

**Received:** 2003.11.25  
**Accepted:** 2004.07.26  
**Published:** 2005.03.01

## Contemporary treatment of ductal carcinoma in situ of the breast

**Kefah Mokbel**

Brunel Institute of Cancer Genetics & Pharmacogenomics, Breast & Endocrine Surgeon at St. George's & The Princess Grace Hospitals, London, United Kingdom

**Source of support:** Cohens Foundation

### Summary

The main controversies surrounding the management of DCIS evolve around the need for adjuvant radiotherapy (RT) after adequate local excision (LE) of localized lesions and the role of adjuvant endocrine therapy.

All randomized controlled trials (RCTs) examining the role of adjuvant RT and tamoxifen after LE were reviewed. The review also included important retrospective studies examining the treatment options for DCIS.

All three RCTs demonstrated that adjuvant RT significantly reduced the incidence of ipsilateral breast tumour recurrence (IBTR) after 'adequate' LE of localised DCIS. Retrospective studies showed that the most significant effect for RT in DCIS was in women with high grade disease, with necrosis, large lesions and/or close margins. Total mastectomy is associated with the lowest rates of IBTR, but there is no evidence that it is superior to LE in terms of overall survival. Tamoxifen may be used in very selected patients with hormone sensitive (ER+) disease when the benefits outweigh the potential risks.

Total mastectomy remains the treatment of choice for multicentric and/or extensive disease. RT significantly reduces the risk of recurrence after adequate LE of localized DCIS. Radiation may be safely omitted after breast-conserving surgery (BCS) in postmenopausal women with low risk DCIS (USC/VNPI score =4-5). Tamoxifen can be considered in high-risk young women (USC/VNPI score =9-12) treated by BCS for ER+ DCIS as long as the potential benefits and adverse effects are explained to the patient.

**key words:**

**DCIS • treatment • radiotherapy • lumpectomy • tamoxifen • mastectomy**

**Full-text PDF:**

[http://www.MedSciMonit.com/pub/vol\\_11/no\\_3/4379.pdf](http://www.MedSciMonit.com/pub/vol_11/no_3/4379.pdf)

**Word count:**

4386

**Tables:**

2

**Figures:**

1

**References:**

65

**Author's address:**

Professor Kefah Mokbel, MS, FRCS, Breast & Endocrine Surgeon at St. George's & The Princess Grace Hospitals, London, U.K., e-mail: kefahmokbel@hotmail.com

## BACKGROUND

Ductal carcinoma in situ (DCIS) of the breast is a heterogeneous group of malignant epithelial proliferations confined within the basement membrane of the mammary ducts [1]. The disease can be sub-classified according to the nuclear grade, presence of necrosis or architectural appearance. The nuclear grade remains the most reproducible and the best single predictor of disease behaviour [1]. Although the natural history of DCIS remains unknown it is estimated that approximately one third of low grade lesions into invasive carcinoma after 30 years if left untreated develop [2]. The risk of subsequent invasive carcinoma development is higher for high grade DCIS. The greater prevalence of DCIS compared with invasive breast cancer in autopsy specimens (8.9% vs. 1.3%) suggests that not all DCIS lesions progress to invasive breast cancer [3]. Despite this encouraging statistic, there are no reliable markers that accurately predict the subsequent development of invasive malignancy [1].

The incidence of DCIS increased significantly in the last two decades due to the widespread adoption of screening mammography [4]. The disease currently accounts for approximately one fifth of all mammographically detected breast cancers [5]. DCIS usually presents as microcalcifications (MCCs) detected by screening mammography, the diagnosis is ideally confirmed by histological examination of stereotactic percutaneous core biopsy specimens [6]. The presence of calcification in the core biopsy specimen radiograph or histological sections considered essential for accurate diagnosis [7]. Although screen film mammography (SFM) is currently the main mode of DCIS detection, full-field digital mammography (FFDM) would seem to be superior to SFM in terms of image quality and sensitivity and reliability in characterising MCC [8]. Furthermore, FFDM allows the use of computer-aided detection (CAD) thus allowing double reading of mammograms [9]. Whereas conventional x-ray mammography remains the mainstay of DCIS detection, contrast-enhanced magnetic resonance imaging (CE-MRI) serves as a useful adjunct to mammography in the detection of residual disease, occult invasion, and multicentricity [10].

The optimal treatment of DCIS is controversial, especially concerning the need for adjuvant radiotherapy (RT) after local excision and the role of endocrine therapy. This article reviews the evidence for the various treatment options and attempts to make treatment recommendations and identify areas which require further research and investigation.

## TOTAL MASTECTOMY

No randomized trials compared total mastectomy with breast conserving surgery (BCS) for DCIS. One randomized study: the NSABP B-06 compared BCS with or without RT with total mastectomy in women with assumingly invasive cancer (less than 4.0 cm) [11]. The study included 78 patients who had DCIS, of whom 51 had BCS (29 of these receiving adjuvant RT) and 27 had total mastectomy. After a median follow up of 39 months, the local recurrence rate was 0% in the mastectomy group, 10.3% in the BCS plus RT group and 22.7% in the BCS alone group [11]. Unfortunately, the small sample size prohibited meaningful conclusions regarding the role of mastectomy.

