CHAPTER 16

Carcinoma in situ

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OVERVIEW

- The number of women with carcinoma in situ continues to increase and comprises approximately 25% of all 'malignancy' detected through screening
- Localised DCIS can be treated by breast-conserving surgery with or without radiotherapy
- The role of hormone therapy in preventing recurrence of DCIS after breast-conserving surgery continues to be investigated
- For patients with larger areas of DCIS, mastectomy with or without breast reconstruction is effective
- Factors that influence local recurrence in DCIS after breast-conserving surgery include completeness of excision, radiotherapy, patient age and histological grade

Carcinoma in situ

Two main types of non-invasive (in situ) cancer can be recognised from the histological pattern of disease and cell type (Table 16.1). Ductal carcinoma in situ is the most common form of non-invasive carcinoma, making up 3–4% of symptomatic and 20–25% of screen-detected cancers. It has increased in frequency because of the widespread use of screening mammography (Figure 16.1). The increase is across all age groups, with a 12% annual increase in the 30–39-year age group and an 18.1% annual increase in women over the age of 50. Ductal carcinoma in situ is characterised by distortion, distention and complete involvement by a similar and neoplastic population of cells of adjacent ducts and lobular units (Figure 16.2). By contrast, lobular carcinoma in situ, now known as lobular intraepithelial neoplasia (LIN), which incorporates what was previously known as lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH), is rare (<1% of screen-detected cancers) and presents as relatively uniform expansion of the whole lobule by regular cells with regular, round or oval nuclei. While each involved lobular unit has a uniform cellular population, the pattern and even cytology often do vary between units, with some intervening ones being minimally involved or uninvolved. Despite the ease of separating these two processes most of the time, there are cases with combined features that should be regarded as having clinical features of both processes.

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Table 16.1 Features of ductal and lobular carcinoma in situ.

	DCIS	LCIS
Average age	Late 50s	Late 40s
Menopausal status	70% postmenopausal	70% premenopausal
Clinical signs	Breast mass, Paget's disease, nipple discharge	None
Mammographic signs	Microcalcifications	None
Risk of subsequent carcinoma	30–50% at 10–18 years	25–30% at 15–20 years
Site of subsequent invasive carcinoma		
Same breast	99%	50–60%
Other breast	1%	40–50%

Previously there was agreement about the criteria distinguishing atypical hyperplasia (with specific histological criteria and validation of clinical implications with follow-up studies) from in situ carcinoma. The heterogeneity of some lesions has led pathologists to incorporate LCIS and ALH into LIN. Discussions about classification of so-called DCIS and atypical ductal hyperplasia (ADH) lesions into a single classification of DIN are ongoing. In general, lesions that involve only a few membrane-bound spaces and that measure less than 2–4 mm in their greatest diameter should be regarded as hyperplastic lesions (with or without atypia) and not in situ carcinoma. There is better agreement about larger lesions. Even if there are greatly enlarged lobular units with partial involvement by foci of ADH, this should not be regarded as DCIS for clinical purposes. They are usually in the 5–8-mm size range, and have not been proven to have the natural history of DCIS.

Ductal carcinoma in situ

Different classifications of ductal carcinoma in situ have been described, and these correlate to some degree with mammographic patterns of microcalcification.

Presentation

Patients with symptomatic ductal carcinoma in situ present with a breast mass, nipple discharge or Paget's disease. Screen-detected carcinoma is most commonly associated with microcalcifications

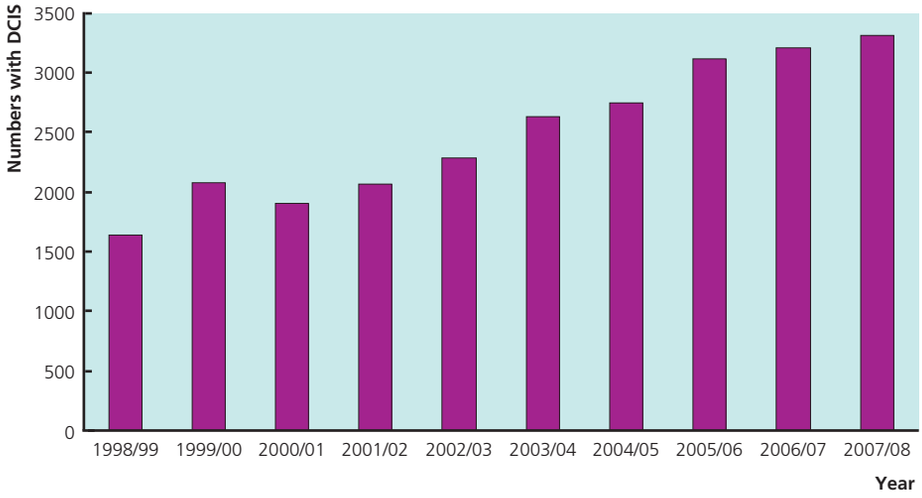

Figure 16.1 DCIS cases detected by breast screening up to 2008 in UK.

