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# A population based study of radiotherapy in a cohort of patients with breast cancer diagnosed between 1996 and 2000

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## ABSTRACT

We studied the use of radiotherapy (RT) (especially secondary RT) in a cohort of 6561 patients in southern Netherlands with invasive breast cancer diagnosed between 1996 and 2000 (median follow-up: 66 months, range 0–107 months). Radiation within 6 months of diagnosis was considered primary RT (PRT). RT given 6 months or later after diagnosis or after PRT was considered secondary RT (SRT). Of all patients, 67% received RT, 3554 only PRT, 323 only SRT and 503 both. The cumulative use of SRT at 100 months was 17%. The 826 patients receiving SRT underwent 1846 courses 0–105 months (median 36) after diagnosis; the retreat rate was 35%. Elderly patients received SRT significantly less often ( $OR_{age\ 50-69} = 0.7$ , 95%CI = 0.6–0.8,  $OR_{age\ \geq 70} = 0.4$ , 95%CI = 0.3–0.5). The following factors increased the chance for SRT: patients from the eastern region ( $OR = 1.3$ , 95%CI = 1.1–1.6); patients who received PRT ( $OR = 1.3$ , 95%CI = 1.0–1.5) and patients who underwent mastectomy including axillary node dissection as well as unresected patients ( $OR = 1.9$ , 95%CI = 1.5–2.4,  $OR = 2.6$ , 95%CI = 1.7–3.9, respectively).

Thirteen percent of all patients with breast cancer received SRT, with a large variation in age and between the 2 RT departments in the region.

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## 1. Introduction

The incidence of breast cancer in the south of Netherlands amounted to 120 per 100,000 women in 2000. Radiotherapy (RT) is an essential part of breast cancer treatment, either as part of the primary treatment within the framework of breast-conserving treatment or mastectomy,<sup>1–3</sup> or for palliation of recurrent or metastatic breast cancer.<sup>4,5</sup> Therefore, patients with breast cancer constitute a large proportion of the patients treated in an RT department.

Of all cancer patients about 50% are likely to receive radiotherapy during the course of their disease.<sup>6,7</sup> This percentage is not derived from population based studies but is nevertheless often used in the process of decision making for estimation of the future capacity of RT equipment and personnel needed. The overall percentage usually consists of a mixture of primary RT (PRT) as part of the initial treatment and secondary RT (SRT) in the case of recurrent disease or metastases without taking into account whether patients had already received primary RT.<sup>6,8</sup> In a population based study of patients

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treated with RT as part of their primary treatment we found that 30% of all cancer patients received PRT.<sup>9,10</sup> For patients diagnosed with breast cancer in 1998–2002 this amounted to 55%.<sup>9</sup> SRT has been studied in our region for all cancer patients diagnosed between 1975 and 1989: 5% of previously non-irradiated patients received RT for recurrent disease or metastases, and about 40% of all irradiated patients had RT again.<sup>11</sup> Recent studies used an evidence-based approach to determine the use of RT as part of primary treatment and for treatment of recurrences or metastases. They estimated that 66–83% of all breast cancer patients received RT during the course of their illness.<sup>12,13</sup>

Since we had already performed several studies on the use of primary RT, we wanted to estimate the percentage of patients receiving RT during their illness, which can also be relevant for planning purposes. We determined, in a population based setting in a region with two large RT departments, the proportion of patients with breast cancer who received RT as part of their primary treatment and as SRT. We explored the influence of patient and tumour characteristics on SRT and variations in referral for SRT.

