

Correlation between the proportion of breast volume involved by locally advanced tumors and invasion of the skin and posterior structures

Parastoo B Dahi, Komal P Dhiran, Constantine A Axiotis, Jeremy Weedon, Mahmoud El-Tamer, Gurinder Sidhu, Albert S Braverman

Parastoo B Dahi, Gurinder Sidhu, Albert S Braverman, Division of Hematology/Oncology, Department of Medicine, Downstate Medical College of the State University of NY, Brooklyn, NY 11203, United States

Komal P Dhiran, Constantine A Axiotis, Division of Surgical Pathology, Kings County Hospital Center, Department of Pathology, Downstate Medical College of the State University of NY, Brooklyn, NY 11203, United States

Jeremy Weedon, Scientific Computing Center, Downstate Medical College of the State University of NY, Brooklyn, NY 11203, United States

Mahmoud El-Tamer, Breast Surgery Service, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, United States

Author contributions: Dahi PB, El-Tamer M and Braverman AS designed the project and wrote the manuscript; Dahi PB, El-Tamer M, Sidhu G and Braverman AS conducted the research; Dhiran KP and Axiotis CA provided pathological expertise; Dahi PB, Dhiran KP, Axiotis CA, Weedon J, El-Tamer M, Sidhu G and Braverman AS approved the manuscript.

Correspondence to: Albert S Braverman, MD, Division of Hematology/Oncology, Department of Medicine, Downstate Medical College of the State University of NY, Box 55, DMC SUNY, 450 Clarkson Ave, Brooklyn, NY 11203, United States. abraverman@downstate.edu

Telephone: +1-718-2701500 Fax: +1-718-2701544

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Abstract

AIM: To evaluate any differences between the percentages of involved breast volume, pathologic attributes, and tumor marker expression of T3 and T4a-c tumors in locally advanced breast cancers (BC).

METHODS: All patients with T3N > 0 and T4a-c BC without evidence of distant metastasis (M0), presenting to the Breast Clinic from 1980 to 2010, were examined

to determine whether their BC's involved $\geq 50\%$ of their breast volumes, defined by gross replacement of at least one hemisphere. Core needle biopsy or post-mastectomy specimens from tumors involving a known percent of breast volume were evaluated for: (1) pathological grades and lympho-vascular invasion (LVI); (2) hormone receptor (ER/PR) expression > 0; and (3) epidermoid growth factor 2 (her2) over-expression (3+) by immune-histochemical staining or fluorescent *in situ* hybridization.

RESULTS: The data base included 98 patients with T3N > 0 M0 and 120 with T4a-c, any N disease, M0 disease. T3 tumor masses involved 50% or more of the breast in 23/98 (24%), and T4a-c tumors 65/120 (54%) ($P < 0.001$). Only 1% of T3 tumors and 23% of T4a-c tumors presented with total breast replacement. There were no significant differences between the pathological attributes and marker expression of the T3 and T4a-c tumors.

CONCLUSION: These data suggest that erosion of the overlying skin or underlying chest wall by some BC may be due to neglect and delay, rather than inherent biological aggressiveness.

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Key words: Breast cancer; Locally advanced breast cancer; Breast cancer size

Peer reviewer: Lu-Zhe Sun, PhD, Professor, Dielmann Endowed Chair in Oncology, Department of Cellular and Structural Biology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr., MC7762, San Antonio, TX 78229, United States

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INTRODUCTION

Locally advanced (stage III) breast cancer (BC) refers to attributes of primary tumors and/or draining nodes which imply the probability of early local and distant relapse. The relevant attributes of the primary tumors are: (1) At least one diameter > 5 cm with associated local nodal involvement (Stage IIIA; T3N1); (2) Invasion of the chest wall (T4a), skin (T4b) or both (T4c) (stage IIIB); and (3) Diffuse breast inflammation with rapid growth and early nodal involvement (T4d)^[1]. T4d tumors are a distinct clinical and pathological entity^[2]. As such tumors are often diffuse, determination of their size, and amount of breast volume they encompass, is not possible.

T3N1 tumors have a significantly better prognosis than T4a-c tumors^[3]. Some of the latter are node negative. The size of many of these tumors suggests very prolonged growth prior to presentation, but histories obtained from patients are not a reliable method of determining their duration. Local invasion may not always be due to intrinsic aggressiveness. Prolonged growth may ultimately lead to replacement of most of the breast by tumor, leading to proximity to adjacent structures, which may facilitate local invasion.

The purpose of this study is to compare local growth, pathological attributes and marker expression in stage III patients with T3 or T4a-c tumors. The data obtained may help elucidate the mechanism of local invasion by breast tumors.

