research article

Is postmastectomy radiotherapy really needed in breast cancer patients with many positive axillary lymph nodes?

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Background. Postmastectomy radiotherapy (PMRT) improves survival by eliminating potential occult lesions in the chest wall and lymphatic drainage area. Meta-analysis has shown that PMRT reduces mortality and local recurrence of patients with node positive breast cancer, but there is no specific data about the effectiveness of PMRT in a sub-group of patients with a high number of positive axillary lymph nodes (PALN). The aim of the study was to analyse the impact of the number of PALN on local and distant metastasis occurrence, overall survival (OS) and distant metastases free survival (DMFS) in patients treated with PMRT.

Patients and methods. We reviewed medical records of 129 consecutive breast cancer patients with PALN, treated at Institute of Oncology Ljubljana with PMRT between January 2003 and December 2004. We grouped patients according to the number of PALN as follows: Group 1 (less than 15 PALN) and Group 2 with more than 15 PALN. All patients received adjuvant systemic therapy according to the clinical guidelines. We analysed number of locoregional (LR) recurrences, distant metastasis, overall survival (OS), progression free survival (PFS) and DMFS.

Results. After the median follow-up time of 11.5 years, the Kaplan-Meier survival analysis of PALN showed significantly shorter OS (p = 0.006), shorter PFS (p = 0.002) and shorter DMFS (p < 0.001) in the group of > 15 PALN. Only one LR was found in the group of patients with more than 15 PALN. In multivariate analysis more than 15 PALN and treatment with anthracycline chemotherapy statistically significantly influenced OS and DMFS. For PFS presence of more than 15 PALN were the only independent factor of shorter survival.

Conclusions. Patients with more than 15 PALN have shorter DMFS, PFS and OS as compared to patients with less than 15 PALN, though they receive the same LR treatment. More studies with higher number of patients included are needed to further evaluate our findings.

Key words: breast cancer; postmastectomy radiotherapy; positive axillary lymph nodes

Introduction

The aim of postmastectomy radiotherapy (PMRT) in breast cancer patients is to improve loco-regional (LR) control and survival by eliminating potential occult lesions in the chest wall and lymphatic drainage area. These benefits have been consistently reported in multiple studies.[1-3] Meta-analysis, made by Early Breast Cancer Trialists' Collaborative Group (EBCTCG), published in Lancet in 2014, has shown that PMRT reduces recurrence and breast cancer mortality in women with one to three positive lymph nodes.[4] There is almost no doubt that the group of breast cancer patients with more than 3 positive axillary lymph nodes (PALN) benefit from PMRT, but it is questionable if the benefit is the same all over the described group.[2] Currently, inadequate data exist to provide answer to this question.

According to our clinical experience, we assumed that patients with many PALN might have a greater chance of already present micrometastatic disease and therefore a greater chance for distant spread than for LR relapse. However, existing TNM classification with 10 lymph nodes as the lower limit of the group with the highest number of PALN might not correspond appropriately to or clinical experiences as it seems to be set too low.[5] Majority of breast cancer patients treated with mastectomy receive systemic therapy within the frame of radical treatment, with impact also on potential subclinical LR lesions, destroying them before they become clinically evident and symptomatic. Moreover, at the time of eventual distant spread, patients receive another line of systemic treatment, which again impact also on potential subclinical LR lesions.

Even though all patients in the studied group received the same kind of LR treatment, we anticipated that patients with many PALN would have less LR relapses than group of patients with smaller number of PALN. We also hypothesized that patients with many PALN might have shorter overall survival and distant metastasis free survival.

In addition to proven benefits, radiation therapy (RT) also has its known side effects. Those need to be over weighted with a benefit of the treatment. Among long known toxicities of RT are skin changes, secondary tumours and lately highly reported cardio-toxic effects.[6-9] In multimodality treatment specific toxicities of each treatment are potentiated, therefore benefit of RT in patients with many PALN should be addressed.