## 2. Methods

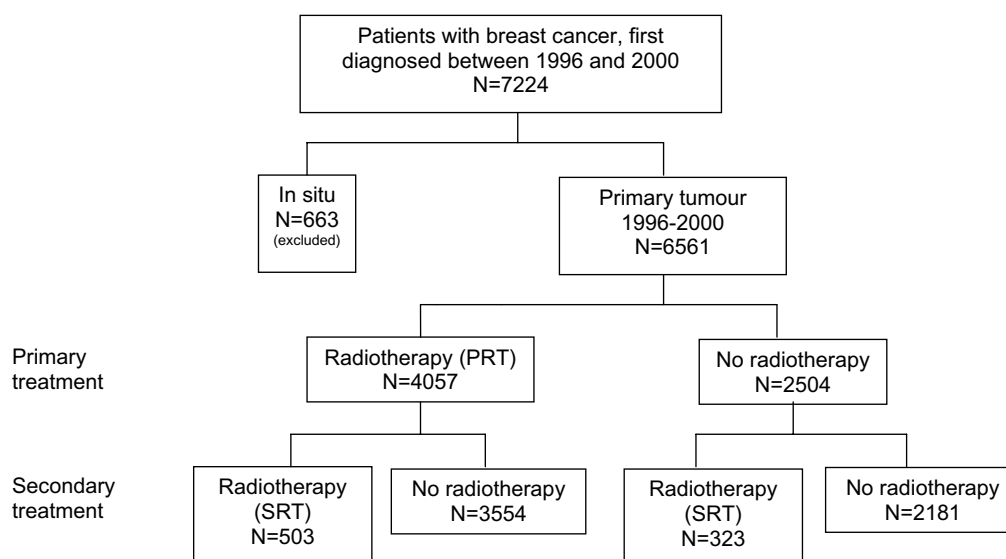
We studied a cohort of patients with a first invasive breast cancer, diagnosed between 1st January 1996 and 31st December 2000 and followed until 1st January 2005. Data were derived from the population based Eindhoven Cancer Registry (ECR), which has recorded data on all patients newly diagnosed with cancer since 1955. The registry covers a large part of South Netherlands with approximately 2.4 million inhabitants in 2004. The medical infrastructure consists of six Pathology Departments, hospital medical records offices in 10 general hospitals and two large RT departments (one in the western (Tilburg) and one in the eastern (Eindhoven) part of the region). Patients never have to travel more than 1 h to an RT department. Trained registry personnel from the ECR

actively collect data on diagnosis, staging, co-morbidity and primary treatment, given or planned within 6 months of diagnosis, from the hospital charts after notification of newly diagnosed cases by the regional Departments of Pathology, Haematology and Radiotherapy as well as the national Registry of Hospital Discharge Diagnoses. An indicator of socioeconomic status (SES) was developed by Statistics Netherlands based on individual fiscal data (economic value of the home and household income) and provided at aggregated levels for each postal code (average of 17 households). Socioeconomic status was categorised 1 (low) to 3 (high), with a separate class for postal codes with a care-providing institution (such as a nursing home).

Cancer registries in The Netherlands usually cover over 95% of all cases, due to the infrastructure of and good access to Dutch health care facilities, together with the multiple source notification procedures used.<sup>14</sup> In both RT Departments, each course of RT is recorded with date of onset, patient characteristics and treatment protocol number indicating the kind of radiation treatment given. Data on all patients with breast cancer who received RT between 1st January 1996 and 1st January 2005 at the two RT Departments were combined with the above-mentioned data from the ECR.

Between 1996 and 2000, a total of 7224 patients were first diagnosed with breast cancer, including sarcomas ( $n = 55$ ) and unknown morphology ( $n = 38$ ). Patients with carcinoma *in situ* ( $n = 663$ ) were excluded. We only considered RT given for the first tumour. Eventually, we included 6561 patients with invasive breast cancer in our analysis (Fig. 1).

Radiation given or planned within 6 months of diagnosis was considered PRT.<sup>15</sup> This includes patients irradiated within 6 months of diagnosis only for metastases as planned primary treatment ( $n = 64$ ). We also included patients who were irradiated as part of primary treatment later than 6 months after diagnosis (in case of prolonged chemotherapy) ( $n = 86$ ). RT given 6 months or later after diagnosis (other than the above) or RT given after a previous course of radiation for



**Fig. 1 – Flow chart of the study population: breast cancer patients diagnosed between 1996 and 2000 in south Netherlands (PTR = primary radiotherapy, SRT = secondary radiotherapy).**

breast cancer (even within 6 months) was considered as delayed or SRT. Patients first irradiated for metastases within 6 months of diagnosis, but for whom this irradiation was not planned as primary treatment, were also considered to have

**Table 1 – Characteristics of patients with breast cancer diagnosed between 1996 and 2000 (n = 6561) receiving primary radiotherapy in south Netherlands**

