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Radiation therapy after breast-conserving surgery: first results of a randomised clinical trial in patients with low risk of recurrence

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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. Between 1991 and 1998, 361 patients (pT1pN0M0, aged 45–75 years, receptor positive, grade I–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 in the analysis. After a median follow-up of 5.9 years, 77 events concerning event-free survival 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 about three times higher in the group with BCS only than in the other three groups. No difference could be established between the four treatment groups for distant disease-free survival rates. It is concluded that even in patients with a favourable prognosis, the avoidance of radiotherapy and tamoxifen after BCS increases the rate of local recurrences substantially.

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

1. Introduction

After breast-conserving surgery (BCS) for breast cancer, postoperative radiotherapy (RT) is given routinely to nearly all patients. The first trial to investigate whether RT is necessary was conducted by the NSABP (study B06). After follow-up of about 9 years a local recurrence (LR) rate of 43% was reported for the group without RT [1], but LR were also observed in patients receiving RT. Obviously, RT cannot prevent all LR 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 [2–7].

Based on prognostic factors for disease-free survival discussed in the literature, and on preliminary analyses of the data from a study for patients with small breast

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cancers by the German Breast Cancer Study Group (GBSG), we tried at the beginning of the 1990s to define a group of patients with a very good prognosis [8]. At that time the potential of tamoxifen (TAM) to increase disease-free survival was regarded as controversial and it was decided to investigate simultaneously the effect of RT and of TAM in a 2×2 factorial design. In order to increase the number of patients, we opened the study to clinics with a strong preference for TAM. Patients from these clinics were randomised in relation to RT only. After about 6 years' median follow-up we report the results of this study for the first time.

2. Patients and methods

In 1991, the GBSG started a randomised clinical trial 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 pT1pN0M0, 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 [9], absence of lymphangiosis carcinomatosa, i.e. extensive lymph-vessel invasion, tumour-free margins 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, the study's independent data-monitoring committee recommended a change in the protocol: patients with grade II tumours could only be randomised between treatment arms BCS + TAM and BCS + RT + TAM. This recommendation was implemented as an amendment to the study protocol. 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 surgical technique has been previously described in detail [10]; the tumour had to be removed with histologically clear margins. The axillary lymph-node status was obtained by lower axillary dissection. There had to be at least 10 lymph nodes in the axillary specimen. RT (with 4–6 MV linear-accelerator photons or telecobalt) was started 2–6 weeks after surgery. Five fractions of 2 Gy per week and a total dose of 50 Gy (reference dose) in 25 fractions (5–6 weeks) were applied to the whole breast. An electron boost of 10–12 Gy (reference dose) in fractions of 2 Gy was delivered to the primary tumour bed. Patients randomised to treatment groups BCS + TAM and BCS + RT + TAM received a daily dose of 30 mg TAM for 2 years.

Randomisation was done centrally by telephone. The centre was used as the stratification criterion, and block randomisation was performed within each centre. 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 both for the treatment comparison with respect to RT and with respect to 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 required was reduced to a total of 550 patients during the course of the study.

The following characteristics had been determined as potential prognostic factors at the time of primary diagnosis: patient's age, menopausal status, tumour location, tumour size, histological tumour type, tumour grade according to Bloom and Richardson [9], oestrogen and progesterone receptor status. Histopathological classification and grading was re-examined centrally in three histopathological reference centres. Methods for determining these factors have been described previously [8].

Patients were followed up at regular intervals to ensure that any kind of recurrence was detected as early as possible. Examinations were performed every 3 months during the first 2 years after operation, every 6 months for the following 3 years, and annually thereafter. Recurrence was defined as local, regional (axillary lymph nodes or supraclavicular region), or distant (metastases in distant sites), 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 also examined; it was defined as the time from primary diagnosis to distance recurrence, contralateral or second cancer and/or death without previous distant recurrence. The effect of the randomised treatments on EFS and DDFS was investigated. In addition, the effect of the following factors on EFS and DDFS was analysed: patient's age in years ($\leqslant$50, 50–59, $\geqslant$60), tumour size in mm ($<$10, $\geqslant$10), tumour grade according to Bloom and Richardson (I, II + III; some patients were regraded to grade III by the reference

pathologist). EFS rates and DDFS rates were calculated according to Kaplan–Meier [11]. 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 [12]. Prognostic factors occurring on more than two levels were coded using dummy variables in order to estimate the relative risks between the different levels separately. *P*-values were based on Wald tests [13,14]. A simultaneous assessment of the effects of treatment and prognostic factors on EFS and DDFS was performed within multiple-regression analyses using the Cox model [12]. 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. In the multiple-regression analysis of the treatment effect, only those patients were included for whom the incorporated prognostic factors were completely documented. Interactive effects between treatment and prognostic factors were not examined.

