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Radiation therapy and tamoxifen after breast-conserving surgery: Updated results of a 2 × 2 randomised clinical trial in patients with low risk of recurrence

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ARTICLE INFO

Article history:
Received 31 July 2009
Available online 29 October 2009

The paper is dedicated to Prof. Dr. Alfred Schauer (Göttingen) on the occasion of his 80th birthday. He has been one of the driving forces for this and for previous studies of the German Breast Cancer Study Group (GBSG) that have led to the introduction of breast-conserving therapy in Germany. He contributed his internationally recognised expertise in the central histopathological assessment of breast tumours.

Keywords:
Breast cancer
Favourable prognosis
Breast-conserving surgery
Radiotherapy
Hormonal therapy
Local recurrence

ABSTRACT

To study the role of radiotherapy and tamoxifen after breast-conserving surgery (BCS) in patients with a favourable prognosis, a clinical trial was initiated by the German Breast Cancer Study Group (GBSG-V). Between 1991 and 1998, 361 patients (pT 1pN0M0, aged 45–75 years, receptor positive, grades I and II) were randomised to radiotherapy (yes/no) and tamoxifen for 2 years (yes/no) in a 2 × 2-factorial design; the exclusion of seven centres (14 patients) left 347 patients for the analysis. First results after a median follow-up of 5.9 years were published. Herein we present updated results after a median follow-up of about 10 years. Hundred and eleven events concerning event-free survival (EFS) have been observed. Since a strong interactive effect between radiotherapy and tamoxifen has been established, the results are presented in terms of the treatment effects for all four treatment groups separately. Mainly due to the presence of local recurrences, the event rate was much higher in the group with BCS only than in the other three groups. No significant difference could be established between the four treatment groups for distant disease-free survival rates (DDFS). Updated results give further evidence that even in patients with a favourable prognosis, the avoidance of radiotherapy and tamoxifen after BCS increases the rate of local recurrences substantially. Rates are about three times higher in the BCS only group. For the two outcomes EFS and DDFS, no important difference could be seen between the three groups with an additional treatment. However, because of the limited sample size with corresponding low power the strength of evidence for such a comparison is weak.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.10.007

1. Introduction

Corresponding to the current treatment recommendations, postoperative radiotherapy (RT) is given routinely to nearly all patients after breast-conserving surgery (BCS) for breast cancer [1]. The first trial to investigate whether RT is necessary was conducted by the NSABP (study B06). The cumulative incidence of a recurrence in the ipsilateral breast 20 years after surgery was 14.3% among the women who underwent irradiation after lumpectomy and 39.2% among those who underwent lumpectomy without irradiation ($P < 0.001$). No significant differences were observed among the three treatment groups (mastectomy, lumpectomy and lumpectomy plus irradiation) with respect to disease-free survival, distant disease-free survival or overall survival. Despite RT some patients will get a local recurrence and a substantial proportion of patients not treated with RT and any other adjuvant will remain free of recurrences. As NSABP-B06 had very wide inclusion criteria, allowing patients to be included with tumours of up to 4 cm and positive nodal status, several trials comparing BCS with and without RT in more selected patient groups were designed in the 1980s [2–8].

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) concluded in their most recent overview that radiotherapy produced similar proportional reductions in local recurrence in all women (irrespective of age or tumour characteristics) and in all major trials of radiotherapy versus not (recent or older; with or without systemic therapy), so large absolute reductions in local recurrence were seen only if the control risk was high [9]. Their interpretation is that avoidance of a local recurrence in the conserved breast after BCS and avoidance of a local recurrence elsewhere (e.g. the chest wall or regional nodes) after mastectomy were of comparable relevance to 15-year breast cancer mortality. Differences in local treatment that substantially affect local recurrence rates would, in the hypothetical absence of any other causes of death, avoid about one breast cancer death over the next 15 years for every four local recurrences avoided, and should reduce 15-year overall mortality.

With a median follow-up time of about 6 years we reported the first results of a trial in patients with low risk for recurrence [10]. Herein we report the updated results for event-free and distant disease-free survival time with a median follow-up of nearly 10 years.