Patients and methods

We reviewed medical records of 129 consecutive breast cancer patients with PALN who were treated at the Institute of Oncology Ljubljana with PMRT between January 2003 and December 2004. All the patients received RT to the thoracic wall and ipsilateral periclavicular region according to clinical guidelines. External beam irradiation was delivered with photons and/or electrons with a total dose of 48 Gy–56 Gy in 5 daily fractions per week.

We grouped patients according to the number of PALN in groups with a low and that with a high number of PALN. Our clinical experiences suggest that the lower limit for N3 class in TNM classification is set too low to reliably predict a greater chance of a distant recurrence.[5]

Therefore, we performed the following grouping for local recurrence: Group 1 (1–3 PALN); Group 2 (4–15 PALN); Group 3 (more than 15 PALN). In further analysis we compared only patients with more than 15 (Group 1) to less than 15 PALN (Group 2).

All patients received adjuvant systemic therapy according to the clinical guidelines. At that time treatment with trastuzumab has not been a part of standard adjuvant treatment yet. However, HER2 was determined in all patients. Additional variables were age, tumour histology, tumour grade, tumour size, estrogen receptor (ER) status, progesterone receptor status (PR), lympho-vascular invasion, peri-neural invasion, adjuvant hormonal therapy, adjuvant chemotherapy and intrinsic subtypes. Breast cancer subtypes were defined based on 2015 St. Gallen Consensus Conference classification but without information on Ki-67, as routine testing was not available at that time, as follows: Luminal A (ER positive, HER2 negative, PR > 20% positive), luminal B (ER positive, HER2 positive or negative, PR < 20%), HER2-overexpression (HER2 positive, ER negative, PR negative), triple negative breast cancer (TNBC) or basal like (ER negative, PR negative, HER2 negative).[10]

Data was analysed with respect to overall survival (OS), progression free survival (PFS) distant metastasis free survival (DMFS) and locoregional free survival (LRFS).
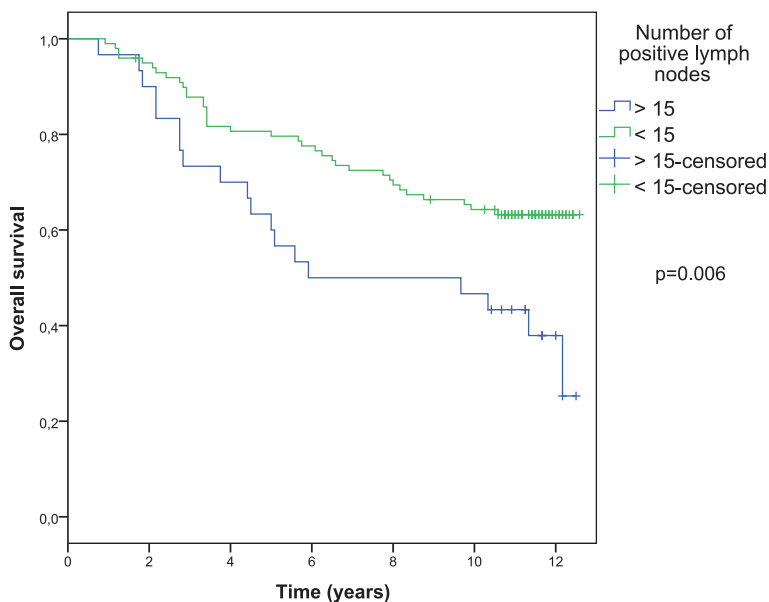

FIGURE 1. Overall survival according to number of positive axillary lymph nodes.

Statistical analysis and ethical consideration

OS time was calculated from the date of surgery to the date of death or last follow up. PFS time was calculated from the date of surgery to the time of first progression, either locoregional or distant. LRFS was calculated from the date of surgery to the first LR progression and DMFS to the event of first distant metastasis. Kaplan-Meier methods were used to estimate survival curves. Log rank tests were used for univariate analysis to compare the survival contribution. In multivariate Cox regression only variables with $p < 0.2$ from univariate analysis were included. Data was calculated using SPSS v.20 statistical package. All p values reported were based on the two-sided hypothesis and were considered statistical significant for values < 0.05 and 95% confidence interval (CI) of hazard ratio (HR) that did not include 1.