MATERIALS AND METHODS

Patient information was obtained from the Kings County Hospital Locally Advanced Breast Cancer Database, including all patients who presented with T3N > 0M0 or T4a-c, any N, M0 tumors. All patients were initially staged by radionuclide bone scanning and either chest films or computerized axial tomography; those with detectable distant metastases were excluded. Patients with diffuse inflammation (T4d) were excluded, but those with localized inflammation due to ulceration were considered T4b or c.

The two longest diameters of each tumor were measured and their product determined. The dimensions from mammography were also noted; these usually corresponded with the measurements from physical examination, but where these parameters were discordant those from mammography were employed. The breast was similarly measured. Data from mastectomy specimens was not usable because almost all of the patients had received neoadjuvant systemic therapy. From these data the volumes of the tumor and the breast were estimated, and confirmed by a second physician. The cases in which the

tumor volume was equal to or greater than 50% of the breast volume could be reliably distinguished from those in whom a smaller proportion of the breast volume was involved; in such cases at least one breast hemisphere was fully replaced. In many cases almost the whole breast was involved by tumor.

The tumors, either as sampled by multiple core needle or incisional biopsies at presentation, or from mastectomy specimens before systemic therapy, were also evaluated for pathological grade, lymphovascular invasion (LVI), hormone receptor and epidermoid receptor-2 (her-2) over-expression. The latter determination was based on American Society of Clinical Oncology (ASCO) criteria^[4]. Estrogen (ER) and progesterone receptor (PR) expression was determined by immunohistochemical (IHC) staining of nuclei and cytoplasm. The tumor specimens were considered positive (1+) if >10% of the tumor cells displayed nuclear ER or PR. Triple negative tumors were those whose ER/PR scores were 0, and which were < 3+ for her2.

The presence or absence of LVI was not noted on many pathology reports, and in such cases was determined from review of slides, or preparation of new slides from archival material. Core needle biopsy material was not deemed sufficient for evaluation of LVI, so that only mastectomy specimens were used for this purpose. Neoadjuvant therapy, mostly with anthracycline based chemotherapy, was administered to 98% of the T3N > 0, and 91% of the T4a-c patients, which may have altered tumor morphology in mastectomy specimens. Evaluation was limited to tissue peripheral to carcinoma, and LVI defined as tumor cells within vessels. Minimal residual disease or ductal carcinoma *in situ* (DCIS) only, were present in some specimens. Equivocal morphologic results were obtained in some cases. The latter were IHC stained with monoclonal antibodies directed against podoplanin, expressed by lymphatic endothelium, and platelet endothelial cell adhesion molecule 1, expressed by blood vessel endothelium^[5].

Determinations of relapse incidence and relapse free survival (RFS) were based on those IIIA and IIIB patients who had neoadjuvant or adjuvant therapy, and definitive surgery. All patients were asked to report to clinic for follow-up every 6 mo for one year following primary treatment, and yearly thereafter, or when they noted signs and symptoms of local and distant relapse.

RESULTS

The criteria for inclusion in the study were patients with T3N > 0M0 or T4a-c, any N, M0. Only patients for whom percentage of breast volume replaced by tumor had been recorded at presentation were included, 98 of whom had T3 and 120 T4a-c tumors. For this reason 10 of 108 T3 and 7 of 127 T4 tumors were excluded. We included patients whose tumor grade was not known, and those for whom LVI could not be determined. We also included those without adequate data concerning ER/PR

and her2 expression.

In some cases these data had not been entered in the database. This was the case with many patients who presented before 1993 for ER/PR, and before 1996 for her2. Electronic charts were introduced in 1997, and hard copy charts for patients presenting earlier were unavailable. Some of these data were obtained from archival material, when available.

The youngest and oldest T3N > 0M0 patients were 26 and 77 years of age, and 26 and 92 for the T4a-c, any N, M0 group. The mean ages of the T3N > 0M0 and the T4a-c, any N, M0 groups are presented in table 1. The oldest T3 patient was 77, while 11% of the T4 patients were > 77 (78-92). The T4a-c patients were significantly older than the T3N > 0 patients. *P* value (< 0.001) was calculated by the Wilcoxon test.

Most T3 tumors involved less than 50% of the breast volume, and most T4a-c tumors involved 50% or more (*P* < 0.001); that is, at least one breast hemisphere was replaced by tumor. The whole breast was involved in a fifth of the T4a-c cases, but in only 1% of the T3 tumors (*P* < 0.001) (Table 1).

