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Effectiveness of Follow-Up for Breast Cancer Patients

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ACADEMIC DISSERTATION
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"Never measure the height of a mountain,
until you have reached the top.
Then you will see how low it was".
Dag Hammarskjöld

"This is not the end. It is not even the
beginning of the end.
But it is, perhaps, the end of the
beginning."
Winston Churchill

To Petteri, Teemu and Ritva.

ABSTRACT

Breast cancer is the most common cancer in women constituting almost one third of all female cases in Finland. The prognosis of patients is good and constantly improving and thus the number of breast cancer survivors under surveillance is also constantly rising. The cost of surveillance is increasing concomitantly. The effectiveness of follow-up for breast cancer patients was here assessed in a randomized study conducted in the oncology unit of Tampere University Hospital.

In this trial the frequency of visits and intensity of follow-up tests were randomized and the effectiveness of follow-up of patients with localized disease after primary treatment evaluated. The study involved altogether 472 consecutive breast cancer patients from the Pirkanmaa area with randomization from May 1991 to December 1995. Patients were followed up at the department of oncology for five years or until the first relapse, either local or distant.

In a prospective setting some common symptoms, i.e. somatic symptoms, pain, cough-dyspnoea, nausea and mental symptoms, fatigue, depression-anxiety and insomnia were recorded in relapse-free patients. Four out of five healthy survivors experienced some symptom(s), but only slight clustering between somatic and mental symptoms was detected. The number of symptomatic patients rose from 38% to 72% in a comparison of the same six symptoms between relapse-free patients in the period from 7 to 12 months from primary treatment and patients experiencing relapse during the six months prior to the diagnosis of relapse.

The sensitivity and specificity of serum tumour marker CA 15-3 and chest X-ray as diagnostic tools in detecting the first local or distant relapse of breast cancer were evaluated. In a prospective setting CA 15-3 was taken every 6th month during the five years of follow-up. This marker could be used with fairly high reliability to rule out relapsing breast cancer with multiple sites or liver metastases, but only one third of first breast cancer recurrences were found by CA 15-3; test specificity was thus high (99%) whereas test sensitivity was low (36%). Likewise, the validity of chest X-ray in detecting intrathoracic relapse was evaluated in arms with routine (chest X-ray taken every 6th month) vs. spontaneous chest X-ray (chest X-ray taken when clinically indicated). Film sensitivity remained low, 11% in the routine vs. 20% in the spontaneous arm, whereas film specificity was higher, 97% in the routine vs. 90% in the spontaneous arm. In addition, no statistically significant differences between arms in disease-free or overall survival were found. Thus, routine compared to spontaneous chest X-ray did not benefit the asymptomatic patient.

The total cost of follow-up was analyzed in the four follow-up arms. The cost of visits and examinations were calculated as well as the cost of detected recurrence per patient in each arm. Neither the frequency of visits nor the intensity of examinations had any effect on overall and disease-free survival. During the mean follow-up of 4.2 years no differences between arms were detected in overall vs. disease-free survival. However, the total cost of follow-up in the arms was different, i.e., the cost per patient and per detected recurrence in the arm with visits every third month with routine examinations was 2269€ vs. 9149€, respectively, and in the arm with visits every sixth month without routine examination 1050€ vs. 4166€, respectively, the difference in total cost between the most and least expensive follow-up being thus 2.2 fold. The reason for the difference in the total cost was explained mainly by the routine examinations in the follow-up.

As a conclusion, after primary treatment relapse-free breast cancer patients suffered considerably from somatic symptoms such as pain, cough-dyspnea and nausea and from mental symptoms such as fatigue, depression and insomnia. The occurrence of symptoms was by no means always associated with relapse of breast cancer. Nonetheless the same symptoms increased significantly during the six months prior to diagnosis of relapse. The sensitivity of tumour marker CA 15-3 in detecting the first relapse was low, as was the sensitivity of chest X-ray in detecting the first intrathoracic relapse in asymptomatic patients. There were no statistically significant differences in disease-free and overall survival between patients in the respective follow-up arms. The least expensive follow-up schedule among equally competent approaches was as good as the most expensive, i.e. no differences in disease-free or overall survival were detected.

CONTENTS

1. ABBREVIATIONS

AFOS	serum alkaline phosphatase
ALAT (GOT)	serum glutamic oxalacetic transaminase
ASAT (GPT)	serum glutamic puruvic transaminase
ASCO	American Society of Clinical Oncology
BCM	breast cancer mucin
BCS	breast conservation surgery
CA 15-3	cancer antigen 15-3
CA 27.29	cancer antigen 27.29
CA 549	cancer antigen 549
CA M29	cancer antigen M29
CA M26	cancer antigen M26
CMAJ	Canadian Medical Association journal
CNS	central nervous system
CEA	carcinoembryonic antigen
CISH	chromogen in situ hybridization
CKs	cytokeratins
CT	computed tomography
CYFRA 21-1	cytokeratin-19 fragments
DCIS	ductal carcinoma in situ
DFI	disease-free interval
DFS	disease-free survival
EGTM	European Group of Tumour Markers
EIC	extensive in situ component
EMCA	epithelial mucin core antigen
ER	estrogen receptor
ESAS	Edmonton Symptom Assessment Scale
ESMO	European Society of Medical Oncology
ESR	erythrocyte sedimentation rate
FISH	fluorescence in situ hybridization
FN	false-negative
FNAB	fine-needle aspiration biopsy
FP	false-positive
GGT	gamma-glutamyl peptidase
GP	general practitioner
HER2	human epidermal growth factor receptor 2
HRT	hormonal replacement therapy
IARC	International Agency for Research on Cancer
LD	serum lactate dehydrogenase
LCIS	lobular carcinoma in situ
LHRH	luteinizing hormone-releasing hormone
M	distant metastases
mAb	monoclonal antibody
MCA	mucin-like carcinoma-associated antigen
MGA	mammaglobin A

MRI	magnetic resonance imaging
MSA	mammary serum antigen
MUC 1	polymorphic epithelial mucin (PEM)
N	nodes
NBI	Nottingham biochemical index
NCC-ST-439	cancer antigen NCC-ST-439
NCCN	National Comprehensive Cancer Network
NPV	negative predictive value
OS	overall survival
QOL	quality of life
PAI-1	plasminogen activator inhibitor type 1
PET	positron emission tomography
PPV	positive predictive value
PR	progesterone receptor
PS	performance status
RFS	relapse-free survival
RU score	relative use score
SNB	sentinel node biopsy
Se	sensitivity
Sp	specificity
T	tumour
TN	true-negative
TP	true-positive
TPA	tissue polypeptide antigen
TPS	tissue polypeptide-specific antigen
TTP	time to progression
UICC	International Union against Cancer Criteria
US FDA	United States Food and Drug Administration
uPA	urokinase plasminogen activator
US	ultrasound
WHO	World Health Organization

2. LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in the text by Roman numerals.

I Kokko R, Hakama M, Väisänen J and Holli K: Occurrence and clustering of mental and somatic symptoms in relapse-free breast cancer patients in comparison to breast cancer patients with relapse (submitted).

II Kokko R, Holli K, Hakama M (2002): Ca 15-3 in the follow-up of localised breast cancer: a prospective study. Eur J Cancer 38: 1189-1193.

III Kokko R, Hakama M and Holli K (2003): Role of chest X-ray in diagnosis of the first breast cancer relapse: a randomized trial. Breast Cancer Res Treat 81: 33-39.

IV Kokko R, Hakama M and K. Holli K (2005): Follow-up cost of breast cancer patients with localized disease after primary treatment: a randomized trial. Breast Cancer Res Treat 93: 255-60.

3. INTRODUCTION

Breast cancer is the most common female cancer in Finland (Cancer Incidence in Finland 2005). Annually over 3800 new breast cancers are diagnosed comprising 32% of all new female cancers, in addition, approximately 300 in situ carcinomas of the breast are detected. The incidence of breast cancer in Finland is 84.0/100 000. The condition is rare in men, only 10–20 new male breast cancers being diagnosed annually. Every year over 800 patients die of breast cancer and breast cancer as a cause of death accounts for 16% of all female cancer deaths (Cancer Incidence in Finland 2005).

The prognosis of breast cancer patients has improved, the relative survival rates being now 87% in 5 years, 77% in 10 years and 70% in 15 years. However, according to the latest estimates from period analysis in the Finnish Cancer Registry the cumulative 40-year relative survival of breast cancer patients diagnosed under the age of 50 is now approximately 43% for all breast cancers, 57% for localized cancers and 24% for cancers with localized spread (Brenner and Hakulinen 2004). Breast cancer thus often behaves like a chronic disease.

The prevalence of patients surviving less than ten years from the primary cancer diagnosis is almost 27 000 (Cancer Incidence in Finland 2005). Regular follow-up for breast cancer patients is recommended at least up to ten years after the primary diagnosis according to guidelines of both the American Society of Clinical Oncology (ASCO) 1998 and European Society of Medical Oncology (ESMO) 2005 (Smith et al. 1999, 2005 ESMO Minimum Clinical Recommendations 2005a), and there are thus many relapse-free women participating in the follow-up schedules. These schedules for women with breast cancer after primary treatment vary considerably and even today a great many asymptomatic women participate in intensive routine follow-up programs including routine and frequent radiological examinations, regular blood tests and frequent clinical visits to detect recurrent disease. There are, however, no evidence-based data to justify this common practice. Large randomized trials have shown no survival benefit from intensive follow-up versus minimal policy follow-up (Rosselli del Turco et al. 1994, GIVIO Investigators 1994). Likewise, Sauer (1997) concludes that follow-up should be symptom-oriented. The first signs to arouse suspicion of relapse are most often the symptoms of the patient, second often findings in physical examinations, and very seldom blood tests and radiological examinations of asymptomatic patients (Pivot et al. 2000).

The aim in following up breast cancer patients after primary treatment is to detect recurrence of the cancer, to give support and reassurance to the patient concerning the disease, to promote rehabilitation, to give feed-back information for evaluation of

treatment efficacy as well as to detect possible late adverse events and toxicities after primary treatment and during possible adjuvant endocrine treatment. A further important aspect is to detect any new primary cancer in the contralateral breast or a relapse in the treated breast or some other cancer, secondary or not, and in a symptomatic patient to confirm or rule out relapse with distant metastases by means of additional examinations. The economic resources of public health care are limited and all actions in health care should be cost-effective, including the follow-up of cancer patients.

The present study assessed the effectiveness of follow-up of breast cancer patients with localized disease after primary treatment in Finland. Symptoms in relapse-free breast cancer patients were evaluated and compared to those experienced by patients with recurrence in a prospective trial (Article I). The efficacy of tumour marker CA 15-3 in detecting the first either local or distant relapse of breast cancer was evaluated in a prospective setting (Article II) and the value of chest X-ray in detecting the first relapse of breast cancer was evaluated in a randomized trial (Article III). In addition, a randomized trial assessed the impact of four different follow-up schedules on disease-free and overall survival. The cost of the different schedules was calculated, i.e. the cost-effectiveness of different follow-up schedules was estimated (Article IV).

4. REVIEW OF THE LITERATURE

4.1 Etiology of breast cancer

The incidence of breast cancer has increased rapidly in developed countries with a higher standard of living. Thus one woman in ten will be stricken with breast cancer during her lifetime. About 20% of women will develop carcinoma in situ during their lifetime and almost a third of these will subsequently experience a relapse, half of these being invasive (Ottesen et al. 2000, 2003).

Multiple environmental factors probably play a major role as causative agents (Doll and Peto 1981). Hormonal factors are likewise implicated; early menarche, nulliparity and late menopause increase the risk of breast cancer, whereas multiparity and long breastfeeding reduce it. Combined hormonal replacement therapy (HRT) for menopausal symptoms increases the risk of breast cancer and the risk is further increased especially after prolonged use (Writing Group for the Women´s Health Initiative Investigators 2002, Chlebowski et al. 2003).

Postmenopausal obesity and alcohol consumption seem to increase the breast cancer risk (Longnecker et al. 1995, Bowlin et al. 1997, Smith-Warner et al. 1998, Biglia et al. 2004, Suzuki et al. 2005) while regular physical exercise may reduce it (Dirx et al. 2001, Lee 2003, Willer 2003, Bauman 2004, Friedenreich 2004, Lagerros et al. 2004).

In addition, 2–11% of breast cancer patients will develop contralateral breast cancer in their lifetime, the risk of this being estimated to be 2-6-fold compared to the risk of women in the general population to develop a first primary breast cancer (Chen et al. 1999, Vaittinen and Hemminki 2000).

Genetic predisposition is estimated to have a role in 5–10% of all cases. Young age at diagnosis, bilateral disease, a family history of breast cancer and cancer of the ovary in close relatives may suggest hereditary breast cancer. Two genes, BRCA1 and BRCA2, have now been identified as markedly increasing the risk of breast cancer and, in addition, the risk of ovarian cancer. There are also other genes, some not yet identified, increasing the genetic predisposition to breast cancer (Claus et al. 1996, Eerola et al. 2001). In developed countries the lifetime excess incidence of breast cancer is 5.5% for women with one affected first-degree relative and 13.3% for women with two (Collaborative Group on Hormonal Factors in Breast Cancer 2001). Nonetheless, eight out of nine breast cancer patients do not have an affected first-degree relative. Also in certain rare genetic syndromes breast cancer can occur as part of the syndrome

(Thull and Vogel 2004). Thus the title breast cancer subsumes a heterogeneous group of diseases with very different causes.

4.2 Diagnosis of breast cancer

Finnish women in the age group 50–59 years are regularly screened every second year. The benefit of screening is proven and more breast cancers are found when smaller at an earlier stage and even in the non-invasive in situ stage. Screening by mammogram for women >50 years of age reduces breast cancer mortality by 19–25% (Hakama et al. 1997, Jatoi 1999, Anttila et al. 2002, Vainio and Bianchini 2002). In younger women aged 40–49 years screening mammograms may also be useful, but are not yet used routinely (Klemi et al. 2003).

Breast cancer suspicion is thus roused in screening mammography or clinically, when the patient or doctor has found a lump in the breast or in the axilla. Today in Finland every 5th breast cancer is found by mammogram. The most common "symptom" (80%) bringing a patient to the doctor is a lump in the breast.

Especially in younger women with firm breasts, ultrasound of the breast increases the accuracy of the mammogram, and both examinations should be made together (Saarenmaa et al. 2001a, b). Fine-needle biopsy (FNB) or true-cut/core biopsy are taken to clarify the cytology or histology of a lesion found in mammogram or ultrasound. Magnetic resonance imaging (MRI) of the breast is still considered experimental, but may give more accurate information in breast cancer of genetic predisposition, in lobular breast cancer and in special problematic cases (Warner et al. 2001, Quan et al. 2003).

In up to 10% of cases breast cancer is primarily diagnosed at an advanced stage (Tampellini et al. 1997), but in the follow-up of patients breast cancer with distant metastases is most often diagnosed on the basis of symptoms, e.g. the cause of bone pain is confirmed to be a destructive lesion in the skeleton, the cause of dyspnoea metastatic pleural effusion, the cause of emesis and upper abdominal pain metastatic involvement of the liver.

4.3 Biology of breast cancer

4.3.1 Clinico-pathological classification

Noninvasive cancers, ca ductale in situ (DCIS) and ca lobulare in situ (LCIS), are regarded as precursor lesions, but today LCIS is increasingly seen as a risk factor for the development of invasive breast cancer (Bodian et al. 1996). LCIS is usually found purely coincidentally in surgical resection of the breast and DCIS is often detected as microcalcifications in mammography.

Invasive ductal cancer is the most common type of invasive breast cancer accounting for 75–80% of cases. This is, however, a particularly heteregeneous group of differently behaving cancers. The cancer cells can be classified as well, moderate or poorly differentiated (WHO grade I–III). Grade I cancer is usually slow-growing and the disease has a good prognosis. In contrast, grade III disease is rapidly growing, the course of the disease is aggressive and the risk of relapse is high, making the prognosis worse (Sainsbury et al. 2000).

Invasive lobular cancer constitutes 15–20% of all breast cancers and according to Li and associates the incidence rate of tumours classified as lobular cancers has increased 1.5-fold (Li et al. 2003). The WHO grading is not always used in lobular cancers but slowly growing and aggressive forms are distinguished. Lobular cancer is often more difficult to detect in mammograms and often has a different metastatic profile from ductal cancer metastasizing in the serous cavities, in the gastrointestinal tract and in the gynecological organs (Korhonen et al. 2004). Generally, the prognosis for ductal and lobular cancers in the same stage is equal, but lobular cancer increases the risk of contralateral disease more than ductal cancer. The risk of contralateral cancer is in any case on average some 3 times greater for all breast cancer patients compared to age-matched women in the general population, and the absolute risk per year of contralateral breast cancer is 0.75% (Prior and Waterhouse 1978).

Usually tubular, cribriform, papillary, medullary, colloidal and mucoid carcinomas are included in the special types of breast cancer and in most cases the prognosis seems better in these subtypes, even in the case of node-positive disease. These subtypes constitute about 5% of all breast cancers (Sainsbury et al. 2000).

Gene expression analyses have identified several breast cancer subtypes including basal-like, HER2 (human epidermal growth factor receptor 2) positive/ER (estrogen receptor) negative, HER2 positive/ER positive, luminal A and luminal B subtypes. Breast cancer-specific survival differs by subtype, with shortest survival in the HER2+/ER- and basal-like types (Carey et al. 2006). Laakso and associates have also detected a subtype basoluminal carcinoma among “basal phenotype” breast cancers. Amplification of HER2 was found almost exclusively in this subgroup with short

relapse-free survival (Laakso et al. 2006). Different gene-expression profiles have been found to predict survival in breast cancer independent of the nodal status, and also a prognostic signature has been detected in lymph node-negative primary breast cancer in gene microarray analyses. Luminal A subtype with good prognosis differs from the basal-like subtype with poor prognosis in gene expression analyses (van de Vijver et al. 2002, Foekens et al. 2006, Sorlie et al. 2006). However, gene microarray assays are not yet in clinical use.

4.3.2 Biological markers

Breast cancers can be classified into two classes with hormone receptor-positive vs. – negative disease. These behave like distinct diseases and the prognosis of a patient with hormone receptor-positive disease is much better than with hormone receptor-negative disease. Routinely, estrogen receptors (ER) and progesterone receptors (PR) are analysed, but very differently in different pathology laboratories. Most often immunohistochemistry/ immunostaining assays are used. Also the cut-off value for positivity differs markedly. With strongly positive estrogen and progesterone receptors the likelihood of a good response to endocrine treatment in breast cancer is excellent, diminishing with weakly positive receptors or if only one kind of receptors are positive (Thorpe et al. 1986).

The receptor tyrosine kinase family has four members (human epidermal growth factor receptors 1-4, HER 1-4). Overexpression of HER 1-3 on the surface of breast cancer cells is associated with poor prognosis, whereas overexpression of HER 4 is associated with better survival (Tovey et al. 2004). Human epidermal growth factor receptor 2 (HER2) is found over-expressed or amplified in 15–20% of breast cancers (Marty et al. 2005). The detection of HER2 receptor on the surface of breast cancer cells is made by immuno-histochemistry, by fluorescence in situ (FISH) or chromogen in situ hybridization (CISH). Reliable results on HER2-status are important in that patients with HER2-positive disease turn a greater risk of early relapse. HER2-positivity also influences in selecting the best treatment for the patient in a metastatic setting and even in the adjuvant setting (Marty et al. 2005, Piccart-Gebhardt et al. 2005, Romond et al. 2005, Joensuu et al. 2006), i.e. trastuzumab is a specific antibody to HER2 and its use improves the prognosis of a patient with HER2-positive disease. Also other HER receptors can be targeted, namely HER1 by gefinitib and erlotinib, and the oral dual tyrosine kinase inhibitor lapatinib inhibits both HER1 and HER2. However, except for trastuzumab more randomized trials are needed for the other targeted therapies before they can be used in clinical practice outside clinical trials (Friess et al. 2005, Johnston and Leary 2006).

Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1) are proteins causally involved in cancer invasion and metastasis. High levels of these proteins have been shown to predict an adverse outcome in breast cancer patients, including those with node-negative disease (Duffy 2002, 2004, Duffy et al. 2004). The prognostic value of uPA/PAI-1 has been validated in a prospective randomized trial with node-negative breast cancer patients, the results showing the prognostic impact of uPA/PAI-1 to be independent of tumour grade, tumour size, surgical treatment and steroid receptor status (Jänicke et al. 2001). Both uPA and PAI-1 have been shown to be stronger predictors of patient outcome than tumour size, grade, receptor status or the age of the patient (Look et al. 2002). Although not yet in routine use, the most immediate benefit of these markers is likely to be in selecting the subgroup of node-negative breast cancer patients failing to benefit, i.e. not needing adjuvant chemotherapy (Harbeck et al. 2002, Duffy et al. 2004). However, this tissue marker must still be considered experimental.

Mammaglobin A (MGA) is a 93 amino acid protein expressed almost exclusively in breast tissue and existing in two molecular forms. The high molecular form has been found to correlate positively with hormone receptors and negatively with tumour grade and proliferation rate. No correlation has been found between MGA proteins and tumour size and nodal status. Its presence is likely to be associated with favourable prognosis in breast cancer and it could be used in detecting micrometastases from breast cancer (O`Brien et al. 2002, 2005).

4.3.3 Clinical staging of breast cancer

The status of ipsilateral axillary lymph nodes is important in invasive breast cancer. In DCIS there is no need for axillary dissection. Axillary lymph node evacuation should always be undertaken if there are palpable nodes in the axilla or pathologic nodes in mammogram or ultrasound of the breast/axilla, or a sentinel node biopsy (SNB) is positive. Preferably at least 10 nodes should be found and dissected to ascertain nodal status. The staging of breast cancer is based on tumour (T) size, nodal (N) status and distant metastases (M) (Table 1).

