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REVIEW

The Role of Radiotherapy in the Conservative Treatment of Ductal Carcinoma in Situ of the Breast

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Abstract Breast-conserving surgery (BCS) followed by radiotherapy (RT) has become the standard of care for the treatment of early-stage (St. I-II) invasive breast carcinoma. However, controversy exists regarding the value of RT in the conservative treatment of ductal carcinoma in situ (DCIS). In this article we review the role of RT in the management of DCIS. Retrospective and prospective trials and meta-analyses published between 1975 and 2007 in the MEDLINE database, and recent issues of relevant journals/handbooks relating to DCIS, BCS and RT were searched for. In retrospective series (10,194 patients) the 10-year rate of local recurrence (LR) with and without RT was reported in the range of 9–28% and 22–54%, respectively. In four large randomised controlled trials (NSABP-B-17, EORTC-10853, UKCCCR, SweDCIS; 4,568 patients) 50 Gy whole-breast RT significantly decreased the 5-year LR rate from

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16–22% (annual LR rate: 2.6–5.0%) to 7–10% (annual LR rate: 1.3–1.9%). In a recent meta-analysis of randomised trials the addition of RT to BCS resulted in a 60% risk reduction of both invasive and in situ recurrences. In a multicentre retrospective study, an additional dose of 10 Gy to the tumour bed yielded a further 55% risk reduction compared to RT without boost. To date, no subgroups have been reliably identified that do not benefit from RT after BCS. In the NSABP-B-24 trial, the addition of tamoxifen (TAM) to RT reduced ipsilateral (11.1% vs. 7.7%) and contralateral (4.9% vs. 2.3%) breast events significantly. In contrast, in the UKCCCR study, TAM produced no significant reduction in all breast events. Based on available evidence obtained from retrospective and prospective trials, all patients with DCIS have potential benefit from RT after BCS. Further prospective studies are warranted to identify subgroups of low-risk patients with DCIS for whom RT can be safely omitted. Until long-term results of ongoing studies on outcomes of patients treated with BCS alone (with or without TAM or aromatase inhibitors) are available, RT should be routinely recommended after BCS for all patients except those with contraindication.

Keywords Breast-conserving therapy · Ductal carcinoma in situ · Endocrine therapy · Prognostic factors · Radiotherapy

Abbreviations

APBI	accelerated partial breast irradiation
BIG	Breast International Group
CCCEN	Comprehensive Cancer Centre East Netherlands
CI	95% confidence interval
DBCG	Danish Breast Cancer Group
DCIS	ductal carcinoma in situ
BCS	breast-conserving surgery
EORTC	European Organization for Research and Treatment of Cancer
ER	estrogen receptor
GEC-ESTRO	Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology
LCIS	lobular carcinoma in situ
LTC	local tumour control
LR	local recurrence
NSABP	National Surgical Adjuvant Breast and Bowel Project
OS	overall survival
PgR	progesterone receptor
RCN	Rare Cancer Network
RT	radiotherapy
RTOG	Radiation Therapy Oncology Group
TAM	tamoxifen
UKCCCR	United Kingdom Coordinating Committee on Cancer Research
USC	University of Southern California
VNPI	Van Nuys Prognostic Index
WBI	whole-breast irradiaton
VEGF	vascular endothelial growth factor

Introduction

Breast-conserving surgery (BCS) followed by radiotherapy (RT) has become the standard of care for the treatment of early-stage (St. I-II) invasive breast carcinoma [1, 2]. There is a consensus that standard treatment of ductal carcinoma in situ (DCIS) is surgical removal with negative margins either by BCS or, if this is not possible, by simple mastectomy [3, 4]. However, controversy exists regarding the value of RT after BCS [3–8]. Before mammographic screening, diagnosis of DCIS was rather incidental, as most cases were identified with a palpable mass, nipple discharge or Paget's disease of the nipple. With the advent of breast-screening, the incidence of DCIS has increased from less than 1% to more than 10% of newly diagnosed breast cancers [5, 6]. The percentage of carcinoma in situ (including DCIS and lobular carcinoma in situ; LCIS) in screened population was reported to be in the range of 8.5 to 26% [6]. Parallelly, during the 20-year period between 1981–2001, the percentage of patients with DCIS treated with BCS increased dramatically from 11% to more than 70% in the USA [9]. However, only less than 40% of patients treated with BCS received postoperative RT [9]. Therefore, there is an emerging need to optimize local treatment strategies for the conservative management of DCIS.

In this article, we review the role of RT in the management of DCIS. Retrospective and prospective trials and meta-analyses published in the MEDLINE database between 1975 and November 2007, and recent issues of relevant journals/handbooks were searched for items relating to DCIS, BCS and RT.

Non-randomised Studies Using Conservative Surgery Alone

BCS without postoperative RT has been widely used for the treatment of DCIS (Table 1) [10–19]. The largest series of 256 patients was reported by Schwartz et al. [18]. At a median follow-up of 66.5 months (range: 12–247 months), there have been 71 second ipsilateral breast recurrences (27.7%), including 26 invasive (37%) and 45 DCIS only (63%) recurrences. The 10-year actuarial local recurrence

(LR) rate was 41% with the long-term projection of LR being as high as 50% at 20 years.

Recently, data of 222 patients who were treated by excision alone for mammographically detected DCIS in 4 institutions from the Boston region were analyzed retrospectively [15]. Patients were treated between 1987 and 2004. Tamoxifen (TAM) was administered to 31% of the cohort. At a median follow-up of 4.6 years, LR was detected in 8.6% of the patients and was evenly distributed between invasive and DCIS recurrences.

Blamey et al. [12] reported on the experience at the Nottingham City Hospital from 1988 through 2000, including 178 women who had been treated with wide local excision alone with circumferential margins clear to a depth of 10 mm. At a median follow-up of 38 months (range: 6–150 months), there were 21 LRs (12%): 12 of them were in situ (57%) and 9 invasive (43%). The actuarial rate of LR was 22% at 10 years.

