentgen therapy (40 patients) was 78% and after radical mastectomy and megavoltage therapy (50 patients) 82%, in stage III correspondingly 15% (27 patients) and 29% (38 patients); these differences were not statistically significant.

Total survival rate in correlation with age. A significant correlation was not found between age and the duration of symptoms before diagnosis. Age was not found to correlate with axillary biopsy findings. Crude 5- and 10-year survival rates in different age groups as well as corrected 5- and 10-year survival rates are shown in Fig. 3.

In stage I, more patients were under 50 years of

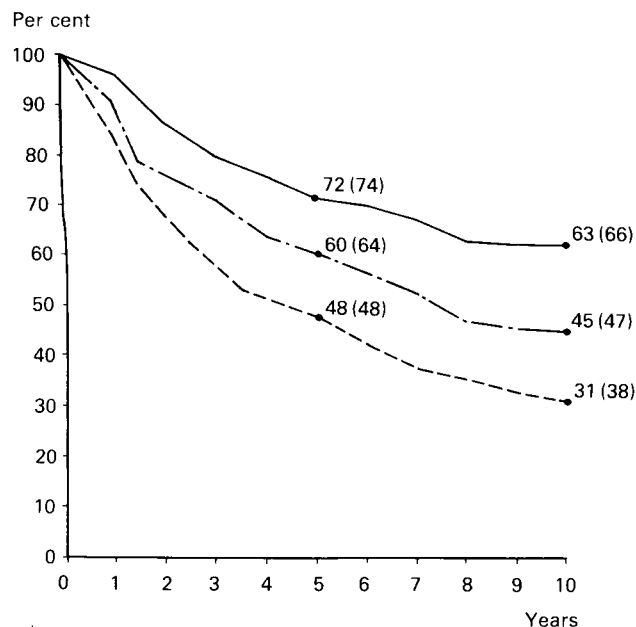


Fig. 3. Crude survival curves by age. Corrected survival rates (in per cent) are given in parentheses. 20–49 years (—). 50–64 years (---). Over 65 years (···).

Table 5

Crude 10-year survival rates by stage and location of the tumour

Location	Stage I		Stage II	
	No. of cases	Survival (per cent)	No. of cases	Survival (per cent)
Lateral	74	80	270	50
Central	10	80	29	38
Medial	29	66	53	45

age than 65 years and over, while more older patients than younger ones were found in stages II and III (Table 8). In stages I to III, patients under 50 years of age were found to have higher survival rates than those over 65 years (Table 8). In stage II patients under 50 years of age, 88% had undergone radical mastectomy, as opposed to 73% of those over 65 years. In stage III the corresponding figures were 100 and 53 per cent.

Prophylactic castration. Of patients in stage I to III 157 were under 50 years of age and in 68 of these castration had been carried out. In stage I the crude 10-year survival rate for patients with prophylactic castration was 73% (11 patients) and without castration 85% (34 patients), in stage II correspondingly 65% (49 patients) and 49% (47 patients) and in stage III 38% (8 patients) and 50% (8 patients).

Table 6*Crude 10-year survival rates by stage and operation method*

	Stage I		Stage II		Stage III	
	No. of cases	Survival (per cent)	No. of cases	Survival (per cent)	No. of cases	Survival (per cent)
Radical mastectomy	95	78	290	47	71	21
Simple mastectomy	13	54	56	50	23	0
Local excision	5	100	6	33	10*	0
Total	113		352		104	

* In 6 cases biopsy only.

