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## Results of adjuvant therapy in postmastectomy breast cancer patients irradiated at the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw between 1985 and 1994

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*Introduction. Between the years 1985 and1994 at the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw two radiotherapy techniques were used in the case of postmastectomy breast cancer patients. In technique "A", in order to limit cardiotoxicity, peripheral nodes only were irradiated, in technique "B" the chest wall was additionally treated. Usually technique "B" was chosen in more advanced cases, but generally the selection of the technique was left to the discretion of the attending physician.*

*Aim. To estimate disease free survival (DFS) and overall survival (OS) with regard to prognostic factors, to evaluate loco-regional failures as related to the radiotherapy technique and to assess early and late morbidity.*

*Material and methods. The retrospective analysis included 507 postmastectomy patients consecutively irradiated for breast cancer in stage IA – IIIB. Median age was 57 years. Median follow-up was 10 years. The incidence of patients with pN1 stage was 90% and with pN0 10%. We applied a total dose of 50 Gy in 25 fractions, over 5 weeks, with Co60 to the supraclavicular area, axillary and internal mammary nodes. The chest wall was irradiated with electrons to a total dose of 46 Gy at 90% izodose in 23 fractions over 5 weeks. Three-dimensional treatment planning of the chest wall was used. Technique "A" and "B" were used in 62% and 38% of patients, respectively. Simultaneously with radiotherapy 67% of patients received chemotherapy (CMF), and/or hormonotherapy (tamoxifen). In 33% of patients no systemic treatment was administered. We analysed the influence of the following prognostic factors: age and hormonal status, additional diseases, duration of symptoms before treatment, breast laterality, T- stage, breast tumour location, carcinoma type, tumour grade, nodal index, extranodal extention and vascular invasion on disease free survival (DFS) and overall survival (OS); in a univariate analysis with the Kaplan-Meier method and in a multivariate analysis with the Cox's proportional-hazards regression model.*

*Results. The 5- and 10-year actuarial DFS and OS for the entire group were 48%, 38% and 62%, 42%, respectively. In univariate analysis: T- stage, breast tumour location, carcinoma type, tumour grade, nodal index, extranodal extention and vascular invasion were statistically significant associated with DFS and/or OS. In multivariate analysis the following prognostic factors had statistically detrimental significant effect on the risk of distant and/or local recurrence of breast cancer: young age (relative risk (RR) 1.36; $p<0.015$), central or medial tumour location (RR 1.47; $p<0.005$), extranodal extention (RR 1.58; $p<0.011$),nodal index (if more than 60% RR=2.26 $p<0.0001$). The same factors (except age) had influence on the risk of death due to breast cancer. During the 5-year of follow-up, in 40% distant failures (DF) and in 6% of patients, isolated loco-regional recurrence (LRR) was found. Throughout follow-up LRR's (isolated or with DF) were recognised in 14% of patients, regardless of the radiotherapy technique. 76% of LRRs appeared during the first 5 years and 90% – during 6.5 years of follow-up. The chest wall recurrence was the most frequent LRR for technique "A" and "B", ocurring in 10% and in 9.3% of pts. respectively. Recurrences in irradiated nodal areas appeared very rarely – in 0.3% – 1.7% of patients. In T1 – T2 pN1 patients, irradiated with technique "A" chest wall recurrence occurred in 11% and in patients with nodal index below 40% – in 8.5%. This data indicates the need of chest wall irradiation in such patients. The tolerance of postmastectomy irradiation was good. Early and late skin reactions were acceptable, although more evident following electron irradiation. In 5.6% of patients who had concurrently received chemotherapy we observed short delays in radiotherapy due to leucopoenia. The following forms of postmastectomy*

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*irradiation late morbidity were observed: in 27 (10%) patients lymphoedema of the arm, in 6 (2.2%) lung fibrosis without symptoms, in one (0.4%) transient brachial plexopathy, in 4 (1.5%) coronary heart disease and in one (0.4) patient – hypothyreosis.*

**Wyniki uzupełniającego leczenia chorych po mastektomii z powodu raka piersi, napromienianych w Centrum Onkologii w Warszawie w latach 1985-1994**

