POSTMASTECTOMY RADIOTHERAPY

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Received September 27th, 2001; received in a revised form January 17th, 2002; accepted February 1st, 2002

INTRODUCTION

The value of postmastectomy radiotherapy (PMRT) has been the subject of long lasting controversy. The results of early clinical trials and retrospective analyses have shown that irradiation is highly effective in reducing the incidence of loco-regional recurrences but does not increase relapse-free and overall survival. However, the results of randomized trials published recently strongly indicate that PMRT improves both relapse-free and overall survival in node positive patients treated with mastectomy and adjuvant systemic therapies. This conclusion is mainly based on the results of the Danish Breast Cancer Cooperative Group (DBCG) Trials 82b and 82c, which are summarized in *Table 1* [1,2]. In breast cancer patients the main cause of deaths are distant metastases, and any treatment which improves survival should reduce the risk of dissemination. The mechanism by which PMRT reduces this risk is the prevention of dissemination from subclinical disease which remains after mastectomy within the scar/chest wall and regional lymph nodes and which is poorly controlled by adjuvant systemic therapy. To demonstrate the existence of the above mechanism one should compare the cumulative risk of distant metastases in patients treated with and without radiotherapy. In the Danish trials such data are not available because it was only the first site of failure that was scored. In *Table 2*, results of the British Columbia Cancer Agency (BCCA) and Stockholm I trials are presented. They show a significant reduction in the incidence of distant metastases in irradiated patients in comparison with the control groups treated with mastectomy alone (Stockholm) or with mastectomy and adjuvant CMF (BCCA) [3,4].

Table 1. Results of DBCG 82b and 82c randomized trials.

Study/treatment	Number of patients	Endpoint (10 year)		
		% LCR relapse	%RFS	%OS
DBCG 82b:				
CMF	856	32	34	45
CMF+RT	852	9	48	54
		p<0.001	p<0.001	p<0.001
DBCG 82C				
TAM	689	35	24	36
TAM+RT	686	10	35	45
		p<0.001	p<0.001	p< 0.03

Table 2. Results of Stockholm I and BCCA randomized trials.

Study/treatment	Number of patients	Endpoint (15 years).			
		% LCR relapse	% distant metastases	% RFS	% OS.
Stockholm I:					
Surgery	120	56	72	18	30
Surgery+RT	118	19	54	33	39
		p<0.0001	p<0.01	p<0.001	p=0.20
BCCA					
CMF	154	33	65	33	46
CMF+RT	164	13	49	50	55
		p<0.003	p<0.006	p<0.007	p=0.07

Proceedings of the Conference “Advances in Radiation Oncology: Diagnosis-Treatment Planning-Clinical Outcome”, Poznań, April 19th – 21st, 2001.

On the other hand, observations have also been reported of individual trials, confirmed by meta-analyses, that PMRT may have a deleterious effect on survival due to an excess of noncancer (mainly cardiac) deaths in irradiated patients. In a recent meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) a significant 4.3% increase in the risk of non-breast cancer deaths was found in irradiated patients in comparison with the control group [5]. However, this meta-analysis included very heterogenous studies with different types of surgical treatment and those with the use of outdated radiotherapy techniques in which large total doses of radiation were delievered to the heart. In some of these studies large doses per fraction were also used, which increases the risk of late complications. An increased risk of cardiovascular mortality is probably caused by accelerated atherosclerosis in irradiated coronary arteries and may be a result of the suboptimal RT technique. In the Stockholm trial the increased mortality from the ischemic heart disease was evident only in patients treated with a tangential photon beams technique, in which a large volume of the heart was irradiated [6]. In the Danish studies, in which electron beams were used to treat the chest wall and parasternal nodes, no excess of cardiac death was found at 12 years of follow-up. No trend was revealed in the increase with time of the hazard rate of morbidity from the ischemic heart disease in relation to radiotherapy use [7]. In *Table 3* the incidence of cardiac mortality in the meta-analysis of the "old trials" of PMRT [8] is presented as compared with the data on cardiac mortality in the "new" DBCG trials.

