DUKTALNI KARCINOM *IN SITU*: AKTUELNI DIJAGNOSTIČKI I TERAPIJSKI PRISTUPI

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REVIEW ARTICLE

DUCTAL CARCINOMA *IN SITU*: CURRENT DIAGNOSTIC AND THERAPEUTIC APPROACHES

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SAŽETAK

Razvoj metoda skrininga značajno je povećao učestalost dijagnostikovanja duktalnog karcinoma *in situ* (DCIS). Iako se odlikuje visokom stopom preživljavanja, DCIS predstavlja klinički izazovan entitet zbog svoje biološke heterogenosti i potencijala za progresiju u invazivni duktalni karcinom (IDC). Mamografija i dalje ostaje primarna dijagnostička metoda, pri čemu su mikrokalcifikacije najčešći nalaz. Lečenje je prvenstveno hirurško – lumpektomijom ili mastektomijom, u zavisnosti od proširenosti lezije. U slučajevima poštednih operacija preporučuje se adjuvantna radioterapija radi smanjenja rizika od lokalnog recidiva, dok se hormonska terapija (tamoksifen i inhibitori aromataze) primenjuje kod hormonski pozitivnih tumora. Disekcija aksilarnih limfnih čvorova ne sprovodi se rutinski, ali može biti indikovana u slučaju mikroinvazije. U novije vreme, aktivni nadzor razmatra se kao alternativa kod pacijentkinja niskog rizika, pri čemu su savremena istraživanja fokusirana na razvoj prognostičkih faktora za precizniju stratifikaciju rizika.

Ovaj rad pruža pregled savremenih multidisciplinarnih pristupa dijagnostike i lečenja DCIS-a, zasnovanih na najnovijim saznanjima iz naučne literature.

Ključne reči: duktalni karcinom *in situ*, mamografija, mastektomija, lumpektomija, hormonska terapija

ABSTRACT

Advancements in breast cancer screening have significantly increased the incidence of ductal carcinoma *in situ* (DCIS) diagnoses. Despite its favorable prognosis, DCIS poses a clinical challenge due to its biological heterogeneity and potential progression to invasive ductal carcinoma (IDC). Mammography remains the primary diagnostic modality, with microcalcifications as the most common radiological finding. Management is primarily surgical, involving either breast-conserving surgery (BCS) or mastectomy, depending on the extent of the lesion. In patients undergoing BCS, adjuvant radiotherapy is recommended to reduce the risk of local recurrence, while hormonal therapy (tamoxifen or aromatase inhibitors) is indicated for hormone receptor-positive tumors. Axillary lymph node dissection is not routinely performed but may be considered in cases with suspected microinvasion. Recently, active surveillance has emerged as a potential alternative for selected low-risk patients. Ongoing research is focused on the identification of prognostic factors to enable more precise risk stratification.

This review provides an overview of current multidisciplinary approaches to the diagnosis and treatment of DCIS, based on the latest scientific evidence.

Keywords: ductal carcinoma *in situ*, mammography, mastectomy, lumpectomy, hormonal therapy

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UVOD

Duktalni karcinom in situ (engl. *ductal carcinoma in situ – DCIS*) predstavlja neinvazivni oblik karcinoma dojke koji se karakteriše proliferacijom malignih epitelnih ćelija unutar duktalnog sistema, bez probijanja bazalne membrane i infiltracije okolnog tkiva [1]. Iako nema metastatski potencijal, DCIS se smatra prekursorom invazivnog duktalnog karcinoma (engl. *invasive ductal carcinoma – IDC*) [1]. Studije pokazuju da 25–60% nelečenih slučajeva DCIS-a može da progredira u IDC [2].

Sa sve učestalijom primenom poštednih operacija dojke (engl. *breast-conserving surgery – BCS*), raste i potreba za preciznom stratifikacijom lezija koje imaju veću šansu da recidiviraju ili progrediraju u IDC. U cilju zadovoljenja ove potrebe, razvijeni su novi klasifikacioni sistemi, koji se prvenstveno zasnivaju na nuklearnom gradusu i prisustvu nekroze [3]. Nekoliko studija je potvrdilo kliničku relevantnost ovog pristupa, pokazujući da su visok nuklearni gradus i/ili prisustvo nekroze (posebno komedo-nekroze) povezani sa većim rizikom od ranog nastanka lokalnog recidiva [4,5].