Table 1. Clinical staging of breast cancer

STAGE	Tumour (T)	Nodes (N)	Distant metastases (M)
0	Tis	N0	M0
I	T1	N0	M0
IIA	T0-1	N1	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0-2	N2	M0
	T3	N1-2	M0
IIIB	T4	N0-3	M0
	T0-4	N3	M0
IV	T0-4	N0-3	M1

4.4 Serum tumour markers in breast cancer

Serum tumour markers have been widely used in the follow-up of localized breast cancer to detect early relapse and to evaluate treatment response in metastatic breast cancer. There are, however, mostly only retrospective data to support this practice. The most widely used serum tumour markers are CA 15-3, CA 27.29, CEA, TPA, TPS, CYFRA 21.1 and HER2 (Table 2).

Table 2. Main serum tumour markers in breast cancer (Duffy 2006).

Marker	Proteins detected
CA 15-3	MUC-1
CA 27.29	MUC-1
CEA	CEA
TPA	Fragments of cytokeratins 8, 18 and 19
TPS	Fragments of cytokeratins 8 and 18
CYFRA 21.1	Fragments of cytokeratins 8 and 19
HER2	Extracellular form of HER-2

4.4.1 MUC1 mucins

MUC1, also known as polymorphic epithelial mucin (PEM), is a large high molecular weight glycoprotein well expressed on the apical surface of most polarized epithelial cells ("wet" epithelia) in different organs, including breast, stomach, pancreas, bladder, ovary and respiratory tract. MUC1 consists of the core protein apomycin, where carbohydrate side-chains are attached. It may play an antiadhesive role. In normal breast tissue MUC1 is expressed in the ducts and acini, but with neoplastic transformation normal cell polarization and tissue architecture is disrupted leading to shedding of MUC1 into the blood, where it can be measured by various immunoassays. A large series of monoclonal antibodies react with the core protein. Circulating MUC1 displays a high degree of heterogeneity, which explains the discordant results obtained by different tests (Cheung et al. 2000, Seregni et al. 2004).

The CA 15-3 test can be considered the "golden" standard; it uses the monoclonal antibodies 115D8 and DF3. Other tests (immunoassay kits) detecting circulating MUC1 are MCA (mucin-like carcinoma-associated antigen), CA 549 (cancer antigen 549), BCM (breast cancer mucin), MSA (mammary serum antigen), EMCA (epithelial mucin core antigen), cancer antigens M26 and M29 and CA 27.29 (cancer antigen 27.29) (Seregni et al. 2004).

4.4.1.1 CA 15-3

The CA 15-3 marker is often false-positive in benign conditions like chronic hepatitis, liver cirrhosis, tuberculosis, sarcoidosis, systemic lupus erythematosus, hypothyroidism and megaloplastic anemia, and may be elevated in other malignancies, e.g., lung, ovarian, endometrial, gastrointestinal and bladder carcinomas (Seregni et al. 2004, Duffy 2006). It may be elevated in normal pregnancy in over 40% of cases (Bombardieri et al. 1993). False-positive elevations are also found in breast cancer patients during granulocyte colony-stimulating growth factor support for intensified adjuvant chemotherapy, values returning to normal in 1–2 months after treatment cessation (Briasoulis et al. 2001).

The tumour marker spike ("spike phenomen") may give false information when the marker is taken too soon after initiating a new treatment for metastatic disease, up to 30% of responding patients showing a transient increase in tumour markers due to cancer cell necrosis induced by treatment 1–3 months after the initiation of a new therapy (Yasaever et al. 1997, Cheung et al. 2000).

Marker sensitivity correlates with the stage of breast cancer (tumour burden), but there is a wide variation in the published results concerning the sensitivity as well as the specificity of this marker in detecting disease recurrence (Table 3).

The sensitivity of CA 15-3 can be enhanced by lowering the cut-off value, but only at the cost of lower specificity. Specificity can be increased by using higher cut-off levels and setting criteria for adequate serial rises (20–66%) in relation to previous value **(**Söletormos et al. 1993, Iwase et al. 1994**)**. However, the magnitude of variation ("critical difference") between successive marker levels constituting a clinically significant change is not well defined. This "critical difference" depends on both the analytical imprecision of the assay and the normal intra-individual biological variation (Söletormos et al. 1993).

CA 15-3 is widely used in practice in follow-up after primary treatment. The purpose behind it is to diagnose relapse (local or distant) earlier and with smaller tumour burden and to improve the survival of the patient by means of earlier treatment. However, the suspicion of local/locoregional relapse usually awakens clinically, and in these situations the sensitivity of CA 15-3 is poor. Pure locoregional relapses are treated with curative intent. When the marker is high in a locoregional relapse of breast cancer the disease should be regarded as occult metastatic disease with shortened lead time to distant metastases (Geraghty et al. 1992).

Table 3. Sensitivity of tumour marker CA 15-3 in different stages of breast cancer and its overall sensitivity and specifity in breast cancer.

Stage	Sensitivity* (%)	Specificity** (%)
I	5–15	
II	20–29	
III	30–45	
IV	54–70	
All	27–31	86–99

*Safi et al.1991, Dnistrian et al. 1991, Geraghty et al. 1992, Söletormos 1993 et al., Bombardieri et al. 1993, Tomlinson et al. 1995, Cheung et al. 2000, Seregni et al. 2004

**Safi et al. 1991, Bombardieri et al. 1993, Tomlinson et al. 1995, Molina et al 1995, Gion et al. 1995

In a review article by Gion the sensitivity of CA 15-3 in breast cancer follow-up was within the range 33–78% (median sensitivity 56%) and specificity 60–98% (median specificity 93%) (Gion et al. 1995). Söletormos and associates found the sensitivity of CA 15-3 to be 44% and the specificity 100% in postoperative follow-up of high-risk breast cancer patients for detection of recurrent disease. The median follow-up time was 747 days and recurrence was detected when the increase in CA 15-3 level was when repeated twice ≥ 26% or once ≥ 66% above the cut-off value (30 IU/ml). In the study 25 recurrences were detected among 90 patients and CA 15-3 detected 11 out of these 25 (Söletormos et al. 1993, 2004). In the postoperative follow-up of 533 breast cancer patients Molina and associates in a prospective trial with a mean follow-up of 6.2 years found the sensitivity of CA 15-3 to be 41% and the specificity 99% in detecting relapse of the disease. The cut-off value for CA 15-3 was higher than usual, i.e. > 60IU/ml. Altogether 91 relapses were detected and CA 15-3 was elevated in none of the 22 cases with locoregional relapse (Molina et al. 1995).

Further, the usefulness of CA 15-3 has been studied in the screening context and in the diagnosis of breast cancer, but the majority of studies have shown no significant elevations in primary localized breast cancer (Safi et al. 1991). According to Seregni there is no use for this marker in screening or in the early diagnosis of breast cancer (Seregni et al. 2004). Nor is there any benefit from CA 15-3 in detecting contralateral breast cancer (Bombardieri et al. 1993).

On the other hand, Ebeling and Molina note a prognostic value for CA 15-3 taken preoperatively in primary breast cancer, and elevated values correlated with early relapse (Ebeling et al. 2002, Molina et al. 2003). Likewise, high preoperative CA 15-3 concentrations have predicted an adverse outcome in 600 breast cancer patients regardless of lymph node status (Duffy et al. 2004). O´Hanlon found an 83% likelihood of stage III breast cancer when CA 15-3 values were over 40 IU/l (O´Hanlon et al. 1995).

In metastatic breast cancer CA 15-3 is according to Tampellini elevated in altogether 61% of patients and, in different metastatic sites, in 72% of liver metastases, 76% of malignant pleural effusions, 63% of pulmonary metastases, 53% of bone metastases and 28% of skin and lymph node metastases (Tampellini et al. 1997). Crippa detected higher values of CA 15-3 with increasing numbers of metastatic sites in the skeleton and when only 1–3 metastatic sites were found in the bones the marker was elevated in only 30% (Crippa et al. 1992). Berruti found CA 15-3 to be more often elevated in visceral than in bony/soft tissue metastases, i.e. 86–95% vs. 33%, respectively (Berruti et al. 1994).

A possible explanation for the marker value in the reference area in advanced disease is a spread presence of antibody against mucins in the sera of patients with

breast cancer (Gourevitch et al. 1995). In metastatic breast cancer there were no differences found between pre- and postmenopausal women (Scaramuzzi et al. 1990).

In the metastatic setting a decrease of CA 15-3 has been found to correlate with favourable therapeutic response (Dnistrian et al. 1991). Likewise, Robertson found changes in CA 15-3 to precede the clinical response (Robertson et al. 1999). In most cases a 25–30% change between successive values or a 66% change as a single value has been regarded as significant change (Söletormos et al. 1993). When the marker value is highly elevated at first recurrence the prognosis is worse (Gion et al. 2002, Tampellini et al. 1997, Berruti et al. 1994), and the persistence of high marker values is also associated with poor prognosis. CA 15-3 has been found useful in following treatment outcome (Depres-Brummer et al. 1995, Pronk et al. 1997, Duffy 2006). However, CA 15-3 alone is not routinely recommended in monitoring the efficacy of treatment and should not be used as the only determinant for treatment decision, but it may be helpful in response monitoring in less easily measurable disease (Smith et al. 1999, ESMO Minimum Clinical Recommendations 2005b, Duffy 2006) as in pleural effusions, ascites and bone metastases. These metastases, not amenable to assessment by UICC (International Union against Cancer) criteria, may constitute 10–40% of all metastases.

No benefit has been detected in using a combination of MUC1 markers but the sensitivity may increase by combining different types of markers (Robertson et al. 1999).

4.4.1.2 CA 27.29

In some cases CA 27.29 may be slightly more sensitive than CA 15-3 (Gion et al. 1999, 2001). CA 27.29 has been approved by the US FDA (United States Food and Drug Administration) for clinical use in the detection of recurrent breast cancer in patients with stage II/III disease. Despite this, guidelines of the American Society of Clinical Oncology 2001 (ASCO guidelines, Bast et al. 2001) and of European Society of Medical Oncology (ESMO guidelines) 2005 do not recommend its use in the routine follow-up of breast cancer.

4.4.2 Oncofetal proteins

4.4.2.1 CEA

Carcinoembryonic antigen (CEA) is a single-chain glycoprotein of 641 amino acids and about one half of the antigen consists of carbohydrates. It is normally found in the embryonic endothermal epithelium and was isolated from malignant tissue in the mid-1960s. CEA may be part of the immunoglobulin gene "superfamily" and is possibly involved in the intercellular or cellular-matrix recognition mechanisms (Cheung et al. 2000, Seregni et al. 2004). CEA is usually measured by different immunoassays.

CEA is commonly used in the follow-up of colorectal cancers, but has been applied in the follow-up of breast cancer, this especially before CA 15-3 was introduced. It is elevated in many other malignancies, including gastrointestinal, liver, pancreas, pulmonary, prostatic and ovarian cancers. It may also be elevated in the elderly and in smokers, and in inflammatory as well as other conditions, including diverticulitis, gastritis, bronchitis, cholangitis, liver abscess and cirrhosis (Cheung et al. 2000). CEA elevations in breast cancer are related to tumour burden, i.e. stage of disease (Table 4).

CEA is not reliable in detecting early breast cancer (Dnistrian et al. 1991). Söletormos compared CA 15-3 and CEA in the follow-up of high-risk breast cancer patients and found the sensitivity of CEA to be much lower compared to CA 15-3, 10% vs. 48% (Söletormos et al. 1993). According to a review by Gion and associates (Gion et al. 1995) the median sensitivity of CEA was 45% (range, 7–89%) and median specificity 71% (range, 39–99%). Molina and associates in their prospective trial evaluated the sensitivities of CA 15-3 and CEA in detecting early recurrences in breast cancer patients and found the sensitivity of CEA to be 46%, of CA 15-3 54% and of both together 64%, specificity being 99% for both single markers (Molina et al 1995). The lead time to CEA elevation was 4.9 months and higher lead time of tumour markers was found with ER-positive (CEA elevated) or PR-positive (CA 15-3 elevated) tumours. The lead time is defined as the time interval between the time-point when the tumour marker test first shows elevated values in an asymptomatic patient to the time-point when the the relapse is verified by symptoms.

Table 4. Sensitivity of tumour marker CEA in breast cancer patients with different stages of disease and in healthy controls (cut-off value < 6ng/ml) (Blamey 1995).

	Sensitivity of CEA (%)
Stage of breast cancer	
I/II	9
III	12
IV	39
Controls	4

Some authors have found addition of CEA to CA 15-3 to be of no additional benefit (Guadagni et al. 2001). In contrast, Robertson found the tumour panel CA 15-3+CEA +/– ESR (erythrocyte sedimentation rate) to provide an objective method to guide therapy in patients with metastatic breast cancer (Robertson et al. 1999). Kurebayashi and associates found time to progression (TTP) in pre-treatment CEA-positive patients to be significantly shorter than in CEA-negative patients in advanced breast cancer. Their prospective study also supported the finding that changes in tumour markers CEA and CA 15-3 correlate with therapy response and a greater than 20% reduction in tumour marker levels to be a favourable predictive factor for time to progression (TTP) during systemic therapy (Kurebayashi et al. 2004). Söletormos monitored different stages of breast cancer with CEA, CA 15-3 and TPA (tissue polypeptide antigen) and the findings suggested that the tumour marker information may be used to discontinue ineffective treatments and thereby reduce unnecessary adverse events (Söletormos et al. 2004).

On the other hand, some prognostic value has been detected for CEA taken preoperatively in primary breast cancer. When comparing pre- and postoperative CEA values in primary breast cancer a decrease in postoperative values was found to be a strong independent prognostic factor for disease-free survival (DFS) and death from disease (Molina et al. 2003, Ebeling et al. 2002).

As a conclusion, tumour marker CEA has proved to be inferior to tumour marker CA 15-3 in breast cancer.

4.4.3 Cytokeratins

The TPA (tissue polypeptide antigen), TPS (tissue polypeptide-specific antigen) and CYFRA 21.1 (cytokeratin fragments 21.1) molecules belong to the family of cytokeratins (CKs). These constitute one of the seven classes of intermediate filaments, which together with microtubules and actin microfilaments make up the cytoskeleton of most eukaryotic cells. Human CKs comprise 20 related polypeptides (CKs 1-20), which can be separated into two subfamilies. CKs 9-20 are the more acidic, type-I CKs, while CKs 1-8 form the neutral/basic type-II group of proteins. Different epithelial cells express characteristic, differentiation-dependent combinations of two or more CKs, with type I and II polypeptides always occurring in stoichiometric amounts, i.e. as "pairs". In simple epithelial cells from many tissues the combinations CK8/CK18 and CK8/CK19 are very often expressed, and are also found in the majority of epithelial breast carcinomas. Tumour marker assay TPA recognizes all three CKs 8, 18 and 19, TPS measures CKs 8 and 18 and Cyfra 21.1 detects CKs 8 and 19 (Seregni et al. 2004).

4.4.3.1 CYFRA 21.1

CYFRA 21.1 is a polypeptide most likely released after cell death, and elevated levels have been found in various malignancies, whereas healthy individuals with abnormal levels are fairly rare (Nakata et al. 2000). However, 20–30% of patients with benign diseases such as cirrhosis, renal failure and infectious lung diseases show higher CYFRA 21.1 levels.

Serum CYFRA 21.1 levels have not differed between receptor-positive vs. –negative breast cancer patients. In a comparison of markers CYFRA 21.1, CA 15-3 and CEA in a retrospective study (n = 173) CYFRA 21.1 had the highest rate of positivity in stages I–IV in breast cancer patients, and in stage IV both CYFRA 21.1 and CA 15-3 were elevated in 83% (10/12) (Nakata et al. 2004). In the same study the sensitivity of CYFRA 21.1 in recurrent breast cancer was much higher than that of CA 15-3 or CEA, respectively 85% vs. 35% vs. 27%. Patients with both pre- and postoperatively elevated values of CYFRA 21.1 had the greatest frequency of recurrence compared to patients with preoperatively high/postoperative normal or preoperative/postoperative normal CYFRA 21.1 values, respectively 67% (5/84) vs. 21% (6/29) vs. 6% (2/3). In metastatic breast cancer the response to chemotherapy might be monitored with CYFRA 21.1.

In contrast to this, Giovanella and associates in a retrospective study involving 194 patients detected no significant improvement in the diagnostic or prognostic evaluation

and follow-up of breast cancer patients by CYFRA 21.1 compared to CEA or CA 15-3 (Giovanella et al. 2002).

The use of CYFRA 21.1 for breast cancer management is thus not justified in clinical practice (Giovanella et al. 2002, Seregni et al. 2004).

4.4.3.2 TPA

Tumour polypeptide antigen TPA is formed during the late S-phase and G-phase of cell division and is released during and immediately after mitosis.

Söletormos in his prospective trial (n=90) investigated the ability of CA 15-3, CEA and TPA to identify, predict and exclude metastases in bone/viscera during the adjuvant treatment and follow-up of high-risk breast cancer patients. It was found that TPA correctly classified only 19% of patients with metastases and 98% of the patients without, i.e. the sensitivity was low and the specificity was fairly high (Söletormos et al. 1993). TPA was inferior to CA 15-3.

4.4.3.3 TPS

Tissue polypeptide-specific antigen TPS is considered to be involved in cell proliferation. The sensitivity of TPS correlates strongly with the stage of breast cancer and has not been found useful in the primary diagnosis of breast cancer (Devine et al. 1995). The sensitivity in detecting early breast cancer was only 16%, its specificity higher 90% (Eskelinen et al. 1997).

In metastatic breast cancer Pronk found TPS helpful in determining response to treatment when a change of more than 25% in serum levels of the marker was taken as significant. However, the study population in question was small (n=60) and not randomized. The association between response and change in marker levels was stronger for CA 15-3 than TPS (Pronk et al. 1997). In contrast, Einarsson found the sensitivity of TPS, CA 15-3 and TPS + CA 15-3 to be high, 81% vs. 79% vs. 92% in 63 metastatic breast cancer patients before starting treatment and even better in visceral/bone metastases compared to soft tissue metastases/locally advanced disease, respectively 94%, 89%, 98% vs. 44%, 50% ,75%. In therapy monitoring TPS correlated better than CA 15-3 with treatment outcome. However, in the study in question there were only a few patients (Einarsson et al. 2000).

TPS has proved to be a good indicator of responding disease, but CA 15-3 was better in finding progressive disease (Jonsson et al. 1995). Robertson observed that in

1/3 of patients developing progressive disease TPS was not an early indicator of disease progression (Robertson et al. 1995a). TPS may indicate the response to applied therapy only after one month independent of the type of metastases, i.e. earlier than CA 15-3 (van Dalen et al. 1996).

In the follow-up of localized breast cancer no reliable data are available to confirm the usefulness of TPS in detecting early recurrences.

4.4.4 Combinations

Anan and associates (2002) studied a tumour panel of TPA + NCC-ST-439 (cancer antigen NCC-ST-439) + CEA/ CA15-3 in the postoperative follow-up of patients with early breast cancer. The authors concluded that serial determinations of these markers are of value in patient selection for radiologic exploration but, in any case, the health benefits and cost-effectiveness of follow-up focused on measurements of tumour markers need to be evaluated in large randomized trials. The study was retrospective, involving 643 patients, and using three of the markers the sensitivity to detect asymptomatic disease progression was 82%.

Tumour panels are mostly used in recurrent disease for therapy monitoring and in clinically ambiguous situations. Nicolini in a retrospective study involving 467 patients derived some clinical benefit from the tumour panel CEA + TPA + CA 15-3 in excluding or confirming suspicious lesions in chest X-rays or liver ultrasound as metastatic. In these situations the positive predictive value (PPV) for thoracic metastases was 92%, for liver metastases 90%, and in both situations negative predictive value (NPV) was 100%, i.e. false-positives were excluded with certainty (Nicolini et al. 2000).

The same tumour panel was also used in recurrent disease (n = 221) with suspicious lesions in the bone scan, chest X-ray and liver ultrasound. PPV for all three sites subject to suspicion of metastatic lesion was 85% (for bone 69%, for liver 83%, for chest 93%), and correspondingly NPV 96% (for bone 98%, for liver 91%, for chest 86%). The study in question was also retrospective but the average follow-up was fairly long, i.e. 86 months. Suspicious lesions were detected in 86% of bone scans, in 57% of chest X-rays and in 40% of liver ultrasounds, but metastases were found in only 14% vs. 9% vs. 5%, respectively. Clinical symptoms (23–53%) were not helpful in predicting metastatic disease. The authors concluded that brief monitoring with this tumour panel was important in confirming/excluding metastatic disease in patients suspected of metastatic disease following common instrumental investigations and particularly important in avoiding false-positive diagnoses (Nicolini et al. 2003a).

The same tumour panel (CEA + TPA + CA 15-3) was also used by Söletormos and associates in three different situations, namely postoperative monitoring, during first chemotherapy and in the follow-up after first-line chemotherapy in metastatic breast cancer patients. They found no extra benefit from CEA and TPA in postoperative follow-up in addition to using CA 15-3 as a single marker. Using all three markers the sensitivity for detecting progression during first-line chemotherapy in breast cancer patients improved from 44% to 69%. In the follow-up after response to first-line chemotherapy the sensitivity of CEA and CA 15-3 together in detecting progression was 68% and TPA had little additive value. The lead time in 90% of patients was shorter than 3 months (Söletormos et al. 2004). Overall, these markers were unreliable in excluding clinical recurrence and progression.