2. Patients and methods

In 1991, the German Breast Cancer Study Group (GBSG) started a randomised clinical trial (GBSG-V) in order to evaluate the role of RT after breast-conserving surgical treatment (BCS) in patients with a low risk of recurrence. The study was planned according to a 2×2-factorial design with four treatment arms: BCS without any further treatment, BCS + RT, BCS + TAM and BCS + RT + TAM. The participating centres had an option for randomisation to all four treatments: randomisation between BCS and BCS + RT and randomisation between BCS + TAM and BCS + RT + TAM. Patients with primary breast cancer, stage pT 1pN0M0, and aged between 45 and 75 years were eligible for the study; further inclusion criteria were: histological tumour grade I or II according to Bloom and Richardson [11], absence of lymphovascular invasion tumour-free margins (at least 2 mm) after BCS, no extensive intraductal component (EIC), positive oestrogen and/or progesterone receptor status ($\geqslant$10 fmol/mg).

After a monitoring analysis performed in 1996, it was decided that patients with grade II tumours could only be randomised between the treatment arms BCS + TAM and BCS + RT + TAM. Because of very slow recruitment in the years 1997 and 1998 the study was closed at the end of 1998. The study was performed with the approval of an ethical committee. Informed consent was obtained from each patient.

- The target sample size was originally a total of 700 patients. It was planned to randomise this number of patients in order to detect a difference of 83–90% in 5-year event-free survival (EFS) rates with a power of 80% (two-sided significance level, 5%). This difference corresponds to a relative risk of 0.56 that was assumed for the treatment comparison with respect to both RT and TAM. For this purpose, the effective sample size, i.e. the expected number of events, should be 96. Due to the longer recruitment period, resulting also in a longer follow-up period as originally planned, the total sample size was reduced accordingly [10].

Patients randomised to TAM received a daily dose of 30 mg for 2 years. More details on the surgical technique, radiation therapy, randomisation, treatment compliance, follow-up intervals and targeted sample size were given in the first report of the study [10]. Recurrence was defined as local, regional (axillary lymph nodes or supraclavicular region) or distant (metastases in distant sites). Further events of failure considered were contralateral breast cancer, second cancer and death without previous recurrence. The first event of failure was classified either as 'local recurrence' (the appearance of local or regional recurrence without simultaneous distant failure) or as 'other event' (distant recurrence contralateral or second cancer and death without previous recurrence). EFS was defined as the time from primary diagnosis to the first event of failure. Distant disease-free survival (DDFS) was defined as the time from primary diagnosis to distant recurrence, contralateral or second cancer and/or death without previous distant recurrence.

EFS rates and DDFS rates were calculated according to Kaplan–Meier analysis [12]. The relative risks between different groups as defined by treatment arm and prognostic factors, with the corresponding 95% confidence intervals (CI), were determined by the Cox regression model [13]. Treatment effects were estimated in univariate Cox models and in Cox models adjusting for age, tumour size and tumour grade. For more details see the first report [10]. From these models, estimates of relative risks with their corresponding 95% CI were calculated. The analyses of the effect of treatment were performed on an intention-to-treat basis. To be consistent with the original analysis, only those patients with information concerning age, tumour size and tumour grade were included in the multivariable regression model (complete case analysis). Potential interactive effects between treatment and prognostic factors were not examined.

Table 1 – Patient characteristics.

Factor	Total $n = 347$
Age	
<50 years	30 (8.6)
50–59 years	131 (37.8)
⩾60 years	186 (53.6)
Tumour size	
<10 mm	72 (22.7)
10–20 mm	241 (76.0)
>20 mm	4 (1.3)
Unknown	30
Hormone receptor status	
ER+ and PR+	269 (80.3)
Only ER+	45 (13.4)
Only PR+	19 (5.7)
ER– and PR–	2 (0.6)
Unknown	12
Tumour grade	
I	154 (47.8)
II	159 (49.4)
III	9 (2.8)
Unknown	25

3. Results

Between March 1991 and December 1998, a total of 361 patients were randomised from 33 institutions. As shown before [10], seven centres (14 patients) were excluded because of lack of cooperation resulting in missing baseline and follow-up data for all patients entered by those centres. These exclusions will not bias any effect. All analyses presented in this paper are based on the remaining 347 patients, who had been entered by 26 institutions. Violation of entry criteria was documented in 21 patients, but none of them was excluded from the intention-to-treat analysis. After randomisation, 5.5% of patients allocated to RT refused to start that treatment whereas 1.9% of patients not allocated to RT did begin it. The corresponding figures for TAM are 1.8% and 6.1%, respectively. Information on compliance with the allocated treatment was not available in 3.5% of patients.