*Wprowadzenie. W Centrum Onkologii w Warszawie w latach 1985-1994 stosowano w radioterapii uzupełniającej u chorych po radykalnej mastektomii z powodu raka piersi dwie techniki napromieniania. W technice A, w celu ograniczenia kardiotoksyczności, napromieniano Co 60 tylko regionalne węzły chłonne, a w technice B napromieniano dodatkowo ścianę klatki piersiowej. Technikę „B" stosowano u chorych z większym zaawansowaniem. Jednakże, ostateczny wybór techniki leczenia był arbitralny.*
*Cel. Ocena przeżycia bezobjawowego i całkowitego, z uwzględnieniem czynników prognostycznych, analiza niepowodzeń loko-regionalnych, z uwzględnieniem techniki radioterapii oraz ocena wczesnych i późnych powikłań.*
*Materiał i metody. Retrospektywną analizą objęto 507 kobiet chorych na raka piersi, napromienianych po mastektomii, w stopniu zaawansowania od IA do IIIB. Mediana wieku wynosiła 57 lat. Mediana obserwacji – 10 lat. U 90% chorych rozpoznano pN1, a u 10% pN0. Okolicę węzłów chłonnych nad- i podobojczykowych, pachowych i przymostkowych napromieniano Co 60, podając całkowitą dawkę 50 Gy w 25 frakcjach w czasie 5 tygodni. Ścianę klatki piersiowej napromieniano wiązką elektronów do dawki całkowitej 46 Gy, obliczanej w izodozie 90%, podanej w 23 frakcjach w czasie 5 tygodni. W radioterapii ściany klatki piersiowej wykorzystywano trójwymiarowe planowanie leczenia. Technikę „A" zastosowano u 62%, a technikę „B" u 38% chorych. U 67% chorych radioterapię skojarzono z jednoczasową chemio- (CMF) lub hormonoterapią (tamoksyfen). U 33% chorych nie stosowano leczenia systemowego. W analizie jednoczynnikowej i wieloczynnikowej zbadano wpływ następujących czynników prognostycznych na ryzyko nawrotów i zgonu z powodu raka piersi: wiek i stan hormonalny chorych, choroby współistniejące, czas wywiadu, strona piersi, wielkość i lokalizacja guza pierwotnego, typ histopatologiczny raka, stopień złośliwości raka, indeks węzłowy, stosunek raka do torebki węzła i tkanki otaczającej, inwazja naczyń. W obliczeniach wykorzystano metodę Kaplana-Meiera i modele proporcjonalnego ryzyka Cox'a.*
*Wyniki. Pięcio- i 10-letnie przeżycie bezobjawowe i całkowite dla całej grupy chorych wyniosło odpowiednio: 48%, 38%, 62% i 42%. W analizie jednoczynnikowej takie czynniki, jak: wielkość i lokalizacja guza pierwotnego, typ histopatologiczny raka, stopień złośliwości raka, indeks węzłowy, stosunek raka do torebki węzła i tkanki otaczającej, inwazja naczyń, okazały się mieć istotny statystycznie związek z przeżyciem bezobjawowym i całkowitym. W analizie wieloczynnikowej czynnikami istotnie statystycznie zwiększającymi ryzyko nawrotu okazały się: młody wiek (ryzyko względne 1,36; $p<0,015$), centralna i przyśrodkowa lokalizacja guza w piersi (ryzyko względne 1,47; $p<0,0005$), naciek torebek węzłów chłonnych (ryzyko względne 1,58; $p<0,011$) i indeks węzłowy (jeśli powyżej 60%, to ryzyko względne 2,26; $p<0,0001$). Te same czynniki, oprócz wieku, miały istotny wpływ na ryzyko zgonu z powodu raka piersi. W ciągu 5 lat obserwacji u 40% chorych wystąpiły przerzuty odległe, a u 6% samodzielne nawroty loko-regionalne. W całym okresie obserwacji nawrót loko-regionalny (samodzielny lub z przerzutem) rozpoznano u 14% chorych, bez względu na rodzaj stosowanej techniki radioterapii. Siedemdziesiąt sześć procent nawrotów pojawiło się w ciągu pięciu lat, a 90% w ciągu 6,5 roku. Najczęściej w obu technikach „A" i „B" wznowę obserwowano w ścianie klatki piersiowej, odpowiednio: u 10% i 9,3% chorych. Nawroty w napromienianych obszarach węzłowych występowały sporadycznie, od 0,3% do 1,7% chorych. Wznowy w ścianie klatki piersiowej u chorych z guzem pierwotnym T1-2 pN1, leczonych techniką „A", wystąpiły u 11% chorych, a u chorych z indeksem węzłowym poniżej 40% u 8,5% chorych. Potwierdza to konieczność napromieniania tych grup chorych na obszar ściany klatki piersiowej. Tolerancja napromieniania była dobra. Wczesne i późne odczyny skórne były akceptowalne. Nieco bardziej były one nasilone po radioterapii elektronowej. U 5,6% chorych leczonych jednoczasowo z CMF zastosowano przerwę w napromienianiu z powodu leukopenii. U 27 (10%) chorych stwierdzono obrzęk kończyny górnej, u 6 (2,2%) zwłóknienie popromienne w płucach nie powodujące objawów klinicznych, u jednej (0,4%) przemijające objawy uszkodzenie splotu ramiennego, u 4 (1,5%) nasilenie choroby wieńcowej i u jednej (0,4%) niedoczynność tarczycy.*

**Key words:** postmastectomy radiotherapy, breast cancer, retrospective analysis
**Słowa kluczowe:** radioterapia po mastektomii, rak piersi, analiza retrospektywna

## Introduction

In Poland breast cancer is the most common malignancy recognised in women (structure index 19.7%, incidence 36). Approximately 11 000 new cases are diagnosed *per annum* [1]. It is estimated that radical mastectomy is performed in some 8000 of these patients, and that some 3500 of those necessitate adjuvant radiotherapy. The main indications for radiotherapy after mastectomy include the involvement of more than 3 axillary lymph nodes and/or the size of the initial tumour exceeding 5 cm [2, 3]. Some authors suggest adjuvant irradiation in patients with only 3 involved lymph nodes, stressing that in these patients the efficacy of irradiation is even higher

[4, 5]. Randomized clinical trials held in the recent years have shown that irradiation not only reduces the risk of recurrence, but also improves overall survival in patients receiving systemic treatment [6-10].

Since the fifties irradiation after mastectomy has been a routine procedure at the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw. Until the seventies we used roentgenotherapy, and later – cobaltotherapy. In the beginning of the eighties we introduced simulators, CT scans and 3D treatment planning. In 1985 we introduced electron beam irradiation of the chest wall in order to minimalize the risk of late complications [11-13].

Irradiation after mastectomy was performed using two different techniques. The first technique – intended to minimalize the complication risks – included only the irradiation of local lymph nodes (the so-called "peripheral" technique). The second technique consisted of irradiation of the lymph nodes and of the chest wall (referred to as the "peripheral + chest wall" technique). After 10 years of patient observation we performed a retrospective analysis of the results.

The aims of this paper are:

1) to evaluate disease-free survival (DFS) and overall survival (OS) including a univariate and multivariate analysis of prognostic factors,
2) to analyse loco-regional failures and to attempt to solve the query – is it rational to refrain from irradiation of the chest wall in selected sub-groups of patients, e.g. T1-T2 tumours with a low nodal index,
3) to evaluate the tolerance of radiotherapy after mastectomy and to analyse the early and the late complications.

