ELSEVIER

European Journal of Cancer 40 (2004) 1545–1553

European Journal of Cancer

www.ejconline.com

Staging in patients with locoregionally recurrent breast cancer: current practice and prospects for positron emission tomography ☆

F.J. van Oost [a,*], J.J.M. van der Hoeven [b,c], O.S. Hoekstra [c,d], A.C. Voogd [a,e], J.W.W. Coebergh [a,f], L.V. van de Poll-Franse [a]

[a] *Eindhoven Cancer Registry, Comprehensive Cancer Center South (IKZ), P.O. Box 231, 5600 AE Eindhoven, The Netherlands*
[b] *Department of Internal Medicine, Ziekenhuis Amstelveen, Amstelveen, The Netherlands*
[c] *Department of Nuclear Medicine/PET, VU University Medical Center, Amsterdam, The Netherlands*
[d] *Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands*
[e] *Department of Epidemiology, Maastricht University, Maastricht, The Netherlands*
[f] *Department of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands*

Received 2 February 2004; received in revised form 17 March 2004; accepted 19 March 2004
Available online 19 May 2004

Abstract

The aim of this study was to describe the extent and yield of daily clinical practice when staging patients with a locoregional recurrence (LRR) of breast carcinoma and to explore the prospects for positron emission tomography (PET). The population-based Eindhoven Cancer Registry was used to select all breast cancer patients in the southeast of the Netherlands with a first episode of LRR between January 1, 1994 and June 30, 2000 ($n = 175$). Additional data concerning staging procedures and follow-up were collected from the medical records. Furthermore, we asked 77 physicians (response: 75%) about their opinions on staging procedures and actual treatment policy. At LRR presentation, 16% of patients were found to have distant metastases. An additional 24% were diagnosed with distant metastases within 18 months. The questionnaire revealed that 33% of clinicians thought that the sensitivity of conventional imaging techniques was too low. We tend to conclude that in daily clinical practice there is a need for more sensitive dissemination tests for patients with a LRR of breast cancer.

Keywords: Breast cancer; Recurrence; Staging; 2-Fluoro-2-deoxy-D-glucose; Positron emission tomography; PET

1. Introduction

Approximately 10% of all patients with breast cancer stage I or II who underwent breast-conserving therapy or mastectomy develop an isolated locoregional recurrence (LRR) within 10 years of treatment of the primary tumour [1]. Women with a LRR of breast cancer have a higher risk of having or developing disseminated disease than those presenting with a primary tumour [2–4]. Until now, validated algorithms are lacking for the diagnostic work-up of distant metastases in LRR.

The yield of current dissemination tests among asymptomatic patients with an early stage of primary breast cancer is low [5–9]. In LRR, the yield of the current staging procedures will probably be low too. Earlier recognition of disseminated disease in these patients may alter treatment policy.

New diagnostic modalities such as 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) have emerged with promising results [10–20] and may be beneficial in patients presenting with LRR. However, one of the first steps in the assessment of new and expensive technology is to obtain knowledge of the

☆ This work was carried out with a grant from the 'College van Zorgverzekeraars' (Board of Health Insurers) and the 'Vereniging Academische Ziekenhuizen' (Association of University Hospitals).
* Corresponding author. Tel.: +31-40-297-1616; fax: +31-40-297-1610.
E-mail address: research@ikz.nl (F.J. van Oost).

0959-8049/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2004.03.012

effectiveness and efficiency of current clinical practice [21]. Therefore, the aim of this study was to obtain representative data on the extent and yield of current daily clinical practice with respect to staging of patients with LRR. In addition, surgeons, radiotherapists and internists responsible for treatment of LRR in two geographical areas in the Netherlands completed a questionnaire to elicit their opinions on staging procedures and current treatment policy in patients with LRR. On the basis of the results of the study, three scenarios were developed estimating the percentage of patients with LRR that might benefit from a PET scan.

2. Patients and methods

2.1. Patients and data collection

The database of the population-based Eindhoven Cancer Registry in the southeast of the Netherlands [22] was used to identify all breast cancer patients with a first episode of isolated invasive LRR between January 1, 1994 and June 30, 2000.

LRR was defined as recurrence in the breast after breast-conserving treatment, in the chest wall (after mastectomy) and/or in the regional axillary and/or parasternal lymph nodes at the site of the primary tumour. Skin metastases were regarded as distant metastases if they did not originate from the locoregional process.

Patients were eligible if they had undergone breast-conserving surgery or mastectomy for primary localised breast cancer. Patients with T4 disease at the time of the primary tumour were excluded since they presumably had not undergone intentionally curative treatment for the primary tumour. Women older than 75 years at the time of LRR were excluded since they are less likely to undergo aggressive local or systemic treatment and as a consequence presumably will not undergo extensive investigations to rule out the presence of metastases. Moreover, patients with clinically overt distant metastases before LRR presentation were also excluded.