In the Danish nation-wide single-arm prospective study of in situ carcinoma of the breast (DBCG 82-IS), a total of 275 women treated with excision alone were registered from 1982 to 1989 [17]. This series included 168 cases of DCIS (with or without accompanying LCIS). Within a median follow-up of 10 years, a crude LR rate of 30.4% (51 cases) was found, of which 49% (25 cases) recurred as invasive carcinomas.

Another single-arm prospective study of wide excision alone for low-risk DCIS was initiated in 1995 at the Dana-Farber/Harvard Cancer Center [19]. Entry criteria included DCIS of grade 1 or 2 with mammographic extent of ≤25 mm treated with wide excision with final margins of ≥1 cm or re-excision without residual DCIS. In 2002, the study was closed to accrual with 158 patients entered, because the number of LRs met the predefined stopping rules. At a median follow-up of 40 months, 13 patients (8.2%) developed a LR as a first site of treatment failure, corresponding to a 5-year actuarial rate of 12%. Nine patients (69%) experienced in situ only and four (31%) invasive LRs.

In other smaller retrospective studies of BCS alone, similar results were found with annual LR rates ranging between 2.5 and 4.1% (see Table 1) [10, 11, 13, 16]. The single study of Lagios et al. [14] reported an annual LR rate of less than 2% (i.e. 1.5%) with an overall LR rate of 22% at 15 years.

As a summary of non-randomised studies on BCS alone, it seems that conservative surgery without RT is far from satisfactory as concerns local tumour control (LTC). Even in highly selected low-risk groups of DCIS, the 10-year ipsilateral breast recurrence rate is unacceptably high (i.e. 22 to 41%; see Table 1). To date, there are insufficient prospective (and retrospective) data to support the hypothesis that excision alone may be the adequate local treatment strategy in patients with low-risk DCIS.

Non-randomised Studies Using Conservative Surgery Plus Radiotherapy

Based on the long-term success of BCS plus RT in the treatment of stage I-II invasive breast carcinoma [1, 2], this treatment strategy was widely tested for DCIS (Table 2) [20–33].

Solin et al. [27] reported the largest multi-institutional series of 1003 mammographically detected DCIS patients treated with BCS and RT. At a median follow-up of

Table 1 Results of non-randomised studies using conservative surgery alone

Author	Institute/city	Patient no.	Median FUP (years)	5-y LR (%)	10-y LR (%)	Annual LR (%)
Schwartz et al. [18]	Philadelphia	256	5.5	24	41	4.1
MacAusland et al. [15]	Boston	222	4.6	9[a]	NR	2.0
Blamey et al. [12]	Nottingham	178	3.2	12[a]	22	2.2
Ottesen et al. [17][b]	DBCG 82-IS	168	10	NR	30[a]	3.0
Wong et al. [19][b]	Dana-Farber/Harvard Cancer Center/Boston	158	3.3	12	NR	2.4
Lagios et al. [14]	San Francisco	79	11	NR	22[c]	1.5
Arnesson et al. [10]	Linköping	38	5	13[a]	NR	2.6
Baird et al. [11]	British Columbia	30	3.2	13[a]	NR	4.1
Carpenter et al. [13]	Guildford	28	3.2	18[a]	23[d]	3.3
Millis et al. [16]	Royal Marsden Hospital	8	10	NR	25[a]	2.5
All patients		1,165	3.2–11	9–24	22–41	1.5–4.1

FUP follow-up period; *LR* local recurrence; *NR* not reported; *DBCG* Danish Breast Cancer Group.
[a] Crude rate
[b] Prospective study
[c] 15-year actuarial rate
[d] 7-year actuarial rate

Table 2 Results of non-randomised studies using conservative surgery plus radiotherapy

Author	Institute/city	Patient no.	Median FUP (years)	5-year LR (%)	10-year LR (%)	Annual LR (%)
Solin et al. [27]	Multi-institutional	1,003	8.5	5	10	1.3
Forquet et al. [29]	Institut Curie/Paris	343	7.7	NR	11[a]	1.4
Nakamura et al. [30]	Univ. Southern California	260	8.8	11	24[b]	2.0
Ben-David et al. [21]	Univ. of Michigan	200	6.2	6	10	1.0
Jhingran et al. [31]	M. D. Anderson/Houston	150	6.3	4	12	1.2
Amichetti et al. [20]	Italian multicentric study	112	6.5	7	9	0.9
Hiramatsu et al. [32]	Joint Center/Boston	76	6.2	4	15	1.5
Ray et al. [26]	Palo Alto	58	5.1	9[c]	11[a]	1.4
McCormick et al. [33]	Memorial Sloan-Kettering	54	3	22[d]	NR	3.7
Stotter et al. [28]	M. D. Anderson/Houston	44	7.7	NR	9	0.9
All patients		2,300	3–8.8	4–22	9–24	0.9–3.7

FUP follow-up period; *LR* local recurrence; *NR* not reported.
[a] 8-year actuarial rate
[b] 12-year actuarial rate
[c] Crude rate
[d] 6-year actuarial rate.

8.5 years (range: 0.2–24.6 years) there were only 100 LRs in the treated breast, yielding a 10-year actuarial LR rate of 10%.

Fourquet et al. [29] reported the experience of the Institute Curie over a 30-year period (1967 to 1996). Among 601 DCIS patients, 343 were treated with wide excision plus RT. Overall 39 LRs (8.8%) were observed during the study period: 9 recurrences (23%) consisted of DCIS only, 27 (69%) contained invasive cancer, and the histology of recurrence was unknown in 2 (8%) patients. The 8-year actuarial rate of LR was 11%.