Table 3. Cardiac mortality in "old" PMRT trials and cardiac mortality and morbidity in DBCG trials.

Study	**No of patients**	**No of cardiac death**		**RH (95% CI), p value**
		PMRT (+)	**PMRT (-)**	
Meta-analysis of 6 "old" trials*	3362	99	67	1.82 (1.32-2.5) p<0.001
DBCG 82b&82c**	3083			
Mortality		12	13	0.84 (0.38-1.83) n.s.
Morbidity:				
Ischemic heart disease		46	49	0.86(.057-1.29) n.s.
Acute myocardial infarction		26	22	1.10(0.62-1.94) n.s.

* Trials: Manchestr Quadrate & Peripheral, Oslo I&II, Heidelberg, Stockholm (mortality for patients who survived at least 10 years).
** follow-up 12 years.

Therefore "the state of art" of PMRT may at present be summarized as follows:

1. PMRT significantly improves the relapse-free and overall survival in high risk breast cancer patients who also receive adjuvant systemic therapies, and
2. PMRT may increase the risk of cardiac deaths, but this effect may be avoided using modern radiotherapy techniques.

However, discussion is continuing and divergent opinions are being formulated on the category of patients who really profit from PMRT and on the optimal technique (treatment volume and dose) and the optimal way of combining radiotherapy with adjuvant systemic treatment. The aim of this paper is to examine these arguments taking into account the data from literature and the results of own retrospective analysis performed in a large group of 1885 patients treated with mastectomy alone or irradiated postoperatively with two dose levels at the Center of Oncology in Krakow [9].

A. The criticism of DBCT 82b, c and BCCA trials.

The Danish and Canadian trials have been criticized for several reasons:

a. The incidence of locoregional recurrences in these trials was very high in comparison with the experience of other centres,
b. The number of axillary nodes removed during mastectomy in the Danish studies was low (7 on average) suggesting that surgical treatment may have been suboptimal and the number of involved nodes underestimated,
c. The systemic therapies used in these studies were suboptimal (low dose intensity CMF, tamoxifen for 1 year) by recent standards.

These objections have led to some doubts, particularly in US, of whether the results of trials which were started in the 70s and the early 80s are relevant to the breast cancer patients treated today [10,11,12]. In this context several important points should be made:

1. The strongest risk factor in the risk of a locoregional failure is the number of metastatic axillary nodes, other factors include tumour size and tumour grade. The analysis performed at the Centre of Oncology in Kraków in a group of 1068 patients treated with mastectomy alone showed that node involvement, tumour size and grade are independent risk factors of locoregional recurrence in a multivariate analysis. *Table 4* shows the risk of locoregional recurrence in subgroups of patients with various combinations of these factors and demonstrates how the incidence of recurrences increases with the number and strength of risk factors [13]. In *Table 5* the incidence of locoregional recurrences in the various clinical series is presented. The data were chosen to illustrate various issues. The results of the old large randomized trials confirm that in node positive patients treated with mastectomy alone long term risk of locoregional recurrence is in fact very high exceeding that seen in a control group of patients from the Danish and Canadian studies [4,14]. In more recent studies from the US, in which adjuvant systemic therapy was used, the risk was found to be considerably lower [15,16]. The long term results of the original Milan study reveal a low but similar risk in both: the CMF and control (mastectomy alone) group, suggesting that chemotherapy was not effective in reducing the risk [17]. There are several reasons why the incidence of locoregional events is various in series of patients with a similar risk factors, e.g. in node positive patients. One of the causes may be the difference in the surgical technnique: incomplete surgery may result in a higher rate of locoregional failure. The distribution of prognostic factors may vary from population to population, especially if the risk category is only broadly defined (e.g. node positive). The incidence of recurrence will be higher in a group in which most patients have many nodes involved in comparison with the group of patients majority of whom has a single or few metastatic lymph nodes. The methods of calculation of the rates may differ, taking into account only the first cause of failure or including also recurrences which appeared with distant metastases or even after distant spread. The statistical methods used will also influence the results: crude incidence will be lower than actuarial cumulative incidence of recurrence.

