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Management of Ductal Carcinoma In Situ Patients Receiving Postoperative Radiotherapy after Breast Conserving Surgery: Hacettepe Experience

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ABSTRACT

We retrospectively evaluated our therapetic results in ductal carcinoma in situ (DCIS) patients treated with postoperative radiotherapy following breast-conserving surgery (BCS). Sixty-seven DCIS patients were treated with curative radiotherapy (RT) after BCS, in our department from December 1998 to January 2008. All patients have been treated with 6 MV photon energy on lineer accelerator machine. Radiotherapy treatment fields were opposed tangential to the whole breast. A total dose of median 50 Gy (48-50 Gy) was delivered in five fractions in a week. In twenty patients, boost dose to the tumour region was applied. Fifty patients received systemic hormonotherapy. Median follow-up time was 44 moths (range 12-122 months). Five-year OS, DFS and local control rates were found as 96%, 97% and 97%, respectively. There was only one ipsilateral breast recurrence in our study (2%). Two patients died due to other causes except disease (3%). Grade III dermatitis was seen in only one patient (2%), and there was no serious acute side effects in 41 patients (63%). There was no late side effect in our patients. Sixty-two patients were alive without evidence of tumour recurrence, with their intact breast and with good cosmesis. Our survival rates and side effects were in consistent with literature, and RT is an effective option for DCIS patients following BCS.

Keywords: Ductal carcinoma In Situ, Radiotherapy, Breast conserving surgery

ÖZET

Duktal Karsinoma İn Situ Olgularında Meme Koruyucu Cerrahi Sonrası Postoperatif Radyoterapi: Hacettepe Deneyimi

Bu retrospektif çalışmada meme koruyucu cerrahi (MKC) sonrası postoperatif radyoterapi uyguladığımız duktal karsinoma in situ (DKİS) olgularında tedavi sonuçlarımız retrospektif olarak değerlendirilmiştir. Anabilim Dalımız'da Aralık 1998 ile Ocak 2008 arasında 67 DKİS olgusuna MKC sonrası küratif radyoterapi uygulanmıştır. Tüm hastalar 6 MV fotonlarla lineer akseleratör cihazı ile tedavi edilmiştir. Radyoterapi iki paralel tanjansiyel alanla tüm memeye uygulanmıştır. Ortanca total doz 50 Gy (48-50 Gy) haftada 5 fraksiyonlar halinde verilmiştir. Yirmi hastada tümör yatağına ek doz uygulanmıştır. Elli olgu sistemik hormonal tedavi almıştır. Ortanca izlem süresi 44 aydır (12-122 ay). 5-yıllık genel sağkalım, hastalıksız sağkalım ve lokal kontrol oranları sırası ile %96, %97 ve %97 olarak saptanmıştır. Çalışmamızda sadece 1 ipsilateral nüks (%2) gözlenmiştir. İki hastamız hastalık dışı nedenlerle kaybedilmiştir (%3). Bir hastada (%2) 3. derece dermatit saptanırken, 41 olguda (%63) hiçbir ciddi akut yan etki saptanmamıştır. Olgularımızda ciddi geç yan etki gözlenmemiştir. Altmış iki olgu iyi kozmetik sonuçla hastalıksız hayattadır. Sağkalım ve yan etki sonuçlarımız literatür ile uyumlu olup, DKİS olgularında MKC sonrası radyoterapi etkin bir tedavi seçeneğidir.

Anahtar Kelimeler: Duktal karsinoma İn Situ, Radyoterapi, Meme koruyucu cerrahi

INTRODUCTION

Ductal carcinoma in situ (DCIS) is characterised by the development of cancerous cells in the milk ducts of the breast, and is a risk factor for invasive breast cancer development. Unlike invasive breast cancer, DCIS either has not yet invaded beyond its intraductal origin or may never invade beyond basal membrane. The diagnosis and management of DCIS is highly complex with many unanswered questions, including the fundamental natural history of untreated disease. 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.[1] 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%.[2]