Table 7*Crude 10-year survival rates by stage and axillary biopsy finding*

Axillary biopsy status	Stage I		Stage II		Stage III	
	No. of cases	Survival (per cent)	No. of cases	Survival (per cent)	No. of cases	Survival (per cent)
No metastatic nodes	66	77	129	61	12	42
Metastatic nodes	16	69	159	34	64	17
No biopsy	31	65	64	52	28	4

Table 8*Crude 10-year survival rates by stage and different age groups*

	Stage I		Stage II		Stage III	
	No. of cases	Survival (per cent)	No. of cases	Survival (per cent)	No. of cases	Survival (per cent)
Under 50 years	45	84	96	57	16	44
50-64 years	44	80	143	48	37	11
65 years and over	24	63	113	37	51	8

Adjuvant cyclophosphamide therapy. The crude 10-year survival rate in stage I with cyclophosphamide was 74% (19 patients) and without cyclophosphamide 77% (94 patients), correspondingly in stage II 45% (108 patients) and 48% (244 patients). In stage III the 10-year survival rate in the adjuvant cyclophosphamide group was 0% (30 patients) and in the group without adjuvant therapy 20% (74 patients).

Histologic grading of infiltrating ductogenic carcinoma. Of all patients, 520 cases had infiltrating ductogenic carcinoma. The intermediate malignancy or grade II was the most common in all clinical

stages (Table 9). A direct correlation between the grade of malignancy and the clinical stage was found: in stage I there were more grade I than grade III cases and in stages III and IV more grade III than grade I cases. In stage II no corresponding interdependence was found. The differentiation grade was not found to be dependent upon the patient's age, nor upon the duration of symptoms before diagnosis. The low and high malignancy grades correlated with the axillary findings. In cases which had microscopically confirmed metastases in axillary lymph nodes (n=233), the grade of malignancy was low in 14% and high in 29%, when no metastases

Table 9

Distribution of infiltrating ductogenic carcinoma by stage and grade

Grade	Stage I		Stage II		Stage III		Stage IV		Total	
	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent	No. of cases	Per cent
I	20	23.0	54	17.1	12	12.5	1	4.8	87	16.7
II	55	63.2	195	61.7	53	55.2	15	71.4	318	61.2
III	12	13.8	67	21.2	31	32.3	5	23.8	115	22.1
Total	87	100.0	316	100.0	96	100.0	21	100.0	520	100.0

were found in the axillary nodes ($n=185$) correspondingly 23% and 16%.

The crude 10-year survival rate for infiltrating ductogenic carcinoma according to the malignancy grade in different clinical stages is given in Fig. 4. For all patients and in clinical stage II, the 10-year survival in grade I was clearly better than in grades II and III.

Complications were reviewed in patients stage I to III. Complications following surgery were registered within one month of the operation. After radical mastectomy (456 patients) chest wound infection was found in 28, necrosis of the wound in 17, infection and necrosis of the wound in 6, fluid accumulation in the operative region in 87 and hematoma in 3 patients. After simple mastectomy (92 patients) chest wound infection was found in 6 and fluid accumulation in 3 patients. Swelling of the arm was recorded as a late complication after radical mastectomy in 107 and after simple mastectomy in 6 patients.

As to complications following postoperative irradiation, changes occurring 3 months after termination of the irradiation have been taken into account. Skin erythema after roentgen therapy was not registered. After irradiation with roentgen therapy (303 patients) 15 cases of skin atrophy and 16 cases of subcutaneous fibrosis were recorded, while pulmonary fibrosis was detected radiologically in 26 cases. After irradiation with megavoltage therapy (214 patients) 22 cases of subcutaneous fibrosis were recorded and in 28 cases pulmonary fibrosis was radiologically detected.

Discussion

General results with different treatment methods. Evaluation of the results of breast carcinoma treat-

ment is made difficult by varying biologic behaviour of the tumour, its differing microscopic classification, staging and primary treatment, and selection of cases for inclusion in a particular series (WATSON 1966, FISHER 1973, ROBBINS 1977, YTREDAL et coll. 1977, VALAGUSSA et coll. 1978).

In the present series the TNM classification (UICC 1974) was used. Crude and corrected 5-year survival rates for all cases were 59% and 60% and at 10-years 45% and 50%, respectively, which corresponds to the results of others (RISSANEN 1969, HAAGENSEN, HAKAMA & RIIHIMÄKI 1974, FERGUSON & MEIER 1976, LEIS 1976). The prognosis seems to be improving slowly, according to the literature, and at least part of the upper shift in survival is due to earlier diagnosis (CUTLER & HEISE 1969). KOULUMIES (1956) reported from the years 1936 to 1948 a 10-year survival of 34 per cent in 866 treated patients with 58 per cent T1 and T2 whereas in the present series 77 per cent of tumours were T1 and T2.

