

Research Article

Outcomes of Tamoxifen Treatment Alone in Patients With Ductal Carcinoma In Situ or Atypical Ductal Hyperplasia Who Refused Surgery

A Retrospective Study

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Objective: Recent trends involving increased screening have led to broad populations being diagnosed with atypical ductal hyperplasia (ADH) or ductal carcinoma in situ (DCIS); as a result, many patients have had to receive surgery followed by standard treatment for ADH or DCIS. The common interest in reducing the use of superfluous invasive treatment has led us to question the necessity of surgical treatment for ADH or DCIS patients in a retrospective review. This work is expected to be a particularly useful reference as there have yet to be any studies describing the outcomes of initial treatment with tamoxifen without curative surgery in Korea.

Methods: The clinicopathological characteristics and oncologic outcomes of 36 patients with DCIS or ADH diagnosis who received initial treatment with tamoxifen between 2013 and 2019 were investigated.

Results: Among 36 patients enrolled, 30 were diagnosed with DCIS and six were diagnosed with ADH. The median age in the included cohort was 47 years old (range, 26–81 years). There was a change in the follow-up strategy including the need for surgery in 13.9% of cases. The median time to surgery in those patients was 32 months (IQR, 17.5–63.5 months). Only one patient had upgraded to a higher nuclear grade, which was a case of ADH upgrading to intermediate DCIS. Three (8.3%) of 36 patients were upstaged to an invasive disease. Of them, two patients were upstaged to microinvasive ductal carcinoma, whereas one patient was diagnosed with metastatic invasive ductal carcinoma.

Conclusion: The use of endocrine therapy without surgery could be a potential treatment strategy in patients with DCIS or ADH. Further validation in larger cohorts and in the context of clinical trials is needed.

Keywords: breast neoplasm; carcinoma; intraductal; noninfiltrating; tamoxifen

1. Introduction

There is a vague boundary for diagnosis between atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS), particularly with low-grade DCIS. Current guidelines dictate that all DCIS patients should be treated upon diagnosis with some combination of surgery, radiation, and endocrine therapy, which is very similar to that

recommended for patients with invasive cancer [1, 2]. Furthermore, the standard treatment for ADH is surgery, such as wide excision [3]. The widespread adoption of population-based breast cancer screening has led to a substantial increase in DCIS incidence; the appropriate treatment of DCIS has emerged as an important research topic [4]. As causing a patient harm by providing them with intensive treatment that does not provide them with any

benefit over a less-intensive or less-invasive alternative treatment goes against the fundamental principles of medicine, it is necessary to reassess the standard treatment for ADH or DCIS to determine if overtreatment can be avoided to preserve patients' quality of life. One study in this area has shown that the treatment that is provided to most women with DCIS is not clearly effective in reducing mortality [5]. Obvious treatment strategies for ADH or DCIS are yet to be validated because it is currently unclear how to predict which cases of DCIS will progress and when they will change to invasive carcinoma [6].

Tamoxifen treatment after DCIS diagnosis can reduce the risk of recurrent disease [3]. Many studies have suggested that management with active surveillance (AS) is an alternative to invasive surgery. According to the AS concept, monitoring and endocrine therapy are safe in low-risk DCIS or ADH. They can help patients consider the range of treatment choices available to them, including approaches both with and without invasive treatment [7, 8].

With the growing trend toward reducing or omitting invasive treatments and surgeries, we questioned the need for surgical intervention in patients with ADH or DCIS. We aimed to determine how many patients were diagnosed with DCIS or ADH through core needle biopsy, vacuum-assisted biopsy, or excisional biopsy and then subsequently managed with AS on tamoxifen without additional surgeries. To date, there has been no research in Korea on the outcomes of initial tamoxifen treatment without curative surgery. Therefore, we ultimately sought to investigate the prognosis and oncologic outcomes of such patients in the present work.