Tokom poslednje decenije, stručne rasprave o najprikladnijem terapijskom pristupu DCIS-u su postale intenzivnije. Iako je hirurška resekcija uz adjuvantnu radioterapiju i dalje predstavlja standardnu terapijsku opciju, kontinuirano se vodi debata o tome da li se određene pacijentkinje, posebno one sa DCIS-om niskog gradusa i povoljnim biološkim karakteristikama, nepotrebno izlažu agresivnim modalitetima lečenja. U poslednje vreme aktivni nadzor se sve češće razmatra kao potencijalna opcija za ove pacijentkinje. Ipak, zbog potrebe za uravnoteženjem rizika od progresije i mogućnosti prekomernog lečenja indolentnih lezija, terapijski protokoli ostaju predmet stručnih debata [6].

Cilj ovog rada jeste da prikaže savremene dijagnostičke i terapijske pristupe DCIS-u, sa posebnim osvrtom na izazove u donošenju optimalnih kliničkih odluka.

DIJAGNOSTIKA

Anamneza i klinički pregled

Klinički pregled je obavezan pre započinjanja radiološke dijagnostike. U kontekstu naslednog rizika za DCIS, posebnu pažnju potrebno je posvetiti detaljnoj porodičnoj anamnezi. Nakon procene rizika, pacijentkinje se po potrebi upućuju na genetsko savetovanje. Nacionalna mreža za sveobuhvatnu borbu protiv raka (engl. *The National Comprehensive Cancer Network – NCCN*) preporučuje rutinsko testiranje ekspresije estrogenskih receptora radi određivanja potencijalne koristi od adjuvantne hormonske terapije, dok testiranje na progesteronske receptore ostaje opciono [6].

INTRODUCTION

Ductal carcinoma in situ (DCIS) is a non-invasive form of breast cancer characterized by the proliferation of malignant epithelial cells within the ductal system, without breaching the basement membrane or infiltrating the surrounding tissue [1]. Although it does not have metastatic potential, DCIS is considered a precursor for invasive ductal carcinoma (IDC) [1]. Studies indicate that 25–60% of untreated DCIS cases may progress to IDC [2].

With the increasing implementation of breast-conserving surgery (BCS), there is an escalating necessity for accurate stratification of lesions with a higher likelihood of recurrence or progression into IDC. To address this need, new classification systems have been developed, primarily based on nuclear grade and the presence of necrosis [3]. Several studies have confirmed the clinical relevance of this approach, demonstrating that high nuclear grade and/or necrosis (especially comedo necrosis) are associated with an increased risk of early local recurrence [4,5].

Over the past decade, professional discussions have intensified regarding the most appropriate therapeutic approach to DCIS. While surgical resection with adjuvant radiotherapy remains the standard treatment option, an ongoing debate concerns whether certain patients (particularly those with low-grade DCIS and favorable biological characteristics) are being unnecessarily exposed to aggressive treatment modalities. Recently, active surveillance has increasingly been considered as a potential option for these patients. However, due to the need to balance the risk of progression against the potential overtreatment of indolent lesions, therapeutic protocols remain a matter of expert debate [6].

This paper aims to present current diagnostic and therapeutic approaches to DCIS, with special emphasis on the challenges of making optimal clinical decisions.

DIAGNOSIS

Anamnesis and Clinical Examination

A clinical examination is mandatory before the initiation of radiological diagnostic procedures. In the context of hereditary DCIS risk, particular attention should be given to detailed family history. Following risk assessment, patients should be referred for genetic counseling when indicated. *The National Comprehensive Cancer Network* (NCCN) recommends routine testing for estrogen receptor expression to determine the potential benefit of adjuvant hormonal therapy, while progesterone receptor testing remains optional [6].