Table 4. Survival and LRF in prognostic subgroups of patients with breast cancer treated with mastectomy alone.

Prognostic subgroup	**No of patients**	**10-year overall survival (%)**	**10-year LCR relapse (%)**
T1 N0 BI	30	96	7
T2 N0 BI	80	92	8
T2 N0 BIII	110	65	23
T2 N(1-3) BI	39	73	27
T2 N(1-3) BII	104	50	29
T2 N≥4 BII	63	41.5	63
T2 N≥4 BIII	37	24	70

Table 5. Incidence of locoregional recurrences in relation to nodal status and treatment method in breast cancer patients treated within various prospective studies.

Study	**Treatment method**	**Nodal status**	**Locoregional recurrence rate (%)**
Manchester	Mastectomy alone	N (-)	16
		N (+)	41.5 (10 - year)
Stockholm I	Mastectomy alone	N (-)	25
		N (+)	56 (15 - year)
BCCA	Mastectomy + CMF	N (1-3)	33
		N≥ 4	46 (15- year)
DBCG 82b	Mastectomy + CMF	N (1-3)	30
		N≥4	42 (10 - year)
DBCG 82c	Mastectomy + TAM	N (1-3)	31
		N≥ 4	46 (10- year)
ECOG	Mastectomy_CMF/P/T	N (1-3)	13
		N≥4	29 (10 - year)
Milan	Mastectomy alone	N (+)	15
	Mastectomy + CMF	N (+)	13 (20 - year)

2. The mean number of nodes removed at surgery in the Danish trials is indeed low and a higher incidence of axillary failure than in other series was observed. It is argued that with more adequate surgery the role of PMRT would become less important. In a recent analysis Iyer et al. demonstrated that the probability of finding a single metastatic node in axilla and the number of metastatic nodes in axilla both increase with the number of nodes found in the specimen and examined [18]. Thus, if only several nodes are removed there is a risk that the real number of involved axillary nodes will be underestimated and patient will be included in the node negative instead of node positive category or in the 1-3 node positive subgroup instead of ≥4 node positive. The small average number of nodes removed in the Danish trial may indeed lead to such underestimation to some extent, however there are the significant differences in the survival and locoregional failure rates between nodal subgroups and survival improvement was found also in patients in whom a higher number of nodes (over 10) was examined. Additionally, in the BCCA trial, in which the average number of nodes was 11, locoregional recurrence rates and the survival benefit were similar to those in the DBCG trials.

3. The adjuvant systemic therapies used in the Danish and Canadian trials should indeed be regarded as suboptimal. However, data from *Table 5* show that a full dose CMF did not reduce the incidence of locoregional failure, and other studies have demonstrated that the addition of radiotherapy to a highly effective adjuvant chemotherapy lowers this incidence [19,20]. Locoregional recurrences appeared to be the cause of failure even in patients who were treated with high dose intensive regimens, followed by BMT, and radiotherapy was included in treatment schedules of these patients [21,22]. In their retrospective analysis of outcome of 857 patients with 10 or more positive lymph nodes Diab et al. found that radiotherapy improved survival only in patients who received adjuvant chemotherapy [23]. It should be pointed out that a significant improvement in the disease free and overall survival observed so far in clinical studies was found almost exclusively in patients who had received systemic therapy. Whelden et al. performed a meta-analysis limited to 18 trials in which the value of PMRT was assessed in patients receiving adjuvant systemic therapies. This meta-analysis also confirmed the improvement of survival in irradiated patients [24]. The above data and other considerations suggest that the positive

effect of radiotherapy on the overall survival would in fact be more pronounced in patients who received more effective systemic chemotherapy that would eradicate a greater proportion of subclinical distant metastases but would be not effective enough in large locoregional subclinical tumours.