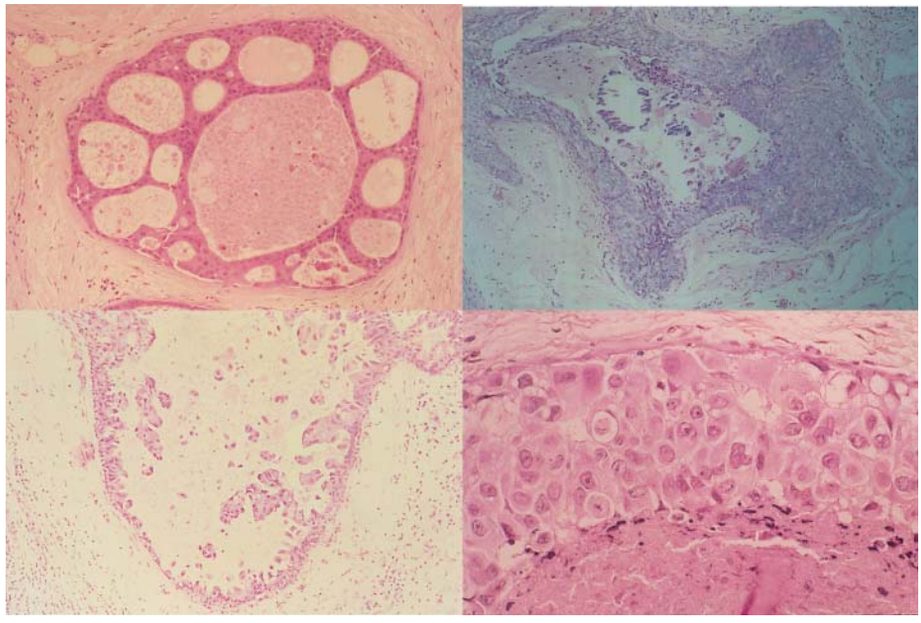

Figure 16.2 Ductal carcinoma in situ: cribiform DCIS (top left); calcification in an area of DCIS (top right); comedo DCIS (bottom left); micropapillary DCIS (bottom right).

Table 16.2 Classification of DCIS.

Histology	Cytology	Necrosis	Calcification
Comedo	High grade	Extensive	Branched
Intermediate	Intermediate	Limited	Limited
Non-comedo*	Low grade	Absent	Microfoci inconsistent

*Cribriform, solid or micropapillary.

(Table 16.2; Figure 16.3), which may be localised or widespread and are characteristically branching within the involved duct system and of variable size and density.

Natural course

Several studies have assessed the risk of subsequent invasive carcinoma in patients in whom ductal carcinoma in situ was not diagnosed by the pathologist or the diagnosis was made but mastectomy was not performed. These studies relate to low-grade carcinoma in situ and show that approximately 40% will develop invasive cancer over a 30-year period, with the majority of these evolving within the first decade. Those who developed invasive cancer did so at the original biopsy site and were in the group where the biopsy was thought not to have removed all the DCIS. Information on the behaviour of inadequately excised intermediate and high-grade DCIS is derived from therapeutic trials documenting local recurrence of DCIS or the development of invasive cancer. This natural history of intermediate and high-grade DCIS is thus continued disease extension and evolution to invasion.

DCIS is a heterogeneous group of lesions, which differ in growth pattern and cytological features, and these different types have marked biological and behavioural differences. Up to 80% of high-grade DCIS overexpress the oncogene or HER2 or erbB2, whereas only 10% of low-grade DCIS express HER2. The presence of a significant amount of oestrogen receptor also differs between

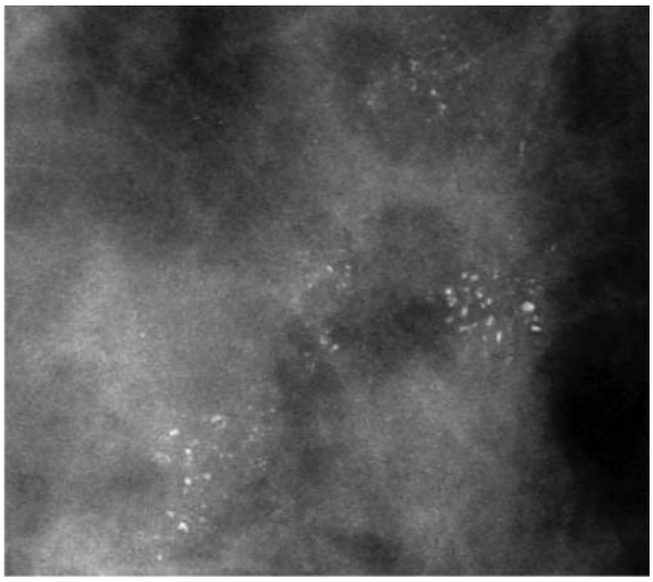

Figure 16.3 Malignant microcalcification that differs in size and density characteristic of DCIS.