Table 1 summarises the most important patient characteristics, more details are given in the first report. In general characteristics were well balanced between treatments. The only remarkable differences observed are for tumour size and tumour grade: among the patients randomised to treatment groups with TAM, a higher percentage had tumours of between 10 and 20 mm in the BCS + TAM group [10]. Median follow-up is 9.9 years (BCS, 9.5; BCS + RT, 10.0; BCS + TAM, 9.2 and BCS + RT + TAM, 9.4). Table 2 shows the distribution of patients according to the location of the first event: 47 patients experienced LR in the ipsilateral breast; 27 of these patients were from the BCS group. In addition, one regional recurrence occurred in the BCS + RT group. In total, 111 patients experienced an event relating to EFS: 46 patients of the BCS group, 26 of the BCS + RT group, 18 of the BCS + TAM group and 21 of the BCS + RT + TAM group, respectively.

EFS rates after 8 years were as follows: 48%, 95% CI (37%, 60%) for BCS; 78%, 95% CI (69%, 86%) for BCS + RT; 78%, 95% CI (67%, 88%) for BCS + TAM and 78%, 95% CI (68%, 87%) for BCS + RT + TAM. Fig. 1 displays the EFS rates for the four treatments investigated. It shows a strong effect of RT and a strong effect of Tam, but both treatments together did not improve over the two single treatments. The corresponding test of interaction between the two treatments was already significant ($P < 0.01$) in the first analysis. Because of the interaction, we have not presented the results of the Cox model in terms of the main effects of RT and of TAM. Instead we present the effects of all four treatment modalities separately by using the BCS-only group as a reference. Table 3 summarises the effects of treatments and prognostic factors on EFS. In the multivariable analysis, BCS + RT, BCS + TAM and BCS + RT + TAM led to significant reductions in the risk of recurrence as compared to BCS alone, with estimated relative risks of 0.36, 0.33 and 0.32, respectively. Age and larger tumour size did not exhibit a distinct effect, but high tumour grade led to a marginally significant increase of risk. The corresponding univariate analyses yielded similar results.

Local recurrences were not counted as events in DDFS and this results in some changes (Table 4) in comparison to the estimated relative risks for EFS. Patients receiving BCS without further treatment still had an increased risk, but the difference was small and no longer significant. In the multivariate model, estimated relative risks were between 0.71 and 0.80. The analysis of DDFS suggests an increased risk for patients aged 60 years or more that was not present in the EFS, but in this pre-defined analysis using three age categories this effect was not statistically significant. DDFS-rates according to treatment modality are displayed in Fig. 2.

With regard to overall survival, 39 deaths have been observed so far (Table 2). Again, for BCS without any further treatment the number of deaths was the largest. The figures are, however, far too small to draw valid conclusions or to perform more comprehensive analyses.

4. Discussion

It is well known that a substantial percentage of patients with a low risk of recurrence may be cured by breast-conserving surgery alone, however, nobody knows how to identify them. Based on the detailed analyses of data from our previous GBSG study (Rauschecker et al. [14]) and based on the discussion of prognostic markers in the literature at that time we tried to define a patient population with a very good prognosis, hypothesising that survival rates will be excellent even without an additional radiotherapy or a systemic treatment.

Concerning treatment and prognostic factors the somewhat disappointing first results [10] were now confirmed with the additional follow-up of about 4 years. Most importantly, it is obvious that BCS alone is no sufficient treatment for many patients. Eight-year EFS rates are only 48% for the BCS group, whereas these rates are nearly 80% in the three groups with additional radiotherapy, tamoxifen or both. As known from other studies for patients with higher risks, also in our highly selected study group the risk for an event is about 3–4 times higher with BCS alone. These severe differences are mainly caused by the large number of local recurrences. Patients treated by hormonal therapy, with or without additional RT,

Table 2 – Location of first event and number of deaths.

