

ORIGINAL ARTICLES

Supraclavicular nodal relapse of breast cancer: Prevalence, palliation, and prognosis

F. L. Ampil¹, M.D.; G. Caldito², Ph.D.; B. D. L. Li³, M.D.; G. V. Burton⁴, M.D.

*Departments of Radiology¹, Biometry², Surgery³, and Medicine⁴
Louisiana State University Health Sciences Center, Shreveport, Louisiana (USA)*

Summary

Purpose: To determine the frequency, palliative effects of radiotherapy (RT) and survival of patients developing supraclavicular nodal relapse (SNR) after definitive surgery for non-disseminated breast cancer (BCa).

Methods: A retrospective study of individuals treated by breast conserving surgery or modified radical mastectomy for Stage I to III BCa at a single institution during a 17-year period (1980-96) was undertaken.

Results: Of the 536 patients studied, 22 (4%) developed SNR. Among the seven symptomatic women, the complete subjective response rate after RT was 71%. Of the 18 evaluable patients with manifest SNRs, tumor regression was complete in 12 (66.6%), partial in one (5.6%), and absent in five (27.8%). The overall median survival was 11.5 months; five patients (23%) survived for at least two years.

Conclusion: Supraclavicular nodal relapse in breast cancer patients occurs infrequently. The application of radiotherapy for palliation of SNR was fully justified by the perceived results even though long-term survival was not often observed.

Key words: Breast cancer; Lymph node; Radiotherapy; Palliation.

Introduction

The occurrence of supraclavicular metastasis in a patient with breast cancer (BCa) is regarded as Stage IV breast cancer with its associated connotation of poor prognosis. Any form of applied treatment for this particular neoplastic stage would have palliation of symptomatic disease as its goal. It was our impression that patients with supraclavicular nodal relapse (SNR) similarly have an adverse outcome.

Reports of radiotherapy (RT) administered for control of locoregional recurrences of BCa are common. Observations conflict regarding the efficacy of employed therapy in controlling the symptoms associated with regional lymphatic recurrences of BCa [1, 2]. Studies examining RT given for palliation of SNR are unfortunately very limited [3, 4].

The objectives of this retrospective study were to establish the frequency of BCa-related SNR, review the results of our radiotherapeutic experience with this special recurrent nodal condition, and determine the survival of this select cohort of patients.

Materials and Methods

Using the hospital's tumor registry data base and reviewing the radiation oncology charts, we searched for cases of SNRs among individuals who underwent definitive surgery for BCa between 1980 and 1996.

Twenty-two women who had been treated for palliation of SNR by RT were identified. The diagnosis of SNR was based on obvious clinical findings and/or histological evidence; two subjects with infraclavicular recurrent disease were included in this identified patient group. One individual underwent breast

irradiation after breast conserving surgery while two other women received locoregional RT following modified radical mastectomy for Stage I or II BCa; the remaining 19 subjects did not receive RT prior to the onset of SNR. Chemotherapy (often consisting of a three-drug combination including cyclophosphamide, methotrexate, 5-fluorouracil, or adriamycin) was administered to five women before and/or after initial surgery usually because of proven metastatic tumor in four or more axillary nodes or Stage 3 BCa.

Patients receiving RT during the period of study were treated by several radiation oncologists with differing treatment philosophies and techniques, explaining the varied applied total doses and dose fractionation. The cobalt-60 teletherapy unit was used to administer daily irradiation before 1981; from 1981 onwards, a six million volt linear accelerator was employed. Irradiation encompassed the SNR lesion plus other local or regional relapse sites. Fractionated total doses ranged from 10 Gy/3 fractions to 50 Gy/25 fractions; the lower dose was prescribed in patients who had received prior locoregional RT.

Responses to treatment were usually determined at the time of completion of RT or several months later. Complete response was defined as the absence of symptoms or tumor mass; partial response signified less intense symptoms or $\geq 50\%$ reduction in size of SNR, and no response meant the absence of symptom improvement or $< 50\%$ regression of the manifested neoplasm.