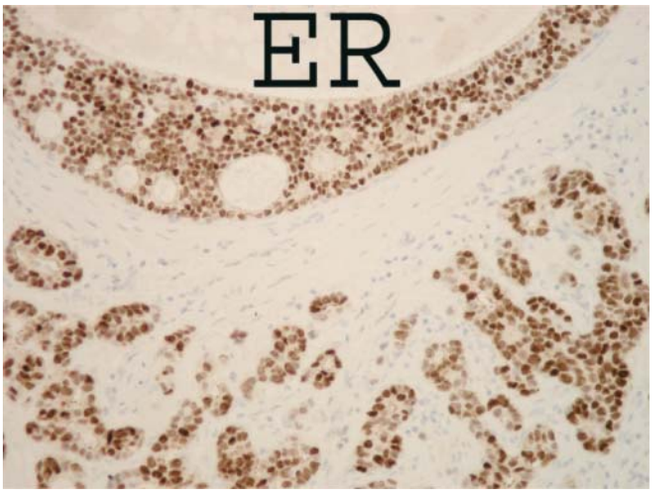

Figure 16.4 An area of DCIS staining strongly positive for oestrogen receptor.

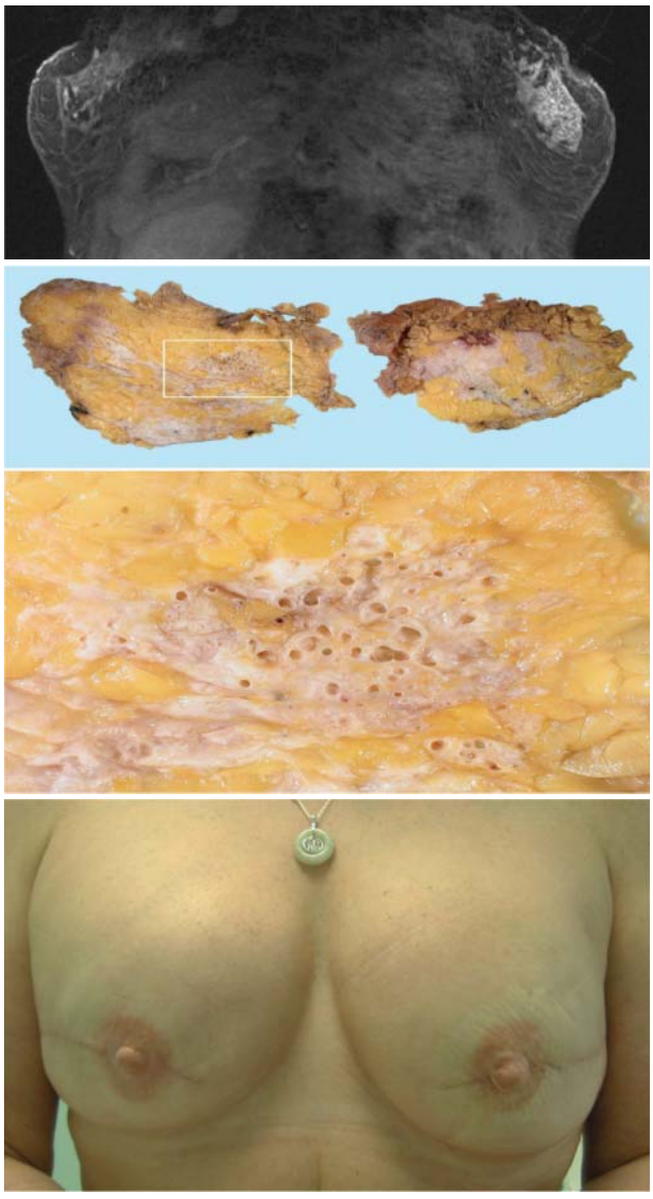

Figure 16.5 Magnetic resonance image (MRI) scan of a patient (top) with a localised area of nodularity in left breast. No abnormality was seen on mammography or ultrasonograpy. Core biopsy showed DCIS and MRI showed a 5 cm area of enhancement that matched the extent of DCIS in the subsequent mastectomy (middle photo). Patient elected to have bilateral mastectomy with immediate reconstruction. Final result after nipple reconstruction and tattooing (bottom).

histological grades, with 50% (range 16–57%) of high-grade DCIS being oestrogen receptor positive compared with 70% (range 70–91%) of low- and intermediate-grade DCIS (Figure 16.4). Pure cases of micropapillary DCIS, although rare, are often extensive within the breast and frequently involve more than a single quadrant.

