Overview of the Randomized Trials of Radiotherapy in Ductal Carcinoma in Situ (DCIS) of the Breast

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

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Abstract

Individual patient data were available for all four of the randomized trials that began before 1995 and compared adjuvant radiotherapy versus no radiotherapy following breast-conserving surgery for DCIS. 3729 women were eligible for analysis. Radiotherapy reduced the absolute 10-year risk of ipsilateral recurrent DCIS by 8.4% (SE 1.2%, 6.5% versus 14.9%, 2p<0.00001) and of ipsilateral invasive cancer by 8.5% (SE 1.3%, 6.9% versus 15.4%, 2p<0.00001). For any ipsilateral breast event (ie, either recurrent DCIS or invasive cancer) radiotherapy reduced the 10-year risk by 15.2% (SE 1.6%, 12.9% versus 28.1%), and it was effective regardless of age at diagnosis, extent of breast-conserving surgery, use of tamoxifen, method of DCIS detection, margin status, focality, grade, comedonecrosis, architecture or tumour size. The proportional reduction in ipsilateral breast events was greater in older than in younger women (2p<0.0004 for difference between proportional reductions; 10year absolute risks: 18.5% versus 29.1% at ages <50 years, 10.8% versus 27.8% at ages 50+ years), but did not differ significantly according to any other factor. Even for women with negative margins and small, low grade tumours the 10-year absolute gain for ipsilateral breast events was 18.0% (SE 5.5, 12.1% versus 30.1%, 2p=0.002). After 10 years of follow-up there was, however, no significant effect on breast cancer mortality, mortality from causes other than breast cancer, or overall mortality.

Introduction

Until the 1980s ductal carcinoma in situ (DCIS) of the breast was usually treated by mastectomy. However, following the introduction of breast-conserving therapy for the treatment of early stage invasive breast cancer, local excision of DCIS with or without radiotherapy to the conserved breast began to be used and, from 1985 to 1990, four randomized trials comparing adjuvant radiotherapy versus no radiotherapy following local excision for DCIS were initiated. We report here an overview of their results based on individual patient data.

Methods

Every 5 years since 1985, evidence from the randomized trials in early breast cancer has been reviewed centrally in a worldwide collaboration between the individuals responsible for them (the Early Breast Cancer Trialists' Collaborative Group, EBCTCG). Two 2005 EBCTCG reports gave the results up to the year 2000 from the trials that began recruitment by 1995 of adjuvant systemic treatments (studying various types of chemotherapy or hormonal therapy) (1) and of local treatments (studying various types of surgery and/or adjuvant radiotherapy) (2). The present report uses similar methods and gives the results up to September 2006 of the trials that began by 1995 of adjuvant radiotherapy versus no radiotherapy following local excision for DCIS.

Trial identification and main outcomes

Trial identification procedures were as in previous EBCTCG reports. Only unconfounded trials were sought (ie, trials in which there was to be no difference between the treatment groups in the extent of surgery or in the use of systemic therapy). Five trials were identified that began by 2000, and brief design details are given in Table 1. One (RTOG 9804) began only in 1999, and is not yet available. The remaining four began in 1985-1990, and have provided information for every patient on characteristics at diagnosis, allocated treatment, time to first event and whether the event was ipsilateral recurrence of DCIS, ipsilateral occurrence of invasive breast cancer, occurrence of contralateral DCIS or invasive breast cancer, or regional or distant metastasis of breast cancer. Information was also provided on cause-specific mortality and incident non-breast primary cancers. It was assumed that any death attributed to breast cancer had been preceded by metastatic breast cancer.

Data management

Data management procedures were as in recent EBCTCG reports (1,2) except that for each woman additional clinical and pathological details were sought about her disease. This information could have been gathered during later pathological review, provided that it was based on material obtained at the time of initial diagnosis or treatment, and provided that samples had not been selected for pathological review according to allocated treatment or outcome.

Statistical analysis

Analyses were based on allocated treatment and were stratified by trial and time since randomization in single years. The analyses of ipsilateral breast events, breast cancer mortality, heart disease mortality, mortality without recurrence, non-breast primary cancer incidence and overall mortality were also stratified by age at randomization in 5 groups (<40, 40-49, 50-59, 60-69, 70+ years). Only two age-groups (<50 and 50+ years, as in previous analyses [2]) were used, however, for

analyses that were also subdivided by other characteristics. Unless otherwise indicated, other aspects of the statistical methods and the formats of the figures are as before (1,2) and are described on the EBCTCG website (www.ctsu.ox.ac.uk/projects/ebctcg).

Collaborative review

A preliminary meta-analysis of these trials was presented and discussed at a meeting of collaborators in September 2006, after which much additional detail was sought about clinical and pathological details and about outcomes. Revised meta-analyses were presented at the NIH State-of-the-Science Conference on DCIS in September 2009 and circulated for comment by collaborating EBCTCG trialists. A draft of the present report was circulated for comment to the trialists in December 2009 and the manuscript was revised in the light of comments received.

Results

A total of 3925 women were randomized and, after exclusion of those who had only a benign lesion at the time of randomization, or who already had microinvasion, invasion, Paget's disease or another cancer present at the time of initial diagnosis, or who had another study-specific protocol violation, a total of 3729 remained eligible for the analysis. 21% of them were randomized during 1985-89, 46% during 1990-95, and 32% during 1995-2000. Median follow-up was 8.9 woman-years. A total of 924 women were reported as having experienced a breast event after randomization, and 74% of the first events were in the ipsilateral breast (see Table 2).

Ipsilateral breast events

Radiotherapy reduced the risk of ipsilateral recurrent DCIS (rate ratio 0.43, SE 0.43, 2p<0.00001) and at 5 years after randomization the absolute reduction was 5.8% (SE 0.9%, 4.6% versus 10.5%) while at 10 years it was 8.4% (SE 1.2%, 6.5% versus 14.9%) (Figure 1). Radiotherapy also reduced the risk of invasive cancer in the ipsilateral breast (rate ratio 0.50, SE 0.08, 2p<0.00001) and at 5 years after randomization the absolute reduction was 5.3% (SE 0.8%, 3.2% versus 8.5%) while at 10 years it was 8.5% (SE 1.3%, 6.9% versus 15.4%). For any ipsilateral breast event (ie, either recurrent DCIS or invasive cancer in the ipsilateral breast) radiotherapy reduced the 5-year risk by 10.5% (SE 1.2%, 7.6% versus 18.1%) and the 10-year risk by 15.2% (SE 1.6%, 12.9% versus 28.1%). The rate of ipsilateral breast events was approximately halved in all four trials, with no evidence of heterogeneity between the proportional reductions (Figure 2).

Radiotherapy was effective in reducing ipsilateral breast events regardless of whether the woman was aged under or over 50 years at diagnosis, whether lumpectomy or sector resection had been performed, and whether or not tamoxifen was to be given to both treatment arms or to neither (Figure 3). For each other characteristic, information was unavailable for many women. Nevertheless, the available information sufficed to show that radiotherapy was effective in reducing ipsilateral breast events regardless of whether the original tumour was detected by mammography only or by clinical symptoms, whether the excised lesion had negative margins, and whether the tumour was unifocal (see Figure 4). Radiotherapy was also effective in reducing ipsilateral breast events irrespective of

histological or nuclear grade (Figure 5), of whether there was comedonecrosis or comedo/solid architecture (Figure 6), and of clinical or pathological tumour size (Figure 7).

Radiotherapy resulted in a larger proportional reduction in the rate of ipsilateral breast recurrence for women aged more than 50 years than for younger women (rate ratios: age <50 years 0.69, SE 0.12, 50+ years 0.38, SE 0.06, 2p=0.0004 for the difference between these proportional reductions), but the proportional reduction did not differ significantly according to any other factor (Figure 8). When the data were subdivided into 5 groups according to age (<40, 40-49, 50-59, 60-69, 70+) the trend in the proportional reduction with age was significant (p=0.02). The difference between the proportional reductions in younger and older women did not appear to be accounted for by differences in histological grade or comedonecrosis (Figure 9), or by differences in nuclear grade or architecture (data not shown).

Women with negative margins and small, low grade tumours were identified *a priori* as a group expected to be at low absolute risk of ipsilateral breast events, for whom radiotherapy might therefore provide little absolute gain. Information was often unavailable on one or more of these factors, however, so only 291 such women could be studied. Among them, the 10-year risk of an ipsilateral event in those allocated not to receive radiotherapy was, however, substantial at 30.1%, and even with this relatively small number of women the effect of radiotherapy was highly significant (rate ratio 0.48, SE 0.17 2p=0.002), with a 10-year absolute gain of 18.0% (SE 5.5%) (Figure 10, left-hand panel).

Other end-points

Radiotherapy reduced the risk of any breast event (ie ipsilateral recurrence of DCIS, ipsilateral occurrence of invasive breast cancer, contralateral occurrence of DCIS or invasive breast cancer, or regional or distant metastasis of breast cancer) (rate ratio 0.59, SE 0.05, p<0.00001), and at 5 years after randomization the absolute reduction was 9.3% (SE 1.3% 11.3% versus 20.7%) while at 10 years it was 11.5% (SE 1.7%, 21.2% versus 32.7%) (Figure 11). In this analysis, which considered first events only, women who were allocated to radiotherapy experienced higher risks compared with those allocated to no radiotherapy for both contralateral and regional or distant events but neither difference was significant (contralateral rate ratio 1.16, SE 0.16 2p>0.1; regional or distant rate ratio 1.51, SE 0.34, 2p>0.1)

A total of 353 women were known to have died during follow-up, 96 from breast cancer, 217 from other causes (including 55 from heart disease) and 40 for whom the cause of death was unknown (Table 3). For breast cancer mortality and for mortality from all causes, women who were allocated to radiotherapy experienced slightly higher risks compared with those allocated to no radiotherapy (breast cancer mortality rate ratio 1.22, SE 0.18, 2p>0.1, all-cause mortality rate ratio 1.11, SE 0.11, 2p>0.1) (Figure 12). Mortality from causes other than breast cancer in the period prior to a breast event and mortality from heart disease were also slightly higher among women allocated to radiotherapy but the effects were not significant (all-cause mortality rate ratio 1.04 SE 0.15, 2p>0.1; heart disease rate ratio: 1.11, SE 0.33, 2p>0.1). A total of 74 non-breast primary cancers were reported during follow-up, but there was no evidence that radiotherapy had any net effect on the incidence of such cancers (rate ratio 0.99, SE 0.20, 2p>0.1).

Discussion

These randomized trials provide strong and consistent evidence that, in the populations studied, radiotherapy after breast-conserving surgery for DCIS approximately halved the rate of ipsilateral breast events during the subsequent decade with little effect on contralateral or distant events. The absolute magnitude of the 10-year risk reduction was 15%, of which about half was due to a reduction in the recurrence of DCIS and about half due to a reduction in the occurrence of invasive breast cancer in the conserved breast. The proportional reduction in the rate of ipsilateral breast events achieved with radiotherapy was greater in older than in younger women but did not differ significantly according to any other factor. The age effect did not appear to be accounted for by younger women being more likely to have high grade lesions or comedonecrosis, and the explanation for it is unknown. A radiotherapy boost was rarely used (Table 1) and so the impact of a boost in DCIS could not be assessed.