Between January 1, 1994 and June 30, 2000, 181 patients who met the inclusion criteria had been recorded with an isolated LRR of breast cancer (approximately 28 patients a year in a population of 500 000 women). In addition to data collected by the Cancer Registry, data from these patients' medical records were registered for a period of 18 months after LRR presentation. This interval would reflect the possible impact of alternative staging tests like PET. We assumed that distant metastases developing after 18 months will probably go undetected by any imaging test. Six patients were excluded from analyses because of a lack of information in the medical records.

Based on the presence or absence of proven distant metastases, patients were divided into three groups for the analysis: (1) patients without distant metastases within 18 months (M0), (2) patients diagnosed with distant metastases by means of the staging procedures at the time of LRR (M1-rec) and (3) patients in whom distant metastases developed within 18 months (M1–18) after the diagnosis of LRR.

The variables 'age', 'complaints', 'interval between primary tumour and LRR' and 'duration of staging' were dichotomised. The age of 50 years was chosen to separate pre- and post-menopausal patients. If patients had complaints at the time of LRR, this would have been described in the medical records. The maximum clinically acceptable duration of staging was set at 4 weeks.

'Staging procedures at the time of the recurrence' included all imaging techniques aimed at distant metastases and will further be referred to as 'staging procedures'. Laboratory tests were also regarded as staging procedures except if ordered preoperatively by an anaesthesiologist. The results of imaging tests were registered as 'normal', 'suspect' or 'confirmative' of metastases, according to the judgement of the attending clinician. Assessment of gamma-glutamyl-transpeptidase (gamma-GT) in combination with alkaline phosphatase was regarded as first-level laboratory dissemination tests since these enzymes are important indicators for liver and bone metastases, respectively. A chest X-ray or computed tomography (CT) in combination with a liver ultrasound or CT and a bone scintigraphy were regarded as first-level imaging tests to screen lungs, liver and skeleton for distant metastases. Staging procedures that were done to verify abnormal first-level test results were regarded as second-level tests. The duration of staging in weeks was calculated from the first suspicion of LRR established by a clinician in the hospital until the date of the definite staging outcome or the date of the last test. Time to distant metastases was defined from the first suspicion of LRR to the date of diagnosis of distant metastases.

2.2. Questionnaire

To see whether staging practice in the eastern Eindhoven Cancer Registry area was representative for other geographical areas and to evaluate the clinical perception of the yield of current staging practice, a questionnaire (Fig. 1) was sent to surgeons ($n = 35$), internists ($n = 36$) and radiotherapists ($n = 6$) in the northwestern and southern regions of the Netherlands, regions that are served by the Amsterdam and Eindhoven Cancer Registries, respectively.

2.3. Statistical analyses

Data were analysed in SAS (version 8.02, SAS Institute Inc., Cary, North Carolina, USA). P values <0.05

Questionnaire: 'Staging in locoregionally recurrent breast cancer'

In this questionnaire 'locoregionally recurrent breast cancer' is defined as:

a) *A local recurrence in the breast after breast-conserving therapy or in the chest wall after mastectomy, whether or not in the skin.*
b) *A regional recurrence in the regional axillary and/or parasternal lymph nodes, whether or not after a complete axillary lymph node dissection.*
c) *a and b combined.*

1. What is your (sub)specialism?

- ❑ surgical oncology
- ❑ internal oncology
- ❑ radiotherapy

2a. Which below mentioned laboratory tests do you request to stage a patient who presents herself with a locoregional recurrence without complaints suggestive for distant metastases?

- ❑ I do not request laboratory tests
- ❑ I request below indicated tests

	Never	Sometimes	Usually	Always
Erythrocyte sedimentation rate				
Haemoglobin / Haematocrit				
Leucocytes/thrombocytes				
Creatinine				
Alkaline phosphatase				
Gamma-glutamyl-transpeptidase (gamma-GT)				
Serum glutamic oxaloacetic transaminase (SGOT) / serum glutamic pyruvic transaminase (SGPT)				
Lactate dehydrogenase (LDH)				
Calcium				
Carcinoembryonic antigen (CEA)				
Cancer antigen 15.3 (CA-15.3)				

2b. Which imaging tests do you use to stage a patient who presents herself with a locoregional recurrence without complaints suggestive for distant metastases?

The aim of this question is to study the 'standard' staging procedures.

- ❑ I do not request imaging procedures
- ❑ I request below indicated imaging procedures

	Never	Sometimes	Usually	Always
Chest X-ray				
Ultrasound of abdomen				
Bone scintigraphy				
Chest computed tomography (CT)				
CT of abdomen				
Chest magnetic resonance imaging (MRI)				
X other if bone scintigraphy result is aberrant				
Ultrasound other				
Other: .....…..				