Robertson and Dixon introduced the concept Nottingham biochemical index (NBI) in therapy monitoring in newly diagnosed breast cancer patients with metastatic disease (Table 5) (Dixon et al. 1991, 1993, Robertson et al. 1999). One of the markers, CA 15-3, CEA or ESR (erythrocyte sedimentation rate), was elevated in 84% of patients at diagnosis and in 96% during therapy. If ESR was not included 12% fewer patients were assessable. Excellent correlations with UICC criteria were found and tumour marker elevations were detected 3–9 months earlier than progressive disease with the UICC criteria. Tumour marker changes were concluded to predict the therapeutic outcome. The use of all three markers allowed the therapy of all patients to be marker-directed and NBI was regarded as a measure of early therapeutic response.

In general, for the postoperative follow-up of a breast cancer patient tumour marker panels are not superior to the single tumour marker CA 15-3.

Table 5. Nottingham Biochemical Index/Scores* for changes in tumour marker concentrations in breast cancer (Robertson et al. 1999).

Tumour marker	Scores for changes in tumour marker values				
	Upper limit of normal value	Non-elevated marker >10%	Marker decrease ≤10%	Stable, marker decrease/increase	Marker >10%
CEA	6 ng/ml	0	–2	+1	+2
CA 15-3	33 IU/l	0	–2	+1	+2
ESR**	20 mm/h	0	–1	+1	+2

*overall biochemical score is summation of the individual score for each marker
**ESR, erythrocyte sedimentation rate

4.4.5 Others

Neu-oncoprotein (HER-2 ectodomain) is the protein product of the neu (cErbB2/HER2Neu) oncogene and has been found in the sera of breast cancer patients and suggested to be a potential candidate as a novel serum tumour marker in breast cancer. Neither Eskelinen nor Robertson found it useful in the diagnosis of breast cancer or in predicting patient outcome (Robertson et al. 1995b, Eskelinen et al. 1997). The negative prognostic significance of high circulating levels of the HER2 ectodomain seems to be related to resistance to chemotherapy, lack of complete response and shorter duration of response (Colomer et al. 2000, Seregni et al. 2004). It might be a surrogate marker to identify patients benefiting from trastuzumab treatment and is possibly useful in monitoring this "target therapy" (Wu 2002).

Haidopoulos in a retrospective study found anti-CEA antibodies in the sera of breast cancer patients to be a more sensitive tumour marker than CEA, and their presence was associated with improved recurrence-free survival (Haidopoulos et al. 2000).

4.4.6 Conclusions from previous studies

The possibility of using tumour markers in the follow-up of breast cancer patients is an attractive prospect. Nonetheless, the sensitivity of these tools has been low even though specificity has been fairly high. Most published data have been retrospective and numbers of patients in the trials small. Also, there has been considerably variation regarding cut-off values of tumour markers distinguishing normal from elevated (pathological) serum levels. While none of the tumour markers or combinations can be considered reliable in excluding or confirming early recurrence of breast cancer in an asymptomatic patient, so far CA 15-3 can be considered a point of reference.

4.5 Treatment of breast cancer patients

4.5.1 Surgery

DCIS is often found in mammography as microcalcifications**,** operated by broad excision followed by radiotherapy or by mastectomy in cases of an extensive in situ component (EIC). Immediate reconstruction of the breast after mastectomy for DCIS is regarded as the ideal treatment.

The primary operation for localized invasive breast cancer can be mastectomy or breast-conserving surgery (BCS), that is resection, depending on the magnitude of the disease, the size of the breast and the age of the patient and, of course, the opinion of the patient. The choice of BCS is increasingly common but there is still place for mastectomy especially in young women who have in any case higher risk of local relapse (Sainsbury et al. 2000) and in older women who may often avoid radiation therapy when mastectomy is done. According to a meta-analysis the 10-year survival rates after BCS and mastectomy in early-stage breast cancer are equal (Morris et al. 1997). Likewise, Poggi and associates found no difference in DFS and OS in eighteen-year results for breast cancer patients treated with mastectomy or breast-conserving surgery combined with radiotherapy (Poggi et al. 2003). Lymphadenectomy of the axilla is usually undertaken directly if there are pathologic nodes in the axilla. Sentinel node biopsy (SNB) is increasingly used, and when the sentinel node is negative and no pathologic nodes are found upon palpation or by radiological examination the surgeon has no need to dissect the nodes in the axilla. In such case the postoperative disadvantages for the arm consequent upon lymph node evacuation can be avoided (Leidenius et al. 2005). The sensitivity of SNB is high, about 95% (Miltenburg et al. 1999, Rutgers 2004a).

Local relapse in the scar can be operated, often with curative intent. In metastatic disease, pathologic fractures can be successfully operatively fixed. In advanced disease a solitary visceral metastatic lesion can sometimes be operated when the disease is otherwise in control, but in advanced breast cancer there are usually multiple metastases in many organs and the only possible means of controlling the disease is systemic treatment with drugs.

4.5.2 Radiotherapy

The aim of postoperative radiotherapy is to reduce the local relapse rate, and after irradiation local relapses have decreased by 2/3 from 30% into 10% (Early Breast Cancer Trialists´ Collaborative Group 2000). The local relapse rate after BCS is especially high in breast cancer patients under aged 35 years and when the tumour contains EIC (Voogd et al. 2001).

Also, breast cancer patients treated with radiotherapy since the year 1970 have evinced better overall survival compared to patients not receiving irradiation. Even 10–20 years after radiotherapy overall survival has been 9%–20% higher for breast cancer patients receiving initial radiotherapy compared to those without radiotherapy (Van de Steene et al. 2000, Whelan et al. 2000, Ragaz et al. 2005).

Today radiotherapy is based on computed tomography planning and the radiation dose to healthy normal tissue can be minimized. After a breast cancer operation the total radiation dose is in the range of 50–60 Grey.

Radiotherapy is recommended in primary localized breast cancer after BCS to the operated breast and in cases of node-positive breast cancer also to the regional lymph node areas in the axillary and clavicular pits. However, some studies show that in T1-2 breast cancers in older patients (>70–75 years of age) conservatively operated with clear margins, adjuvant radiotherapy could be omitted without substantially increasing the risk of relapse or be replaced by adjuvant tamoxifen (Hughes et al. 2004, Carlson et al. 2005, Livi et al. 2005). After mastectomy radiotherapy is delivered to the thoracic wall if the tumour has been extensive and to the regional nodes in node-positive cases. However, debate persists as to whether irradiation could be omitted in cases with only <3 positive axillary nodes (Overgaard 2001).

Radiotherapy is also beneficial after resection of DCIS. The 4-year local relapse-free rate among patients with resected DCIS and postoperative radiotherapy has been 7% higher compared to the patients with resection only, 91% vs. 84%. Irradiation reduced the risk of local relapse equally for invasive (40%) and non-invasive (35%) cancers (Julien et al. 2000).

In a distant metastatic setting, palliative radiotherapy can be successfully applied to painful bony metastases, to prevent skeletal complications and also to treat cerebral metastases.

4.5.3 Drug treatment

Neoadjuvant chemotherapy with antracycline/taxane-based regimens can be given preoperatively before primary surgery; at least four cycles should be given. Indications for neoadjuvant treatment are locally advanced disease or inflammatory breast cancer. A meta-analysis of neoadjuvant vs. adjuvant systemic treatment in breast cancer was recently published and no difference was found in terms of survival (Mauri et al. 2005). In clinical practice, however, adjuvant chemotherapy is more common compared to neoadjuvant chemotherapy.

Adjuvant medical treatment is used increasingly, even very small carcinomas with aggressive features and without axillary involvement being treated (Goldhirsch et al. 2005). The intrinsic tumour features, the age, other chronic diseases and general condition of the patient serve as individual selection criteria for different treatments.
Patients under 35 years of age should all be treated, preferably with combined consecutive chemo-endocrine therapy; following chemotherapy endocrine therapy should also be given in cases with hormone receptor positive disease. Younger patients

benefit from chemotherapy more than older ones and all premenopausal patients can be included in the group of young patients. In the adjuvant setting antracycline- and taxane-based polychemotherapy for 4–6 courses has become both more common and more beneficial (Cole et al. 2001, Early Breast Cancer Trialists` Collaborative Group 2005, Trudeau et al. 2005). Breast cancer patients < 50 years of age when diagnosed and treated with polychemotherapy for six months have an annual breast cancer death rate reduced by 38% and in the age group 50-69 years at diagnosis the reduction rate is 20%. At 15 years from diagnosis of breast cancer, recurrence is reduced by 12% in younger women and by 4% in older women and, likewise, mortality is reduced by 10% and 3%, respectively (Early Breast Cancer Trialists` Collaborative Group 2005).

After chemotherapy hormone receptor-positive patients gain additional benefit from the selective estrogen receptor modulator (SERM) tamoxifen used for 5 years, which also lowers the risk of hormone receptor positive contralateral breast cancer. Adjuvant tamoxifen for 5 years reduces the annual breast cancer death rate by 31%, largely irrespective of the use of chemotherapy and of age. Combined adjuvant polychemotherapy for six months and tamoxifen for 5 years in hormone receptor-positive breast cancer reduce the mortality of breast cancer patients throughout the next 15 years from diagnosis by 57% in younger and by 45% in older patients (Early Breast Cancer Trialists` Collaborative Group 2005).

Premenopausal patients with hormone receptor-positive disease also benefit from ovarian ablation, which may be caused either by irradiation or by luteinizing hormone-releasing hormone analogs (LHRH analogs). Postmenopausal patients have a wider range of alternatives in adjuvant endocrine treatment; besides tamoxifen there are aromatase inhibitors and some patients may benefit from extended adjuvant endocrine treatment for over 5 years (Goss et al. 2003, Coombes et al. 2004, ATAC Trialists 2005, Carlson et al. 2005, Mouridsen and Robert 2005). Adjuvant treatments with trastuzumab monoclonal antibody combined with chemotherapy have yielded excellent results in reducing relapses during the first follow-up years in HER2-positive breast cancer patients (Piccart-Gebhardt et al. 2005, Romond et al. 2005, Joensuu et al. 2006). Adding adjuvant trastuzumab to adjuvant polychemotherapy for one year has given an absolute benefit of 8–12% in DFS at 2 vs. 3 years from randomization, and in the above-mentioned study by Romond and associates the risk of death was also reduced by 33%.

In advanced disease the same drugs are used but with palliative intent (Table 6). For bony metastases systemic treatments with bisphosphonates are in general use.

Table 6. Commonly used endocrine therapies in metastatic breast cancer (ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of locally recurrent or metastatic breast cancer (MBC) 2005b).

Endocrine therapy group	Treatment
Selective estrogen receptor modulators (SERMs)	tamoxifen, toremifen
Luteinizing hormone-releasing hormone analogs (LHRH analogs)	goserelin, leuprorelin, triptorelin, buserelin
Third generation aromatase inhibitors	
non-steroidal	anastrozole, letrozole
steroidal	exemestane
Estrogen receptor antagonist	fulvestrant
Progestins	medroxyprogesterone acetate, megestrol acetate
Androgens	fluoxymesterone

4.6 Prognosis

4.6.1 Overall prognosis

The prognosis of breast cancer is constantly improving. In 2005, the 5-year, 10-year and 15-year relative survival rates of breast cancer patients in Finland were 87%, 77% and 70%, respectively (Finnish Cancer registry 2005). Nevertheless, Saphner and associates estimate the average annual hazard rate of recurrence for breast cancer in the post-treatment years 5–12 as still 4.3% per year (Saphner et al. 1996).

Regardless of the major improvement in prognosis over time breast cancer among patients diagnosed under the age of 50 often remains a chronic disease involving increased mortality throughout at least 40 years after diagnosis even in patients with localized disease. In this age group in Finland the cumulative 40-year relative survival is now approximately 43% for all breast cancers combined, 57% for localized cancers and 24% for cancers with regional spread (Brenner and Hakulinen 2004).

4.6.2 Node-negative vs. node-positive breast cancer

According to Shapiro the 20-year relapse-free survival (RFS) in T1N0 vs. T2N0 are 74–79% and 63–64%, respectively (Shapiro and Recht 2001). Recurrence occurs even in stage I (T1N0) in 10–30% of cases within 10 years and in stage II in 40–50% of cases within 5 years (Tomiak and Piccart 1993). In stage II the tumour is over 2 cm or axillary nodes are positive. The risk for relapse is higher in N+ than in N- disease, i.e. in the first year 5% vs. 1%, in the second year 7% vs. 3%, in the third and fourth year 10% vs. 5% (Wheeler et al. 1999). Newer evidence, however, suggests better prognosis in N+ disease with few positive nodes, that is, when only <3 of axillary nodes are affected the prognosis might be almost as good as in node-negative patients (Overgaard 2001). Other factors affecting survival of breast cancer patients are tumour size, grade and HER2 status as well as hormone receptor status (Tables 7 and 8).

4.6.3 Local vs. distal relapse

Nixon and associates in a retrospective analysis of 716 breast cancer survivors primarily treated by BCS and radiotherapy and with median follow-up of 134 months observed that the 10-year local relapse rate was not related to histologic grade but that the distant recurrence rate was significantly higher as grade increased (Nixon et al. 1996). In any case local relapse of breast cancer is often followed by distant relapse. Doyle and associates studied 10-year survival after local relapse (n = 112) in breast cancer patients primarily treated with BCS and radiotherapy and found OS to be 69% and freedom from distant metastasis to be 47% (Doyle et al. 2001).

4.6.4 Contralateral vs. second(ary) cancer

In addition of contralateral breast cancers patients with breast cancer suffer from secondary cancers. In a study by Fowble and associates the 10-year cumulative incidence of second cancers among 1253 breast cancer patients with stage I–II disease treated with breast conservation surgery and radiation therapy was 16%. Young age and family history predicted contralateral breast cancer and older age predicted an increased risk of non-breast cancer, the most common types of second non-breast malignancies being skin cancers, gynecologic malignancies and gastrointestinal malignancies, that is, colorectal and pancreatic cancers (Fowble et al. 2001).

Likewise, in situ carcinomas of the breast increase the risk of contralateral breast cancer. The cumulative probability at 10 years of being diagnosed with contralateral

breast cancer among women diagnosed with DCIS has been estimated to be 7% and among women with LCIS 7–14%, respectively (Claus et al. 2003, Chuba et al. 2005). LCIS seems to increase the risk of invasive breast cancer equally in both the ipsilateral and the contralateral breast. In these invasive cancers the proportion of lobular invasive breast cancer is increased to about one fourth (23%) and the proportion of ductal invasive cancer reduced to 50% (Chuba et al. 2005).

4.6.5 Survival in advanced (M1) breast cancer

More frequent and more intensive adjuvant treatments often delay the relapse of breast cancer after the first two years. However, up to 80% of recurrences appear during 5 years (Wheeler et al. 1999) and the median survival of patients with metastatic disease is still 2–3 years. In advanced disease the disease-free interval, limited metastatic disease and the location of metastases have an influence on overall survival. The survival of patients with visceral metastases, especially in the liver, is poorest and patients with bone-only metastases have longer median survival. Also, patients with hormone receptor-positive metastatic disease have longer median survival compared to patients with receptor-negative metastatic disease (Tables 7 and 8) (Joensuu and Toikkanen 1992). Tumour marker CA 15-3 and number of metastatic sites are not independent prognostic factors in metastatic disease (Tampellini et al. 1997), but in primary breast cancer high preoperative CA 15-3 is of prognostic value (Ebeling et al. 2002, Molina et al. 2003, Duffy et al. 2004).

Table 7. Factors affecting the survival of breast cancer patients (Joensuu and Toikkanen 1992).

Factor	5-year survival rate (%)
Tumour size	
<2cm	92
2–5cm	75
>5 or T4	58
Grade	
I	97
II	79
III	59
Axillary nodes	
pN0	93
pN+	62
Estrogen receptors	
<25 fmol/mg protein	65
>25 fmol/mg protein	88
Progesterone receptors	
<60 fmol/mg protein	69
>60 fmol/mg protein	90

Table 8. Factors associated with favorable prognosis in metastatic breast cancer (ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of locally recurrent or metastatic breast cancer (MBC) 2005b)

ER/PR positive tumour
Long disease-free interval (>1–2 years)
No visceral involvement
Limited metastatic disease, no bulky disease
HER2-negative tumour

4.7 Follow-up of breast cancer patients

4.7.1 Purpose of follow-up

The main aim in routine follow-up is early detection and treatment of curable recurrences of breast cancer, that is, local relapses, locoregional relapses or contralateral breast cancer. Evaluation of primary and adjuvant therapies and monitoring for long-term complications are also important aspects of follow-up. Patient rehabilitation and psychological support of patients belong likewise to the follow-up, as well as family and patient risk counselling (Tomiak and Piccart 1993). Rutgers defines the aim of follow-up as detection of curable disease, but it must comply with the needs of the patient (Rutgers 2004b). Important to patients is reassurance, information and with new symptoms prompt access to a medical specialist.

In stage I–II breast cancer 30% of patients face a relapse (Jacobs et al. 2001), and the relapses are distant in 70% of cases and local in 20%, and second primaries (contralateral and treated breast) constitute 10% of cases. Of local relapses 10-30% can be permanently cured and 70% of second primary cancers caught at an early stage are curable. Annually second primary cancers are detected in 0.4–0.8% of cases. Altogether about 60% of local relapses are found by physical examination (Hannisdal et al. 1993, de Bock et al. 2004a). Risk factors for local relapse after breast conservation are involved margins, EIC, patient age < 35 years, lymphatic or vascular invasion and high histological grade. After mastectomy axillary lymph node involvement, lymphatic or vascular invasion, histological grade III and tumour > 4cm in diameter belong to the risk factors for local relapse (Voogd et al. 2001, Sainsbury et al. 2000).

The local relapse rate in DCIS treated with mastectomy is 0–4%, in DCIS after BCS 16% and in DCIS after BCS and radiotherapy 10% at 5 years (Julien et al. 2000). In invasive cancers (T1-2, N0-1) the primary surgical operation (mastectomy vs. BCS) has not been seen to affect the local relapse rate, 10% at ten years (Rutgers 2004a). In locally advanced breast cancer even after multimodality treatment the risk of local relapse has been high, 20–30%. Jager and associates detected 60% of local relapses after mastectomy within the first three years (Jager et al. 1999). The prognosis of local relapse depends on the initial tumour parameters (T, N), disease-free interval (DFI) and the extent of relapse ("the smaller the better"). Local relapses are most often detected by a physician and thus regular follow-up visits by a doctor can be considered beneficial.

Distant metastases are found synchronous with or subsequent to a local relapse in 10–30% of cases (Mansfield et al. 1995). Unfortunately breast cancer with distant metastases is not a curable disease. The diagnosis of distant metastases is usually made

on the basis of the patient´s symptoms, and searching for distant metastases by routine investigations will not improve the life expectancy of the patient and may even be harmful (Rutgers 2004b). Metastatic disease is only exceptionally detected on routine visits and by physical examination, more often on internal attendance.

During follow-up visits the long-term consequences of adjuvant treatments can be detected, namely after surgery shoulder problems, lymph edema and neuralgia of the arm. After irradiation, in addition, radiation pneumonitis and painful sensations in the breast, after chemotherapy fatigue, amenorrhea, menopausal symptoms, occasionally congestive heart failure, cognitive deficits and rarely leukemias can be detected and treated (Shapiro and Recht 2001).

Muss and associates have studied the awareness of patients concerning follow-up and state that only 1/3 of patients understood the significance of history-taking in the follow-up visits, 2/3 of patients understood the purpose of physical examination and 92% of patients believed that early detection of distant metastases improved survival and treatment results. Patients thought that blood tests and imaging procedures were more important than history-taking in detecting metastatic disease (Muss et al. 1991).

Taken together, the aim of routine follow-up can not be detecting disease with distant metastases but finding curable local relapses or new primary cancers and treating patients´ symptoms caused by disease or treatment.

4.7.2 Symptoms in relapse-free breast cancer patients

The symptoms of relapse-free breast cancer patients have been little studied and most of the studies have been retrospective, concerning aspects of quality of life (QOL). These investigations have usually involved only a few patients and study participants have completed a mailed interview often only once.

In clinical practice breast cancer survivors suffer a great number of symptoms and disease recurrence with distant metastases is frequently found based on these. However, no comparison has been made to establish how much more common and more severe these symptoms are preceding the diagnosis of metastatic disease.

Bloom JR and associates studied QOL of young breast cancer survivors who were under 50 years of age at diagnosis. The study comprised an interview immediately after the primary diagnosis and a second interview of 185 relapse-free patients after 5 years from this. The authors concluded that 92% of relapse-free patients had good or excellent general health at this time-point. Better physical QOL was associated with reporting fewer chronic conditions, being employed and having been treated with chemotherapy. Better mental QOL was also associated with fewer chronic conditions and a smaller decrease in emotional support (Bloom JR et al. 2004). In contrast, Tchen and associates

found that adjuvant chemotherapy may cause more moderate or severe cognitive impairment in breast cancer patients aged below 60 years compared to age/education matched controls, 16% vs. 4%, respectively. In the 100 breast cancer patients in question a strong correlation between fatigue, menopausal symptoms and QOL was found, but none of the symptoms was significantly associated with the presence of cognitive dysfunction. The evaluation was made after completion of at least three courses of chemotherapy and assessment included neuropsychological tests and quality of life questionnaires (Tchen et al. 2003).

Ganz has also evaluated late health effects of treatment on younger women with breast cancer. The author found physical functions to be fairly good at 6 years after the initial diagnosis, but the youngest women, aged 25–34 years, experienced poorer mental heath and less vitality. The study involved 577 relapse-free patients who were under 50 years (mean age 43.5 y) at diagnosis of primary breast cancer, current mean age 49.5 years at the time of the mailed survey, six years after the initial diagnosis (Ganz et al. 2003).