Treatment

Symptomatic DCIS usually involves much larger areas of the breast than carcinoma in situ detected by screening and has traditionally been treated by mastectomy (Figure 16.5). Such treatment is associated with excellent long-term outcomes (99% survival at five years). With the advent of breast screening and the use of conservative surgery for invasive carcinoma, wide local excision has been increasingly used for localised carcinoma in situ (Table 16.3). The relative merits of wide excision and mastectomy should be discussed with each individual patient (Figure 16.6). There is an increasing trend to treat DCIS regardless of size and grade by breast-conserving surgery if feasible with or without postoperative radiotherapy.

Radiotherapy after breast-conserving surgery for DCIS

Four randomised trials involving almost 3000 women have shown an approximate 50% reduction in the rate of ipsilateral tumour

Table 16.3 Recommended treatment for ductal carcinoma in situ.*

Localised carcinoma in situ (≤4 cm)**/**

- Wide local excision (WLE)^
- Ensure that mammographic lesion has been completely excised with clear histological margins (at least 1 mm)
- Re-excise if margins are involved
- Consider mastectomy if DCIS >4 cm in size or if micropapillary
- Postoperative radiotherapy especially if ER/PR negative)
- Consider tamoxifen, 20 mg a day if ER positive

Widespread carcinoma in situ (>4 cm)**/**

- Mastectomy (with or without breast reconstruction)
- Tamoxifen not indicated after mastectomy
- Radiation not indicated after mastectomy

*Outside trials of experimental treatments.
**Extent of carcinoma can be estimated in 80% of patients by measuring extent of malignant microcalcification on mammograms.
***Size per se is not an indication for WLE or mastectomy, larger lesions can be treated by WLE in larger breasts.
^Complete excision to clear margins.

Figure 16.6 Mammogram of recurrent DCIS seen as microcalcification adjacent to the metal clip, in a patient treated by wide excision alone.

recurrence, but as yet no effect on all-cause or breast cancer mortality was seen, with 10% mortality at 10 years in both groups (Figures 16.7–16.9). Disease recurrence is a function of residual disease remaining after initial treatment, because it occurs in the same region and is usually of the same grade as the initial lesion. In many randomised series not all patients had clear margins. The 1–2% of patients who developed life-threatening recurrent invasive disease have been equally distributed between the treated and untreated groups in clinical trials. High-grade DCIS has the highest rate of local recurrence and the greatest benefit from adjuvant radiotherapy (Figure 16.10). Lesions over 4 cm are not always easy to excise by wide local excision. Larger lesions have been reported to have a higher rate of local recurrence, and therefore mastectomy has been advocated for large or extensive areas of DCIS. In fact, the majority of studies show no clear relationship between extent of DCIS and recurrence (Figure 16.11). Providing that all disease can be excised to clear margins by breast-conserving

Table 16.4 Risk factors for recurrence of DCIS.

Risk factor	Bad prognosis feature	
Excision margins	Margins <1 mm after breast-conserving surgery	
Tumour grade	High grade (III)	
Comedo necrosis	Present	
Histological type	Poorly differentiated	
Patient age	Younger age at diagnosis ≤40 years	
Biological markers	*Negativity*	*Positivity*
	Oestrogen receptor	HER2 (erb-B2)
	Progesterone receptor	
	Bcl2	P21
	?erbB4	P53
		Ki67
Patient presentation	Symptomatic	
Tumour size	Not significant	

surgery with or without therapeutic mammoplasty, then breast conservation appears safe even in large DCIS lesions. Axillary surgery is not indicated in localised DCIS; however, axillary node metastases are seen in 1% of high-grade lesions over 4 cm in size, even when invasion cannot be detected histologically. In patients having mastectomy for large areas of DCIS, sentinel node biopsy following a subareolar injection or an axillary sampling procedure is reasonable.

Margin width

Data from three randomised trials have analysed margin status and margin width after local excision of DCIS correlated with recurrence. Clear circumferential margins (greater than 1 mm) were associated with a reduction in the risk of recurrence by 30–50% compared with involved margins (Table 16.4). Although some have argued that wider margins greater than 1 cm obviate the need for radiotherapy, even in patients with such margins radiotherapy reduces local recurrence rates. Wider margins result in a greater-volume excision, which leads to a poorer cosmetic result. Recent results from the overview showed similar rates of local recurrence and benefits from radiotherapy for wide local excision or sector excision (removing more tissue and excising the ducts segmentally).