2. Materials and Methods

2.1. Patient Selection. We retrospectively investigated patients who had been diagnosed with either DCIS or ADH and who had initially received endocrine therapy with tamoxifen without any oncologic surgery from 2013 to 2019 in Samsung Medical Center. For the current study, we selected patients who had been the subject of AS with regular imaging follow-up and endocrine therapy. To exclude a high-risk group for hereditary breast cancer, we did not select any patients with a family history of breast cancer. The investigated patients were treated with tamoxifen without curative surgery based on patient's preference, most likely related the need for a more extensive surgery due to the broad distribution of the DCIS lesions.

We included pathologic variations of low-, intermediate-, and high-grade DCIS, ADH, DCIS vs. ADH, or intraductal papilloma (IDP) with ADH. Diagnostic modality was set by lumpectomy without any pathologic information of tumor mass margin from excisional biopsy, vacuum-assisted biopsy, or core needle biopsy. Patients who exhibited a clear and definite margin negative result after lumpectomy were excluded. At the time of diagnosis, other radiologic modalities, including bilateral mammogram, breast ultrasonography, and breast magnetic resonance imaging (MRI), had been performed. However, breast ultrasonography or breast MRI was considered to be unnecessary whether or not there were any residual lesions in radiologic description such

as mammography. AS proceeded with mammography, breast ultrasonography, or breast MRI at 3–6-month intervals.

The data to be analyzed in the present study were collected using a protocol approved by the Institutional Review Board (IRB) of Samsung Medical Center, Korea (IRB file number: 2023-05-087-001).

2.2. Definitions of Biologic Factors. Patients were divided into three groups (under 40 years old, from 40 to 49 years old, and over 49 years old) according to their age at the time of diagnosis. Regarding follow-up outcomes, AS was defined as regular imaging surveillance with or without endocrine therapy. Surgery was managed while the event of progression of disease was defined by physical examination or radiologic findings.

With DCIS demography, the hormone receptor (HR) expression level was determined based on positive cell proportion after immunohistochemical cell (IHC) staining. Regarding HR, estrogen receptor (ER) and progesterone receptor (PR) expression were considered to be positive with positive cell proportion $\geq 1\%$, while they were considered to be negative with positive cell proportion $< 1\%$. Human epidermal growth factor receptor 2 (HER2) positivity was defined as an intensity of 3+ by IHC. A score of 2+ was interpreted as equivocal. A staining test result of 0/1+ was considered negative. Results were considered to be positive for HER2 amplification when the ratio of HER2 to CEP17 was > 2.0 . For Ki-67 level, results were considered to be positive when 20.0% of cells showed staining and based on identification of the following criteria in at least one core. We reviewed the clinicopathologic characteristics of patients and biologic factors such as Ki-67, ER, PR, and HER2. The pathologic tumor stage was assessed according to the seventh American Joint Committee on Cancer (AJCC). Surgical pathology reports were reviewed to assess upstaging to invasive disease.

2.3. Statistics. The chi-square test and Fisher's exact test were used to statistically analyze the differences in the up-stage rates to invasive carcinoma among different clinicopathological variables and subtypes. Statistical significance was defined as $p < 0.05$. All statistical analyses were executed using R (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Overall Patient Demographics. In total, 36 patients in the DCIS or ADH cohort were identified as having received initial treatment with tamoxifen. The patient demographics are listed in Table 1. The median follow-up duration for 36 patients included in this analysis was 54 months (IQR, 41.75–66.50 months). Their median age was 47 years old (range, 26–81 years). The median period of tamoxifen administration was 58.5 months (IQR, 47.25–60.00 months), while the dosage of tamoxifen was 20 mg daily in all cases. There were not any thromboembolic events related to tamoxifen. Two patients could not complete therapy with tamoxifen due to other side effects including musculoskeletal

TABLE 1: Patient demographics.