## Material

The study group consisted of 507 consecutive women with breast cancer after mastectomy who had been irradiated at the 2nd Department of Radiotherapy of the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw (referred to as Institute of Oncology) between the years 1985 and 1994. Indications for postoperative radiotherapy included metastases in axillary lymph nodes found after lymphadenectomy and/or tumour size over 5 cm. According to the protocol only post-menopausal women were to be qualified for postoperative irradiation, however there were some exceptions. These included women with multiple nodal involvement, and/or with histopathologically highly malignant tumours (G3). These patients account for some 12% (62/507) of the entire group. Patient characteristics are presented in Table I. A vast majority of patients were over 50 years of age (70%) and postmenopausal (88%). The youngest patient was 29, the oldest – 78. Median age was 57 years. Almost half of the patients (45%) had at least one concomitant disease – diabetes, arterial hypertension or coronary heart disease. A majority of the patients (91%- 462/507) had been operated in general surgical wards. Only 9% of the patients (45/507) had undergone mastectomy at the Institute of Oncology in Warsaw. 70% (354/507) had undergone mastectomy *modo* Patey, 17% (85/507) – mastectomy *modo* Halstedt and 1% (4//507) – *modo* Urban. In 12% of patients (64//507) operated outside the Institute of Oncology residual breast tissue was found despite "so-called" radical mastectomy. In over 2/3 of the patients the mastectomy was performed more than six months after the first symptoms of breast cancer. 89% of patients reported with a tumour over 2 cm in size, in 25% of patients the tumour was over 5 cm in diameter or the skin was infiltrated. The relatively small number of excised lymph nodes (7 on average) from the axilla caused difficulties in making therapeutic decisions. In order to assess the advancement of the disease we checked surgical protocols and consulted almost all histo-pathological specimens. In 66% of cases invasive ductal carcinoma was diagnosed, in 16% – invasive lobular carcinoma and in 5% of cases – other types of breast cancer with a better

**Table I. Clinical characteristics of 507 patients (pts)**

| Factor | | Number of pts. (%) |
|---|---|---|
| Age (yrs.) 29–78 (median: 57) | | 153 (30) |
| | < 50 | 354 (70) |
| | >= 50 | |
| Pre-menopausal | | 62 (12) |
| Postmenopausal | | 445 (88) |
| Additional | no | 277 (55) |
| diseases | yes | 230 (45) |
| Anamnesis (mths.) | | 136 (27) |
| 1–48 mths. | = < 6 | 371 (73) |
| (median: 4) | > 6 | |
| Breast laterality: | right | 245 (48) |
| | left | 262 (52) |
| Breast tumour location: | | |
| lateral quadrants | | 66 (13) |
| central location | | 279 (55) |
| medial quadrants | | 162 (32) |
| I° T1pN0 | | 8 (2) |
| II°A T1pN1 | | 47 (9) |
| T2pN0 | | 33 (7) |
| II°B T2pN1 | | 293 (57) |
| T3pN0 | | 8 (2) |
| III°A T3pN1 | | 80 (16) |
| III°B T4pN1 | | 38 (7) |
| Carcinoma type: | | |
| ductal invasive | | 332 (66) |
| lobular invasive | | 81 (16) |
| good prognostic group | | 27 (5) |
| | no data | 67 (13) |
| No. of nodes removed: 0–36 | | |
| (median: 7) | 1-6 | 169 (33) |
| | >6 | 292 (58) |
| | no data | 46 (9) |
| No. of nodes involved: 0–28 | | |
| (median: 3) | 1-3 | 218 (43) |
| | 4-8 | 157 (31) |
| | => 9 | 86 (17) |
| | no data | 46 (9) |
| Extranodal extention: | | |
| | no | 127 (25) |
| | yes | 380 (75) |
| Tumor Grade: | | |
| | G I | 14 (3) |
| | G II | 200 (39) |
| | G III | 82 (16) |
| | no data | 211 (42) |
| Vascular invasion: | | |
| | no | 370 (73) |
| | yes | 137 (27) |

prognosis. In 13% of patients receiving preoperative chemotherapy it had been impossible to diagnose the histopathological type of the tumour. 90% of the entire group (458/507) presented an axillary lymph node metastases. The remaining 49 patients (10%) appeared not to have nodal involvement – however the analysed specimens from these patients contained, on average, less than 6 lymph nodes, or, in some cases – the number of lymph nodes was unknown, and therefore they also underwent postoperative irradiation. Third pathological grade, vascular invasion and extranodal extension were recognised in 16%, 27% and 75%, respectively.

### Postoperative irradiation

In all patients postoperative irradiation was started some 2-3 months after mastectomy. Two different techniques of irradiation were used. In the first technique – referred to as "peripheral" (A) – the irradiated field included axillary, supra- and infraclavicular lymph nodes without the chest wall. In the second technique – the so-called "peripheral and chest wall" technique we irradiated the lymph nodes and the postmastectomy chest wall. Patients with lesser advancement and a higher complication risk were qualified for technique A and patients with further advancement were qualified for technique B. However, the final choice of treatment was arbitrary and depended also on the accessibility to the CT – computed tomography and to the accelerator. Radiotherapy was planned on the simulator. Supra- and infraclavicular nodes were irradiated with Co60 with one frontal field, with a 10 degree lateral rotation in order to avoid irradiating the pharynx and the oesophagus. We used individual shields for the larynx and the entire head of the humerus. We administered a total dose of 50 Gy in 25 fractions calculated for the 100% isodose. The dose was increased in the centre of the axillary fossa from an additional backward field, using the isocentric technique without altering the position of the patient. This allowed to achieve a total isodose of 50 Gy in 25 fractions within the centre of the AP distance of the axilla over the same treatment time. The internal mammary nodes were irradiated with a mixed beam – a total dose of 30 Gy of Co60 calculated for the 100% isodose in 15 fractions and a total dose of 18 Gy of a 12 or 15 MeV electron beam calculated for the 80% isodose in 9 fractions. The chest wall and the internal mammary nodes were irradiated with an electron beam. We performed 3D planning with CT sections of the chest wall taken every 2 cm. The planning treatment volume (PTV) was inserted at each scan. The Helax planning system allowed to calculate the energy and the electron beam angles. We used individual wax boluses to shape the electron beam so that the chest wall (PTV) would be in the 80% isodose, and to diminish the volumes of critical organs (heart, lungs). We administered a total dose of 46 Gy calculated for the 80% isodose in 23 fractions. In 313/507 patients (62%) we irradiated the lymph nodes only (technique A), while in 194/507 patients (38%) the irradiated area also included the chest wall (technique B).