Factors predicting recurrence after wide local excision of ductal carcinoma in situ (Table 16.4)

Randomised trials have indicated that symptomatic high-grade lesions, comedo necrosis and incomplete excision of DCIS are associated with a higher rate of local recurrence. In addition, young age (less than 50 years) (Figure 16.9) at diagnosis is associated with an increased risk of local recurrence in several DCIS trials. Local recurrence is in the form of invasive cancer in up to 50% of cases, while the remainder are recurrent DCIS. The EORTC study indicated that invasive carcinoma developing after excision of high-grade DCIS is more likely to be node positive compared with low- or intermediate-grade invasive 'recurrence', regardless of whether radiotherapy is given (Figure 16.10). Size does not appear to be

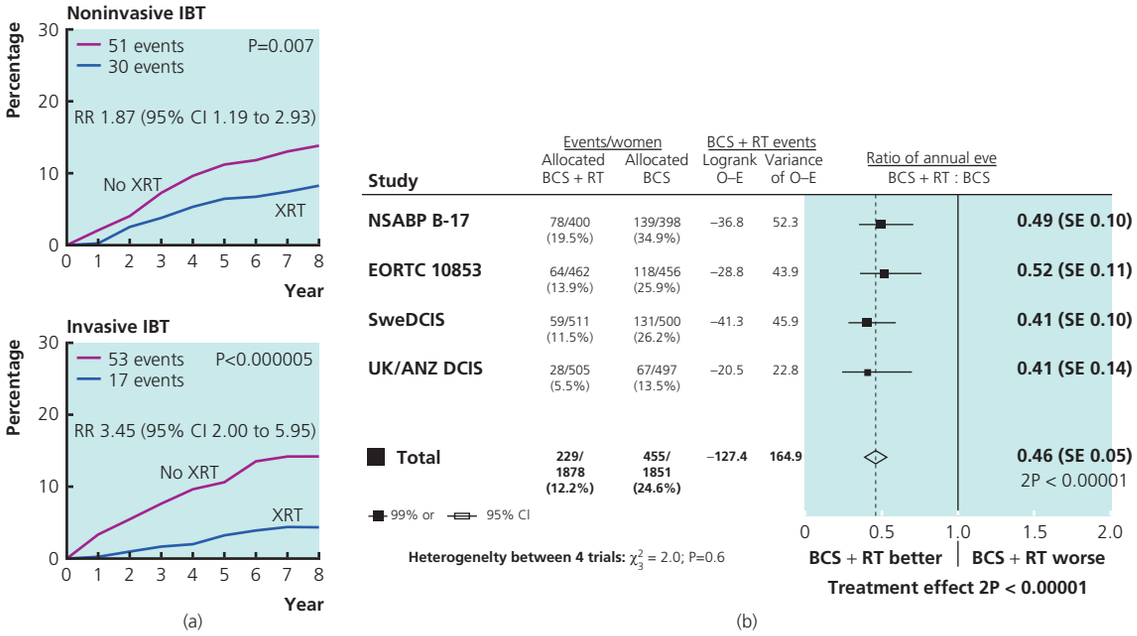

Figure 16.7 (a) Cumulative incidence of all ipsilateral breast tumour recurrences, of non-invasive and invasive ipsilateral breast tumour recurrences, and of all other first events in women treated by lumpectomy or lumpectomy and radiation therapy in National Surgical Adjuvant Breast Project Protocol B—17. *p* values are comparisons of average annual rates of failure. CI = confidence interval; IBT = ipsilateral breast tumor; L = lumpectomy; RR = relative risk; XRT = radiation therapy. (b) Effect of radiotherapy (RT) after breast-conserving surgery (BCS): ratio of annual event rates of any ipsilateral breast event by trial. (c) Effect of radiotherapy (RT) after breast-conserving surgery (BCS) (four trials, start dates 1985–90, 3729 women): 10-year cumulative risks of any ipsilateral breast event (i.e. recurrent DCIS or invasive cancer).

important in breast-conserving surgery providing that radiotherapy is given.

Adjuvant endocrine therapy

Two studies have examined the benefit of tamoxifen in preventing local recurrence (Figure 16.12). In the American B24 trial (Table 16.5), the significant reduction in local recurrence from tamoxifen was due predominantly to a 40% reduction in women under 50 years of age; older women had a smaller (20%) non-significant reduction. The UK/ANZ trial found a 30% reduction in recurrent DCIS but not in invasive cancer development in tamoxifen-treated patients, but this study included few patients under 50 years of age. A pathological review of ER status in a subset of the American trial indicates that tamoxifen reduced the risk of recurrence in ER-positive DCIS by 60% (RR 0.41; 95% CI 0.26–0.65), but did not affect relapse rate in ER-negative DCIS. There is thus no indication for using tamoxifen in women with ER-negative DCIS or after mastectomy for DCIS.

Ongoing trials are examining the management of DCIS in specific subgroups (e.g. oestrogen receptor-positive DCIS, HER2-positive DCIS) to provide a basis for individualisation of treatment in this condition. One such trial is the International Breast Interventional Study II comparing anastrazole, an aromatase inhibitor, with tamoxifen in women with oestrogen receptor-positive DCIS.

