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Vascular Density and the Response of Breast Carcinomas to Mastectomy and Adjuvant Chemotherapy

Efi Protopapa, George S. Delides and László Révész

Using morphometric analysis of histological preparations, in a retrospective study vascular indices, expressing the extent of vascularisation, were determined for a number of mammary carcinomas. The indices were found to be related to the survival of the patients treated with modified radical mastectomy in combination with pre- and postoperative chemotherapy, the cases with low indices having the shorter survival. The impaired access of the cytotoxic agents to cells in the deficiently vascularised tumours was considered as an explanation. It was concluded that determination of vascular density in tumours may have a prognostic value in regard to the treatment response, and may be helpful in choosing the appropriate treatment.
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INTRODUCTION

STAGING AND histological grading of tumours are most commonly used for the selection of treatment and indication of the prognosis of the neoplastic disease. Despite identical treatment of tumours of the same stage and similar histological classification, frequently greatly varying treatment responses can be observed. These observations can be interpreted as indicating that factors not included in the staging and grading may play an important role in defining the result of treatment. Currently, the characterisation of the factors with predictive value for the tumour treatment response is subject to extensive research [1].

In 1968 Kolstad [2] reported that the results of radiotherapy for cancer of the uterine cervix were closely related to the vascular density in the tumours, as determined by colposcopic measurements. Richly vascularised cases responded to treatment better than cases with a poor vascularisation. These observations were subsequently confirmed by authors who used different morphometric methods for the retrospective evaluation of the vascularity in histological sections of biopsy specimens from cervical carcinomas [3–5]. The vascularity was also found to be related to the radiotherapy response of nasopharyngeal carcinomas [6], carcinomas of the rectum [7] and the bladder [8]. These and some other related observations were discussed in a recent review [9].

The presence of radioresistant cells in extended hypoxic areas, which may occur in the poorly vascularised cases, has been put forward as an explanation for the failure of radiotherapy [2, 10]. In view of the known radiobiological "oxygen effect", the radiosensitivity of cells under hypoxic conditions can be decreased by a factor up to about 3 in comparison to the well oxygenated cells.

It is conceivable that, being less accessible to the blood circulation, the cells in the less well vascularised tumours will show resistance besides radiotherapy, to parenteral or oral treatment with cytostatic drugs. The determination of the extent of vascularisation may, therefore, have a prognostic value also for chemotherapy. In an attempt to investigate this possibility, in a retrospective study we determined the vascular density in a number of mammary carcinomas which were treated surgically in combination with neo-adjuvant chemotherapy, and the vascularity was then related to the survival of the patients. This paper reports the results.

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PATIENTS AND METHODS

Patients

A total of 26 patients with mammary tumours were included in the study, treated at the Metaxas Memorial Cancer Institute in the period between 1978 and 1982. They were selected according to the following criteria: (a) they were premenopausal cases, aged between 35 and 50 years; (b) the tumours were

2–5 cm in diameter, and were ductal invasive grade II carcinomas; (c) the patients underwent modified radical mastectomy; (d) at least two of the excised axillary lymph nodes were metastatically infiltrated and there was no evidence of any secondaries elsewhere; (e) chemotherapy was administered both before and after mastectomy; and (f) radiotherapy was given solely in a few cases to the metastases which eventually developed following mastectomy.

Chemotherapy

Chemotherapy was administered in cycles, one cycle comprising a regimen with oncovin, cyclophosphamide and doxorubicin in doses 1.4, 350 and 30 mg/m^2, respectively, on the first day, and 5-FU and methotrexate in doses of 350 and 20 mg/m^2, respectively, on the second day. As a rule, one cycle was given 2 weeks before mastectomy, and five additional cycles postoperatively during a 5 month period.

Determination of vascularity index

Paraffin-embedded archival tumour material, preserved at the Pathology Department of the Metaxas Hospital, was cut serially in 5 μm thick sections and stained with haematoxylin and eosin and Masson's trichrome. As a routine, one to two slides with a total of 10 randomly chosen microscopic visual fields were scored using 400 × magnification. In order to assure identical diameters of the microscopic field as required for our particular morphometry [11], all measurements were carried out with the same microscopic equipment. In any field, the capillaries were identified and their number was related to the tumour volume. This was estimated in the same field by using the method of "point counting" [12] and by applying Delesse's principle [12] according to which the *volume* fraction occupied by a constituent is proportional to its *areal* profile. Necrotic and haemorrhagic areas and cavernous formations were omitted. The morphometry was aided by a computer programmed appropriately for digital image analysis.

The vascularity index (V_i) expressing the number of vessels per percentage of neoplastic tissue was calculated according to the following formula:

$$V_i = \frac{\frac{V1}{T1} + \frac{V2}{T2} + \ldots\ldots + \frac{Vn}{Tn}}{n}$$

where $V1 \ldots Vn$ is the number of vessels per optical field; $T1 \ldots Tn$ is the percentage of tumour per optical field; and n the number of optical fields scored.