There is a consensus that standard treatment of ductal carcinoma in situ (DCIS) is surgical removal of lesion with negative margins either by breast conserving surgery (BCS) or, if this is not possible, by simple mastectomy. However, controversy exists regarding the value of radiotherapy (RT) after BCS particularly for low-risk cases.[3] Regarding the surgical management of DCIS, the preffered choice of many women and surgeons is BCS. However, the main risk of inadequately removing all the DCIS is either a recurrence of DCIS or the development of invasive breast cancer later even with a risk of progression to metastatic disease. Radiotherapy (RT) is applied to the whole breast after BCS to reduce the risk of developing recurrent disease (either DCIS or invasive breast cancer).[1-3] Three large multicenter randomized control trials (RCTs) have documented the benefits of RT after BCS with 50 to 60% reduction of the risk of local recurrence (LR).[4] However, only less than 40% of patients treated with BCS received postoperative RT.[5]

Recently, several studies showed that RT after BCS is an effective option for local control with acceptable toxicity. However, the debate remains whether there is a low-risk group in which RT could be omitted safely. Several studies have used a decision model to examine DCIS treatment strategies, but none modeled DCIS as a heterogeneous disease with different recurrence risks. Therefore, there is an emerging need to optimize local treatment strategies for the conservative management of DCIS. In this study, we retrospectively evaluated our DCIS patients treated with radiotherapy after BCS.

Table 1. Characteristics of the patients

	Number of Patients (%)
Age	
<40 age	5 (8)
40-60 age	45 (69)
>60 age	15 (23)
Menapausal status	
Premenaposal	28 (43)
Postmenaposal	37 (57)
Symptoms at diagnosis	
Mass	26 (40)
Nipple discharge	4 (6)
Pain	3 (5)

PATIENTS AND METHOD

Sixty-seven DCIS patients were treated with curative RT after BCS, in our department from December 1998 to January 2008. One patient who did not complete RT and one patient lost to follow-up excluded from the study. Data of remaining 65 DCIS patients analyzed retrospectively. Some characteristics of the patients are summarized in Table 1.

The median age was 53 years (range, 27-72 years). Twenty-eight patients were premenopausal (43%), and others were postmenopausal period. Thirty-two patients were diagnosed with screening mammograpy (49%). Breast conserving surgery was lumpectomy in 41 patients and excisional biopsy in 17 patients. Tumor characteristics including histological type, nuclear grade, width of the surgical margin, lesion size, receptor status, comedonecrosis presency are shown in Table 2.

All patients have been treated with 6 MV photon energy on linear accelerator machine. Radiotherapy treatment fields were parallel opposed tangential to the whole breast. A median total dose of 50 Gy (Range, 48-50 Gy) was delivered in five fractions in a week. In 20 patients, boost dose to the tumor

Table 2. Characteristics of the tumors

	Number of Patients (%)
Tumor size	
<15 mm	39 (60)
16-40 mm	24 (37)
>40 mm	2 (3)
Grade	
Grade I	13 (20)
Grade II	16 (25)
Grade III	21 (32)
Unknown	15 (23)
C-erbB2 (IHC)	
2+ 3 (5)	
3+ 5 (8)	
Negative	29 (44)
Unknown	28 (43)
Surgical margin	
Negative	64 (98.5)
Close (<1mm)	1 (1.5)
Comedonecrosis	
Present	20 (31)
Absent	32 (49)
Unknown	13 (20)
Receptor status	
ER+	4 (6)
PR+	4 (6)
ER+PR+	37 (57)
ER-PR-	6 (9)
Unknown	14 (21.5)

DCIS: Duktal Carsinoma In Situ
LCIS: Lobuler Carsinoma In Situ
ER: Estrogen Receptor
PR: Progesteron Receptor
DCISmic: Duktal Carsinoma In Situ Microinvazive

Table 3. Systemic and hormonal therapy

	Number of Patients (%)
Hormonotherapy	
Present	50 (77)
Absent	15 (23)
Hormonotherapy	
Tamoxifen	45 (90)
Aromatase inhibitor	5 (10)

region was applied. Fifty patients received systemic hormonotherapy (Table 3).

All patients were examined after every five fractions, once in a week during RT. After the end of RT, patients were followed every 3 months for the first 2 years, every 6 months for the following 3 years and once a year after the end of the fifth year. Physical examination, complete blood count, chest X-ray, serum biochemical analyses were performed in every follow-up visits. Mammography and breast ultrasonograpy were performed in every 6 months.