In these trials, in most of which tamoxifen was not given, 12.9% of women allocated to radiotherapy had an ipsilateral breast event within the first decade. This risk is similar to that in a large multi-institutional series of women diagnosed up to 1995 and given breast-conserving surgery with radiotherapy (14), suggesting that the women in these trials were reasonably typical of women diagnosed with DCIS during that era. Since then, breast screening has become more common, so in recent years women diagnosed with DCIS tend to have smaller lesions. In addition, greater attention is now paid to achieving negative surgical margins. Both factors are associated with a lower rate of ipsilateral breast events in the absence of radiotherapy. Therefore, there has been considerable interest in identifying patients with favourable features for whom the rate of ipsilateral breast events in the absence of radiotherapy is so low that radiotherapy can reasonably safely be omitted (15, 16, 17).

In the data available from these trials, it was not possible to subdivide the women with negative margin status according to margin width, so women with close (<2 mm) surgical margins had to be included with other women who had wider margins. Nor was it possible to subdivide women with tumours smaller than 20 mm according to tumour size. Therefore, all women with negative margin status and low-grade tumours smaller than 20 mm were combined in our "low-risk" group. These criteria are less stringent than those used in recent non-randomized studies (15,16,17) to define low risk, which could well explain the higher risk of ipsilateral breast events in the "low-risk" women in these trials. The trial results suggest, however, that no matter what the underlying rate of ipsilateral breast events may be for particular categories of women, it will be approximately halved by radiotherapy.

The risks of a contralateral breast event and of a regional or distant breast event both appeared to be somewhat larger among the women allocated to radiotherapy than among the controls. Neither of these increases was statistically significant and so chance may be the explanation for them. However, the analyses presented in this paper consider only first events and make the assumption that women who experience an ispilateral breast event are no more or less likely than other women to experience a regional, distant, or contralateral event. This independence assumption cannot be verified from the data. If women with more aggressive disease are at greater risk of all three types of event, then, as the predominant effect of the radiotherapy is on ipsilateral events, the apparent slight increase in the risk of contralateral and regional or distant events may be an artefact accounted for by events that would, in the absence of radiotherapy, have occurred after an ipsilateral breast event. The analysis of any breast event does not depend on the independence assumption and confirms the efficacy of radiotherapy in reducing breast events overall.

In these randomized trials the risk of death from breast cancer was non-significantly greater in the women allocated to radiotherapy than in the women allocated to breast conserving surgery only, as was the risk of death from all causes. Breast cancer mortality is unlikely to be affected by the issues referred to in the previous paragraph, while mortality from all causes cannot be affected by it. Therefore, as the differences are not significant, chance seems a likely explanation for them.

Among the much larger numbers of women in the trials of radiotherapy following breast-conserving surgery for early invasive breast cancer, radiotherapy had little effect on breast cancer mortality during the first few years of follow-up, but by 15 years about one breast cancer death was avoided for every four local recurrences avoided in the first 5 years (2). Theoretically, if about the same 1 to 4 ratio applied to ipsilateral invasive cancers following breast-conserving therapy for DCIS, then radiotherapy might be expected to reduce breast cancer mortality by an absolute amount of about 1 or 2% by year 15 or 20, which the present trials can neither exclude nor confirm.

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Conflict of interest

The writing committee and secretariat declare that they have no conflict of interest.

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References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365(9472):1687-717.

2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366(9503):2087-106.

3. Fisher B, Costantino J, Redmond C, et al: Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. N Engl J Med 1993;328(22):1581-6.

4. Fisher B, Dignam J, Wolmark N, et al: Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol 1998;16(2):441-52.

5. Fisher ER, Dignam J, Tan-Chiu E, et al: Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Eight-year Update of Protocol B-17. Intraductal carcinoma. Cancer 1999; 86:429-38.

6. Julien JP, Bijker N, Fentiman IS, et al: Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet 2000;355(9203):528-33.

7. Bijker N, Peterse JL, Duchateau L, et al: Histological type and marker expression of the primary tumour compared with its local recurrence after breast-conserving therapy for ductal carcinoma in situ. Br J Cancer 2001;84(4):539-44.

8. Bijker N, Peterse JL, Duchateau L, et al: Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: analysis of European Organization for Research and Treatment of Cancer Trial 10853. J Clin Oncol 2001;19(8):2263-71.

9. 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(21):3381-7.

10. Emdin SO, Granstrand B, Ringberg A, et al: SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncol 2006;45(5):536-43.

11. Ringberg A, Nordgren H, Thorstensson S, et al: Histopathological risk factors for ipsilateral breast events after breast conserving treatment for ductal carcinoma in situ of the breast--results from the Swedish randomised trial. Eur J Cancer 2007;43(2):291-8.

12. Holmberg L, Garmo H, Granstrand B, et al: Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. J Clin Oncol 2008;26(8):1247-52.

13. Houghton J, George WD, Cuzick J, Duggan C, Fentiman IS, Spittle M: Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet 2003;362(9378):95-102.

14. Solin LJ, Fourquet A, Vicini FA, et al: Long-term outcome after breastconservation treatment with radiation for mammographically detected ductal carcinoma in situ of the breast. Cancer 2005;103(6):1137-46.

15. Wong JS, Kaelin CM, Troyan SL, et al: Prospective study of wide excision alone for ductal carcinoma in situ of the breast. J Clin Oncol 2006;24(7):1031-6.

16. Hughes LL, Wang M, Page DL, et al: Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2009;27(32):5319-24.

17. Silverstein MJ, Lagios MD, Groshen S, et al: The influence of margin width on local control of ductal carcinoma in situ of the breast. N Engl J Med 1999;340(19):1455-61.

Table 1: Randomised trials comparing radiotherapy versus the same management without radiotherapy following breast-conserving surgery for

ductal carcinoma in situ (DCIS) of the breast.

Year code, study name (references)	Entry dates	No. of women randomised	No. of women eligible for analysis*	Median follow- up (yrs)	Mammo- graphic detection	Breast and axillary surgery	Negative surgical margins required	Central pathological review	Breast radiotherapy
Data available fo	r overview								
NSABP B-17 (3, 4, 5)	1985-1990	818	798	16.5	80%	Local excision (37% axillary dissection)	Yes (13% involved/unknown) [†]	623 (76%)	50 Gy (2 Gy/f) 9% with boost
EORTC 10853 (6, 7, 8, 9)	1986-1996	1010	918	10.4	72%	Local excision (20% axillary dissection)	Yes (16% "not free", <1mm, involved or unknown) [†]	824 (82%)	50 Gy (2 Gy/f) 5% with boost
SweDCIS (10, 11, 12)	1987-1999	1067	1011	8.4	79%	Sector resection (17% axillary dissection)	No (11% positive, 9% unknown) [†]	271 (25%)	50 Gy (2 Gy/f)(80%) or 48 Gy (2.4 Gy/f) (13%) or 54 Gy (2 Gy/f), 2 wk gap (7%) Boost not recommended
UK/ANZ DCIS‡ (13)	1990-1998	1030	1002	4.8	100%	Local excision (No axillary dissection)	Yes	0 (0%)	50 Gy (2 Gy/f) Boost not recommended
Data not yet avai	lable								
RTOG 9804	1999-2006	636	-	-	ns	Local excision (No axillary dissection)	Yes	0 (0%)	50.4 Gy (1.8 Gy/f) or 50 Gy (2 Gy/f) or 42.5 Gy (2.656 Gy/f) Boost not recommended

Abbreviations: f, fraction; Gy, Gray; ns, not specified.

* After exclusion of women with a benign lesion only or with microinvasion, invasion, Paget's disease, other cancer present at randomisation, or other study-specific protocol violation.

† Including information from later pathological reviews, provided that that it was based on material obtained at the time of initial diagnosis or treatment and provided that samples had not been selected for pathological review according to allocated treatment or outcome.

‡ Microinvasion (< 1mm) allowed, present in 0.3%. A total of 1694 women were randomised in this trial. However, 664 were women randomised in a comparison of tamoxifen versus not. They have therefore been excluded from the present overview. 540 of the 1002 women included in the overview were randomised to radiotherapy and tamoxifen versus tamoxifen alone, while the remainder were randomised to radiotherapy versus not.</p>

Years since randomisation	Allocated BCS+RT (n=1878)	Allocated BCS (n=1851)	Total (n=3729)
	((= : ••• :)	(
Any breast event			
0-4	196	359	555
5-9	116	141	257
10+	55	57	112
Total	367	557	924
Any ipsilateral brea	ast event as first event		
0-4	131	311	442
5-9	61	111	172
10+	37	33	70
Total	229	455	684
Any contralateral t	preast event as first event*		
0-4	47	35	82
5-9	42	24	66
10+	16	22	38
Total	105 ⁺	81†	186
Regional or distan	t event as first event		
0-4	18	13	31
5-9	13	6	19
10+	2	2	4
Total	33	21	54
Woman-years unti	I first breast event, or end of	follow-up if no event	
0-4	8199	. 7662	15,861
5-9	4785	4150	8935
10+	2457	2080	4537
Total	15,441	13,892	29,333

Table 2: Numbers of women for whom a breast event during follow-up was reported.

* Includes 4 RT and 6 No RT where a contralateral and ipsilateral event occurred within 7 days of each other. [†] 77 RT and 56 No RT events were due to invasive cancer. Table 3: Total numbers of deaths and non-breast primary cancers reported during follow-up (including

events reported after a breast event).

Years since randomisation	Allocated BCS+RT (n=1878)	Allocated BCS (n=1851)	Total (n=3729)
All causes of death			
0-4	48	45	93
5-9	63	65	128
10+	75	57	132
Total	186	167	353
Breast cancer death			
0-4	14	16	30
5-9	21	17	38
10+	17	11	28
Total	52	44	96
Heart disease death			
0-4	9	10	19
5-9	7	11	18
10+	10	8	18
Total	26*	29*	55
All other known causes	of death		
0-4	18	17	35
5-9	30	32	62
10+	37	28	65
Total	85	77	162
Unknown cause of dea	th		
0-4	7	2	9
5-9	5	5	10
10+	11	10	21
Total	23	17	40
Non-breast primary car	ocers		
0-4	11	10	21
5-9	10	13	23
10+	17	13	30
Total	38	36	74
	th or and of follow up		
Woman-years until dea 0-4	8600	8520	17,120
5-9	5634	5631	11,265
5-9 10+	3329	3413	6742
Total	17,563	17,564	35,127

* Left-sided breast cancer 8 BCS + RT versus 10 BCS, right-sided 10 versus 6, unknown side 8 versus

Figure 1: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) (4 trials, start dates 1985-90, 3729 women): 10-year cumulative risks of ipsilateral recurrent DCIS, ipsilateral invasive cancer, and any ipsilateral breast event.



Figure 2: Effect of radiotherapy (RT) after breast-conserving surgery (BCS): Ratio of annual event rates of any ipsilateral breast event by trial.



Figure 3: Effect of radiotherapy (RT) after breast-conserving surgery (BCS): 10-year cumulative risks of any ipsilateral breast event by age at diagnosis, extent of surgery, and use of tamoxifen (3729 women). Women given sector resection were from either the Swedish BCCG trial (1011 women) or the EORTC 10853 trial (135 women), and women using tamoxifen were all in the UK/ANZ DCIS trial. Information on estrogen and progesterone receptor status was not available.