Retrospective studies have shown that total mastectomy for DCIS is superior to BCS plus adjuvant RT in terms of disease free survival (DFS) [12–14]. Silverstein et al. [12] reported a disease-free survival (DFS) rate of 98% for mastectomy compared with 81% for BCS plus RT ( $p=0.0004$ ). In a recent meta-analysis by Boyages et al, the recurrence rate was 1.4% for mastectomy (95% CI=0.7–2.1) compared with 8.9% (95% CI=6.8–11) for BCS plus RT and 22.5% (95% CI=16.9–28.2) for BCS alone [13]. More recently Tunonde-Lara et al. reported similar results [14]. In a study of 676 patients with DCIS, the authors reported a local recurrence rate of 2.6% for the mastectomy group (94 months of follow up), 7.5% for the BCS plus RT group (79 months of follow up) and 14.5% for the BCS group (86 months of follow up) [14]. Involved surgical margins and young age were predictive of local recurrence after BCS [15,16]. Local recurrence after mastectomy can be attributed to the presence of undiscovered foci of invasive carcinoma, development of a new primary breast carcinoma in the breast tissue remaining on the skin flaps after the mastectomy procedure, or to residual foci of DCIS remaining in breast tissue after mastectomy. Intra-operative specimen radiography can be performed to ensure complete excision of mammographic microcalcifications [17].

Despite the superiority of mastectomy in terms of local control, there is no evidence however that total mastectomy is superior to BCS in terms of overall and breast cancer – specific survival [12–14]. Therefore, it is argued that total mastectomy is an over-treatment for DCIS in the light of the overwhelming evidence that BCS combined with adjuvant RT for invasive cancer achieves similar survival rates to total mastectomy [18–19]. However, unlike invasive breast cancer, no randomized controlled trials (RCTs) exist comparing total mastectomy with BCS for DCIS. Nevertheless, mastectomy may be indicated for multi-centric DCIS, large lesions (> 4cm), centrally located disease, inadequate margins after BCS, in patients who prefer to have mastectomy and if adjuvant RT is thought to be contra-indicated [20]. The optimal management of DCIS, however, should take into consideration the individual's risk of local recurrence associated with BCS and the impact of mastectomy on health-related quality of life. All patients requiring or requesting total mastectomy for DCIS should be offered the option of immediate breast reconstruction (IBR) which is associated with a psychological benefit [21], a similar oncological outcome [22], a superior cosmetic result [22] and cost-savings [23] compared with delayed reconstruction. IBR is facilitated by skin-sparing mastectomy (SSM) approaches and the use of autologous tissue for volume replacement (Figure 1) without compromising oncological outcome [22].

The evidence for the oncological safety of SSM comes from descriptive retrospective studies [17,22,24]. In a study of 95 patients undergoing SSM and IBR for DCIS, Rubio et al reported 3 (3%) recurrences after a median follow up of 3.7 years [17]. In this study intra-operative specimen radiography was useful for assessing margin status and for identifying the location of microcalcifications within tissue slices. After a minimal follow up period of 6 years, Spiegel et al. reported no recurrences in 44 patients who had SSM plus IBR for DCIS [24]. IBR after mastectomy for DCIS is also facilitated by the fact that such patients do not usually require post-mastectomy RT or chemotherapy, both of which



**Figure 1.** This 51 year old woman had right skin-sparing mastectomy and immediate reconstruction using the LD myocutaneous flap followed by reconstruction and tattooing of the nipple areola complex for extensive DCIS.

represent important considerations in patients undergoing IBR [25,26].

### ADJUVANT RT

The aim of BCS for localized DCIS is complete excision with clear margins and cosmetically acceptable result. The role of adjuvant RT after BCS for DCIS has been controversial. The evidence regarding the need for adjuvant RT after local excision of DCIS comes from prospective RCTs and retrospective (non-randomized) three studies.

### RCTs

Three prospective RCTs investigated the role of adjuvant RT after local excision of DCIS: the NSABP-B17 trial [27,28], the EORTC 10853 trial [29] and the UK, Australia, and New Zealand (UK/ANZ) DCIS trial [30]. In the NSABP-B17, 818 patients with localized DCIS were randomized to either excision alone or excision plus adjuvant RT. After a mean follow up of 90 months, the investigators observed a significant reduction in both invasive (from 13.4% to 3.9%,  $p < 0.0001$ ) and non-invasive (from 13.4% to 8.2%,  $p = 0.007$ ) ipsilateral breast tumour recurrence (IBTR) associated with the use of adjuvant RT. Although all patients subgroups benefited from the addition of RT, the benefit was maximal in patients with comedonecrosis. These authors observed no significant difference in regional and distant recurrence or mortality between the two study arms. This study has been criticized however for its unsatisfactory definition of clear margins, lack of requirement of specimen radiography, indetermination of tumour size and incomplete tissue processing of DCIS specimens. In this trial, margins were considered to be free when 'the tumour was not transected. Assessments indicating lesions to be 'close' or 'too close' were not considered to represent margin involvement.