3. Are you satisfied with the yield of the imaging tests? (more than one answer possible)

- ❑ Yes
- ❑ No, because the sensitivity is too low
- ❑ No, because the false-positivity is too high
- ❑ No, because I need too many tests
- ❑ No opinion

4. Which policy do you carry out in case of a locoregionally recurrent breast carcinoma? (more than one answer possible)

- ❑ Resection if technically possible, irrespective of the presence of distant metastases
  - ❑ and if possible followed by radiotherapy
  - ❑ followed by systemic therapy (hormonal/chemotherapy)
- ❑ Resection only in the absence of distant metastases
  - ❑ and if possible followed by radiotherapy
  - ❑ followed by systemic therapy (hormonal/chemotherapy)

Fig. 1. Questionnaire sent to physicians treating breast cancer patients.

were considered statistically significant. The χ^2 test was used to detect differences in patient characteristics between the groups. Logistic regression analyses were used to study treatment choice and predictive values of diagnostic tests, with adjustment for age.

2.4. Scenarios for use of PET

An estimate was made of the percentage of patients with LRR that might benefit from a PET scan in order to plan studies about the accuracy of PET in the most

relevant target population. We calculated the percentage of patients with distant metastases that can be detected by PET at the time of diagnosis of LRR, and 6 and 18 months earlier than by conventional techniques. In the first calculation, we assumed that FDG PET detects all the metastases that are imaged by conventional staging techniques, in the second and third we assumed that FDG PET is able to detect metastases 6 or 18 months earlier than conventional techniques.

Approximately 6% of the Dutch population (16 million inhabitants in total) live in this part of the southeast of the Netherlands. The study period covered 6.5 years. By multiplying the numbers from our scenarios by a factor of 2.56 ($=(100/6)/6.5$), an estimate was made of the annual number of patients who might qualify for PET scanning nationwide, based on the selection criteria in this study. On the basis of the PET literature, we assumed that PET does rarely miss patients diagnosed with distant metastases by means of conventional tests.

3. Results

We investigated the medical records of 175 patients. The mean age of these LRR patients was 55 years (range: 32–74 years). Fifty-eight percent developed LRR after breast-conserving therapy, 40% after mastectomy and in 2% the initial surgical approach could not be identified. Most patients (73%) presented with a local, 19% with a regional and 7% with a local as well as a regional recurrence. Twenty-eight (16%) patients were diagnosed with distant metastases at the time of LRR (M1-rec); during follow-up 42 (24%) others proved to have distant metastases within 18 months (M1–18).

In M1–18 and M1-rec patients, the interval between primary tumour and LRR was more often less than 3 years compared with patients in the M0 group (Table 1). Patients in the M1-rec group more often had regional lymph node recurrences, primary tumours larger than pT1 and complaints compared with patients in the M0 group. M1–18 patients more often had local recurrences with mastitis carcinomatosa and/or multiple foci and this group consisted of relatively younger women compared with M0 patients. No statistically significant differences in regional lymph node stage of the primary tumour were observed between the three patient groups.

Twelve M0 patients, 3 M1–18 patients and 0 M1-rec patients were not staged with imaging techniques at all. In the total group of LRR patients, the median number of imaging tests was three (range: 0–13), with a median staging period of four weeks (range: 0–21 weeks).

The first-level laboratory dissemination tests (gamma-GT and alkaline phosphatase) and imaging tests (chest X-ray or CT in combination with a liver ultrasound or CT and bone scintigraphy) were performed more often in patients with distant metastases (M1-rec) compared with patients without distant metastases at the time of LRR (M0/M1–18; Table 2). There was no difference between the M0 and the M1–18 group in the percentage of patients who underwent these tests. In LRR patients without complaints suggestive of distant metastases ($n = 143$), first-level laboratory dissemination tests and imaging tests were performed in 56% and 62% of cases, respectively.

Patients in the M1–18 and M1-rec groups with metastases in bone, liver or lungs/pleural cavity not proven at the time of diagnosis of LRR, but detected within 6 months, had been screened for these metastases during the staging procedures at LRR presentation in 75% (bone scintigraphy), 50% (liver ultrasound/CT) and 89% (chest X-ray/CT) of the cases, respectively.

An increased risk of distant metastases within 6 months was found in patients with an aberrant gamma-GT or lactate dehydrogenase (LDH) laboratory test result and/or with a chest X-ray or bone scintigraphy giving rise to suspicion of metastases at the time of LRR (Table 3).

Patients with distant metastases diagnosed during staging (M1-rec) less often underwent locoregional surgery and were more likely to receive systemic treatment compared with patients without distant metastases diagnosed at the time of LRR (M0/M1–18; Table 4). Three out of 7 patients (43%) in the M1-rec group with a recurrence in the breast after breast-conserving therapy underwent a mastectomy in contrast to 72 out of 83 (87%) in the M0/M1–18 group.

Twenty-nine percent of patients without metastases at the time of diagnosis of LRR were diagnosed with distant metastases within 18 months (M1–18), half of them within 6 months (Fig. 2). The percentage of patients who underwent first-level staging procedures did not differ between these groups. Survival after 8 months was equally poor for M1–18 and M1-rec patients (88% and 89%, respectively).