Location of first event	Therapy				
	BCS $n = 79$	BCS + RT $n = 94$	BCS + TAM $n = 80$	BCS + RT + TAM $n = 94$	Total $n = 347$
No event	33	68	62	73	236
Ipsilateral breast					
Invasive	26	8	6	5	45
In situ	1	1	0	0	2
Ipsilateral lymph nodes	0	1	0	0	1
Distant metastases	6	5	2	0	13
Contralateral breast	3	2	0	3	8
Second carcinoma non-breast	3	7	3	4	17
Several locations	2	0	2	0	4
Death without recurrence	5	2	5	9	21
Total	46	26	18	21	111
All events (DDFS)	22	18	13	17	70
All deaths	16	6	7	10	39

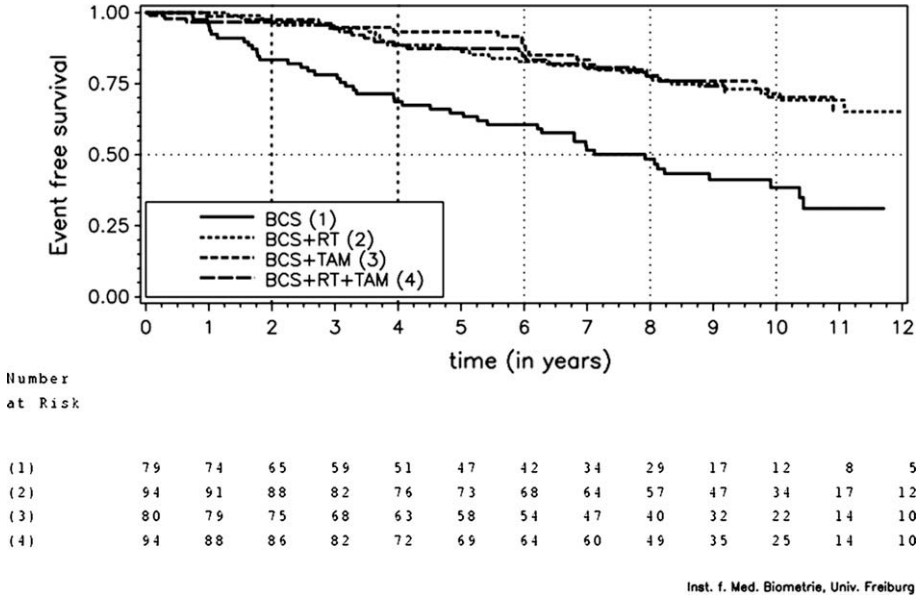

Fig. 1 – Event-free survival.

have EFS rates comparable to those of the RT group. However, because of the limited sample size with corresponding low power the strength of evidence for such a comparison is weak.

In agreement to our earlier report, the effect of treatment is no longer significant if distant disease-free survival is considered as the end-point. Hazard ratios indicate that treatment with RT, tamoxifen or both may reduce the risk of a DDFS event by about 20–30%. The number of deaths is highest in the BCS group, but altogether the amount of information is too small for a more detailed analysis. For the two outcomes EFS and DDFS we do not see important differences between the three groups with an additional treatment. However, this cannot be translated into a formal statement on equivalence between them.

Another trial (BASO , [15]) including only patients with excellent prognosis has a similar design. In patients randomised between all 4 treatments local recurrence rates at 10 years are 1.1% if Tam and RT are given, 4.8% if Tam only is given, 5.5% if RT only is given and 16.6% if neither is given. Unfortunately, data on distant disease-free survival and overall survival are not given.

The study by Pötter et al. [16] addressed a comparable patient population but with somewhat relaxed criteria for patient selection. They found an increased risk of local relapse when radiotherapy was omitted; in this study, endocrine treatment was given to all patients.

The issue of replacing RT by TAM was investigated in the B-21 study of the NSABP [8]. After lumpectomy for tumours of $\leqslant 1$ cm patients were treated either with TAM, RT or both.

Table 3 – Effect of therapy and prognostic factors on event-free survival.[a] Multivariate analysis on complete case population with 313 patients and 108 events.