Treatment related complications were recorded as acute when they occured within the treatment period or during 90 days after the end of the therapy and as late after then. Toxicity was graded according to Radiation Therapy Oncology Group (RTOG), Europen Organistaion for Research and Treatment of Cancer (EORTC) common toxicity criteria.[6]

Statistical Analysis: All the data were collected in a database and were verified by a second independent person. According to the findings on last follow-up, patients were classified as "no evidence of disease" if labaratory and physical examination is normal, "alive with disease" if signs of relapse were detected and "exitus of other causes" if patient died from other causes except disease. "Disease-free survival (DFS)" was defined as the time from surgery to the occurence of the first relapse either local or distant, and "overall survival (OS)" was defined as the time from surgery to death due to breast cancer or other causes.

Descriptive statistics were generated for all study variables, including mean and standart deviaton (SD) or median and range for continuous variables and relative frequencies and percentages for categorical variables. The distribution of the data was tested for normality by the Kolmogorov-Smirnov test. Two-tailed significance was defined as $p<0.05$. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows version 15 (SPSS Inc, Chicago, Illinois, USA). DFS and OS rates were calculated using the Kaplan-Meier method. There was only one local recurrence in our study, and therefore we could not perform univariate or multivariate analysis for prognostic factor assessment.

Table 4. Treatment-related acute side effects

	Number of Patients (%)
Dermatitis	
Grade I	15 (23)
Grade II	8 (12)
Grade III	1 (2)

RESULTS

Median follow-up time was 44 moths (range, 12-122 months). Five-year OS, DFS and local control rates were found as 96%, 97% and 97%, respectively. There was only one ipsilateral breast recurrence (2%). Two patients died due to other causes except disease (3%).

The patient with ipsilateral breast recurrence was 40 years old at the time of DCIS diagnosis. The tumor was <15 mm in size, and all surgical margins were negative (with 4 mm tumour free margin). Whole breast RT (50 Gy) was applied after excisional biopsy. She received adjuvant Tamoxifen for five years after the RT due to estrogen and progesteron receptor positivity. Forty-three months after the diagnosis, breast cancer developed in the same breast but not in the primary tumor localization. Mastectomy was applied and she is alive without evidence of disease 12 months after the tumor recurrence.

Treatment-related acute side effects are listed in Table 4. Grade III dermatitis was seen in only one patient (2%), and there were no acute side effects in 41 patients (63%). There was no late side effect in our patients. Sixty-two patients were alive without evidence of tumour recurrence, with their intact organ and with good cosmesis.

DISCUSSION

Mastectomy and local excision with radiotherapy are both effective local therapeutic approaches in patients who have DCIS. Although outcomes between mastectomy and BCS or BCS+RT were not studied in a randomized fashion, several observational studies compared them. Current data demonstrate that long-term survival is similar with either approach. There is a higher local recurrence risk for DCIS with local excision and radiation therapy (12%, half of whom have invasive cancer) than in patients who choose mastectomy (about 1%).[7] However mastectomy serves to reduce body image concerns, sexual function problems, and other psychosocial sequela after surgery.

Randomized clinical trials show that RT after local excision reduces the risk of both invasive and noninvasive local recurrence, compared with local excision alone.[9,10,11] Mature results of 4 multicentric randomised studies evaluating local and systemic treatment strategies for DCIS have been published.[8] 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 The EORTC trial found the 10-year local relapse-free rate was 85% with adjuvant radiotherapy compared to 74% without (HR 0.53, log rank $p < 0.001$). The SweDCIS trial found the absolute risk reduction was 16% at 10 years, corresponding to a relative risk (RR) of 0.40 (95% CI 0.30 to 0.54), for all ipsilateral breast events. The NSABP trial found the cumulative incidence of all ispilateral events at 12 years was 31.7% in the control group compared to 15.7% in the RT group (RR 0.43; 95% CI 0.32 to 0.58, $p < 0.000005$). The EORTC trial found the risk of invasive local recurrence was reduced by 42% ($p= 0.0065$). The NSABP trial found that invasive breast tumor recurrence was reduced from 16.8% to 7.7% ($P < 0.0001$). The SweDCIS found ipsilateral invasive disease was reduced from 12.3% to 7.2%.[9,10,11] In the United Kingdom, Australia, New Zealand DCIS Trial (UK/ANZ Trial), 1701 women who underwent excision of DCIS with clear margins were randomly assigned to RT (yes or no), and/or to tamoxifen versus placebo, using a two by two factorial design. The UKCCCR trial found the absolute risk of all ipsilateral events was reduced by 8.9% (from 13.7% in the control group to 4.8% in the RT group). The UKCCCR trial found that incidence of ipsilateral invasive disease was reduced from 5.3% to 2.5%.[12] In these four multicentric randomised trials that evaluated adjuvant radiotherapy in 3665 patients with DCIS submitted to BCT showed that adjuvant RT leads to a significant reduction (60%) in the risk of a local (invasive and DCIS) in-breast recurrence. In spite of the reduced recurrence, the overall mortality and breast cancer mortality rates