3.1. Questionnaire

The questionnaire was returned by 75% ($n = 58$) of the clinicians. Fifty-four percent of clinicians in the southeast of the Netherlands indicated that they usually or always determined alkaline phosphatase in combination with gamma-GT in LRR patients without complaints suggestive of distant metastases. This result was comparable to the results obtained from medical records in this area (56%), but not to the results from the total group of respondents (71%). With respect to the first-level imaging tests (chest X-ray/CT, liver ultrasound/CT and bone scintigraphy), a discrepancy existed between results from the medical records and the questionnaire in the southeast of the Netherlands (62% versus 92%, respectively), but not between the geographical areas (southeast: 92%; total group of respondents: 88%).

Table 1
Clinical characteristics of patients with locoregionally recurrent (LRR) breast cancer ($n = 175$)

	Group					
	M0[a] ($n = 105$)		M1–18[b] ($n = 42$)		M1-rec[c] ($n = 28$)	
	n	(%)	*n*	(%)	*n*	(%)
Recurrence						
Local	81	(77)	32	(76)	14	(50)
Regional	19	(18)	6	(14)	9	(32)
Locoregional	4	(4)	4	(10)	5	(18)
Local;regional?	1	(1)	0	(0)	0	(0)
P-value (versus M0)			*0.483*		*0.011*	
Mastitis carcinomatosa[d]						
Yes	5	(6)	8	(22)	3	(16)
No/unknown	81	(94)	28	(78)	16	(84)
P-value (versus M0)			*0.007*		*0.138*	
Number of foci[d]						
Solitary	59	(69)	16	(44)	8	(42)
Multiple	23	(27)	18	(50)	10	(53)
Unknown	4	(5)	2	(6)	1	(5)
P-value (versus M0)			*0.038*		*0.080*	
pT stage PT[e]						
pT1	62	(59)	23	(55)	6	(21)
pT2/T3	32	(30)	17	(40)	20	(71)
Unknown	11	(10)	2	(5)	2	(7)
P-value (versus M0)			*0.349*		*0.0004*	
Age at time of LRR						
<50	27	(26)	25	(60)	11	(39)
⩾50	78	(74)	17	(40)	17	(61)
P-value (versus M0)			*0.0001*		*0.158*	
Interval PT-LRR (years)						
0–<3	38	(36)	24	(57)	16	(57)
⩾3	67	(64)	18	(43)	12	(43)
P-value (versus M0)			*0.020*		*0.045*	
Complaints at time of LRR						
Yes	7	(7)	6	(14)	19	(68)
No	70	(67)	28	(67)	8	(29)
Unknown	28	(27)	8	(19)	1	(4)
P-value (versus M0)			*0.262*		*<0.0001*	

[a] M0, patients without distant metastases within 18 months of LRR.
[b] M1–18, patients with distant metastases within 18 months of LRR.
[c] M1-rec, patients diagnosed with distant metastases by means of the staging procedures at the time of LRR.
[d] Only registered for local/locoregional recurrence.
[e] PT, primary tumour.

Table 2
First-level staging procedures in patients with locoregionally recurrent (LRR) breast cancer

	Alkaline phosphatase + gamma-GT[a]		Chest X-ray/CT[b] + liver ultrasound/CT + bone scintigraphy	
	n	(%)	*n*	(%)
M0[c]($n = 105$)	56	(53)	64	(61)
M1–18[d] ($n = 42$)	23	(55)	28	(67)
M1-rec[e] ($n = 28$)	23	(82)	24	(86)
P-value	*0.005*		*0.048*	

[a] Gamma-GT, gamma-glutamyl-transpeptidase.
[b] CT, computed tomography.
[c] M0, patients without distant metastases within 18 months of LRR.
[d] M1–18, patients with distant metastases within 18 months of LRR.
[e] M1-rec, patients diagnosed with distant metastases by means of the staging procedures at the time of LRR.

Table 3
Predictive value of test results (aberrant/suggestive of metastases) in diagnosing distant metastases within 6 months

	Patients without distant metastases at locoregionally recurrent (LRR) breast cancer presentation (M0[a] + M1–18[b])		
	Normal-aberrant	RR[c]	(95% CI[d])
Laboratory			
Erythrocyte sedimentation rate	61–31	3.2	(0.96–10)
Haemoglobin	117–10	2.9	(0.75–11)
Haematocrit	92–11	2.7	(0.71–10)
Leucocytes	72–12	2.7	(0.68–11)
Thrombocytes	22–2	#	
Creatinine	100–7	#	
Alkaline phosphatase	88–6	3.8	(0.58–24)
Gamma-GT[e]	71–10	8.5	(1.8–39)
SGOT[f]	64–3	#	
SGPT[g]	75–2	#	
LDH[h]	43–10	5.9	(1.1–32)
Calcium	36–3	#	
CEA[i]	16–5	#	
CA-15.3[j]	4–0	#	
Imaging[k]			
Chest X-ray	120–4	11	(1.2–95)
Bone scintigraphy	74–21	3.5	(1.0–12)
Liver ultrasound	102–1	#	

Relative risk could not be calculated.
[a] M0, patients without distant metastases within 18 months of LRR.
[b] M1–18, patients with distant metastases within 18 months of LRR.
[c] RR, relative risk adjusted for age.
[d] 95% CI, 95% Confidence Interval.
[e] Gamma-GT, gamma-glutamyl-transpeptidase.
[f] SGOT, serum glutamic oxaloacetic transaminase.
[g] SGPT, serum glutamic pyruvic transaminase.
[h] LDH, lactate dehydrogenase.
[i] CEA, carcinoembryonic antigen.
[j] CA-15.3, cancer antigen 15.3.
[k] Confirming imaging results were excluded from analyses.