Patient characteristics	Primary radiotherapy		
	No (n = 2504) (%)	Yes (n = 4057) (%)	Total (n = 6561) (%)
Age at diagnosis			
≤49 years	554 (22)	1142 (28)	1696 (26)
50 t/m 69	1002 (40)	2059 (51)	3061 (47)
≥70+	948 (38)	856 (21)	1804 (28)
Number of concomitant diseases			
None	1188 (47)	2441 (60)	3629 (55)
One	580 (23)	889 (22)	1469 (22)
2+	387 (16)	372 (9)	759 (12)
Unknown	349 (14)	355 (9)	704 (11)
Socioeconomic status			
Low	687 (28)	977 (24)	1664 (25)
Middle	927 (37)	1669 (41)	2596 (40)
High	660 (26)	1249 (31)	1909 (29)
Institution <sup>a</sup>	195 (8)	131 (3)	326 (5)
Unknown	35 (1)	31 (1)	66 (1)
Stage at diagnosis			
I	897 (36)	1713 (42)	2610 (40)
II	1135 (45)	1815 (45)	2950 (45)
III	133 (5)	390 (10)	523 (8)
IV	176 (7)	105 (3)	281 (4)
Unknown	163 (7)	34 (1)	197 (3)
Second breast tumour			
No	2377 (95)	3847 (95)	6224 (95)
Yes	127 (5)	210 (5)	337 (5)
Vital status 1st January 2005			
Alive	1664 (66)	3068 (76)	4732 (72)
Deceased	840 (34)	989 (24)	1829 (28)
Surgery <sup>b</sup> (western region)			
BCS + AC	42 (3)	1227 (67)	1269 (39)
BCS	62 (4)	32 (2)	94 (3)
MRM + AC	1074 (76)	510 (28)	1584 (49)
MRM	63 (4)	25 (1)	88 (3)
No surgery	176 (12)	41 (2)	217 (7)
Surgery (eastern region)			
BCS + AC	53 (5)	1632 (73)	1685 (51)
BCS	51 (5)	35 (2)	86 (3)
MRM + AC	840 (77)	502 (23)	1342(41)
MRM	28 (3)	18 (1)	46 (1)
No surgery	115 (11)	35 (2)	150 (5)
Radiotherapy department			
Western region	1417 (57)	1835 (45)	3252 (50)
Eastern region	1087(43)	2222 (55)	3309 (50)
Secondary radiotherapy			
No	2181 (87)	3554 (88)	5735 (87)
Yes	323 (13)	503 (12)	826 (13)

a Institution: patients living in an institution (i.e. nursing home).

b BCS = Breast conserving surgery, AC = axillary clearance, MRM = modified radical mastectomy.

received SRT (n = 57). When data from the RT institutes were compared with data from the ECR, we found that PRT was not registered in the ECR in 136 cases (2% of the total cohort). We included them in our analysis as part of the PRT group. RT registered in the ECR for 2 patients who were treated later than 6 months (25 and 51 months) after diagnosis was considered to be SRT.

Twenty-one patients were treated with a combination of hyperthermia and external RT for recurrent breast cancer, all administered in the RT department at the Western region, which is a top level reference department for superficial hyperthermia.<sup>16</sup> Eleven of these patients received previous PRT at the same department, and 9 in the other; 1 had previous SRT for recurrent breast cancer in the same institute.

The retreat rate is defined as the number of radiation courses given after the first course divided by the number of all first courses either as PRT or as SRT (=number of patients irradiated).

Characteristics of patients who did or did not receive PRT are listed in Table 1. For surgery, we distinguished between patients from the western and the eastern region. We used logistic regression analysis to estimate the chance of receiving SRT adjusting for age, number of concomitant conditions, socioeconomic status, stage, second breast tumour, RT institute, primary surgical treatment and prior PRT. We assessed the number of patients receiving SRT, and the number and type of secondary radiation treatments (for recurrent or for metastasised disease) they received.

The cumulative use of any RT (PRT or SRT) over time was calculated according to the Life Table Method,<sup>17</sup> starting on the date of diagnosis and ending on the date of start of RT, or censored on the date of death or 1st January 2005 whichever occurred first. In total 1543 patients were censored on 1st January 2005. The cumulative use of SRT was calculated by means of the same method: follow-up for patients who received PRT (n = 4057) started on the last day of primary RT (according to the definition, these patients were at risk for SRT after having received PRT); follow-up for patients who received no PRT (n = 2385, 119 patients died within 6 months of diagnosis) started 6 months after diagnosis (by definition patients without PRT were at risk for SRT 6 months after diagnosis). Follow-up of both groups ended on the date of initiating SRT, date of death or 1st January 2005, whichever occurred first. These two groups were compared by means of the log-rank test.