Age at diagnosis

Extent of breast-conserving surgery







Figure 4: Effect of radiotherapy (RT) after breast-conserving surgery (BCS): 10-year cumulative risks of any ipsilateral breast event by detection method (2619 women), margin status (3355 women) and focality (1526 women). Women for whom the surgical margins were close (<2 mm) were classified as having negative surgical margins.



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5

Years since randomisation

10

0

5 10 Years since randomisation 15

Method of DCIS detection

15

Figure 5: Effect of radiotherapy (RT) after breast-conserving surgery (BCS): 10-year cumulative risks of any ipsilateral breast event by histological (1794 women) and nuclear (1617 women) grade.



21

Figure 6: Effect of radiotherapy (RT) after breast-conserving surgery (BCS): 10-year cumulative risks of any ipsilateral breast event by comedonecrosis (1332 women) and architecture (1388 women).





Architecture



Figure 7: Effect of radiotherapy (RT) after breast-conserving surgery (BCS): 10-year cumulative risks of any ipsilateral breast event by clinical tumour size (1192 women) and pathological tumour size (1631 women).



Clinical primary tumour size





Figure 8: Effect of radiotherapy (RT) after breast-conserving surgery (BCS): Ratio of annual event rates of any ipsilateral breast event by various patient and tumour characteristics.

