POSTOPERATIVE ADJUVANT RADIATION THERAPY IN BREAST CANCER PATIENTS WITH 10 OR MORE POSITIVE AXILLARY LYMPH NODES.

Nan SUNTORNPONG, M.D.

ABSTRACT

This study was performed to analyse the outcome of postoperative adjuvant radiation therapy (RT) for breast cancer patients with10 or more involved axillary nodes receiving adjuvant chemotherapy. Seventy - five patients treated at Division of Radiation Oncology, Department of Radiology, Siriraj Faculty of Medicine from January 1978 to March 1995 were retrospectively reviewed with the median follow-up period 25 months. The overall survival and disease-free survival were 54.5 % and 25.9% respectively. Adjuvant RT significantly decreased locoregional disease-free survival but not improved distant disease-free survival or overall survival compared to those of systemic therapy alone. The role of RT on distant control in this high risk group of patients need more studies to be confirmed.

INTRODUCTION

The most important single factor in determining prognosis of breast cancer is the presence or absence of axillary lymph node involvement. The disease-free survival and overall survival rates of patients are closely related to total number of involved nodes.[1]

Four or more positive axillary nodes is one of the high risk features in breast cancer indicating need for radiation therapy (RT) in addition to chemotherapy.[2] This retrospective study was performed to assess the impact of adjuvant locoregional RT on the management of breast cancer patients with very high number of positive axillary nodes metastases (ie. 10 or more) which is a high risk factor for both locoregional and distant failure.

MATERIALS & METHODS

One-hundred and seven breast cancer patients with 10 or more positive axillary nodes metastases treated at Division of Radiation Oncology, Department of Radiology, Siriraj Faculty of Medicine between January 1978 and March 1985 were retrospectively reviewed by charts and letters. Thirty-two patients were excluded from the analysis due to incomplete or no adjuvant systemic therapy in 30 and immediately lost after RT in 2.

Of 75 evaluable patients, the median age was 50 years (range 26-78) . The pathology in all were invasive ductal carcinoma except scirrhous carcinoma in 1 and invasive apocrine gland in 1. The 1988 AJCC staging system was used to classify in all cases. The patient characteristics divided into 2 groups according to type of postoperative adjuvant therapy were given in Table1

Division of Radiation Oncology, Department of Radiology, Siriraj Faculty of Medicine, Mahidol University, Bangkok 10700, Thailand.

Table 1. Patient characteristics

Variables	Systemic therapy alone No. of patients (%)	Systemic &radiation therapy No. of patients (%)
Total no. of patients	22	53
Age *<=40	11(21)	9(41)
>40	42(79)	13(39)
Stage+ II	15(31)	9(38)
III, IV #	34(69)	15(62)
No. of involved nodes <=20	38(72)	13(59)
>20	15(28)	9(41)

* Two patients had simutaneous bilateral breast cancer (stage IIIB and IIB, IIIA and IIB)
+ unknown stage in 5 patients
# Stage IV from metastases to supraclavicular node at diagnosis

All patients underwent modified radical mastectomy with neoadjuvant chemotherapy given before surgery in 3 cases (2 stage IIIB and 1 stage IV). The median number of involved axillary nodes in this study was 13 (range 10 to 44).

All patients received adjuvant systemic therapy after surgery with chemotherapy alone in 59, hormonal therapy (Tamoxifen) alone in 10 and combined chemotherapy and hormonal therapy in 6 (Tamoxifen in 5, irradiation castration in 1).

The chemotherapy regimens consisted of CMF (Cyclophosphamide 100mg/m^2 PO day 1-14 ,Methotrexate 40mg/m^2 IV day1 and 8, 5 Fluorouracil 600 mg/m^2 IV day 1 and 8 ,repeated on a 28-day cycle as described by Bonadonna et al [3]) in 52 patients and CAF (C and F as above, Adriamycin 50 mg/m^2 IV day 1 and 8) in 7 patients.

Adjuvant postoperative external radiation therapy (RT) following systemic therapy was delivered to 53 (71%) patients.The treatment volume consisted of chest wall and regional lymph nodes (axillary,internal mammary chain (IMC), supraclavicular node) in all except 2 patients with T2N1 and T0N2 disease who received only RT to regional lymph nodes. The total dose to each portal was 50 Gy except one patient received boost dose to primary tumor bed to total 66 Gy. All fields were given by Co60 machine with 2 Gy a fraction, 5 fraction a week except IMC in one patient treated by electron. Twenty-two patients in this study received incomplete or no adjuvant RT at all.