Nakamura et al. [30] examined a database of 260 patients treated for DCIS with excision and RT between 1979 and 2002 at either the Van Nuys Breast Center or the University of Southern California Comprehensive Cancer Center. The median follow-up for all patients was 105 months. Forty-eight patients (18%) had recurrence in the treated breast and 22 of these (46%) were invasive. At 12 years, the actuarial LR rate was 24%.

The University of Michigan retrospective series consisted of 198 patients with 200 DCIS lesions treated with BCS and RT [21]. Median follow-up was 6.2 years (range: 0.8–18.2 years). The 5- and 10-year cumulative rates of in-breast only failure were 6% and 10%, respectively.

The M. D. Anderson Cancer Center reported 150 patients with DCIS treated with surgical excision and RT between 1980 and 1997 [31]. At a median follow-up of 63 months (range: 7–288 months), 12 patients (8%) had LR. The actuarial rate of LR at 5 and 10 years was 4% and 12%, respectively.

In the retrospective North-Italian multi-institutional study, data of 112 women with DCIS were collected [20]. At a median follow-up of 66 months, 8 LRs (7%) were observed, 4 intraductal and 4 invasive. A 5- and 10-year actuarial LR rate of 7% and 9% was obtained.

In other retrospective studies of BCS plus RT (with smaller sample sizes), similar results were found with annual LR rates of less than 2% (see Table 2) [23, 26, 28, 32], except McCormick et al. [33], who reported an actuarial LR rate of 22% at 6 years in a series of 54 patients. The study patients were treated between 1977 and 1988 and the majority of these patients had unknown (60%) or close/involved (10%) surgical margins.

The collective experience obtained from retrospective studies of DCIS suggests that excision with clear surgical margins followed by whole-breast irradiation (WBI) yields acceptable LTC (i.e. annual LR rate <2%), comparable to that achieved in early-stage invasive breast carcinomas [1].

Comparative Non-randomised Studies of Conservative Surgery with or without Radiotherapy

Several retrospective non-randomized studies (including single-institutional and multicenter experience) have been published in the literature comparing LTC for DCIS patients treated with or without RT after conservative surgery (Table 3) [22–25, 34–47].

The Van Nuys/University of Southern California Experience

The largest retrospective comparative series (909 patients) was reported by Silverstein et al. [42, 43]. Of all, 326 patients underwent mastectomy, 237 excision plus RT, and 346 excision alone. Selection between treatment options

Table 3 Results of comparative non-randomised studies of conservative surgery with or without radiotherapy

Author	Institute/city	Patient no. by treatment	Median FUP (years)	5-year LR (%)	10-year LR (%)	Annual LR (%)
Boyages et al. [56]	Meta-analyis	*RT:* 1452	5.2	8.9	NR	1.7
		OBS: 1148	5.7	22.5	NR	3.9
Silverstein et al. [42, 43]	Van Nuys/Univ. Southern California	*RT:* 237	8.8	12	20	2.0
		OBS: 346	5.8	19	28	2.8
Cutuli et al. [36]	French multicentric study	*RT:*435	7.6	9	14[b]	1.7
		OBS: 136		24	31[b]	3.9
van der Velden et al. [45]	Cancer Center East Netherlands	*RT:* 153	4.9	9	NR	1.8
		OBS: 237		25	NR	5.0
Omlin et al. [39]	RCN multicentric study	*RT:* 150 (boost)	6	NR	14	1.4
		166 (no boost)		NR	28	2.8
		OBS: 57		NR	54	5.4
Vargas et al. [47]	William Beaumont Hospital	*RT:* 313	7	6	9	0.9
		OBS: 54		13	42[b]	5.2
Mascarel et al. [25]	Inst. Bergonié/ Bordaux	*RT:* 155	5.9	9[a]	NR	1.5
		OBS: 212		15[a]	NR	2.5
Meijnen et al. [38]	The Netherlands Cancer Institute	*RT:* 119	6.7	NR	9[b]	1.1
		OBS: 91		NR	16[b]	2.0
Chan et al. [35]	Manchester	*RT:* 27	3.9	11[a]	NR	2.8
		OBS: 178		16[a]	NR	4.1
Cataliotti et al. [34]	Florence Hospital	*RT:* 97	7.6	6	11	1.1
		OBS: 105		13	22	2.2
Park et al. [40]	Joint Center/Boston	*RT:* 136	8.7	3	NR	0.6
		OBS: 59	8	10	NR	2.0
Ringberg et al. [41]	South Sweden Breast Cancer Group	*RT:* 66	6.2	6	NR	1.2
		OBS: 121		21	NR	4.2
Jha et al. [24]	Newcastle	*RT:* 94	7.3	1[a]	NR	0.1
		OBS: 30		17[a]	NR	2.3
Van Zee et al. [46]	Memorial Sloan-Kettering/New York	*RT:* 65	6.2	10[c]	NR	1.7
		OBS: 92		21[c]	NR	3.5
Dixon [37]	Edinburgh Breast Unit	*RT:* 38	6.3	11[a]	NR	1.7
		OBS: 95		17[a]	NR	2.7
Fisher ER et al. [22]	NSABP-B-06[d]	*RT:* 27	6.9	7[a]	NR	1.0
		OBS: 21		43[a]	NR	6.2
Gallagher et al. [23]	Harvard/Boston	*RT:* 4	8.1	0[a]	NR	0
		OBS: 13	8.3	38.5[a]	NR	4.6
All patients		*RT:* 3734	3.9–8.8	0–12	9–28	0–2.8
		OBS: 2995	3.9–8.3	10–43	16[b]–54	2.0–6.2

FUP follow-up period; *LR* local recurrence; *RT*: radiotherapy; *OBS* observation; *NR* not reported; *RCN* Rare Cancer Network
[a] Crude rate
[b] 8-year actuarial rate
[c] 6-year actuarial rate
[d] subgroup of patients from the NSABP-B-06 trial found to have DCIS on central pathology review

was not based on randomisaton. Until 1988, all patients who elected breast conservation were advised to receive breast irradiation. Treatment policy was changed in 1989, and patients with surgical margins clear by at least 1 mm were offered careful clinical follow-up without RT. The 10-year actuarial LR rates after BCS with or without RT were 20% and 28%, respectively (p=0.06). Median times to LR were 57 and 25 months, respectively (p<0.01). It is to be noted that significantly more patients had close (<1 mm) margins in the RT group compared to the group treated with excision alone (35% vs. 19%). Furthermore, the mean follow-up of patients treated with excision alone was 36 months less than that of patients treated with RT. Nevertheless, in a multivariate analysis, the addition of RT after excision reduced the relative risk of LR by 55% (p=0.0002).