### 3. Results

In our cohort of 6561 patients with breast cancer diagnosed between 1996 and 2000 (median follow-up 66 months, range 0–107 months), 4380 (67%) patients received RT between 1st January 1996 and 1st January 2005: 3554 (54%) only PRT, 323 (5%) only SRT and 503 (8%) both (Fig. 1). Five hundred and three patients who received PRT and 120 patients who received only SRT were irradiated twice or more. The retreat rate was 35% (1523/4380). The patient characteristics are listed in Table 1. About half of all patients underwent breast-conserving surgery and half mastectomy. In the eastern region, a higher percentage received breast-conserving surgery and was referred for PRT. Five percent of the patients

( $n = 337$ ) developed a second breast tumour between 1st January 1996 and 1st January 2005, 146 (43%) of whom received PRT for the second tumour. Six patients developed a second tumour in the ipsilateral breast, but with other morphology or at another sublocalisation, 331 in the contralateral breast. For 105 patients the second tumour was diagnosed within 1 month of the first, for 82 of these patients on the same day. In this study, we only considered RT given for the first tumour ( $n = 57$ ). The odds for receiving SRT are shown in Table 2. Patients aged 50 years or older received SRT significantly less often (OR = 0.7, 95% CI = 0.6–0.8 and OR = 0.4, 95%CI = 0.3–0.5 for patients 50–69 years and 70 years or older, respectively). Patients with an initial tumour stage higher than stage I

**Table 2 – Odds of receiving secondary radiotherapy for patients with breast cancer diagnosed between 1996 and 2000 ( $n = 6561$ ) in south Netherlands, each variable adjusted for all others**

	Odds-ratio	95% CI	p-value
Age at diagnosis			
≤49 years	1		
50 t/m 69	0.7	0.6–0.8	<0.0001
≥70+	0.4	0.3–0.5	<0.0001
Number of concomitant diseases			
None	1		
One	0.9	0.8–1.1	0.5
2+	0.8	0.6–1.1	0.1
Unknown	1	0.7–1.2	0.7
Socioeconomic status			
Low	1		
Middle	1	0.9–1.3	0.7
High	1.1	0.9–1.4	0.4
Institution <sup>a</sup>	0.8	0.5–1.3	0.4
Unknown	1.4	0.7–2.9	0.4
Stage at diagnosis			
I	1		
II	2.2	1.8–2.7	<0.0001
III	2.9	2.1–3.9	<0.0001
IV	8	5.5–11.5	<0.0001
Unknown	0.9	0.5–1.7	0.8
Radiotherapy department			
Western region	1		
Eastern region	1.3	1.1–1.6	0.0003
Primary radiotherapy			
No	1		
Yes	1.3	1.0–1.5	0.02
Second breast tumour			
No	1		
Yes	1	0.7–1.5	0.8
Surgery <sup>b</sup>			
BCS + AC	1		
BCS	1.6	0.9–2.8	0.09
MRM + AC	1.9	1.5–2.4	<0.0001
MRM	1.7	1.0–3.0	0.07
No surgery	2.6	1.7–3.9	<0.0001

a Institution: patients living in an institution (i.e. nursing home).

b BCS = Breast conserving surgery, AC = axillary clearance, MRM = modified radical mastectomy.

**Table 3 – Number of secondary radiation courses (range: 0<sup>a</sup>–105 months after primary diagnosis) per patient in a cohort of breast cancer patients diagnosed between 1996 and 2000 ( $n = 6561$ ) in south Netherlands**

Number of secondary radiotherapy courses	Number of patients (%)	Total number of secondary radiotherapy courses	Cumulative number of secondary radiotherapy courses
1	438 (53)	438	438
2	166 (20)	332	770
3	76 (9.2)	228	998
4	47 (5.7)	188	1186
5	44 (5.3)	220	1406
6	14 (1.7)	84	1490
7	13 (1.6)	91	1581
8	11 (1.3)	88	1669
9	5 (0.6)	45	1714
10	4 (0.5)	40	1754
11	6 (0.7)	66	1820
12	0 (0)	0	1820
13	2 (0.2)	26	1846
Total	826 (100)	1846	1846

a 0 months after diagnosis: patients first irradiated for metastases within 6 months of diagnosis, but for whom this irradiation was not planned as primary treatment.