Further, Ganz conducted two prospective studies of QOL in breast cancer survivors (Ganz et al. 1996, 2002). In the earlier study 139 relapse-free patients were interviewed after one year from initial surgery and after two (n = 94) or three years (n = 88) a mailed survey was made. Maximal recovery from the physical and psychosocial trauma of cancer treatment had occurred but many symptoms had remained or even worsened with time. Global QOL was poorer at three years compared to one year. The QOL of breast cancer survivors was nonetheless better than that of other patients with chronic conditions (Ganz et al. 1996). In the more recent study two surveys were made of the same relapse-free breast cancer patients, the first at a mean of 3.4 years from diagnosis (mean age of patients at initial survey 55.6 years) and the second at a mean 6.3 years from diagnosis; 763 relapse-free patients responded to the second mailed survey. Physical and emotional well-being were both excellent, the minimal changes between baseline and follow-up assessments reflecting expected age-related changes. Survivors with past adjuvant systemic therapy had poorer QOL and past chemotherapy was detected to be a statistically significant predictor of poorer current QOL (Ganz et al. 2002).

Dow conducted a mailed survey evaluating the QOL of 294 breast cancer survivors at average 68.5 months from diagnosis of breast cancer; 81% (238) of patients were disease-free. The median age of these patients was 50.0 years. The QOL, including all domains, physical, psychological, social and spiritual well-being, improved with time when comparing time under 3 years vs. time between 3–5 years vs. over 5 years from the initial diagnosis. The patients did, however, experience long-term changes in

all QOL domains after completion of therapy, affecting overall QOL adversely (Dow et al. 1996).

Dorval studied the long-term QOL of 98 relapse-free breast cancer patients by telephone interview, comparing it to the QOL of population controls of the same age and residential area but without cancer. On average 8.8 years had passed since the initial diagnosis of breast cancer. He found QOL to be equally good in both groups with the exception of arm problems and sexuality. The conclusion was that relapse-free patients do not need organized late psychosocial follow-up (Dorval et al. 1998).

In contrast, Holzner found reduced QOL, especially in emotional, social and sexual functioning, in relapse-free breast cancer patients not only after initial treatment at 1–2 years but also after a long post-treatment survival after 5 years. Fatigue, insomnia and pain were reported by patients even more after 5 years than between years 2–5. The study was cross-sectional, covering 87 patients with a median age of 53.9 years. On average 4.7 years had passed from primary treatment (Holzner et al. 2001).

For the most part the QOL of breast cancer patients some years after primary therapy appeared to be fairly good, with symptoms reducing over time. Younger patients with past chemotherapy remained symptomatic for a longer time, but most treated patients enjoyed good QOL. Since recurrent disease with distant metastases is suspected mostly on the grounds of new symptoms, the assumption can be made that survivors` symptoms will rapidly increase when distant relapses are diagnosed.

4.7.3 Visits and tests in the follow-up

Most authors and guidelines recommend routine follow-up of breast cancer patients after primary treatment (ASCO and ESMO guidelines) (Table 9**)**. In the first years more frequent follow-up is recommended; after 5 years annual follow-up is considered adequate but must be maintained for lifetime (Dershaw et al. 1992, Rosen et al. 1993). In fact, the majority of breast cancer patients desire follow-up for lifetime (de Bock et al. 2004b). Breast cancer patients have excess mortality even after 40 years from diagnosis (Brenner and Hakulinen 2004) and also for this reason the lifelong follow-up of breast cancer patients may in some cases be beneficial for palliation of symptoms detected.

Table 9. Recommended surveillance programs following primary treatment of early breast cancer (Mollick and Carlson 2004).

	PROFESSIONAL ORGANIZATION				
	ASCO (1998)	NCCN (2000)	Canada (1998)	Australia (2002)	ESMO (2001)
History, physical exam.	every 3–6 months for 3 years; 6–12 months for 2 years; annually beyond 5 years	every 4–6 months for 5 years; annually beyond 5 years	frequency individualized; at least every 12 months	every 3 months for 1 year; every 6 months for 4 years; annually beyond 5 years	every 3–6 months for 3 years; every 6–12 months for 2 years; annually beyond 5 years
Mammogram, conserv. breast	6 months following completion of breast irradiation, then as per contralateral breast	6 months after completion of breast irradiation, then as per contralateral breast	yearly	6–12 months after completion of breast irradiation, then as per contralateral breast	every 1–2 year
Mammogram, contralat. breast	yearly	yearly	yearly	yearly	every 1–2 years

4.7.3.1 Visits

Holli has studied the number of consultations attended by patients under surveillance (Holli and Hakama 1989, 1993). Patients were found to make twice as many visits to a doctor as recommended, 16 per patient in the first five follow-up years, a median 6.3 visits in the first year and a median 3.5 visits in years 4–5. The continuity of the patient/doctor relationship was poor; after 5 years patients had met on average 10 doctors (Holli and Hakama 1989, 1993).

Donnelly considers follow-up in hospital ineffective and unnecessary and would prefer follow-up in general practice after two years (Donnelly et al. 2001). Grunfeld in her randomized trial found no increase in time to recurrence detection and no increase in anxiety or no deterioration in QOL in patients in general practitioner (GP)-led vs. specialist-led follow-up. In addition, GP-led follow-up was well accepted by most patients. However, 1/3 of patients refused to participate in the trial. About 60% of GPs felt they needed more training in the examination of the irradiated breast (Grunfeld et al. 1995a, 1995b and 1996). A more recent trial by Grunfeld and associates brought out no differences in medical or in psychosocial health outcomes when comparing the post-operative follow-up of breast cancer patients led by family physician or specialist. The randomized trial involved 968 patients with an average follow-up of 3.5 years (Grunfeldt et al. 2006).

The risk of recurrence in breast cancer is not constant, being at its highest, 13%, between follow-up years 1–2 and then diminishing during years 2-5 and being annually after the 5th year 4.3% (Saphner et al. 1996). The risk for local relapse is higher in younger patients (Nixon et al. 1994), and in general younger, i.e. premenopausal, patients, especially under the age 35 years, should be followed more frequently, as should those with node-positive disease and/or grade III disease.

Incurable distant metastases are diagnosed for the most part during the first five years, but further, most potentially curable local relapses are detected in the first years of follow-up. Dewar and associates found half (48%) of all relapses to be detected on routine visits, and of these about 3/4 were local. In contrast, Pivot and associates found only one in four breast cancer relapses to be diagnosed on routine visits and 2/3 of these through history and physical examination (Pivot et al. 2000). Local relapses in breast cancer were asymptomatic in half of cases according to Dewar and Kerr and Loong and associates, but according to Perrone and associates even 2/3 of cases with local relapse were asymptomatic (Dewar and Kerr 1985, Loong et al. 1998, Perrone et al. 2004). On the other hand, only a minority (5%) of breast cancer patients with distant metastases were found to be asymptomatic and recurrence with distant metastases was most often

detected on interval visit (Schapira 1993, Loong et al. 1998). About 90% of all breast cancer relapses were detected based on symptoms (58%) or physical examination by patient/doctor (32%), whereas only 10% of them were based on specific tests. About 15% of all relapses were detected purely by physical examination (Schapira 1993).

Asymptomatic local relapses are often found early in clinical examinations and thus survival in these cases is better than that with symptomatic local relapses (Perrone et al. 2004). According to Dewar and Kerr the risk of synchronous distant metastases was significantly smaller, 11% vs. 47%, when local relapse was detected on routine visit as against interval visit, and thus the survival of patients with local relapse detected on scheduled visit was better. Unfortunately, however, at only 1% of follow-up visits (66/6764) were relapses eligible for curative treatment found and only 39% of these patients remained disease-free. A successfully treated relapse was thus detected at only 0.4% of routine visits. The authors concluded that routine follow-up might be maintained less frequently without compromising the benefit of the patient (Dewar and Kerr 1985).

The bones are the commonest site of metastases. All metastases in the central nervous system (CNS), 95% of bony metastases, 63% of pulmonary metastases and 51% of liver metastases are symptomatic (Table 10) (Pivot et al. 2000). In an earlier trial intrathoracic relapses were detected almost equally frequently as asymptomatic (54%) or as symptomatic (46%) (Hietanen 1986). No differences in DFS or in OS were detected between patients with symptomatic vs. asymptomatic distant relapses at diagnosis. Likewise, no influence on DFS and OS was found regardless of whether the distant relapses were diagnosed on routine vs. interval visit (Pivot et al. 2000).

Table 10. Metastatic sites and locations of first detected metastases with symptoms in breast cancer patients (n = 1125) (Pivot et al. 2000).

Site (%)	Location of first metastases, %	Symptoms with first metastases, %
Bones (42)	38	95
Lung/pleural (36)	18	63
Nodes (20)	14	9
Liver (13)	7	51
Chest wall/skin (22)	16	5
Breast (5)	2	0
Central nervous system (1)	1	100
Other (8)	4	88
Multiple (53)	–	–

4.7.3.2 Blood tests

In clinical practice, in addition to serum tumour markers, blood tests are performed in general in the follow-up of breast cancer patients even if their sensitivity in catching relapses is poor. Pandya found the first indicator of relapse in 12% of cases to be elevated values in blood chemistry, most often serum alkaline phosphatase (AFOS). Tests included, in addition of AFOS, lactate dehydrogenase (LD), glutamic oxalacetic transaminase (GOT, ALAT), glutamic pyruvic transaminase (GPT, ASAT) and bilirubin. Chemistry elevations were seen in 12% of bone metastases and 32% of liver metastases, but in most cases the first indicators (74%) were symptoms or clinical findings. Elevated chemistry values were seen in 9%, 16% and 9% in the first three follow-up years, respectively (Pandya et al. 1985). Mansi found AFOS to be elevated in 52% and gamma-glutamyl peptidase (GGT) to be elevated in 34% of relapsed patients at some time during follow-up, but in patients without relapse AFOS or ALAT was also elevated in 64% of patients (Mansi et al. 1988). Schapira showed AFOS to be elevated in 59% of patients with bone metastases, but also in one third of patients without (bone) metastases. Altogether, in only 6% of cases was the method of detection for relapse blood chemistry (Schapira 1993). Crivellari evaluated the relationship of six blood tests to the occurrence of overt metastatic disease. During the 6-month period after relapse AFOS was elevated in 20% of any metastases, in 32% of bone metastases, and in 71% of liver metastases. Correspondingly, GGT and ALAT were elevated only in liver recurrences and then in 62% and in 75% of cases, respectively. During the disease-free period 3–6% of patients (n = 4105) under surveillance yielded elevated values; most often AFOS was elevated. No benefit in detecting metastatic breast cancer was derived from use of blood tests for creatinine, calcium and bilirubin. As a conclusion, the author stated AFOS to be most effective among these blood tests in distinguishing patients with relapse from those without (Crivellari et al. 1995). Likewise, Joseph evaluated detection methods for breast cancer recurrence and in 3% of patients the recurrence was detected on the basis of elevated liver function tests, AFOS being elevated in 2% of cases in bone metastases and in 1% of cases in liver metastases (Joseph et al. 1998). Norum noted ALAT and GGT to be frequently elevated in the post-treatment period without recurrence, but in 25% of cases AFOS was of use in detecting liver metastases (Norum and Andreassen 2000).

Taken together, blood tests have been reviewed retrospectively and most reported results are rather old but nonetheless showed lack of sensitivity and specificity in detecting the early relapse of breast cancer in asymptomatic patients.

4.7.3.3 Imaging examinations

Except for mammography the sensitivity of imaging examinations has been modest in detecting early relapse in an asymptomatic breast cancer patient. Nevertheless, in the assessment of a lump in the breast ultrasound of the breast with biopsy is beneficial and in dense breasts and in younger patients ultrasound improves the sensitivity of the mammography (Saarenmaa et al. 2001a, b). Boccardo concludes from the results of the Working Group on the Clinical Aspects of Follow-up that the only beneficial radiological examination in routine follow-up is the mammogram up to the age of 70 years (Boccardo et al. 1995). Rutgers suggests a reasonable compromise in scheduling routine mammograms, namely annually until the age of 60 and thereafter every second year until the age of 70 years. Younger breast cancer patients after BCS have a higher risk of local relapse or new primary/contralateral breast cancer and for them annual mammograms are of benefit, whereas for older patients with mastectomy biannual mammograms might be the best choice (Rutgers 2004b).

Screening mammography is recommended up to the age of 70 years (IARC 2002). In addition, Parvinen and associates have found mammography screening in Finland to be benefial also in females over the age of 70 years (Parvinen et al. 2006). Mortality from breast cancer was reduced by 47% in women aged 65–69 years at entry when screened. The risk for recurrent breast cancer for patients in age group 40–74 years screened for breast cancer was likewise reduced (Immonen-Räihä et al. 2005). After 5 years the recurrence rate was 16% in the screened group and in the non-screened group 28%. In addition, Kauhava and associates estimated that about one third of the costs of fatal breast cancer were avoidable by means of mammography screening (Kauhava et al. 2006).

In spite of their poor sensitivity and specificity radiological tests are in common use in clinical practice. The skeleton has been found to be the first site of breast cancer relapse in 38% (426/1126) of cases and 95% of the metastases in bones were symptomatic (Table 10) (Pivot et al. 2000). In asymptomatic breast cancer patients bone scan was the detection method for bony metastases in only 3% of cases compared to a rate of 86% with a combination of bone scan and physical examination in symptomatic patients (Schapira 1993).

The first locations of metastases have been observed to be lung and pleural cavity in 19% of cases (208/1125). These metastases were symptomatic in 63% (Pivot et al 2000). The detection rate in chest X-ray for pulmonary metastases in asymptomatic breast cancer patients has been <1% (Chen et al. 2000, Hurria et al. 2003), and

according to Schapira chest X-ray was the detection method for breast cancer recurrence in 3% of cases (Schapira 1993).

The liver is according to Pivot and associates the first metastatic site in about 7% (74/1125) of cases in breast cancer. Liver metastases presented with symptoms in half (51%) of cases (Table 10). The first detection methods for liver metastases in asymptomatic patients were laboratory tests in 39%, radiological examinations in 31% and physical examination in 20% of cases when retrospectively assessed. Metastases in the liver were detected on scheduled visit in one third of cases, but only 1% of liver metastases were found by routine liver scan or blood tests. The routine use of radiological examination to detect liver metastases in breast cancer patients was not beneficial (Pivot et al. 2000).

In symptomatic patients the relapse of breast cancer is sought by native X-rays, ultrasound and bone scans and supplemented with computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) (Musumeci 1995). In symptomatic patients the clinical benefit of these tests is much higher compared to routine tests in asymptomatic patients (Table 11).

Indeed, the corner stones in visits are history-taking and physical examination of patients (Pivot et al. 2000). Symptoms reported by the patient arouse the suspicion of distant metastases and pathologic findings in physical examination can lead to the diagnosis of local recurrence (Schapira 1993). The role of blood tests and imaging examinations is modest by reason of lack of sensitivity and specificity in asymptomatic patients. Effective interventions can be initiated for depression, sexual dysfunction or menopausal symptoms when detected on visits. Even reassuring the patient to be "cancer-free" improves social functioning and enhances self-esteem (Jacobs et al. 2001).

Table 11. Radiological flow chart in symptomatic patients with suspicion of metastatic disease (Musumeci 1995).

Site	Procedures
Chest	X-ray→CT
Breast	X-ray→US→MR
Bone	Scan→X-ray→CT/MRI
Liver	US→CT→MRI
Brain	MRI
Spinal cord	X-ray→MRI

4.7.4 Cost of follow-up

Three types of economic analysis can be distinguished in health care (Macones et al. 1999, Coast 2004), namely cost-minimization, cost-effectiveness and cost-benefit analysis. In the published literature most often only the costs of follow-up are estimated without specific economic analysis.

Schapira and Urban have calculated the costs in minimalist vs. intensive surveillance for 5 years in the follow-up of breast cancer patients by evaluating some follow-up studies retrospectively. The costs were estimated according to the year 1990 in US dollars. The cost per patient was 5.6 times higher in intensive follow-up compared to the minimalist strategy, which included only routine physical examinations and annual mammogram, 5735 USD vs. 1025 USD. Altogether 86% of recurrences were found on the basis of symptoms reported by the patient or detected on physical examination by a doctor. By comparison, the overall difference in cost between intensive and minimal surveillance strategies would pay approximately 29% of the cost of screening by annual or biannual mammography for all women aged 40 years and older in the USA. Such a program would be expected to reduce breast cancer mortality by 30%, while the intensive surveillance program is not expected to reduce breast cancer mortality at all (Schapira and Urban 1991).

Mapelli and associates have estimated the follow-up costs of breast cancer patients in intensive vs. basic arms resembling the follow-up arms in the GIVIO randomized trial. Only direct costs were evaluated and for 5 years. Over 1300 patients participated in the trial and no difference in outcome (DFS, OS) was found between follow-up arms. However, the costs were estimated to be 5.1 times higher in the intensive compared to the basic arm (Mapelli et al. 1995).

Grunfeldt and associates have studied GP- vs. specialist-led follow-up of breast cancer patients for 18 months and noted no difference between the groups in time to detection of recurrences, in anxiety/depression or QOL of patients (Grunfeldt et al. 1996). They also made a cost minimization analysis and found the average cost in hospital-based follow-up to be 2.9 times higher. Especially clinical visits were 4.2 times more expensive in hospital than in primary care, even though the duration of the clinical visit by a specialist in the hospital was shorter. More tests were made by GPs as against specialists, blood tests 5 times and chest X-rays 3 times more often. Nonetheless no difference was found in the total costs of diagnostic tests. Thus the lower health service cost of primary care was attributable to the lower cost of a physician visit. The impact of excess costs of tests and false-positive test results would in any case have to be

evaluated before it could be concluded with certainty that primary care follow-up is the less costly option overall (Grunfeldt et al. 1999).

Most recurrences of breast cancer are found due to symptoms and often as interval relapses, and for that reason patient-initiated follow-up might be superior in terms of economic benefits compared to GP- or specialist-led follow-up (Brown et al. 2002). Brown and associates in a small (n = 61) randomized study assessed patient-initiated vs. standard follow-up of breast cancer patients with good prognosis after at least one year of primary treatment. Patients in the patient-initiated follow-up arm contacted the breast cancer nurse when needed and those in the standard follow-up made routine visits to a general practitioner. The mean time from treatment was 47 vs. 50 months and the mean age of patients was 63 vs. 68 years. Follow-up was only 12 months and assessments of QOL and psychological mortality (depression and anxiety) were made at 6 and 12 months. No difference in these aspects was found between the two arms. Only three phone calls were made to the study nurse. There was no difference between arms in the number of relapses. It is of note that half of the patients approached refused to participate. In this trial no costs were analyzed, but this small study showed that expenses could be reduced by patient-initiated follow-up when no routine visits to a doctor are made and the patient contacts the nurse by phone on clinical grounds.

Will and associates have estimated the life-time costs of breast cancer treatment in Canada in patients diagnosed in 1995 (Table 12). Breast cancer patients with all stages were included (Will et al. 2000). In recent years the cost of components in life-time total cost has, of course, probably already changed and is constantly changing by reason of new treatment modalities for breast cancer patients with both localized and advanced disease.

Table 12. Components of life-time costs in breast cancer patients during different periods of treatment (Will et al. 2000).

By period of treatment	(%)	By modality	(%)
Initial treatment	34	Hospitalization	63
Local recurrence	5	Radiotherapy	11
Follow-up (5 years)	7	Follow-up (5 years)	7
Radiotherapy of metastases	9	Hormonal therapy	6
Ongoing care (3 months from dg		Chemotherapy	5
as far as 3 months before death)	18	Diagnosis/staging	3
Terminal care		Surgery	3
(3 months before death)	27	Others	3
TOTAL	100	TOTAL	100

The follow-up costs constituted 7% of all life-time costs and the costs of hospitalization comprised the largest item. The average undiscounted life-time costs were 1.6 times higher in the advanced compared to the early stage (Will et al. 2000).

Holli and associates report stage II–IV breast cancer patients to have more than twice as many outpatient visits and inpatient hospital days compared to stage I patients during the first five years. Only breast cancer-related visits were analyzed. The costs can be seen to be directly related to the numbers of visits and hospital days (Holli et al. 1996).

Legorreta likewise concluded that the total cost of medical care during the four years of follow-up were directly related to the clinical stage of breast cancer at diagnosis, with higher costs in stage III–IV compared to stage 0–I. Breast cancer patients identified by screening mammography are likely to consume fewer health care resources than patients identified by other means (down-staging effect of screening mammography) and this is directly related to differences in medical expenditures for breast cancer (Legorreta et al. 1996). Kauhava and associates also found population-based mammography screening programmes to reduce the costs of hospital treatment of breast cancer (Kauhava et al. 2004).

Hensley and associates studied the follow-up of breast cancer survivors with a median follow-up of 12.2 years. A survey was sent to 245 stage II patients with good performance status, i.e. PS 1-2. During the last year 87% of patients had been checked by a specialist (70% medical oncologist, 15% surgeon) and 78% had made 1–2 visits during the last year while 4% had made no visits. Screening tests had been carried out frequently during the preceding year, i.e. in addition to mammogram, 91% had blood tests, 59% chest X-ray, 18% bone scan, 11% CT and almost one half tumour markers. The majority of the patients were white and insured, and 45% had at least some college education. Tests were made more often for patients visiting a medical oncologist, for those with lower income or of younger age. The median annual cost of follow-up per survivor was estimated to be 630 USD and expensive tests were over-used compared to the follow-up guidelines (Hensley et al. 2005).

No studies are available concerning the follow-up of breast cancer patients led solely by a cancer nurse, but in a study by Brown and associates (Brown et al. 2002) patients in different follow-up arms made routine visits to a general practitioner or phoned the study nurse when experiencing clinical problems. The study nurse then arranged consultation with a doctor when needed.