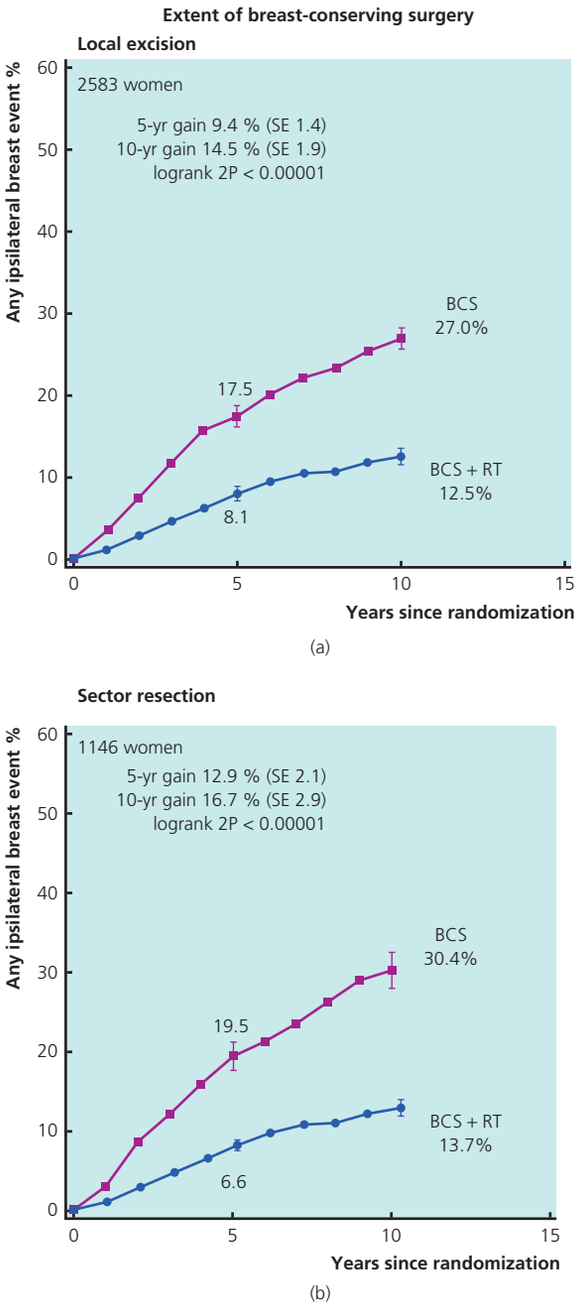

Figure 16.8 Effect of radiotherapy (RT) after breast-conserving surgery (BCS): 10-year cumulative risks of any ipsilateral breast event by extent of surgery. Women given sector resection were from either the SweDCIS trial (1011 women) or the EORT 10853 trial (135 women). Vertical lines indicate 1 SE above or below the 5 and 10 percentages.

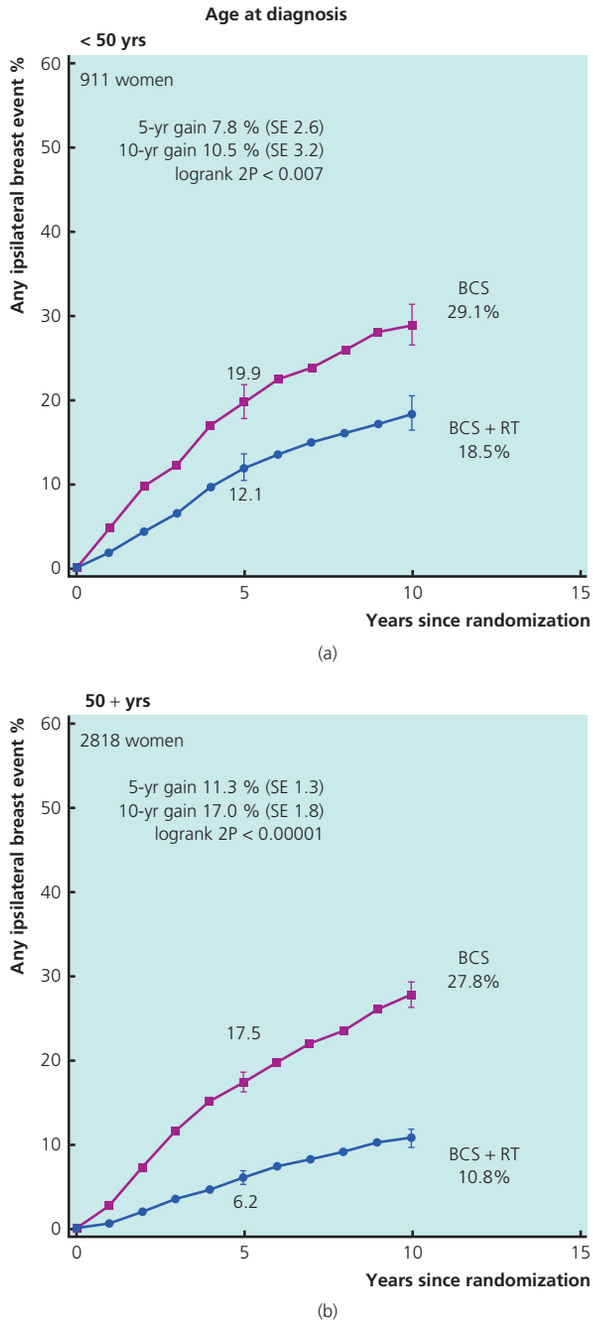

Figure 16.9 Effect of radiotherapy (RT) after breast-conserving surgery (BCS): 10-year cumulative risk of any ipsilateral breast event by age at diagnosis.