Variables	n (%)
Age	
< 40	5 (13.9)
40–49	18 (50.0)
49 <	13 (36.1)
Total	36 (100.0)
Diagnosis	
ADH	6 (16.7)
DCIS	30 (83.3)
Low	13 (43.3)
Intermediate	14 (46.7)
High	2 (6.7)
Unknown	1 (3.3)
Total	36 (100.0)
Diagnostic method	
CNBx	8 (22.2)
VABB	16 (44.4)
Excisional Bx	12 (33.3)
Total	36 (100.0)
Location	
Lt.	17 (47.2)
Rt.	17 (47.2)
Bilateral	2 (5.6)
Total	36 (100.0)

Abbreviations: ADH, atypical ductal hyperplasia; CNBx, core needle biopsy; DCIS, ductal carcinoma in situ; VABB, vacuum-assisted breast biopsy for breast cancer.

pain. They had taken tamoxifen for 6 months and 4 years each with AS without any evidence of recurrence.

Of the included patients, 30 patients were diagnosed with DCIS and six patients were diagnosed with ADH. In terms of the age distribution, five (13.9%) patients below the age of 40 years old were diagnosed, 18 (50.0%) patients between 40 and 49 years old were diagnosed, and 13 (36.1%) patients over 49 years old were diagnosed. DCIS or ADH was pathologically proven in 12 (33.3%) patients by excisional biopsy, 16 (44.4%) patients by vacuum-assisted biopsy, and eight (22.2%) patients with core needle biopsy. Two (5.6%) patients were bilateral cases.

3.2. DCIS Clinicopathologic Characteristics. DCIS patients ($n = 30$) were analyzed in terms of various clinicopathologic characteristics, which are presented in Table 2. Regarding pathologic results in terms of nuclear grade in particular, DCIS cases were most commonly low grade (43.3%) and intermediate grade (46.7%); there were only two (6.7%) patients with a high-grade DCIS, while there was just one (3.3%) pathologically unknown case. ER-positive (28/30, 93.3%) and PR-positive (26/30, 86.7%) patients comprised the dominant group. Half (15/30, 50.5%) of the DCIS patients were HER2-negative (0, 1+), while 10% (3/30) of DCIS patients were HER2-positive. Over two-thirds (22/30, 73.3%) of DCIS patients presented a high score of Ki-67.

3.3. Oncologic Outcomes. The follow-up results and oncologic outcomes are presented in Tables 3 and 4. The rate of cases in which there was a change in the follow-up strategy

TABLE 2: DCIS patient demographics.

	n (%)
ER	
Positive	28 (93.3)
Negative	0 (0.0)
Unknown	2 (6.7)
Total	30 (100.0)
PR	
Positive	26 (86.7)
Negative	2 (6.7)
Unknown	2 (6.7)
Total	30 (100.0)
HER2	
Negative	15 (50.0)
Equivocal	6 (20.0)
Positive	3 (10.0)
Unknown	6 (20.0)
Total	30 (100.0)
Ki-67	
≤ 20%	22 (73.3)
> 20%	2 (6.7)
Unknown	6 (20.0)
Total	30 (100.0)
Nuclear grade	
Low	13 (43.3)
Intermediate	14 (46.7)
High	2 (6.7)
Unknown	1 (3.3)
Total	30 (100.0)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

TABLE 3: Follow-up result.

	n (%)
Surgery after progression	5 (13.9)
Continue AS	30 (83.3)
de novo Stage 4	1 (2.8)
Total	36 (100.0)

Abbreviation: AS, active surveillance.