3. Results

Between March 1991 and December 1998, a total of 361 patients were randomised from 33 institutions. As shown in Fig. 1, 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. All analyses presented in this paper are based on the remaining 347 patients, who had been entered by 26 institutions: 79 patients were allocated to BCS, 94 to BCS + RT, 80 to BCS + TAM and 94 to BCS + RT + TAM. 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.

Entry criteria were violated for the following reasons: 4 patients had tumours larger than 20 mm, in 9 patients the grading re-examination by the reference pathologist resulted in a grade III classification, 2 patients had negative hormone receptor status and in 6 patients fewer than 10 lymph nodes were examined. No patients were excluded from the analyses; they were performed strictly according to the intention-to-treat principle.

Table 1 presents a description of the most important patient and tumour characteristics, which are in general well-balanced between the treatment groups. The only remarkable differences observed are for tumour size and tumour grade: among patients randomised to treatment groups with TAM, a higher percentage had tumours of between 10 and 20 mm in the BCS + TAM group. Likewise, a somewhat larger percentage of grade II tumours was observed in the BCS + RT + TAM group.

Median follow-up was 5.9 years (BCS, 6.8 years; BCS + RT, 6.3 years; BCS + TAM, 5.0 years; BCS + RT + TAM, 4.9 years). During this time, 77 events occurred in relation to the endpoint EFS. Despite extra efforts we do not have complete follow-up for all patients, especially among those receiving TAM. Table 2

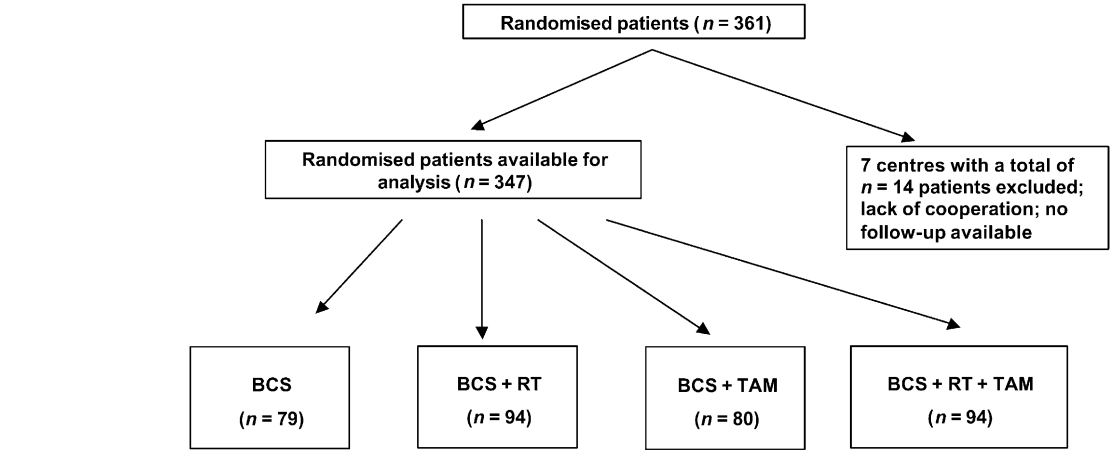

Fig. 1. Flow chart of study participants. BCS, breast-conserving surgery; RT, radiotherapy; TAM, tamoxifen.