In the EORTC trial [29], 1010 patients with localized DCIS were randomized. After a median follow up of 4.25 years, the investigators observed that adjuvant RT had achieved significant reductions in all IBTR (hazard ratio [HR]=0.62,  $p = 0.005$ ) and invasive recurrence rates, however the reduction in DCIS recurrence failed to reach a statistical significance ( $p = 0.06$ ). Furthermore, the authors reported an unexpected significant increase in contra-lateral breast cancer

in the irradiated group, though this may represent a spurious finding, given the low standard doses used and short follow up. It has been suggested that the method of delivery of RT in the EORTC study may explain this finding [31]. The authors of the EORTC study found involved margins to be the most significant risk factor for local recurrence (HR=2.07,  $p = 0.0008$ ). Other risk factors included young age ( $< 40$ , HR=2.14,  $p = 0.02$ ), poor differentiation and symptomatic detection [32]. Although the risk of invasive recurrence was similar for high, intermediate and low grade lesions, the incidence of subsequent metastatic disease was different: 41%, 15% and 5% respectively in these subgroups. Unfortunately both trials did not employ recommendations from the 1997 DCIS Consensus Conference on Pathology for specimen processing [20].

In the UK/ANZ DCIS trial [30], which has a factorial 2x2 design, 1701 patients were randomised to RT and tamoxifen. After a median follow up of approximately 52.6 months, (range: 2.4–118.3 months) the investigators observed that adjuvant RT was associated with a significant reduction (HR=0.38,  $p < 0.0001$ ) in all IBTR events (invasive or DCIS). RT reduced the risk of ipsilateral DCIS by 64% ( $p = 0.0004$ ) and ipsilateral invasive cancer by 55% ( $p = 0.01$ ). The reductions in relative risks observed in this study were greater than those reported by the EORTC trial (35% and 40% respectively) but the reduction in the relative risk of ipsilateral invasive recurrence is smaller than that reported by the NSABP B-17 (71%).

This difference might be explained by the difference in age distribution between the two trials. Patients entered in the UK/ANZ trial were older and more likely to be screen-detected than those recruited for the NSABP B-17 trial. The UK/ANZ trial authors do intend to perform a pathological review of margin width and tumour grade within the context of the study to identify those tumours which may not require adjuvant radiotherapy. Furthermore, they are planning to report breast cancer and non-breast cancer mortality over the next 10 years.

The results of these three prospective trials are summarised in Table 1.

### Non-randomised studies

In contrast to RCTs which aim to answer one or two simple questions, retrospective studies often address several issues and therefore can answer more questions. Consistent with the findings of RCTs, most non-randomized studies reported similar results and showed that adjuvant RT after BCS significantly decreased the incidence of IBTR [12–14,16,33–35]. These studies identified positive margins, high nuclear grade, young age ( $< 40$  years), and symptomatic detection as risk factors for local relapse. The overall recurrence rate for BCS alone was 22.5% (95% CI=16.9–28.2) versus 8.9% (95% CI=6.8–11) for BCS plus adjuvant RT [13].

Approximately 50% of recurrences after BCS for DCIS are invasive [36]. In order to identify a subgroup of patients who can be safely spared adjuvant RT and its potential complications, Using a prospective database of 706 women who had BCS for pure DCIS and 12 year follow up, Silverstein designed a prognostic index known as the

**Table 1.** Summary of the three RCTs comparing LE alone with LE plus RT for localised DCIS.

Trial	Number of evaluable patients	Median or mean follow up (years)	HR of invasive IBTR, RT vs. no RT	HR of non-invasive IBTR, RT vs. no RT
NSABP-B17	818	7.5	0.29 (p<0.0001)	0.61 (p=0.007)
EORTC 10853	1002	4.25	0.60 (p=0.04)	0.65 (p=0.06)
UK DCIS	1694	4.38	0.45 (p=0.01)	0.36 (p=0.0004)

No – number; HR – hazard ratio; RT – radiotherapy; IBTR – ipsi-lateral breast tumour recurrence; LE – local excision.

**Table 2.** The USC/Van Nuys Prognostic Index. The first horizontal represents USC/VNPI scores and the index is calculated by adding the scores of the various parameters (USC/VNPI varies between 4 and 12).

Parameter	1	2	3
Size (mm)	< or =15	15.1–40	>40
Margins (mm)	= or >10	2–9	<1
Pathology	Non HG No necrosis	Non HG with necrosis	HG with necrosis
Age (years)	>60	40–60	<40

HG – high grade.