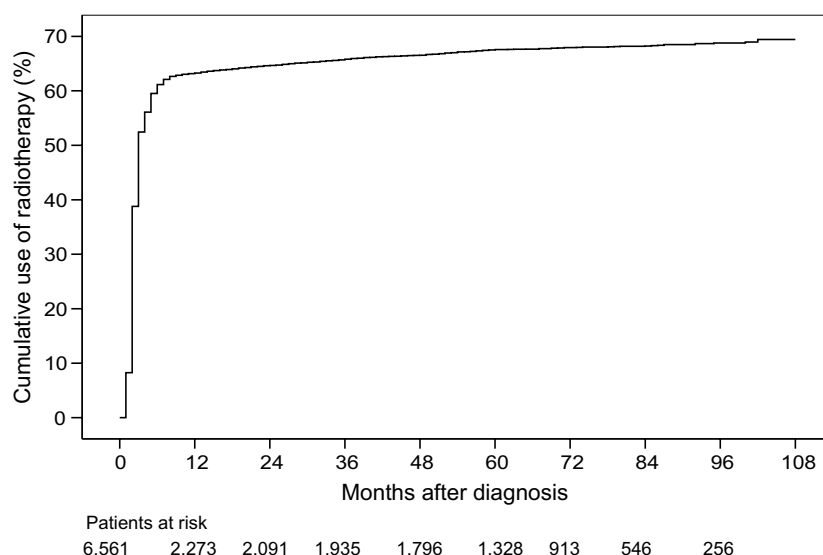
received SRT significantly more often (stage II: OR = 2.2, 95%CI = 1.8–2.7, stage III: OR = 2.9, 95%CI = 2.1–3.9, stage IV: OR = 8, 95%CI = 5.5–11.6). Patients from the eastern region were referred more often for SRT (OR = 1.3, 95% CI = 1.1–1.6). Patients who received PRT had a slightly higher chance of receiving SRT (OR = 1.3, 95%CI = 1.0–1.5). Patients who underwent mastectomy including axillary node dissection and patients who did not undergo surgery had SRT significantly more often (OR = 1.9, 95%CI = 1.5–2.4, OR = 2.6, 95%CI = 1.7–3.9, respectively).

Of 826 patients receiving SRT, 138 (17%) had the first course of SRT for a recurrence and 688 for metastases; they underwent 1846 courses in total, with a range of 0–101 months (median 36 months) after primary diagnosis: 174 courses for relapsed breast tumours and 1672 courses for metastases. Seventy-four percent of these patients had more than one secondary treatment (median = 3) (Table 3).

Fig. 2 shows the cumulative use of RT, either PRT or SRT. Of all patients at risk, 4035 (61%) had RT within the first 6 months of diagnosis. After 101 months 4380 patients had received RT, or 67% of the patients at risk. In Fig. 3, the cumulative use of SRT is shown separately for patients who did or did not receive previous PRT. The total cumulative use of SRT was 17% 100 months after start of follow-up. The cumulative chance to have SRT was slightly higher for patients who did not receive prior PRT ( $p = 0.2$ ).

#### 4. Discussion

We studied the percentage of patients with breast cancer in a cohort diagnosed between 1st January 1996 and 1st December 2000 in our region who received either primary or secondary RT. With a median follow-up of 66 months, 67% of all breast



**Fig. 2 – Cumulative use of radiotherapy (primary or secondary) in a cohort of breast cancer patients (n = 6561) diagnosed between 1996 and 2000 in south Netherlands.**

cancer patients received RT at some point in the course of their illness. This is similar to an evidence-based estimation for optimal RT utilisation in Canada, while an evidence-based study in Australia calculated a higher level.<sup>12,13</sup> However, reported actual RT utilisation rates were much lower (25–50%),<sup>18,19</sup> except in the state of New South Wales, Australia (71%), which was the only study that included patients who had their first RT late during the course of their disease.<sup>20</sup>

We found that patients older than 50 years of age had a significantly lower chance of receiving SRT than did younger patients. Manders and colleagues described the clinical management of women with metastatic breast cancer, demon-

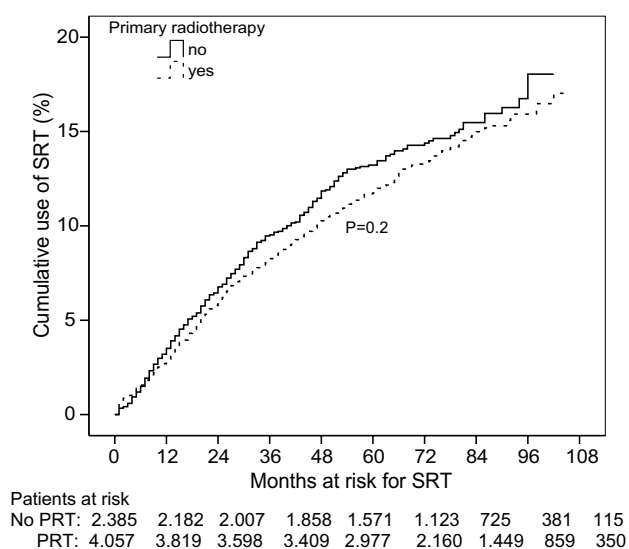
strating that patients aged 70 years or older were less likely to receive both chemotherapy or RT.<sup>21</sup> Elderly patients were also treated less often with primary irradiation, sometimes related to co-morbidity.<sup>22,23</sup>