Table 1
Patient characteristics

Factor	No. of patients (%)				
	BCS ($n=79$)	BCS + RT ($n=94$)	BCS + TAM ($n=80$)	BCS + RT + TAM ($n=94$)	Total ($n=347$)
Age					
< 50 years	8 (10.1)	6 (6.4)	9 (11.3)	7 (7.5)	30 (8.6)
50–59 years	27 (34.2)	41 (43.6)	28 (35.0)	35 (37.2)	131 (37.8)
⩾60 years	44 (55.7)	47 (50.0)	43 (53.7)	52 (55.3)	186 (53.6)
Tumour size					
< 10 mm	16 (21.3)	25 (27.8)	11 (15.1)	20 (25.3)	72 (22.7)
10–20 mm	56 (74.7)	64 (71.1)	62 (84.9)	59 (74.7)	241 (76.0)
> 20 mm	3 (4.0)	1 (1.1)	0 (0.0)	0 (0.0)	4 (1.3)
Unknown	4	4	7	15	30
Tumour location					
Lateral	46 (59.7)	57 (61.3)	49 (63.6)	56 (61.5)	208 (61.5)
Medial/central	31 (40.3)	36 (38.7)	28 (36.4)	35 (38.5)	130 (38.5)
Unknown	2	1	3	3	9
Number of lymph nodes examined					
< 10 mm	2 (2.7)	3 (3.3)	1 (1.4)	0 (0.0)	6 (1.9)
10–14 mm	27 (36.0)	34 (37.8)	26 (35.6)	28 (35.4)	115 (36.3)
⩾15 mm	46 (61.3)	53 (58.9)	46 (63.0)	51 (64.6)	196 (61.8)
Unknown	4	4	7	15	30
Hormone receptor status					
OR + and PR +	59 (77.6)	78 (83.9)	63 (80.8)	69 (78.4)	269 (80.3)
Only OR +	14 (18.4)	8 (8.6)	10 (12.8)	13 (14.8)	45 (13.4)
Only PR +	3 (4.0)	6 (6.4)	4 (5.1)	6 (6.8)	19 (5.7)
OR− and PR−	0 (0.0)	1 (1.1)	1 (1.3)	0 (0.0)	2 (0.6)
Unknown	3	1	2	6	12
Tumour grade					
I	39 (52.7)	45 (50.0)	37 (49.3)	33 (39.8)	154 (47.8)
II	33 (44.6)	43 (47.8)	35 (46.7)	48 (57.8)	159 (49.4)
III	2 (2.8)	2 (2.2)	3 (4.0)	2 (2.4)	9 (2.8)
Unknown	5	4	5	11	25
Histological type					
Ductal	35 (46.7)	56 (62.2)	43 (58.9)	46 (58.2)	180 (56.8)
Inv. lobular	17 (22.7)	13 (14.4)	9 (12.3)	12 (15.2)	51 (16.1)
Com./crib.	3 (4.0)	2 (2.2)	3 (4.1)	3 (3.8)	11 (3.5)
Pap./tub.	12 (16.0)	17 (18.9)	12 (16.4)	13 (16.5)	54 (17.0)
Others	8 (10.6)	2 (2.3)	6 (8.2)	5 (6.3)	21 (6.6)
Unknown	4	4	7	15	30
Second resection					
No	49 (63.6)	58 (62.4)	53 (67.1)	58 (63.0)	218 (63.9)
Yes	28 (36.4)	35 (37.6)	26 (32.9)	34 (37.0)	123 (36.1)
Unknown	2	1	1	2	6

BCS, breast-conserving surgery; RT, radiotherapy; TAM, tamoxifen; OR, oestrogen; PR, progesterone

shows the distribution of patients according to the location of the first event: 32 patients experienced LR in the ipsilateral breast; 23 of these patients were from the BCS group. In addition, one regional recurrence occurred in the BCS + RT group. In total, 77 patients experienced an event relating to EFS: 36 patients of the BCS group, 18 of the BCS + RT group, 9 of the BCS + TAM group and 14 of the BCS + RT + TAM group, respectively. EFS rates after 5 years were as follows: 64%, 95%-CI (53%, 75%) for BCS; 86%, 95%-CI (78%, 94%) for BCS + RT; 92%, 95%-CI (86%, 99%) for BCS + TAM and 84%, 95%-CI (75%, 93%) for BCS + RT + TAM. Fig. 2 displays the EFS rates for the four treatments investigated.

Table 3 summarises the effects of treatments and prognostic factors on EFS. In the multivariate 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 0.35, 0.25 and 0.38, respectively. Age did not exhibit a distinct effect, larger tumour size and high tumour grade led to a marginally significant increase of risk. The corresponding univariate analyses yielded similar results. We have not presented the results of the Cox

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	43	76	71	80	270
Ipsilateral breast					
- invasive	22	3	2	3	30
- in situ	1	1	0	0	2
Ipsilateral lymph nodes	0	1	0	0	1
Distant metastases	4	5	2	0	11
Contralateral breast	1	2	0	2	5
Second carcinoma					
non-breast	3	5	3	4	15
Several locations	2	0	1	0	3
Death without recurrence	3	1	1	5	10
Total	36	18	9	14	77
All events (DDFS)	15	14	7	11	48
All deaths	8	4	3	6	21

BCS, breast-conserving surgery; RT, radiotherapy; TAM, tamoxifen; DDFS, distant death-free survival

model in terms of the main effects of RT and of TAM, since we observed a very strong interactive effect between RT and TAM ($P=0.0052$; data not shown). This was due to the fact that the majority of events occurred in the BCS-only group whereas comparably few events occurred in the other three treatment groups. We therefore present the effects of all four treatment modalities separately by using the BCS-only group as a reference (Table 3).