University of Southern California/Van Nuys Prognostic Index (USC/VNPI) [37]. The initial index was introduced in 1996 and combined tumour size, margin width, nuclear grade and the presence/absence of necrosis Age was subsequently included in a modified version of the index (<40, 40–60 and >60 years) in order to improve the accuracy of the index in predicting local failure (Table 2) [37]. There was no statistical difference in the 12-year local recurrence-free survival in patients with VNPI scores of 4, 5, or 6, regardless of whether or not RT was used (P>0.05). Patients with VNPI scores of 7, 8, or 9 received a statistically significant average 12% to 15% local recurrence-free survival benefit when treated with RT (P=0.03). Patients with scores of 10, 11, or 12, although showing the greatest absolute benefit from RT, experienced local recurrence rates of almost 50% at 5 years. These observations suggest that RT can be omitted after LE in patients with scores 4, 5 or 6 and that mastectomy with or without IBR should be considered in patients with scores 10, 11, or 12. Patients with intermediate scores (7, 8, or 9) should be considered for treatment with radiation therapy or be re-excised if margin width is less than 10 mm and cosmetically feasible.

Other investigators found the percentage of DCIS-positive blocks a more significant predictor of local recurrence than the original VNPI [38]. Moreover, the USC/VNPI has not been prospectively validated.

Despite the controversy regarding the role of the VNPI in the complex treatment selection process, Silverstein and colleagues provided further evidence for the importance of the margin width in the treatment of DCIS [39]. They retrospectively examined data for 469 patients with DCIS,

256 of whom were treated with excision alone and 213 received adjuvant RT after local excision. These two groups were not randomized. The authors employed accurate measurements of samples, including 3-dimensional reconstructions, to achieve precise data on margin width. After a mean follow-up of 81 months, the authors observed that with a margin width of 10 mm or more, the incidence of IBTR was only 2.3% and there was no significant benefit from adding adjuvant RT. However, the group of patients with a 10 mm margin who did not have RT had significantly smaller lesions than those who had RT (median tumour size =9 mm versus 12.5 mm respectively). With margins of 1 to 9 mm, the relative risk of IBTR for local excision alone was 1.49 (non-significant, p=0.24). Similarly in this group, the tumour size was significantly higher in the RT arm (14.5 mm) than in the excision alone arm (8 mm). Furthermore, the rate of comedonecrosis was higher in 1–9 mm margin group than in the 10 mm margin group. The group of patients who had a margin width of less than 1 mm, the relative risk (RR) of IBTR was significantly increased (RR=2.54, p=0.01) when RT was omitted. However, this group of patients had larger cancers and a higher incidence of comedonecrosis than any of the other groups. Therefore, it is difficult to draw meaningful conclusions from this retrospective study as the three groups with different margin widths differed significantly in other factors known to influence local recurrence.

Moreover, the importance of margin width in determining local control after BCS for DCIS is controversial. Neuschartz and colleagues [40] have recently shown that a tumour margin width >1 mm is associated with a low recurrence rate at 5 years for either BCS alone or BCS plus RT (10.9% vs. 4.6%, p=ns). For all cases, these authors also observed that lesion size >15 mm and margin width < or =1mm were associated with increased local recurrence.

Chan et al. [41] also reported that the cut-off in terms of involved margins was <1 mm and that there was no significant difference in the rates of local recurrence in patients treated by local excision with margins between 1–5 mm, 5–10 mm or >10mm. The issue of margin width is further complicated by the fact that different methods of assessing surgical margins have been used, including selected tangential sections, the margin shaving, and cavity peel methods.

In the future trials should adopt uniform criteria for margin evaluation.

However, these retrospective studies taken together, suggest that adjuvant RT may be safely omitted in patients with ad-



equately excised (margin width = or >1 mm), small (<15 mm) non-high grade DCIS not associated with significant necrosis. However, the effect of these parameters and especially margin-width on local recurrence should be evaluated in prospective RCTs that adopt uniform and practical methods in estimating the size of DCIS and margin width.

It is worth-noting that the margin width represents one parameter for which no accurate data were provided by the RCTs outlined above. Another important finding from Silverstein's stratification of data according to margin width comes from the group with clearance <1 mm.

Although adjuvant RT significantly decreased the incidence of IBTR from 58% to 30%, such a recurrence rate would still be unacceptably high, suggesting that excision plus RT is not the optimal treatment for this sub-group of patients. Rather, further local excision or total mastectomy with or without immediate reconstruction would be preferred.

