E9. Optimal management of ductal and lobular carcinomas *in situ* of the breast

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Ductal carcinoma *in situ*

Ductal carcinoma *in situ* (DCIS) is a proliferation of malignant mammary ductal cells without basement membrane involvement. With the increasingly widespread use of mammography, its reported incidence has increased by 200% over the last 20 years in the USA [1].

The 'historical' management options for DCIS are total mastectomy, breast-conserving surgery (BCS) alone and BCS with 50 Gy whole-breast irradiation (BCS+RT) [2].

Mastectomy

Mastectomy remains the treatment providing optimal control rate. Recurrences occur when there is lack of knowledge of invasive carcinoma foci and/or insufficient tissue resection.

Breast-conserving surgery

BCS, even in selected series including small lesions with complete excision, leads to a local recurrence (LR) rate of about 25% at 7 years, with 40–45% being invasive LR [3].

Breast-conserving surgery with radiotherapy

In infiltrating breast carcinoma, several randomised trials and the Oxford meta-analysis have shown a 70% reduction in LR (from 30% to 10%) by addition of radiotherapy (RT) [4]. Thus, this approach has also been used widely in DCIS.

In several large series, the 10-year LR rate was approximately 11%, but with large heterogeneities due to selection criteria, extent of surgery and RT modalities (total dose/boost) [5].

Three randomised trials (NSABP B-17, EORTC 10583 and UK/ANZ) have investigated the role of RT after BCS [6–8]. The first two trials, including, respectively, 818 and 1010 women [6,7], randomised BCS versus BCS+RT with a similar scheme. The third trial [8] used a 2×2 factorial design in 1701 women recruited by screening programs to assess the effectiveness of adjuvant RT and tamoxifen. The results are shown in Table 1. Globally, RT reduced LR rates by 57%, 45% and 52%.

In both the National Surgical Adjuvant Breast and Bowel Project (NSABP) and European Organisation for Research and Treatment of Cancer (EORTC) trials, the efficiency of RT was observed in all categories of patients. Young age (less than 40 years) and incomplete/doubtful excision remain the most important LR risk factors [5,9]. Margin width was the most predictive LR factor in Silverstein's experience [10]. In a retrospective analysis of 583 patients treated by BCS (346) and BCS+RT (237), the LR rates varied widely according to excision margins and use of RT: 73% (BCS) versus 35% (BCS+RT) in case of margins <1 mm ($P = 0.002$); 28% (BCS) versus 16% (BCS+RT) in case of margins 1–10 mm ($P = 0.05$); and 6% (BCS) versus 3% (BCS+RT) in case of margins >10 mm (not significant [ns]).

Table 1. Results of trials comparing breast-conserving surgery alone (BCS) with BCS plus radiotherapy (BCS+RT)

	NSABP B-17		EORTC 10583		UK/ANZ	
	BCS	BCS+RT	BCS	BCS+RT	BCS	BCS+RT
Patients (*n*)	403	410	500	502	502	522
LR *n*	124	61	83	53	69	29
	31.7	15	16.6	10.5	13.7	5.5
In situ LR (*n*)	57	29	43	29	30	14
Invasive LR (*n*)	67	32	40	24	39	15
Follow-up (mo)	129		51		53	

RT, radiotherapy; BCS, breast conserving surgery; LR, local recurrence; NSABP, National Surgical Adjuvant Breast and Bowel Project; EORTC, European Organisation for Research and Treatment of Cancer; DCIS, ductal carcinoma *in situ*.

In another study [11], RT reduced LR rates from 28% to 21%, but in the BCS+RT group, there were more unfavourable lesions with larger median size (15 mm versus 10 mm, $P = 0.01$), almost double 'limit' excisions (<1 mm margin: 35% versus 19%, $P < 0.001$), and also very different follow-up times: 106 months versus 70 months in the BCS group ($P < 0.001$). Therefore, BCS+RT is considered the standard treatment, with a 1% annual risk of LR and 98% 15-year specific survival [11].

However, mastectomy remains the safest option in large lesions with doubtful/incomplete excision, because invasive local recurrences can lead to axillary involvement and metastases in approximately 15% of cases.

Tamoxifen

The role of tamoxifen is still under debate. The NSABP B-24 trial [6] showed a significant reduction of LR, from

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11% to 8%, but not in case of free margins (9% versus 7%) and women older than 50 years (8% versus 6%). Moreover, the efficiency of tamoxifen was only present in cases of positive oestrogen receptors (about 75% of cases) [12]. On the other hand, the UK/ANZ trial failed to show the benefit of tamoxifen [8]. Presently, two trials (IBIS II and NSABP B-35) are investigating the potential role of anastrazole versus tamoxifen in DCIS after BCS+/–RT.

Lobular carcinoma *in situ*

Lobular carcinoma *in situ* (LCIS) represents 1–2% of all breast cancers. The exact significance of LCIS has remained uncertain, ranging from a mere marker of subsequent carcinoma to a real pre-cancerous lesion [13]. LCIS is sometimes discovered as an 'incidental finding' around benign lesions such as fibroadenomas or cysts. However, LCIS can be revealed by several radiological features. Several authors have observed a recent increase in LCIS incidence [14] and others have identified some 'aggressive' subtypes [15–17].