(e) Age at diagnosis $(\chi^2_{-} = 12.4; 2p = 0.4004)$ (f) Surgery $(\chi^2_{+} = 0.7; 2p = 0.4)$ Local accision 1 199/128 307/1297 -928 1126 (h) Surgery $(\chi^2_{+} = 0.7; 2p = 0.4)$ Local accision 1 199/128 307/1297 -928 1126 (c) Tamoxi 14277 30282 1-928 -1126 (c) Tamoxi 14277 30283 1-107 115 (c) Tamoxi 14277 30283 1-107 1-15 (c) Tamoxi 14277 30283 1-107 1-15 (c) Tamoxi 14283 2-108 7-74 (c) Tamoxi 14283 2-22 2-20 304 (c) Tamoxi 14171 1-102 2-21101 -88 806 (c) 100 Multifocal 42180 80197 -220 304 (c) Tamoxi 12883 2-20 -03) (c) Histological grade ($\chi^2_{+} = 0.5; 2p = 0.6$) Low 51/484 1204 2-221101 -88 806 (c) 100 Multifocal 2-222 2-22797 7-167 2-5 (c) Mistological grade ($\chi^2_{-} = 0.5; 2p = 0.6$) Low 51/484 12031 2-26 80-53 (c) Comedoxi 13/1185 248/1204 -724 875 (c) Actister 12 2078 8-74 4-9 (c) Actister 12 2078 1-226 8-21 (c) Actister 12 2078 1-226 8-21 (c) Actister 12 2078 1-22	Characteristic	Events/ Allocated BCS+RT	Women Allocated BCS		T events nkVarianc of O-E	e Ratio of annua BCS+RT : I	
50+ yrs 135/1422 330/1386 108.3 112.9 0-38 (sc 0.06) (b) Surgery ($\chi^2_1 = 0.7; 2p = 0.4$) 0-48 (sc 0.07) Sector 70582 148684 46.1 5.8 0-48 (sc 0.07) Colspan="2">Colspan="2">0-43 0-46 (sc 0.07) Colspan="2">0-43 0-46 (sc 0.07) Colspan="2">0-44 0-46 (sc 0.07) Colspan="2">Colspan="2">0-43 0-46 (sc 0.07) Colspan="2">0-43 <th>(a) Age at diagno</th> <th>sis ($\chi_1^2 =$</th> <th></th> <th></th> <th>004)</th> <th>_</th> <th></th>	(a) Age at diagno	sis ($\chi_1^2 =$			004)	_	
Local excision 199/1298 207/1297 - 328 1128 - 0-48 (se 0-07) Sector 70982 148/354 - 46-1 528 - 0-42 (se 0-09) (c) Tamoxifen use $(\chi_1^2 = 0.3; 2p = 0.6)$ Neither Tamox. 213/600 422/138 -1162 154-3 Detection method $(\chi_1^2 = 0.6; 2p = 0.4)$ Mamography 199/1013 27/1867 -772 98-7 - 0-46 (se 0-07) Clinical symptoms 57/301 100316 - 238 374 - 0-33 (se 0-12) Unknown method 36/562 84/548 -276 28-7 - 0-33 (se 0-12) Unknown method 36/562 84/548 -276 28-7 - 0-33 (se 0-12) Unknown status 17/185 46/189 -145 15-1 - 0-46 (se 0-05) Unknown status 17/185 46/189 -145 15-1 - 0-46 (se 0-05) Unknown status 17/185 46/189 -145 15-1 - 0-38 (se 0-12) Unknown status 17/185 46/189 -145 15-1 - 0-38 (se 0-12) Unknown status 17/185 46/189 -145 15-1 - 0-38 (se 0-13) Unknown status 17/185 46/189 -145 15-1 - 0-38 (se 0-13) Unknown status 17/185 46/189 -145 15-1 - 0-38 (se 0-13) Unknown status 17/185 46/189 -145 15-1 - 0-38 (se 0-13) Unknown grade 129/562 272070 -70-1 670 - 0-44 (se 0-10) Unknown grade 129/562 272070 -70-1 670 - 0-44 (se 0-12) Unknown grade 129/56 272070 -70-1 670 - 0-44 (se 0-12) Unknown grade 129/56 272070 -70-1 670 - 0-44 (se 0-12) Unknown grade 129/56 272070 -70-1 670 - 0-44 (se 0-12) Unknown grade 80/1049 200/1063 -647 775 - 0-40 (se 0-68) (f) Cornectonecrosis ($\chi_1^2 = 0.5; 2p = 0.4$) Present 50/321 89/305 -200 32-1 - 0-43 (se 0-13) Unknown grade 80/1049 200/1063 -647 775 - 0-44 (se 0-12) Unknown grade 80/1049 200/1063 -647 775 - 0-44 (se 0-13) Unknown comedo. 112/1173 22/118 -724 875 - 0-44 (se 0-13) Unknown arch. 102/1172 25/1189 -723 817 - 0-41 (se 0-13) Unknown 172/127 5327/1282 -892 120.8 - 0-43 (se 0-13) Unknown 112/141 139/482 -548 726 - 0-44 (se 0-13) Unknown 112/141 139/482 -548 726 - 0-44 (se 0-13) Unknown 112/141 139/482 -548 726 - 0-44 (se 0-13) Unknown 112/147 225/1189 -723 817 - 0-41 (se 0-06) 20-50 mm 111/94 2590 -85 82 - 0-49 120 mm 46/509 -364 85 82 - 0-46 (se 0-05) 120 mm 46/509 -364 85 82 - 0-46 (se 0-13) Unknown 108/1040 257/1059 -619 803 - 0-46 (se 0-06) 145 (se						-	. ,
(c) Tamoxifen use $(\chi^2 = 0.3; 2p = 0.6)$ Neither Tamox. 0.46 (se 0.06) Both Tamox. 14277 33283 -10.7 11.5 0.39 (se 0.19) (d) Detection method $(\chi^2 = 0.6; 2p = 0.4)$ Mamography 139(10)3 271,897 -77.2 98.7 0.46 (se 0.07) (d) Detection method $(\chi^2 = 0.6; 2p = 0.4)$ Mamography 139(10)3 271,897 -77.2 98.7 0.46 (se 0.07) (e) Margin status $(\chi^2 = 0.0; 2p = 0.6)$ Negative 189(1513 323(1465 -91.4 119.1 0.46 (se 0.06) Involved 43/180 86/167 -22.0 30.4 0.48 (se 0.13) Unknown status 17/165 46/189 -14.5 15.1 0.39 (se 0.17) (f) Focality $(\chi^2_1 = 0.2; 2p = 0.6)$ 134/538 -0.0 48.2 0.44 (se 0.10) Multifical 54/258 98/212 -39.1 35.5 0.39 (se 0.11) Unknown focality 11/11/102 22/1101 -68.5 60.6 0.44 (se 0.10) Unknown grade 12/282 -0.5; 2p = 0.5) 0.51 (se 0.15) 0.51 (se 0.15) 0.51 (se 0.15) Unknown grade 82/028 96/305 -28.8 35.3	(b) Surgery (χ_1^2 = Local excision			-82-8	112.6	_	0·48 (se 0·07)
Neither Tamox. 215/1601 422/1588 -1182 154-3 - 0.46 (se 0.06) Boht Tamox. 14/277 33283 -107 115 0.39 (se 0.19) (d) Detection method ($\chi^2_{2} = 0.6; 2p = 0.4$) - 0.46 (se 0.06) 0.46 (se 0.07) Clinical symptoms 57/801 100/318 -238 37.4 0.46 (se 0.07) Clinical symptoms 57/801 100/318 -238 37.4 0.46 (se 0.06) Involved 43/180 86/197 -220 30.4 0.46 (se 0.06) Unknown status 17/185 48/189 -14.5 15.1 0.38 (se 0.12) Unknown focality 111/1102 222/101 -55 80.6 0.44 (se 0.01) Multifocal 64/235 99/212 -33.1 35.5 0.38 (se 0.17) Unknown focality 111/1102 222/110 -55 25.3 0.448 (se 0.02) Pathology: (g) Histological grade ($\chi^2_{+} = 0.5; 2p = 0.5$) 0.51 (se 0.15) 0.51 (se 0.15) Unknown grade 29/365 -28.8 35.3 0.444 (se 0.12) Intermediate 21/1	Sector	70/582	148/564	-46-1	52·8		0.42 (SE 0.09)
Neither Tamox. 215/1601 422/1588 -1182 154-3 0.46 (se 0.06) Boht Tamox. 14/277 33283 -107 115 0.39 (se 0.19) (d) Detection method ($\chi^2_1 = 0.6$; $2p = 0.4$) 0.46 (se 0.06) 0.46 (se 0.07) Clinical symptoms 57/801 100/318 223 as 37.4 0.46 (se 0.07) Clinical symptoms 57/801 100/318 228 as 37.4 0.46 (se 0.06) Involved 43/180 89/197 -220 30.4 0.46 (se 0.06) Involved 43/180 89/197 -220 30.4 0.46 (se 0.06) Unknown status 17/185 48/189 -14.5 15.1 0.38 (se 0.12) Unknown focality 1111/102 222/101 -58 80.6 0.44 (se 0.10) Multifocal 54/235 99/212 -39.1 55 0.38 (se 0.13) Unknown focality 1111/102 222/101 -56 26.0 0.51 (se 0.15) Unknown focality 111/102 22/17 -167 24.5 0.51 (se 0.15) Unknown grade 20/95 27/207 -70.1 97.0 <th>(a) Tomovifon up</th> <th>$a/a^2 = 0$</th> <th>21 2n - 1</th> <th>0 6)</th> <th></th> <th></th> <th></th>	(a) Tomovifon up	$a/a^2 = 0$	21 2n - 1	0 6)			
(d) Detection method $(\chi^2_1 = 0.6; 2p = 0.4)$ Marmography 188/101 27/187 77.2 987 Clinical symptoms 57/301 100/316 28.8 37.4 Unknown method 36/582 84/58 27.6 28.7 Unknown method 36/582 84/58 27.6 28.7 (e) Margin status $(\chi^2_1 = 0.6; 2p = 0.8)$ Negative 169/1513 323/1465 91.4 119.1 Unknown status 17/185 46/189 14.5 15.1 Unknown status 17/185 46/189 14.5 15.1 Unknown focality 111/1102 222/101 58.5 80.6 Pathology: (g) Histological grade $(\chi^2_1 = 1; 2p = 0.3)$ Low S1/483 174/429 24.6 25.3 Unknown grade 129/58 392/12 33.1 35.5 Unknown grade 129/58 392/12 33.1 35.5 Unknown grade 129/58 392/12 33.1 35.5 Unknown grade 129/58 292/12 33.1 35.5 Unknown grade 129/58 292/12 33.1 35.5 Unknown grade 129/58 292/12 33.1 35.5 Unknown grade 129/58 27/2707 7-0.1 97.0 (h) Nuclear grade $(\chi^2_1 = 0.5; 2p = 0.5)$ Low S1/463 992/103.11 22.5 39.6 Unknown grade 88/1049 209/103.11 22.5 39.6 (h) Comedonecrosis $(\chi^2_1 = 0.6; 2p = 0.4)$ Present 66/341 124/342 37.4 44.9 (h) Comedonecrosis $(\chi^2_1 = 0.6; 2p = 0.4)$ Present 66/341 124/342 37.4 44.9 (h) Architecture $(\chi^2_1 = 0.6; 2p = 0.4)$ Present 66/341 124/342 37.4 44.9 (h) Comedonecrosis $(\chi^2_1 = 0.6; 2p = 0.4)$ Present 66/341 124/342 37.4 44.9 (h) Comedonecrosis $(\chi^2_1 = 0.6; 2p = 0.4)$ Discover 69/501 124/342 37.4 44.9 (h) Comedonecrosis $(\chi^2_1 = 0.6; 2p = 0.4)$ Present 66/341 124/342 37.4 44.9 (h) Comedonecrosis $(\chi^2_1 = 0.6; 2p = 0.4)$ Discover 69/501 119.1193 249/1204 72.4 87.5 (h) Clinical tumour size $(\chi^2_1 = 0.2; 2p = 0.6)$ 1.20 mm 11/94 25/90 8.5 8.1 (h) Clinical tumour size $(\chi^2_1 = 0.2; 2p = 0.6)$ 1.20 mm 11/94 25/90 8.8 5.8 1 (h) Clinical tumour size $(\chi^2_1 = 0.2; 2p = 0.6)$ 1.20 mm 11/94 25/90 8.8 5.8 1 (h) Clinical tumour size $(\chi^2_1 = 0.2; 2p = 0.6)$ 1.20 mm 11/94 25/90 8.8 5.8 1 (h) Chinel tumour size $(\chi^2_1 = 0.2; 2p = 0.2)$ 1.20 mm 11/94 25/90 8.8 5.8 1 0.43 (se 0.18) 0.43 (se 0.18) 0.44 (se 0.06	Neither Tamox.	215/1601			154-3	-	0·46 (SE 0·06)
Marmography 196/105 27/1967 772 967 100 0-46 (55 0-7) Clinical symptoms 57/801 100/316 -238 37.4 0-53 (55 0-12) Unknown method 38/52 80/318 -238 37.4 0-53 (55 0-12) Unknown method 38/52 80/318 -238 37.4 0-53 (55 0-12) Unknown status ($\chi_1^2 = 0.0; 2p = 0.6$) Involved 43/180 86/197 -220 30.4 0-46 (55 0-07) Unknown status 17/185 46/199 -145 151 0-38 (55 0-13) Unknown status 17/185 46/199 -145 151 0-38 (55 0-05) Unknown focality 111/1102 222/1101 -565 80-6 0-44 (55 0-13) Unknown focality 111/1102 222/1101 -565 80-6 0-48 (55 0-13) Unknown grade 120/55 27 2707 -70-1 07.0 0-44 (55 0-13) Unknown grade 120/55 27 2707 -70-1 07.0 0-44 (55 0-13) Unknown grade 21/72 47/171 -134 17.4 0-46 (55 0-13) Unknown grade 86/1049 209/1083 -647 71.5 0-440 (55 0-13) Unknown grade 86/1049 209/1083 -647 71.5 0-440 (55 0-13) Unknown grade 86/1049 209/1083 -647 71.5 0-440 (55 0-13) Unknown grade 86/1049 209/1083 -520 92.1 0-44 (55 0-13) Unknown grade 86/1049 209/1083 -547 71.5 0-440 (55 0-13) Unknown grade 86/1049 209/1083 -547 71.5 0-440 (55 0-13) Unknown grade 86/1049 209/1083 -647 71.5 0-440 (55 0-13) Unknown grade 86/1049 209/1083 -520 92.1 0-54 (56 0-13) Unknown grade 86/1049 209/1083 -547 71.5 0-440 (55 0-13) Unknown grade 86/1049 209/1083 -547 71.5 0-440 (55 0-13) Unknown grade 86/1049 209/1083 -520 92.1 0-54 (56 0-13) Unknown grade 92.1 92.1 92.1 92.5 0-45 10-44 (55 0-17) Zizer: (k) Clinical tumour size ($\chi_1^2 = 0-2; 2p = 0-5$) 1-20 mm 119/4 22500 -85 82 0-02 (j) Architecture ($\chi_2^2 = 0-2; 2p = 0-5$) 1-20 mm 119/4 22500 -85 82 0-02 Unknown 112/172 237/182 -723 81.7 0-41 (55 0-63) 20-50 mm 119/193 282/128 -824 1208 0-448 (55 0-03) 20-50 mm 119/193 282/128 -842 1208 0-448 (55 0-03) 20-50 mm 119/193 282/128 -842 1208 0-448 (55 0-03) 20-50 mm 119/193 193/62 -544 724 0-45 (55 0-63) 20-50 mm 13/107 37/111 -132 11.8 0-33 (55 0-13) 0-46 (55 0	Both Tamox.	14/277	33/263	-10.7	11.5		0·39 (se 0·19)