Mamografija

Tokom rane faze implementacije skrininga, incidencija DCIS-a je porasla za više od 500% [7]. Danas DCIS čini 20–25% svih novodijagnostikovanih karcinoma dojke [8].

Mikrokalcifikacije predstavljaju najčešću mamografsku manifestaciju DCIS-a. Prema podacima Dershaw-a i sar., mamografijom se njihovo prisustvo detektuje u 98% slučajeva [9]. Slične nalaze izneli su i Stomper i sar., naglašavajući njihov karakterističan izgled [10]. U njihovoj studiji, kalcifikacije povezane sa DCIS-om opisane su kao pleomorfne, tipično grupisane i često raspoređene u linearne ili segmentne obrasce koji prate raspored mlečnih kanala. Ovi obrasci, karakteristični za maligne procese, pomažu u razlikovanju istih od kalcifikacija povezanih sa benignim promenama, koje su uglavnom okrugle i nasumično raspoređene [9,10].

Još jedan ključni aspekt preoperativne procene DCIS-a jeste procena rasprostranjenosti mikrokalcifikacija. Iako mamografija može pružiti dragocene informacije o njihovom prisustvu, često potcenjuje veličinu same lezije, naročito kod DCIS-a niskog i srednjeg gradusa. U studijama koje su koristile samo standardne bilateralne mamografske projekcije (mediolateralne i kraniokaudalne), veličina lezije bila je potcenjena i do 2 cm [11]. Pored toga, peritumoralna inflamacija i/ili fibroza takođe mogu dovesti do pogrešnog tumačenja mamografskih nalaza usled prisustva periduktalnih masa sa mikrokalcifikacijama, čak i u odsustvu invazije [12]. Stoga mamografija sama po sebi nije dovoljna za procenu tumorske invazije bazalne membrane, što je inače ključna razlika između DCIS-a i IDC-a. Radi smanjenja rizika od potcenjivanja lezije i pogrešnog tumačenja peritumoralnih promena, preporučuje se rutinska primena mamografije sa uvećanjem i/ili kompresijom [13].

Magnetna rezonanca (MRI)

Morfološki obrasci maligniteta uočeni na MRI-u slični su onima nađenim mamografijom. Najčešći nalaz jeste nenodularno pojačanje signala, grupisano ili linearno, koje prati duktalnu distribuciju u dojci [13,14].

Neke studije su pokazale da se osetljivost MRI-a za detekciju DCIS-a kreće u rasponu od 70–100% [15,16]. Senzitivnost iste varira u zavisnosti od histološkog tipa tumora, pri čemu je viša kod tumora visokog gradusa. Iako MRI ima visoku senzitivnost, njena specifičnost je niža i kreće se od 37–75% [17]. Niska specifičnost i veća stopa lažno pozitivnih rezultata mogu se pripisati benignim lezijama koje takođe pokazuju pojačanje signala na MRI-u. Neke studije su pokazale povećanje specifičnosti kada se uzmu u obzir kinetika pojačanja, budući da maligne lezije obično pokazuju rano i brzo pojačanje signala [18].

Mammography

During the early phase of screening implementation, the incidence of DCIS diagnoses increased by more than 500% [7]. Currently, DCIS accounts for 20–25% of all newly diagnosed breast cancer cases [8].

Microcalcifications represent the primary mammographic manifestation of DCIS. According to Dershaw *et al.*, mammography detected their presence in 98% of cases [9]. Similar findings were reported by Stomper *et al.*, who particularly emphasized their distinctive appearance [10]. In their study, calcifications associated with DCIS were described as pleomorphic, typically clustered, and often arranged in linear or segmental patterns following the distribution of breast ducts. These patterns, characteristic of malignant processes, help distinguish them from calcifications related to benign changes, which are generally round and randomly distributed [9,10].