Table 4
Therapy at the time of locoregionally recurrent breast cancer presentation in patients with (M1-rec) and without (M0/M1–18) distant metastases

	Group				M1-rec	
	M0/M1–18 ($n = 147$)		M1-rec ($n = 28$)		RR[a]	(95% CI[b])
	n	(%)	*n*	(%)		
Surgery	134	(91)	14	(50)	0.10	(0.04–0.25)
RT[c]	54	(37)	8	(29)	0.68	(0.28–1.7)
Hormonal therapy[d]	48	(33)	16	(57)	2.8	(1.2–6.4)
Chemotherapy	20	(14)	11	(39)	4.4	(1.7–11)
Surgery only	60	(41)	0	(0)	–	
Systemic therapy only	7	(5)	10	(36)	11	(3.8–33)
Surgery and RT	22	(15)	1	(4)	0.21	(0.03–1.6)
Surgery and syst[e]	24	(16)	9	(32)	2.4	(0.97–6.0)
Surgery and RT and syst	28	(19)	4	(14)	0.72	(0.23–2.2)

[a] RR, relative risk adjusted for age.
[b] 95% CI, 95% Confidence Interval.
[c] RT, radiotherapy (not included if it was only radiation of distant metastases).
[d] Ovariectomy and X-castration also counted as hormonal therapy.
[e] Syst, systemic therapy (hormonal and/or chemotherapy).

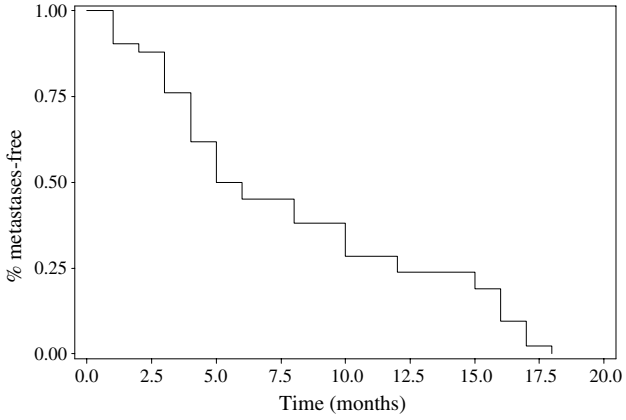

Fig. 2. Distant metastases-free period of patients with distant metastases within 18 months (M1–18) after locoregionally recurrent breast cancer presentation.

Forty-four percent of all respondents indicated that they were not satisfied with the yield of the conventional imaging techniques. Thirty-three percent indicated that the sensitivity was too low, 14% needed too many tests, 7% believed there were too many false-positives and 7% of the clinicians did not have an opinion.

Seventy-one percent of all respondents chose a resection of the LRR only in the absence of distant metastases. In addition, 9% indicated that (in principle) they would choose this latter option, but in exceptional circumstances (predominantly if local problems were expected) they would also perform a resection in the presence of distant metastases.

3.2. Scenarios for the use of PET

Three scenarios were developed for the use of PET:

1. As a substitute for the current, mostly protracted staging process: all patients with a LRR are supposed to qualify for PET. A total of 448 patients in the Netherlands would undergo PET scanning annually for the indication LRR; this would detect distant metastases in 16-28-40% of patients (assuming that FDG PET detects all metastases confirmed by conventional techniques at the time of diagnosis of LRR, 6 or 18 months earlier, respectively).
2. After a negative conservative screening (84% of the total group): 376 patients would undergo PET scanning and this could alter the stage of disease in 0-14-29% of patients.
3. As in 2, but only in patients with the high-risk profile used in our study:
   (a) younger than 50 years of age (pre-menopausal),
   (b) interval between primary tumour and recurrence less than 3 years,
   (c) local recurrence with mastitis carcinomatosa or multiple foci,
   (d) increased gamma-GT or LDH or a suspicious chest X-ray or bone scintigraphy result without proof of metastases during further staging.

In this scenario, 282 patients would undergo PET scanning which would result in a change of stage in 0-18-35% with LRR.

4. Discussion

This study shows that current staging practice at the time of LRR identified distant metastases in 16% of patients, while another 24% were detected within 18 months after this diagnosis. This result is consistent with an earlier publication showing that at least 20% of LRR patients develop distant metastases within 18 months of diagnosis of the recurrence [23]. In the M1–18 group, staging procedures were no less extensive than in the M0 group. In contrast, the M1-rec group appeared to be subjected more frequently to first-level staging procedures. Existence of abnormal initial screening test results in these patients may have been the reason for performance of at least the complete set of first-level laboratory and imaging tests.