Unknown method 30:552 84/548 -27.6 28.7 0.38 (st 0.12) (e) Margin status ($\chi^2_{-} = 0.6$; $2p = 0.8$) Negative ($\chi^{2}_{-} = 0.6$; $2p = 0.8$) Involved 43/180 86/197 -22.0 30.4 0.46 (st 0.06) Involved 43/180 86/197 -22.0 30.4 0.46 (st 0.13) Unknown status 17/185 46/189 -14.5 15.1 0.38 (st 0.17) (f) Focality ($\chi^2_{+} = 0.2$; $2p = 0.6$) Multifocal 54/235 99/212 -33.1 35.5 0.39 (st 0.17) Unknown focality 111/1102 222/1101 -58.5 80.6 0.44 (st 0.10) Multifocal 54/235 99/212 -33.1 35.5 0.39 (st 0.11) Unknown focality 111/1102 222/1101 -58.5 80.6 0.44 (st 0.10) Multifocal 54/235 99/212 -33.1 35.5 0.39 (st 0.11) Unknown grade 128/056 272/979 -79.1 87.0 0.44 (st 0.13) Intermediate 27/215 45/226 -10.2 17.1 0.55 (st 0.16) Unknown grade 128/056 272/979 -79.1 87.0 0.44 (st 0.17) (h) Nuclear grade ($\chi^2_{-} = 0.5$; $2p = 0.5$) Low 52/228 98/306 -28.8 35.3 0.44 (st 0.12) Intermediate 21/172 47/171 -13.4 17.4 0.46 (st 0.17) High 64/229 10/31 -25.6 39.6 0.44 (st 0.12) Unknown grade 88/1048 209/1083 -84.7 7.5 0.44 (st 0.07) (j) Architecture ($\chi^2_{-} = 0.3$; $2p = 0.4$) Present 68/341 124/342 -37.4 44.9 0.43 (st 0.10) Unknown comedo. 113/113 248/1204 -72.4 87.5 0.44 (st 0.07) Size: (k) Clinical tumour size ($\chi^2_{-} = 0.2$; $2p = 0.6$) 1-20 mm 10/73 129/368 -38.1 52.7 0.49 (st 0.13) Other 80/486 139/489 -38.1 52.7 0.49 (st 0.13) Other 80/486 139/489 -38.1 52.7 0.49 (st 0.13) Other 80/486 139/489 -38.1 52.7 0.49 (st 0.13) Other 110/73 129/362 -36.8 36.1 0.43 (st 0.11) 20-50 mm 11/04 25/00 85 82 0.43 (st 0.11) 20-50 mm 11/04 25/00 8-5 82 0.448 (st 0.02) 1.20 mm 110/73 129/362 -54.8 72.6 0.43 (st 0.11) 20-50 mm 13/107 37/111 -132 11.8 0.33 (st 0.18) 0.468 (st 0.08) 1.70tal 2289 4557 -127.4 164.8 0.456 (st 0.05) 2.9 < 0.0001 1.20 mm 13/107 37/111 -132 11.8 0.33 (st 0.18) 0.468 (st 0.08) 1.70tal 2289 4557 -127.4 164.8 0.466 (st 0.05) 2.9 < 0.0001	(d) Detection met Mammography	thod (χ ² 136/1015				_	0·46 (se 0·07)
(e) Margin status ($\chi^2 = 0.0$; $2p = 0.8$) Negative 168/1513 3231/455 91.4 119-1 0.46 (sc 0.06) Involved 43/180 86/197 22.0 30.4 0.48 (sc 0.13) Unknown status 17/185 46/189 14.5 15.1 0.38 (sc 0.17) (f) Focality ($\chi^2_1 = 0.2$; $2p = 0.6$) Unificeal 64/235 99/212 33.1 35.5 0.39 (sc 0.11) Unknown focality 11/1102 2221101 58.5 80.6 0.44 (sc 0.10) Pathology: (g) Histological grade ($\chi^2_1 = 1.1$; $2p = 0.3$) Low 51/463 1.744.5 15.1 0.55 (sc 0.18) Intermediate 27/215 45/226 10.2 17.1 0.55 (sc 0.18) High 42/244 64/217 16.7 24.5 0.51 (sc 0.15) Unknown grade 129/056 272/979 -79.1 87.0 0.44 (sc 0.07) (h) Nuclear grade ($\chi^2_1 = 0.5$; $2p = 0.5$) Low 55/262 89/306 -5.8 35.3 0.44 (sc 0.12) Intermediate 21/172 47/171 13.4 17.4 0.46 (sc 0.12) Intermediate 21/172 47/171 13.4 17.4 0.46 (sc 0.12) Unknown grade 86/1049 209/1083 64.7 71.5 0.44 (sc 0.12) Unknown grade 86/1049 209/1083 64.7 71.5 0.44 (sc 0.10) Absent 60/321 83/305 20.0 32.1 0.44 (sc 0.10) Absent 60/321 83/305 20.0 32.1 0.44 (sc 0.10) Other 80/468 139/469 38.1 52.7 0.44 (sc 0.10) Unknown arch. 102/112 23/1180 47.2 3 81.7 0.44 (sc 0.07) (j) Architecture ($\chi^2_1 = 0.5$; $2p = 1.0$) Comedo/solid 47/220 61/21 8/305 20.0 32.1 0.44 (sc 0.07) (j) Architecture ($\chi^2_1 = 0.5$; $2p = 0.6$) 1-20 mm 46/509 10/311 25.6 39.6 0.44 (sc 0.10) Other 80/468 139/469 38.1 52.7 0.44 (sc 0.10) Unknown arch. 102/112 23/1180 47.2 3 81.7 0.44 (sc 0.07) Size: (k) Clinical tumour size ($\chi^2_2 = 0.2$; $2p = 0.6$) 1-20 mm 13/107 37/111 192(52 12.8 1.5 0.45) 0.45 (sc 0.13) 0.45 (sc 0.08) (1) Pathological tumour size ($\chi^2_2 = 1.3$; $2p = 0.2$) 1-20 mm 13/107 37/111 192(52 54.6 2.4 0.45) 100/100 0.25/1059 61.9 80.3 0.446 (sc 0.08) 0.46 (sc 0.08		57/301	100/316	-23-8	37.4		
Negative 169/1513 323/1465 -91.4 119.1 -	Unknown method	36/562	84/548	-27.6	28.7		0-38 (SE 0-12)
Involved 43/180 86/197 -220 30.4 0.48 (st 0.13) Unknown status 17/185 46/189 -14.5 15.1 0.38 (st 0.17) (f) Focality ($\chi_1^2 = 0.2; 2p = 0.6$) 64/541 134/538 -40.0 48.2 0.44 (st 0.10) Multifocal 54/235 99/212 -33.1 35.5 0.44 (st 0.10) 0.39 (st 0.11) Unknown focality 111/1102 222/101 -58.5 80.6 0.44 (st 0.10) 0.39 (st 0.11) Unknown focality 111/1102 222/101 -58.5 80.6 0.48 (st 0.13) 0.48 (st 0.10) Unknown forade 27/215 45/225 -10.2 17.1 0.45 (st 0.13) 0.55 (st 0.18) High 42/244 64/217 -16.7 24.5 0.51 (st 0.15) 0.54 (st 0.12) Intermediate 27/17 -18.4 77.4 0.44 (st 0.12) 0.46 (st 0.17) 0.44 (st 0.17) High 64/329 10/311 -25.6 35.3 0.44 (st 0.17) 0.43 (st 0.17) Unknown grade 86/104 209/1083 -84.7 71.5 0.43 (st 0.17) 0.43 (st	(e) Margin status Negative	$(\chi_{-1}^2 = 0.0)$			119-1		0·46 (se 0·06)
(1) Focality $(\chi_1^2 = 0.2; 2p = 0.6)$ Unifocal 54/235 99/212 33.1 355 0.400 452 0.44 (st 0.10) Multifocal 54/235 99/212 33.1 355 0.439 (st 0.11) Unknown focality 111/1102 222/1101 586 80.6 0.44 (st 0.08) Pathology: (g) Histological grade $(\chi_1^2 = 1.1; 2p = 0.3)$ Low 31/463 7/4/429 246 253 0.38 (st 0.13) Intermediate 27/215 45/226 10.0 17.1 0.44 (st 0.07) Unknown grade 129/956 272/970 .70.1 07.0 0.44 (st 0.07) (h) Nuclear grade $(\chi_1^2 = 0.5; 2p = 0.5)$ Low 52/28 96/306 288 35.3 0.44 (st 0.07) (h) Nuclear grade $(\chi_1^2 = 0.5; 2p = 0.5)$ Low 52/28 96/306 288 35.3 0.44 (st 0.12) Intermediate 21/172 47/171 13.4 17.4 0.46 (st 0.07) High 64/329 103/311 256 39.6 0.42 (st 0.12) Unknown grade 88/1049 209/1083 647 71.5 0.44 (st 0.01) Present 66/364 124/322 37.4 44.9 0.43 (st 0.10) Nuknown comedo.113/1133 248/1204 .72.4 87.5 0.40 (st 0.08) (j) Comedo.recursis $(\chi_1^2 = 0.0; 2p = 1.0)$ Comedo./solid 47/220 81/213 29.5 0.49 (st 0.13) Unknown comedo.113/1133 248/1204 .72.4 87.5 0.44 (st 0.07) Size: (k) Clinical tumour size $(\chi_1^2 = 0.2; 2p = 0.6)$ 1.20 mm 48/509 103/499 30.6 36.1 0.43 (st 0.11) 20.50 mm 11/94 2590 4.5 8.2 0.43 (st 0.11) 20.50 mm 11/94 2590 4.5 8.2 0.44 (st 0.02) (l) Pathological tumour size $(\chi_1^2 = 1.3; 2p = 0.2)$ 1.20 mm 11/97 17/111 132 118 0.43 (st 0.01) 0.44 (st 0.02) 1.20 mm 13/107 37/111 132 211.8 0.3 0.44 (st 0.02) 1.20 mm 13/107 37/111 132 211.8 0.446 (st 0.08) 0.43 (st 0.11) 0.53 (st 0.22) 0.47 (st 0.08) 0.48 (st 0.08) 0.46 (st 0.08) 0.46 (st 0.09) 0.46 (st 0.05) 0.46 (st 0.05) 0.46 (-	43/180	86/197	-22-0	30-4		
Unifocal 1 44 (se 0-10) Multifocal 54/236 99/212 33 1 35 5 0.44 (se 0-10) Multifocal 54/236 99/212 33 1 35 5 0.48 (se 0-08) Pathology: (g) Histological grade ($\chi_1^2 = 1.1; 2p = 0.3$) Low 31/483 174/82 246 25 3 0.48 (se 0-08) High 42/244 64/217 1.67 245 0.51 (se 0-15) Unknown grade 129/956 272/979 79-1 97.0 0.44 (se 0-12) Intermediate 21/172 47/171 1.34 17.4 0.46 (se 0-17) High 64/229 103/311 256 39.6 0.52 (se 0-12) Unknown grade 86/1049 209/1083 64.7 71.5 0.40 (se 0-08) (i) Comedonecrosis ($\chi_1^2 = 0.5; 2p = 0.4$) Present 66/364 124/372 477.4 49 0.43 (se 0-10) Absent 50/321 83/205 20.0 32.1 0.44 (se 0-07) (i) Architecture ($\chi_1^2 = 0.5; 2p = 1.0$) Comedo./solid 47/220 81/213 21.3 29.5 0.49 (se 0-13) Other 80/486 139/469 38.1 52.7 0.44 (se 0-07) (i) Architecture ($\chi_1^2 = 0.2; 2p = 1.0$) Comedo./solid 47/220 81/213 21.3 29.5 0.49 (se 0-13) Other 80/486 139/469 38.1 52.7 0.44 (se 0-17) Size: (k) Cilinical tumour size ($\chi_1^2 = 0.2; 2p = 0.6$) 1-20 mm 11/94 25/90 8.5 82 Other/unknown 172/1275 327/1282 89.2 120.8 0.43 (se 0.11) 20-50 mm 13/107 37/111 132 11.8 0.43 (se 0.11) Other/unknown 106/1040 225/1059 61.9 80.3 0.448 (se 0.05) (i) Pathological tumour size ($\chi_1^2 = 1.3; 2p = 0.2$) 1-20 mm 110/731 193/24 57.4 72.6 0.448 (se 0.05) (i) Pathological tumour size ($\chi_1^2 = 1.3; 2p = 0.2$) 1-20 mm 110/731 193/26 54.8 72.6 0.448 (se 0.05) (i) Pathological tumour size ($\chi_1^2 = 1.3; 2p = 0.2$) 1-20 mm 110/731 193/66 54.8 72.6 0.448 (se 0.05) (i) Pathological tumour size ($\chi_1^2 = 1.3; 2p = 0.2$) 1-20 mm 110/731 193/62 54.8 72.6 0.448 (se 0.05) (i) Pathological tumour size ($\chi_1^2 = 1.3; 2p = 0.2$) 1-20 mm 110/731 193/62 54.8 72.6 0.448 (se 0.05) (i) Pathological tumour size ($\chi_1^2 = 1.3; 2p = 0.2$) 1-20 mm 110/731 193/62 54.8 72.6 0.448 (se 0.05) (i) Pathological tumour size ($\chi_1^2 = 0.3; 2p = 0.2$) 1-20 mm 110/731 193/24 25.0 1.418 0.433 (se 0.13) 0.464 (se 0.05) (i) Pathological tumour size ($\chi_1^2 = 0.3; 2p = 0.6$) 1-20 mm 13/107 37/111 1.32 11.8 0.33 (se 0.18) 0.464 (se	Unknown status	17/185	46/189	-14.5	15-1		