### ADJUVANT TAMOXIFEN

The role of adjuvant tamoxifen in patients with DCIS remains unclear. The NSABP-B24 study [42] randomized 1804 patients treated with lumpectomy and RT to placebo or tamoxifen (20 mg/day for 5 years). The authors observed a significant reduction in breast cancer events at 5 years in the tamoxifen group (8.2 vs. 13.4,  $p=0.0009$ ). The cumulative incidence of all invasive breast cancer events in tamoxifen group was 4.1% at 5 years (2.1% ipsilateral, 1.8% contra-lateral and 0.2% regional/distant), however the reduction in non-invasive breast cancer events was non-significant. Furthermore, there was no overall survival benefit associated with tamoxifen use. On the other hand, tamoxifen significantly reduced the incidence of IBTR when the margins were positive and DCIS contained comedo-necrosis. Among the potential subgroups, no data was reported regarding the oestrogen receptor (ER) and progesterone receptor (PgR) status which is the best predictor of response to tamoxifen therapy. These preliminary results of the UK/ANZ DCIS trial [30] demonstrated that among patients not receiving RT ( $n=1053$ ) adjuvant tamoxifen did not significantly reduce the incidence of ipsilateral invasive breast cancer events (5% vs. 4%,  $p=0.26$ ) nor that of DCIS (6% vs. 9%,  $p=0.1$ ). However the total number of DCIS events (ipsilateral and contralateral) was significantly reduced by tamoxifen (6% vs. 10%,  $p=0.03$ ). Among patients receiving RT ( $n=523$ ), there was no significant difference between the two groups. These observations differ substantially than those reported by the only other trial investigating this issue; the NSABP B-24 trial [42]. This discrepancy might be explained by the difference in age distributions and hormone receptor status between the two trials. Both trials demonstrate that tamoxifen is more effective in reducing the incidence of IBTR in women aged 50 years or younger [30]. Only 9.5% of patients in the UK/ANZ DCIS trial were under the age of 50 compared with 33.5% for the NSABP-B24 trial. The investigators of the UK/ANZ DCIS trial have not provided any data regarding tamoxifen effects in relation to the hormone receptor status.

Dr Allred and colleagues have recently presented a subgroup analysis in relation to the ER status derived from the NSABP B-24 study during the 25<sup>th</sup> San Antonio Breast Cancer

Symposium (December 2002) [43]. The ER status was determined for 628 patients who had BCS for DCIS followed by adjuvant RT. In ER positive tumors (77%), tamoxifen significantly reduced the incidence of all breast cancer events ( $RR=0.41$ , 95%  $CI=0.25-0.65$ ,  $p=0.0002$ ). This effect was not seen in patients with ER negative disease ( $RR=0.80$ ,  $p=0.51$ ). However, in view of the small number of events in the ER negative group ( $n=36$ ), a small benefit in the group could not be excluded with certainty. Another limitation of this retrospective analysis was the lack of standardization of ER testing. In this study, the ER results from contributing institutions were significantly more likely to be negative than those from the central reference laboratory, where ER status was determined by

immunohistochemistry ( $p=0.016$ ). Furthermore no survival advantage has been demonstrated for tamoxifen use. The intended pathological review of the UK/ANZ trial may shed further light on this issue.

Since premenopausal women have a higher risk of recurrence after BCS for DCIS [13,32] and a lower risk of developing endometrial carcinoma with tamoxifen therapy [27,42], then it may be reasonable to recommend tamoxifen to younger women who had BCS for high risk DCIS especially if the tumour is ER and/or PgR positive. Moreover, patients undergoing BCS and RT for localized DCIS are at an increased risk of developing invasive breast cancer, it has been suggested that tamoxifen may be added to BCS and adjuvant RT as a chemo-preventative agent [4]. However such a policy requires the acceptance of the controversial NSABP-P1 trial [45].

Since tamoxifen use is associated with excess mortality related to endometrial cancer and thrombo-embolic episodes especially in postmenopausal patients [46], therefore it is not currently possible to identify subgroups of postmenopausal patients with DCIS for whom the benefits outweigh the risks.

### FUTURE RESEARCH

#### Hormonal therapy

The potential therapeutic role of third and fourth generation selective estrogen receptor modulators acting as ER down-regulators (e.g. fulvestrant), or as pure anti-estrogens (e.g. EM-652) [47] and third generation aromatase inhibitors [48] in women with hormone receptor positive DCIS should be investigated by RCTs. The preliminary results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial [49] have demonstrated that adjuvant anastrozole is superior to tamoxifen in postmenopausal women with ER positive early breast cancer in terms of DFS, prevention of contra-lateral breast cancer and adverse effects. Zhang et al. have recently shown that aromatase expression in the stromal and tumour cells is significantly higher for DCIS than for invasive carcinoma [50]. Such data suggest that third generation aromatase inhibitors are promising as an adjuvant therapy for hormone sensitive DCIS in postmenopausal patients.

#### Cyclo-oxygenase 2 (Cox-2)

The cyclooxygenase (COX) enzyme system is composed of two isoenzymes, COX-1 and COX-2. Recent sources of ex-

perimental and epidemiological evidence suggest a significant role for the COX enzymes, particularly COX-2, in the pathogenesis of breast cancer [51]. Cox-2 expression has been detected in most breast tumours including DCIS [51]. This would seem to translate into a potentially viable role for Cox-2 inhibitors in the treatment of DCIS and prevention of breast cancer, but also raises issues regarding safety and tolerability of these drugs [52].

### Sentinel node biopsy (SNB)

Recent studies have demonstrated that the SNB, which utilizes a simple principle, is a reliable and minimally invasive method for determining the status of the regional lymph nodes in patients with clinically node-negative breast cancer. The technique has been widely used in the management of patients with early breast cancer despite the lack of long-term data from randomised controlled trials which are currently in progress [53]. Although neither formal axillary node dissection nor SNB is appropriate for all cases of DCIS, the role of the SNB in high-risk lesions (e.g. the presence of micro-invasion and lesions >4 cm) and in patients undergoing mastectomy is worth investigating [54–56].