Silverstein et al. [42, 43, 48] found that among 30 possible prognostic factors evaluated nuclear grade, tumour

size, margin width, comedo necrosis, and patient age were significant predictors of LR. Combining these predictors they built the original Van Nuys Prognostic Index (VNPI), which was later modified (USC/VNPI) and offered this as a simple and clinically reliable scoring system supporting the treatment decision-making process (Tables 4 and 5). According to their treatment guidelines, patients with low (i.e. 4 to 6) USC/VNPI scores can be treated with excision alone, as no significant increase in LTC was observed with RT. Patients with intermediate (i.e. 7 to 9) scores showed an average of 10 to 15% LR-free survival benefit with the addition of RT. Although patients with high (i.e. 10 to 12) scores showed the greatest absolute benefit from RT, they experienced LR rates of almost 50% at 5 years. Thus, these patients were proposed as candidates for mastectomy with the option of immediate reconstruction.

Although the VNPI (and USC/VNPI) was validated by the results of Silverstein's group [42–44, 49], it should be tested in prospective randomized trials before being generally accepted [50, 51]. Indeed, in some other retrospective and prospective series, a significant benefit of RT was observed in patients with low VNPI scores [25, 41, 52–54]. In a recent analysis by MacAusland et al. [15], neither the VNPI nor the margin width alone were found to be valid tools to assist in the stratification of patients with different risks of LR at 5 years after excision alone. The group of the University Hospital of South Manchester confirmed that the VNPI score predicted LR-free survival, but 78% of their patients clustered into the group with moderate risk of LR [55]. The authors concluded that the VNPI lacked discriminatory power in subgrouping patients by LR risk, therefore it cannot be used to stratify patients for adjuvant RT after BCS. Based on the shortcomings of the VNPI, Fisher et al. [50] concluded that justification was lacking for its use as a part of the strategy for the treatment of DCIS.

French Multi-center Experience

Cutuli et al. [36] analysed the results of 716 women treated in 8 French Cancer Centres from 1985 to 1992. Among these patients 571 underwent BCS with (n=435) or without (n=136) RT. The 8-year LR rates were 13.9% and 31.3%, respectively (p=0.0001). LRs were invasive in 60% and 59% in the two groups, respectively. The rate of distant metastases was 1.4% in the BCS plus RT group, whereas it was 4.4% in the BCS alone group. Among the 60 cases with invasive LR, 20% developed distant metastases. In multivariate analysis, young age (<40 years) and incomplete excision were significant factors for LR in the BCS plus RT group.

Comprehensive Cancer Centre East Netherlands (CCCEN) Experience

Recently, van der Velden et al. [45] reported outcomes after different treatment strategies for DCIS for a geographically defined population in East Netherlands. A total of 798 patients were treated between 1989 and 2003 in eight hospitals of the CCCEN. Among these, 237 patients were treated with BCS alone, and 153 with BCS followed by RT. The 5-year LR rate was 25% for the BCS only group, and 9% for the BCS plus RT group (p<0.01). In multivariate analysis the only histopathologic variable significantly related to LR was the presence of comedo necrosis.

Retrospective Multicentre Study of the Rare Cancer Network

Recently, the Rare Cancer Network evaluated the outcome data of young (≤45 years) women with DCIS treated with BCS [39]. Records of 373 patients taken from 1978 to 2004 were analysed retrospectively. Patients were treated in 18 institutions from 11 countries. Fifty-seven women (15%) were treated with BCS alone. 166 patients (45%) received WBI (median dose: 50 Gy) without tumour bed boost, and 150 (40%) received WBI with boost up to a median total dose of 60 Gy. The 10-year actuarial rate of LR was 54% in patients given no RT, 28% in those given RT without boost, and 14% in those given RT with boost. RT without boost decreased the relative risk of LR with 67%. Tumour bed boost further decreased the risk of recurrence with 55%.

William Beaumont Hospital Series

The largest single-institution experience was reported from the William Beaumont Hospital [47]. Between 1981 and 1999, 367 patients were managed with BCS (54 without

Table 4 The modified USC/VNPI scoring system

Predictor	Score		
	1	2	3
Size (mm)	≤15 mm	16–40	≥41
Margin width (mm)	≥10	1–9	<1
Pathologic classification	NG 1–2 without necrosis	NG 1–2 with necrosis	NG 3
Age (years)	>60	40–60	<40

USC/VNPI: University of Southern California/Van Nuys Prognostic Index; NG: nuclear grade.

Table 5 Treatment guidelines by the modified USC/VNPI scoring system

Score	Treatment
4–6	Excision alone
7–9	Excision + RT
10–12	Mastectomy

USC/VNPI University of Southern California/Van Nuys Prognostic Index; *RT*: radiotherapy

and 313 with adjuvant RT). Of these 313 patients, 298 (95%) also received a supplemental boost of 16 Gy to the tumour bed. The 5-year LR rate with or without RT was 6% and 13%, respectively. On multivariate analysis breast RT reduced the risk of LR with 82%. Other negative predictors for LR were younger age, low (≤9 MeV) electron boost energy, and final surgical margins ≤2 mm. Furthermore, LR was found to be associated with increased rates of distant metastasis and breast cancer death.