The study has been approved by Institutional Review Board Committee and Ethics Committee and conducted in accordance with the declaration of Helsinki.
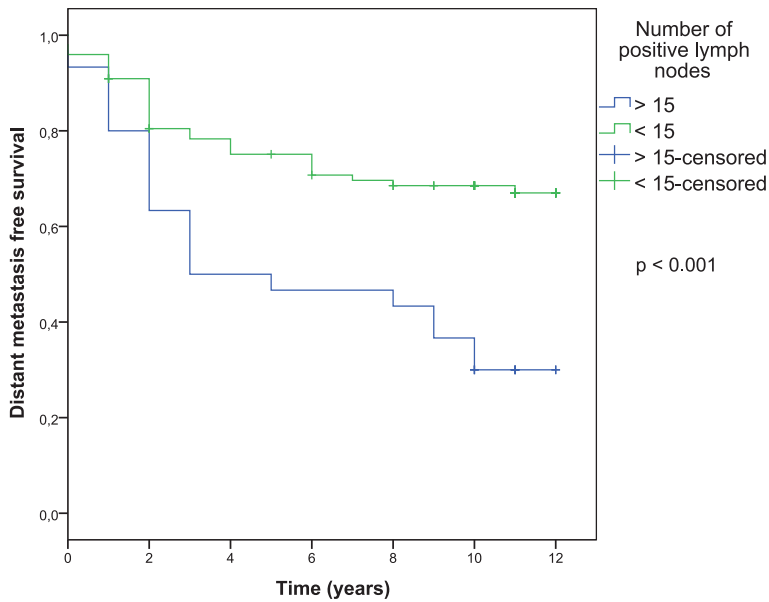
Results

The median follow-up time was 11.5 years. Patients' characteristics are presented in Table 1. Median age of breast cancer patients was 56 years and majority had invasive ductal carcinoma (80.7%). Beside to mastectomy, patients also had lymph node dissection. Mean number of examined lymph nodes was 19 (SD 8.1). With respect to breast cancer subtype Luminal A was predominant (47.3%), followed by luminal B (31%), HER2 group (12.4%) and TNBC (9.3%). HER2 positive patients were present in 28.7%. All ER positive patients (77.5%) received hormonal therapy (HT). Adjuvant chemotherapy was delivered to 83% of patients.
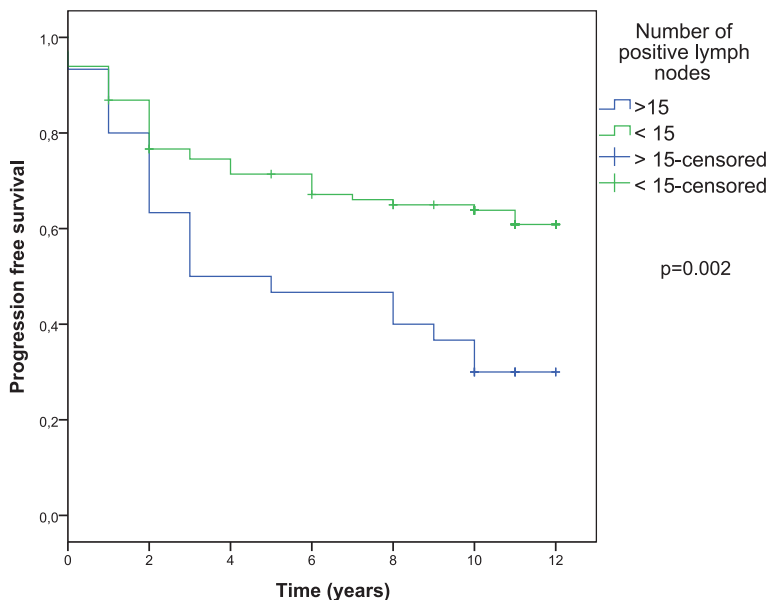
Kaplan-Meier survival analysis for lymph node groups with > 15 PALN (30 patients) *vs.* < 15 PALN (99 patients) showed significant difference in median OS survival. For the group with > 15 PALN was 5.9 years (SD 3.6), while for the group with < 15 PALN median time was not reached at the time of analysis (p = 0.006) as shown on Figure 1. The number of LR recurrences occurred as follows: 5 (17%) in group with 1–3 PALN, 4 (5.7%) in group 4–15 PALN and the lowest number was in the group with the highest number of PALN–Group 3; only 1 recurrence (3.3%). Further analysis was not performed due to low number of events. Distant me-