### Systemic treatment

In 167/507 patients (33%) no systemic treatment was administered. In the remaining 340/507 patients (67%) postoperative irradiation was administered together with chemo- or hormonotherapy. In 284/445 postmenopausal patients (64%) tamoxifene was administered for 5 years as adjuvant therapy. The estrogen and progesterone receptors had not been evaluated in a vast majority of patients. In 192/507 patients (38%) postoperative chemotherapy was applied. 88 patients (17%) received 6 courses of the CMF programme (cyclophosphamide 100 mg/m$^2$ orally on days 1-14; methotrexate 40 mg/m$^2$ i.v. on day 1 and 8; 5-fuorouracil 600 mg/m$^2$ i.v. on day 1 and 8) every 28 days. The remaining 104 patients (21%) received complex preoperative chemotherapy due to poor prognosis – 12 courses according to the Ansfield programme (cyclophosphamide 100 mg/m$^2$ orally day 1-14; prednisone 45-15 mg/day; methotrexate 30 mg/m$^2$ i.v. and 5-fuorouracil 500 mg/m$^2$ i.v. every 7 days and vincristine 1 mg i.v. every 7 days). After mastectomy these patients additionally received 3 courses according to the CMF programme and tamoxifene.

Observation was terminated in December 2001. The observation time varied between 7 and 15.5 years (median – 10 years). Late complications were analysed according to the RTOG-EORTC and NCI Common Toxicity Criteria-CTC.

### Statistical methods

The first stage included a univariate analysis with a calculation of the 5- and 10-year DFS and OS using the Kaplan-Meier method [14]. We analysed the following prognostic factors: age and hormonal status, concomitant diseases, duration of case history, breast laterality, size and location of the primary tumour, histological grade, nodal index (ratio of involved nodes in all dissected), extranodal extension and vascular invasion.

In the second stage we performed a multivariate analysis using Cox's proportional hazards model [15]. We used stepwise elimination for the modelling, excluding factors for which the p value was the highest, but not lower than 0.1. The level of statistical significance was assumed for $\alpha = 0.05$.

In the next stage we checked the frequency and structure of the first failures during a 5-year observation period. We also registered loco-regional failures (isolated and/or with simultaneous distant failures) throughout the observation period in relation to the applied irradiation technique. The cumulated frequency of loco-regional failures was calculated according to the Kaplan-Meier method [14].

## Results

In the entire group of 507 breast cancer patients irradiated after mastectomy 273 (54%) died. An analysis of the causes of death had shown that 244 (48%) of patients had died of breast cancer dissemination. 5 patients (1%) died due to other causes, i.e. stroke, heart disease, ovarian cancer, colorectal cancer and lung cancer. In 24 cases (5%) we failed to discover the cause of death. Among the 234 survivors (46%) 201 patients (40%) are symptom-free and 33 (6%) have reported with symptoms of the malignancy. In 21 patients (4%) we have diagnosed cancer of the second breast.

### DFS and OS in view of univariate and multivariate analysis of the prognostic factors

The probability of 5- and 10-year DFS and OS in the entire group of patients was 48%, 38% and 62%, 42%, respectively.

In the course of the univariate analysis we found that the following prognostic factors had a statistically significant impact on DFS and OS: size and location of the primary tumour, histological type, nodal index, the infiltration of the nodal capsule and surrounding tissue and vascular invasion – Table II. The histopathological grade of the tumour did not affect the risk of recurrence, but it had a statistically significant impact on OS. All

**Table II. 5 and 10 – year disease free survival (DFS) and overall survival (OS) in 507 postmastectomy breast cancer patients as related to prognostic factors**

| Prognostic factors | Number of pts. | 5 year DFS%()* | 10 year DFS%()* | 5 year OS%()* | 10 year OS%()* |
|---|---|---|---|---|---|
| Total group | 507 | 48 (44;52) | 38 (34;42) | 62 (58;66) | 42 (38;46) |
| Age: | | | | | |
| 29-45 | 88 | 36 (26;46) | 25 (17;33) | 57 (47;67) | 33 (23;43) |
| 46-55 | 133 | 52 (44;60) | 44 (36;52) | 68 (60;76) | 50 (42;58) |
| 56-65 | 184 | 42 (36;48) | 33 (26;40) | 57 (50;64) | 36 (28;44) |
| 66-77 | 102 | 60 (50;70) | 44 (35;55) | 66 (58;74) | 45 (33;57) |
| | | | p.=0.02 | | p.=0.06 |
| Breast tumour location: | | | | | |
| lateral quadrants | 66 | 67 (56;78) | 48 (38;58) | 78 (68;88) | 50 (40;60) |
| central and medial quadrants | 441 | 45 (41;49) | 36 (32;40) | 60 (56;64) | 41 (36;46) |
| | | | p.=0.012 | | p.=0.02 |
| T1+T2 | 381 | 51 (46;56) | 40 (35;45) | 67 (62;72) | 45 (39;51) |
| T3+T4 | 126 | 38 (30;46) | 28 (20;36) | 48 (39;57) | 31 (23;39) |
| | | | p.=0.001 | | p.=0.001 |
| I° | 8 | 87 | 87 | 100 | 90 |
| IIA | 80 | 67 (57;77) | 59 (47;71) | 78 (69;87) | 62 (50;74) |
| IIB | 301 | 49 (43;55) | 42 (36;48) | 62 (58;66) | 43 (37;49) |
| IIIA | 80 | 43 (32;54) | 33 (23;43) | 50 (40;60) | 34 (24;44) |
| IIIB | 38 | 29 (15;43) | 20 (4;36) | 36 (22;50) | 21 (9;33) |
| | | | p.=0.01 | | p.=0.01 |
| Carcinoma type: | | | | | |
| ductal invasive | 332 | 46 (41;51) | 37 (31;43) | 63 (58;68) | 40 (35;45) |
| lobular invasive | 81 | 55 (44;66) | 40 (28;52) | 70 (60;80) | 56 (44;68) |
| good prognostic group | 27 | 70 (54;86) | 50 (36;66) | 79 (63;95) | 60 (42;78) |
| no data | 67 | 34 (23;45) | 26 (15;37) | 43 (31;55) | 26 (15;37) |
| | | | p.=0.005 | | p.=0.005 |
| Extranodal extension: | | | | | |
| No | 127 | 65 (58;72) | 54 (44;64) | 76 (68;84) | 59 (49;69) |
| Yes | 380 | 42 (37;47) | 32 (27;37) | 58 (53;63) | 36 (30;42) |
| | | | p.=0.001 | | p.=001 |
| Tumour Grade: | | | | | |
| G I + G II | 214 | 44 (37;51) | 33 (26;40) | 63 (57;69) | 38 (31;45) |
| G III | 82 | 44 (33;55) | 32 (21;43) | 51 (40;62) | 32 (21;43) |
| no data | 211 | 53 (46;60) | 43 (36;50) | 66 (60;72) | 50 (43;57) |
| | | | p.=0.17 | | p.=0.01 |
| Vascular invasion: | | | | | |
| No | 370 | 50 (54;46) | 40 (44;36) | 65 (61;69) | 46 (42;50) |
| Yes | 137 | 40 (44;36) | 27 (19;35) | 54 (46;62) | 31 (22;40) |
| | | | p.=0.016 | | p.=0.049 |
| Nodal Index^ | | | | | |
| <40% | 215 | 63 (57;69) | 51 (44;58) | 74 (68;80) | 57 (49;65) |
| 40-60% | 72 | 39 (28;50) | 32 (20;44) | 63 (57;69) | 38 (26;50) |
| >60% | 174 | 34 (27;31) | 21 (14;28) | 48 (40;56) | 24 (16;32) |
| | | | p.=0.001 | | p.=0.001 |

