THE INSTITUTE OF ONCOLOGY, LJUBLJANA

FIVE-YEAR SURVIVAL OF PATIENTS WITH BREAST CANCER AND AXILLARY LYMPH NODE METASTASES TREATED BY POSTOPERATIVE IRRADIATION AND ADJUVANT CHEMOTHERAPY

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Abstract — Five-year survival of patients with operable breast cancer and metastases in the axillary lymph nodes was studied. Following modified radical mastectomy (Maden-Patey), the patients were treated either by postoperative irradiation or adjuvant chemotherapy according to CMF schedule. In 169 patients treated by adjuvant chemotherapy the 5-year survival was found to be 72 %, whereas in 126 patients receiving postoperative irradiation it was 60 % ($p = 0.04$). Five-year survival in patients without evidence of disease (NED) treated by adjuvant chemotherapy was 61 %, and in irradiated patients 50 % ($p = 0.02$). Statistically significant better survival of patients receiving adjuvant chemotherapy ($p < 0.05$) was found only in those with tumors smaller than 2 cm, and less than 3 or less than 7 positive axillary lymph nodes, respectively.

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Introduction — In Europe, North America and also in our country breast cancer still represents the most common form of cancer in women. According to the data of the Cancer Registry of Slovenia for the year 1984, there were 612 newly detected breast cancer patients in Slovenia. The incidence per 100 000 women was 51.2 (1). Surgery still remains the treatment of choice in patients with operable breast cancer. Ten-year survival in patients with operable breast cancer treated by radical or modified radical mastectomy ranges from 50 % to 60 % (2, 3).

The surgical treatment was combined with postoperative irradiation with the intent to eliminate possible micrometastases in the thoracic wall and regional lymph nodes, and thus cure the patient. Nevertheless, in spite of several studies, the relevance of postoperative irradiation has not been fully explained. Most authors report no significant improvement in the survival of patients treated by postoperative irradiation despite a smaller number of local recurrences (4, 5).

According to Montague (6), postoperative irradiation may result in a prolonged survival in individual patients with operable breast cancer and metastases in the axillary lymph nodes.

At the Institute of Oncology in Ljubljana, the survival of patients with operable breast cancer treated by radical mastectomy and postoperative irradiation was not found to be longer than that in patients treated by radical mastectomy alone (7).

Most patients with operable breast cancer die from metastases and not from local recurrence despite the radical local treatment. This finding supports the hypothesis that cancer is not a local, but rather a systemic disease. Therefore, patients after mastectomy require an additional systemic treatment (8, 9).

The studies carried out by the end of 70's and the beginning of 80's showed that adjuvant systemic treatment resulted in an improved survival and disease-free survival in individual patients with operable breast cancer only (10, 11, 12, 13).

The aim of the present study was to establish possible differences in the survival of patients with operable breast cancer: treated by postoperative irradiation or adjuvant chemotherapy.

Patients and methods — The study comprised the patients with operable breast cancer and axillary lymph node metastases (T_1-$T_{3a}N_1$-$N_{1b}M_0$), treated at the Institute of Oncology in Ljubljana by postoperative irradiation or adjuvant chemotherapy according to CMF schedule following radical or modified radical mastec-

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tomy. In the group with postoperative irradiation there were 126 patients, of these 38 (30 %) were irradiated on an ortovoltage X-ray machine with the energy of 180 Kv to the five fields as follows: parasternally, two tangent fields onto the thoracic wall, supraclavicular and axillary fields. The irradiation was performed in two courses, the daily dose being 250 r. Skin dose after the completed first course amounted to 10950 r, and after the second 9750 r. Another 88 (70 %) patients were irradiated with Cobalt to the following three fields: parasternal, supraclavicular and axillary. Tumor dose was 4400 cGy, and daily dose 200 cGy. Postoperative adjuvant chemotherapy according to the CMF schedule was applied in 169 patients Cyclophosphamide 100 mg/m^2 1—14 days per os; MTX 40 mg/m^2 i.v. on day 1 and 8; 5-FU 600 mg/m^2 on day 1 and 8 i.v.). The chemotherapy cycle was repeated 12 times, every 4 weeks. Only the patients with pathohistologically verified axillary lymph node metastases were included. Metastases before mastectomy were exluded by clinical. laboratory, X-ray and radionuclide examinations. All the patients with advanced breast cancer (T_{3b}-T_4N_2-N_3M_1), and those with negative axillary lymph nodes, as well as the patients receiving either irradiation, chemo- or immunotherapy prior to mastectomy, the patients postoperatively treated by irradiation and chemotherapy, and the patients entering for adjuvant therapy after the 42nd postoperative day were excluded from the study. The follow up was 60 months after mastectomy.