Factor	Univariate			Multivariate		
	RR	CI	P-value	RR	CI	P-value
Therapy						
BCS	1		0.0001	1		0.0001
BCS + RT	0.36	0.22–0.58		0.36	0.22–0.59	
BCS + TAM	0.34	0.19–0.62		0.33	0.18–0.61	
BCS + RT + TAM	0.33	0.18–0.57		0.32	0.18–0.58	
Age						
<50 years	1		0.117	1		0.675
50–59 years	1.08	0.50–2.33		1.08	0.49–2.38	
⩾60 years	1.58	0.76–3.30		1.28	0.59–2.74	
Tumour size						
<10 mm	1		0.018	1		0.085
⩾10 mm	1.80	1.07–3.04		1.59	0.94–2.71	
Tumour grade						
I	1		0.046	1		0.045
II + III	1.48	1.00–2.18		1.52	1.01–2.28	

[a] All analyses are stratified according to modus of randomisation (all four treatments ($n = 224$); BCS versus BCS + RT ($n = 41$); BCS + TAM versus BCS + RT + TAM ($n = 48$)).

Table 4 – Effect of therapy and prognostic factors on distant disease-free survival.[a] Multivariate analysis on complete case population with 313 patients and 68 events.

Factor	Univariate			Multivariate		
	RR	CI	P-value	RR	CI	P-value
Therapy						
BCS	1			1		
BCS + RT	0.67	0.36–1.25	0.601	0.72	0.38–1.36	0.731
BCS + TAM	0.69	0.33–1.46		0.71	0.33–1.53	
BCS + RT + TAM	0.76	0.38–1.52		0.80	0.39–1.62	
Age						
<50 years	1			1		
50–59 years	1.15	0.39–3.45	0.023	1.07	0.36–3.21	0.107
⩾60 years	2.28	0.82–6.37		1.85	0.66–5.22	
Tumour size						
<10 mm	1			1		
⩾10 mm	1.49	0.79–2.78	0.216	1.29	0.68–2.46	0.433
Tumour grade						
I	1			1		
II + III	1.88	1.12–3.13	0.016	1.69	1.00–2.87	0.051

[a] See Table 3.

In contrast to our and many other studies with EFS as the primary end-point, the B-21 study selected time free from an ipsilateral breast tumour recurrence (IBTR) as first event, considering both invasive and non-invasive IBTRs as an event. Patients (1009) were randomised and 187 had an EFS event, 77 of them had IBTRs. IBTR rates per 1000 woman-years were 22.8 (TAM), 11.7 (RT) and 4.4 (RT + TAM). The authors conclude that in women with tumours <1 cm, IBTR occurs with enough frequency after lumpectomy to justify considering RT, regardless of tumour ER status, and TAM plus RT when tumours are ER positive.

Results of our study are in reasonable agreement with the literature. Omitting radiotherapy results in a severely increased risk of local recurrences, whereas the effect of distant disease-free and overall survival is much lower. Fyles et al. [17] showed a significant reduction of local recurrences by radiotherapy in patients receiving tamoxifen, however this advantage did not transfer to the rate of distant relapses (4.5% in the RT group, 4.0% without RT, $P = 0.69$).

In older (⩾70 years) patients receiving tamoxifen (97% ER positive tumours) radiation prevented local or