B. Which patients should be treated with PMRT?

Patients with multiple (≥4) metastatic axillary nodes have the highest risk of locoregional recurrence, and the use of PMRT in this group was often recommended even before the survival benefit was proven. The use of irradiation in patients with few (1-3) nodes involved is still the subject of discussion despite the convincing evidence from the Danish and BCCA trials [25, 26]. In the US a large multicenter randomized trial was initiated to examine the value of PMRT in this subgroup. In *Table 6* absolute and proportional survival benefits in the Danish and BCCA studies are presented. The data from this table strongly suggest that patients with a less advanced disease (1 – 3 positive lymph nodes) are more likely to benefit from PMRT in terms of survival than those with four or more lymph nodes involved. This hypothesis can be explained on the assumption that the number of positive nodes correlate with both risk of dissemination and the tumour burden of micrometastatic disease. Thus patients with 1-3 nodes involved are firstly at a lower risk of distant dissemination, which if exists it is more likely to be controlled by adjuvant systemic therapy. Similarly, the locoregional tumour burden may be smaller in patients with 1–3 than in those with >3 nodes involved then PMRT would be more effective in eradicating the subclinical disease in locoregional sites and thus preventing secondary dissemination. This is keeping in with the results of the meta-analysis published by Van de Steene et al., in which the survival benefit was found in patients with favourable crude survival corresponding to the patients with a smaller number of involved nodes [27].

Table 6. Survival benefit in patients treated with PMRT within DBCG and BCCA studies, in realtion to degree of nodal involvement.

Study	**Nodal involvement**	**Absolute survival benefit**	**Proportional survival benefit**
DBCG 82b*	N+ (1-3) N+ ≥ 4	8% 12%	17% 15%
DBCG 82c*	N+ (1-3) N+ ≥ 4	11% 7%	20% 8.5%
BCCA **	N+ (1- 3) N+ ≥ 4	14% 13%	27% 16%

* benefit in overall survival
** benefit in systemic disease free survival.

C. What is the optimal technique of PMRT?

The discussion on the value of PMRT includes the issue of technique with respect of treatment volume and dose.

C.1. The treatment volume includes the chest wall and regional (axillary, supraclavicular, parasternal) lymph nodes. The problem under discussion has been whether irradiaton of all these regions is necessary or equally important. Irradiation of the chest wall is not controversial because the majority of the recurrences develop in this area, and the involvement of scar and lymphatics within the chest wall represents an early spread in comparison with lymph node metastases and thus the risk of distant spread is lower. This is illustrated by

the data presented in *Table 7*. The percentage of recurrences occuring with concomitant distant metasaeses is higher in patients who develop nodal (supracalvicular) recurrence than in patients with chest wall recurrence. These data indicate that chest wall irradiation is likely to contribute to survival improvement. The impact of irradiation of regional nodes on survival has been less certain. There are few data on the relative incidence of local versus regional recurrences because in many publications local and regional failures are scored together. *Table 8* shows the proportions of local and regional recurrences in several series of patients treated with mastectomy alone or with mastectomy and systemic therapy. In patients treated with mastectomy alone regional recurrences are equally or more frequent than local recurrences. In patients receiving systemic therapies the ratio of local to regional recurrences seems to be reversed, regional recurrences still occurring quite frequently.

Table 7. Proportion of local/regional recurrence with concomitant distant failure (DF) in breast cancer patients treated with adjuvant systemic therapy.

Study	**No of patients**	**Proportion of local/regional recurrence +DF**	
		Chest wall	**Supraclavicular**
DBCG 82c [2] (Tam alone arm)	686	17/123 (14%)	8/29 (27%)
ECOG (4 trials)[15]	2016	67/198 (34%)	49/113 (43%)

Table 8. Frequency and proportion of local and regional recurrences in node positive breast cancer patients treated with mastectomy alone or with mastectomy and systemic therapies.

Study/treatment	**No of patients**	**No of L-R recurrence**	**% local**	**% regional**
Kraków (mastectomy alone)* [9]	483	193	42%	58%
NSABP B-04 (mastectomy alone)[28]	292	61	51%	49%
DBCG 82c (mastectomy + TAM)[2]	686	254	53%	47%
ECOG (4 trials:mastectomy +adjuvant therapy) [15]	2016	456	53.5%	46.5%

* retrospective analysis: 10-year actuarial LRR rates.