Another key aspect of preoperative DCIS assessment is evaluating the extent of tumor microcalcifications. Although mammography can provide valuable information about their presence, it may underestimate lesion size, particularly in low- and intermediate-grade DCIS. In studies using only standard bilateral mammography in mediolateral and craniocaudal projections, lesion size was underestimated by as much as 2 cm [11]. Additionally, peritumoral inflammation and/or fibrosis may lead to misinterpretation of mammographic findings due to the presence of a periductal mass with microcalcifications, even in the absence of invasion [12]. Therefore, mammography alone is insufficient for determining whether the basement membrane has been breached, a distinction critical for differentiating DCIS from IDC. To minimize the risk of lesion underestimation and misinterpretation of peritumoral changes, the routine use of magnification or compression mammography is recommended [13].

Magnetic Resonance Imaging (MRI)

The morphological patterns of malignancy observed on MRI are similar to those seen on mammography. The most common finding is non-nodular enhancement, which may appear as clustered or linear, following the ductal distribution within the breast [13,14].

Some studies have demonstrated that MRI sensitivity for detecting DCIS ranges from 70–100% [15,16]. Sensitivity varies according to tumor histology, being higher in high-grade tumors. Although MRI sensitivity is high, its specificity is lower, ranging from 37–75% [17]. The low specificity and higher rate of false positives may be attributed to benign lesions that also exhibit enhancement on MRI. Some studies have shown improved specificity when enhancement kinetics are

Iako se MRI ne koristi rutinski kod svih pacijentkinja sa DCIS-om, ona može pružiti vredne informacije u preoperativnoj proceni rasprostranjenosti bolesti, kao i u detekciji istovremenih lezija u kontralateralnoj dojci.

Ultrazvuk

Na ultrazvuku se DCIS obično prikazuje kao hipoehogena lezija nepravilnog oblika i slabo definisanih ivica. Ove lezije obično ne pokazuju značajnu vaskularizaciju na Doppler-u, što pomaže u njihovom razlikovanju od IDC-a [19]. Ultrazvuk može igrati važnu ulogu u detekciji i proceni rasprostranjenosti DCIS-a kada su mamografski nalazi nejasni (npr. nekalcifikovane lezije, visoka gustina dojki). Yuan i sar. su pokazali da kombinacijom ove dve dijagnostičke metode dolazi do povećanja osetljivosti u detekciji DCIS-a za 10–15% [20].

Biopsija

Uprkos napretku u sferi dijagnostičkog imidžinga, konačna dijagnoza DCIS-a može se postaviti isključivo histopatološkom analizom uzoraka tkiva dobijenih biopsijom. Izbor metode biopsije zavisi od karakteristika same lezije, kao što su njena veličina, prisustvo mikrokalcifikacija i palpabilnost. Biopsiju treba izvoditi samo kada je indikovana, a na osnovu kliničkih i radioloških nalaza (BI-RADS 4–5), i nakon adekvatnog izbora metode [12].

Najčešće korišćene tehnike biopsije su biopsija iglom velikog promera (engl. core *needle biopsy – CNB*) i vakuum-asistirana biopsija (engl. *vacuum-assisted biopsy – VAB*), koje se izvode uz mamografsku, ultrazvučnu ili MRI navigaciju, u zavisnosti od vidljivosti same lezije [21,22].

Stereotaksična CNB je standardni pristup za nepalpabilne mikrokalcifikacije otkrivene mamografijom, dok se biopsija vođena ultrazvukom preferira za sonografski vidljive lezije [22]. Kada perkutane metode nisu izvodljive ili ne obezbeđuju adekvatne uzorke, primenjuje se otvorena biopsija uz navođenje žicom, posebno kod difuznih ili duboko lociranih promena. Ova tehnika omogućava preciznu lokalizaciju i eksciziju sumnjivih lezija uz poštovanje onkoloških i estetskih principa [6].