Institut Bergonié, Bordeaux Experience

Mascarel et al. [25] studied the LR rate in their retrospective series of 367 patients by applying the VNPI. One hundred and fifty five patients (42%) had RT, while 212 (58%) were treated with BCS alone between 1971 and 1995. At a median follow-up of 71 months, 14 LRs (9%) occured in the BCS plus RT group, whereas 32 (15.1%) in the BCS only group. In accordance with the findings of Silverstein et al. [42, 43], in the subgroup of patients with intermediate VNPI (score 5 to 7) RT reduced the LR rate from 19.4% to 13.8%. However (contrary to Silverstein's results) all LRs (n=17; 12.7%) in the low VNPI group (with score 3 or 4) occured in the patients who received no RT.

In all other retrospective comparative series (with smaller sample sizes) RT reduced the annual LR rate from 2.0–6.2% to 0–2.8%, and none of the studies identified a subgroup of patients who would not benefit from RT after BCS (see Table 3) [14, 22–24, 34, 35, 38, 40, 41, 46].

Meta-analysis of Retrospective Studies

In 1998, Boyages et al. [56] published a meta-analysis of available retrospective studies of different local treatments for DCIS (although the patients and early results of the prospective randomised NSABP-B-17 trial was also included in the analysis). Overall 1,148 patients treated with BCS alone and 1452 women treated with BCS plus RT were included. The meta-analysis suggested a LR rate of 22.5% (with 95% confidence interval [CI] of 16.9 to 28.2%) for studies employing BCS alone, and 8.9% (CI: 6.8 to 11.0%) for BCS with RT. These figures indicated a clear and statistically significant difference between the recurrence rates of the two treatment options, despite the likelihood that patients undergoing BCS alone were more likely to have smaller, and possibly low-grade lesions with clear margins. The authors also cautioned against the routine use of the VNPI without further clinical validation.

Randomised Studies

To date, mature results of 5 multicentric randomised studies evaluating local (and systemic) treatment strategies for DCIS have been published [50, 52–54, 57–62]. In 3 of these trials (NSABP-B-17, EORTC-10853, and SweDCIS trials) outcome of patients treated with BCS alone was compared to that of BCS followed by RT [52, 58, 59]. One study (NSABP-B-24 trial) evaluated the possible benefit from the addition of TAM to RT [60]. Finally, the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) assessed the effectiveness of adjuvant RT and TAM in a 4-arm trial [61]. Design and outcome of these trials are summarized in Table 6.

NSABP-B-17 Trial

The earliest randomised DCIS trial (conducted from 1985 to 1990) was designed to assess the value of RT after BCS [59]. The trial compared excision alone with excision and postoperative breast RT. Radiotherapy consisted of 50 Gy WBI given in 25 fractions. Only 9% of patients in the RT arm received 10 Gy boost to the tumour bed. Overall 818 women with DCIS removed with pathologically free margins were enrolled. However, inking of specimen margins and specimen mammography were not routinely used in that era. Thus, on central pathology review 17% of patients had uncertain or involved margins [53]. The 12-year rate of LR was 31.7% after excision and 15.7% after excision plus RT ($p<0.000005$) [50]. Seventy-six percent of all LRs were found to be at the same site as the index DCIS [53]. The 12-year overall survival (OS) was virtually identical in the two groups (86% and 87%, respectively) [50]. Predictive factors for LR were analyzed in the 8-year follow-up report [53]. In univariate analysis, nuclear grade, comedo necrosis, margin status, and histologic tumour type were significant prognostic variables for LR. In multivariate analysis, only comedo necrosis was found to be an independent predictor for LR. However, in each prognostic subgroup an overall benefit from the use of RT was observed.

EORTC-10853 Trial

The EORTC conducted a trial similar to NSABP-B-17 between 1986 and 1996 [52, 62]. Overall 1010 patients with DCIS lesions up to 5 cm and removed with free

Table 6 Design and outcome of randomised DCIS studies

Study	Study period	Median FUP (years)	Patient no. By treatment arm	5-year LR (%)	10-year LR (%)	Annual LR (%)	RR
NSABP-B-17 [50, 53, 59]	1985–90	10.8	*RT:* 413	10.4	15.7%[a]	1.3	0.43
			OBS: 405	20.9	31.7%*	2.6	1
EORTC-10853 [52, 62]	1986–96	10.5	*RT:* 507	9[c]	15	1.5	0.53
			OBS: 503	16[c]	26	2.6	1
SweDCIS [54, 58]	1987–99	5.2	*RT:* 526	7	NR	1.4	0.33
			OBS: 520	22	NR	4.4	1
NSABP-B-24 [50–60]	1991–94	6.9	*RT+TAM:* 902	6	7.7[b]	1.1	0.69
			RT: 902	9.3	11.1[b]	1.6	1
UKCCCR [61]	1990–98	4.4	*RT+TAM:* 316	6.6[d]	NR	1.5	NR
			RT: 267	8.2[d]	NR	1.9	0.38[f]
			TAM: 567	17.8[d]	NR	4.0	0.90 (NS)[g]
			OBS: 544	21.9[d]	NR	5.0	1
All studies:	1985–99	4.4–10.8	*RT+TAM:* 1218	6–6.6	7.7[b]	1.1–1.5	0.69[e]
			RT: 2615	7–10.4	11.1[b]-15.7*	1.3–1.9	0.33–0.53
			TAM: 567	17.8	NR	4	0.90 (NS)
			OBS: 1972	16–22	26–31.7	2.6–5	1

NSABP National Surgical Adjuvant Breast and Bowel Project; *EORTC* European Organization for Research and Treatment of Cancer; *UKCCCR* United Kingdom Coordinating Committee on Cancer Research; *FUP* follow-up period; *LR* local recurrence; *RR* relative risk; *RT* radiotherapy; *TAM* tamoxifen; *OBS* observation; *NR* not reported; *NS* not significant.