Irradiation of regional nodes alone was very popular and even overrated in the past, when so called “peripheral irradiation” was recommended in lower risk (1-3 positive nodes) patients. The value of this type of PMRT was studied in several randomized trials, e.g. in the Oslo II trial. An interesting point often forgotten today is that in this trial adjuvant systemic treatment was applied in the form of ovarian ablation, which is an effective form of adjuvant therapy as demontrated by EBCTCG metaanalysis. In the Oslo II trial an improvement of survival connected with decreased incidence of distant metastess was in fact noted, it was, however, offset in longer follow-up by an increased risk of cardiac deaths resulting from high dose to parasternal nodes given with direct photon beam with relatively high dose per fraction of 2.5 Gy. Nevertheless the results of Oslo II study indicate that

irradiation of regional nodes may contribute to survival benefit [29,30]. One should also stress that in DBCG and BCCA trials, in which survival benefits were demonstrated, regional nodes had been treated.

Of all nodal areas treated in breast cancer patients the irradiation of internal mammary nodes has been most controversial [31,32,33,34,35). The arguments for and against are summarized in *Table 9*, and the incidence of IMN involvement from surgical series is presented in *Table 10*. Recently, retrospective analyses were published in which the value of IMN irradiation has been negated [36]. This study, however, included a large proportion of early, mainly node negative patients, and only a small proportion of patients IMN were treated, therefore the conclusions may not be relevant to high risk patients treated with mastectomy [37]. It should also be stressed that in all the recent randomized trials which demontrated survival benefit with PMRT the whole volume at risk, including IMN, was irradiated. The value of IMN irradiation has been the subject of clinical trials, especially of a large study of EORTC, which is still recruiting patients. Early results of SFRO randomized trial do not show survival advantage of IMN irradiation after mastectomy [38].

Table 9. Arguments for and against irradiation of internal mammary nodes (IMN).

FOR	**AGAINST**
1. High incidence of IMN involvement in surgical series. 2. IMN were irradiated in trials in which survival benefit was demonstrated. 3. With modern technique dose to the heart may be minimize.	1. Very low incidence of clinical parasternal recurrence. 2. Lack of the direct evidence from randomized trials. 3. It complicates the technique and increases the dose to heart.

Table 10. Incidence of IMN involvement in relation to location of primary tumour and axillary nodes status.

Axillary nodes	**Localisation in breast**	
	Outer	**Inner/central**
N (-) negative	5%	10%
N (+) positive	20%	50%

C.2. The optimal dose of PMRT is also an important issue, although recently it has been less commonly discussed. The dose of 45 – 50 Gy is usually recommended following classical Fletcher estimation which is presented in *Table 11* [39]. The recent EBCTCG meta-analysis showed that radiotherapy reduces the risk of locoregional recurrence on average by two thirds and did not demonstrate any significant difference in relation to the dose and technique [5]. This, however, is not consistent with other reports, which suggest that the dose response relationship for the control of a sublicnical disease does exist in breast cancer *(Table 12)*. *Tables 13* and *14* show the results of analysis performed in our own material on the effectiveness of PMRT in preventing local (chest wall) and regional (nodal) recurrences in relation to dose and degree of nodal involvement [8]. These data suggest that: (a) there is a dose–response relationship, (b) effectiveness of PMRT is lower in preventing chest wall failures than in preventing lymph node failures