The median follow-up period in this study was 25 months (range 3-115 months). The overall survival (OS), locoregional disease-free survival (LRDFS)and distant disease-free survival (DDFS) were estimated by Kaplan-Meier method. Log-rank test were used to determine the variables that univariately predictive of these outcome.

RESULT

The patient characteristics in this study showed that there were higher proportion of other poor prognostic factors (young age <= 40 year, more than 20 positive axillary nodes) in systemic therapy alone group than that in systemic and RT group.

Pattern of failure

Of the 75 patients, 48 (64%) experienced treatment failure by the time of analysis.. The predominant sites were distant-only (69%) while locoregional-only comprised only 23 % of all failures. The pattern of first failures was shown in Table 2

Table 2. Pattern of first failure

Site of first failure	Systemic therapy No. of patient	Systemic & RT No. of patient
Total no. of patients	22	53
Locoregional only	7	4
Distant only	10	23
Locoregional & distant	4	-

Twenty-nine (78%) of all first distant failure occured within 2 years after initial treatment while 13 (87%) of all first locoregional failure occured within the same period. The median time to first distant and locoregional failure were 20 months (range 2 to 105) and 14 months (range 3-77) respectively.

Three patients in this study developed contralateral breast cancer during follow-up at 8,12 and 24 months after initial treatment. The pathology were similar to those of previous cancer in all.

Survival

For all 75 patients, 28 (37%) have died by the time of analysis.The causes of death were unknown in 3 and from distant metastases to lung in 15, liver in 7 and brain in 3. patients.

The 5-year OS for all patients in this study was 54.5 %. The 5- year DFS was 25.9% (Fig. 1)

Postoperative RT significantly reduced locoregional failure. At 5 years, LRDFS in systemic therapy alone group and combined systemic-RT group were 90.5% and 38.6% respectively ($P = < 0.001$). (Fig.2)

The 5-year DDFS and OS were not different between 2 groups. The DDFS in systemic therapy alone group and combined systemic-RT group were 15.1% and 42.3%. respectively ($P= 0.09$) (Fig .3). The OS were 61.2% and 51.5% respectively ($P= 0.46$) (Fig.4)