Unifical a 4/541 134/538 -40.0 48.2 - 0 -44 (se 0-10) Multifocal 54/235 99/212 -331 35.5 - 0.39 (se 0-11) Unknown focality 111/1102 222/1101 -58.5 80.6 - 0.48 (se 0.08) Pathology: (g) Histological grade ($\chi_1^2 = 1.1; 2p = 0.3$) Low 31/463 7/4/29 -24.6 25.3 - 0.38 (se 0-13) Intermediate 27/215 45/226 -10.2 17.1 - 0.55 (se 0-18) High 42/244 64/217 -16.7 24.5 - 0.51 (se 0-15) Unknown grade 129/956 272/979 -79-1 97.0 - 0.44 (se 0-07) (h) Nuclear grade ($\chi_1^2 = 0.5; 2p = 0.5$) Low 52/328 96/306 -28.8 35.3 - 0.44 (se 0-12) Intermediate 21/172 47/171 -13.4 17.4 - 0.46 (se 0-17) High 64/229 103/311 -25.6 39.6 - 0.52 (se 0-12) Unknown grade 86/1049 209/1083 -64.7 71.5 - 0.40 (se 0-08) (i) Comedonecrosis ($\chi_1^2 = 0.8; 2p = 0.4$) Present 50/321 83/305 -20.0 32.1 - 0.44 (se 0-17) (j) Architecture ($\chi_1^2 = 0.0; 2p = 1.0$) Comedo/solid 47/220 81/213 -21.3 29.5 - 0.44 (se 0-07) (j) Architecture ($\chi_1^2 = 0.2; 2p = 1.0$) Comedo/solid 47/220 81/213 -21.3 29.5 - 0.49 (se 0-13) Other 80/486 139/469 -38.1 52.7 - 0.44 (se 0-10) Unknown arch. 102/1172 235/1169 -72.3 81.7 - 0.41 (se 0-07) Size: (k) Clinical tumour size ($\chi_1^2 = 0.2; 2p = 0.6$) 1-20 mm 11/94 25/90 -8.5 8.2 - 0.35 (se 0.22) Other/unknown 172/1275 327/1282 -89.2 120.8 - 0.43 (se 0.11) 20-50 mm 13/107 37/111 -13.2 11.8 - 0.43 (se 0.11) 20-50 mm 13/107 37/111 -13.2 11.8 - 0.43 (se 0.11) 20-50 mm 13/107 37/111 -13.2 11.8 - 0.43 (se 0.12) 1-20 mm 110/731 193/622 -54.8 72.6 - 0.47 (se 0.68) 20-50 mm 13/107 37/111 -13.2 11.8 - 0.43 (se 0.13) Other/unknown 106/1040 225/1059 -61.9 80.3 - 0.46 (se 0.05) 1-20 mm 13/107 37/111 -13.2 11.8 - 0.43 (se 0.13) 0.46 (se 0.05) 20-50 mm 13/107 37/111 -13.2 11.8 - 0.43 (se 0.13) 0.46 (se 0.05) 20-50 mm 13/107 37/111 -13.2 11.8 - 0.43 (se 0.13) 0.46 (se 0.05) 20-50 mm 13/107 37/111 -13.2 11.8 - 0.46 (se 0.05) 20-60 m 13/107 37/111 -13.2 11.8 - 0.46 (se 0.05) 20-646 (se 0.05) 20-65 -1-0 -15 -20		0.2.2-	0.6)				-
Unknown focality 111/1102 222/1101 -58-5 80-6 - 0-48 (se 0-08) Pathology: (g) Histological grade ($\chi_1^2 = 1.1; 2p = 0.3$) Low 31/483 7 74/29 -24-6 25-3 - 0-38 (se 0-13) Intermediate 27/215 45/226 -10-2 17.1 - 0-55 (se 0-18) High 42/244 64/217 -16-7 24-5 - 0-51 (se 0-15) Unknown grade 129/956 272/979 -79-1 97.0 - 0-44 (se 0-07) (h) Nuclear grade ($\chi_1^2 = 0.5; 2p = 0.5$) Low 52/328 96/306 -28-8 35-3 - 0-44 (se 0-12) Intermediate 21/172 47/171 -13-4 17.4 - 0-46 (se 0-17) High 64/329 103/311 -25-6 39-6 - 0-52 (se 0-12) Unknown grade 86/1049 209/1063 -84-7 71.5 - 0-40 (se 0-08) (i) Comedonecrosis ($\chi_1^2 = 0.6; 2p = 0.4$) Present 66/364 1 124/342 -37.4 44-9 - 0-43 (se 0-10) Absent 50/321 83/305 -20-0 32-1 - 0-44 (se 0-07) (i) Architecture ($\chi_1^2 = 0.6; 2p = 1.0$) Comedo/solid 47/220 81/213 -21-3 29-5 - 0-44 (se 0-13) Other 80/486 139/469 -38-1 52-7 - 0-49 (se 0-13) Other 80/486 139/469 -38-1 52-7 - 0-49 (se 0-13) Other 80/486 139/469 -38-1 52-7 - 0-49 (se 0-10) Unknown arch. 102/1172 235/1169 -72-3 81-7 - 0-49 (se 0-10) Unknown arch. 102/1172 235/1169 -72-3 81-7 - 0-41 (se 0-07) Size: (k) Clinical tumour size ($\chi_1^2 = 0-2; 2p = 0-6$) 1-20 mm 119/4 25/80 -8-5 8-2 - 0-3 Other/unknown 172/1275 327/1262 -89-2 120-8 - 0-43 (se 0-11) Other/unknown 172/1275 327/1262 -89-2 120-8 - 0-43 (se 0-10) Other/unknown 106/1040 225/1059 -61-9 80-3 - 0-44 (se 0-05) Total 229/ 455/ -127.4 164-8 - 0-46 (se 0-08) 29% or -> 95% Cl - 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 - 0 -				-40-0	48-2	_	0·44 (se 0·10)
Pathology: (g) Histological grade $(\chi^2_1 = 1.1; 2p = 0.3)$ Low 31/463 74/429 246 25-3 0-38 (se 0-13) Intermediate 27/215 45/226 10.2 17.1 0-55 (se 0-18) High 42/244 64/217 16-7 24-5 0-51 (se 0-15) Unknown grade 129/956 272/979 79.1 97.0 0-44 (se 0-07) (h) Nuclear grade $(\chi^2_1 = 0.5; 2p = 0.5)$ Low 52/328 99/306 288 35-3 0-44 (se 0-12) Intermediate 21/172 47/171 134 17.4 0-46 (se 0-17) High 64/329 103/311 25-6 39.6 0-52 (se 0-12) Unknown grade 86/1049 209/1063 -64-7 71.5 0-40 (se 0-08) (i) Comedonecrosis $(\chi^2_1 = 0.8; 2p = 0.4)$ Present 66/364 124/342 -37.4 44-9 0-43 (se 0-10) Absent 50/321 83/305 -20.0 32-1 0-54 (se 0-13) Unknown comedo.113/1193 248/1204 -72.4 87.5 0-49 (se 0-13) Unknown arch. 102/1172 235/1169 -72.3 81.7 0-49 (se 0-10) Unknown arch. 102/1172 235/1169 -72.3 81.7 0-49 (se 0-10) Unknown arch. 102/1172 327/1262 -89.2 120.8 0-43 (se 0-11) 20-50 mm 11/0/3 1 193/682 -54.8 72.6 0-43 (se 0-11) 20-50 mm 11/0/3 1 193/682 -54.8 72.6 0-43 (se 0-10) 0 -41 (se 0-07) Size: (k) Clinical tumour size $(\chi^2_1 = 0.2; 2p = 0.6)$ 1-20 mm 11/0/3 1 193/682 -54.8 72.6 0-43 (se 0-11) 20-50 mm 11/0/3 1 193/682 -54.8 72.6 0-43 (se 0-10) 0 -41 (se 0-07) Size: (k) Clinical tumour size $(\chi^2_1 = 0.2; 2p = 0.6)$ 1-20 mm 11/0/3 1 193/682 -54.8 72.6 0-43 (se 0-11) 20-50 mm 11/0/3 1 193/682 -54.8 72.6 0-43 (se 0-11) 20-50 mm 11/0/3 1 193/682 -54.8 72.6 0-47 (se 0.08) 0 -43 (se 0-11) 20-50 mm 11/0/3 1 193/682 -54.8 72.6 0-47 (se 0.08) 0 -46 (se 0.05) 2p < 0-0001 = 99% 97 = 95% Cl 0 0-5 10 15 2.9	Multifocal	54/235	99/212	-33-1	35-5		0-39 (se 0-11)
(g) Histological grade ($\chi_1^2 = 1.1; 2p = 0.3$) Low 31/483 1/74/429 246 253 0.38 (st 0.13) Intermediate 27/215 45/228 10.2 17.1 0.55 (st 0.18) High 42/244 64/217 16.7 24.5 0.51 (st 0.15) Unknown grade 129/956 272/979 70.1 97.0 0.44 (st 0.15) Unknown grade ($\chi_1^2 = 0.5; 2p = 0.5$) Low 52/228 96/306 28.8 35.3 0.44 (st 0.12) Intermediate 21/172 47/171 1.34 17.4 0.46 (st 0.17) High 64/329 103/311 25.6 39.6 0.52 (st 0.12) Unknown grade 86/1049 209/1083 64.7 71.5 0.40 (st 0.08) (i) Comedonecrosis ($\chi_1^2 = 0.8; 2p = 0.4$) Present 66/364 124/322 37.4 44.9 0.43 (st 0.10) Absent 50/321 83/305 20.0 32.1 0.44 (st 0.07) (j) Architecture ($\chi_1^2 = 0.0; 2p = 1.0$) Comedo./solid 47/220 81/213 21.3 29.5 0.49 (st 0.13) Other 80/466 139/469 38.1 52.7 0.49 (st 0.13) Other 80/466 139/469 38.1 52.7 0.49 (st 0.13) Other 80/466 139/469 38.1 52.7 0.49 (st 0.10) Unknown arch. 102/1172 235/1169 72.3 81.7 0.41 (st 0.07) Size: (k) Clinical tumour size ($\chi_1^2 = 0.2; 2p = 0.6$) (1) Pathological tumour size ($\chi_1^2 = 1.3; 2p = 0.2$) 1-20 mm 11/9/4 25/90 -8.5 8.2 0.43 (st 0.11) 20-50 mm 11/9/4 25/90 -8.5 8.2 0.43 (st 0.11) 20-50 mm 11/9/4 25/90 -8.5 8.2 0.43 (st 0.11) 20-50 mm 11/9/3 193/882 -5.4.8 72.6 0.43 (st 0.01) 0.43 (st 0.11) 20-50 mm 13/107 37/111 13.2 11.8 0.33 (st 0.18) Other/unknown 106/1040 225/1059 61.9 80.3 0.46 (st 0.05) 2p < 0.0001 Total 229/ 455/ -127.4 164.8 0.46 (st 0.05) 2p < 0.0001		111/1102	222/1101	-58-5	80-6		0-48 (se 0-08)
High 42/244 64/217 -16.7 24.5 0.51 (ste 0.15) Unknown grade 129/956 272/979 -76.1 97.0 0.44 (ste 0.07) (h) Nuclear grade (χ^2 = 0.5; 2p = 0.5) 0.44 (ste 0.12) 0.44 (ste 0.12) Intermediate 21/172 47/171 -13.4 17.4 0.46 (ste 0.12) Intermediate 21/172 47/171 -13.4 17.4 0.46 (ste 0.12) Unknown grade 86/1049 209/1063 -64.7 71.5 0.40 (ste 0.08) (i) Comedonecrosis (χ^2 = 0.8; 2p = 0.4) 0.43 (ste 0.10) 0.52 (ste 0.12) 0.40 (ste 0.08) (i) Comedonecrosis (χ^2 = 0.8; 2p = 0.4) 0.43 (ste 0.10) 0.54 (ste 0.13) 0.44 (ste 0.07) (j) Architecture (χ^2 = 0.0; 2p = 1.0) 0.54 (ste 0.13) 0.44 (ste 0.07) 0.44 (ste 0.07) (j) Architecture (χ^2 = 0.2; 2p = 0.6) -72.3 81.7 0.44 (ste 0.13) Other 80/486 139/469 -38.1 52.7 0.44 (ste 0.13) Other 80/486 139/469 -72.3 81.7 0.44 (ste 0.07) Size: <	(g) Histologica						0·38 (se 0·13)
Unknown grade 129/956 272/979 -78-1 97-0 0 0-44 (sc 0.07) (h) Nuclear grade $(\chi_1^2 = 0.5; 2p = 0.5)$ 96/06 -28-8 35-3 0-44 (sc 0.12) Intermediate 21/172 47/171 -13-4 17-4 0-46 (sc 0.12) High 64/329 103/311 -25-6 39-6 0-52 (sc 0.12) Unknown grade 86/1049 209/1063 -64-7 71-5 0-40 (sc 0.08) (i) Comedonecrosis (χ_1^2 =0-8; 2p = 0-4) 0-43 (sc 0.10) 0-54 (sc 0.13) Present 66/364 124/342 -37-4 44-9 0-43 (sc 0.10) Absent 50/321 83/305 -20-0 32-1 0-54 (sc 0.13) Unknown comedo. 113/1193 248/1204 -72-4 87-5 0-44 (sc 0.07) (j) Architecture ($\chi_1^2 = 0-0; 2p = 1-0)$ 0-43 (sc 0.13) 0-44 (sc 0.07) 0-44 (sc 0.07) Silze: (k) Clinical tumour size ($\chi_1^2 = 0-2; 2p = 0-6)$ 0-44 (sc 0.07) 0-44 (sc 0.07) Silze: (k) Clinical tumour size ($\chi_1^2 = 1-3; 2p = 0-2$) 0-44 (sc 0.06) 0-43 (sc 0.11) 1-20 mm 11/94 <t< td=""><td>Intermediate</td><td>27/215</td><td>45/226</td><td>-10-2</td><td>17.1</td><td></td><td>0·55 (se 0·18)</td></t<>	Intermediate	27/215	45/226	-10-2	17.1		0·55 (se 0·18)
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	High	42/244	64/217	-16.7	24.5		0.51 (SE 0.15)
Low 52/328 96/306 -28-8 35.3 - 0-44 (se 0.12) Intermediate 21/172 47/171 -13.4 17.4 - 0-46 (se 0.17) High 64/329 103/311 -25.6 39.6 - 0.52 (se 0.12) Unknown grade 86/1049 209/1063 -64.7 71.5 - 0.40 (se 0.08) (i) Comedonecrosis (χ_1^2 = 0-8; 2p = 0-4) Present 66/364 12/4/342 -37.4 44.9 - 0.43 (se 0.10) Absent 50/321 83/305 -20.0 32.1 - 0.54 (se 0.13) Unknown comedo. 113/1193 248/1204 -72.4 87.5 - 0.440 (se 0.07) (i) Architecture (χ_1^2 = 0-0; 2p = 1-0) Comedo/solid 47/220 81/213 -21.3 29.5 - 0.49 (se 0.13) Other 80/486 139/489 -38.1 52.7 - 0.49 (se 0.11) Unknown arch. 102/1172 235/1169 -72.3 81.7 - 0.41 (se 0.07) Size: (k) Clinical tumour size (χ_1^2 = 0.2; 2p = 0.6) 1-20 mm 46/509 103/499 -30.6 36.1 - 0.43 (se 0.11) 20-50 mm 11/94 25/90 -8.5 8.2 - 0.48 (se 0.6) (I) Pathological tumour size (χ_1^2 = 1.3; 2p = 0.2) 1-20 mm 110/731 193/882 -54.8 72.6 - 0.47 (se 0.08) Other/unknown 106/1040 225/1059 -61.9 80.3 - 0.46 (se 0.05) 2p < 0.0001 Total 229/ 455/ 187 (24.6%) = 99% or $\Rightarrow 95\%$ Cl 0 - 0.5 1.0 1.5 2.0	Unknown grade	129/956	272/979	-79-1	97-0		0-44 (se 0-07)