The type of biopsy was not found to have a significant effect on the prognosis, although the survival in stages II and III was better when the tumour had been diagnosed by frozen section than in those diagnosed by preoperative biopsy. Other authors have also found that no correlation exists between survival and the type of biopsy or interval from biopsy to operation (SCHEEL 1953, ABRAMSON 1966, BAKER 1977). The duration of symptoms before diagnosis and the location of the primary tumour had no significant influence on the prognosis, which is in agreement with other recent reports (BRINKLEY & HAYBITTLE 1975, E. FISHER et coll. 1977, MEYER et coll. 1978, VALAGUSSA et coll.).

During the first seven decades of this century the principal methods of treatment of breast carcinoma

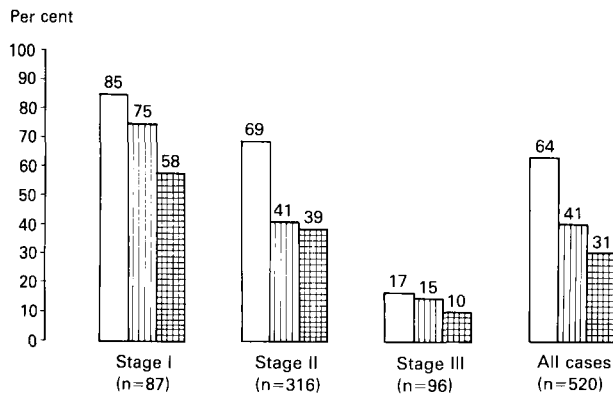


Fig. 4. Crude 10-year survival rates (in per cent) of patients with infiltrating ductogenic carcinoma of the breast, by stage and grade of the tumour. All cases include also stage IV. Grade I (□). Grade II (▨). Grade III (▩).

have been radical mastectomy which may be followed by radiation therapy or by simple mastectomy and radiation therapy (FORREST 1977). In the present series, in which simple mastectomy was performed in most of the older patients and during the early years also in a majority of the patients, the two surgical procedures followed by radiation therapy gave similar results in stages I and II.

The effect of postoperative irradiation on the prognosis was analysed by comparing patients treated with conventional roentgen irradiation and megavoltage therapy after radical mastectomy. In stages I-III the survival of patients given postoperative megavoltage therapy was better than that of those given roentgen irradiation.

Particularly in stage II, megavoltage irradiation seems to improve the prognosis. At 8 years, survival was higher after treatment with radical mastectomy and megavoltage irradiation than after the same operation and roentgen irradiation. This is probably due to the fact that megavoltage therapy enables a greater tumoricidal dose to be given to the occult micrometastases. However, the tumoricidal doses both with conventional roentgen irradiation and with megavoltage therapy were inadequate according to FLETCHER (1972). In stage II with metastatic axillary nodes HØST & BRENNHOVD (1977) found a significantly higher 5-year survival after radical mastectomy combined with megavoltage irradiation than after radical mastectomy alone. Furthermore, patients stage II who had undergone radical mastectomy and received megavoltage irradiation had a higher 5-year survival than those given roentgen irradiation, but not significantly.

Axillary lymph node metastases decreased sur-

vival in stages I-III, as has been noted previously (HAAGENSEN, FISHER et coll. 1975).

Neither prophylactic castration nor adjuvant cyclophosphamide, both without randomization, improved survival in the present series. A parallel result concerning prophylactic castration was found by RAVDIN et coll. (1970) in a controlled series. NISSEN-MEYER et coll. found that a short-term adjuvant cyclophosphamide course immediately after surgery improved the 10-year survival. In the present series the daily doses of cyclophosphamide were low and the duration of treatment was short. The recent results with long-term combined chemotherapy (BONADONNA) indicate that a clear correlation exists between the response rate and the doses of the cytostatic agents.