and (c) effectiveness decreases with the number of positive lymph nodes (possibly due to a larger subclinical tumour burden). This observation is keeping in with the reports of Fletcher et al., who also found that 50 Gy to the chest wall was relatively ineffective in patients with massive lymph node involvement, and who even recommended the use of higher dose to that area [40,41]. In the published results of recent trials all local (chest wall) and regional (nodal) recurrences have been scored together and it is impossible to confirm whether PMRT is not equally effective in controlling local and nodal recurrences. The data from DBCG 82c seem to confirm that the chest wall disease may be more difficult to eradicate (73% control) than the nodal disease (82% control) [2]. There is also little data on whether the effectiveness of adjuvant systemic therapies is similar or different in both localisations. Obviously, more complete eradication of locoregional subclinical disease with systemic therapy and irradiation should result in better survival preventing more effectively the secondary distant dissemination. With this respect, however, one should note that in BCCA trial a lower dose of 35 Gy resulted in a lower reduction of incidence of locoregional recurrence but the gain in survival was the same as in the Danish trials, in which doses of 46 – 50 Gy were applied [1,2,3]. The question whether chest wall and nodes sholud be treated with the same or different doses requires additional studies.

C.3. Since PMRT may have an adverse effect on survival due to an increased risk of cardiac deaths careful treatment planning is essential to minimize this risk. The modern PMRT techniques with individual CT imaging, three dimensional planning, with the use of electron or mixed beams make it possible to reduce dose to the heart to very low level [33,42].

Table 11. Control of subclinical nodal involvement in relation to dose.

Dose (number of patients)	**% control**
30 – 35 Gy (89 pts)	60 – 70 %
40 Gy (120 pts)	80 – 90%
50 Gy (273 pts)	➢ 90%

Table 12. Dose response relationship in postmastectomy radiotherapy.

Study	**Dose**	**Axillary nodes status**	**Reduction in recurrence risk**
BCCA	35 – 37 Gy	N+ (1-3) N+ ≥ 4	70% 54%
Stockholm I	45 Gy	N (-) N (+)	80% 66%
DBCG 82b	46 – 50 Gy	N (-) N+ (1-3) N+ ≥ 4	82% 77% 67%
DBCG 82c	46 – 50 Gy	N (-) N+ (1-3) N+ ≥ 4	74% 81% 76%

Table 13. Effectivenses of PMRT in reduction the risk of local (chest wall) recurrence in relation to the dose and involvement of axillary nodes.

Number of nodes involved	Treatemnt method and dose	Number of patients	Local recurrence rate (%)	Reduction in recurrence risk
	OP alone	265	15.5	
1 – 3	OP+ RT (40 Gy)	208	5.7	63%
	OP+ RT (50 Gy)	55	3.6	77%
≥ 4	OP alone	173	23	
	OP+ RT (40 Gy)	304	16	30%
	OP+ RT (50Gy)	77	10.5	55%

Table 14. Effectiveness of PMRT in reduction the risk of regional (nodal) recurrence in relation to the dose and involvement of axillary nodes.

Number of nodes involved	Treatment method and dose	Number of patients	Nodal recurrence rate (%)	Reduction in recurrence risk.
	OP alone	265	18.8	
(1 – 3)	OP+RT (40 Gy)	208	7.2	62%
	OP+RT (50 Gy)	55	3.6	81%
≥ 4	OP alone	173	36	
	OP+RT (40Gy)	304	18	55%
	OP+RT (50Gy)	77	5.2	86%

CONCLUSIONS

1. PMRT is indicated in all node positive breast cancer patients.
2. Chest wall and regional lymph nodes should be treated with the dose of 45 – 50 Gy with classical fractionation.
3. Careful individual treatment planning should be used to minimize dose to the heart.
4. Optimal solution of combining PMRT with adjuvant systemic therapies requires further studies.

REFERENCES

1. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Engl J Med. 1997;337:949–55.
2. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, Andersson M, et al. Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999;353:1641–48.
3. Ragaz J, Jackson SM, Le N, Plenderleith IH, Spinelli JJ, Basco VE, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal patients with breast cancer. N Eng J Med 1997;337:956–62.
4. Arriagada R, Rutquist LE, Mattsson A, Kramar A, Rotstein S. Adequate locoregional treatment for early breast cancer may prevent secondary dissemination. J Clin Oncol 1995;13:2869–78.
5. EBCTCG. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet 2000;355: 1757–70.