4.7.5 Conclusion from follow-up studies

Few follow-up studies have been made concerning the surveillance of breast cancer patients and even fewer prospective or randomized studies. Most have been retrospective and the numbers of patients have been rather small, while in the retrospective materials many confounding factors can be suspected. Two large randomized studies from the 1990s have been made in Italy. They are multicenter studies and of a general nature concerning overall survival. So far the results have not been confirmed in other trials from different countries and, in addition, the different components of follow-up incurring costs have not been analyzed in any detail.

5. AIMS OF THE STUDY

The general aim of the present study was to evaluate the effectiveness and the disadvantages of different follow-up schedules for breast cancer patients with localized disease after primary treatment and to establish a cost-effective follow-up schedule for clinical use.

The specific aims were as follows:

1. To evaluate certain common symptoms in recurrence-free breast cancer patients during follow-up and to compare the occurrence of these symptoms between relapse-free patients and patients with recurrence (article I).
2. To evaluate the sensitivity and specificity of diagnostic methods in detecting the first relapse (articles II, III).
3. To evaluate the impact of the intensity and amount of services during follow-up on health outcome measured by DFS and OS (articles III, IV).
4. To compare the total cost of different schedules in the follow-up of breast cancer patients (article IV).

6. PATIENTS AND METHODS

6.1 Study cohort

Consecutive breast cancer patients with localized disease after primary treatment were randomized (Figure 1) at the oncology department of Tampere University Hospital by simple random sampling into four different follow-up schedules (A, B, C, D). The different schedules were explained personally to patients and their oral informed consent was obtained as was then the common practice in Finland. The patients were reassured that all clinically necessary tests to detect a relapse could also be used on clinical grounds in the follow-up schedules without routine tests. Randomization was made by phone-call to the secretary of the oncology unit, who did not take part into the treatment or follow-up of the patients. The randomization time continued from May 1991 to December 1995. The patients were followed at the Department of Oncology for five years or until the first relapse either local or distant. The follow-up study was approved by the Tampere University Ethical Committee.

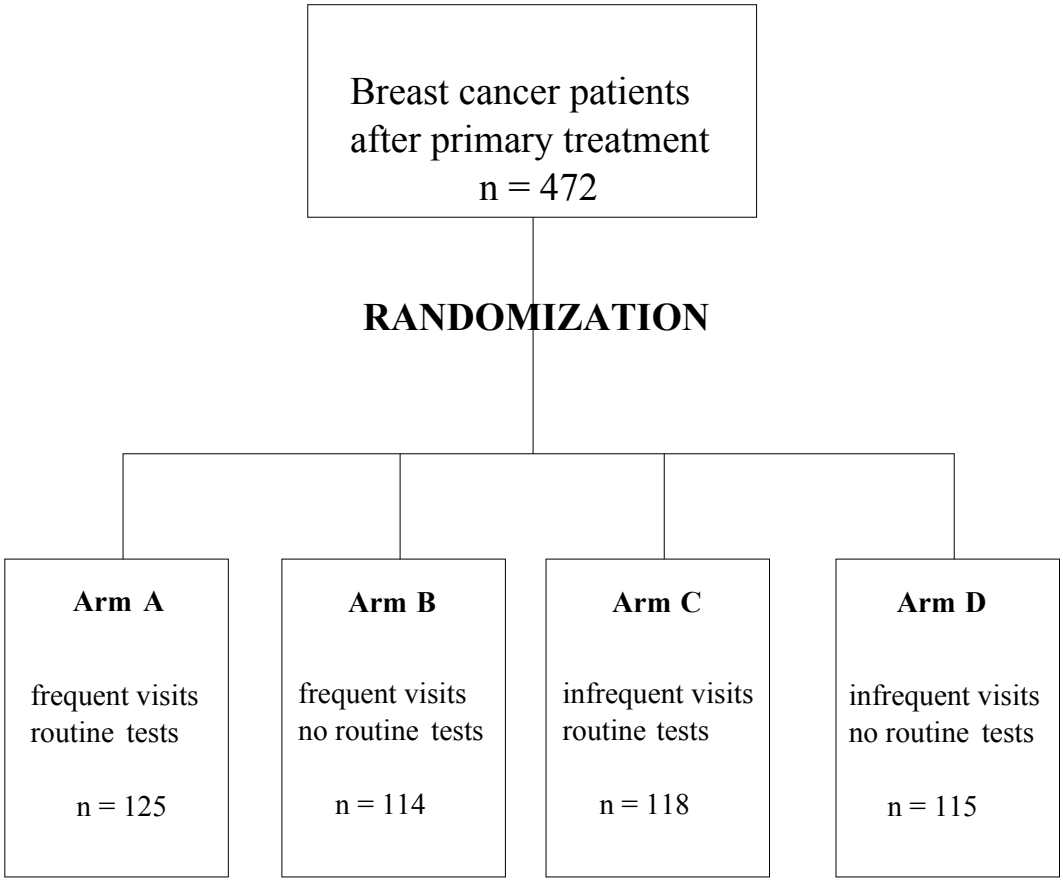

Figure 1. Randomization schedule in the Tampere breast cancer follow-up study.

The study population comprised 472 patients from the Tampere University Hospital district, i.e. the Pirkanmaa region. The median age of the patients was 58 years and 27% of them were pre-menopausal. Most had invasive cancer with or without axillary lymph node metastases, but a few per cent had non-invasive ductal cancer in situ; in other words the study patients had stage Tis/T1-4, N0-1, M0 disease. About 3% of breast carcinomas were over 5 cm in diameter (T3-4) and node-positive disease (N1) was found in about 22% of patients. Estrogen receptors were positive in 2/3 of tumours and one half of the tumours were also progesterone receptor-positive (Table 13).

The randomization process itself made for some imbalance between arms; in arm A the number of patients was higher than in the other arms and, in addition, the median age of the patients in arms A and B was a few years lower than in arms C and D. This entire study was a part of a larger follow-up study where power calculations were not made in 1991. The total number of patients in the follow-up schedules was planned up to 600, 150 in each arm, the main outcomes being quality of life, cost and recurrences. Initially it was estimated that the number of 600 patients would be clinically enough in order to get the answers to the main questions (symptoms, cost and recurrences, not survival). In consequence of new large adjuvant trials beginning in the clinic the number of patients here remained at 472. The randomization time to this study was not lengthened due to changing adjuvant treatments for breast cancer. These new treatments might have constituted confounding factors in this follow-up study in making the patient population imbalanced. The cohort can be considered a representative spectrum of breast cancer in the Pirkanmaa area (Table 13). The incidence of breast cancer in the Tampere University Hospital district (Pirkanmaa region) has been high: over 300 cases annually in the years 1999-2003 (Cancer Incidence in Finland, 2005).

This study consisted of four sub-studies (articles I–IV), in which the number of patients was different but all the sub-studies concerned the same patient population (n = 472) (Figure 1). In the first article, dealing with 6 specific symptoms of relapse-free patients, the number of patients was reduced to 435 because the first 6 months at the beginning and also the last 6 months at the end of the study period were withdrawn to exclude symptoms from the primary treatment and from occult metastases. The occurrence of the six symptoms was also compared between these 435 relapse-free patients and 123 relapsed patients among all 472 study patients. In the second article, dealing with CA 15-3 the number of patients was 243 (follow-up arms A+C), in the third, dealing with chest X-ray, the total was 472, but the group was divided into two (follow-up arms A+C vs. B+D). The fourth article, dealing with cost, included the whole population divided into four subgroups (A, B, C, D) (Table 14).

Table 13. Clinical characteristics of the breast cancer patient material (n = 472) in different follow-up arms.

Characteristics	Arms			
	A (%)	B (%)	C (%)	D (%)
N	125	114	118	115
Median age (y)	56.9	56.8	59.7	60.5
Menopausal status				
Pre	44 (35)	34 (30)	26 (22)	23 (20)
Post	81 (65)	78 (68)	92 (78)	91 (79)
Not known	-	2 (2)	-	1 (1)
Tumour				
Tis, T1-2	121 (97)	110 (96)	115 (97)	111 (97)
T3-4	4 (3)	4 (4)	3 (3)	4 (3)
Nodal status				
N0	89 (71)	92 (81)	92 (78)	95 (83)
N1	36 (29)	22 (19)	26 (22)	20 (17)
ER status				
Positive	83 (66)	71 (62)	75 (64)	70 (61)
Negative	29 (23)	22 (20)	25 (21)	28 (24)
Unknown	13 (11)	21 (18)	18 (15)	17 (15)
PR status				
Positíve	69 (55)	58 (51)	61 (52)	67 (58)
Negative	43 (35)	34 (30)	41 (35)	31 (27)
Unknown	13 (15)	22 (19)	16 (13)	17 (15)
Histology				
Invasive ca	116 (93)	101 (89)	112 (95)	99 (90)
DCIS	9 (7)	13 (11)	6 (5)	16 (14)

Table 14. Number of patients in the sub-studies and mean follow-up time.

Publication	N	Mean follow-up (y)
I	435	3.2
II	243	4.2
III	472 (243 vs. 229)	3.8
IV	472 (125 vs. 114 vs. 118 vs. 115)	4.2

6.2 Follow-up schedules in the study

There were 4 follow-up arms and the variable elements in the follow-up were the frequency of visits and the number of diagnostic tests. In the so-called routine arms (A, C) diagnostic tests were made regularly in asymptomatic patients, and in the so-called spontaneous arms (B, D) tests were made only when clinically needed, i.e. in symptomatic patients or by reason of clinical findings. Additional diagnostic tests were allowed in all arms, that is, the trial did not limit tests on the grounds of the need of the patient or tests the doctor deemed necessary (Figure 1, Table 15).

Clinical visits were made every third month in arms A and B and every sixth month in arms C and D. After 3 years of follow-up the frequency of clinical visit was every sixth month in all arms. The visit always included physical examination of the patient made by a hospital doctor, either specialist in oncology or specializing in this field. Also, patients always had the possibility of additional visits on clinical grounds and also the possibility to contact the doctor by phone between follow-up visits.

At 6 months interval, immediately prior to the clinical visit, the patients were interviewed regarding symptoms by the same study nurse. The trained nurse ascertained especially somatic symptoms such as pain, cough (including dyspnea) and nausea and mental symptoms such as fatigue, depression (including anxiety) and insomnia. These somatic symptoms were considered suggestive of possible distant metastases and the presence vs. absence of somatic or mental symptoms was considered to affect the quality of life. The intensity of these symptoms had to be severe enough, i.e. affecting daily well-being, to be designated as prevalent in this study. The patient defined the intensity of the symptom and the study nurse rated its severity on a local scale ranging from 0 to 10. The symptom asked had to score over 4 on this scale to be estimated to affect daily well-being. The local scale used resembled the Edmonton Symptom Assessment Scale (ESAS) in common use in palliative medicine (Bruera et al. 1991, Chang et al. 2000).

Table 15. Follow-up schedules in different study arms.

	Arms			
	A	B	C	D
Tests	(months)			
Clinical visit*	3	3	6	6
Reg. blood tests**	3	#	6	#
CA 15-3	6	#	6	#
Chest X-ray	6	#	6	#
Mammogram	12	#	12	#
Bone scan	24	#	24	#
Liver ultrasound	24	#	24	#
Interview***	6	6	6	6

\# when clinically indicated
* after follow-up of 3 years every 6 months
** ESR, HB, WBC, platelet count, Ca^{2+}, alat, afos
*** symptoms

6.3 Evaluation of symptoms in relapse-free vs. relapsed patients

To evaluate the symptoms of relapse-free breast cancer patients the first six months after randomization were excluded to ensure that symptoms from the primary therapy had dissipated and the last six months in the follow-up were excluded to rule out the possibility that occult metastases were causing symptoms. After these reductions 435 evaluable patients without relapse were left and the mean follow-up time was 3.2 years (from enrolment 3.8 years).

Six specific symptoms were evaluated more precisely even though many further symptoms were asked in the interview by the same study nurse every sixth months. The representative somatic symptoms chosen were pain, cough (including dyspnea) and nausea, since these commonly arouse the suspicion of metastatic disease. The skeleton is the most common site of distant metastases and pain is the commonest symptom of bone metastases. Intrathoracic, especially pulmonary-pleural metastases are also common and when symptomatic the most common symptom may be a cough, often combined with dyspnea. Nausea as a symptom in follow-up is in most cases associated with metastases in the liver.

The representative mental symptoms chosen were fatigue, depression (including anxiety) and insomnia. These three are often inter-dependent but were here considered

as separate symptoms because they were asked separately in the study questionnaire. Anxiety is a common symptom in a cancer patient under follow-up and in this study anxiety was included in the depression category. Likewise, fatigue is common in cancer patients and might be considered as both a somatic and a mental symptom but was here included in the mental group (Table 16). As mentioned above the intensity of a given symptom had to be rated over 4 on a local scale from 1 to 10 to be considered prevalent, i.e. affecting daily well-being.

In this prospective study the occurrence of these six symptoms was evaluated at intervals of six months and cumulatively for 4 years. On evaluation symptoms were asked from the preceding six months. In addition, clustering of these mental vs. somatic symptoms with each other was calculated. Their occurrence in the time period from 7 to 12 months was also compared to their occurrence in the time period from 0 to 6 months from primary treatment with a view to detect the symptoms due to primary treatment. Further, the occurrence of these symptoms was compared between relapse-free patients (n = 435) and the patients relapsing (n = 123 of 472) during the preceding six months in order to detect the symptoms caused by the relapse. The time period for this comparison was chosen from 7 to 12 months from the beginning of follow-up, i.e. from primary treatment, for relapse-free patients with an interview at 12 months from primary treatment and for relapsed patients the preceding 6 months before the diagnosis of the relapse with an interview at the time of the relapse (article I).

In the sub-study on chest X-ray in detecting the first intrathoracic relapse it was also evaluated how often the patient with this relapse was asymptomatic vs. symptomatic. Pain, cough and dyspnea were considered representative symptoms for intrathoracic metastases (article III).

Table 16. Symptoms assessed in relapse-free patients.

Symptoms	
Somatic	Mental
Pain	Fatigue
Cough*	Depression**
Nausea	Insomnia

* including dyspnea
** including anxiety

6.4 Diagnostic tests used to detect the first relapse

Serum tumour marker CA 15-3 and chest X-ray were used to detect the first relapse of breast cancer. The sensitivity, the specificity, and the negative and positive predictive values of the tumour marker were estimated as well as the validity of the chest-X ray.

6.4.1 Tumour marker CA 15-3

CA 15-3 was chosen as being the most commonly used tumour marker and there are no reliable data attesting the superiority of newer markers. In addition, the test was in general use in Finland during the study period. This tumour marker was analyzed prospectively in 243 out of 472 study patients in routine arms (A+C) every 6 months; in 229 patients of the spontaneous arms (arms B+D) the test was thus not taken routinely. Tumour marker analysis was made by immunoradiometry and values ≥ 40 IU/l were considered positive.

The validity of CA 15-3 in detecting the first relapse was estimated in relation to both the patients and the tests, both patient and test sensitivity and specificity being calculated. The test sensitivity was estimated with restriction of positivity to the preceding 12 months from the diagnosis of the relapse. The sensitivity of CA 15-3 was also analyzed in detecting the first relapse at different sites, including locoregional and distant metastases and cancer of the contralateral breast.

The diagnostic significance of CA 15-3 was estimated in terms of positive predictive value (PPV) and negative predictive value (NPV) only with respect to patients (Table 17).

Table 17. Validity of serum tumour marker CA 15-3 in patients and tests in detecting the first relapse of breast cancer in the follow-up of breast cancer patients.

CA 15-3	In patients (n)	In tests (n)
Sensitivity	relapsed patients with CA 15-3 ≥ 40 / all relapsed patients	CA 15-3 ≥ 40 / all tests in relapsed patients
Specificity	relapse-free patients with CA 15-3 < 40 / all relapse-free patients	CA 15-3 < 40 / all tests in relapse-free patients
Positive predictive value	relapsed patients / all patients with CA 15-3 ≥ 40	
Negative predictive value	relapse-free patients / all patients with CA 15-3 < 40	

6.4.2 Chest X-ray

The efficacy of chest X-ray in detecting the first intrathoracic relapse was evaluated in a randomized setting. In routine arms (A+C) with 243 patients a chest X-ray was taken every 6 months and in the remainig 229 patients in the spontaneous arms (B+D) only when clinically needed. Pulmonary, pleural, mediastinal and bone metastases seen on the chest X-ray were regarded as intrathoracic metastases. The distribution of these into bony vs. pure pleuro-pulmonary metastases was analyzed. We also estimated how often intrathoracic metastases caused symptoms. Pain, dyspnea and cough were regarded as possible symptoms of intrathoracic metastases when the severity was rated over 4 on the local scale from 1 to 10.

The validity of the chest X-ray was estimated by calculating separately the sensitivity and specificity for both chest X-rays and individual patients, since each patient underwent several X-rays. The diagnostic significance of the chest X-ray was estimated by calculating PPV and NPV for both X-rays and patients (Table 18).

Table 18. Validity of chest X-ray in detecting the first intrathoracic relapse of breast cancer in the follow-up of breast cancer patients.

Chest-X-ray	Patient	Chest X-ray film
Sensitivity	relapsed patients with true positive X-ray / relapsed patients	true positive X-rays in relapsed patients / X-rays in relapsed patients
Specificity	relapse-free patients with true negative X-ray / relapse-free patients	true negative X-rays in relapse-free patients / X-rays in relapse-free patients
PPV	relapsed patients with true positive X-ray / patients with true positive or false positive X-ray	true positive X-rays / true positive and false positive X-rays
NPV	relapse-free patients with true negative X-ray / patients with true negative or false negative X-rays	true negative X-rays / true negative and false negative X-rays

6.5 Evaluation of survival of study patients

The primary endpoints were disease-free survival (DFS) and overall survival (OS). These health outcomes were analyzed for each follow-up arm at 5 years. The endpoints were analyzed by life table method.

6.6 Calculation of costs of follow-up

The total cost of follow-up per arm and per patient was estimated for different follow-up schedules. The number of patients evaluated was 472 and the mean follow-up time was 4.2 years. The mean cost of follow-up per patient in each study arm was calculated by dividing the total cost incurred in the arm by the number of patients in it. Further, the mean cost of follow-up per detected relapse was calculated. The mean cost of detected relapse was calculated by dividing the total cost in the arm by the number of relapses in it.

The distribution of total follow-up cost into cost of contacts and cost of examinations was estimated in every arm. The cost of contacts included costs of outpatient visits and phone calls. The distribution of total examination cost into subclasses was also analyzed in the different arms. The subclasses analyzed were blood tests (regular blood tests and CA 15-3), chest X-rays, mammograms, liver ultrasounds, bone scans and others (miscellaneous).

Costs were estimated from the hospital perspective and only costs on an outpatient basis associated with breast cancer were included. Indirect costs (travel, sick leave) were not estimated. The monetary costs were estimated in Euros according to the 2003–2004 charge list of Tampere University Hospital (Table 19). Disease-free and overall survival was also estimated separately in all four arms.

Table 19. Tampere University charge list (2003–2004).

Facility	Price (€)
Outpatient visit	56
Phone call	23
Chest X-ray	31
Liver ultrasound	65
Bone scan	244
Mammogram	60
Blood tests*	28
CT examination	237
MRI examination	404
FNAB**	35
Core biopsy	150

*$HB^{€}$, $WBC^{€}$, platelet count$^{€}$, $ESR^{€}$, $Ca^{2+€}$, $AFOS^{€}$, $ALAT^{€}$, CA 15-3 ($^{€}$=regular blood tests)
**FNAB, fine-needle aspiration biopsy

7. RESULTS

7.1 Role of symptoms

Relapse-free breast cancer patients experienced cumulatively a great many symptoms during the mean follow-up time of 3.2 years (article I). At 36 months, the cumulative mean number of mental symptoms per patient was 2.43 and that of somatic symptoms per patient 1.95. Even at this late time point after primary treatment patients without relapse still suffered increased symptoms affecting daily well-being (Figure 2a).
The mean number of mental symptoms per patient was highest at 24 months, 0.47, with a diminishing trend over time. In contrast, the mean number of somatic symptoms per patient was highest at six months, 0.39, and after twelve months the mean number of somatic symptoms per patient remained fairly constant without any significant decreasing trend (Figure 2b). The severity of symptoms, as mentioned above, had to be over 4 on a local scale from 1 to 10 to be marked as prevalent.

The ratio of mental to somatic symptoms was ≥ 1 up to two years, indicating that mental symptoms dominated at the beginning of follow-up. Correspondingly, the same ratio persisted < 1 in late follow-up after two years, indicating the permanence of somatic symptoms. Thus, after many years from the primary treatment breast cancer survivors still increasingly had somatic symptoms, but mental health was improving over time (Figure 2c).