RESULTS

A follow-up of the 26 patients included in this study showed that 6 (group A) died within 2 years after the initiation of the treatment, and another 6 (group B) after 2, but within 5 years. The cause of death was, in all cases, metastatic dissemination of the disease. 14 of the patients (group C) survived free from the disease for at least 10 years after the diagnosis.

Table 1 shows the mean vascularity index of the tumours in the three groups. In processing the data, a normal distribution of the values was assumed. The data indicate that the tumours of those surviving longest (group C) had the greatest vascular density, and that the density was considerably lower in the case of those in groups A and B with limited survival. As indicated in Table 2, the differences between the vascular indices in group C and group A or B are statistically highly significant, while no significant difference exists between group A and B in regard to vascularity.

Table 1. Vascularity index for the mammary tumours of patients who survived < 2 (Group A), > 2 < 5 (Group B) and > 10 years (Group C) after mastectomy and treatment with cytostatic drugs

Group	No. of patients	Mean vascularity index ± S.E.M.
A	6	0.217 ± 0.083
B	6	0.392 ± 0.073
C	14	0.922 ± 0.046

DISCUSSION

Neo-adjuvant chemotherapy is not universally used as a standard treatment for breast carcinomas, and the protocol described here is actually no longer in use in our clinic either. However, for the purpose of our study we found this protocol had a particular advantage permitting the retrospective analysis of the relationship between the effect of chemotherapy and vascular density in this particular type of tumour.

The data obtained can be interpreted as indicating that a significant relationship exists between the vascularity in mammary tumours and the survival after mastectomy combined with chemotherapy preceding as well as following surgery. Greater vascular density was seen to be associated with longer survival. A similar relationship has been reported between the vascularity of some other types of tumour and the results of radiotherapy [9]. While the relationship can, in the latter cases, be satisfactorily explained by the particular radioresistance of the cells in the deficiently vascularised and, consequently, less well oxygenated neoplastic tissue [13, 14], the preoperative impaired access of the cytotoxic agents to cells in the tumours with inadequate vascularisation may explain the results reported here. Determination of the vascular density may thus have a prognostic value in regard to the effect of both chemo- and radiotherapy, although possibly for different reasons.

In view of the selective toxicities of the antineoplastic agents toward oxygenated and hypoxic cells [15], information on the vascular supply in the tumours may also have the additional advantage of permitting the choice of appropriate drug.

Due to the limited experience available so far, no generalisations can yet be made regarding the importance of the vascularity index as a prognostic parameter. More data with different types of tumour in different stages and exposed to varying treatment are necessary to reach a final conclusion. If further studies confirm the predictive value of vascular density indicated

Table 2. Statistical significance of the differences between the vascularity index of the tumours in the groups indicated in Table 1.

Groups compared	d.f.	t	P
A to B	10	1.43	0.21
(A + B) to C	24	8.39	$< 10^{-4}$

t-test was used for the calculations.

by the investigations made so far, the possibility of making improved prognosis would permit a more individualised treatment of patients than practised today.

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Psychosocial Adjustment Among Husbands of Women Treated for Breast Cancer; Mastectomy vs. Breast-conserving Surgery

M. Omne-Pontén, L. Holmberg, R. Bergström, P.O. Sjödén and T. Burns

Psychosocial adjustment was measured among 56 spouses of women operated for breast cancer. Of 69 eligible husbands, 56 participated. Twenty women underwent breast-conserving surgery (BCT) and 36 had a mastectomy (MT). An interview was conducted with each woman and her husband separately, 4 and 13 months after surgery. Two instruments were used; SBAS (Social Behaviour Assessment Schedule) and a scale (TB) constructed specifically for the study. The husbands of the women in the MT group were significantly more depressed after 4 months and reported complaints related to their wives's disease more often than did those in the BCT group. After 4 months, the marital relation was assessed as more positive in the MT group. A total of 48% of the husbands in the sample expressed some emotional distress during the investigation period, which is similar to levels seen among breast cancer-operated women themselves. Overall, only marginally better scores were seen for husbands married to women who had undergone breast-conserving surgery. Few researchers have studied psychosocial reactions in the breast cancer patient's family. Since patterns of social support empirically influence the rehabilitation of the cancer patient, this field of investigation is important.
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INTRODUCTION

PSYCHOSOCIAL REACTIONS in husbands to women with breast cancer have rarely been investigated. In a controlled follow-up study, Maguire [1] found that husbands of breast cancer patients experienced significantly more distress before and after surgery than did a group of men whose wives had been treated for a benign breast disease. The results were similar in a study by Northouse [2] who performed a descriptive, longitudinal study of couples, where the women underwent a mastectomy. Northouse [2] also found that the psychosocial problems persisted over time for both the men and women (18 months postsurgery). In Maguire's study [1], 36% of the husbands still had symptoms of anxiety 1 year after their wives had been treated for breast cancer.

In a retrospective study, Baider *et al.* [3] investigated whether less mutilating breast surgery influenced the husband's own