6. Rutqvist LE, Lax I, Fornander T, Johansson H. Cardiovascular mortality in a randomized trial of adjuvant radiation therapy versus surgery alone in primary breast cancer. Int J Radiat Oncol Biol Phys. 1992;22:887–96.

7. Hojris I, Overgaard M, Christensen JJ, Overgaard J. Morbidity and mortality of ischemic heart disease in high risk breast cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. Lancet 1999;354: 1425–30.

8. Cuzick J, Stewart H, Rutquist L, Houghton J, Edwards R, Redmond C, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol 1994;12:447-53.

9. Korzeniowski S. The value of postoperative radiotherapy in patients with breast cancer treated with radical mastectomy. [Ph.D. thesis] Kraków: Centrum Onkologii, 1991.

10. Recht A, Bartelink H, Fourquet A, Fowble B, Haffty BG, Harris JR, et al. Postmastectomy radiotherapy: Questions for the twenty-first century. J Clin Oncol 1998;16:2886–9.

11. Harris JR, Halpin-Murphy P, McNeese M, Mendenhall NP, Morrow M, Robert NJ. Consensus statement on postmastectomy radiation therapy. Int J Radiat Oncol Biol Phys. 1999;44:989–90.

12. McNeil C. Postmastectomy radiation: Back to center stage? J Natl Cancer Inst 1999; 91:1800-1.

13. Korzeniowski S, Dyba T, Skołyszewski J. Classical prognostic factors for survival and loco-regional control in breast cancer patients treated with radical mastectomy alone. Acta Oncol 1994;33:759–65.

14. Easson EC. Postoperative radiotherapy in breast cancer*. in* Forrest APM, Kunkler PB (edt) *Prognostic factors in breast cancer* Edinburgh and London Ltd. 1968:118–27.

15. Recht A, Gray R, Davidson NE, Fowble BL, Solin LJ, Cummings FJ, et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with and without tamoxifen without irradiation: experience of the Eastern Cooperative Oncology Group. J Clin Oncol 1999:17:1689–700.

16. Recht A. Locoregional failure rates in patients with involved axillary nodes after mastectomy and systemic therapy. Sem Radiat Oncol 1999;9:223–9.

17. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclphosphamide, methotrexate and fluorouracil in node positive breast cancer: the results of 20 years of follow-up. N Engl J Med 1995;332:901–6.

18. Iyer RV, Hanlon A, Fowble B, Freedman G, Nicolaou N, Anderson P, et al. Accuracy of the extent of axillary nodal positivity related to primary tumor size, number of involved nodes, and number of nodes examined. Int J Radiat Oncol Biol Phys 2000:47: 1177–83.

19. Griem KL, Henderson IC, Gelman R, Ascoli D, Silver B, Recht A, et al. The 5 – year results of randomized trial of adjuvant radiation therapy after chemotherapy in breast cancer patients treated with mastectomy. J Clin Oncol 1987;5:1546–55.

20. Sykes HF, Sim DA, Wong CJ, Cassady JR, Salomon SE. Locoregional recurrence in breast cancer after mastectomy and adriamycin based adjuvant chemotherapy: evaluation of the role of postoperative radiotherapy. Int J Radiat Oncol Biol Phys 1989; 16:641–7.

21. Marks LB, Halperin EC, Prosnitz LR, Ross M, Vredenburgh JJ, Rosner GL, et al. Postmastectomy radiotherapy following adjuvant chemotherapy and autologous bone marrow transplantation for breast cancer patients with greater than or equal to 10 positive axillary nodes: Cancer and Leucemia Group B. Int J Radiat Oncol Biol Phys 1992: 23:1021–6.

22. Bucholtz TA, Tucker SL, Moore RA, Mc Neese MD, Strom EA, Jhingrin A, et al. Importance of radiation therapy for high risk breast cancer patients treated with high-dose chemotherapy and stem cell transplant. Proc 41st ASTRO meeting. Int J Radiat Oncol Biol Phys 1999;45:230.

23. Diab SG, de Moor CA, Clark GM et al. Radiation therapy improves survival by decreasing local failure in breast cancer patients with 10 or more positive axillary lymph nodes treated with mastectomy. Proc ASCO 1997;16:130a.

24. Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML, et al. Does locoregional radaition therapy improve survival in breast cancer? A meta-analysis. J Clin Oncol 2000;18:1220–29.

25. Fowble B. Postmastectomy radiation in patients with one to three positive axillary nodes receiving chemotherapy: an unresolved issue. Sem Radiat Oncol 1999;9:230–40.

26. Kuske RR Adjuvant irradiation after mastectomy in women with one to three positive axillary nodes: then no; now yes. Sem Radiat Oncol 1999;9:254-8.

27. Van de Steene J, Soete G, Storme G. Adjuvant radiotherapy for breast cancer significantly improves overall survival: the missing link. Radiother Oncol 2000;55:263–72.

28. Fischer B, Redmonde C, Fisher ER, et al. Ten year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med 1985;111:674-81.

29. Host H, Brenhoved IO, Loeb M. Postoperative radiotherapy in breast cancer – long term results from the Oslo study. Int J Radiat Oncol Biol Phys 1986;12:727–32.

30. Auquier A, Rutqvist LE, Host H, Rotstein S, Arriagada R. Post-mastectomy megavoltage radiotherapy: the Oslo and Stockholm trials. Eur J Cancer 1992;28:433–37.

31. Fletcher GH, Mantague ED. Does adequate irradiation of internal mammary chain and supraclavicular nodes improve survival rates? Int J Radiat Oncol Biol Phys 1978;4: 482–92.

32. Arriagada R, Le MG, Mouriesse H, Fontaine F, Dewar J, Rochard F, et al. Long term effect of internal mammary chain treatemnt: results of a multivariate analysis of 1195 patients with operable breast cancer and positive axillary nodes. Radiother Oncol 1988;11:213–22.

33. Kuske RR. Adjuvant chest wall and nodal irradiation: maximize cure, minimize late cardiac toxicity. J Clin Oncol 1998;16:2579–82.

34. Freedman GM, Fowble BL, Nicolaou N, Sigurdson ER, Torosian MH, Boraas MC, et al. Should internal mammary lymph nodes in breast cancer be a target for radiation oncologist? Int J Radiat Oncol Biol Phys 2000;46:805–14.

35. Marks LB, Hebert ME, Bentel G, Spencer DP, Sherouse GW, Prosnitz LR. To treat or not to treat the internal mammary nodes: a posisible compromise. Int J Radiat Oncol Biol Phys 1994;29:903–9.

36. Fowble B, Hanlon A, Freedman G, Nicolaou N, Hoffman J, Sigurdson E, et al. Internal mammary node irradiation neither decreeases distant metastases nor improve survival in stage I and II breast cancer. Int J Radiat Oncol Biol Phys 2000;47:883–94.

37. Buchholtz TA. Internal mammary lymph nodes: to treat or not to treat. Int J Radiat Oncol Biol Phys. 2000;46:801–3.

38. Romestaing P, Echochard R, Hennequin C, et al. The role of internal mammary chain irradiaiton on survival after mastectomy for breast cancer – results of a phase III SFRO trial. Proc 19th ESTRO Meeting, Radiother Oncol 2000;56 (suppl 1) S85.

39. Fletcher GH. Local results of irradiation in the primary management of localized breast cancer. Cancer 1972;29:545–51.

40. Fletcher GH Mc Neese MD, Oswald MJ. Long term results for breast cancer patients treated by radical mastectomy and postoperative radiation without adjuvant chemotherapy: an update. Int J Radiat Oncol Biol Phys 1989;17:11–4.

41. McNeese, Fletcher GH, Levitt SH. Breast cancer, In: Levitt SH, Tapley ND, editors. Technological basis of radiation therapy: practical clinical application, 2nd edition. Philadelphia: Lea and Febiger, 232–47.

42. Hardenbergh PH, Bentel GC, Prosnitz LR, Marks LB. Postmastectomy radiotherapy: toxicities and techniques to reduce them. Sem Radiat Oncol 1999;9:259–68.