Axillary lymph node metastasis and survival in breast cancer patients with concurrent cardio-cerebral-vascular disease

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DECLARATIONS

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Summary

Objectives Dissemination of tumour cells occurring both spontaneously or caused by diagnostic biopsy procedures is the most serious complication of solid malignancies. In the present work we focus on local tumour spread and how this complication of cancer disease can be counteracted.

Design From a cohort of 864 breast cancer patients we selected those who died of their primary cancer and those who died because of a simultaneously existing cardio-cerebral-vascular disease (CCVD) and were exposed to anticoagulants.

Setting The study was based on breast cancer patients diagnosed at Karolinska University Hospital during 1991 ($n = 519$) and 1997–1998 ($n = 345$).

Main outcome measures Axillary lymph node metastasis (ALNM) and survival of breast cancer patients with concurrent CCVD.

Results Breast cancer patients belonging to the group that died of CCVD showed ALNM at the time of tumour diagnosis in 27% of the cases compared with 68% diagnosed in the group that died of their breast cancer ($p < 0.0001$). Likewise we observed a highly significant ($p < 0.0001$) difference in mean survival time with an average of 102 months in the group of breast cancer patients who died of CCVD and an average of 61 months in the group who died of breast cancer.

Conclusion The data presented herein indicate that breast cancer patients regularly involved in treatment with anticoagulants because of simultaneously existing CCVD develop ALNM significantly less frequently and have an increased average survival time compared with breast cancer patients not suffering from CCVD.

Introduction

There is a general agreement that more than 90% of cancer patient deaths are related to distant metastases. This means that not only the primary tumour itself but the disseminated cells of the tumour determine the fate of the vast majority of cancer patients. Thus, in order to significantly decrease the death rate of cancer patients one of the urgent tasks in the field of cancer research is to develop procedures efficiently reducing the risk of tumour cell dissemination.

It is also well known that malignant solid tumours behave significantly different regarding clinical aggressiveness and the occurrence of clinically detectable metastases. A few commonly known examples are pancreatic carcinomas with a high risk to spread tumour cells and kill the vast majority of patients within a five-year period[1] and papillary thyroid carcinomas presenting low frequencies of clinically detectable distant metastases even 10–20 years after diagnosis of the primary tumour which is also related to a favourable prognosis.[2]

One of the highly significant differences of these two tumour types is the degree of genomic instability with more or less all of the pancreatic carcinomas showing pronounced genomic instability[3] and more or less all of the papillary carcinomas presenting a low degree of genomic instability at the time of diagnosis.[4]

Other types of malignancies, e.g. breast and prostate carcinomas, can be subdivided into two main groups which are characterized by either a high or low degree of genomic instability[5,6] which in turn is strongly correlated to clinical aggressiveness and patient survival.

Taken together, these data indicate that distant metastases occur in both highly and lowly aggressive cancer variants but that the time period from diagnosis of the primary tumour to the clinical occurrence of distant metastases, in turn determining patient survival, can differ significantly. This difference in growth activity contributes that disseminated cancer cells – both local and distant – are frequently not diagnosed resulting in inadequate treatment decisions. Thus, tumour cell dissemination either occurring spontaneously during tumour progression or caused by, for example, diagnostic needle or surgical biopsy seems to be an under-estimated risk factor especially in the patient group with tumours exhibiting a low degree of genomic instability.

In the present work we mainly focused on the phenomenon of local tumour spreading and how this serious complication of cancer disease can be counteracted.

Diagnostic needle biopsy procedures

Achieving a decisive morphologic diagnosis is compulsory when a patient presents an unknown lesion. In a majority of cases needle biopsies will be performed. Today needle biopsies can be subdivided into fine needle aspiration biopsy (FNAB) and core needle biopsy (CNB) for which methodologies and equipment differ substantially. FNAB relies solely on needles with a diameter of 0.5–0.8 mm in order to aspirate representative malignant single cells or cell complexes whereas CNB utilizes needles in the range of 1.2–3 mm or more to cut blocks of tissue from the suspicious lesion. FNAB is considered to be the less invasive and more patient-friendly method.[7–9] Certain advantages of CNB, however, namely the possibility to acquire preoperative information on the state of invasion, histological grade and receptor status have lead to CNB being the method of choice in most malignancies. Numerous case reports of malignant needle track seeding have been published for different tumours[10–14] and increasing caution is observed in highly aggressive malignancies, e.g. in the pancreas.[15]

It has also been shown that tumour manipulation during breast cancer surgery results in tumour cell dissemination into the vascular circulation.[16] A high count of CTC in peripheral blood was found to decrease breast cancer patient survival.[17] However, it is difficult to determine the true incidence of tumour cell dissemination in biopsy procedures. From the time of tumour cell spread until the development of clinically detectable metastases, several years can elapse and the detected lesions are indistinguishable from those occurring spontaneously. Tracing needle channels in surgically removed organs containing only parts of the track is difficult. Furthermore the task is complicated by postoperative treatment, e.g. radiotherapy and drugs reducing relapse

due to spontaneous spread or induced by the biopsy. At the time of diagnosis some tumours have not yet established cellular alterations inevitably necessary for local or distant tumour growth. However, there are tumour subgroups which at the earliest clinically detectable stage have already gained metastasizing properties and in which the biopsy induced dissemination of tumour cells may have implications on patient survival. At present these subgroups cannot be identified by non-invasive, for example imaging, methods but only by morphological, immunochemical or preferentially molecular analysis of the tumour cells.