[a] 12-year actuarial rate

[b] 7-year actuarial rate

[c] 4-year actuarial rate

[d] Crude rate —note, that all breast events (ipsilateral plus contralateral) were reported together

[e] Risk reduction compared to RT alone;

[f] Risk reduction compared to no RT (including patients treated with or without TAM)

[g] Risk reduction compared to no TAM (including patients treated with or without RT).

margins were randomised to excision only or excision plus RT. However, at central pathology review pathologic margin status was involved or close (≤1 mm) in 8.5% and not specified in 13.5% of patients [57]. Radiotherapy consisted of 50 Gy WBI and only 5% of the patients received a tumour bed boost (median dose of 10 Gy). The 10-year rate of LR was 26% after excision alone and 15% after excision plus RT ($p<0.0001$) [52]. The 10-year OS rate was 95% in both arms. In multivariate analysis, young age (≤40 years), symptomatic detection of DCIS, grade 2 or 3 DCIS, solid or cribriform growth pattern, and margins that were not free (positive, ≤1 mm or unknown) were associated with an increased risk of LR [52, 57]. Similarly to the findings of the NSABP-B-17 trial [50, 53], RT reduced the risk of LR in all clinical and pathologic subgroups with a homogenous treatment effect across the levels of all factors considered [52, 57].

SweDCIS Trial

The third randomised trial comparing BCS to BCS and RT was conducted by the Swedish Breast Cancer Group [41, 58]. Between 1987 and 1999, 1046 patients were randomized either to RT or control. In the RT arm, treatment could be given either continuously (50 Gy over 5 weeks given in 25 fractions) or as a split course treatment (54 Gy given in two series with a gap of 2 weeks). No boost radiation was given to the tumour bed. Although the study protocol recommended radical surgery, microscopically uninvolved margins were not mandatory. Thus, surgical margins were positive and unknown in 112 (11%) and 94 (9%) patients, respectively. The 5-year cumulative incidence of LR was 7% in the RT group and 22% in the control group ($p< 0.0001$). Distant metastasis or breast cancer death occured in 9 cases in each treatment group. In multivariate analysis, a high nuclear grade and the presence of necrosis were found to be associated with a higher risk for developing LR. Radiotherapy conferred a reduction in LR in all subsets of patients, with even stronger effect in the absence of necrosis. The investigators could not delineate a group without RT which would have an annual risk of LR less than 2%.

NSABP-B-24 Trial

The NSABP-B-24 trial examined the effect of TAM for patients with DCIS treated with BCS and RT [50, 60]. Between 1991 and 1995, 1,804 patients were randomised to

receive TAM or placebo concurrently with RT. The same RT regimen was used as in the B-17 trial. However, women with DCIS excised with positive margins were also eligible for the study. As a consequence, among the study population 16% were enrolled with positive (and 10% with unknown) surgical margins. At the last update, the 7-year LR rate was 11.1% in the RT plus placebo group and 7.7% in the RT plus TAM group (p=0.02) [50]. Tamoxifen also significantly decreased the rate of all contralateral breast tumours (4.9% vs. 2.3%; p=0.01).

According to a later subgroup analysis, TAM reduced the risk of all breast cancer events by 59% (p=0.0002) in estrogen receptor (ER) positive tumours, which effect was not significant in patients with ER negative DCIS [8]. Age less than 50 years, positive margin status, clinically palpable tumours, and presence of comedo necrosis were significantly associated with a higher risk of LR [50, 60]. The 7-year OS was 95% in both groups. There was only a nonsignificant increase in the incidence of endometrial cancer in the TAM group (0.78% vs.0.33%; p=0.38).

UKCCCR Trial

The UKCCCR trial was aimed to assess the effectiveness of both adjuvant RT and TAM [61]. Between 1990 and 1998, 1,701 patients who underwent excision of DCIS with clear margins were randomised using a 2 × 2 factorial design, in which patients could be allocated to receive RT or not and/or to receive TAM or not. Radiotherapy consisted of 50 Gy WBI in 25 fractions over 5 weeks without a tumour bed boost. In the analysis of the effect of RT (1,030 patients), at a median follow-up of 4.4 years, the crude rate of LR was 5.6% with and 13.6% without RT (p<0.0001). In the TAM comparison (1,576 patients), the crude rate of LR was 12.8% with and 14.6% without TAM (p=NS). As the results showed no significant difference in the LR rates between patients in the control and TAM groups, the authors did not recommend the routine use of TAM in women older than 50 years with DCIS. There were too few deaths for a meaningful analysis of the cause of death by treatment arms.

Meta-analysis of Randomized Trials

Recently, Viani et al. [63] published a meta-analysis of the 4 randomised trial evaluating the value of RT in the treatment of DCIS. The pooled results of 3665 patients showed a 60% risk reduction of both invasive and in situ LRs with RT. There were no differences in distant metastasis and death rates between the RT and the observation arms. However, the likelihood of contralateral breast cancer was 1.53-fold higher in RT arms (3.85% vs. 2.5%; p=0.03). Although patients with high-grade DCIS and positive margins benefited most from the addition of RT, the authors could not identify a subgroup of women who did not need to be treated with RT.

Controversial Issues in the Treatment of DCIS-Ongoing Clinical Trials

Although both retrospective data and prospective randomised trials confirmed that all patients with DCIS have potential benefit from RT after BCS, there are several controversial issues in the treatment of DCIS, which should be explored in further prospective trials.

Is Radiotherapy Mandatory for all Women with DCIS Treated with BCS?