Age and survival. In patients under 50 years of age, both crude and corrected survival rates were higher than in patients of 65 years old and over; a similar result has been published by HAKAMA & RIIHIMÄKI and also by MUELLER et coll. (1978). In the same clinical stage the prognosis for younger patients was better than for older ones. In stage III all patients under 50 years of age underwent radical mastectomy, which probably explains the difference in prognosis between the youngest and the oldest age group. In stages I and II the reason remains unknown. In the literature, youth, i.e. under 30 or under 50 years of age, at the time of diagnosis has not been found to impair survival, contrary to the general opinion (WATSON, MUELLER et coll., PATTERSON 1978).

Histopathology of infiltrating ductogenic carcinoma. Of all microscopic diagnoses 88 per cent were infiltrating ductogenic carcinomas; in the literature this percentage varies from 50 to 87 per cent (SCHJØDT 1966, KUZMA 1971, ZIPPEL 1977, FISHER 1978). The differentiation degree of the carcinoma did not correlate with the patient's age nor with the duration of symptoms. There was more of grade I in stage I and when no metastatic axillary nodes were found, whereas there was more of grade III in stages III and IV and when metastatic axillary nodes were present. With a lower malignancy grade, breast carcinoma has a better prognosis (BLOOM & RICHARDSON 1957, WOLFF 1966, TOUGH et coll. 1969, BLOOM & FIELD 1971, FISHER 1978), as was found in the present series. Grading reflects the potential malignancy of the tumour and helps in recognizing those cases in which the possibility of dissemination is greatest (BLOOM & RICHARDSON).

Complications. Surgical complications were found markedly more frequently after radical than after simple mastectomy. The most common early complications after radical mastectomy were fluid accumulation (19%), and infection or necrosis of the wound (11%), the former being reported in the literature in 7 to 40 per cent and the latter in 18 to 50 per cent of cases (ZINTEL & NAY 1964, SAY & DONEGAN 1974, FEIGENBERG et coll. 1977, BUDD et coll. 1978). The most common late complication after radical surgery is swelling of the arm (HEALEY 1971, HAAGENSEN). In the literature the frequency of swelling after radical mastectomy and radiation therapy varies between 30 and 46 per cent (TREVES 1957, NIAS 1960, GREGL et coll. 1967, RISSANEN), being in this investigation 23 per cent.

The most common complications after radiation therapy were pulmonary fibrosis (10%) and subcutaneous fibrosis (7%). Relatively low radiation doses reduced the complications. In the literature, irradiation complications vary considerably according to the irradiation technique and fractionation schema (HEINZE & FEIL 1970, HAGEN & KOLBENSTVEDT 1972, FLETCHER et coll. 1973).

Conclusion

The prognosis for breast carcinoma was found to be highly dependent upon the clinical stage at the time of diagnosis. Metastatic axillary nodes impaired survival in clinical stages I–III. In stage II after radical mastectomy the prognosis was better with postoperative megavoltage irradiation than with roentgen irradiation, and it appears that postoperative megavoltage irradiation improves the survival. The prognosis was not affected by adjuvant single cyclophosphamide treatment and prophylactic castration. Duration of symptoms, type of biopsy and location of the tumour were of no significance for the prognosis. In all cases the prognosis was better for patients under 50 years of age than for patients over 50. In infiltrating ductogenic carcinoma there was a markedly higher 10-year survival in the grade I group than in grade II and grade III groups. The immediate complications of surgical treatment and the side effects of postoperative radiation therapy were slight.

SUMMARY

A retrospective review of 590 patients with breast carcinoma of all clinical stages is presented. The patients

were treated mainly with radical mastectomy and postoperative irradiation. The overall 5- and 10-year survival rates were 59% and 45%, in stage I 83% and 76%, in stage II 64% and 47%, in stage III 29% and 14% and in stage IV 5% and 0%, respectively. Treatment methods, prognostic factors and differentiation grade of infiltrating ductogenic carcinoma have been analysed and the effect of these factors on the treatment results in different clinical stages is presented.

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