LR 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 treatment effect was no longer significant. In the multivariate model, estimated relative risks were between 0.61 and 0.95; the latter value indicates that DDFS rates were similar for patients treated either with BCS only or with BCS + RT + TAM. The analysis for DDFS suggests an increased risk for patients aged 60 years or more that was not present in the EFS, but this effect was not-statistically significant. DDFS-rates according to treatment modality are displayed in Fig. 3.

With regard to overall survival, 21 deaths have been observed so far (Table 2). Again, for BCS without any further treatment the number of deaths was largest. The figures are, however, far too small to draw valid conclusions or to perform more comprehensive analyses.

Table 3
Effect of therapy and prognostic factors on event-free survival*: multivariate analysis on complete case population with 311 patients and 76 events

Factor	Univariate			Multivariate		
	RR	CI	P	RR	CI	P
Therapy						
BCS	1		0.0001	1		0.0001
BCS + RT	0.35	0.20–0.62		0.35	0.19–0.62	
BCS + TAM	0.28	0.13–0.59		0.25	0.12–0.56	
BCS + RT + TAM	0.39	0.21–0.75		0.38	0.19–0.74	
Age						
< 50 years	1		0.327	1	0.38–2.38	0.790
50–59 years	1.00	0.41–2.47		0.95	0.46–2.74	
⩾60 years	1.42	0.60–3.36		1.13		
Tumour size						
< 10 mm	1	0.96–3.45	0.067	1		
⩾10 mm	1.82			1.58	0.83–3.01	0.166
Tumour grade						
I	1	0.89–2.24	0.138	1		0.061
II + III	1.42			1.59	0.98–2.58	

BCS, breast-conserving surgery; RT, radiotherapy; TAM, tamoxifen: RR, relative risk; CI, confidence interval. *All analyses are stratified according to mode of randomisation (all four treatments ($n=223$); BCS versus BCS + RT ($n=40$); BCS + TAM versus BCS + RT + TAM ($n=48$)).

4. Discussion

In the last years several randomised trials have demonstrated without doubt that the rate of LR will substantially increase if patients do not receive RT after BCS [2–7,15–17]. Published LR rates for groups without RT vary substantially between studies, ranging from about 13% [15]) to about 39% [17]. A substantial part of this variation may be explained by differences in patient selection criteria, length of follow-up and differences in further adjuvant treatment. Other factors, e.g. tumour-free margin, type of surgical technique, consideration of events and ways of analysis, may also play a part, but scientific evidence for their identification is limited. According to the literature, the rate of LR can be reduced by a factor of about 3–4 by breast irradiation.

This figure also corresponds to the results observed in our study, insofar as we must admit that we failed to

Table 4
Effect of therapy and prognostic factors on distant disease-free survival*: multivariate analysis on complete case population with 311 patients and 47 events

Factor	Univariate			Multivariate		
	RR	CI	P	RR	CI	P
Therapy						
BCS	1		0.777	1		0.747
BCS + RT	0.81	0.39–1.68		0.83	0.40–1.73	
BCS + TAM	0.63	0.25–1.59		0.61	0.24–1.58	
BCS + RT + TAM	0.92	0.41–2.07		0.95	0.42–2.17	
Age						
< 50 years	1		0.202	1		0.258
50–59 years	1.03	0.29–3.64		0.96	0.27–3.42	
⩾60 years	1.78	0.54–5.86		1.61	0.48–5.35	
Tumour size						
< 10 mm	1		0.215	1		0.257
⩾10 mm	1.66	0.74–3.72		1.60	0.71–3.62	
Tumour grade						
I	1		0.130	1		0.228
II + III	1.59	0.87–2.88		1.45	0.79–2.67	

BCS, breast-conserving surgery; RT, radiotherapy; TAM, tamoxifen: RR, relative risk; CI, confidence interval. *All analyses are stratified according to mode of randomisation (all four treatments ($n = 223$); BCS versus BCS + RT ($n = 40$); BCS + TAM versus BCS + RT + TAM ($n = 48$)).