The two groups were almost identical in pathological grade and hormone receptor expression (Table 1). There were no significant differences between her2 expression, triple negativity and LVI. Of the T3 patients 13 (22%) and of the T4a-c 17 (28%) were triple negative. Of 96 available Hematoxylin-Eosin stained slides, 18 contained only minimal residual disease or DCIS. Of the 78 specimens containing sufficient tumor for evaluation, 31 cases were positive and 21 cases negative for LVI. The morphology of 26 cases was equivocal, and these were IHC stained to determine whether or not LVI was present; 22 were informative. The results are presented in Table 1. *P* values were calculated by Fisher's exact test.

More than 90% of all patients received neoadjuvant systemic therapy, and the rest post-operative treatment. Relapse was defined as either distant metastases, confirmed by imaging, or by regional recurrence, such as supraclavicular nodes or the brachial plexus syndrome; chest wall recurrences were not included. The analysis of the two patient groups for relapse incidence and RFS was limited to those who had definitive surgery: 72/98 (74%) of the stage IIIA and 81/120 (68%) of the IIIB patients. Of the IIIA patients 38%, and of the IIIB patients 51% ultimately relapsed at distant or regional sites. The Kaplan-Meier curves of RFS are presented in Figure 1. Although more of the IIIB patients relapsed the difference was not significant (*P* = 0.097).

DISCUSSION

Prolonged growth resulting from neglect has been assumed to be an explanation for local invasion by BC's, but the unreliability of patient histories has made it difficult to confirm this hypothesis^[6-7]. It is supported by the much higher incidence of locally advanced BC's amongst women in non-industrialized nations, or in those with limited

Table 1 Comparison between the attributes of 98 patients with T3N > 0M0 breast tumors and 120 patients with T4a-c, any N, M0 tumors

BC	T3N>0	%	T4a-c	%	P value
Age Mean	51	-	58	-	< 0.001
≥ 50% BV	23/98	24	65/120	54	< 0.001
WB	1/98	1	21/99	21	< 0.001
Grade III	51/82	62	51/84	61	0.874
ER> 0	36/63	57	38/67	57	1
PR> 0	29/63	46	31/67	46	1
ER/PR> 0	27/63	43	33/67	49	0.486
Her2+	25/58	42	21/60	35	0.455
Triple neg	13/59	22	17/60	28	0.528
LVI	6/33	18	11/40	28	0.403

BC: Breast cancers; BV: Breast volume; WB: Whole breast; ER: Estrogen receptor; PR: Progesterone receptor; Her2+: Epidermoid growth factor receptor 2; LVI: Lymphovascular invasion.

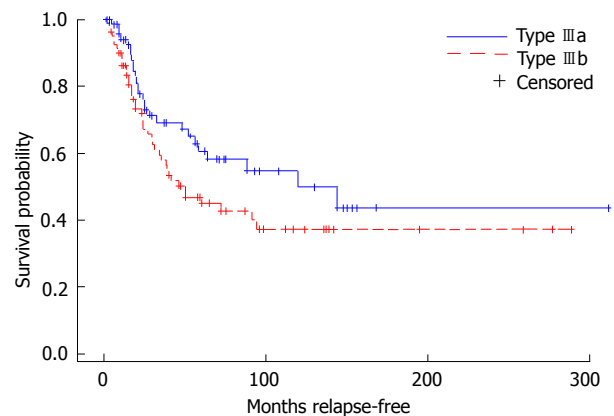


Figure 1 A Kaplan-Meier plot was constructed to compare relapse rate of type IIIa (*n* = 72) vs type IIb (*n* = 81). The log-rank test of comparison of groups yielded *P* = 0.097.

use of, or access to screening or regular medical care^[8].

The percentage of breast volume involved by a tumor is a function of the ratio of tumor to breast size. We compared the amount of breast volume replaced by tumor in patients with large breast cancers (T3) and in those whose cancers, regardless of size, had grossly invaded the skin or chest wall (T4a-c). We found that cancers which invaded local structures more often replaced 50% or more of the breast volume than large cancers (T3) which remained within the breast. Replacement of most of the breast may bring the tumor cells close enough to adjacent structures to facilitate their invasion. We and others^[9-11] have found physical examination a reliable method of determining breast tumor size and percentage of the breast involved by tumor; the results correlate well with those obtained by mammography^[12].

Pathological attributes and marker expression were similar in the two groups. Thus, an important role for neglect and prolonged tumor growth in the pathogenesis of local invasion is suggested by these data. But other biological differences may exist between them; we have not excluded differences between gene expressions in the

two groups.

There may still be a role for constitutively rapid growth in the tendency of some T4a-c tumors to occupy large breast volumes, and for intrinsic differences in the ability of tumor cells to invade adjacent structures.