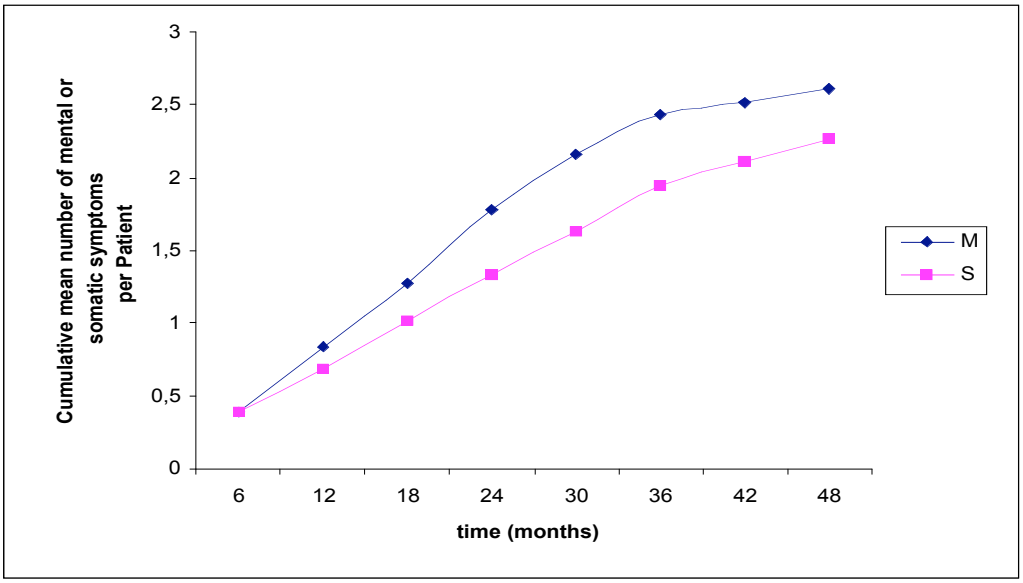

Figure 2a.

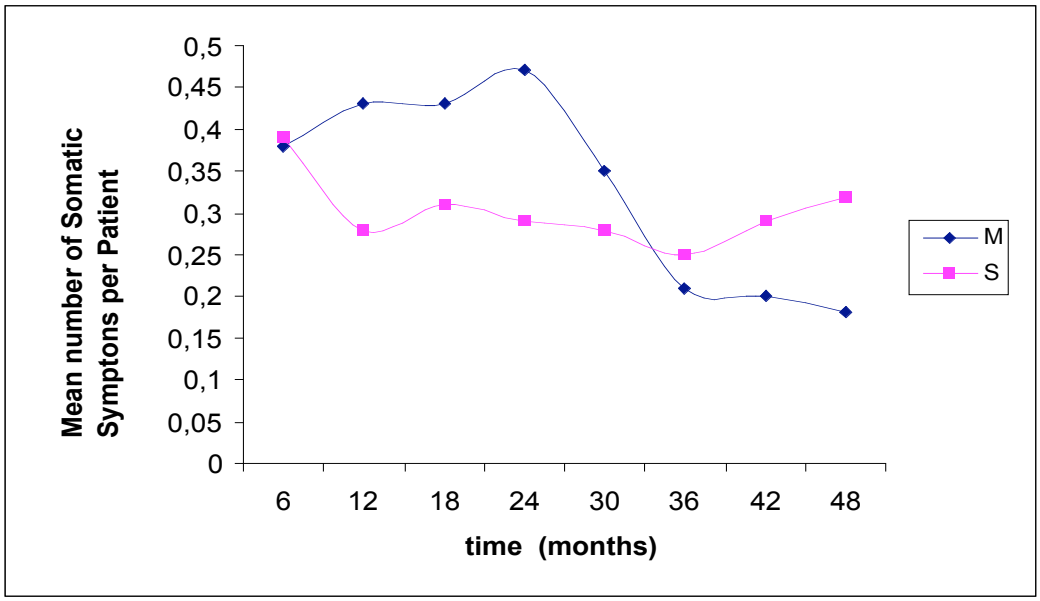

Figure 2b.

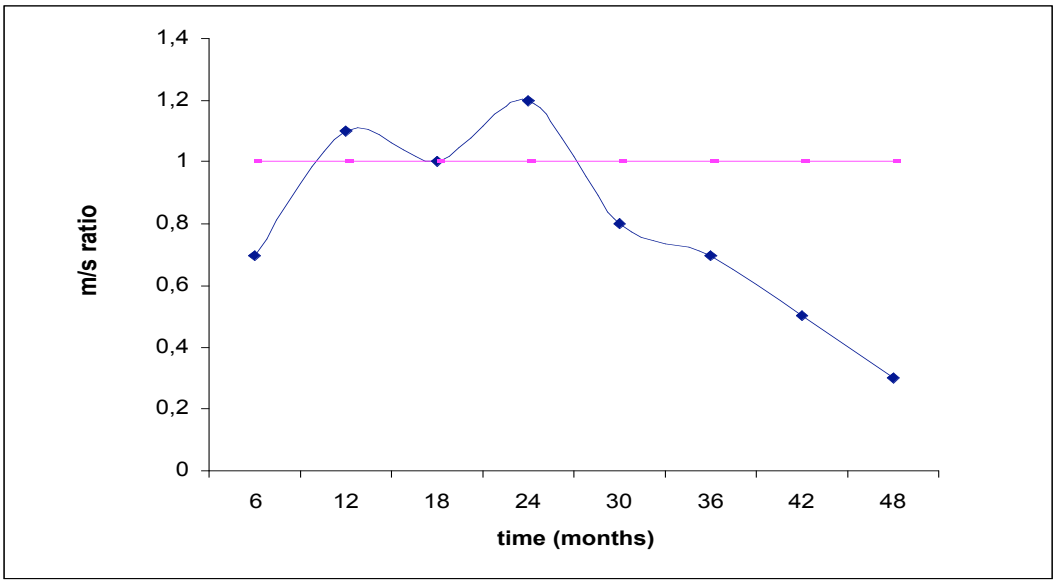

Figure 2c.

Figure 2 a,b,c. Cumulative mean number (Figure 2a) and mean number (Figure 2b) of mental (M) or somatic (S) symptoms per patient and the ratio of mental to somatic symptoms (m/s ratio) (Figure 2c) among 435 relapse-free breast cancer patients during follow-up in the Tampere breast cancer study.

Only 19% of relapse-free patients were asymptomatic during the mean follow-up time of 3.2 years. Cumulatively, altogether 67% of patients suffered from at least one somatic symptom, i.e. pain, cough-dyspnea or nausea. Likewise, mental symptoms were also common, with 61% of patients manifesting at least one mental symptom cumulatively, namely fatigue, depression-anxiety or insomnia. Almost one half of

patients (47%) experienced simultaneously at least one somatic and one mental symptom (Table 20). Only minor clustering of symptoms was detected; the kappa coefficient remained low (range 0.12–0.28), average kappa being 0.26 (Figure 3, Table 21).

Table 20. Number and percentage of asymptomatic and symptomatic relapse-free patients during the follow-up period of 3.2 years in the Tampere breast cancer follow-up study.

Patients	N	%
All	435	100
Asymptomatic	83	19
With somatic symptoms only*	87	20
With mental symptoms only**	61	14
With somatic and mental symptoms	204	47

*pain, cough-dyspnea, nausea
**fatigue, depression-anxiety, insomnia

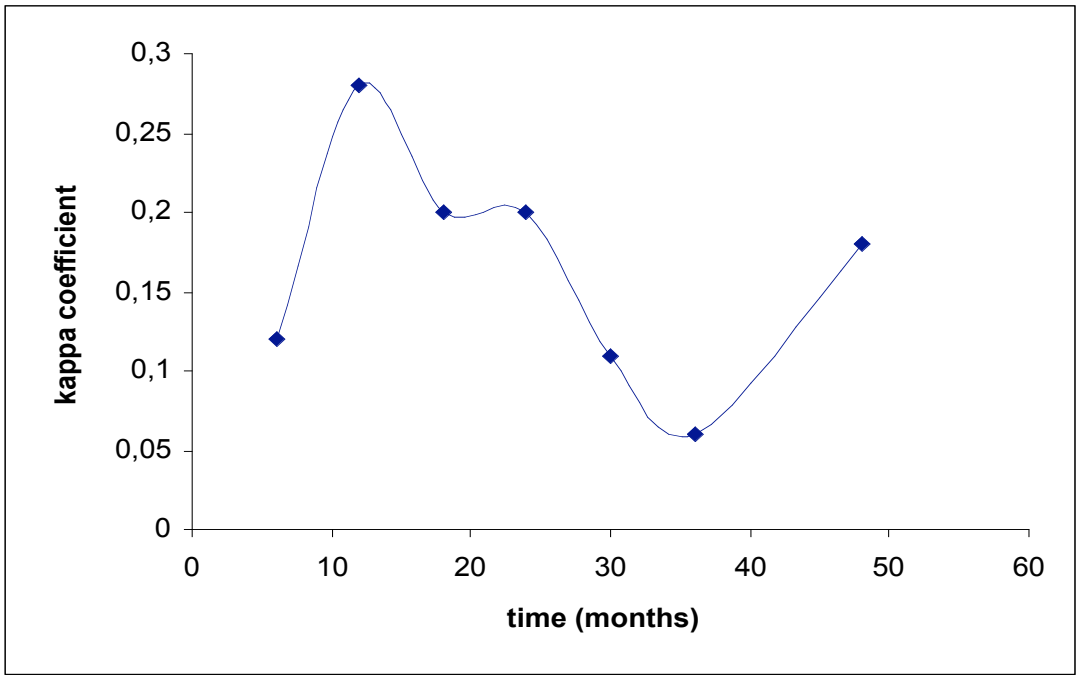

Figure 3. Kappa coefficient between patient-reported mental and somatic symptoms in relapse-free breast cancer patients (n = 435) during the Tampere breast cancer follow-up study.

Table 21. Kappa coefficient between patient-reported mental and somatic symptoms in relapse-free breast cancer patients (n = 435) during the mean follow-up period of 3.2 years in the Tampere breast cancer follow-up study.

Time (months)	Kappa coefficient (0.0–1.0)
6	0.12
12	0.28
18	0.20
24	0.20
30	0.11
36	0.06
48	0.18
average (cumulative)	0.26

When comparing the occurrence of symptoms in relapse-free breast cancer patients in the time period from 7 to 12 months to the period from 0 to 6 months from primary treatment, somatic symptoms had diminished by 9% but every fourth patient at 7–12 months from primary treatment still experienced at least one somatic symptom. In the time period from 7 to 12 months the number of asymptomatic patients had increased by 10% compared to the period from 0 to 6 months from primary treatment; about 2/3 (62%) of the patients were asymptomatic during the second half of the first follow-up year (Table 22).

The symptoms of 123 patients with recurrence out of all 472 patients were also evaluated. In the six months preceding the diagnosis of breast cancer relapse 2/3 (66%) of patients experienced somatic symptoms and 1/3 (36%) mental symptoms (Table 22). Only every fourth patient (28%) was without symptoms. When comparing the symptoms of relapse-free patients in the time period from 7 to 12 months after primary treatment to those of patients during the six months prior to diagnosis of relapse the relative proportion of asymptomatic patients had decreased from 62% to 28%, i.e. by 34%. During the six months prior to breast cancer relapse especially somatic symptoms alone but also somatic and mental symptoms combined had increased compared to the symptoms of relapse-free breast cancer patients at 7–12 months after the primary treatment (Table 22).

Table 22. Symptomatic and asymptomatic relapse-free vs. relapsed patients in the Tampere breast cancer follow-up study.

	Relapse-free patients				Patients with relapse	
	At 0–6 months		At 7–12 months		At 0-6 months prior to the relapse	
Patients	N	(%)	N	(%)	N	(%)
All	435	(100)	435	(100)	123	(100)
Asymptomatic	228	(52)	268	(62)	34	(28)
With somatic symptoms only*	96	(22)	56	(13)	44	(36)
With mental symptoms only**	64	(15)	61	(14)	8	(6)
With somatic and mental symptoms	47	(11)	50	(11)	37	(30)

*pain, cough-dyspnea, nausea
**fatigue, depression-anxiety, insomnia

7.2 Role of diagnostic tests

7.2.1 Efficacy of tumour marker CA 15-3

A total of 1294 marker tests were made among these 243 patients, a median of 5.3 per patient. Relapse of breast cancer was detected in 24% (59/243) of patients. About 1/3 (21/59) of the relapses were detectable with CA 15-3 with a mean lead time of 89 days and median lead time 18 days. About every 8th marker test was positive in relapsed patients; 3% of patients yielded false-positive test results and 1% of tests were false-positive. With elevated CA 15-3 the recurrent disease could be confirmed in about 4 out of 5 patients (PPV) and, correspondingly, with CA 15-3 in normal limits in about 4 out of 5 patients it could be excluded (NPV) (Table 23).

Table 23. Sensitivity, specificity and positive and negative predictive values of CA 15-3 in detecting the first relapse.

Factor	Patient (%)	Test (%)
Sensitivity	36	13
Specificity	97	99
PPV	78	–
NPV	82	–

The sensitivity of CA 15-3 was higher in liver, bone and multiple metastases while, in contrast, sensitivity was lower in lung, lymph-node and skin metastases; in all four liver metastases it was elevated and in all five lung metastases it was within normal limits. Three contralateral breast cancers were detected and in none of them was CA 15-3 elevated (Table 24). However, the number of cases was small and no definite conclusions can therefore be drawn.

Table 24. CA 15-3 sensitivity in breast cancer relapses at different sites (n = 59).

Relapse Site	CA 15-3 elevated* (n)	Patient sensitivity (%)
Any	21/59	36
Liver-only	4/4	100
Bone-only	7/15	47
Multiple	7/13	54
Lymph nodes-only	1/5	20
Skin-only	1/14	7
Lung-only	0/5	0
Contralateral breast-only	0/3	0

* ≥ 40 IU/l

7.2.2 Efficacy of chest X-ray

The numbers of chest X-rays taken were 1429 in the routine arm (A+C combined) and 411 in the spontaneous arm (B+D combined), the mean number of chest X-rays per patient being thus 5.9 in routine and 1.5 in spontaneous arm (article III). The follow-up schedules have been elucidated in the foregoing (Table 15, page 62).

Among the 472 patients some relapse was detected in 123 (26%) patients, 59/243 (24%) in the routine arm and 64/229 (28%) in the spontaneous, intrathoracic relapse being found in 30/243 (12%) patients and in 22/229 (10%) patients in the routine vs. spontaneous arm. In both arms about 1/3 of the intrathoracic metastases comprised pleuro-pulmonary and 2/3 of bony metastases. The relapse was in most cases symptomatic, 90% vs. 86% in the routine and spontaneous arms, respectively. Thus, between arms there was no significant difference in the occurrence of symptoms of intrathoracic metastases (Table 25). Pain was the commonest symptom in 59% of metastatic cases, dyspnea and cough combined occurring in 13% and all three symptoms in 28% of cases.

Table 25. Relapses among breast cancer patients, number of chest X-rays and findings on chest X-rays in study arms.

Event	Routine arm (%)	Spontaneous arm (%)
Number of patients	243 (100)	229 (100)
Number of chest X-rays	1429	411
Mean number of chest X-rays/patient	5.9	1.8
Mean number of chest X-rays/ patient year	1.5	0.5
Number of patients with some relapse	59 (24)	64 (28)
Number of patients with intrathoracic relapse	30 (12)	22 (10)
pleuro-pulmonary	10 (4)	6 (3)
bony	20 (8)	16 (7)
with symptoms*	27	19
visible in chest X-ray	9	8
Number of patients with false-positive chest X-ray	32	28

*symptoms: pain, cough, dyspnea

Film and patient sensitivity of chest X-ray in detecting the first relapse (intrathoracic relapse) were both low, in the range of 11–36%. Likewise, both the film and patient specificity remained low, in the range of 85–97%.

Correspondingly, positive predictive values were low, 21–22%. Negative predictive values were higher, 89–93% (Table 26).

Table 26. Validity of chest X-ray in detecting inthrathoracic relapse as the first relapse of breast cancer.

	Arms	
Chest X-ray	routine	spontaneous
Sensitivity		
Patient	30	36
Film	11	20
Specificity		
Patient	85	86
Film	97	90
Positive predictive value		
Patient	22	22
Film	21	22
Negative predictive value		
Patient	90	92
Film	93	89

7.3 Disease-free and overall survival of patients

No impact of the intensity and amount of services of follow-up on health outcome was detected. However, the number of patients altogether and in different arms was rather small. When considering the role of chest X-ray in detecting the first relapse of breast cancer no statistically significant difference in survival was observed between the groups with or without routine chest X-ray (article III). The mean follow-up was 3.8 years and in the group with routine chest X-ray intrathoracic relapse was detected two months earlier, the mean time to progression being 1.9 years in the routine arm and 2.1 years in the spontaneous arm. Correspondingly, disease-free survival (DFS) was 86% in the routine arm and 89% in the spontaneous. Overall survival (OS) was better in the routine arm than in the spontaneous arm, 88% vs. 85% but no statistically significant difference was found (Figures 4 and 5).

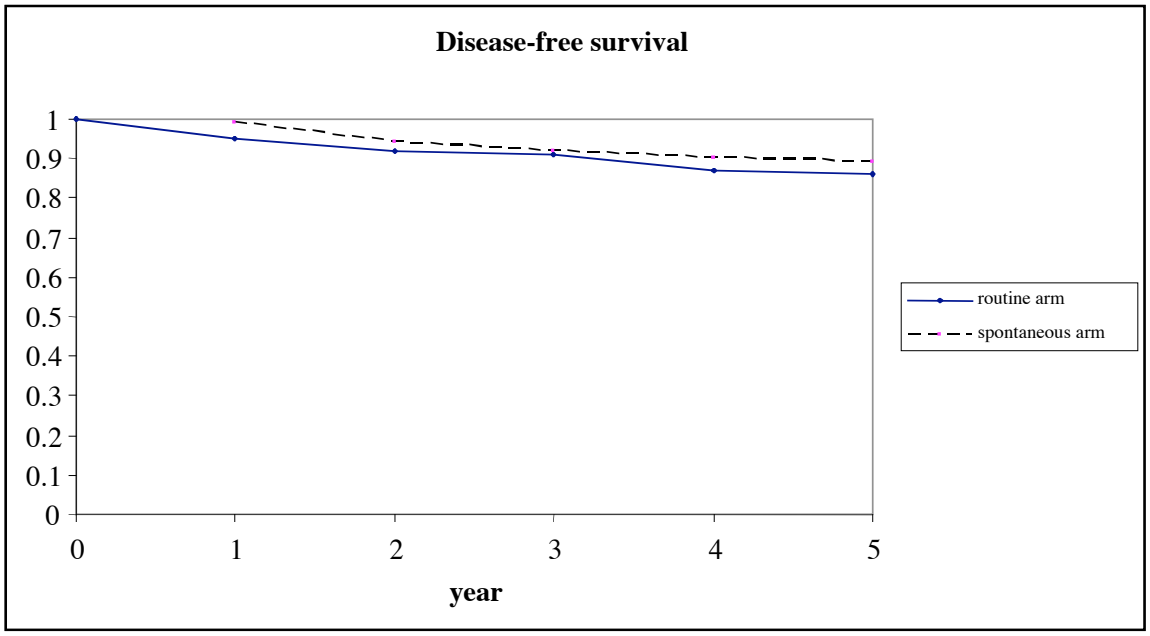

Figure 4. Disease-free survival in the routine (A+C) and in the spontaneous (B+D) arms in the Tampere breast cancer study.

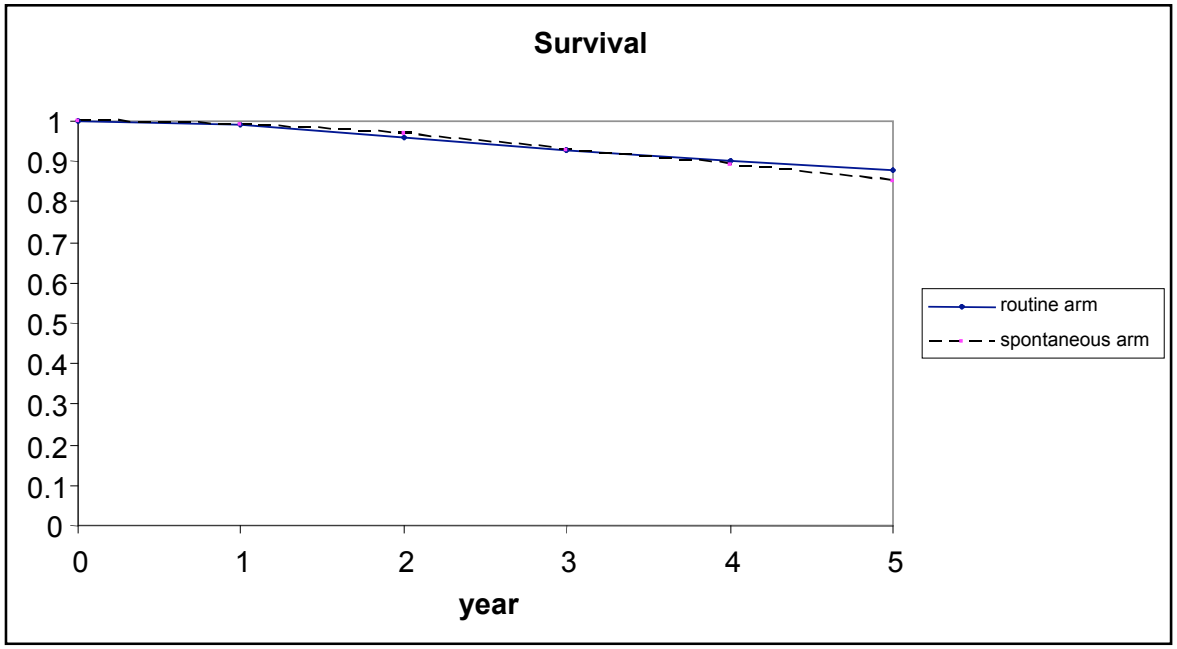

Figure 5. Overall survival in the routine (A+C) and in the spontaneous (B+D) arms in the Tampere breast cancer study.

When comparing the four differently followed arms with a mean follow-up of 4.2 years (article IV) no statistically significant differences in DFS or OS at 5 years fared, that is, not even now did the intensity or the amount of services of follow-up play any role on health outcome. Patients making infrequent visits every sixth month without any routine tests were fared as well as those making visits every third month with routine tests. Altogether 123 patients experienced recurrence of breast cancer and among all 472 patients DFS was 72% and OS 81% at five years (Table 27).