### Mammary ductoscopy

Mammary ductoscopy (MD) is an emerging technique that allows direct visualization of the mammary duct system using sub-millimeter microendoscopes, and that produces sharp and clear video images and ductal washings for cytological analysis [57]. There is a growing body of evidence that MD may have a role in the management of women with pathological nipple discharge [57] and guiding breast conserving surgery for DCIS [58].

Further research with carefully designed clinical trials is required to confirm these potential applications of MD including its utility in DCIS detection and treatment of DCIS by combining radiofrequency (RF) or LASER with MD [57,59]. The therapeutic role of these ablative techniques (LASER and RF) using stereotactic delivery is also worth investigating.

### Molecular markers

Gene expression profiling and proteomics have the potential to characterize the complex genetic alterations that typify DCIS in a way that reflects the complexity of the regulatory mechanisms involved and allows a more accurate prediction of biological behaviour and clinical outcome [60,61]. These techniques may accurately identify a subgroup of DCIS lesions which are likely to progress to invasive disease and therefore guide therapeutic strategies. The potential role of certain molecular markers such as p53, vascular endothelial factor and Her-2 in determining the biological behaviour and outcome of DCIS also requires further investigations [62,63].

### Imaging

Recent evidence suggests that functional imaging such as CE-MRI and scintimammography (using Tc-99m MIBI) can serve as a useful adjunct to structural imaging in the detection and characterisation of DCIS [10,64]. Further research

is needed to evaluate both the diagnostic and therapeutic roles of functional imaging in the management of DCIS.

### Intra-operative RT

Since that most local recurrences after BCS are in the index quadrant then whole-breast RT may not always be necessary. If the volume of breast tissue to be irradiated is limited, RT may be performed intraoperatively. Intraoperative RT delivered with electrons at the total isodose 21 Gy could potentially replace standard external RT course of external RT after BCS for DCIS [65]. This approach reduces irradiation to the skin, subcutaneous tissue, and contralateral breast and lung and the inconvenience to patients. RCTs evaluating the potential of this strategy are clearly needed.

### CONCLUSIONS

Total mastectomy remains the treatment of choice for multicentric and/or extensive disease. Radiotherapy significantly reduces the risk of recurrence after adequate local excision of localized DCIS. Achieving clear surgical margins is essential for adequate local excision. Radiotherapy may be safely omitted after breast-conserving surgery for postmenopausal women with low risk DCIS (USC/VNPI score =4–5). Tamoxifen can be considered in high-risk young women (USC/VNPI score =9–12) treated by breast-conserving surgery for hormone receptor positive DCIS as long as the potential benefits and adverse effects are explained to the patient.

### Acknowledgements

I would like to thank Lady Sharon Hawrel-Cohen and the Cohens Foundation for supporting our research program.

### REFERENCES:

- Shoker BS, Sloane JP: DCIS grading schemes and clinical implications. *Histopathology*, 1999; 35: 393–400
- Page DL, Dupont WD, Rogers LW et al: Continued local recurrence of carcinoma 15-25 years after a diagnosis of low grade ductal carcinoma in situ of the breast treated by biopsy. *Cancer*, 1995; 76: 1197–200
- Welch HG, Black WC: Using autopsy series to estimate the disease "reservoir" for ductal carcinoma in situ of the breast: how much more breast cancer can we find? *Ann Intern Med*, 1997; 127: 1023–28
- Ernster VL, Barclay J, Kerlikowske K et al: Incidence of and treatment for ductal carcinoma in situ of the breast. *JAMA*, 1996; 275: 913–18
- Moss SM, Michel M, Patnick J et al: Results from the NHS breast screening programme 1990-1993. *J Med Screen*, 1995; 2: 186–90
- Verkooijen HM: Core Biopsy After Radiological Localisation (COBRA) Study Group. Diagnostic accuracy of stereotactic large-core needle biopsy for nonpalpable breast disease: results of a multicenter prospective study with 95% surgical confirmation. *Int J Cancer*, 2002; 99: 853–59
- Dahlstrom JE, Jain S: Histological correlation of mammographically detected microcalcifications in stereotactic core biopsies. *Pathology*, 2001; 33: 444–48
- Fischer U, Baum F, Obenauer S et al: Comparative study in patients with microcalcifications: full-field digital mammography vs screen-film mammography. *Eur Radiol*, 2002; 12: 2679–83
- Bazzocchi M, Facecchia I, Zuiani C et al: Application of a computer-aided detection (CAD) system to digitalized mammograms for identifying microcalcifications. *Radiol Med (Torino)*, 2001; 101: 334–40
- Hwang ES, Kinkel K, Esserman LJ et al: Magnetic resonance imaging in patients diagnosed with ductal carcinoma-in-situ: value in the diagnosis of residual disease, occult invasion, and multicentricity. *Ann Surg Oncol*, 2003; 10: 381–88