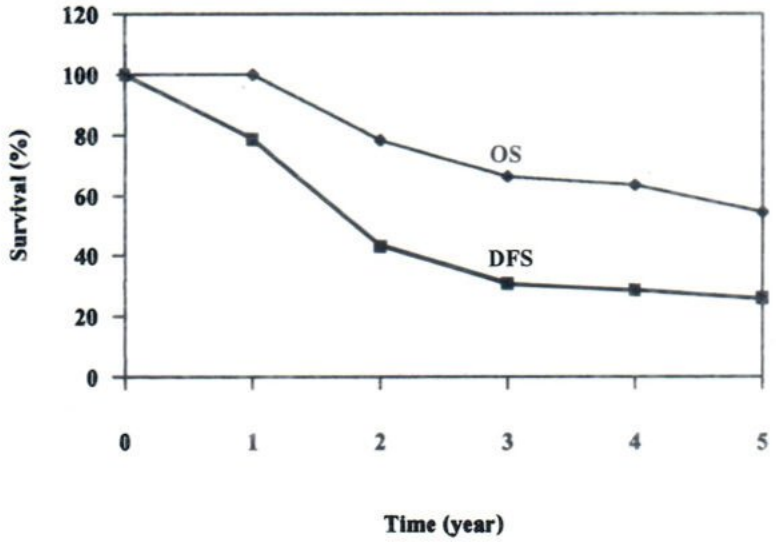

Fig.1 Overall survival and disease-free survival of all patients

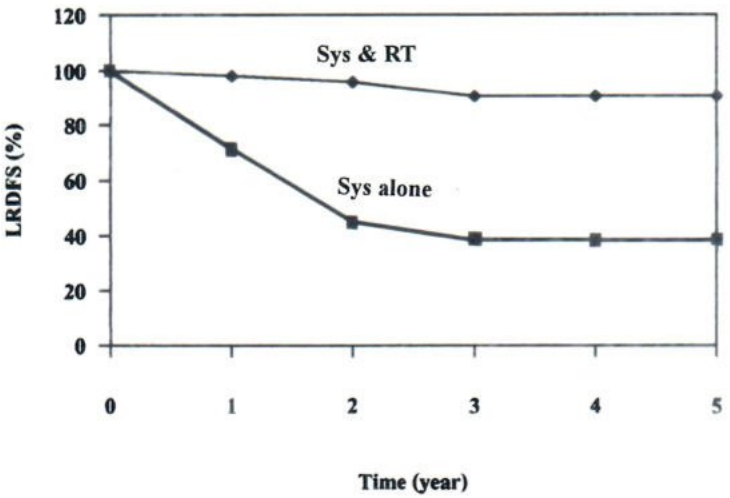

Fig.2 Locoregional disease-free survival of Sys & RT VS Sys alone group

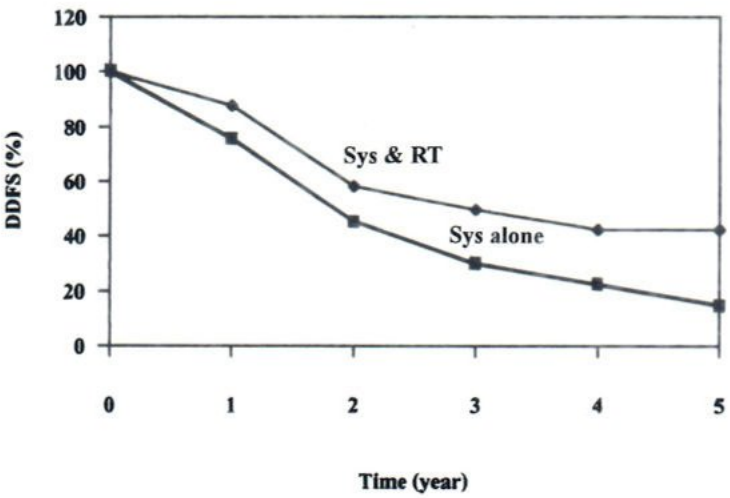

Fig.3 Distant disease-free survival of Sys & RT VS Sys alone group

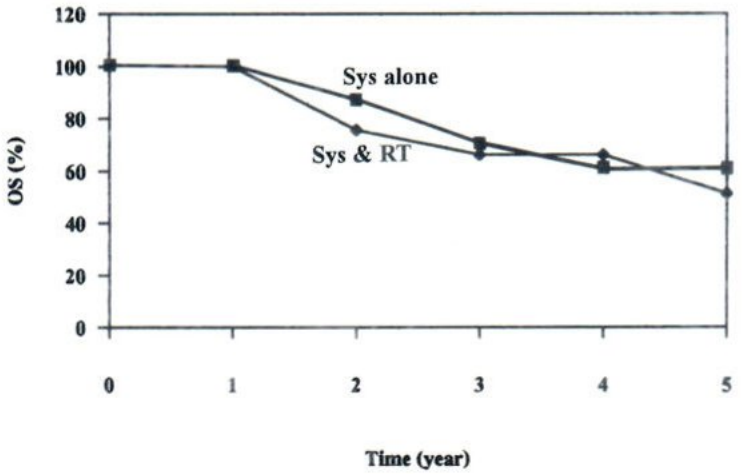

Fig.4 Overall survival of Sys & RT VS Sys alone group

DISCUSSION

The most consistent prognostic factor for survival and recurrence after primary surgery for operable breast cancer is number of involved axillary nodes. The historical data from randomised trials in patients with 10 or more positive nodes receiving standard dose chemotherapy indicated less than 50% 5-year relapse-free survival rates.[4] The 5 –year disease-free survival of the patients given mostly CMF regimen in the present study was 25.9% with 64% of all patients experienced disease failure at least at one site during follow –up period.

The role of RT as an effective modality for locoregional control have been proven by several prospective randomised trials. The 2 most important factors predicting for locoregional recurrence were number of positive nodes and primary tumor size. Locoregional recurrence rates in the patients with 4 or more positive nodes receiving adjuvant CMF regimen without and with RT were 20-64% and 10-22% respectively[5] depending on follow-up time. The LRDFS in this study supported the significant benefit of adjuvant RT.