Statistic significance in the 5-year survival and 5-year survival without evidence of disease in patients treated either by adjuvant chemotherapy or postoperative irradiation was calculated using log-rank test (14). The life-table method was used for graphic analysis.

Results — The characteristics of patients with operable breast cancer and metastases in the axillary lymph nodes are presented in Table 1.

The were 169 patients treated by adjuvant chemotherapy (ChT) and 126 by postoperative irradiation (RT). Both groups were correlated by age, tumor size, menstural status, number of positive axillary lymph nodes, hormone receptors and malignancy grade.

Patients with adjuvant chemotherapy had statistically significantly longer 5-year survival than those treated by postoperative irradiation (ChT 72 ± 3 %; RT 60 ± 4 %; p = 0.04) (Table 2, Fig. 1).

Patients	All	%	ChT	%	RT	%
	295	%	169	57 %	126	43 %
Age						
< 40	56	19 %	35	21 %	21	43 %
40—49	111	38 %	68	40 %	43	34 %
> 50	128	43 %	66	39 %	62	49 %
Tumor size						
≤ 2	65	22 %	39	23 %	26	21 %
> 2	230	78 %	130	77 %	100	79 %
Menopause						
premenopausal	175	59 %	115	67 %	60	48 %
postmenopausal	93	31 %	40	25 %	53	42 %
perimenopausal	27	10 %	14	8 %	13	10 %
Lymph nodes						
≤ 3	153	52 %	85	50 %	68	54 %
> 3	142	48 %	84	50 %	58	46 %
Hormone receptors						
HR$^+$	72	25 %	64	38 %	8	6 %
HR$^-$	65	22 %	57	34 %	8	6 %
HRn	158	53 %	48	28 %	110	88 %
Malignancy grade	221		138		83	
I	19	9 %	12	9 %	7	8 %
II	146	66 %	96	69 %	50	61 %
III	56	25 %	30	22 %	26	31 %

Table 1 — Characteristics of patients with operable breast cancer and axillary lymph node metastases treated by adjuvant chemotherapy (ChT) and postoperative irradiation (RT)

Patients	All	%	Dead	Alive	% ± SD	p
ChT	169	57 %	48	121	72 % ± 3	
RT	126	43 %	50	76	60 % ± 4	0.04
Total	295		98	197		

Table 2 — Five-year survival in patients with operable breast cancer and axillary lymph node metastases treated either by ChT or RT

Five-year survival without evidence of disease was statistically significantly better in patients receiving adjuvant chemotherapy than in those treated by postoperative irradiation (ChT 61 ± 4 %; RT 50 ± 4 %; p = 0.02) (Table 3, Fig. 2).

Patients with adjuvant chemotherapy were distributed into subgroups according to tumor size, number of positive axillary lymph nodes, malignancy grade, tumor size in the breast, hormone receptor, menopausal status and age.

Statistically significant differences in the 5--year survival ($p < 0.05$) were established only in patients with tumors smaller than 2 cm (ChT 92 ± 4 %; RT 54 ± 10 %; p = 0.001) (Table 4) and

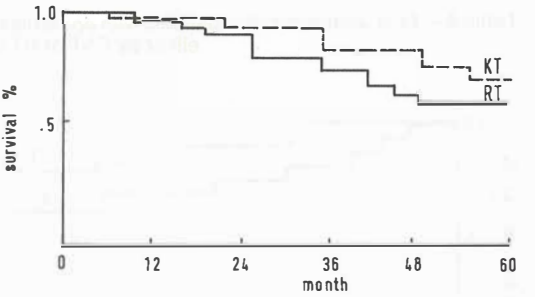

Fig. 1 — Five-year survival in patients with operable breast cancer and axillary lymph node metastases treated either by ChT or RT

Patients	All	%	Recurrence	NED	% ± SD	p
ChT	169	57 %	66	103	61 % ± 4	
RT	126	43 %	63	63	50 % ± 4	0.02
Total	295		129	166		

Table 3 — Five-year survival without evidence of disease in patients with operable breast cancer and axillary lymph node metastases treated either by ChT or RT

in patients with less than 3 positive axillary lymph nodes (ChT 86 ± 4 %; RT 75 ± 5 %; p = 0,05) (Table 5).

Sixty five patients had tumor measuring 2 cm or less. There were 39 patients (60 %) treated by adjuvant ChT and 26 (40 %) by postoperative irradiation (ChT 82 ± 6 %; RT 50 ± 10 %; p = 0.004) (Fig. 3).

Less than 3 positive axillary lymph nodes were found in 85 (56 %) patients with adjuvant chemotherapy, and 68 (44 %) patients with postoperative irradiation (ChT 82 ± 4 %; RT 65 ± 6 %; p = 0.01) (Fig. 4).