11. Fisher ER, Sass R, Fisher B et al: Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). II. Relation of local breast recurrence to multicentricity. *Cancer*, 1986; 57: 1717-24
12. Silverstein MJ, Barth A, Poller DN et al: Ten-year results comparing mastectomy to excision and radiation therapy for ductal carcinoma in situ of the breast. *Eur J Cancer*, 1995; 31: 1425-27
13. Boyages J, Delaney G, Taylor R: Predictors of local recurrence after treatment of ductal carcinoma in situ: a meta-analysis. *Cancer*, 1999; 85: 616-28
14. Tunon-de-Lara C, de-Mascarel I, Mac-Grogan G et al: Analysis of 676 cases of ductal carcinoma in situ of the breast from 1971 to 1995: diagnosis and treatment-the experience of one institute. *Am J Clin Oncol*, 2001; 24: 531-36
15. Lagios MD, Margolin FR, Westdahl PR, Rose MR: Mammographically detected duct carcinoma in situ: frequency of local recurrence following tylectomy and prognostic effect of nuclear grade on local recurrence. *Cancer*, 1989; 63: 618-24
16. Schwartz GF, Finkel GC, Garcia JC, Patchefsky AS: Subclinical ductal carcinoma in situ of the breast. Treatment by local excision and surveillance alone. *Cancer*, 1992; 70: 2468-74
17. Rubio IT, Mirza N, Sahin AA et al: Role of specimen radiography in patients treated with skin-sparing mastectomy for ductal carcinoma in situ of the breast. *Ann Surg Oncol*, 2000; 7: 544-48
18. Veronesi U, Banfi A, Del Vecchio M et al: Comparison of Halsted mastectomy with quadrantectomy, axillary dissection, and radiotherapy in early breast cancer: long-term results. *Eur J Cancer Clin Oncol*, 1986; 22: 1085-89
19. Fisher B, Bauer M, Margolese R et al: Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med*, 1985; 312: 665-73
20. Schwartz GF, Solin LJ, Olivetto IA et al: The Consensus Conference on the Treatment of In Situ Ductal Carcinoma of the Breast, April 22-25, 1999. *The Breast Journal*, 2000; 6: 4-13
21. Al-Ghazal SK, Sully L, Fallowfield L, Blamey RW: The psychological impact of immediate rather than delayed breast reconstruction. *Eur J Surg Oncol*, 2000; 26: 17-19
22. Singletary SE: Skin-sparing mastectomy with immediate breast reconstruction: the M.D. Anderson Cancer Center experience. *Ann Surg Oncol*, 1996; 3: 411-16
23. Khoo A, Kroll SS, Reece GP et al: A comparison of resource costs of immediate and delayed breast reconstruction. *Plast Reconstr Surg*, 1998; 101: 964-68
24. Spiegel AJ, Butler CE: Recurrence following treatment of ductal carcinoma in situ with skin-sparing mastectomy and immediate breast reconstruction. *Plast Reconstr Surg*, 2003; 111: 706-11
25. Rogers NE, Allen RJ: Radiation effects on breast reconstruction with the deep inferior epigastric perforator flap. *Plast Reconstr Surg*, 2002; 109: 1919-24
26. Petit J, Rietjens M, Garusi C: Breast reconstructive techniques in cancer patients: which ones, when to apply, which immediate and long term risks? *Crit Rev Oncol Hematol*, 2001; 38: 231-39
27. Fisher B, Constantino 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: 1581-86
28. 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: 441-52
29. Julien J-P, Bijker N, Fentiman S et al: Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomized phase III trial 10853. *Lancet*, 2000; 355: 528-33
30. No author listed: 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: 95-102
31. Silverstein MJ, Lagios MD: Benefits of irradiation for DCIS: a Pyrrhic victory. *Lancet*, 2000; 355: 510-11
32. 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 the European Organization for Research and Treatment of Cancer Trial 10853. *J Clin Oncol*, 2001; 19: 2263-71
33. Kestin LL, Goldstein NS, Martinez AA et al: Mammographically detected ductal carcinoma in situ treated with conservative surgery with or without radiation therapy: patterns of failure and 10 year results. *Ann Surg*, 2000; 231: 235-45
34. Cutuli B, Cohen-Solal-le Nir C, De Lafontan R et al: Ductal carcinoma in situ of the breast; results of conservative and radical treatments in 716 patients. *Eur J Cancer*, 2001; 37: 2365-72
35. Solin LJ, Kurtz J, Fourquet A et al: Fifteen year results of breast-conserving surgery and definitive breast irradiation for the treatment of ductal carcinoma in situ of the breast. *J Clin Oncol*, 1996; 14: 754-63
36. Sakorafas GH, Tsiotou AG: Ductal carcinoma in situ (DCIS) of the breast: evolving perspectives. *Cancer Treat Rev*, 2000; 26: 103-25
37. Silverstein MJ: The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast. *Am J Surg*, 2003; 186: 337-43