It is controversial whether a small (i.e. few percent) absolute gain in LTC without any survival benefit in the treatment of low-risk DCIS outweighs the potential morbidity, costs, and inconvenience associated with RT. Several ongoing trials were designed to clarify this issue [3, 8, 64]. The Radiation Therapy Oncology Group (RTOG) 9804 trial is comparing excision plus TAM plus RT to excision plus TAM alone for patients with grade 1–2 DCIS up to 2.5 cm diameter with clear margins of at least 3 mm. The UK DCIS II is a similar randomised trial comparing RT plus endocrine therapy with endocrine therapy alone for low-risk (ER positive, grade 1–2 and less than 30 mm, or grade 3 and less than 15 mm) DCIS. The randomised Hungarian DCIS trial that tests the possibility of avoiding RT in low risk cases and the role of tumour bed boost after WBI in high risk cases will be described later in this manuscript [65, 66].

Which Patients with DCIS Need a Tumour Bed Boost after BCS and WBI?

It has been shown in several prospective randomized trials on the treatment of invasive breast carcinoma that the addition of a boost dose after 50 Gy WBI significantly reduced the risk of LR [67, 68]. In the EORTC boost versus no boost trial, a boost dose of 16 Gy decreased the 10-year LR rate from 10.2% to 6.2% (p<0.0001) [67]. The absolute risk reduction by boost was the largest (from 23.9% to 13.5%) in patients ≤40 years of age. However, in the RT arms of all randomised DCIS trials, 50 Gy WBI without tumour bed boost was recommended [52, 58, 59]. One retrospective series of young (≤45 years) patients with DCIS suggested a similar magnitude of risk reduction (from 28% to 14% at 10 years) by 10 Gy boost irradiation [39]. Nonetheless, these findings should be confirmed in prospective randomized trials. The Breast International Group

(BIG) 3–07 trial is planning to compare the effectiveness of WBI (50 Gy in 25 fractions or 42.5 Gy in 16 fractions) to WBI plus 16 Gy boost.

Is Accelerated Partial Breast Irradiation A Valid Option for the Treatment of DCIS?

Pathological whole-organ studies of Holland et al. [69] suggested that typically DCIS is not a multicentric disease. This concept is supported by clinical data showing that LR after excision of DCIS appears in the vicinity of the index lesion in the majority (i.e. in 76% to 94%) of cases [20, 34, 41, 47]. Based on these findings, the necessity of giving WBI for all patients after BCS has been questioned, and several centers have evaluated the efficacy of accelerated partial breast irradiation (APBI) [70, 71]. In several Phase I-II studies [70, 71] and the Hungarian Phase III trial [72], APBI has been shown to produce similar LTC to standard WBI at least for a selected group of patients with early-stage invasive breast carcinoma. However, the experience with APBI is primarily derived from experience with invasive carcinoma, and there are no published series of APBI specifically for DCIS. An initial report on a Phase II APBI study using the MammoSite balloon catheter for pure DCIS has been published recently [73]. In that study, there were 2 LRs in 100 patients at a median follow-up of 9.5 months. The ongoing multicenter Phase III APBI trial of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) addresses this controversial issue and eligible patients for this study are enrolled by stratification according to the histologic type of the cancer (in situ versus invasive) [70]. A similar Phase III trial (NSABP-B-39/RTOG-0413) has also been activated in the United States [71].

Which Patients with DCIS Benefit from Adjuvant Hormonal Therapy?

The role of adjuvant TAM in patients with DCIS remains controversial due to the conflicting results of the NSABP-B-24 and the UKCCCR trials [50, 61]. As described previously in detail, while TAM provided a clear benefit in the NSABP-B-24 trial, the UKCCCR trial found only a non-significant effect in regard of all breast cancer events. Potential reasons for the different outcomes of these trials may be the higher rates of relatively young (<50 years) patients, low grade and ER positive tumours in the NSABP-B-24, as compared to the same parameters in the UKCCCR Trial [50, 61]. Treatment with TAM is associated with an excess incidence of endometrial cancer, thrombo-embolic events, and fatal stroke, although, these toxic effects are predominant in the higher age group. There is a need to identify those subgroups of patients with DCIS for whom the benefit of adjuvant TAM by decreasing the risks of LR and contralateral breast cancer would outweigh the risk of toxicity [74]. Thus, taking into account both the higher efficiency and the reduced toxicity, the use of TAM in premenopausal women with close/involved margins and ER positive DCIS, seems reasonable [8]. The superiority of modern aromatase inhibitors in invasive breast cancer, especially the striking effect on the incidence of contralateral breast cancer, and also the different toxicity profile, promoted the testing of aromatase inhibitors in DCIS. Interestingly, the expression of the aromatase enzyme in tumour cells was higher in DCIS than in invasive cancer [75]. The clinical significance of HER2 overexpression typical in high grade DCIS, and related resistance to TAM in invasive cancers, is not known. Thus, the use of aromatase inhibitors in postmenopausal patients with DCIS could be a promising option. To explore this possibility, the NSABP-B-35 and the IBIS II randomised trials comparing adjuvant TAM to anastrozole, and the NCIC MAP.3 testing exemestane were initiated [76].

Is There a Role for Molecular Prognostic Factors in the Treatment of DCIS?

During the last decade, numerous molecular markers have been identified to characterize breast carcinoma. Some of these makers (e.g. ER, PgR, HER-2/neu) have been proven to have prognostic significance and therapeutic implications in invasive carcinomas [77, 78]. In contrast, there is insufficient information available concerning the prognostic significance of biologic markers in DCIS [78–80]. It is likely that distinct molecular elements have a role in the genesis of DCIS and may be associated with the risk of LR after local therapy [80]. There are some data suggesting that overexpression of certain biologic markers (such as HER-2/neu, p53, Ki-67, VEGF, and p-21) in DCIS lesions may be associated with a higher risk for developing LR and/or progressing into an invasive carcinoma [77, 78]. On the contrary, the higher expression of bcl-2 and E-cadherin have been linked to better differentiation and less aggressive behaviour of DCIS [78, 81]. The expression of other markers (e.g. p16, p27, and TGF-β) have been documented in DCIS, but their prognostic significance is still uncertain [78].