Also the patients with less than 8 positive axillary lymph nodes treated by adjuvant chemothe-

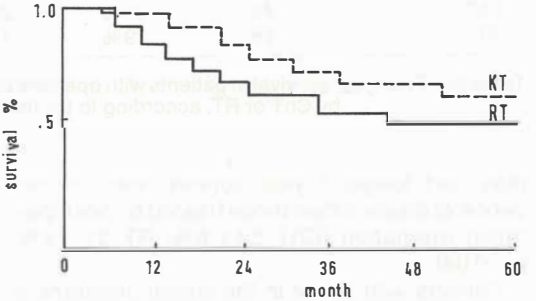

Fig. 2 — Five-year survival without evidence of disease in patients with operable breast cancer and axillary lymph node metastases treated either by ChT or RT

Tumor size	All	%	Dead	Alive	% ± SD	p
Tumor 2 cm	65		15	50		
ChT	39	60%	3	36	92% ± 4	0.001
RT	26	40%	12	14	54% ± 10	
Tumor 3—4 cm	163		58	105		
ChT	96	59%	31	65	68% ± 5	0.2
RT	67	41%	27	40	60% ± 6	
Tumor 4 cm	67		25	42		
ChT	34	51%	14	20	59% ± 8	0.4
RT	33	49%	11	22	67% ± 8	

Table 4 — Five-year survival in patients with operable breast cancer and axillary lymph node metastases treated either by ChT or RT according to tumor size

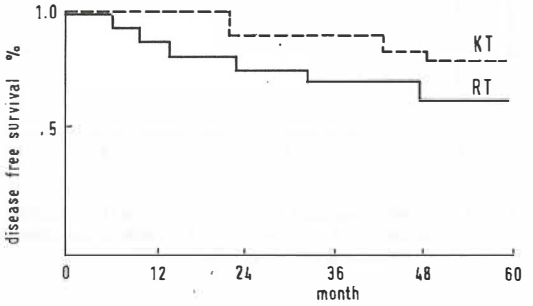

Fig. 3 — Five-year survival in patients with operable breast cancer and axillary lymph node metastases without evidence of disease, treated either by ChT or RT, with tumors smaller than 2 cm.

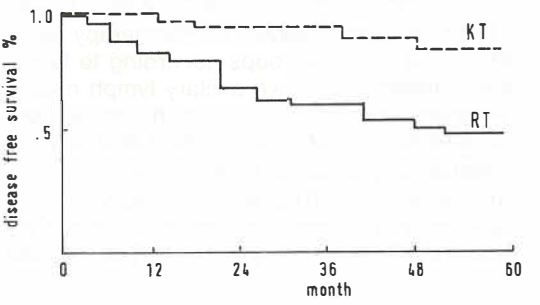

Fig. 4 — Five-year survial in patients with operable breast cancer and axillary lymphn node metastases without evidence of disease, treated either by ChT or RT, with less than 3 involved lymph nodes.

No. of l. n.	All	%	Dead	Alive	% ± SD	p
3 lymph n.	153		29	124		
ChT	85	56%	12	73	68% ± 4	0.05
RT	68	44%	17	51	75% ± 5	
4—7 lymph n.	68		30	38		
ChT	39	57%	14	25	64% ± 8	0.1
RT	29	43%	16	13	45% ± 9	
8 lymph n.	74		39	35		
ChT	45	61%	22	23	51% ± 7	0.4
RT	29	39%	17	12	41% ± 9	

Table 5 — Five-year survival in patients with operable breast cancer and axillary lymph node metastases treated by ChT or RT, according to the number of involved axillary lymph nodes

rapy had longer 5-year survival without evidence of disease than those treated by postoperative irradiation (ChT 54 ± 8%; RT 31 ± 9%; p = 0.04).

Patients with tumor in the lateral quadrant of the breast, treated by ChT, had longer survival than those treated by RT (ChT 58 ± 5%; RT 46 ± 5%; p = 0.04) (Table 6).

Discussion — The patients treated by adjuvant chemotherapy were found to have longer 5-year survival and 5-year survival without evidence of disease than those treated by postoperative irradiation. Considering the prognostic factors, statistically significant differences were found only in patients with tumors smaller than 2 cm, or in those with less than 3 or 7 affected lymph nodes.