38. de Mascarel I, Bonichon F, MacGrogan G et al: Application of the van nuys prognostic index in a retrospective series of 367 ductal carcinomas in situ of the breast examined by serial macroscopic sectioning: practical considerations. *Breast Cancer Res Treat*, 2000; 61: 151-59
39. Silverstein MJ, Lagios MD, Groshen S et al: The influence of margin width on local control of ductal carcinoma of the breast. *N Engl J Med*, 1999; 340: 1455-61
40. Neuschatz AC, DiPetrillo T, Safaii H et al: Margin width as a determinant of local control with and without radiation therapy for ductal carcinoma in situ (DCIS) of the breast. *Int J Cancer*, 2001; 96: 97-104
41. Chan KC, Knox WF, Sinha G et al: Extent of excision margin width required in breast conserving surgery for ductal carcinoma in situ. *Cancer*, 2001; 91: 9-16
42. Fisher B, Dignam J, Wolmark N et al: Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet*, 1999; 353: 1993-2000
43. Mokbel K: Recent advances in breast cancer: the 25<sup>th</sup> Annual San Antonio Breast Cancer Symposium. *Curr Med Res Opin*, 2003; 19: 143-46
44. Fisher B, Land S, Mamounas E et al: Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the national surgical adjuvant breast and bowel project experience. *Semin Oncol*, 2001; 28: 400-18
45. Fisher B, Costantino JP, Wickerham DL et al: Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*, 1998; 90: 1371-88
46. Ragaz J, Coldman A: Survival impact of adjuvant tamoxifen on competing causes of mortality in breast cancer survivors, with analysis of mortality from contralateral breast cancer, cardiovascular events, endometrial cancer, and thromboembolic episodes. *J Clin Oncol*, 1998; 16: 2018-24
47. Elkak AE, Mokbel K: Pure antiestrogens and breast cancer. *Curr Med Res Opin*, 2001; 17: 282-89
48. Mokbel K: The evolving role of aromatase inhibitors in breast cancer. *Int J Clin Oncol*, 2002; 7: 279-83
49. The ATAC Trialists Group: Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet*, 2002; 359: 2131-39
50. Zhang Z, Yamashita H, Toyama T et al: Semi-quantitative immunohistochemical analysis of aromatase expression in ductal carcinoma in situ of the breast. *Breast Cancer Res Treat*, 2002; 74: 47-53
51. Singh-Ranger G, Mokbel K: The role of cyclooxygenase-2 (COX-2) in breast cancer, and implications of COX-2 inhibition. *Eur J Surg Oncol*, 2002; 28: 729-37
52. Singh-Ranger G, Mokbel K: Current concepts in cyclooxygenase inhibition in breast cancer. *J Clin Pharm Ther*, 2002; 27: 321-27
53. Singh-Ranger G, Mokbel K: The evolving role of sentinel lymph node biopsy for breast cancer. *Eur J Surg Oncol*, 2003; 29: 423-25
54. Klauber-DeMore N, Tan LK, Liberman L et al: Sentinel lymph node biopsy: is it indicated in patients with high-risk ductal carcinoma-in-situ and ductal carcinoma-in-situ with micro-invasion? *Ann Surg Oncol*, 2000; 7: 636-42
55. Cox CE, Nguyen K, Gray RJ et al: Importance of lymphatic mapping in ductal carcinoma in situ (DCIS): why map DCIS? *Am Surg*, 2001; 67: 513-19
56. Intra M, Veronesi P, Mazzarol G et al: Axillary sentinel lymph node biopsy in patients with pure ductal carcinoma in situ of the breast. *Arch Surg*, 2003; 138: 309-13
57. Mokbel K, Elkak A: The evolving role of mammary ductoscopy. *Curr Med Res Opin*, 2002; 18: 30-32
58. Dooley WC: Routine operative breast endoscopy for bloody nipple discharge. *Ann Surg Oncol*, 2002; 9: 920-23
59. Dowlatshahi K, Francescatti DS, Bloom KJ: Laser therapy for small breast cancers. *Am J Surg*, 2002; 184: 359-63

60. Luzzi V, Holschlag V, Watson MA: Expression profiling of ductal carcinoma in situ by laser capture microdissection and high density oligonucleotide arrays. *Am J Pathol*, 2001; 158: 2005–10
61. Wulfkuhle JD, Sgroi DC, Krutzsch H et al: Proteomics of human breast ductal carcinoma in situ. *Cancer Res*, 2002; 62: 6740–49
62. Heiken TJ, Farolan M, D'alessandro S, Velasco JM: Predicting the biologic behaviour of ductal carcinoma in situ: An analysis of molecular markers. *Surg*, 2001; 30: 593–601
63. Hoque A, Sneige N, Sahin AA et al: Her-2/neu gene amplification in ductal carcinoma in situ of the breast. *Cancer Epidemiol Biomarkers Prev*, 2002; 11: 587–90
64. Cwikla J, Buscombe JR, Hilsenrath AJ: Detection of DCIS using 99mTc-MIBI scintimammography in patients with suspected primary breast cancer, comparison with conventional mammography. *Nucl Med Rev Cent East Eur*, 2000; 3: 41–45
65. Veronesi U, Gatti G, Luini A et al: Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery. *Arch Surg*, 2003; 138: 1253–56