identify a group with such a low rate of LR that it made RT unnecessary. In the three arms receiving RT, TAM or RT + TAM we observed only as small number of LR as a first event, but this rate was increased substantially in the group with BCS only. In the analysis of EFS we estimated an increased risk of about 3, whereas the three other groups had similar EFS rates. Despite the small sample size this effect is highly significant. At the present stage, our data cannot make a substantial contribution to the current debate about whether TAM can eventually replace breast irradiation or whether the combination of TAM and breast irradiation may lead to further benefit in patients with a very low risk of recurrence [18,19]. The data observed so far do not suggest a large difference between the three treatment groups BCS + RT, BCS + TAM and BCS + RT + TAM, but the small number of events in these groups does not allow us to draw reliable conclusions.

Furthermore, the analysis shows that tumour size and tumour grade still have a prognostic effect in this highly selected group. Currently the effects are not significant, but this is also most probably due to the limited power of the study.

Concerning the assessment of treatment the results are different for DDFS, where LR are not considered as an event. Event rates in the BCS + TAM are slightly smaller (but not statistically significant) than in the other three groups, in which similar results are observed. These results confirm that RT can prevent LR, but it is not known whether this has any important implications for DDFS and overall survival. Because of the small number of deaths an analysis of overall survival is not reasonable within the current follow-up status. We will also need more mature follow-up information before a sensible assessment of the role of TAM will be possible. Recently, the NSABP presented the results of

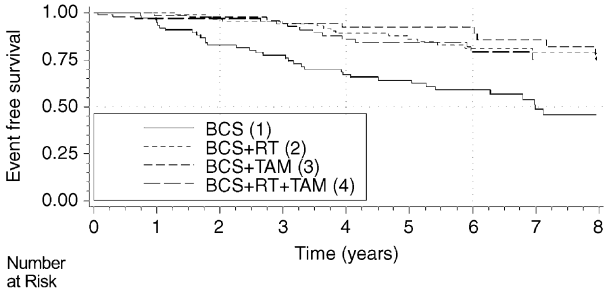

Fig. 2. Event-free survival rate (EFS) by treatment group. BCS, breast-conserving surgery; RT, radiotherapy; TAM, tamoxifen.

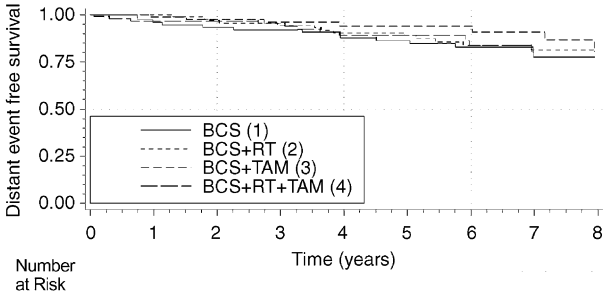

Fig. 3. Distant disease-free survival rate (DDFS) by treatment group. BCS, breast-conserving surgery; RT, radiotherapy; TAM, tamoxifen.

their three-arm trial comparing RT, TAM and RT + TAM in a population with tumours of less than 1 cm [15]. Concerning LR they observed a 49% lower hazard rate in the RT arm compared to TAM. TAM + RT reduced the rate by 63% in comparison to RT only, and by 81% compared to TAM. Despite these large reductions in LR from the combination of RT + TAM, they found nearly identical rates of death in the three groups. This is in agreement with the results of all randomised trials: a reduction in, or avoidance of, LR could not be translated into an apparent advantage with respect to overall survival. One has, however, to take into account that the power of single trials is too low to be able to detect a survival advantage of reasonable magnitude. In a meta-analysis based on individual patient data, the Early Breast Cancer Trialists' Collaborative Group [20] demonstrated that breast cancer mortality was significantly reduced by RT but other, particularly vascular, mortality was significantly increased, resulting in a slight improvement in overall survival (56.6% versus 54.5% at 10 years). In a pooled analysis of 13 published randomised trials Vinh-Hung and colleagues [21] estimated the relative excess mortality as 8.6% (95%-CI (0.3%, 17.5%)) if RT is omitted. We believe that more information can only be gained by a meta-analysis based on updated individual patient data, including all trials. In addition, analyses of several large studies appropriately modelling the occurrence of LR in the framework of multi-state models may help to provide more insight into this issue [22].

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Appendix

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