The mean age of our patients with locally invasive tumors was 58, while that of the patients with T3 tumors was 51. Yet the tumors of younger BC patients are generally more aggressive^[3]. For example, the mean age of 127 patients with constitutively aggressive inflammatory carcinomas (T4dM0) was 50 (data not presented). Our T4a-c patients may have been older than T3 or T4d patients because more years had elapsed between tumor onset and presentation for medical treatment.

The incidence of distant metastases at presentation or subsequent distal relapse of T4a-c tumors is similar to that of inflammatory carcinomas^[3]. Prolonged growth and local invasion may themselves facilitate the development of such metastases. Alternatively, tumors which invade local structures may be constitutively prone to distant spread. Of interest is the fact that T4 tumors are the only subsets of BC whose distant relapse rate may be independent of nodal involvement^[3].

As previously reported^[3], there is a significant difference between the incidences of distant metastases at presentation in patients presenting with T3N1 and T4a-c tumors; 8.8% and 42% in this study. Thus, the stage III B (T3N1M0) patients in this study may represent a subset of T4a-c patients with less aggressive disease. This may, in part, explain the fact that the differences between relapse rates and survival curves of the III A and B patients were not significant. Earlier studies^[3] showed a poorer prognosis for III B (T4a-c) patients, but the adjuvant therapy for many of the patients reported here included innovations, such as taxanes, anti-her2 agents, and aromatase inhibitors. The longest recorded follow-up periods were for patients who had relapsed. Many of our patients reside in the Caribbean; although some continue to report for yearly follow-up at our clinic, those who relapse are more likely to do so. Most of these data were obtained from patients of African-Caribbean origin, and may not be the same in other groups.

We conclude that the behavior of locally advanced primary BC's is likely to be related, in part, to their duration and growth. Intracellular attributes facilitating invasion of adjacent structures may exist, but their existence cannot be assumed until demonstrated.

COMMENTS

Background

Any or all of the following attributes define locally advanced (stage III) breast cancer: (1) large (> 5) cm size with involved lymph nodes in the axilla (stage III A); (2) tumors which have grossly invaded adjacent skin or chest wall (stages III Ba-c), tumors which are inflammatory (stage III Bd); (3) locally advanced breast tumors are also defined by the absence of distant metastases at presentation (stage IV), as detected by imaging of bones, lungs or liver. Stage III tumors are more likely to relapse at distant sites after surgery and radiation than stage I or II tumors; (4) the cells of inflammatory (stage III Bd) tumors are known to be rapidly growing, abnormally invasive and aggressive. This is not

necessarily true of stage III A and III Ba-c tumors. In such patients large size and local invasion may be due to prolonged neglect of the tumor by the patient or her physicians, or the inaccessibility of adequate screening procedures. But because of the unreliability of patients' histories, it is difficult to reliably document neglect in most cases.

Research frontiers

An approved molecular technique called gene expression analysis can give us detailed information about which genes are active in specific breast tumors. Especially in the case of tumors which have not involved lymph nodes in the axilla, expression of some genes is correlated with subsequent distant relapse. But there is little data correlating gene expression with the prognosis of locally advanced breast tumors. Thus, whether any tumor became large or locally invasive because of neglect, or due to intrinsic aggressiveness, cannot be determined. Some of the factors which seem to correlate with aggressiveness are: Failure to express hormone receptors. Over-expression of the epidermoid growth factor receptor 2 (her2). Failure to express both her2 and hormone receptors: triple negativity

Innovations and breakthroughs

T3N1 tumors have a significantly better prognosis than T4a-c tumors. Local invasion may not always be due to intrinsic aggressiveness. Prolonged growth may ultimately lead to replacement of most of the breast by tumor, leading to proximity to adjacent structures, which may facilitate local invasion.

Applications

In this study authors compared several hundred patients with either large (III A) and/or locally invasive (III Ba-c) tumors by the following criteria: (1) did the tumor occupy > 50% of the total breast volume? (2) the pathological grade of the tumor; high grade tumors may be more aggressive; (3) invasion of small blood or lymphatic vessels by tumor; (4) hormone receptor expression by tumor cells; (5) her2 expression by tumor cells; (6) triple negativity of the tumor for estrogen and progesterone receptors and her2. None of these criteria distinguished stage III A and III Ba-c tumors except the first. That is, stage III A tumors, however large, usually involved < 50% of breast volume, whereas most stage III Ba-c tumors did involve > 50% of the breast volume, and many involved the whole breast.

Peer review

This paper is well written and interesting to the readers.

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