* 95% confidence limit

^Nodal Index: total number of axillary nodes involved divided by the number of axillary nodes excised

other analysed factors (age, hormonal status, concomitant diseases, duration of case history and the breast laterality) had no influence either on DFS or OS.

In the multivariate analysis the following factors were found to have a statistically significant influence on recurrence: age, location of the primary tumour, nodal index and the infiltration of the nodal capsule and surrounding tissue – Table III.

Younger patients – up to 45 years of age – had an almost twice as high risk of recurrence and death as compared to older patients. Only patients between 55 and 65 years of age formed an exception, as in their case the risk of recurrence was similar to that found in younger women. Patients with central or medial tumour location within the breast had a 1.5 times higher risk of recurrence than patients with lateral tumour location. The risk of recurrence was also 1.5 times higher in patients with extracapsular nodal infiltration. The greatest risk of recurrence was observed in patients with the highest nodal index – patients with a nodal index of over 60% had a 2.3 times higher risk of recurrence than patients with the nodal index below 40% – Table III.

In the course of an analysis of the factors influencing the death risk we found that in this case practically the same factors are significant, except for age. Patient with central or medial tumour location have a 60% higher

**Table III. Cox's model factors and the risk of recurrence of breast cancer or death**

| Variable | Relative risk | P – value |
|---|---|---|
| Age [29, 45]– ref. | | 0.007 |
| [45, 55] | 0.638 | 0.015 |
| [55, 65] | 0.813 | 0.225 |
| [65, 77] | 0.528 | 0.002 |
| Lateral – ref. vs central or medial quadrants | 1.472 | 0.005 |
| No extranodal extension – ref. vs extranodal extension | 1.585 | 0.011 |
| Nodal Index | | |
| <40 – ref. | | <0.0001 |
| 40-60 | 1.767 | 0.002 |
| >60 | 2.262 | <0.0001 |

**Table IV. Cox's model factors and the risk of death due to breast cancer**

| Variable | Relative risk | P – value |
|---|---|---|
| Lateral – ref. vs central or medial quadrants | 1.382 | 0.041 |
| No extranodal extension – ref. vs extranodal extension | 1.740 | 0.049 |
| Nodal Index | | |
| <40 – ref. | | <0.0001 |
| 40-60 | 1.481 | 0.0457 |
| >60 | 2.197 | <0.0001 |

death risk than patients with lateral tumour location. Extracapsular nodal infiltration increases the patients' death risk by 70%, as compared to patients without capsular infiltration. Patients with a nodal index below 40% are at a 1.5 or twofold lesser risk of death than patients with the nodal index of between 40%-60% and over 60% respectively. All other prognostic factors, such as the patients' hormonal status, concomitant diseases, duration of case history, the breast laterality, the size of the primary tumour, the histopathological type and grade of the tumour were found to be statistically non-significant in the multivariate analysis.

10-year DFS in the entire group irradiated according to technique A and B was 40% (34;46), 32% (26, 38), respectively, with a 95% confidence interval – Figure 1.

## Analysis of failures

During the first 5 years of observation a recurrence of the malignancy was observed in 226 patients (46%) – in 197 of these (40%) we observed distant failures, in 29 (6%) – isolated loco-regional recurrence. It was proved that distant metastases are the main cause of failure (197/226 – 87%) as compared to only 13% within the loco-regional area. In 18 cases (62%) the recurrence was limited to the thoracic wall, in 6 (21%) – it was found in the regional lymph nodes and in the remaining 5 (17%) it

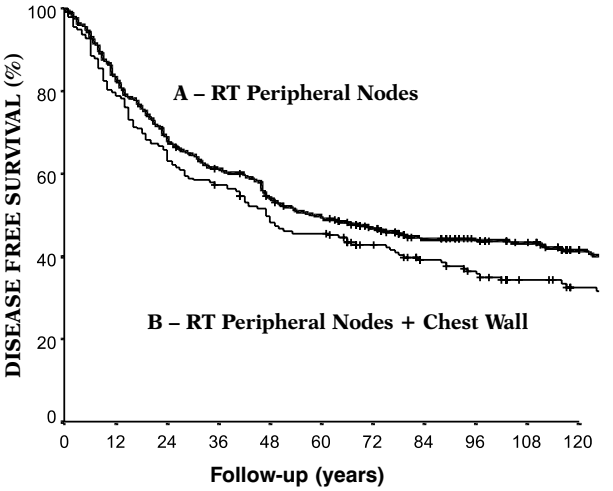


**Figure 1.** Disease free survival in respect to the radiotherapy technique in postmastectomy breast cancer patients

was located both in the lymph nodes and in the thoracic wall.