Survival was estimated from the time of diagnosis of SNR until death or date of last contact with the patient. The 95% confidence interval was determined for observed proportions, and the standard error of the mean for average values.

Results

In the 17-year period of this study, 536 individuals underwent definitive surgery for BCa, and of these, 22 (4%) developed SNR. The average interval between initial surgery and detection of SNR was 39 ± 7.8 months (range 3 to 164 months).

The mean patient age was 55 ± 1.9 years (range 39 to 69 years). SNR appeared alone (11 patients) or with simultaneous recurrence in the anterior chest wall (6 patients), axillary region (3 patients), internal mammary region (1 patient), or with relapse in the anterior chest wall and axilla (1 patient).

Because of the inherent constraints of a retrospective study, not all of the desired information was available from the medical records. With respect to the site of BCa, the tumor was located in the lateral quadrant of the breast (7 patients), central quadrant (3 patients), or medial quadrant (2 patients); the BCa site was not recorded in ten patients. Moreover, the size of SNR was less than 2 cm in three patients, between 2 cm to 4.9 cm in six patients, 5 cm or larger in three patients, described as "mass/node/induration" in six patients, and not characterized in four women.

Of the 21 evaluable women, 14 (66.6%) were not symptomatic from their SNRs. Table 1 summarizes the observed manifestations of SNR – mostly consisting of pain and palpable, recurrent disease in the supraclavicular fossa – and beneficial effects of palliative RT. We found a positive correlation between applied total RT dose and objective response to therapy. Among the 18 evaluable patients, the perceived complete response rates were $44 \pm 35\%$ (4/9) and $89 \pm 22\%$ (8/9) with < 40 Gy and ≥ 40 Gy dose, respectively ($p < 0.05$); the corresponding number of patients with described SNR sizes of 3 cm or larger were five women and three women.

The overall survival rate at one year was $50 \pm 22\%$ (11/22) and at two years $23 \pm 18\%$ (5/22).

The overall median survival was 11.5 months. Because not all recurrences are followed immediately by generalized neoplastic disease dissemination and death, we attempted to identify factors which might indicate the need for a more or less aggressive management plan in patients with BCa-related SNR. With regard to factors examined for prognostic importance, none was found to be an independent predictor of an adverse outcome (Table 2); admittedly, the number of evaluated cases was small and sometimes skewed.

Table 1. — *Results of treatment.*

Symptoms and Signs ^a	Pretreatment	Post-treatment ^b		
		CR	PR	NR
Pain	(6)*	(4)	—	(2)
Numbness	(1)	(1)	—	—
Tumor/Mass**	(18)	(12)	(1)	(5)

* () refers to the number of evaluable patients; **Includes an indurated lesion observed in one patient; ^aNeck, shoulder, or arm pain, numbness of the upper limb; ^bCR = Complete response; PR = Partial response; NR = No response.

Discussion

The supraclavicular lymph nodes are in direct extension of the lymphatic drainage of the apex of the axilla [3]. The observed rate of supraclavicular recurrence has been closely correlated with axillary nodal status. One study reports that of 716 patients treated by radical mastectomy, 4% of the women with negative axillary nodes and 13% with positive axillary histology developed ipsilateral SNR [5].

Table 2. — *Analysis of prognostic factors.*

Variable	Median survival (mos)	p value
Age		
< 60 yrs (14)*	7 [3-20]**	0.24
≥ 60 yrs (8)	17 [2]	
Number of positive axillary nodes		
0 to 3 (12)	18.5 [11]	0.08
≥ 4 (10)	5 [3-12]	
Distant metastasis***		
Absent (15)	12 [8-22]	0.53
Present (3)	2 [1-17]	
Onset of supraclavicular nodal relapse****		
≤ 2 yrs (10)	5 [2-20]	0.28
> 2 yrs (12)	14.5 [6-22]	
Objective response to radiotherapy		
Complete (12)	14.5 [5-22]	0.61
Incomplete or none (6)	13 [8]	

* () refers to the number of evaluable patients; ** [] refers to the 95% confidence interval; ***Distant metastasis present at the time of supraclavicular nodal relapse; ****Supraclavicular nodal relapse relative to initial surgery for breast cancer.