In the study of Ringberg et al. [77] mutated p53 and elevated Ki-67 levels were significantly associated with a higher risk of LR. However, in a series of 151 patients treated with BCS alone at the Thomas Jefferson University in Phiadelphia, no significant association was found between the expression of a wide variety of biologic markers including ER, PgR, HER-2/neu, Ki-67, p21, and bcl-2, and the rate of LR [81].

Cytokeratin profile also seems to hold promise as prognostic marker in DCIS [82]. Recently, Tang et al.

[83] found that DCIS can be subdivided into 3 subgroups (e.g. luminal, basal/stem, and null) according to the expression patterns of cytokeratin cell origin markers. Also, high-grade DCIS were significantly more often of the basal and stem cell subtypes. Several studies have found that invasive breast cancers of luminal subtype have a better prognosis than those expressing the features of the basal/stem cell subtypes. However, clinical applicability of these informations for DCIS is not clear yet.

Despite significant controversies, molecular biologic markers may provide useful information in addition to traditional histopathologic prognostic factors. Zaugg et al. [80] suggested the retrospective analysis of potential molecular key targets from biopsy materials collected in carefully designed DCIS clinical trials. In the future, molecular profiling and simultaneous evaluation of multiple genes will be of special interest and might help to identify individual risk-adapted management strategies for patients with DCIS [64, 78].

The Hungarian Multicentric Randomised DCIS Trial

The Hungarian multicentric randomised trial (activated in May 2000) is an ongoing 6-arm clinical study evaluating some of the above mentioned controversial issues in the treatment of DCIS [65, 66]. The design of the study is summarized in Fig. 1. Eligibility criteria include patients with DCIS (without microinvasion or lymph node involvement if staged for nodal status and with or without accompanying LCIS or Paget's disease of the nipple) treated with any type of BCS using modern pathological tissue processing (including specimen mammography and inking of the specimen margins) according to the recommendations of the 1997 Consensus Conference on the Classification of DCIS [84]. Patients eligible for the study are being randomised to 6 arms of the trial according to stratification to risk groups after full informed consent. Low and intermediate-risk patients (grade 1–2 lesions without comedo necrosis and excised with free margins of at least 5 mm) are randomised to observation or 50 Gy WBI. High-risk patients (non-high grade lesions with comedo necrosis and/or grade 3 tumours and/or lesions with free margins of less than 5 mm) are allocated to receive 50 Gy WBI or 50 Gy WBI plus 16 Gy tumour bed boost. Very high-risk patients (i.e. patients with microsopically involved surgical margins) are randomised to 50 Gy WBI plus 16 Gy tumour bed boost or reoperation (reexcision plus RT or mastectomy alone). Adjuvant endocrine therapy (TAM or aromatase inhibitor) is recommended by the study protocol for all patients with ER positive lesions. Besides routine ER and PgR determination, central pathology review including the evaluation of the molecular markers HER-2/neu, Ki-67, p53, and bcl-2 is carried out. To date, 278 patients have been enrolled in the study. Preliminary results on clinical outcome and central pathology review have been reported recently in abstract form [65, 66].

Summary

Based on available evidence obtained from retrospective and prospective clinical trials, all patients with DCIS have potential benefit from RT after BCS. Further prospective studies are warranted to identify subgroups of low-risk patients with DCIS for whom RT can be safely omitted. Until long-term results of ongoing studies on outcome of BCS alone (with or without endocrine therapy) in special subgroups of patients will be available, RT should be routinely recommended after BCS for all patients except those with contraindication.

The role of adjuvant endocrine therapy in patients with DCIS remains controversial. It is not yet clear which subgroups of patients might benefit the most in regard of reduction of risks of both LR and contralateral breast cancer that would outweight the risks of TAM. However, it seems reasonable to consider TAM for premenopausal patients with ER positive DCIS who have a high risk of LR and lower risk of adverse events from TAM.

The role and indication of aromatase inhibitors, boost irradiation of the tumour bed, and accelerated partial breast irradiation in the treatment of DCIS should be further explored in ongoing and future clinical studies.

Identification of specific molecular prognostic markers associated with the biological behaviour and prognosis of

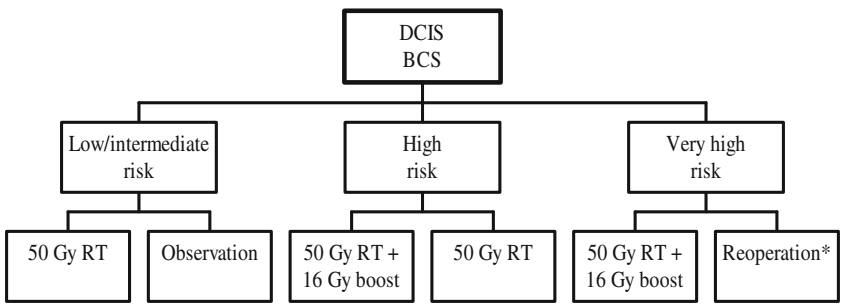

Fig. 1 Design of the Hungarian multicentric randomised DCIS trial. *DCIS* ductal carcinoma in situ; *BCS* breast-conserving surgery; *RT* radiotherapy. *Asterisk* reoperation—mastectomy without RT or reexcision with clear margins plus RT following randomisation in the risk group indicated by the combined analysis of all pathology findings

DCIS will help to clarify controversial issues in the management of DCIS and contribute to a more individualized treatment of patients diagnosed with DCIS.

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