Socioeconomic status did not affect the chance to receive SRT in our cohort (Table 2), while in the USA large treatment disparities were found.<sup>24</sup> However, socio-economic disparities in the Netherlands are relatively small and medical insurance covers cancer treatment for 99% of the population.<sup>25</sup>

The chance to receive RT for an invasive carcinoma may have been influenced by a previous carcinoma in situ (CIS). According to the national guidelines duct carcinoma in situ (DCIS) should be treated with breast-conserving surgery, including RT, or alternatively with a simple mastectomy on indication.<sup>26</sup> Currently, 49% of patients with DCIS are irradiated but in 1996 this was only 20%.<sup>27</sup> After breast-conserving therapy, including irradiation for a previous DCIS, no standard RT is possible for a new invasive tumour in the same breast. As a result patients with an invasive carcinoma after earlier treatment for DCIS are more likely to undergo a mastectomy without irradiation. DCIS forms 8% (in 1996) to 10% (in 2003) of all new breast tumours.<sup>28</sup>

In our cohort 337 (5%), patients developed a second breast tumour between 1st January 1996 and 1st January 2005. This percentage was also found in another population based study.<sup>29</sup> Because we only considered RT given for the first tumour, we excluded these second tumours, 43% of which received PRT, from our cohort. If these patients received SRT, we distinguished for which tumour on the basis of data from the RT departments. Only SRT for the first tumour was included in our study. A second breast tumour did not influence the chance of receiving SRT for the first tumour.

When a local recurrence occurs after mastectomy (66% of patients primarily undergoing a mastectomy received no PRT), the recurrent tumour can often be treated with SRT. Patients with a recurrence after breast conserving treatment (97% of whom received PRT) are usually not suited for RT



**Fig. 3 – Cumulative use of secondary radiotherapy for patients who did or did not receive primary radiotherapy in a cohort of breast cancer patients (n = 6561) diagnosed between 1996 and 2000 in south Netherlands (PTR = primary radiotherapy, SRT = secondary radiotherapy).**



for their recurrence. Therefore, a mastectomy will commonly be the first treatment of choice. Some of these patients are eligible for regional lymph node irradiation. Superficially located recurrent breast cancer in a previously irradiated area can be treated with RT in an adapted fractionation schedule combined with hyperthermia as radiosensitiser.<sup>16</sup>

In the eastern region, a higher percentage of patients were treated with breast-conserving surgery, which leads to a higher percentage of patients receiving PRT in that region. This can be explained by variations in surgical management, which are larger in the western region than in the eastern region.<sup>30,31</sup> This variation in referral for radiotherapy was observed not only for PRT but also for SRT.

Patients with a higher stage, usually treated with mastectomy including axillary node dissection, have a higher risk for metastases amenable to RT. Patients who did not have any surgery at all had a significantly higher chance of receiving SRT, probably because almost 50% of them had a stage IV tumour at diagnosis, thus a higher risk for symptomatic metastases amenable to RT. Eventually, skeletal metastases occur in 20–40% of patients with breast cancer.<sup>32,33</sup> RT relieves pain in most cases, is effective in spinal cord decompression and can prevent a pathological fracture in the case of lytic lesions of the bone cortex.<sup>34–36</sup> It also improves quality of life and may prolong median survival for most patients with symptomatic brain metastases which occur in 10–20% of women with metastatic breast cancer.<sup>37</sup>

The cumulative use for SRT was slightly higher for patients who did not receive prior PRT (Fig. 3), but after adjustment, the chance of receiving SRT was 30% higher for patients with prior PRT in comparison with patients without prior PRT (OR = 1.3, Table 2). This can partly be explained by the differences in stage distribution and variations in surgical procedures.