High $64/329$ $103/311$ $-25-6$ $39-6$ -52 (se 0.12) Unknown grade $86/1049$ $209/1063$ -64.7 71.5 0.40 (se 0.08) (i) Comedonecrosis (χ_1^2 $= 0.8$; $2p = 0.4$) 0.43 (se 0.10) 0.43 (se 0.10) Absent $50/321$ $83/305$ -20.0 32.1 0.43 (se 0.10) Absent $50/321$ $83/305$ -20.0 32.1 0.44 (se 0.07) (j) Architecture ($\chi_1^2 = 0.0$; $2p = 1.0$) Comedo./solid $47/220$ $81/213$ -21.3 $29-5$ 0.44 (se 0.07) (j) Architecture ($\chi_1^2 = 0.0$; $2p = 1.0$) Comedo./solid $47/220$ $81/213$ -21.3 $29-5$ 0.44 (se 0.07) Size: (k) Clinical tumour size ($\chi_1^2 = 0.2$; $2p = 0.65$) 0.43 (se 0.11) 0.43 (se 0.11) 0.43 (se 0.11) 20-50 mm $11/94$ $25/90$ -85 8.2 0.43 (se 0.11) 0.43 (se 0.11) 20-50 mm $11/94$ $25/90$ -85 8.2 0.43 (se 0.18) 0.44 (se 0.06) (i) Pathological tumour size ($\chi_1^2 = 1.3$; $2p = 0.2$) 0.43 (se 0.18) 0.44 (se 0.08	(h) Nuclear grad Low	$de_{52/328}(\chi_{1}^{2} = 0)$			35-3		0·44 (se 0·12)
Unknown grade $86/1049$ $209/1063$ -647 71.5 0.40 (se 0.08) (i) Comedonecrosis (χ^2_1 = 0.8; 2p = 0.4) 124/342 -37.4 44.9 0.43 (se 0.10) Absent $50/321$ $83/305$ -20.0 32.1 0.43 (se 0.10) Absent $50/321$ $83/305$ -20.0 32.1 0.44 (se 0.07) (j) Architecture (χ^2_1 = 0.0; 2p = 1.0) $Comedo./solid$ $47/220$ $81/213$ -21.3 29.5 0.49 (se 0.13) Other $80/486$ $139/469$ -38.1 52.7 0.441 (se 0.07) Unknown arch. $102/1172$ $235/1169$ -72.3 81.7 0.43 (se 0.11) Unknown arch. $102/1172$ $235/1169$ -72.3 81.7 0.43 (se 0.11) Unknown arch. $102/1172$ $235/1169$ -30.6 36.1 0.43 (se 0.10) Unknown $172/1275$ $327/1262$ -89.2 120.8 0.43 (se 0.11) 20-50 mm $11/973$ $193/682$ -54.8 72.6 0.47 (se 0.08) 20-50 mm $13/107$ $37/111$ -13.2	Intermediate	21/172	47/171	-1 3·4	17-4		0·46 (se 0·17)
(i) Comedonecrosis $(\chi_1^2 = 0.8; 2p = 0.4)$ Present 66/364 124/342 -37.4 44.9 Absent 50/321 83/305 -20.0 32.1 Unknown comedo. 113/1193 248/1204 -72.4 87.5 (i) Architecture $(\chi_1^2 = 0.0; 2p = 1.0)$ Comedo./solid 47/220 81/213 -21.3 29.5 Other 80/486 139/469 -38.1 52.7 Unknown arch. 102/1172 235/1169 -72.3 81.7 Size: (k) Clinical tumour size $(\chi_1^2 = 0.2; 2p = 0.6)$ 1-20 mm 11/94 25/90 -8.5 8.2 Other/unknown 172/1275 327/1262 -89.2 120.8 (I) Pathological tumour size $(\chi_1^2 = 1.3; 2p = 0.2)$ 1-20 mm 13/107 37/111 -13.2 11.8 Other/unknown 106/1040 225/1059 -61.9 80.3 Total 229/ 85% or 2 95% Cl 90 0.5 1.0 1.5 2.0	High	64/329	103/311	-25.6	39.6		0.52 (SE 0.12)
Instant 00300 124042 0.44 443 0-40 (st 0.10) Absent 50/321 83/305 -20.0 32.1 0-54 (st 0.13) Unknown comedo. 113/1193 248/1204 -72.4 87.5 0-49 (st 0.13) (j) Architecture ($\chi_1^2 = 0.0$; $2p = 1.0$) 0-44 (st 0.07) 0-44 (st 0.07) (j) Architecture ($\chi_1^2 = 0.0$; $2p = 1.0$) 0-49 (st 0.13) 0-44 (st 0.07) Unknown arch. 102/1172 235/1169 -72.3 81.7 0-49 (st 0.13) Unknown arch. 102/1172 235/1169 -72.3 81.7 0-43 (st 0.10) Unknown arch. 102/1172 235/1169 -72.3 81.7 0-43 (st 0.10) Size: (k) Clinical tumour size ($\chi_1^2 = 0.2$; $2p = 0.6$) 0-43 (st 0.11) 0-43 (st 0.11) 20-50 mm 11/94 25/90 -8.5 8.2 0-48 (st 0.06) (l) Pathological tumour size ($\chi_1^2 = 1.3$; $2p = 0.2$) 0-47 (st 0.08) 0-43 (st 0.11) 100/731 193/682 -54.8 72.6 0-47 (st 0.08) 20-50 mm 13/107 37/111 -13.2 11.8 0-33 (st 0.18) 0-46 (st	Unknown grade	86/1049	209/1063	-64.7	71.5	-0-	0·40 (se 0·08)
Unknown comedo. 113/1193 248/1204 -72:4 87.5 (i) Architecture $(\chi_{1}^{2} = 0.0; 2p = 1.0)$ Comedo./solid 47/220 81/213 -21:3 29:5 Other 80/486 139/469 -38:1 52:7 Unknown arch. 102/1172 235/1169 -72:3 81.7 Size: (k) Clinical tumour size $(\chi_{1}^{2} = 0.2; 2p = 0.6)$ 1-20 mm 48/509 103/499 -30:6 38:1 20-50 mm 11/94 25/90 -8:5 8:2 Other/unknown 172/1275 327/1262 -89:2 120.8 (I) Pathological tumour size $(\chi_{1}^{2} = 1.3; 2p = 0.2)$ 1-20 mm 13/107 37/111 -13:2 11:8 Other/unknown 106/1040 225/1059 -61:9 80:3 Total 229/ 1878 (12-2%) 455/ 99% or \Rightarrow 95% Cl 0 0-5 1-0 1.5 2.0	(i) Comedonecı Present	rosis (χ ² _{66/364} 1	= 0-8; 2 124/342	p = 0-4 -37-4	4) 44·9		0·43 (se 0·10)
(i) Architecture $(\chi_1^2 = 0.0; 2p = 1.0)$ Comedo./solid 47/220 81/213 -21.3 29.5 0-49 (se 0.13) Other 80/486 139/469 -38.1 52.7 0-49 (se 0.13) Unknown arch. 102/1172 235/1169 -72.3 81.7 0-41 (se 0.07) Size: (k) Clinical tumour size $(\chi_1^2 = 0.2; 2p = 0.6)$ 1-20 mm 46/509 103/499 -30.6 36.1 0-43 (se 0.11) 20-50 mm 11/94 25/90 -8.5 8.2 0-48 (se 0.06) (I) Pathological tumour size $(\chi_1^2 = 1.3; 2p = 0.2)$ 1-20 mm 110/731 193/682 -54.8 72.6 0-48 (se 0.06) (I) Pathological tumour size $(\chi_1^2 = 1.3; 2p = 0.2)$ 1-20 mm 13/107 37/111 -13.2 11.8 0-448 (se 0.06) Total 229/ 455/ -127.4 164.8 0-46 (se 0.05) 2p < 0.0001 = 99% or \rightarrow 95% Cl 0-45 1-0 1-5 2-0	Absent	50/321	83/305	-20-0	32.1		0·54 (se 0·13)
Comedo./solid 47/220 81/213 -21-3 29-5 0-49 (se 0.13) Other 80/486 139/469 -38-1 52-7 0-49 (se 0.13) Unknown arch. 102/1172 235/1169 -72-3 81-7 0-49 (se 0.10) Size: (k) Clinical tumour size ($\chi_1^2 = 0.2$; $2p = 0.6$) 0-43 (se 0.11) 0-43 (se 0.11) 20-50 mm 11/94 25/90 -8-5 8-2 0-35 (se 0.22) Other/unknown 172/1275 327/1262 -89-2 120-8 0-48 (se 0.06) (I) Pathological tumour size ($\chi_1^2 = 1.3$; $2p = 0.2$) 0-47 (se 0.08) 0-47 (se 0.08) 0-47 (se 0.08) 20-50 mm 130/07 37/111 -13-2 11.8 0-43 (se 0.11) 0-50 mm 13/107 37/111 -13-2 11-8 0-48 (se 0.06) Total 229/ 1876 455/ 1851 -127-4 164-8 0-46 (se 0.05) $2p < 0.00001$ 99% or \sim 95% Cl 0 0-5 1-0 1-5 2-0	Unknown comedo). 113/1193	248/1204	-72-4	87.5	- <u>-</u>	0·44 (se 0·07)
Unknown arch. 102/1172 235/1169 -72-3 81-7 Size: (k) Clinical tumour size $(\chi_1^2 = 0.2; 2p = 0.6)$ 1-20 mm 46/509 103/499 -30-6 36-1 20-50 mm 11/94 25/90 -8-5 8-2 Other/unknown 172/1275 327/1262 -89-2 120-8 (I) Pathological tumour size $(\chi_1^2 = 1.3; 2p = 0.2)$ 1-20 mm 110/731 193/682 -54-8 72-6 20-50 mm 13/107 37/111 -13-2 11-8 Other/unknown 106/1040 225/1059 -61-9 80-3 Other/unknown 106/1040 225/1059 -61-9 80-3 Total 229/ 455/ -127-4 164-8 99% or \rightarrow 95% Cl 0 0-5 1-0 1-5 2-0		$(\chi^2_{1} = 0.0)$; 2p = 1 81/213	• 0) -21·3	29.5		0·49 (se 0·13)
Size: (k) Clinical tumour size $(\chi_1^2 = 0.2; 2p = 0.6)$ 1-20 mm 46/509 103/499 -30.6 36.1 20-50 mm 11/94 25/90 -8.5 8.2 Other/unknown 172/1275 327/1262 -89.2 120.8 (I) Pathological tumour size $(\chi_1^2 = 1.3; 2p = 0.2)$ 1-20 mm 110/731 193/682 -54.8 72.6 0.43 (se 0.11) 0.35 (se 0.22) 0.48 (se 0.06) 0.47 (se 0.08) 0.47 (se 0.08) 0.43 (se 0.11) 0.33 (se 0.18) 0.46 (se 0.08) 0.46 (se 0.05) 2p < 0.0001 99% or \sim 95% Cl 0 0 0 0 0 0 0 0 0 0 1.5 2.0	Other	80/486	139/469	-38-1	52.7	_	0.49 (SE 0.10)
(k) Clinical tumour size $(\chi_1^2 = 0.2; 2p = 0.6)$ 0.43 (se 0.11) 1-20 mm 46/509 103/499 -30.6 36.1 0.43 (se 0.11) 20-50 mm 11/94 25/90 -8.5 8.2 0.35 (se 0.22) Other/unknown 172/1275 327/1262 -89.2 120.8 0.48 (se 0.06) (I) Pathological tumour size $(\chi_1^2 = 1.3; 2p = 0.2)$ 0.47 (se 0.08) 0.47 (se 0.08) 20-50 mm 13/107 37/111 -13.2 11.8 0.43 (se 0.11) 20-50 mm 13/107 37/111 -13.2 11.8 0.43 (se 0.08) Other/unknown 106/1040 225/1059 -61.9 80.3 0.46 (se 0.08) Total 229/ 1878 455/ (12.2%) -127.4 164.8 0.46 (se 0.05) 2p < 0.00001	Unknown arch.	102/1172	235/1169	-72-3	81.7	-0-	0·41 (se 0·07)
20-50 mm 11/94 25/90 -8-5 8-2	(k) Clinical tum						0·43 (se 0·11)
(I) Pathological tumour size ($\chi_1^2 = 1.3$; 2p = 0.2) 1-20 mm 110/731 193/682 -54.8 72.6 20-50 mm 13/107 37/111 -13.2 11.8 Other/unknown 106/1040 225/1059 -61.9 80.3 Total 229/ 455/ -127.4 164.8 99% or \sim 95% Cl 99% or \sim 95% Cl 0 0.5 1.0 1.5 2.0							
1-20 mm 110/731 193/682 -54.8 72.6 - 0.47 (SE 0.08) 20-50 mm 13/107 37/111 -13.2 11.8 - 0.33 (SE 0.18) Other/unknown 106/1040 225/1059 -61.9 80.3 - - 0.46 (SE 0.08) Total 229/ 1878 (12.2%) 455/ 1851 (24.6%) -127.4 164.8 - 0.46 (SE 0.05) 2p < 0.00001	Other/unknown	172/1275	327/1262	- 89 ·2	120.8		0.48 (SE 0.06)
20-50 mm $13/107$ $37/111$ $-13\cdot2$ $11\cdot8$ - 0.33 (se 0.18) Other/unknown $106/1040$ $225/1059$ $-61\cdot9$ $80\cdot3$ - 0.46 (se 0.08) Image: Total $229/1059$ $455/1059$ $-127\cdot4$ $164\cdot8$ 0.46 (se 0.050) $2p < 0.00001$ 1878 1851 $(24\cdot6\%)$ 0.05 1.0 1.5 2.0	(I) Pathological	tumour s	size $(\chi_1^2)_{193/682}$			-2)	0.47 (se 0.08)
Other/unknown 106/1040 225/1059 -61.9 80.3 -1 0.46 (se 0.08) ■ Total 229/ 1878 (12.2%) 455/ 1851 (24.6%) -127.4 164.8 - 0.46 (se 0.05) 2p < 0.00001							
■ 10.01 1878 1851 12.74 104.0 2p < 0.00001 (12.2%) (24.6%) 0 0.5 1.0 1.5 2.0	Other/unknown	106/1040			80-3	- <u>t</u>	
■ 10.01 1878 1851 12.74 104.0 2p < 0.00001							0 40 / 0 0-1
0 0.5 1.0 1.5 2.0	Total	1878	1851	-127.4	164.8	\$	• •
BCS+RT better BCS+RT worse	-∎-99% or <>>95% Cl				0	0.5 1.0	1.5 2.0
						BCS+RT better	BCS+RT worse