During the entire period of observation (median of 10 yrs.) loco-regional recurrence (isolated or simultaneous with distant failures) was found in 71/507 patients (14%). 54 cases (74%) of recurrences were observed during the first 5 years, and 90% – during 6.5 years – Figure 2. We

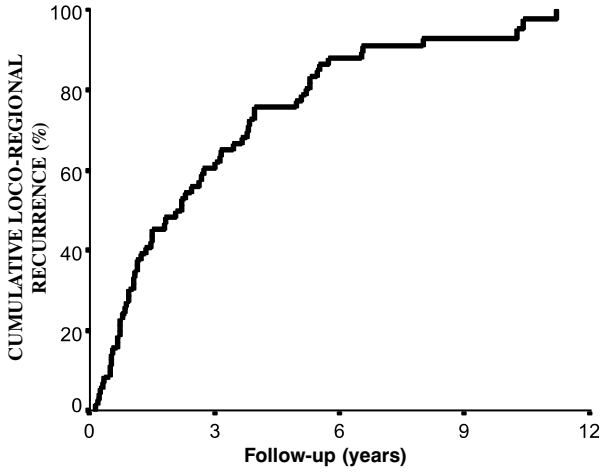


**Figure 2.** Cumulative loco-regional recurrence in 71/507- 14%, postmastectomy breast cancer patients

found no difference as to the frequency of loco-regional failure between patients from group A and group B (44/313 – 14% – vs. 27/194 – 14%) – see Table V.

In both groups the most common site of recurrence was the chest wall – 10% and 9.3%, respectively. Recurrences within the different nodal sites were observed sporadically (0.3-1.7% of patients) – see Table V.

We enhanced the analysis of loco-regional failures within the chest wall by determining the influence of the T stage and pN (as measured by the nodal index) and their relation to the applied irradiation technique. We found that in the case of patients with T1-T2 tumours and nodal metastases these failures occurred in 11% of

**Table V. Rate and localization of loco-regional failures (LRF) in relation to the radiotherapy technique**

| RT Technique | N | LRF in regions (%) CW | CW+PN | Sup/inf.clavicular | Axilla | Parasternal | Total |
|---|---|---|---|---|---|---|---|
| "A" PN alone | 313 | 33 (10) | 4 (1.5) | 2 (0.7) | 4 (1.5) | 1 (0,3) | 44 (14) |
| „B" PN + CW | 194 | 18 (9.3) | 2 (1) | 3 (1.7) | 2 (1) | 2 (1) | 27 (14) |
| Total | 507 | 51 (10) | 6 (1.2) | 5 (1) | 6 (1.2) | 3 (0.6) | 71 (14) |

N -Number of pts.; RT – radiotherapy; PN – Peripheral nodes; CW – chest wall; Sup/inf.clavicular – supra and/or infra clavicular region

patients from group A and 8% of patients from group B. Patients with T3-T4 tumours had an identical (15%) ratio of chest wall recurrence, regardless of the irradiation technique- Table VI.

We also observed that the recurrence risk grew with the increase of the nodal index, although more rapidly in group B. Even with a low nodal index (below 40%) chest wall recurrence occurred in 8.5% of patients from group A – Table VII.

## Treatment tolerance and early and late complications

Among the 507 patients undergoing postoperative irradiation 22 (4.3%) women failed to complete treatment – 15 developed distant failures, 3 had stroke and 4 presented with exacerbation of previously observed heart disease.

In 218/507 patients (43%) the total treatment time was lengthened to more than 6 weeks. The main cause of elongation was the long waiting list for the electron beam irradiation of the chest wall or of the internal mammary lymph nodes. Treatment delays were also caused by apparatus failures and conservation jobs.

Among the 485 patients who had completed treatment 40 (8.2%) reported complications which necessitated treatment delays. The most common cause for these delays was leucopoenia (leukocyte count below 2500/mm$^3$), which occurred in 27/485 patients (5.6%), who were all concurrently receiving CMF chemotherapy.

Early skin reactions after Co60 treatment were moderate (grade 1 and 2 in the RTOG-EORTC scale). However, 17% of patients irradiated with the electron beam to the chest wall and 3% irradiated with the same technique to the internal mammary nodes developed severe skin reactions in the form of moist desquamation (grade 3).

An analysis of late complications was carried out in 269 patients, who had survived at least 5 years without disease recurrence. Late skin reactions within the Co60 treated areas were all grade 1. Minor teleangiectasiae (grade 2) were observed on the chest wall and in the sternal region in 73% of patients. Grade 3 late skin reactions on the chest wall were observed only in 3% of patients. In 27 patients (10%) we observed lymphoedema of the upper extremity. In 10 cases (3.7%) the diameter of the unilateral upper arm was 4 cm greater than the diameter of the contralateral arm.

**Table VI. Chest wall recurrence in relation to the radiotherapy technique and T-stage in 458 patients with pN1**

| T-stage | Radiotherapy Technique "A" N | "A" Chest wall recurrence (%) | "B" N | "B" Chest wall recurrence (%) |
|---|---|---|---|---|
| T1 + T2 | 244 | 27 (11) | 96 | 8 (8) |
| T3 + T4 | 39 | 6 (15) | 79 | 12 (15) |
| Total | 283 | 33 (12) | 175 | 20 (11) |

**Table VII. Chest wall recurrence in relation to radiotherapy technique and nodal index in 461 patients with a stated number of nodes**

| Nodal Index | Radiotherapy Technique "A" N | "A" Chest wall recurrence (%) | "B" N | "B" Chest wall recurrence (%) |
|---|---|---|---|---|
| < 40 | 141 | 12 (8.5) | 74 | 3 (4) |
| 40 – 60 | 45 | 4 (9) | 27 | 2 (7) |
| >60 | 98 | 13 (13) | 76 | 10 (13) |
| Total | 284 | 29 (10) | 177 | 15 (8.5) |

In 40/269 patients (15%) we observed late complications arising from adjuvant treatment after mastectomy. The most common disorders included haematological problems observed in 12% of patients (grade 2-3 according to NCI CTC) which lasted from 6 to 12 months. In 8.5% of patients we observed recurrent infections which deteriorated the quality of life (erysipelas, herpes zoster, abscesses). Post-irradiative pulmonary fibrosis with no clinical symptoms was observed in 6 patients (2.2%). Transient brachial plexopathy was observed in 1 patient (0.4%) and exacerbation of coronary heart disease necessitating treatment was observed in 4 patients (1.5%), all irradiated on the left side of the chest. We observed no exacerbation of coronary heart disease in patients irradiated to the right side of the chest. Post-irradiative hypothyrosis was observed in 1 case (0.4%).