A potential drawback of our study is the median follow-up time for our cohort (66 months, range 0–107), which is not very long for a population of breast cancer patients. However, we were unable to study an earlier cohort, because data were incomplete before 1996. Although the development of loco-regional recurrences after 5 years is not uncommon,<sup>38</sup> the majority of recurrences and distant relapses occur in the first 5 years.<sup>39–41</sup> Generally, breast cancer often behaves as a chronic disease for many patients, resulting in prolonged survival with metastases.<sup>41,42</sup> Patients with metastasised disease may be referred for the first SRT many years after the first appearance of the disease and can be treated with irradiation on different localisations until their death. Only 28% of patients in our cohort had died on 1st January 2005. So, whereas the majority of SRT for recurrent breast cancer will occur within our study period, illustrated by the levelling off of the total referral rate (PRT and SRT) after the first year of follow-up (Fig. 2), the cumulative use of SRT (17% at 100 months after the start of follow-up) will undoubtedly continue to increase slowly over subsequent years.

## 5. Conclusions

The required capacity for RT for breast cancer is likely to be higher than the cumulative rates calculated now, requirements also need to be based on RT for DCIS (now 10% of all breast can-

cers, 50% of whom receive RT), and the RT for second primary breast cancer. Furthermore, there was a relatively low rate of breast-conserving surgery (and thus PRT) attributable to several referring specialists<sup>30,31</sup> and there was also some undertreatment of elderly patients.<sup>22,23</sup> This approach to the investigation of radiotherapy consumption stimulates discussion on optimal treatment and clinical justification of treatment variations. Therefore, continued monitoring and discussion with referring specialists is highly warranted.

## Conflicts of interest statement

The authors declare that they have no conflicts of interest.

## REFERENCES

- Whelan TJ, Julian J, Wright J, Jadad AR, Levine ML. Does locoregional radiation therapy improve survival in breast cancer? A meta-analysis. *J Clin Oncol* 2000;**18**:1220–9.
- Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. *J Natl Cancer Inst* 2004;**96**:115–21.
- Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000;**355**:1757–70.
- van der Sangen MJ, Coebergh JW, Roumen RM, Rutten HJ, Vreugdenhil G, Voogd AC. Detection, treatment, and outcome of isolated supraclavicular recurrence in 42 patients with invasive breast carcinoma. *Cancer* 2003;**98**:11–7.
- McQuay HJ, Carroll D, Moore RA. Radiotherapy for painful bone metastases: a systematic review. *Clin Oncol (R Coll Radiol)* 1997;**9**:150–4.
- van Daal WA, Bos MA. Infrastructure for radiotherapy in The Netherlands: development from 1970 to 2010. *Int J Radiat Oncol Biol Phys* 1997;**37**:411–5.
- Porter A, Aref A, Choudounsky Z, et al. A global strategy for radiotherapy: a WHO consultation. *Clin Oncol (R Coll Radiol)* 1999;**11**:368–70.
- Moller TR, Brorsson B, Ceberg J, et al. A prospective survey of radiotherapy practice 2001 in Sweden. *Acta Oncol* 2003;**42**:387–410.
- Vulto A, Louwman M, Rodrigus P, Coebergh JW. Referral rates and trends in radiotherapy as part of primary treatment of cancer in South Netherlands, 1988–2002. *Radiother Oncol* 2006;**78**:131–7.
- Lybeert ML, Louwman M, Coebergh JW. Stable overall referral rates of primary radiotherapy for newly diagnosed cancer patients in the ageing population of South-Eastern Netherlands, 1975–1998. *Radiother Oncol* 2004;**73**:101–8.
- de Jong B, Crommelin M, van der Heijden LH, Coebergh JW. Patterns of radiotherapy for cancer patients in south-eastern Netherlands, 1975–1989. *Radiother Oncol* 1994;**31**:213–21.
- Foroudi F, Tyldesley S, Walker H, Mackillop WJ. An evidence-based estimate of appropriate radiotherapy utilization rate for breast cancer. *Int J Radiat Oncol Biol Phys* 2002;**53**:1240–53.
- Delaney G, Barton M, Jacob S. Estimation of an optimal radiotherapy utilization rate for breast carcinoma: a review of the evidence. *Cancer* 2003;**98**:1977–86.
- Schouten LJ, Hoppener P, van den Brandt PA, Kottner JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol* 1993;**22**:369–76.