TABLE 1. Patients' characteristics

Patients characteristics	No patients	%
	129	100
Age (years)		
Median	56	
Q1-Q3	48-64	
Histology		
IDC	104	80.7
ILC	25	19.3
Tumour size		
T1	29	9.3
T2	79	45.7
T3	21	45.0
Histological grade		
G1	12	9.3
G2	59	45.7
G3	58	45.0
Lymphovascular invasion		
Yes	54	41.9
No	64	49.6
N/A	11	8.5
Perineural invasion		
Yes	20	15.5
No	83	64.3
N/A	26	20.2
No. of positive axillary lymph nodes (PALN)		
1-3	29	22.5
4-15	70	54.3
>15	30	23.2
No. of PALN according to N category		
N1	29	22.5
N2	47	36.5
N3	53	41.0
Estrogen receptor		
Positive	100	77.5
Negative	29	22.5
Progesteron receptor		
Positive	85	65.9
Negative	44	34.1
HER–2 overexpression		
Positive	37	28.7
Negative	92	71.3
Adjuvant hormone therapy		
Yes	101	78.3
No	28	21.7
Adjuvant chemotherapy		
Yes	108	83.7
No	21	16.3
Adjuvant chemotherapy with anthracyclines		
Yes	99	76.7
No	30	23.2
Breast cancer subtype		
Luminal A	61	47.3
Luminal B	40	31.0
Her2-overexpression	16	12.4
Triple negative breast cancer (TNBC)	12	9.3

FIGURE 2. Distant metastasis free survival according to number of positive axillary lymph nodes.

FIGURE 3. Progression free survival according to number of positive axillary lymph nodes.

tastases developed in 52 patients with no statistical difference between groups with more than 15 *vs.* less than 15 PALN (p = 0.48). Patients with the high number of PALN had significantly shorter DMFS (median 3.0 years, CI 0.1–8.3; for the group with < 15 PALN not reached; p < 0.001) and PFS (median 3.0 years, CI 0.1–7.6; for the group with < 15 PALN not reached; p < 0.002) (Figure 2, 3).

Multivariate analysis showed two variables with significant influence on OS, adjuvant chemotherapy with anthracyclines (p = 0.005, HR = 0.39, CI 0.20–0.75) and group of patients with more than 15 positive PALN (p = 0.002, HR = 2.52, CI 1.38–4.57). For PFS only more than 15 PALN showed significant influence (p = 0.003, HR = 2.24). None of the investigated factors independently influenced LRF. Adjuvant chemotherapy with anthracyclines (HR = 0.51) and more than 15 PALN (HR 3.05) were also statistically significant for DMFS. We found no significant influence of the breast cancer subtypes on any of the categories analysed.

Discussion

Patients with more than 15 PALN had shorter PFS, OS and DMFS. On the other hand, treatment with anthracyclines showed increased DMFS and OS. In our analysis only one patient experienced LR in the group with more than 15 PALN.

Published data provides evidence that the most significant prognostic factor for OS in patients with early-stage breast cancer is the presence or absence of axillary lymph node involvement. Furthermore, there is a direct relationship between the number of involved axillary nodes and the risk for distant recurrence.[11,12] More than three decades ago Fisher *et al*. reported that the 5-year OS for patients with node-negative disease was 82.8% compared with 73% for 1–3 positive nodes, 45.7% for 4–12 positive nodes, and 28.4% for ≥13 positive nodes.[13] Nowadays we use more potential systemic therapy and there are substantial improvements in OS of patients with clinically localized breast cancer.[14] But in spite of better systemic treatment, the number of PALN remains a negative prognostic factor for breast cancer patients.