TABLE 4: Oncologic outcome.

	n (%)
Upstage rate to invasive disease	3/36 (8.3)
MIDC	2 (66.7)
Metastatic IDC	1 (33.3)
Upgrade rate to higher nuclear grade	1/36 (2.8)

Abbreviations: IDC, invasive ductal carcinoma; MIDC, microinvasive ductal carcinoma.

after surgery was 13.9% (5/36). Most (31/36, 86.1%) patients were followed up with under AS without any invasive procedures. Details on patients who required surgery are presented in Table 5. The median time to surgery was 32 months (IQR, 17.5–63.5 months). Only one patient was upgraded to a higher nuclear grade, which was a case of ADH upgrading to intermediate DCIS. Three (8.3%) of the 36 patients were upstaged to an invasive disease. Of them, two patients were upstaged to microinvasive ductal

TABLE 5: Operation cases.

Number	Preoperation diagnosis	Operation type	Postoperation diagnosis	Time to operation (months)
1	DCIS intermediate	BCS only	MIDC	47
2	DCIS low	BCS only	LCIS	32
3	DCIS intermediate	NSM SLNB	MIDC	28
4	IDP with ADH	BCS only	DCIS intermediate	80
5	DCIS intermediate	BCS only	DCIS intermediate	7

Abbreviations: ADH, atypical ductal hyperplasia; BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; IDP, intraductal papilloma; LCIS, lobular carcinoma in situ; MIDC, microinvasive ductal carcinoma; NSM, nipple-sparing mastectomy; SLNB, sentinel lymph node biopsy.

carcinoma, whereas one patient was ultimately diagnosed with metastatic invasive ductal carcinoma; none of these three patients received any surgeries. One patient was found to have lobular carcinoma in situ (LCIS). Regarding the final pathologic report of operation cases, the upstage rates by demographics and pathology variables are given in Table 5. When considering demographic and pathologic variables (Table 6), only age was found to be associated with upstaging to an invasive disease ($p = 0.045$). Of the patients with an upstage, 40% were under 40 years old. The patients who upstaged to invasive disease had to receive appropriate treatment as recommended per guidelines. Therefore, we changed the treatment strategy from AS to proper treatment in those patients. There was no case of cancer-related mortality in the follow-up period considered in our study.

3.4. Specific Case Review. Herein, we discuss the case of a metastatic patient who had the worst outcome in included patients. She had multiple microcalcifications in the left breast that were detected by mammography. Low-grade DCIS was proven by excisional biopsy. Multiple calcifications led to the need for total mastectomy, which both her and her doctor considered to be an excessive approach. With the aim of decreasing both invasiveness and the risk of complications, the patient and the doctor decided that the patient would not undergo any surgical procedure. Eventually, these multiple calcifications turned to metastatic invasive carcinoma with bilateral breast cancer after 6 years from diagnosis, and the patient had to receive palliative chemotherapy. In this case, we believe that the patient should have received a mastectomy. We recommend that surgical treatment be pursued if a patient has multiple DCIS lesions with broad distribution of microcalcifications.

4. Discussion

This study is one of the first reports in Korea addressing the outcomes of initial tamoxifen treatment without any oncologic surgery in patients with DCIS or ADH. Among the 36 patients who received initial tamoxifen treatment for DCIS or ADH who were retrospectively considered in the current study, five subsequently underwent invasive surgical treatment. Three patients were upstaged to invasive disease, and two of these were found to have microinvasive ductal carcinoma. One patient did not undergo surgery, as she was diagnosed with invasive carcinoma with multiple metastases

TABLE 6: Upstage rate to invasive disease.