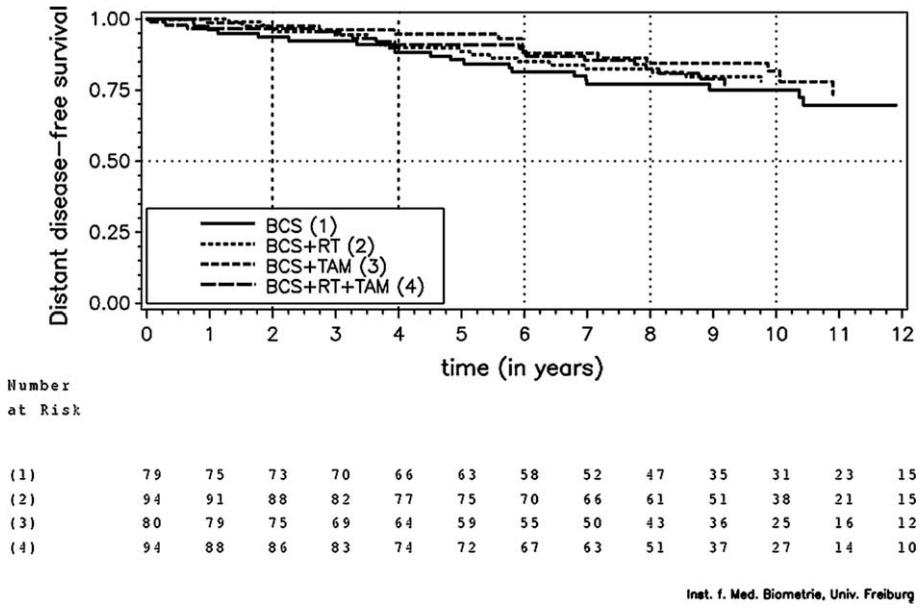

Fig. 2 – Distant disease-free survival.

regional recurrences (after 5 years median follow-up <1% compared to 5% without RT) but survival rates are identical [18].

In a recently published Swedish study [19] radiotherapy did not increase long-term distant disease-free and overall survival rates after mastectomy in ER + patients treated with tamoxifen [19]. Patients were randomised between RT, Tam and RT + Tam. Cumulative incidence rate of loco-regional recurrences as first event at 20 years were significantly reduced by radiotherapy. Rates were 18.5% in the Tam-only group, versus 5.3% (RT + Tam) and 6.7% (RT) in the radiotherapy groups. Concerning cumulative incidence of systemic disease, radiotherapy alone has the highest rates; in receptor positive patients 20 years rates are 54% (RT), 40% (RT + Tam) and 41% (Tam). Concerning overall mortality the differences are negligible. In all patients, cumulative incidence rates of the treatment groups do not show any difference within the first 15 years. Results after 15 years vary more but are uncertain because of the low number of patients. In subgroups of patients with better prognosis (node negative) results are also nearly identical in the first 10 years, the 20 years rates are best in the TAM- only group. However, results at 20 years are very uncertain.

The most recent review of the Early Breast Cancer Trialists' Collaborative Group [9] and studies cited clearly illustrate that more data is needed to answer questions concerning the best combination of radiation therapy and hormonal treatment for patients with breast cancer. Issues start with the definition of subgroups defined by prognostic and predictive factors and the most relevant outcome.

The updated results of our study provide further evidence that even in patients with a favourable prognosis, the avoidance of both radiotherapy and systemic treatments after BCS increases the rate of local recurrences substantially.

Conflict of interest statement

None declared.

Acknowledgement

This study was supported by Deutsche Krebshilfe e.V.

Appendix

The following were participants in the German Breast Cancer Study Group: study coordination: H. Bojar, Düsseldorf; J. Dunst, Halle; W. Guski, Berlin; K. Hübner, Frankfurt; M. Kaufmann, Frankfurt; H. Rauschecker, Rosenheim; R. Sauer, Erlangen; W. Sauerbrei, Freiburg; A. Schauer, Göttingen; C. Schmoor, Freiburg; M. Schumacher, Freiburg; K.-J. Winzer, Berlin.

Centres including more than 10 patients: Charité Universitätsmedizin Berlin CCM (Chirurgie); Zentralkrankenhaus Bremen-Nord, Bremen; Universitätsklinikum Erlangen; Universitätsklinikum Göttingen (Chirurgie); Allgemeines Krankenhaus Hagen; Universitätsklinikum Halle; Diakonissenkrankenhaus Karlsruhe; Klinikum Osnabrück.

Further centres including patients: Kreiskrankenhaus Albstadt; Oskar-Ziethen-Krankenhaus, Berlin; Städtisches Klinikum, Brandenburg; Kreiskrankenhaus Ebersberg; Universitätsklinikum Frankfurt am Main; Städtisches Kreiskrankenhaus Friedrichshafen; Universitätsklinikum Greifswald (Chirurgie); Evangelisches Krankenhaus Hagen; Allgemeines Krankenhaus Harburg, Hamburg; Städtisches Krankenhaus Hanau; Universitätsklinikum Heidelberg; Kreiskrankenhaus Henningsdorf; Universitätsklinikum Kiel; Frankenwaldklinik GmbH, Kronach; Städtisches Klinikum Passau; Martin-Luther-Krankenhaus, Schleswig; EN-Süd-Klinikum GmbH Martfeld-Krankenhaus Schwelm; Krankenhaus Wermelskirchen GmbH, Wermelskirchen.

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