The impact of local therapy on survival of patients with breast cancer has been debated for decades. In breast cancer, three theories of cancer spread in breast cancer exist.[15] More than hundred years ago dr. Wiliam Halsted believed that breast cancer begins as a strictly local disease and that tumour cells only spread haematogenously to other organs at a later stage.[16] Unfortunately, only 12% of patients treated with radical mastectomy, survived 10 years. The poor outcome with the Halstedian approach, as well as the observation that 20%–30% of node-negative patients ultimately develop metastatic disease, led to the »systemic view« theory, proposed by dr. Bernard Fisher.[17,18] He believed that breast cancer is systemic disease and if distant

metastases were destined to develop, such metastases already exist at the time of diagnosis of the breast cancer.

Neither Halstedian nor the systemic view could have explained the course of the disease for all breast cancer.[15] A third hypothesis, the "spectrum" theory, synthesized aspects of both opposing approaches. As Punglia *et al.* wrote in their article, »this theory holds that for many breast cancers there is a time when tumor cells have not metastasized to distant sites but that it is generally not known whether this time has passed at the point of diagnosis for any patient«. They also wrote that this theory acknowledges that the greater the likelihood that systemic spread has occurred at the time of diagnosis in a patient, the lower the likelihood that local therapy will influence the patient's survival.[15] The results of our analysis are in accordance with their theory showing that patients with higher number of PALN have low number of LR recurrences and greater likelihood for shorter OS.[11,12,13] With regards to the spectrum theory and explanation of Punglia *et al.*, it seems that in the subgroup of patients with many PALN local treatment has a minor impact.

Punglia *et al.* also pointed out, that contribution of improved LR control to survival depends on the effectiveness of systemic treatment.[15] Later on, Poortmans added to this factor also the component of metastatic risk of primary tumour and he concluded that with combining both components, the contribution of improved LR treatment to the final outcome can be estimated.[19] We agree that metastatic potential of different breast cancer tumours is very heterogenic, as is disease itself. It is well known that different breast cancer subtypes have different OS and in our opinion this is the component that really needs to be explored.[20] However, in our analysis we didn't show any significant difference in breast cancer subgroups regarding PALN and OS, probably due to small number of patients in each subgroup.

Based on our analysis, it seems that our results fit best to the spectrum theory. We grouped patients according to the number of PALN in groups with a low and that with a high number of PALN. Interestingly, Fisher in his article grouped patients very similar as we did.[13] It seems that if the number of PALN is very high, the chance of haematogenic relapse at distant sites is higher than the chance of lymphogenic local relapse and the time to evident haematogenic distant metastases is shorter than the time to local lymphogenic relapse which is in line with the theory of Punglia and collegues.[15]

Finally, it is also in concordance with the results of our multivariate analysis, showing that adjuvant chemotherapy with antracyclines and more than 15 PALN predict for shorter DMFS.

Our study was limited with a small number of patients. According to clinical guidelines, all patients with a high number of PALN are treated with PMRT; therefore, it was not possible to compare studied patients with a cohort treated without RT. For the future, trials comparing our results with a cohort of patients treated also with adjuvant trastuzumab would be interesting. Trastuzumab, with proven important impact on overall survival, became a part of adjuvant treatment in 2005, soon after our cohort was treated.[21] We assume that it might further diminish a need for PMRT in HER2 positive breast cancer patients due to its very potent systemic effectiveness.

Conclusions

Patients with more than 15 PALN have shorter OS, PFS and DMFS compared to patients with less than 15 PALN though they receive the same LR therapy. They also have the smallest number of LR recurrences. Our results suggest that systemic treatment with anthracyclines is important component of adjuvant treatment for patients with higher number of PALN and radiation treatment might be questionable in this group, but studies with larger number of patients would be needed to answer this question.

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