Upstage rate to invasive disease	Upstage ($n = 3$, 8.3%)	No upstage ($n = 33$, 91.7%)	<i>P</i> value
Age			0.045
< 40	2 (40.0)	3 (60.0)	
40–49	1 (5.6)	17 (94.4)	
50 ≤	0 (0.0)	13 (100.0)	
Nuclear grade			0.681
Low	2 (15.4)	11 (84.6)	
Intermediate	1 (7.1)	13 (92.9)	
High	0 (0.0)	2 (100.0)	
Unknown	0 (0.0)	7 (100.0)	
Ki-67			0.612
≤ 20	3 (13.6)	19 (86.4)	
> 20	0 (0.0)	2 (100.0)	
Unknown	0 (0.0)	12 (100.0)	
HER2			0.534
Negative	2 (13.3)	13 (86.7)	
Equivocal	1 (16.7)	5 (83.3)	
Positive	0 (0.0)	3 (100.0)	
Unknown	0 (0.0)	12 (100.0)	
ER			1.000
Positive	3 (10.7)	25 (89.3)	
Negative	0 (0.0)	0 (0.0)	
Unknown	0 (0.0)	8 (100.0)	
PR			1.000
Positive	3 (11.5)	23 (88.5)	
Negative	0 (0.0)	2 (100.0)	
Unknown	0 (0.0)	8 (100.0)	
Diagnostic method			0.873
CNBx	1 (12.5)	7 (87.5)	
VABB	1 (6.2)	15 (93.8)	
Excisional Bx	1 (16.7)	11 (91.7)	

Abbreviations: CNBx, core needle biopsy; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; VABB, vacuum-assisted breast biopsy for breast cancer.

at de novo Stage 4. Only one patient experienced an upgrade to a higher nuclear grade.

In most clinical trials comparing between AS and standard surgery in low-risk DCIS, the inclusion criterion for age is generally over 45 years old. By contrast, our study includes patients as young as in their twenties. No patients over 50 years old were upstaged to an invasive disease or upgraded to a higher nuclear grade. Thus, DCIS or ADH patients with older age who have substantial competing risk at operations could consider AS as a viable management strategy [9]. As we included patients younger than 45 years in a distinct group, the upstaging rate to invasive disease was 8.3%, which was considerably low compared to that found in

trials such as LORIS, COMET, LORD, and LORRETA for those with low-risk DCIS. Their observed upstaging rate ranged from 12% to 25% [10, 11].

One study retrospectively reviewed patients with vacuum-assisted biopsy-proven DCIS and found that there is a low DCIS upstaging rate in women eligible for AS trials (6%–10%) and that all patients with upstaging to invasive disease are early in stage as well as node-negative [12]. Reviewing our cases, two out of three cases finally turned out to be microinvasive carcinoma, which is a pathologic status that can be seen before other features of invasive carcinoma, and they were considered as very early stage and node-negative. Although upstaging occurred in some cases, most of them fortunately exhibited an early stage of the disease. This result supports that AS is safe in low- or intermediate-grade DCIS.

Generally, in DCIS patients meeting LORIS criteria (age ≥ 46 years, screen-detected calcifications, nipple discharge absence, minimal family history, non-high-grade DCIS) undergoing excision without RT, the 10-year invasive ipsilateral breast cancer recurrence (IBTR) rate was 6%, which is a considerably lower risk for IBTR [13]. One study showed that approximately 20% of women with core biopsy-proven non-high-grade DCIS have invasive cancer at excision and that patients who are managed without excision are expected to incur a higher invasive cancer rate [8]. Reviewing our cases, the diagnostic method was not found to be correlated to upstaging or upgrading rate to a higher nuclear grade.

The selection for AS in DCIS or ADH patients must be made carefully while considering the initial experience of tamoxifen administration before curative surgery. The identification of occult invasive disease or accurate prediction of the risk of progression to invasive disease has been shown to be key to ensuring AS [14]. Recent studies have shown that younger age, tumor size and grade, and comedonecrosis are consistently related to DCIS recurrence [3]. One research study identified some risk factors for invasive recurrences after a diagnosis of pure DCIS. After competing risk analysis for invasive in-breast recurrence, the significant factors have been found to include lesion size > 5 cm (hazard ratio = 1.59), while the significant factors for breast cancer mortality have been found to include age at diagnosis (hazard ratio = 1.04) and diffuse disease (hazard ratio = 6.02) [15]. The most important risk factor is age. Although AS for those with an older age is a more relieved treatment option, ADH or DCIS patients who are younger than 45 years old have the option of noninvasive and oncological safe management of disease with reliable results. Lesion size and distribution are also important factors for prognosis. Considering the metastatic outcomes observed in our case, multiple and diffuse lesions should be considered when conducting curative surgeries. By considering those factors and making predictions with preoperative imaging modality, we could establish precise criteria with which to select appropriate patients for AS.