With respect to the neoplastic site in the breast, inner quadrant primary growths are apparently less likely to produce supraclavicular recurrent disease; the inner quadrant was the primary site in only 11% of the 174 SNR cases from the Christie Hospital [3] (an observation akin to our finding from the limited number of evaluated patients).

In the present study, the incidence of SNR during a 17-year period in which non-conserving or conserving breast surgery was performed for BCa was 4%. The reported SNR incidences following conservative surgery [1, 2, 6] range from less than 1% to 5% and, after mastectomy 12% to 27% (as summarized in the report of Jackson [3]).

In general, SNR does not immediately threaten a patient's life but it poses a considerable problem. First, the morbid effects of uncontrolled regional relapse can greatly influence the quality of life as documented in approximately 32% to 62% of cases from other institutional experiences [1, 2, 7]; our observation of close to a third of the studied women (7/22) being symptomatic is in agreement with the preceding consideration. In the report of McKinna *et al.* [1], lymphedema of the arm was the foremost severe symptom of SNR, followed by pain in the hand or arm and sensory or motor changes in the upper limb respectively. In contrast, pain was the main complaint in the very few symptomatic women in the present series. Second, the development of SNR in BCa is a harbinger of distant metastases. In one study only seven of 81 patients who developed supraclavicular metastases as the first and only clinical evidence of recurrence did not subsequently suffer relapse or metastases elsewhere [3].

RT is widely recognized as a palliative method of treatment in symptomatic patients with incurable, Stage IV BCa. Recently, several authors [1, 2] have reported conflicting observations concerning the effectiveness of palliative therapy of regional lymphatic relapses; McKinna and associates [1] found that only 5% (out of the 41 women who experienced morbidity from regional recur-

Table 3. — Radiotherapy (RT) for supraclavicular nodal relapse (SNR) of breast cancer: review of the literature.

Author	No. patients	Subjective*	Response Objective*	SNR control	Comment
Jackson [3]	112	—	CR (67) 60% PR (21) 19% IR (24) 21%	60%	'Radical' treatment (3 weeks) achieved greater palliation than shorter therapy (single treatment or 2 weeks). No complication observed after RT.
Madoc-Jones <i>et al.</i> [4]	23	—	CR (18) 78%	78%	Higher (≥ 40 Gy) RT doses resulted in more complete objective responses than lower doses (< 40 Gy)
This series	22	CR (5) ^a 71% NR (2) 29%	CR (12) 66.6% PR (1) 5.6% NR (5) 27.8%	—	

*CR (Complete response meant complete disappearance of symptoms or tumor); PR (Partial response meant less intense symptoms/ $\geq 50\%$ regression of tumor/regression or disappearance of tumor with recurrence, or no alteration but remaining symptom free); IR/NR (Inadequate/No response meant the absence of symptom improvement/ $< 50\%$ regression of tumor/regression and later growth causing symptoms and inconvenience); * () Refers to the number of evaluable patients.

rences) gained complete and permanent control of all symptoms prior to death or last follow-up after the employment of several therapeutic modalities (e.g., palliative surgery, radiotherapy, systemic treatment). On the other hand, Recht *et al.* [2] concluded (after analyzing the likelihood of regional nodal failure in 1,624 patients with Stage I or II BCa managed by conservative surgery and RT) that the symptoms of regional nodal relapse can be controlled with treatment in most but not all patients; significant pain and other distressing symptoms at last follow-up or death were present in 32% of the 38 individuals with regional nodal failures.