Literature on LCIS treatment is rare [13,18], but options are the same as for DCIS, although BCS+RT was reported in detail in only one study [19]. Mastectomy gives an almost 100% cure rate. BCS alone gives an average 15% of subsequent invasive LR (at 10–15 years). In a recent French retrospective study [20] including 135 cases treated by BCS (with a 9-year median follow-up), 24 LRs occurred (10 *in situ* and 14 invasive), corresponding to 13% and 24% of LR rates at 5 and 10 years, respectively. Moreover, among 30 women treated by BCS+RT, only 1 invasive LR was observed. No clinical or pathological LR risk factors were identified. These results are similar to others in the literature. LCIS is not always an 'indolent' disease and, in several cases, it looks like DCIS, but with a longer relapse time. Several aggressive subtypes (i.e. pleiomorphic) are now defined by pathologists. Both mastectomy and CS+RT could be seen as possible options instead of simple lumpectomy. The role of tamoxifen is not yet clearly established, but in the NSABP P-1 chemoprevention trial, it reduces the subsequent risk of invasive BC [6].

References

[1] Nakhlis F, Morrow M. Ductal carcinoma in situ. *Surg Clin N Am* 2003, **83**, 821–839.

[2] Baxter N, Virning BA, Durham JB, Tuttle TM. Trend in treatment of ductal carcinoma in situ of the breast. *J Natl Cancer Inst* 2004, **96**, 443–448.

[3] Macdonald HR, Silverstein MJ, Mabry M, *et al.* Local control in ductal carcinoma in situ treated by excision alone: incremental benefit of larger margins. *Am J Surg* 2005, **190**, 521–525.

[4] Early Breast Cancer Trialist's Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000, **355**, 1757–1770.

[5] Cutuli B, Cohen-Solal-Le Nir C, De Lafontan B, *et al.* Breast conserving therapy for ductal carcinoma in situ. The French cancer center's experience. *Int J Radiat Oncol Biol Phys* 2002, **53**, 868–879.

[6] Fisher B, Land S, Mamounas E, Dignam J, Fisher ER, Wolmark N. 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**, 400–418.

[7] Bijker N, Peterse JL, Duchateau L, *et al.* Risk factor for recurrence and metastasis after breast conserving therapy for ductal carcinoma in situ: analysis of European Organisation for Research and Treatment of Cancer trial 10853. *J Clin Oncol* 2001, **19**, 2263–2271.

[8] Houghton J, George WD, Cuzick J, *et al.* Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in UK, Australia and New Zealand. Randomized controlled trial. *Lancet* 2003, **362**, 95–102.

[9] Solin L, Fourquet A, Vicini FA, *et al.* Long term outcome after breast-conservative treatment with radiation for mammographically detected ductal carcinoma in situ of the breast. *Cancer* 2005, **103**, 1137–1146.

[10] Silverstein MJ. Margin width as a sole predictor of local recurrence in patients with ductal carcinoma in situ of the breast. In Silverstein MJ, Recht A, Lagios M, eds. *Ductal Carcinoma In Situ of the Breast, 2nd edition.* Philadelphia: Lippincott Williams and Wilkins, 2002, 482–493.

[11] Cutuli B, Fourquet A, Luporsi E, *et al.* Standards, Options and Recommendations for the management of ductal carcinoma in situ of the breast (DCIS): update 2004. Available from www.fnclcc.fr

[12] Allred DC, Bryant J, Land S, *et al.* Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS. Findings from NSABP protocol B-24. *Breast Cancer Res Treat* 2002, **76**, s36.

[13] Anderson BO, Rinn K, Georgian-Smith D, Lawton T, Li CI, Moe RE. Lobular carcinoma in situ. In Silverstein MJ, Recht A, Lagios M, eds. *Ductal Carcinoma In Situ of the Breast, 2nd edition.* Philadelphia: Lippincott Williams and Wilkins, 2002, 615–634.

[14] Li C, Anderson BO, Daling JR, Moe RE. Changing incidence of lobular carcinoma in situ of the breast. *Breast Cancer Res Treat* 2002, **75**, 259–268.

[15] Ottesen GL, Graversen HP, Blichert-Toft M, Christensen IJ, Andersen JA. Carcinoma in situ of female breast. 10 year follow-up results of a prospective nationwide study. *Breast Cancer Res Treat* 2000, **62**, 197–210.

[16] Sigal-Zafrani B, Vincent-Salmon A, Penault Llorca F, Sastre-Garau X. Lobular neoplasia. *Ann Pathol* 2003, **23**, 547–553.

[17] Bratthauer GL, Moinfar F, Stamatakos MD, *et al.* Combined E-cadherin and high molecular weight cytokeratin immunoprofile differentiates lobular, ductal and hybrid mammary intraepithelial neoplasias. *Hum Pathol* 2002, **33**, 620–627.

[18] Fisher ER, Land SR, Fisher B, Mamounas E, Gilarski L, Wolkmar N. Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project. Twelve-year observations concerning lobular carcinoma in situ. *Cancer* 2004, **100**, 234–244.

[19] Cutuli B, De Lafontan B, Quetin P, Mery E. Breast-conserving surgery and radiotherapy: a possible treatment for lobular carcinoma in situ? *Eur J Cancer* 2005, **41**, 380–385.

[20] Cutuli B, Levy C, Lemanski C, *et al.* Lobular carcinoma in situ (LCIS). Discovery modalities, treatments and long-term outcome. *Breast Cancer Res Treat*, in press.