Table 27. Disease-free survivors (%) and overall survivors (%) and number of relapsed patients in the different follow-up arms in the Tampere breast cancer study (mean follow-up 4.2 years).

	Arms				
Event	A	B	C	D	All
Disease-free survivors (%)	74	67	73	72	72
Overall survivors (%)	82	74	85	84	81
Patients (n)	125	114	118	115	472
With relapse (n)	31	35	28	29	123

7.4 Cost-effectiveness of follow-up

7.4.1 Number of visits and examinations

Study patients made 5454 visits and 450 phone calls altogether. The total number of visits included routine, extra and consultation visits on an outpatient basis. The mean number of visits per patient was 14 in arms A and B, and 9 in arms C and D.

Altogether 7547 examinations were carried out. Blood tests comprised 44%, chest X-rays 27%, mammograms 8%, bone scans 7%, liver US 6% and other examinations 5% of the total number of examinations**.** About 3/4 of examinations were made in routine arms A and C, that is, 85% of liver ultrasounds, 79% of bone scans, 75% of chest X-rays and 74% of blood tests. Between mammograms and other examinations made no difference between arms was noted (Table 28).

Table 28. Number of patients, outpatient visits, phone calls and examinations by follow-up arms and mean number of outpatient visits, phone calls and examinations per patient in the Tampere breast cancer study.

	Follow-up arms				
Event	A	B	C	D	All
Patients (n)	125	114	118	115	472
Outpatient visits	1883	1569	1065	1018	5454
mean/patient	15.1	13.8	9.0	8.9	11.6
Phone calls	128	116	108	98	450
mean/patient	1.1	1.1	0.9	0.9	1.0
Chest X-ray	833	284	698	218	2033
mean/patient	6.7	2.5	5.9	1.9	4.3
Liver US	208	42	174	28	452
mean/patient	1.7	0.4	1.5	0.2	1.0
Bone scan	210	66	186	38	500
mean/patient	1.7	0.6	1.6	0.3	1.1
Mammogram	244	207	190	186	827
mean/patient	2.0	1.8	1.6	1.6	1.8
Blood tests	1624	505	859	367	3355
mean/patent	13.0	4.4	7.3	3.2	7.1
Other diagnostic tests	115	101	77	87	380
mean/patient	0.9	0.9	0.7	0.8	0.8

7.4.2 Cost of follow-up

The mean total cost of follow-up per patient was 1632€ (range, 1051–2269€). The mean cost of contacts per patient (visits and phone calls together) was 669€ (range, 515–831€) and the mean cost of examinations per patient was 963€ (range, 536–1438€). As expected, arm A (routine examinations with a visit every third month) was the most expensive and arm D (no routine examinations with visits every sixth month) the least expensive. The total follow-up cost per patient in the least expensive arm D was only 46% of the corresponding cost in the most expensive arm A (Table 29, Figure 6).

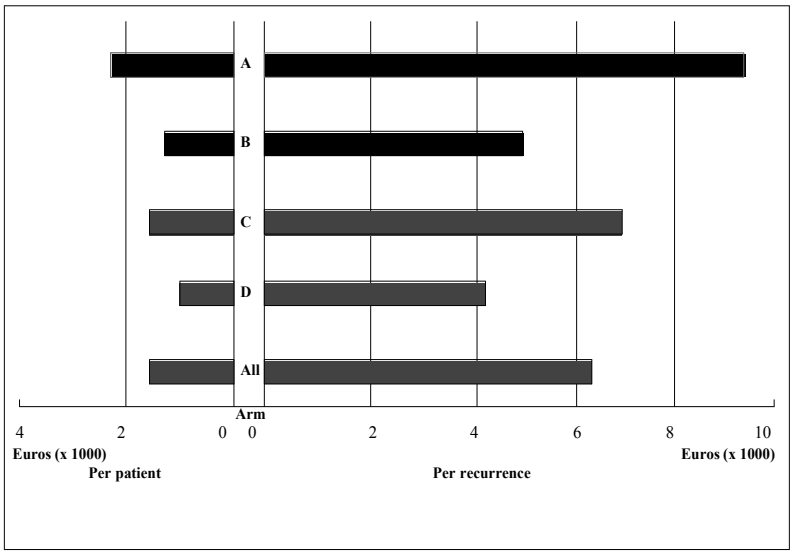

Figure 6. Total cost (€) of follow-up per patient and per recurrence in the different arms in the Tampere breast cancer follow-up study.

Among all 472 patients cost of contacts accounted for 41% and cost of examinations 59% of total costs (Table 29). Contact costs were highest in arm A with frequent visits and routine tests and lowest in arm D with infrequent visits and no routine tests. Thus, in arm A contacts accounted for 37% and examinations 63% of total follow-up costs and in contrast in arm D the total cost was equally distributed between contacts (49%) and examinations (51%) (Figures 7 and 8).

The greatest differences in examination costs among the arms were observed in the cost of bone scans, blood tests and chest X-rays. Altogether bone scans (mean cost 258€) and blood tests (mean cost 199€) constituted almost half of the mean examination cost per patient (963€) among all patients, whereas chest X-rays and liver ultrasounds combined constituted 20% of this total. When comparing the different follow-up arms bone scans comprised 15–34%, blood tests 17–25%, chest X-rays 11–16% and liver ultrasounds 3–8% of total examination costs (Figure 8, Table 29).

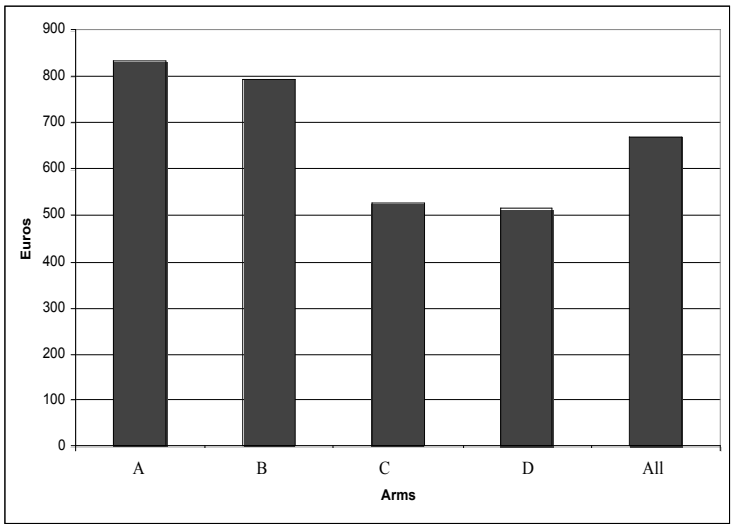

Figure 7. Total costs (€) of contacts (visits and phone calls) per patient in the different arms in the Tampere breast cancer follow-up study.

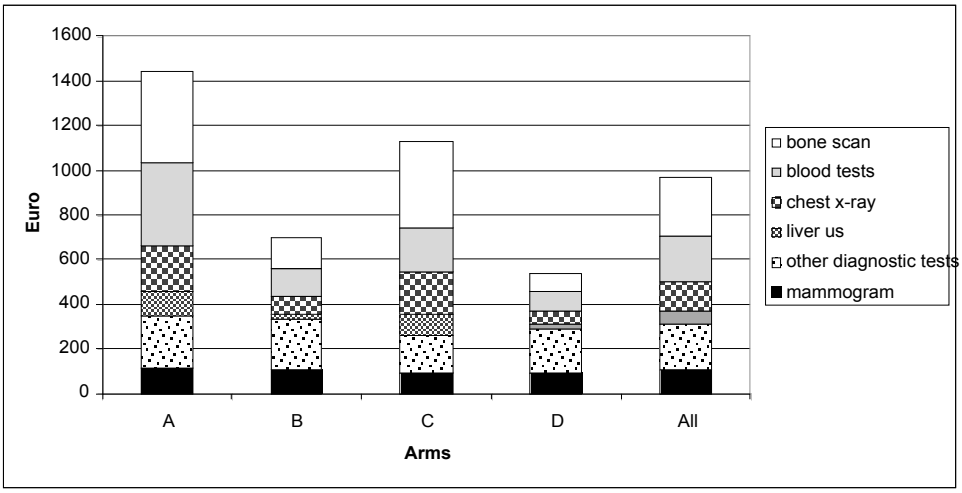

Figure 8. Total cost (€) of examinations per patient in the different arms in the Tampere breast cancer follow-up study.

Table 29. The mean cost (€) of contacts and examinations per followed patient in the different arms in the Tampere breast cancer study.

Event	Arms				
	A (n=125) (%)	B (n=114) (%)	C (n=118) (%)	D (n=115) (%)	Al (n=472) (%)
Contacts	831 (37)	794 (53)	526 (32)	515 (49)	669 (41)
Examinations	1438 (63)	699 (47)	1130 (68)	535 (51)	963 (59)
Chest X-ray	207	77	183	59	134
Liver US	108	24	96	16	62
Bone scan	410	141	385	81	258
Mammogr.	117	109	97	97	105
Blood tests	364	124	204	89	199
Others	232	224	165	194	204
Total follow-up	2269 (100)	1493 (100)	1656 (100)	1050 (100)	1632 (100)

7.4.3 Cost of detected recurrence

Altogether 123 recurrences were found, 31 in arm A, 35 in arm B, 28 in arm C and 29 in arm D (Table 30). The mean cost per detected recurrence among all 472 patients was 6261€. As expected, it was highest in arm A and lowest in arm D, 9149€ in arm A, 4864€ in arm B, 6980€ in arm C and 4166€ in arm D (Table 30, Figure 6). Nevertheless no statistically significant differences in DFS or OS were found between the arms (Table 27).

7.4.4 Relative use scores

In addition, we estimated relative use scores (RU scores) for expenditure per patient on contacts, examinations and total follow-up. The cost in the least expensive arm D was used as reference score and valued at 1. In this way the highest scores in cost per patient were found in arm A, 1.6 in contacts, 2.7 in examinations and 2.2 in total follow-up. Likewise, RU scores for expenditure per detected recurrence were estimated with a score for total follow-up, and they were in the range from 2.2 (arm A) to 1.0 (arm D) (Table 31).

Table 30. Number of relapsed patients and mean follow-up cost per recurrence in study patients in the Tampere breast cancer follow-up study.

	Arms				
Event	A	B	C	D	All
Patients (n)	125	114	118	115	472
With relapse	31	35	28	29	123
Mean cost (€) per relapse	9149	4864	6980	4166	6261

Table 31. Relative use scores (RU scores) of contacts, examinations and total follow-up per patient (pt) and per recurrence (rec) in the study arms (arm D as reference arm) in the Tampere breast cancer study.

Arm	RU score					
	Contacts		Examinations		Total follow-up	
	per pt	per rec	per pt	per rec	per pt	per rec
A	1.6	1.6	2.7	2.7	2.2	2.2
B	1.5	1.3	1.3	1.1	1.4	1.1
C	1	1.1	2.1	2.2	1.6	1.7
D	1	1	1	1	1	1

8. DISCUSSION

Breast cancer is a common disease affecting one woman in ten. The 5-year survival rates are constantly increasing and overall survival is improving. Factors contributing to these outcomes include mammography screening programs and adjuvant treatments (Berry et al. 2005). The number of breast cancer survivors under follow-up is already enormous and is steadily increasing, entailing pressure on limited health care resources and professionals. Breast cancer with distant metastases remains incurable and in that setting only palliative treatment is possible. Breast cancer localized at diagnosis may relapse even after decades and some cases can be regarded as chronic diseases, in that even after forty years from the initial diagnosis over-mortality is observed (Brenner and Hakulinen 2004). The diagnosis of breast cancer embraces very differently acting disease entities. Indolent breast cancer is cured purely by surgery, while aggressive breast cancer kills the patient in a short time in spite of intensive therapy. Adjuvant treatment of breast cancer usually improves the prognosis, but nevertheless some cancers treated with adjuvant therapy relapse after a couple of years. "Chronic breast cancer" sensitive to treatment gives the patient many good years of living but the disease nonetheless leads to death. Surprisingly, very silent breast cancer can relapse after decades from the primary diagnosis. For these reasons there is a need for (individualized) follow-up for breast cancer patients after primary treatment.

This thesis comprises four articles concerning the follow-up of 472 patients in a single institution. The patients were randomized into four different follow-up schedules. The mean follow-up time was over 4 years. The symptoms (pain, cough-dyspnea, nausea; fatigue, depression-anxiety, insomnia) of relapse-free patients were analyzed and compared with symptoms of patients with relapse in a prospective setting (article I). The effectiveness of follow-up was studied by analyzing the validity of CA 15-3 (article II) and chest X-ray (article III) in detecting the first recurrence of breast cancer. The costs of follow-up were calculated in the four different follow-up schedules per patient and per detected recurrence. Further, disease-free survival and overall survival in the follow-up arms were estimated.

8.1 Symptoms of breast cancer patients

After primary treatment breast cancer patients suffer from many symptoms attributable to primary surgical, radiotherapy and adjuvant chemotherapy. Many adverse symptoms disappear soon after cessation of therapy, but some late inconveniences persist even for years, possibly permanently (Partridge et al. 2003). Symptoms due to primary treatment, relapsing disease and/or fear of relapse are inter-related; for example healthy breast cancer survivors suffer from many symptoms impairing QOL. QOL studies have brought out prolonged physical, social, spiritual and psychological symptoms in breast cancer survivors (Dow et al. 1996, Holzner et al. 2001, Ganz et al. 2002).

To the author´s knowledge there are no studies comparing the occurrence of the common symptoms pain, cough (including dyspnea), nausea, fatigue, insomnia and depression (including anxiety) in relapse-free patients. These symptoms are common in women generally, but can also be looked upon as common findings in relapsing breast cancer patients with distant metastases. In such cases the somatic symptoms might predispose to fatigue, insomnia and depression-anxiety. In this study (article I) these symptoms were evaluated in 435 relapse-free patients and were found to be particularly common in breast cancer survivors. After six months from the end of primary treatment and during the mean follow-up time of 3.2 years only one out of five patients was asymptomatic with respect to somatic symptoms pain, cough-dyspnea or nausea and the mental symptoms fatigue, insomnia or depression-anxiety. Almost every second patient had simultaneously at least one of both somatic and mental symptoms during follow-up. These mental and somatic symptoms occurred quite independently of each other. Mental symptoms showed a decreasing trend as time passed, whereas the prevalence of somatic symptoms was more constant. We assumed that symptoms caused by primary treatment would be minimal half a year from cessation of primary treatment, but we nonetheless detected harm probably due to primary treatment lasting for years. In addition, the intensity of these symptoms was rated as affecting daily living, that is, they were rather severe. The abundance of these symptoms in healthy breast cancer survivors in itself justifies the follow-up of breast cancer patients, since many of the symptoms can be alleviated by effective symptomatic treatment. Of course the follow-up of patients itself does not dispose of the symptoms.

Some interventions in follow-up might reduce these inconveniences. Scheier and associates found that very short-term interventions could enhance both physical and psychological functioning among younger breast cancer patients, ending with adjuvant chemotherapy for early breast cancer. Both active educational and nutritional interventions compared to standard follow-up improved the primary outcomes physical

and mental functioning and depressive symptoms, and after four sessions the results remained at 9 months post-intervention in both active groups (Scheier et al. 2005). Instructions for weight control with an emphasis on exercise are important after primary treatment of breast cancer, as there are trends towards poorer prognosis in overweight patients and in patients with treatment-related weight gain (Rock and Demark-Wahnefried 2002). Likewise, the guidelines of Canadian Medical Association journal (CMAJ) emphasize the importance of discussing with patients the topics of cognitive functioning, fatigue, weight management, osteoporosis and sexual functioning and subsequent pregnancy (Grunfeldt et al. 2005).

The occurrence of these six symptoms among relapse-free breast cancer patients in the period from 7 to 12 months from primary treatment and breast cancer patients sustaining a relapse during the six months prior to the diagnosis of relapse was compared. The number of symptomatic patients had increased by 34%, i.e. over 2/3 of patients had symptoms in the six months prior to confirmation of the relapse, whereas only 1/3 of relapse-free patients from 7 to 12 months from primary treatment when asked at one year were symptomatic. Severe symptoms affecting daily life increased significantly preceding the relapse. As expected, somatic symptoms dominated prior to the relapse. The results of this study are in line with other findings confirming that relapse of breast cancer comes with symptoms (Pivot et al. 2000).

Symptom-oriented follow-up of relapse-free breast cancer patients gives the possibility through effective treatment of these symptoms to improve the health-related quality of life of survivors. However, by no means always is the occurrence of symptoms a sign of cancer relapse but can be due to late treatment effects or other factors not-related to cancer.

8.2 Tumour marker CA 15-3

The idea of following breast cancer patients with localized disease by serum tumour marker is fascinating, as is the prospect of diagnosing early relapse by a specific tumour marker. However, there are so far no data to show that early diagnosis of distant metastases can cure the disease or at least significantly improve survival with good QOL. In most cases distant metastases are diagnosed on the basis of symptoms in the patient (Pivot et al. 2000). There are no data to show that the survival of patients with distant metastases is superior when the metastases are diagnosed in asymptomatic as against symptomatic stage. The elevated marker CA 15-3 when used in routine follow-up is most frequently detected in an asymptomatic patient, leading to additional

confirmatory or excluding examinations. Often no metastases are found, which makes for anxiety of patients and the need to repeate the examinations in the near future.

On the other hand, preoperative elevated values of CA 15-3 in primary breast cancer may be of prognostic value for early relapse (Duffy et al. 2004).

The mean lead time between elevated CA 15-3 and confirmation of the first relapse of breast cancer by imaging examinations was here 89 days (range 0-1091), but the median lead time was only 18 days (article II). Likewise, in other studies published the mean lead time has varied in a range between 1–9 months (Jäger 1993, Söletormos et al. 1993, Molina et al. 1995). Using CA 15-3 does not bring the diagnosis of first relapse significantly earlier.

Multiple metastatic disease and large tumour burden correlate with elevated tumour marker CA 15-3 values (Bast et al. 2001, Berruti et al. 1994). Thus in detecting the first relapse of breast cancer the sensitivity of CA 15-3 might be low.

During the 12 months preceding the diagnosis of contralateral breast cancer CA 15-3 was not elevated in any of the contralateral breast cancer even though only three contralateral cancers among 243 patients were found in the mean follow-up of 4.3 years (article II). Likewise, the sensitivity of CA 15-3 was poor in detecting locoregional relapse during the 12 months preceding diagnosis; in other words CA 15-3 was here elevated in lymph node relapses in only one out of five cases. In a study by Molina and associates CA 15-3 was elevated in none of their 22 locoregional relapses (Molina et.al. 1995).

Only every third relapse of breast cancer was detectable on the basis of elevated tumour marker CA 15-3, while the marker failed to reveal two out of three relapses (article II). The test was in fact taken only every sixth month and the cut-off value was ≥ 40 IU/l. The test sensitivity was even lower, 13%, compared to patient sensitivity (36%). Considerable expenses were thus incurred in the use of CA 15-3. In the above-mentioned study by Molina and associates CA 15-3 was elevated (>60IU/l) in half of the cases at confirmed diagnosis of breast cancer relapse (Molina et al. 1995).

In this present study CA 15-3 was elevated in all liver metastases and in half of multiple-site and bone metastases, but not at all in lung-only metastases. In fact, only 4 liver metastases and 5 lung metastases were found as first metastases, the number of cases being thus rather small. Our results were in line with those of Molina and Söletormos concerning metastases in the liver and bone, but not in lung-only metastases. CA 15-3 was elevated in 2/3 of bone metastases and in 3/4 of liver metastases, and in half of pulmonary and multiple-site metastases (Molina et al. 1995). Söletormos detected elevated CA 15-3 in half of breast cancer patients with metastases in bone/viscera (Söletormos et al. 1993).

Breast cancer with distant metastases is an incurable condition. No large randomized trials have been undertaken to show that starting systemic treatment for patients with elevated CA 15-3 without any other confirmation of distant metastases gives any benefit to patients by improving survival. Two small randomized trials, both involving ≤ 50 patients in the 1990s, were conducted with treatment of medroxyprogesterone (MPA) and tamoxifen (Jäger 1993, Kovner et al. 1994) with short follow-up and, in addition, two small studies have been carried out by Nicolini and associates, with 28 and 68 participants, respectively (Nicolini et al. 1997, 2003b). Dixon and associates in one small randomized study (n = 67) with marker-directed chemotherapy found better disease stabilization, quality of life and survival (Dixon et al. 1991, 1993). No reliable conclusions can be drawn from these small trials and so far improved OS has not been reliably demonstrated.

Neither the American Society of Clinical Oncology nor the European Society of Medical Oncology guidelines recommend tumour markers routinely for the follow-up of primary breast cancer (Bast et al. 2001, ESMO Minimum Clinical Recommendations for diagnosis, adjuvant treatment and follow-up of primary breast cancer 2005). In contrast, the European Group on Tumour Markers (EGTM) recommends serial CA 15-3/CEA determinations for the early detection of recurrence in patients with breast cancer and no evidence of disease if the detection of recurrent or metastatic disease would alter clinical management (Molina et al. 2005). There are however so far no data showing that serial measurements of tumour markers results in better patient outcome, as we lack effective (salvage) treatments to cure metastatic breast cancer.

Gene expression profiling analyses are under intensive research and these profilings have already been found to predict clinical outcome and recurrence of tamoxifen-treated node-negative breast cancer (Van de Vijver et al. 2002, Paik et al. 2004). In the future these analyses might be helpful in assessing both individual therapy and follow-up for the individual breast cancer patient.