We know of only a few studies that have been published reporting the usefulness of RT applied for palliation of BCa-related SNRs [3, 4]. With respect to the results achieved by RT, the 66.6% complete disappearance of tumor in this series is similar to those reported by other investigators [3, 4] (Table 3). The majority of the treated patients seemingly attain durable objective responses. The Groupe Europeen de Curietherapie [6] noted that regional control of SNR was realized in 69% (18/26) of the women through the application of "salvage treatment". Complete relief of pain was achieved in several of our symptomatic patients. Our data was retrospective; no information was available to assess the post-RT complications. However, the likelihood of brachial neuropathy as a consequence of supraclavicular RT is small, about less than 1% to 2% [6, 8]. This particular treatment-related neurological condition was seen most often with administered doses ranging from 55 Gy to 70 Gy; the high doses were ascribed to faulty treatment technique (such as overlapping treatment fields) rather than the delivery of excessive doses [6].

With regard to prognosis, the majority of women who experience SNR will die from their disease (as was found to be true in the present series). In the Christie Hospital study [3], 80% of the SNR patients were dead within three years of appearance of recurrent disease; when local relapses simultaneously occurred with SNR, the outlook was even worse — 80% of the women were dead within two years. Likewise, Fowble and colleagues [9] analyzed 31 individuals with regional failures after breast conserving therapy, and found that "supraclavicular recurrence was associated with a poor prognosis; none of our patients is alive NED." Multivariate analysis of the results

of our study did not reveal the most influential parameter affecting the prognosis of patients with SNR of BCa.

In conclusion, although SNR of BCa does not often occur, the impact of the morbidity of SNR may seriously compromise the patient's dignity and ability to interact with family and friends during their final months. Our standard of palliative care using RT (in light of our observations) shall continue to consist of offering a more prolonged course of therapy (40 Gy to 50 Gy/4 to 5 weeks) to those women in whom the anticipated survival is not less than 6 months, and fewer treatments (30 Gy/2 weeks) to those debilitated yet symptomatic individuals with widespread metastatic disease.

References

- [1] McKinna F., Gothard L., Ashley S., Ebbs S.R., Yarnold J.R.: "Lymphatic relapse in women with early breast cancer: a difficult management problem". *Eur. J. Cancer*, 1999, 35, 1065.
- [2] Recht A., Pierce S.M., Abner A., Vicini F., Osteen R.T., Love S.M., Silver B., Harris J.R.: "Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma". *J. Clin. Oncol.*, 1991, 9, 988.
- [3] Jackson S.M.: "Carcinoma of the breast — the significance of supraclavicular lymph node metastases". *Clin. Radiol.*, 1966, 17, 107.
- [4] Madoc-Jones H., Nelson A.J., Montague E.D.: "Evaluation of the effectiveness of radiotherapy in the management of early nodal recurrences from adenocarcinoma of the breast". *Breast, Diseases of the Breast*, 1976, 2, 31.
- [5] Veronesi U., Valagussa P.: "Inefficacy of internal mammary node dissection in breast cancer surgery". In: Yarnold J.R.: *Radiother. Oncol.*, 1981, 2, 79.
- [6] Pierquin B., Mazon J.J., Glaubiger D.: "Conservative treatment of breast cancer in Europe: Report of the Groupe Europeen de Curietherapie". *Radiother. Oncol.*, 1986, 6, 187.
- [7] Bedwinek J.M., Fineberg B., Lee J., Ocwieja M.: "Analysis of failures following local treatment of isolated local-regional recurrence of breast cancer". *Int. J. Radiat. Oncol. Biol. Phys.*, 1981, 7, 581.
- [8] Mendenhall N.P., Devine J.W., Mendenhall W.M., Bland K.I., Million R.R., Copeland E.M. III.: "Isolated local-regional recurrence following mastectomy for adenocarcinoma of the breast treated with radiation therapy alone or combined with surgery and/or chemotherapy". *Radiother. Oncol.*, 1988, 12, 177.
- [9] Fowble B., Solin L.J., Schultz D.J., Goodman R.L.: "Frequency, sites of relapse, and regional node failures following conservative surgery and radiation for early breast cancer". *Int. J. Radiat. Oncol. Biol. Phys.*, 1989, 17, 703.

Address reprint requests to:

F. L. AMPIL, M.D.

Division of Therapeutic Radiology

Louisiana State University Health Sciences Center

1501 Kings Highway

Shreveport, Louisiana 71130 (USA)