According to the perception of clinicians, first-level imaging tests were performed more often than observed in the medical records. This discrepancy might be explained by the fact that the questionnaire gives a simplistic reflection of everyday reality. In daily practice, a complex combination of patient and tumour characteristics determines if clinicians request imaging tests.

Diagnosing distant metastases at the time of LRR had a clear effect on treatment of patients: they received more systemic therapy and less locoregional surgery. This attitude to surgery was confirmed by the outcome of the questionnaire. However, the results also showed that a substantial proportion of patients with a local recurrence after breast-conserving therapy and proven distant metastases underwent a salvage mastectomy. It is likely that in these cases locoregional control of the disease process was needed. In our opinion, aggressive local treatment is not warranted in cases of disseminated cancer, unless required to palliate local symptoms. If not, the local recurrence may be used as a parameter to monitor the effect of systemic treatment.

Furthermore, a proportion of patients in the M1–18 group had a very poor prognosis, but distant metastases could obviously not be diagnosed at the time of LRR. We propose two possible explanations why the presence of these distant metastases could not be verified at the time of LRR: (1) the dissemination process was less extensive compared with M1-rec patients; (2) the growth rate of tumour cells in M1–18 patients was lower than in M1-rec patients, making lesions too small for conventional imaging techniques. In addition, 50–89% of M1–18 and M1-rec patients with metastases in liver, bone or lungs/pleural cavity identified within 6 months, but not diagnosed at

LRR presentation were screened for these metastases during the staging procedures at the time of LRR. This result is in accordance with the opinion of 33% of clinicians who thought that the sensitivity of conventional imaging techniques was too low. This outcome warrants a study of more sensitive imaging techniques such as whole body magnetic resonance imaging (MRI), -CT, -PET and the combination of PET/CT. Antoch and colleagues [24] concluded that PET/CT was superior to whole body MRI in overall tumour node metastases (TNM) staging in 98 patients with different tumours. TNM stage was correctly determined by PET/CT in 75 patients compared with MRI in 53 patients. In our discussion, we will focus on FDG PET, but similar scenarios might be considered for other technologies.

The potential value of FDG PET has been studied for purposes including diagnosis of primary and locally recurrent breast cancer, for staging of axillary lymph nodes, for detection of distant metastases and in clinical problem cases [10–20,25–32]. All studies consistently showed high variability in FDG uptake in breast cancer, ranging from very intense to no uptake at all. In general, lobular breast cancers (approximately 15% of all breast cancers [33]) show lower FDG uptake than ductal breast cancers [34,35].

The issue of diagnosing distant metastases of breast cancer with FDG PET has been addressed in several studies [12–19,36,37]. Schirmeister and colleagues [19] performed whole body FDG PET and conventional staging (chest X-ray, bone scintigraphy and liver ultrasound) in 117 patients with relatively small primary tumours (mean 2.3 cm). Seven of them appeared to have distant metastases, and in four of them this could only be detected after the PET scan. Van der Hoeven and colleagues [38] performed PET scans in 48 patients with locally advanced breast cancer (LABC) after conventional staging techniques ruled out the presence of metastases. In 8% of these patients, PET detected metastases which were not detected earlier. Another 8% had a normal PET scan at entry, but developed metastases within 1 year after start of therapy which consisted of neoadjuvant chemotherapy, mastectomy and radiotherapy. Patients with LABC are more comparable to those with LRR regarding the likelihood of developing metastases within 18 months of diagnosis. Until now, a prospective study is lacking comparing the yield of FDG PET with the combination of conventional lung- (chest X-ray or CT), skeleton- (bone scintigraphy) and liver screening (liver ultrasound or CT) in patients with LRR.

A great advantage of FDG PET is that the procedure is not organ-specific and that, as a consequence, patients can be staged with one investigation. Assuming enough PET capacity, the duration of staging procedures might be shortened. Staging with FDG PET can also influence treatment policy since the results of our study show that the detection of distant metastases has a clear effect on therapy and survival. This influence has also been described in the literature [16,20]. It is not known how much earlier FDG PET might discover distant metastases in comparison with other staging procedures, but it is not likely to be much more than 18 months. On the other hand, it needs to be established whether false-positive results will degrade the potential benefit of a new technology. False-positivity with FDG PET is related to aspecific tracer uptake (inflammation) and to confirmation issues (i.e. finding anatomical substrates for the suspected metastases identified by PET) [39].

Efficient use of imaging tests (i.e. application in a high-risk subset of patients) to demonstrate disseminated disease may be further enhanced by micro-array profiles [40]. At present, these data are confined to patients at primary presentation.

Despite the limited size of our study, we tend to conclude that in daily clinical practice there is a need for more sensitive dissemination tests for patients with a LRR of breast cancer in order to provide them with more tailored treatment. The present study provides baseline data necessary for planning studies using potentially more effective diagnostic methods such as FDG PET. On the basis of our scenarios and assuming that there are approximately 100 hospitals in the Netherlands, 3 to 5 patients with a LRR of breast cancer would qualify annually for PET per medium-sized hospital.