## Discussion

At present it is believed that chest wall irradiation after mastectomy is a necessity, because most loco-regional recurrences are found in this area, and therefore such treatment affects not only local success but also increases patient survival. However, there are no conclusive literature reports concerning regional lymph node irradiation, mostly arising from the risk of morbidity [16].

In view of our own experiences and the reports of other authors [17] our policy concerning postoperative radiotherapy has been altered in 1995. All patients who qualify for radiotherapy after mastectomy are treated with the "peripheral + chest wall" technique (i.e. B). Such an approach has been rendered possible by the availability of modern methods of radiotherapy planning with the use of 3D and treatment with the electron beam. The "peripheral" technique, which was widely used in the years 1985-1994, was introduced due to the anticipation of treatment toxicity during time of the widespread enthusiasm for adjuvant chemotherapy. At that time Bonadonna reported his results, according to which he achieved an improvement in the survival of postmenopausal breast cancer patients after adjuvant chemotherapy according to the CMF programme and without radiotherapy [18]. Stjernsward in 1974 [19] and Cusick in 1987 [20] reported an increased risk of death in irradiated patients. In view of their findings the general opinion turned in favour of chemotherapy, while postoperative radiotherapy became less common. This caused postoperative radiotherapy to be limited and practically administered only in postmenopausal women, as in this group of patients the CMF programme proved less effective [18]. In a further analysis Rudqvist [21] and Cuzick [22] reported that the main cause of the increased death ratio after radiotherapy is connected to cardiovascular complications in fact associated with old-fashioned techniques and exceeding doses applied to the coronary vessels. This was later confirmed in large epidemiological population studies. It was proven that irradiation of patients with cancer of the left breast was associated with a 20% higher death risk due to cardiovascular causes, as compared to patients irradiated for cancer of the right breast [23]. Because of these literature reports at the Institute of Oncology in Warsaw we had also decided to limit the use of postoperative radiotherapy among premenopausal patient, and we introduced the "peripheral" technique (A) in which (in order to limit potential cardiotoxicity) only the regional lymph nodes were irradiated. Qualification was arbitrary; however there was a tendency to apply technique A in less advanced cases and technique B (which included the regional lymph nodes and the chest wall) in more advanced cases. In the entire studied group 10-year DFS for patients irradiated according to the A and B method was 40% and 32%, respectively, which is probably associated with the fact that patients referred for technique B had more advanced disease.

Our analysis has confirmed the commonly known fact that the main cause of failure in breast cancer is associated with distant metastases. Among the 46% of failures observed in the first 5 years distant metastases were responsible for 40% of failures, and loco-regional recurrence only 6%. This can result from too less aggressive adjuvant systemic treatment. At present a majority of the analysed patients would have been receiving treatment, probably with the use of anthracyclines or taxoids. Tamoxifene was administered only to 30% of patients, and in the majority of cases the estrogen and progesterone receptors were not investigated. It is common knowledge that the presence of these receptors is a predictive factor in the treatment of breast cancer and their concentration is a condition for hormonotherapy [23, 24].

In Poland breast cancer is responsible for the highest ratio of cancer-induced mortality in women [1] and in the course of population studies it is still reported that the results of breast cancer treatment in Poland are worse the average European results [25]. Our material is representative for the time period, during which it had been observed. 5- and 10-year prognosed DFS and OS for patients consecutively irradiated between the years 1985 and 1994 was 48%, 38% and 62%, 42%, respectively. However, the results of treatment depend upon numerous prognostic factors, especially advancement of the disease, and therefore the comparison of these results is very difficult (Table II).

An analysis of failures has shown that recurrences within the chest wall are more common (2.8 times more likely) than nodal recurrences – Table V. We believe that in the case of patients with nodal metastases the chest wall should be irradiated even in the case of smaller tumours – pT1-pT2, and the same can be said for patients with a low nodal index. To support this it is worth stressing that in group A recurrences were observed in 11% and 8.5% of cases, respectively – Table VI and VII.

In 1995 we abandoned the A technique. Patients referred for postoperative radiotherapy are irradiated to the chest wall with an electron beam. It is well known that the frequency of recurrences within the chest wall increases with an increase in the size of the primary

tumour and with the increase of the advancement of the disease within the axillary fossa [26, 27]. We have also observed such correlations. In patients with T3-T4 tumours or with a nodal index of over 60% we observed 15% and 13% of chest wall recurrences, respectively – Table VI and VII. In this group of patients an increase of the radiation dose should be considered. There probably exists a group of postmastectomy patients with axillary lymph node metastases who are not in need of postoperative irradiation. The problem lies in patient stratification and in the individual selection of such persons – and, as an issue, requires further research [26, 28-31].

The analysis of the time of the occurrence of loco-regional failures (both isolated and simultaneous with distant recurrence) has shown, that 76% of these appeared in the first 5 years of observation, and as many as 90% in the first 6.5 years of observation. Literature data report 70% of failures during the first 3 years and 80-90% of failures during the first 5 years [24, 27, 32].

Recht et al. [24] have published an analysis of 10-year loco-regional failure rate in a group of 2016 patients participating in four randomised studies performed by the Eastern Cooperative Oncology Group. After mastectomy due to breast cancer the patients received adjuvant chemo- and/or hormonotherapy without radiotherapy. The authors observed 13% of isolated loco-regional failures, while the 10-year cumulated risk of isolated and simultaneous failures was estimated to be 28.7% in patients with more than 3 lymph nodes involved. In our material similar percentages were much lower – 6% and 14% respectively, and we associate this with radiation therapy. However, our analysis is retrospective and therefore all comparisons with the cited data are superficial and cannot form the base for conclusions.