Tumor site	All	%	Recurrence	NED	%±SD	p
Lateral quadrant	194		92	102		
ChT	105	54%	44	61	58%± 5	0.04
RT	89	40%	48	41	46%± 5	
Central quadrant	25		8	17		
ChT	16	64%	5	11	69%±12	0.9
RT	9	36%	3	6	67%±16	0.9
Medial quadrant	68		23	45		
ChT	43	63%	14	29	67%± 7	0.6
RT	25	37%	9	16	64%±10	

Table 6 — Five-year survival in patients with operable breast cancer and axillary lymph node metastases, without evidence of disease, treated either by ChT or RT, according to the site of tumor in the breast

Opinions on the importance of postoperative irradiation in patients with oprable breast cancer are differing (4, 5, 6). Most authors believe that post-operative irradiation does not prolong the survival in patients with operable breast cancer and axillary lymph node metastases (4, 5, 15). Also, there has been no statistically significant difference in the survival of patients postoperatively irradiated on either a high-energy X-ray machine or Cobalt (16). Systemic ocult micrometastases are often present at diagnosis of breast cancer, and therefore postoperative irradiation cannot prolong the survival in these patients. Still, it is possible that in some patients ocult micrometastases affect only locoregional lymph-nodes which are within the irradiation field. In such cases, postoperative irradiation could destroy these metastases, and subsequently result in a prolonged survival (17). However, untill now no such group of patients with locoregional lymph node involvement, in whom postoperative irradiation would be sensible, has been reported.

Statistically insignificant differences i the survival of patients with tumors exceeding 2 cm or with more than 3 positive axillary lymph nodes are most probably due to the appearance of chemotherapy-resistant cell clones; on the other hand, a longer survival of some patients with postoperative irradiation whould also be considered as a possible cause of this.

Patients with tumor in the lateral quadrant of the breast treated by adjuvant chemotherapy had statistically significantly longer survival without evidence of disease than the patients treated by postoperative irradiation. Perhaps, postoperative irradiation destroyed possible micrometastases in the parasternal lymph nodes, which are more likely to appear in tumors situated in the central quadrant than in those situated in the lateral quadrant (18).

Possible difference in the survival between both adjuvant treatment groups has disappeared owing to the prolonged survival of postoperatively irradiated patients with tumor in the mediastinal or cental quadrant.

Based on ther results of NSABP study on 1665 patients treated by radical mastectomy or radical mastectomy and postoperative irradiation, no difference in the survival according to the tumor site could be established (18, 19).

There have been many reports published in the past few years on the results of postoperative clinical studies on adjuvant chemotherapy (10, 11, 19, 20). In these studies the survival of patients with operable breast cancer and axillary lymph node metastases treated by radical mastectomy or radical mastectomy and adjuvant chemotherapy has been correlated. Their results are similar to ours. However, no statistically significant longer survival (16) has been established in premenopausal patients treated by adjuvant chemotherapy, for the difference with other authors.

In our study the survivaly of patients treated by either postoperative irradiation or adjuvant chemotherapy have been correlated. The obtained results can be compared with those of other studies on adjuvant chemotherapy, considering that many studies comparing the survival of patients with radical mastectomy, and those with radical mastectomy and postoperative irradiation, has not established any statistically significant differences in the survival (2, 5, 15).

Conclusion — Adjuvant systemic treatment has the potential of prolonging survival in some of the patients with operable breast cancer only. Every adjuvant treatment represents a severe strain on the patients. Therefore, it is of essential importance that the decision on adjuvant systemic treatment application is made only after the

relevant prognostic factors (i.e. the number of positive axillary lymph nodes, tumor size, grade of malignancy, menopausal status, hormone receptors) as well as patients's psychophysical condition have been carefully considered.

Povzetek

5-LETNO PREŽIVETJE BOLNIC Z RAKOM DOJKE IN POZITIVNIMI PAZDUŠNIMI BEZGAVKAMI ZDRAVLJENIH S POOPERATIVNIM OBSEVANJEM IN DOPOLNILNO SISTEMSKO KEMOTERAPIJO

Avtor je ocenil 5-letno preživetje bolnic z operabilnim rakom dojke in zasevki v pazdušnih bezgavkah. Po modificirani radikalni mastektomiji (Maden-Patey) so bile bolnice zdravljene s pooperativnim obsevanjem ali dopolnilno sistemsko kemoterapijo po shemi CMF. Petletno preživejte 169 bolnic zdravljenih z dopolnilno sistemsko kemoterapijo je bilo 72 %, 126 bolnic zdravljenih s pooperativnim obsevanjem pa 60 % ($p = 0,04$). Petletno preživetje bolnic brez znamenj bolezni zdravljenih z dopolnilno sistemsko kemoterapijo je bilo 61 % in s pooperativnim obsevanjem 50 % ($p = 0,02$). Statistično značilno daljše preživetje bolnic z dopolnilno sistemsko kemoterapijo ($p < 0,05$) je ugotovil le pri skupini bolnic s tumorjem od 2 cm ali manj kot tremi oziroma manj kot 7 pozitivnimi bezgavkami.

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