Acknowledgements

The authors would like to thank the registration team of the Eindhoven Cancer Registry for their dedicated data collection of local recurrence and Annette Mills for her suggestions regarding the editing of this paper. We are also indebted to all clinicians who responded to the questionnaire.

This work was carried out with a grant from the 'College van Zorgverzekeraars' (Board of Health Insurers) and the 'Vereniging Academische Ziekenhuizen' (Association of University Hospitals).

References

1. Voogd AC, Nielsen M, Peterse JL, *et al*. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol* 2001, **19**, 1688–1697.
2. Veronesi U, Marubini E, Del Vecchio M, *et al*. Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. *J Natl Cancer Inst* 1995, **87**, 19–27.
3. Fisher B, Anderson S, Fisher ER, *et al*. Significance of ipsilateral breast tumour recurrence after lumpectomy. *Lancet* 1991, **338**, 327–331.
4. Elkhuizen PH, van de Vijver MJ, Hermans J, Zonderland HM, van de Velde CJ, Leer JW. Local recurrence after breast-conserving therapy for invasive breast cancer: high incidence in young patients and association with poor survival. *Int J Radiat Oncol Biol Phys* 1998, **40**, 859–867.

5. Samant R, Ganguly P. Staging investigations in patients with breast cancer: the role of bone scans and liver imaging. *Arch Surg* 1999, **134**, 551–553, discussion 554.
6. Ravaioli A, Tassinari D, Panzini I, Milandri C, Amadori D. Staging of breast cancer: it is time to break with tradition and initiate the evidence-based-medicine age. *J Clin Oncol* 2001, **19**, 1234.
7. Yeh KA, Fortunato L, Ridge JA, Hoffman JP, Eisenberg BL, Sigurdson ER. Routine bone scanning in patients with T1 and T2 breast cancer: a waste of money. *Ann Surg Oncol* 1995, **2**, 319–324.
8. Chen EA, Carlson GA, Coughlin BF, Reed WP, Jr JL, Garb JL. Routine chest roentgenography is unnecessary in the work-up of stage I and II breast cancer. *J Clin Oncol* 2000, **18**, 3503–3506.
9. Barry MC, Thornton F, Murphy M, Younis F, Watson RG. The value of metastatic screening in early primary breast cancer. *Ir J Med Sci* 1999, **168**, 248–250.
10. Comans EF, Hoekstra OS, Hoekman K, van der Hoeven JJ, Golding RP, Teule GJ. Added value of positron emission tomography with fluoro-18-deoxyglucose as the tracer (FDG-PET) in clinical problem cases in oncology. *Ned Tijdschr Geneeskd* 2000, **144**, 1520–1528.
11. Bender H, Kirst J, Palmedo H, *et al*. Value of fluoro-18-deoxyglucose positron emission tomography in the staging of recurrent breast carcinoma. *Anticancer Res* 1997, **17**, 1687–1692.
12. Cook GJ, Houston S, Rubens R, Maisey MN, Fogelman I. Detection of bone metastases in breast cancer by 18FDG PET: differing metabolic activity in osteoblastic and osteolytic lesions. *J Clin Oncol* 1998, **16**, 3375–3379.
13. Dose J, Bleckmann C, Bachmann S, *et al*. Comparison of fluorodeoxyglucose positron emission tomography and 'conventional diagnostic procedures' for the detection of distant metastases in breast cancer patients. *Nucl Med Commun* 2002, **23**, 857–864.
14. Eubank WB, Mankoff DA, Vesselle HJ, *et al*. Detection of locoregional and distant recurrences in breast cancer patients by using FDG PET. *Radiographics* 2002, **22**, 5–17.
15. Hubner KF, Smith GT, Thie JA, Bell JL, Nelson HS, Hanna WT. The potential of F-18-FDG PET in breast cancer. Detection of primary lesions, axillary lymph node metastases, or distant metastases. *Clin Positron Imaging* 2000, **3**, 197–205.
16. Kim TS, Moon WK, Lee DS, *et al*. Fluorodeoxyglucose positron emission tomography for detection of recurrent or metastatic breast cancer. *World J Surg* 2001, **25**, 829–834.
17. Lonneux M, Borbath II, Berliere M, Kirkove C, Pauwels S. The place of whole-body PET FDG for the diagnosis of distant recurrence of breast cancer. *Clin Positron Imaging* 2000, **3**, 45–49.
18. Moon DH, Maddahi J, Silverman DHS, Glaspy JA, Phelps ME, Hoh CK. Accuracy of whole-body fluorine-18-FDG PET for the detection of recurrent or metastatic breast carcinoma. *J Nucl Med* 1998, **39**, 431–435.
19. Schirrmeister H, Kuhn T, Guhlmann A, *et al*. Fluorine-18 2-deoxy-2-fluoro-D-glucose PET in the preoperative staging of breast cancer: comparison with the standard staging procedures. *Eur J Nucl Med* 2001, **28**, 351–358.