An evaluation of 5-year and 10-year DFS and OS probability has confirmed the influence of classical prognostic factors associated with the advancement of the disease. In a univariate analysis we did not confirm the worse prognosis of patients with cancer of the left breast as compared with patients with cancer of the right breast. Patients with central and medial location of the tumour have poorer prognosis than patients with lateral location. These observations have also been reported by other authors [33, 34]. Maybe this arises from the higher probability of dissemination via the internal mammary lymph nodes to the mediastinum and further, and maybe the phenomenon is associated with cardiotoxicity. However, we did not observe increased cardiotoxicity or an increased risk of death due to cardiac reasons. Only in 4 patients (1.5%) did we observe exacerbation of coronary heart disease which demanded treatment and which was associated with prior irradiation to the left side of the chest. However in 25 patients (5%) we were unable to determine the cause of death.

In a multivariate analysis we had found that younger patients (below 45 years of age) with a medial primary tumour location and numerous nodal metastases with extracapsular extension have the highest risk of recurrence and/or death due to breast cancer. The nodal index was found to be the most important prognostic factor. Patients in whom the nodal factor is higher than 60% have 2.3 times higher risk of recurrence and a twofold higher risk of death than patients in whom the nodal index was below 40%.

When we compare the present results with the results obtained in the course of breast cancer treatment at the Institute of Oncology in Warsaw and in Cracow in the eighties we cannot fail to notice that despite the time lapse the results have remained unchanged in the different prognostic subgroups [35, 36]. Patients below the age of 46, with a central location of the tumour originally over 5 cm in diameter and with numerous (>3) involved nodes with extracapsular extension have poor prognosis. Korzeniowski [35] stresses the influence of the histopathologic grade not only as a risk factor of distant failures, but also as a risk factor of loco-regional recurrence. In the multivariate analysis performed in our material the histopathological grade did not statistically significantly influence prognosis. Maybe this arises from the fact that the number of patients in whom the histopathologic grade was microscopically determined was rather low.

Complications necessitating treatment delay were observed in 40/485 patients (8.2%). The main cause of such delays was leucopoenia in patients receiving concomitant chemotherapy. No optimal methods of combining radio- and chemotherapy in postmastectomy patients have been reported. Basing upon our experiences at present we begin radiotherapy 4 weeks after the completion of chemotherapy in order to achieve better treatment tolerance.

Excessive skin reactions and pharyngeal reactions were seldom the cause for treatment delay – 2.6% and 1.4% of patients, respectively. A majority of early skin reactions observed in the studied group were noted as stage 1 and 2. Nevertheless, in view of the individual observation of patients we have decreased the total dose from 46 Gy calculated in the 80% isodose in 23 fractions to 45 Gy calculated in the 90% isodose in 20 fractions. We have also changed the PTV isodose from 80% to 85%.

Every patient treated at the Institute of Oncology undergoes individual and group rehabilitation. Maybe this is the reason why lymphoedema of the unilateral upper extremity is observed only in 10% of patients.

We observed no clinically significant post-irradiation pulmonary fibrosis. The relatively low ratio of cardiotoxicity (1.5%) may be proof of correct treatment planning, which includes shielding the heart. Nonetheless, late cardiovascular complications should be assessed over an observation period longer than 10 years [10]. Transient symptoms of post-irradiation brachial plexopathy were observed only in one patient (0.4%). We observed no permanent plexopathy. This suggests that we apply a correct technique of supraclavicular and axillary lymph node irradiation. These sites were irradiated using the isocentric technique, without changing the position of the patient. Patient repositioning during radiotherapy is

the main cause of complications, as the fields overlap and the dose applied to the brachial plexus exceeds its tolerance.

In the last five years there has been an increase in the interest concerning the postmastectomy irradiation. Danish and Canadian studies have shown that adjuvant radiotherapy not only provides better loco-regional control but also improves the 10- and 15-year survival rate, as compared to patients receiving only adjuvant chemotherapy [6-8]. The introduction of modern methods of 3D treatment planning to limit the risk of late complications – especially pulmonary and cardiac [28, 37, 38]. Nevertheless, these issues demand careful and scrutinizing research because, at present, all patients with nodal metastases receive systemic treatment. Despite the fact, that communications concerning an improvement of patient survival after postoperative radiotherapy have not yet been confirmed by many scientists, especially the Americans, nobody questions the necessity to administer adjuvant radiotherapy to postmastectomy breast cancer patients who report with a number of poor prognostic factors, especially with the use of modern treatment methods.

## Summary

1. 5- and 10-year prognosed DFS and OS for patients consecutively irradiated between the years 1985 and 1994 was 48%, 38% and 62%, 42%, respectively.
2. The significant ratio of distant failures among the total number of failures (87% during the first 5 years) confirms the necessity of more effective systemic therapy.
3. The most important prognostic factor influencing the risk of recurrence and of death is the nodal index (the ratio of involved lymph nodes among all dissected). If it exceeds 60% the risk of recurrence and/or death due to breast cancer is 2.2 times higher than in patients with a nodal index of 40%.
4. The relatively low percentage of isolated loco-regional recurrences (6% in 5 years) confirms the efficacy of radiotherapy in the analysed group. Loco-regional failures (both isolated and simultaneous with distant recurrences) were observed in 14% of patients – 76% of these failures appeared in the first 5 years of observation, and as many as 90% in the first 6.5 years of observation. Both in the case of technique A and B the most often recurrence was observed within the chest wall – 10% and 9.3% of patients, respectively. Nodal recurrences were observed sporadically – in 0.3-1.7% of patients.
5. The significantly more common local failures (in the entire observation period – median of 10 yrs.) confirm the need for irradiation of the chest wall in postmastectomy patients with a T1-T2 primary tumour (11% of recurrences) and axillary node involvement (even with a nodal index below 40% – 8.5% of recurrences). In 1995 the A technique has been abandoned at the Institute of Oncology in Warsaw, and the irradiated fields include the chest wall and the regional lymph nodes.
6. The relatively low ratio of late complications (1.5% cardiotoxicity and 10% lymphoedema of upper extremity) allows to pronounce the technique used in the Institute of Oncology as safe. It must, however, be kept in mind that in order to provide a reliable analysis of cardiotoxicity the observation period should be longer than 10 years.

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