15. Vulto JCM, Louwman MW, Poortmans P, et al. population based study of radiotherapy in a cohort of patients with rectal cancer diagnosed between 1996 and 2000. *Eur J Surg Oncol* 2007; doi:10.1016/j.ejso.2007.02.019.
16. Vernon CC, Hand JW, Field SB, et al. International Collaborative Hyperthermia Group. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. *Int J Radiat Oncol Biol Phys* 1996;35:731–44.
17. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. *J Chronic Dis* 1958;8:699–712.
18. Hill DJ, White VM, Giles GG, Collins JP, Kitchen PR. Changes in the investigation and management of primary operable breast cancer in Victoria. *Med J Aust* 1994;161:110–1 [114, 118 passim].
19. Luke C, Chapman P, Priest K, Roder D. Use of radiotherapy in the primary treatment of cancer in South Australia. *Australas Radiol* 2003;47:161–7.
20. NSW radiotherapy management information system report 2000. Sydney: New South Wales Health Department; 2001. *Statewide Services Development Branch* 2001.
21. Manders K, van de Poll-Franse LV, Creemers GJ, et al. Clinical management of women with metastatic breast cancer: a descriptive study according to age group. *BMC Cancer* 2006;6:179.
22. Vulto AJ, Lemmens VE, Louwman MW, et al. The influence of age and comorbidity on receiving radiotherapy as part of primary treatment for cancer in South Netherlands, 1995 to 2002. *Cancer* 2006;106:2734–42.
23. Louwman WJ, Janssen-Heijnen ML, Houterman S, et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population based study. *Eur J Cancer* 2005;41:779–85.
24. Voti L, Richardson LC, Reis I, Fleming LE, Mackinnon J, Coebergh JW. The effect of race/ethnicity and insurance in the administration of standard therapy for local breast cancer in Florida. *Breast Cancer Res Treat* 2006;95:89–95.
25. Ministry of Health, Welfare and Sport; 2007. <http://www.minvws.nl/dossiers/>zorgverzekering/onverzekerden> [cited 15 March 2007].
26. Oncoline, oncological guidelines; 2007. <http://www.oncoline.nl> [cited 15 March 2007].
27. Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853—a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *J Clin Oncol* 2006;24:3381–7.
28. IKCnet, Network of knowledge of the Comprehensive Cancer Centers; 2006. [www.ikcnet.nl](http://www.ikcnet.nl) [cited 15 March 2007].
29. Gao X, Fisher SG, Emami B. Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: a population based study. *Int J Radiat Oncol Biol Phys* 2003;56:1038–45.
30. Vulto JC, Louwman WJ, Poortmans PM, Coebergh JW. Hospital variation in referral for primary radiotherapy in South Netherlands, 1988–1999. *Eur J Cancer* 2005;41:2722–7.
31. Siesling S, van de Poll-Franse LV, Jobsen JJ, Repelaer van Driel OJ, Voogd AC. Trends and variation in breast conserving surgery in the southeast and east of the Netherlands over the period 1990–2002. *Ned Tijdschr Geneesk* 2005;149:1941–6.
32. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. *Br J Cancer* 1987;55:61–6.
33. Tubiana-Hulin M. Incidence, prevalence and distribution of bone metastases. *Bone* 1991;12(Suppl. 1):S9–S10.
34. Nielsen OS, Munro AJ, Tannock IF. Bone metastases: pathophysiology and management policy. *J Clin Oncol* 1991;9:509–24.
35. van der Linden YM, Steenland E, van Houwelingen HC, et al. Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: results on survival in the Dutch Bone Metastasis Study. *Radiother Oncol* 2006;78:245–53.
36. Rades D, Veninga T, Stalpers LJ, et al. Prognostic factors predicting functional outcomes, recurrence-free survival, and overall survival after radiotherapy for metastatic spinal cord compression in breast cancer patients. *Int J Radiat Oncol Biol Phys* 2006;64:182–8.
37. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. *J Clin Oncol* 2004;22:3608–17.
38. van der Sangen MJ, van de Poll-Franse LV, Roumen RM, et al. The prognosis of patients with local recurrence more than five years after breast conservation therapy for invasive breast carcinoma. *Eur J Surg Oncol* 2006;32:34–8.
39. van Tienhoven G, Voogd AC, Peterse JL, et al. Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. *Eur J Cancer* 1999;35:32–8.
40. Holzel D, Engel J, Schmidt M, Sauer H. A model for primary and secondary metastasis in breast cancer and the clinical consequences. *Strahlenther Onkol* 2001;177:10–24.
41. Chung CT, Carlson RW. Goals and objectives in the management of metastatic breast cancer. *Oncologist* 2003;8:514–20.
42. Solomayer EF, Diel IJ, Meyberg GC, Gollan C, Bastert G. Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis. *Breast Cancer Res Treat* 2000;59:271–88.