However, the impact of adjuvant RT on improved distant control and survival from those trials is still controversial. The inconsistent outcome is due to : inadequate number of patients in each study to detect modest benefit, inclusion of low or intermediate risk patients for whom RT would be minimal benefit, lack of adjuvant systemic therapy and nonqualified RT technique resulting in high complication.

Recently, Overgard et al reported improved DFS and OS by postoperative RT in randomised trial of 1708 high risk premenopausal women receiving CMF irrespective of tumor size, number of involved node or grade.[6] Ragaz et al also reported improved systemic DFS by Adjuvant RT and CMF in 318 node positive premenapausal patients. No significant difference in locoregional and systemic DFS were observed between group of patients with 1-3 and 4 or more positive nodes.[7]

Postoperative RT in this study showed trend to prolong DDFS even no statistic significance reached but this caused no effect on OS. Higher number of patients is required. For more confirmative result. RT technique in this study was similar to that used in general at present. Almost all patients in our division received RT to IMC postoperatively but some were treated by electron instead of photon to reduce cardiac dose. No severe or fatal cardiac complication from RT presented in this study except 3 cases with unknown causes of death.

The selected patients with 10 or more positive nodes have been sparsely studied for benefit of RT. Diab et al studied retrospectively in 618 patients of this criteria. At first, they mentioned that all patients with this very high risk can be assumed to have systemic disease at diagnosis so benefit of RT on distant control and survival should be less expected than that in low risk patients. The result in their study showed significant reduced locoregional failure, improved distant control and OS by combined RT and systemic therapy. They suggested that prolonged survival may be due to decreased secondary systemic spread from improved locoregional control.[8]

Gina et al also reported benefit of RT on locoregional failure and DFS in this high risk patients when combined with adjuvant chemotherapy including high dose regimen with autologous reserve.[9]

The standard adjuvant therapy for patients with 10 or more positive nodes at present is still conventional doxorubicin-based chemotherapy. The results of high dose chemotherapy with hematopoietic stem-cell support from 2 recent randomised trials[10, 11] contradicted the promising early results.Therefore, it should not be given in routine clinical practice now. If the benefit of RT on distant control and survival in this group of patients can be proven consistently in the future, its role can be considered as part of the intensive therapy for the patients with very poor prognostic factor.

REFERENCES

1. Nenoto T, Vana J, Bedwan R et al. Management and survival of female breast cancer : results of a national survey by the Americal College of Surgeon. Cancer 1980; 45: 2917-21.
2. Perez CA, Fields JN. Role of radiation therapy for locally advanced and inflammatory carcinoma of the breast. Oncology 1987; 1: 81-90.
3. Bonadonna G, Brusamolino E, Valagussa P et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Eng J Med 1976;294 :405-10.
4. Perez CA, Taylor ME .Breast: Tis, T1 and T2 Tumors. In : Perez CA, Brady LW (eds), Principles & Practice of Oncology, 3rd ed. J.B. Lippincott Co. 1997: 1269-1414.
5. Fowble B. Postmastectomy radiation : then and now. Oncology 1997; 11:213-31.
6. Overgaard M, Hansen PS, Overgaard J et al.Postoperative radiotherapy in high risk premenopausal women with breast cancer who receive adjuvant chemotherapy. N Eng J Med 1997; 337:949-55
7. Ragaz J, Jackson SM, Le N et al. Adjuvant radiaotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Eng J Med 1997;337: 956-62.
8. Diab SG, Hilsenbeck SG, Moor C et al. Radiation therapy and survival in breast cancer patients with 10 or more positive axillary lymph nodes treated with mastectomy. J Clin Oncol 1998;16:1655-60.
9. Jabro G, Wazer D, Erban J et al. The importance of loregional radiotherapy with conventional or high dose chemotherapy in the management of breast cancer with >=10 positive axillary nodes. Proc ASTRO 1997; 39:(abstr.2045)
10. Hortobagyi GN, Bazdar AU, Chaplin R et al. Lack of efficacy of adjuvant high-dose (HD) combination chemotherapy (CT) for high-risk primary breast cancer. (HRPBC: a randomised trial) .Proc ASCO 1998;17: (abstr 417).
11. Rodenhuis S, Richel DJ, Wall E et al. Randomised trial of high-dose chemotherapy and haemopoietic progenitor-cell support in operable breast cancer with extensive axillary lymph-node involvement. Lancet 1998; 352: 515-19