Another is looking at the value of using trastuzumab concurrently with radiotherapy as a radiosensitizing agent.

Lobular intraepithelial neoplasia (lobular carcinoma in situ/atypical lobular hyperplasia)

Most studies that have reported on this range of lesions have noted that the lobular units involved lack the continuous involvement of adjacent lobular units and ducts that characterise DCIS. There is no proof that patients with larger lesions or those with more pleomorphic cytology have a higher risk of breast cancer development than women with more localised or less pleomorphic lobular carcinoma in situ (LCIS) lesions. Controversy does exist however as to whether the natural history of pleomorphic LIN is more similar to that of DCIS. More studies are needed.

Presentation is often an incidental finding during a breast biopsy and there are no characteristic clinical or mammographic

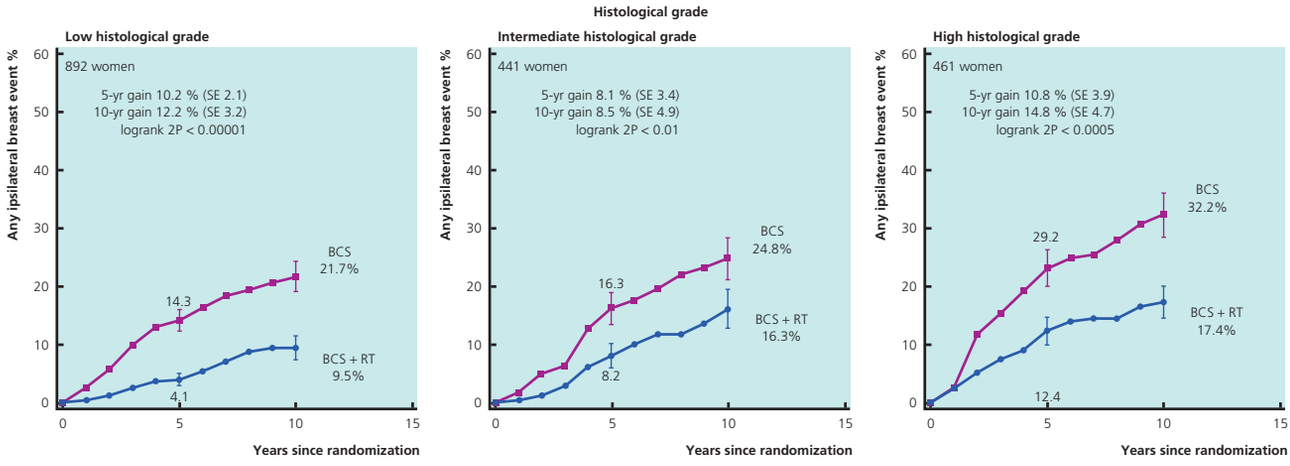

Figure 16.10 Effect of radiotherapy (RT) after breast-conserving surgery (BCS): 10-year cumulative risks of any ipsilateral breast event by histological grade (1794 women). Vertical lines indicate 1 SE above or below the 5 and 10 percentages.