A review of nine phase II trials and a meta-analysis of two randomized trials suggested that the initial response rate to preoperative endocrine therapy exceeded 50%–60% for

patients with ER positive disease, thus showing the feasibility and safety of preoperative endocrine therapy for breast cancer patients [16]. The clinical management of DCIS is heterogeneous. The clinical significance of microinvasion in DCIS remains elusive. Although a specific subgroup of patients who could be appropriately treated with or without excision is yet to be identified, the risk of overtreatment is of primary concern, since a proportion of DCIS cases never progress to invasive breast cancer [17]. One study has suggested that microinvasive carcinoma has two progressive pathways: a “low-grade luminal pathway” and a “high-grade HER2 pathway.” While HER2-positive cases show unique characteristics such as high-grade, comedo, high TIL, and cluster-like invasion, low-grade luminal cases showed relatively low-grade characteristics [18, 19]. All of our cases that were ultimately upstaged after AS with additional surgical treatment were microinvasive carcinomas, with no such cases of invasive carcinoma. If the case was a luminal-type DCIS, which is considered to be a lower grade than HER2 type, then AS can be selected as a more reasonable and safer option.

The present study has some limitations that must be noted. Fundamentally, there are few cases of DCIS or ADH patients in Korea in which AS can be attempted. It is necessary to conduct a nationwide multicenter study enrolling abundant cases with statistical consideration to overcome these limitations. However, the period of tamoxifen administration for patients in our study was nearly 5 years, which was considered to be a sufficiently long time for statistically significant analyses. Second, this was a retrospective study. Patients were not selected on a randomized basis. We did not stratify patients according to a balanced number. The results of these small-scale studies cannot always be generalized. Therefore, it is essential to verify the initial results through larger clinical trials and to evaluate the effectiveness and safety across diverse patient populations. The final limitation is the heterogeneity of the patients included in the study. Nearly one-third of the included cohort underwent excisional biopsy, which could have had a therapeutic impact on clinical outcomes. There was no statistical difference in outcomes according to diagnostic modalities, although the small number of patients should be acknowledged.

At present, there is a growing impulse to unburden the management of DCIS, including the use of nonoperative approaches for low-grade and intermediate-grade DCIS (low-risk DCIS). Indeed, there have been several clinical trials considering the decision-making process of low-risk DCIS patients with AS instead of traditional treatment, such as Comparison of Operative versus Monitoring and Endocrine Therapy (COMET) in the United States [7], LORIS in the United Kingdom [8], LORD in Europe [20], and LORETTA in Japan [21]. By highlighting these trends of treatment for low-grade DCIS, our study's findings can help inform enhanced AS for low-grade DCIS or ADH.

5. Conclusion

AS with tamoxifen administration could be a reasonable option for patients who refuse standard care of surgical treatment for DCIS or ADH with a luminal type or of lower

grade, and for older patients, with the ultimate purpose of reducing the risk of recurrence and preventing breast cancer mortality.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Statement

Study data were collected using a protocol approved by the Institutional Review Board (IRB) of Samsung Medical Center, Korea (IRB file number 2023-05-087).

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Conceptualization: Jeong Eon Lee and Youngji Kwak Data curation: Byung Joo Chae, Jonghan Yu, Jeong Eon Lee, Seok Won Kim, Seok Jin Nam, and Jai Min Ryu. Investigation: Youngji Kwak Methodology: Youngji Kwak Supervision: Jeong Eon Lee Writing—original draft: Youngji Kwak Writing—critical revision of the manuscript for important intellectual content: Youngji Kwak and Jeong Eon Lee.

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