In conclusion, in the present study CA 15-3 was likewise not found suitable for routine use in follow-up after primary treatment, as was indicated in the recommendations of ASCO and ESMO. It seems that CA 15-3 can be used to rule out or confirm relapsing breast cancer with liver, bone or multiple-site metastases when clinical suspicion has arisen, but very seldom is the same true concerning pulmonary metastases of breast cancer. Tumour markers, including CA 15-3, are evidently not sufficiently sensitive to detect micrometastatic disease, locoregional relapse or contralateral breast cancer, as they are not associated with a large tumour burden. Besides, effective therapeutic approaches in metastatic breast cancer are still lacking, making the need for early detection of distant recurrence questionable (Nicolini et al. 1997).

8.3 Regular blood tests

Among the 472 patients (article IV) one half had regular blood tests (including AFOS) taken. The DFS and OS of patients with regular blood tests were not improved compared to survival among patients without regular blood tests. In any case, routine blood tests incurred considerable expenses and a large proportion of resources were used.

Regular blood tests have not helped in catching the early relapse of breast cancer and in only 3–6% was the diagnosis of relapse made on the basis of blood tests (Schapira 1993, Joseph et al. 1998). The best but modest results are gained from the use of the enzyme alkaline phosphatase, but elevated values of AFOS are even more frequently false-positives rather than the first sign of relapse in asymptomatic patient.

Loprinzi and associates demonstrated that the demand for medically inappropriate testing could be reduced by patient education, leading the patient to understand that avoiding blood tests is not therapeutic nihilism, but that there simply are no blood tests shown to improve quality or quantity of life. The fact is that patients appreciate honesty in their doctor (Loprinzi et al. 2000).

8.4 Chest X-ray and other imaging tests

Nine out of ten patients with intrathoracic relapse manifested symptoms (pain, dyspnea, cough) when the diagnosis was made; the first suspicion of intrathoracic relapse thus obviously arose because of symptoms in both follow-up arms with or without routine chest-X ray (article III). Most often intrathoracic relapse as first relapse of breast cancer was found symptomatic. Correspondingly Pivot and associates have found that in 90% of cases relapse with distant metastases (including thoracic metastases, i.e. bony, pleural and pulmonary ones) was detected on the basis of symptoms or upon physical examination, and no survival benefit could be shown in patients with distant asymptomatic versus distant symptomatic metastases. In over 60% of cases pulmonary or pleural relapse (excluding bony intrathoracic relapses) was associated with symptoms (Pivot et al. 2000).

Intrathoracic relapse was found about two months earlier in the arm with routine chest X-ray, whereas no survival benefit was detected between the arms (article III). Only about every third patient with intrathoracic relapse was found by chest X-ray and, moreover, in this study chest X-ray in an asymptomatic patient detected a relapse in only 0.7% of patients. These results are in line with those obtained by other

investigators. According to groups under Chen and Hurria chest X-ray detected metastatic disease < 1% in asymptomatic patients (Chen et al. 2000, Hurria et al. 2003). However, in the present study (article III) the role of chest X-ray was evaluated in detecting the first intrathoracic relapse.

In this follow-up study no significant differences in DFS and OS between arms were found. The total number of patients was however under 500. In a large randomized follow-up study in Italy DFS was found better in the arm with routine chest X-ray compared to that without, whereas no difference in OS was found. In the study in question Rosselli Del Turco and associates evaluated the effectiveness of early detection of intrathoracic and bone metastases in reducing mortality in breast cancer patients under/up to the age of 70 years. They randomized 1243 women into two arms, a clinical follow-up group with visits including physical examination and annual mammogram vs. an intensive follow-up group with routine chest X-ray and bone scan every 6 months in addition to visits and mammograms. No routine blood tests or QOL measurements were made. Detection of isolated intrathoracic and bony metastases was increased in the intensive arm, 18% vs. 11%, while no difference was noted for other sites. Thus, the 5-year DFS was higher in the clinical group but no difference was observed in 5-year mortality, i.e. 19% vs. 20%. They concluded that chest X-ray and bone scan should not be undertaken routinely in the follow-up of breast cancer patients but should be limited to patients with suspicious symptoms or findings (Rosselli Del Turco et al. 1994). Ten-year follow-up data on this trial were available in 1999 and not even then was any significant difference in overall survival detected, the 10-year mortality rate being in the clinical arm 31.5% and in the intensive arm 34.8% (Palli et al. 1999).

As a conclusion, taking chest X-ray in an asymptomatic patient is a waste of money and intrathoracic metastases can be found on the basis of symptoms without compromising overall survival.

The costs of imaging examinations (besides chest X-rays, abdominal ultrasounds, bone scans and mammograms) were evaluated (article IV) in all follow-up arms, but not directly their validity for diagnosis of the first relapse of breast cancer. Nonetheless, indirectly it seems that there was no influence of these examinations on the length of life of the patient because in the differently followed arms no significant differences in survival emerged. It should however be borne in mind that the number of patients was not very high in the follow-up arms (range, 114–125).

8.5 Follow-up visits

In clinical practice the follow-up of breast cancer patients has not considerably changed during recent decades and even today many patients attend a clinic every third month for years, often undergoing numerous unnecessary examinations. Bloom and associates (Bloom BS et al. 2004) studied how breast cancer patients are managed in practice and found that in only a few per cent of cases were breast cancer guidelines and evidence-based data obeyed. Likewise, Paradiso and associates (Paradiso et al. 1995) concluded in their questionnaire survey that diagnostic tests performed in the preceding 12 months of follow-up reported by the patients confirmed a routine follow-up for breast cancer, which tended to utilize uncritically almost all diagnostic possibilities available. The patient survey was sent to 284 patients being followed after primary treatment for breast cancer; 154 patients (54%) replied and returned the survey.

This present study study with 472 patients was a randomized study and the participants were patients in a single institution. The randomization time period was not too long, i.e. the primary treatments of the patients were established and did not differ excessively. There were only few patients who refused to attend the follow-up trial. In addition, the mean follow-up time was fairly long, 4.2 years and furthermore follow-up was maintained in the same single institution. Besides, two important points are that the cost of follow-up was estimated concomitantly with the follow-up prospectively in different follow-up arms and the total cost was analyzed in cost subgroups. These aspects represent the advantages of this follow-up study, the drawback being the rather small number of patients in the different arms, which for practical reasons could not be extended.

Follow-up of breast cancer is difficult to study in randomized trials, which take years for results to be completed. Collins and associates (2004) undertook a structured review of follow-up trials in breast cancer published between 1989 and 2001 and from 4418 articles identified only 38 eligible for review inclusion; 34 published and 4 unpublished manuscripts. Only 5 out of these 38 studies had employed a randomized controlled trial design. This notwithstanding, randomized studies assessing the follow-up of breast cancer patients are important for both patients and health care. The benefit of these studies for patients could be better survival and QOL and for health care cost-effective follow-up.

In the last decade two large randomized trials involving over 1200 patients each have in fact been made in this setting concerning minimalist vs. intensive follow-up of breast cancer patients. Both showed no survival benefit for asymptomatic patients

between intensive vs. clinical arm after 5 years of follow-up (GIVIO investigators 1994; Rosselli Del Turco et al. 1994, previous page).

The GIVIO investigators randomized 1320 breast cancer patients under the age of 70 years into two arms, control with clinical visits including physical examination and annual mammogram vs. intensive, including, in addition, bone scans, liver ultrasounds, chest X-rays and blood tests regularly. It was not stated which tests were included in regular blood tests. QOL measurements were also made in both groups regularly. At a median follow-up of 71 months no significant difference (2%) was found in OS (80% vs.78%) or QOL, nor in time to detection of recurrence between arms. In any case, however, at all four assessments of QOL over 70% of patients expressed the desire to be seen frequently by a physician and undergo diagnostic tests even if symptom-free. The investigators concluded that breast cancer patients do not benefit from frequent diagnostic tests added to routine medical surveillance; follow-up based on routine implementation of a battery of diagnostic tests is not superior to a clinical follow-up (GIVIO investigators 1994).

Emens and Davidson (2003) have also reviewed the cost-effectiveness of intensive surveillance of breast cancer survivors and found no significant impact on overall survival or quality of life for women with early-stage breast cancer.

In article IV no statistically significant differences in DFS (range 67%–74%) or OS (range 74%–85%) were found between the four follow-up arms including 472 patients at a mean follow-up at 4.2 years; patients followed by visits only every sixth month without routine tests (except mammograms) had survival comparable to intensively followed-up patients with visits every three months including routine tests. Nor was any difference in survival found among patients followed without routine examinations by visits either every third or sixth month. However, the QOL between the differently monitored patients was not analyzed at all.

This result is in line with the results of GIVIO investigators (1994) and of Rosselli Del Turco and associates (1994). Nor did Gulliford and associates find any additional benefit for patients with breast cancer in frequent (standard follow-up visits) vs. seldom (once a year or every second year) routine visits in the follow-up. In both groups mammograms were taken regularly and in the group making less frequent visits patients were checked only after mammography. Altogether 193 patients were evaluable while 7% of patients refused to participate in the trial. Median follow-up was 16 months and mailed questionnaires were sent to patients at six months and then annually. In the trial in question the time from primary diagnosis was < 2 years in 20% of patients and > 5 years in 60% of patients. No increase in the number of phone calls and use of physician services was seen in the group of seldom visits compared to the other group. In both groups about 90% of the patients found the psychological effect of the clinic visit

reassuring. In the frequent group one fourth and in the non-frequent group one third preferred a less frequent future visit schedule (Gulliford et al. 1997).

Jacobs and associates (2001) found only minimal medical effects from routine follow-up in a simulation model of follow-up of breast cancer patients. The benefit of follow-up, i.e. gain in life expectancy, for patients aged 40 years was 73 days and aged 60 years 37 days compared to no follow-up. Social, physical, psychological and quality of life (QOL) aspects could not be included and estimated in this model and this may be the justification for current follow-up policies. The authors recommend specialist-led follow-up during the first post-treatment year and thereafter easy access to health care facilities in the case of symptoms or concern. Anyway, regular mammograms should be done.

Follow-up visits of breast cancer patients could be made to general practioner instead of hospital specialists. In addition, the expenses of follow-up might thus be reduced. Grunfeldt and associates compared routine follow-up led by general practitioners vs. specialists at hospital in a randomized trial; 296 breast cancer patients with stage I–III were involved and at least 3 months had passed from the end of primary treatment. The mean ages of the patients were 59 years vs. 62 years. Three questionnaires were mailed to patients at the beginning, at mid-trial between 6–12 months and at the end of study. Follow-up was for 18 months and during this time no delay was found in the detection of recurrence between the two arms. Recurrence was detected in 6.8% of patients in the general practice group and in 10.8% in the hospital group. Neither increase in anxiety nor deterioration in health-related quality of life of patients was detected between the groups (Grunfeldt et al. 1996). The total cost of follow-up was lower in primary care. In fact at the onset one in three eligible patients did not wish to be involved in the trial.

In a more recent randomized follow-up study covering 968 patients no differences were found in the health outcome of breast cancer patients followed by family physician versus hospital specialist. Median follow-up in the study was 3.5 years (Grunfeldt et al. 2006).

Rojas and associates in their review of follow-up strategies on women treated for early breast cancer conclude that a recent update (4 randomized trials of GIVIO investigators 1994, Rosselli del Turco et al. 1994, Grunfeldt et al. 1996 and Gulliford et al. 1997) confirms regular physical examination and yearly mammogram (minimalist follow-up) to be as effective as more intensive methods of examination (intensive follow-up) in detecting recurrent breast cancer. In this review altogether over 3000 women were included (Rojas et al. 2006)

As a conclusion, the benefit of patients with localized breast cancer under surveillance was equally good in intensive vs. non-intensive arms; no difference in

disease-free or overall survival was found either between follow-up arms with frequent vs. infrequent visits or between follow-up arms with or without routine tests. It seems that clinical visits every sixth month without routine examinations would appear to be the best choice during the first years after primary treatment of breast cancer.

8.6 Patients` conceptions of follow-up

In this study conceptions of patients concerning follow-up were not studied. However, in terms of good follow-up the patient is the main target and should benefit from it. Therefore, the conceptions of patients should thus be considered and some studies have been conducted with this in mind.

Asymptomatic patients with localized breast cancer under surveillance desire frequent visits and routine examinations even though frequent testing can lead to increased anxiety (Paradiso et al. 1995, Partridge et al. 2003, de Bock et al. 2004b). In a survey by Paradiso and associates 71% of patients confirmed that periodic follow-ups generated anxiety (Paradiso et al. 1995). Also > 50% of patients in a cross-sectional survey with postal questionnaire sent to over 100 patients without any sign of relapse of breast cancer after 2–4 years after primary surgical treatment and under routine follow-up hoped for routine life-long follow-up every 6th month (De Bock et al. 2004b). In the GIVIO trial frequent visits with testing was also the hope of patients under follow-up.

In general, patients are used to routine visits and believe that early detection of metastatic disease is beneficial. They rely more on tests than their own well-being to reflect the general attitudes in health care. Muss and associates (1991) studied the awareness of patients in this respect. The authors state that only 1/3 of patients understood the significance of history-taking in follow-up visits and 2/3 of patients understood the purpose of physical examination. Most patients, 92%, believed that early detection of distant metastases improved survival and treatment results. Patients thought blood tests and imaging procedures to be more important than history-taking in detecting metastatic disease (Muss et al. 1991). It is hard for clinicians under this pressure not to make some tests for certainty. This brings up one important aspect of follow-up, namely giving appropriate guidance and information to patients.

8.7 Cost of follow-up

The total costs in the four follow-up arms and differences in costs between the arms were calculated and, in addition, estimations were made per patient (article IV). Cost

estimations were made on an outpatient basis and from the hospital perspective. The total costs per patient would have been even higher if travel expenses and absences from work had been included in the costs. Now the mean total cost per patient among the 472 participants was 1632€ during the mean follow-up of 4.2 years. The total cost in the most expensive arm (2269€) was 2.2 times higher compared to the cheapest (1050€). The cost of contacts (including visits and phone calls) per patient was 1.6 times higher and that of examinations 2.7 times higher in the most expensive compared to the least expensive arm. Much more money was spent on examinations than on visits in arms with routine investigations, whereas in those without routine investigations about half of the cost went both on contacts and on examinations. The total cost of follow-up would most likely be much higher in other countries where public health is not supported by the state as in Finland.

The cost per detected recurrence was also estimated and among the 472 patients the cost per detected recurrence was 6261€. Between the most and least expensive arms the difference in cost per detected recurrence was doubled (2.2).

Most importantly, between arms no statistically significant differences in DFS and in OS were found, survival in the arm with visits every 6th month without routine tests being equal to that in the arm with visits every third month with routine tests. However, one has to remember that there were only some hundred patients (range, 114–125) in each of the four follow-up arms and the number of all patients for follow-up was under five hundred (n = 472).

Among all tests, quantitatively, blood tests and chest X-rays were performed most. The conclusion can be drawn that the clinical need for these tests based on symptoms and findings is about 25% from the amount of tests taken in the intensive arms. The three groups of most expensive tests were bone scans, blood tests and chest X-rays, which made up almost half of the examination costs in the intensive arms. A great-deal of money can be saved without compromising the survival of patients by reducing/discounting the performance of these tests in asymptomatic patients. Besides money, very likely other expenses as well as the use of different resources can be reduced, for instance travel expenses, absences from work and time consumption for examinations among patients and health care personnel. By reducing routine visits to one every 6th month with additional visits made on clinical grounds cost can be reduced by almost 40%. By combining these reductions in visits and examinations the total cost of follow-up could be reduced by half (54%). QOL was not evaluated and this study does not reveal whether patients would have had more mental support with more frequent visits.

The results of this randomized follow-up study concerning cost of follow-up are in line with theoretical calculations. Cost analyses have usually comprised only theoretical

calculations of what follow-up with visits and examinations woud cost. Costs between minimalist vs. intensive surveillance in the follow-up of breast cancer patients have also been calculated by Schapira and Urban, as well as by Mapelli and associates, the cost per patient being estimated to be 5.6 times higher in intensive vs. basic follow-up for five years (Schapira and Urban 1991). Mapelli calculated the cost differences when the follow-up schedule would have corresponded to that in the large randomized GIVIO trial, where no difference in OS was found between patients in the standard versus intensive arm. The authors estimated the ratio of intensive to minimum follow-up cost to be 3:1 (up to 5:1) during a five-year follow-up (Mapelli et al. 1995). In the present study the total cost of follow-up was also analyzed in different sectors of follow-up, i.e contacts and examinations. Moreover, the cost of examinations was estimated separately in different parts of examinations, namely chest X-rays, liver ultrasounds, bone scans, mammograms and blood tests. No publications were found concerning such detailed cost estimation of follow-up examinations in real life.

In addition, the cost of follow-up, other expenses and resources used in the follow-up can probably be reduced by transferring the follow-up of breast cancer patients after primary treatment to primary outpatient care outside hospitals. Grunfeldt evaluated the differences in the follow-up cost between hospital and primary care and found the cost to be 2.9 times higher in hospital-based follow-up (Grunfeldt et al. 1999). However, the follow-up time in that case was only 18 months.

Follow-up costs could most likely be reduced even further by transferring (some) visits to a doctor to the cancer nurse.

8.8 Conclusion

In conclusion, the findings in this study suggest that routine visits every 6th month supplemented with additional visits/phone calls seem to be as good as visits every third month in respect of disease-free and overall survival during the first four years after primary diagnosis of breast cancer. Additional tests, including blood tests, tumour markers, chest X-rays and other imaging examinations apart from routine mammograms should be made on clinical grounds. Intensive routine testing in asymptomatic breast cancer patients does not improve survival but compromises the cost-effectiveness of follow-up. In any case, the most important point is that the well-informed patient with breast cancer knows where to turn when suspicious symptoms or findings arise and then has access without delay to assessment.

9. SUMMARY

Breast cancer is the most common female cancer, constituting almost one third of all female cancers in Finland. The prognosis of patients with breast cancer is good and constantly improving, and the number of breast cancer survivors under surveillance is thus also on the increase. The cost of surveillance is correspondingly rising. The effectiveness of follow-up for breast cancer patients was here assessed in a randomized study in the oncology unit of Tampere University Hospital.

In this trial the frequency of visits and intensity of follow-up tests were randomized and the effectiveness of follow-up of breast cancer patients with localized disease after primary treatment was evaluated. The study involved altogether 472 consecutive breast cancer patients from the Pirkanmaa area with randomization from May 1991 to December 1995. Patients were followed up at the Department of Oncology for five years or until the first relapse, either local or distant.

In a prospective setting some common symptoms, i.e. somatic symptoms, pain, cough-dyspnea, nausea and mental symptoms, fatigue, depression-anxiety and insomnia were recorded in relapse-free patients. Four out of five healthy survivors experienced some symptom(s), but only slight clustering between somatic and mental symptoms was detected. The number of symptomatic patients rose from 38% to 72% in a comparison of the same six symptoms between relapse-free patients in the period from 7 to 12 months from primary treatment and patients experiencing relapse during the six months prior to the diagnosis of relapse.

The sensitivity and specificity of serum tumour marker CA 15-3 and chest X-ray as diagnostic tools in detecting the first local or distant relapse of breast cancer were evaluated. In a prospective setting CA 15-3 was taken every 6th month during the five years of follow-up. This marker could be used with fairly high reliability to rule out relapsing breast cancer with multiple sites or liver metastases, but only one third of first breast cancer recurrences were found by CA 15-3; test specificity was thus high (99%) whereas test sensitivity was low (36%). Likewise, the validity of chest X-ray in detecting intrathoracic relapse was evaluated in arms with routine (chest X-ray taken every 6th month) vs. spontaneous chest X-ray (chest X-ray taken when clinically indicated). Film sensitivity remained low, 11% in the routine vs. 20% in the spontaneous arm, whereas film specificity was higher, 97% in the routine vs. 90% in the spontaneous arm. In addition, no statistically significant differences were found between arms in disease-free or overall survival. Thus, routine compared to spontaneous chest X-ray did not benefit the asymptomatic patient.

The total cost of follow-up was analyzed in the four follow-up arms. The costs of visits and examinations were calculated as well as the cost of a detected recurrence per patient in each arm. Neither the frequency of visits nor the intensity of examinations had any effect on overall and disease-free survival. During the mean follow-up of 4.2 years no differences between arms in overall vs. disease-free survival were detected. However, the total cost of follow-up in the respective arms was different; the costs per patient and per detected recurrence in the arm with visits every third month with routine examinations were 2269€ vs. 9149€, respectively, and in the arm with visits every sixth month without routine examination 1050€ vs. 4166€, respectively, the difference in total cost between the most and least expensive follow-up being thus 2.2 fold. The reason for the difference in total cost was explained mainly by the routine examinations in the follow-up.

As a conclusion, after primary treatment relapse-free breast cancer patients suffered considerably from the somatic symptoms pain, cough-dyspnea and nausea and from the mental symptoms such as fatigue, depression and insomnia. By no means always was the occurrence of symptoms associated with relapse of breast cancer. Nonetheless, the same symptoms increased significantly during the six months prior to diagnosis of relapse. The sensitivity of tumour marker CA 15-3 in detection of the first relapse was low, as was the sensitivity of chest X-ray in detecting the first intrathoracic relapse in an asymptomatic breast cancer patient. There were no statistically significant differences in disease-free and overall survival between patients in the respective follow-up arms. The least expensive follow-up schedule among equally competent approaches was as good as the most expensive schedule, i.e. no differences in disease-free or overall survival were detected.

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12. ERRATUM

Original Article II: Ca 15-3 in the follow-up of localised breast cancer: a prospective study. On side 1191 beneath table 3 [a] Ca 15-3 elevated < 40 IU/l should read Ca 15-3 elevated ≥ 40 IU/l.

13. ORIGINAL PUBLICATIONS

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