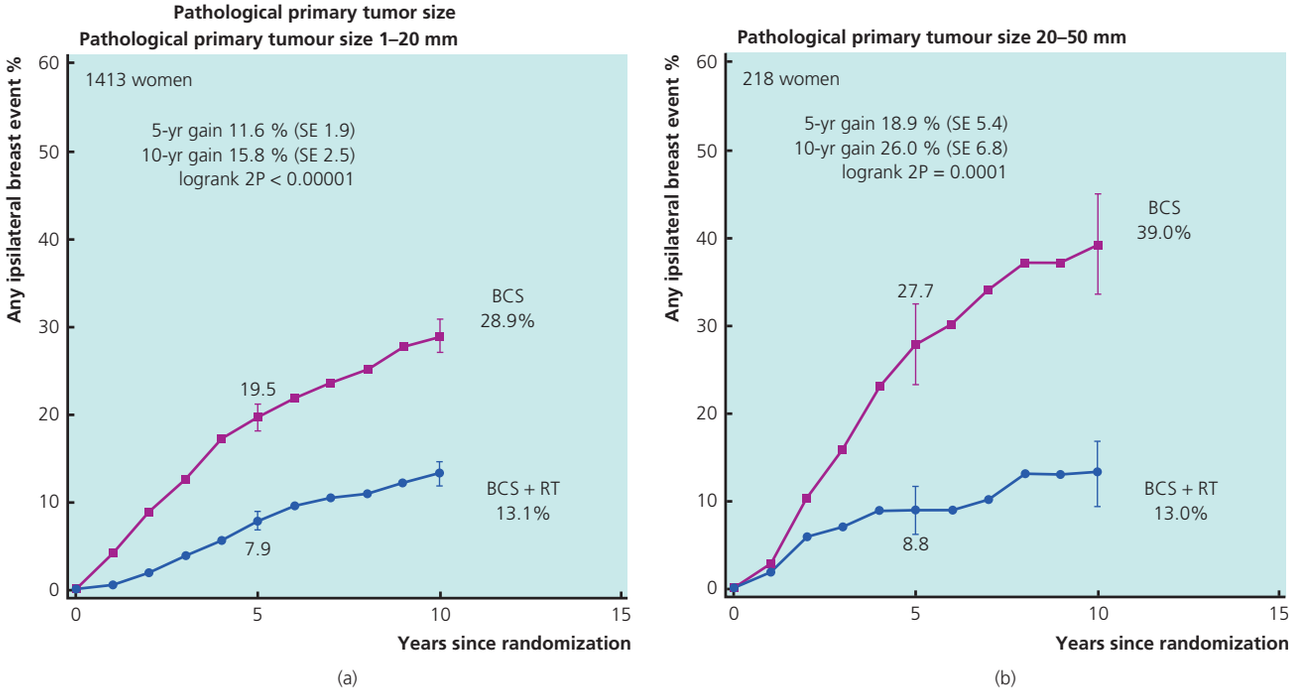

Figure 16.11 Effect of radiotherapy in relation to pathological size. Providing that radiotherapy is given, larger lesions appear to have similar rates of local events after breast-conserving surgery (BCS) and radiotherapy (RT).

features. It is the associated features of dense mammary tissue, enlarged lobular units and calcifications that are visible on mammograms and explain the increased incidence in the screening population.

Natural course

About 15–20% of women with a diagnosis of lobular intraepithelial neoplasia (LIN) will develop breast cancer in the same breast, and a further 10–15% will develop an invasive carcinoma in the contralateral breast.

Treatment

There are four possible approaches to LIN observation: with yearly bilateral mammography; treating the patient with a preventive agent; entering the patient into a trial of treatments to prevent breast cancer; or bilateral mastectomy. Bilateral mastectomy should be confined to women who experience severe anxiety that significantly reduces their quality of life. In the National Surgical Adjuvant Breast and Bowel Project tamoxifen breast cancer prevention trial, there was a 56% reduction in the risk of invasive cancer in patients diagnosed with LCIS who received tamoxifen. Ongoing trials are evaluating anastrozole in postmenopausal women with LIN.

Table 16.5 Recurrence rates for localised DCIS treated by wide local excision and radiotherapy in a randomised trial of tamoxifen (National Surgical Adjuvant Breast and Bowel Project B-24).

Cumulative recurrence rate at five years				
Type of recurrence	**Cumulative placebo (n = 902)**	**Tamoxifen (n = 902)**	**Odds ratio (95% CI)**	**P value**
Ipsilateral non-invasive	5.1	3.9	0.82 (0.53 to 1.28)	0.43
Ipsilateral invasive	4.2	2.1	0.56 (0.32 to 0.95)	0.03
All breast cancer events (includes contralateral disease)	13.4	8.2	0.63 (0.47 to 0.83)	0.0009

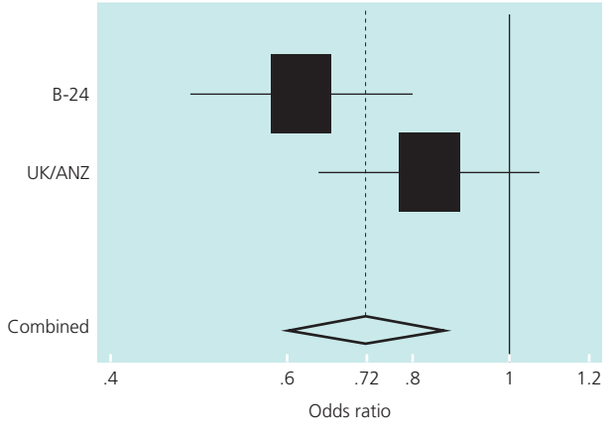

Figure 16.12 Tamoxifen trial overview in DCIS.

Acknowledgement

The source of the data for the graph of rate of development of cancer after excision or excision and radiotherapy is Fisher, B., Constantino, J., Redmond, C. *et al.* (1993) Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *New England Journal of Medicine*, **328**, 1581–1586. The data are reproduced with permission of the journal.

Further reading

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