Figure 9: Effect of radiotherapy (RT) after breast-conserving surgery (BCS): Ratio of annual event rates of any ipsilateral breast event by age and histological grade and age and comedonecrosis.

Age and histological grade

Category	Events/ Allocated BCS+RT	Women Allocated BCS		T events kVariance of O-E	e <u>Ratio of annua</u> BCS+RT :	
(a) Age at diagno	osis < 50	yrs				
Low hist. grade	9/81 (11·1%)	13/87 (14·9%)	-2.4	5.2		0.63 (se 0.35)
Inter. hist. grade	9/47 (19·1%)	15/43 (34·9%)	-4.1	5.4		0.47 (se 0.30)
High hist. grade	18/70 (25·7%)	16/46 (34·8%)	-3-1	7·2		0.65 (SE 0.30)
Unknown hist. grade	58/258 (22·5%)	81/279 (29·0%)	-11-2	33.5		— 0·72 (se 0·15)
■ (a) Subtotal	94/ 456 (20·6%)	125/ 455 (27∙5%)	-20.8	51.3	\triangleleft	0·67 (SE 0·11) 2p = 0·004
Heterogeneity betwe	een 4 catego	ries: $\chi_3^2 = 0$	•9; p = 0•	В		
(b) Age at diagno	osis 50+ y	yrs				
Low hist. grade	22/382 (5·8%)	61/342 (17·8%)	-22.2	20.2		0·33 (se 0·13)
Inter. hist. grade	18/168 (10·7%)	30/183 (16·4%)	-6.1	11.7		
High hist. grade	24/174 (13⋅8%)	48/171 (28·1%)	-13-6	17.4		0·46 (se 0·17)
Unknown hist. grade	71/698 (10·2%)	191/700 (27·3%)	-68-0	63-4	-0-	0·34 (se 0·08)
(b) Subtotal	135/ 1422 (9·5%)	330/ 1396 (23⋅6%)	-109-9	112.7	\oplus	0·38 (SE 0·06) 2p < 0·00001
Heterogeneity betwo	een 4 catego	ries: $\chi_3^2 = 4$	•0; p = 0∹	3		
	229/ 1878 (12·2%)	455/ 1851 (24·6%)	-130.7	164.0	\diamond	0·45 (SE 0·05) 2p < 0·00001
🚽 99% or < 95% Cl				<u> </u>		<u> </u>
Difference between treatment effects i				0 007	0.5 1. BCS+RT better	0 1.5 2.0 BCS+RT worse
Heterogeneity wit	hin subtotals	s: χ ₆ ² = 4·8;	p = 0·6		Treatment effect	rt 2p < 0.00001

Age and comedonecrosis

present (2 Comedonecrosis 2 absent (2 Unknown comedo. 4 (1	6/105 24-8%) 1/105 20-0%) 7/246 9-1%) 94/	39/92 (42·4%) 30/110 (27·3%) 56/253 (22·1%)	-10·9 -4·3 -6·0	15·0 12·2		0-48 (se 0-18)
Comedonecrosis 2 present (2 Comedonecrosis 2 absent (2 Unknown comedo. 4 (1 (2) (a) Subtotal (2) Heterogeneity between 3	6/105 24-8%) 1/105 20-0%) 7/246 9-1%) 94/	39/92 (42·4%) 30/110 (27·3%) 56/253	-4.3			
present (2 Comedonecrosis 2 absent (2 Unknown comedo. 4 (1 (2) (2) (2) (2) (2) (2) (2) (2) (2) (2)	14-8%) 1/105 20-0%) 7/246 9-1%) 94/	(42·4%) 30/110 (27·3%) 56/253	-4.3			
absent (2 Unknown comedo. 4 (1 (a) Subtotal (2 Heterogeneity between 3	20·0%) 7/246 9·1%) 94/	(27·3%) 56/253		12.2		0.70 (SE 0.24)
(1 ■ (a) Subtotal (2 Heterogeneity between 3	9·1%) 94/		-6-0		ł	
(2) (2) (2) (2) (2) (2) (2) (2) (2) (2)				24.5	o	0·78 (se 0·18)
	456 20∙6%)	125/ 455 (27·5%)	-21.2	51.7	\Leftrightarrow	0.66 (SE 0.11) 2p = 0.003
(b) Age at diagnosis	3 categori	ies: $\chi_2^2 = 2$ ·	2; p = 0-	3		
	s 50+ y	rs				
	0/259 5·4%)	85/250 (34·0%)	-26.5	29-9		0·41 (se 0·12)
	9/216 3∙4%)	53/195 (27·2%)	-15-6	19-9		0·46 (se 0·16)
	6/947 7·0%)	192/951 (20∙2%)	-66 ·4	63 ∙0	-0-	0·35 (se 0·08)
	I35/ 1422 9∙5%)	330/ 1396 (23-6%)	-108-5	112-8	\Leftrightarrow	0·38 (SE 0·06) 2p < 0·00001
Heterogeneity between	3 categori	ies: $\chi_2^2 = 1$.	3; p = 0-	5		
—	29/ 1878 2·2%)	455/ 1851 (24·6%)	-129.7	164.5	\$	0·45 (se 0·05 2p < 0·00001
- 🗗 99% or <> 95% Cl				L		L
Difference between treatment effects in 2 s	subtotals:	χ <mark>²</mark> = 10⋅8;	2p = 0.0	0 101	0 0.5 1 BCS+RT better	0 1.5 2.0
Heterogeneity within a		-	-			BCS+RT worse

Heterogeneity between 6 categories: $\chi_5^2 = 14.3$; p = 0.01

Figure 10: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 724 women with negative margin status and pathological tumour size 1-20 mm according to nuclear grade: 10-year cumulative risks of any ipsilateral breast event.



Figure 11: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 3729 women: 10-year cumulative risks of any breast event, any contralateral breast event and any regional or distant event.



Figure 12: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 3729 women: 10-year cumulative risks of breast cancer mortality, mortality without a breast event (ie mortality from causes other than breast cancer in the period prior to a breast event), and any death. (Analysis based on first events only)