were not decreased for RT arm (30/1711= 1.75%) compared to observation arms (33/1954 = 1.68%).[13] However if we look at the results of the trials of radiotherapy following breast-conserving surgery for early invasive breast cancer, we will see effect of radiotherapy on breast cancer mortality. After 15 years follow-up, about one breast cancer death was avoided for every four local recur-rences avoided in the first 5 years. Theoretically, if about the same 1:4 ratio applied to DCIS, then radiotherapy might be expected to reduce breast cancer mortality by an absolute amount of about 1% or 2% by year 15 or 20.[14] In consistent with literature, we demonstrated excellent local control rates with acceptable morbidity and good cosmesis with RT after BCS for DCIS patients. Five-year OS, DFS and local control rates were 96%, 97% and 97%, respectively.

In the largest retrospective comparative series reported by Silverstein et al, thirty possible prognostic factors evaluated.[15] There were 909 patients in this study. Of all, 326 patients underwent mastectomy, 237 excision plus RT, and 346 excision alone. 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). In a multivariate analysis, the addition of RT after excision reduced the relative risk of LR by 55% (p= 0.0002). Nuclear grade, tumor size, margin width, comedo necrosis, and patient age were found as significant predictors of LR in this study. Combining these predictors they built the original Van Nuys Prognostic Index (VNPI). 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. So mastectomy was recomended treatment strategy in these patients.[16] Although the VNPI (and USC/VNPI) was validated by the results of Silverstein's group , it should be tested in prospective randomized trials before being generally accepted.[17] We could not analysed prognostic factors in our study, because there was only one recurrent disease in our study.

With the available information of randomized controlled trials, there was no evidence of excess deaths attributable to the addition of RT, either due to vascular disease, pulmonary toxicity, or second malignancies. Rate of death due to any cause was low in both arms of all trials and was similar between trials. However, if long-term toxicity due to RT does occur, a longer follow-up period may be required to show such an effect. In the early stage breast cancer studies, a significant excess of non-breast-cancer mortality in irradiated women (risk ratio 1.12, SE 0.04, p= 0.001) was shown. It was slight during the first 5 years, but continued after year 15. The excess mortality was mainly from heart disease (risk ratio 1.27, SE 0.07, p= 0.0001) and lung cancer (rate ratio 1.78, SE 0.22, p= 0.0004).[18] However, RT side effects based on the result of early stage breast cancer patients could not accurately reflect that in DCIS patients receiving BCS with RT. The actual development of disease (such as vascular disease or malignancy) was not reported, only cause of death. As RT techniques continue to improve, such as the use of modern megavoltage regimen, small fraction sizes, and with computed tomography treatment planning exposure of nearby normal tissues is reduced also potentially decrease RT side effects.4 We observed no serious late effects due to the RT.

Solin et al. reported RT effect in DCIS in the largest multi-institutional series of 1003 mammographically detected DCIS patients treated with BCS and RT. At a median follow-up of 8.5 years there were only 100 LRs in the treated breast, yielding a 10-year actuarial LR rate of 10%.[19] The experience of the Institute Curie over a 30-year period (1967 to 1996) was reported.[20] 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%. 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.9 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. 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. Although, RT is shown to be effective on local tumor, BCS without postoperative RT has been widely used for the treatment of DCIS. The largest series of 256 patients was reported by Schwartz et al.[21] 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 rate was 41% with the long-term projection of local recurrence being as high as 50% at 20 years. Blamey et al 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.[22] At a median follow-up of 38 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 1998, Boyages et al. published a meta-analysis of available retrospective studies of different local treatments for DCIS.[23] 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% for studies employing BCS alone, and 8.9% 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.

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. No subgroups have been reliably identified that do not 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.9

Until the natural history and biology of DCIS and important therapeutic risk stratifications has been clearly defined, our study and currently available literature supports that RT is an effective and tolerable treatment strategy after BCS in the management of DCIS.

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