20. Yap CS, Seltzer MA, Schiepers C, *et al*. Impact of whole-body 18F-FDG PET on staging and managing patients with breast cancer: the referring physician's perspective. *J Nucl Med* 2001, **42**, 1334–1337.
21. Herder GJ, Verboom P, Smit EF, *et al*. Practice, efficacy and cost of staging suspected non-small cell lung cancer: a retrospective study in two Dutch hospitals. *Thorax* 2002, **57**, 11–14.
22. Voogd AC, van Beek MW, Crommelin MA, Kluck HM, Repelaer van Driel OJ, Coebergh JW. Management of early breast cancer in southeast Netherlands since 1984. A population-based study. Regional Breast Cancer Study Group. *Acta Oncol* 1994, **33**, 753–757.
23. Voogd AC, van Tienhoven G, Peterse HL, *et al*. Local recurrence after breast conservation therapy for early stage breast carcinoma: detection, treatment, and outcome in 266 patients. Dutch Study Group on Local Recurrence after Breast Conservation (BORST). *Cancer* 1999, **85**, 437–446.
24. Antoch G, Vogt FM, Freudenberg LS, *et al*. Whole-body dual-modality PET/CT and whole-body MRI for tumor staging in oncology. *Jama* 2003, **290**, 3199–3206.
25. Adler LP, Crowe JP, al-Kaisi NK, Sunshine JL. Evaluation of breast masses and axillary lymph nodes with [F-18] 2-deoxy-2-fluoro-D-glucose PET. *Radiology* 1993, **187**, 743–750.
26. Greco M, Crippa F, Agresti R, *et al*. Axillary lymph node staging in breast cancer by 2-fluoro-2-deoxy-D-glucose-positron emission tomography: clinical evaluation and alternative management. *J Natl Cancer Inst* 2001, **93**, 630–635.
27. Noh DY, Yun IJ, Kim JS, *et al*. Diagnostic value of positron emission tomography for detecting breast cancer. *World J Surg* 1998, **22**, 223–227, discussion 227–8.
28. van der Hoeven JJ, Hoekstra OS, Comans EF, *et al*. Determinants of diagnostic performance of [F-18]fluorodeoxyglucose positron emission tomography for axillary staging in breast cancer. *Ann Surg* 2002, **236**, 619–624.
29. Yang SN, Liang JA, Lin FJ, Kao CH, Lin CC, Lee CC. Comparing whole body (18)F-2-deoxyglucose positron emission tomography and technetium-99m methylene diphosphonate bone scan to detect bone metastases in patients with breast cancer. *J Cancer Res Clin Oncol* 2002, **128**, 325–328.
30. Avril N, Dose J, Janicke F, *et al*. Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. *J Clin Oncol* 1996, **14**, 1848–1857.
31. Scheidhauer K, Scharl A, Pietrzyk U, *et al*. Qualitative [^{18}F]FDG positron emission tomography in primary breast cancer: clinical relevance and practicability. *Eur J Nucl Med* 1996, **23**, 618–623.
32. Avril N, Rose CA, Schelling M, *et al*. Breast imaging with positron emission tomography and fluorine-18 fluorodeoxyglucose: use and limitations. *J Clin Oncol* 2000, **18**, 3495–3502.
33. Li CI, Anderson BO, Daling JR, Moe RE. Trends in incidence rates of invasive lobular and ductal breast carcinoma. *Jama* 2003, **289**, 1421–1424.
34. Crippa F, Seregni E, Agresti R, *et al*. Association between [^{18}F]fluorodeoxyglucose uptake and postoperative histopathology, hormone receptor status, thymidine labelling index and p53 in primary breast cancer: a preliminary observation. *Eur J Nucl Med* 1998, **25**, 1429–1434.
35. Avril N, Menzel M, Dose J, *et al*. Glucose metabolism of breast cancer assessed by 18F-FDG PET: histologic and immunohistochemical tissue analysis. *J Nucl Med* 2001, **42**, 9–16.
36. Ohta M, Tokuda Y, Suzuki Y, *et al*. Whole body PET for the evaluation of bony metastases in patients with breast cancer: comparison with 99Tcm-MDP bone scintigraphy. *Nucl Med Commun* 2001, **22**, 875–879.
37. Suarez M, Perez-Castejon MJ, Jimenez A, *et al*. Early diagnosis of recurrent breast cancer with FDG-PET in patients with progressive elevation of serum tumor markers. *Q J Nucl Med* 2002, **46**, 113–121.
38. van der Hoeven JJ, Krak NC, Hoekstra OS, *et al*. 18F-2-fluoro-2-deoxy-d-glucose positron emission tomography in staging of locally advanced breast cancer. *J Clin Oncol* 2004, **22**, 1253–1259.
39. Hoekstra CJ, Stroobants SG, Hoekstra OS, *et al*. The value of [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography in the selection of patients with stage IIIA-N2 non-small cell lung cancer for combined modality treatment. *Lung Cancer* 2003, **39**, 151–157.
40. van de Vijver MJ, He YD, van't Veer LJ, *et al*. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med* 2002, **347**, 1999–2009.