Platelets and cancer

Several studies have shown that cancer cells receive a helping hand from platelets that protect and feed disseminated tumour cells, making it easier for cancer to metastasize. However, the role of platelets in the biopsy procedure has yet to be determined. Dislocated tumour cells that are spread locally or into the periphery could become more resistant to the immune system by acquiring a protective coat of platelets.[18] Since platelets seem to protect and growth stimulate disseminated tumour cells it can be suggested that the presently used traumatic diagnostic cell and tissue biopsy procedures, causing bleeding in association with biopsy-related blood vessel injury, may initiate tumour cell spread of a still local tumour disease.

Materials and Methods

In two consecutive materials of breast cancer patients, one from 1991 ($n = 519$) and another one from 1997–1998 ($n = 345$), we have analysed patients who died because of their breast cancer and patients who died of cardio-cerebral-vascular disease (CCVD). All data concerning cause of death were retrieved from the Swedish Cause of Death Register and are shown in Table 1. The primary morphologic diagnosis in all patients was based on FNAB technique and was confirmed histopathologically in material from the operated breast. Since there were no known differences between the two groups we could merge them into one. The follow-up time in the material from 1991 and 1997–1998 was 17 and 10 years, respectively. Multiple tumour disease parameters have been analysed. In this report we focus on tumour size, axillary lymph node metastases (ALNM) and DNA index in breast cancer patients that died either of their primary cancer or due to CCVD. DNA index was based on the DNA content of normal diploid epithelial cells. All patients were treated according to standard protocols based on clinical stadium and tumour aggressiveness.

Statistical calculations were performed using the STATISTICA software package (StatSoft, Inc., Tulsa, OK, USA). Statistical significance for categorical variables was calculated using χ^2-test and independent t-test was used for continuous ones. Statistical significance was assumed if $p < 0.05$.

Table 1
Cause of death according to the Swedish Cause of Death Register

Cause of death	*Patient material from 1991 (n = 519)*	*Patient material from 1997–1998 (n = 345)*
Breast cancer	147	52
CCVD	81	22
Other types of cancer	37	12
Others	34	14

Results

The two selected patient groups were statistically inseparable with respect to tumour size and DNA index, two objective parameters specifying malignancy potential. In spite of this conformity, the patient groups differed significantly in ALNM positivity. Patients in the group that died of CCVD showed ALNM positivity in 27% of the cases, as compared to 68% in the group that died of the primary cancer ($p < 0.0001$). We also observed a significantly increased survival time in the CCVD patient group (102 months) compared with patients who died of breast cancer (61 months). Clinical and cytometric data of the patients are shown in Table 2.

Table 2
Clinical and cytometric data of breast cancer patients who died of their primary tumour or of CCVD (material from 1991 and 1997–98)

	Patients who died of breast cancer (n = 126)	*P value*	*Patients who died of CCVD (n = 64)*
Tumour size [mm ± SD]	24.43 ± 13.04	n.s.	22.56 ± 10.62
ALNM positivity	68%	p < 0,0001	27%
DNA index [DI ± SD]	1.56 ±0.46	n.s.	1.55 ± 0.51
Survival [month ± SD]	61.45 ± 44.46	p < 0,0001	102.13 ± 59.80

Discussion

Dissemination of cancer cells followed by metastatic growth is the most serious complication of solid malignancies. Therefore, there is an urgent need to introduce procedures making it possible to prevent cancer cells from spreading. One well-known efficient course of action is early detection and removal of the entire tumour when it is still in the stage of *in situ* or early locally invasive growth. Other possible procedures are those that eliminate the risk of tumour spread during diagnostic tissue sampling and those preventing disseminated tumour cells from surviving and growing. Since only a minority of solid malignancies are detected at the *in situ* or early locally invasive stage and the fact that diagnostic needle or surgical biopsies are generally necessary to obtain a final pretreatment diagnosis it is evident that techniques used today are inappropriate to reach this goal. This is clear from numerous studies reporting local seeding in connection with diagnostic sampling of tumour tissue.[10–15] A striking example is a comprehensive study of Hansen *et al.*[19] who showed that preoperative manipulation of the primary breast tumour using either FNAB or CNB techniques resulted in an increase of sentinel node metastases with as much as 50%.

In the present study we investigated the incidence of ALNM and patient survival in 864 breast cancer patients who were preoperatively diagnosed by means of FNAB, i.e. the most patient-friendly, minimally traumatic sampling procedure. From this patient cohort we selected those who died because of their breast cancer disease and those who died because of a simultaneously existing CCVD, i.e. patients who at the time of FNAB sampling and until death at least periodically were exposed to anticoagulants. A decisive advantage of the present study is that both the average size and the DNA index of the primary breast cancers, well known to be highly correlated to ALNM positivity and malignancy potential, were statistically the same in the compared patient groups. With this in mind, the highly significant difference (68% versus 27%) in ALNM positivity at the time of diagnosis and survival time (61 versus 102 months) in the two patient categories indicate that anticoagulant treatment seems to counteract tumour cell seeding in turn improving patient survival.

The data presented herein are in line with data obtained from studies in cancer patients[20] and experimental animals injected with highly malignant tumour cells[21] showing that anticoagulants counteract activation of platelets and by doing so inhibit platelet-cancer cell interaction resulting in reduced metastatic growth of disseminated cancer cells.

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