Biopsija limfnog čvora stražara (engl. *sentinel lymph node biopsy – SLNB*)

Iako neki autori zagovaraju rutinsku SLNB kod pacijentkinja sa povećanim rizikom za IDC, drugi se protive ovom pristupu zbog niske učestalosti aksilarnih metastaza i visokih stopa preživljavanja kod pacijentkinja sa čistim DCIS-om (97–99%) [23]. NCCN preporučuje selektivnu primenu SLNB kod pacijentkinja koje su planirane za mastektomiju ili za BCS u regijama dojke koje bi mogle ugroziti normalnu limfnu drenažu aksile

considered, as malignant tumors typically display early and rapid signal enhancement [18].

Although MRI is not routinely utilized in all DCIS patients, it can provide valuable information in the preoperative assessment of disease extent and in detecting synchronous lesions in the contralateral breast.

Ultrasound (US)

On ultrasound, DCIS typically appears as a hypoechoic lesion with an irregular shape and poorly defined margins. These lesions usually do not exhibit significant vascularization on *Doppler* imaging, which helps distinguish them from IDC [19]. Ultrasound can play an essential role in detecting and assessing DCIS extent when mammographic findings are inconclusive (e.g., non-calcified lesions, high breast density). Yuan *et al.* demonstrated that combining these two modalities increases DCIS detection sensitivity by 10–15% [20].

Biopsy

Despite advancements in diagnostic imaging, definitive diagnosis of DCIS can only be established through histopathological analysis of tissue samples obtained via biopsy. The choice of biopsy method depends on lesion characteristics, such as size, presence of microcalcifications, and palpability. Biopsy should be performed only when indicated, based on clinical and radiological findings (BI-RADS categories 4–5), and following appropriate method selection [12].

The most commonly used techniques are core needle biopsy (CNB) and vacuum-assisted biopsy (VAB), performed under mammographic, ultrasound, or MRI guidance, depending on lesion visibility [21,22].

Stereotactic CNB is the standard approach for non-palpable microcalcifications detected via mammography, while ultrasound-guided biopsy is preferred for sonographically visible lesions [22]. When percutaneous methods are not feasible or yield inadequate samples, wire-guided open biopsy is utilized, especially for diffuse or deeply located changes. This technique allows accurate localization and excision of suspicious lesions while adhering to oncological and aesthetic principles [6].

Sentinel Lymph Node Biopsy (SLNB)

Although some authors advocate for routine SLNB in patients at increased risk of IDC, others oppose this approach due to the low incidence of axillary metastases and the high survival rates observed in patients with pure DCIS (97–99%) [23]. The NCCN recommends selective use of SLNB in patients scheduled for mastectomy or BCS in breast regions that could compromise normal axillary lymph drainage (e.g., upper outer

(npr. gornji spoljašnji kvadrant) [6]. U takvim slučajevima, SLNB treba razmotriti tokom primarne hirurške intervencije, jer se nakon mastektomije ne može izvesti. Zlatni standard za ovu proceduru jeste metoda dvostruke modalnosti, tj. upotreba radioaktivnog izotopa u kombinaciji sa metilenskim plavetnilom [24].

TERAPIJA

Poslednjih godina raste interesovanje za manje invazivne terapijske pristupe DCIS-u. Klinička ispitivanja kao što su *LORIS*, *LORD* i *COMET* istražuju aktivni nadzor kao alternativu hirurškom lečenju kod pažljivo odabranih pacijentkinja sa niskorizičnim oblicima bolesti [25–27]. Rani rezultati ovih studija ukazuju na terapijske ishode uporedive sa konvencionalnim načinom lečenja, barem na kratkoročnom nivou. Ipak, kod približno 20% pacijentkinja kod kojih je prvobitno dijagnostikovan niskorizični DCIS, nakon hirurške ekscizije je otkriven IDC [28]. Zbog toga, aktivni nadzor zahteva stroge kriterijume selekcije pacijentkinja i dosledno praćenje.

Radi bolje individualizacije lečenja, razvijeni su različiti prognostički alati koji pomažu u stratifikaciji rizika i donošenju adekvatnih terapijskih odluka. Među tradicionalnim alatima, *Van Nuys prognostički indeks* kombinuje veličinu tumora, širinu hirurške margine, nuklearni gradus i prisustvo komedo-nekroze, kako bi se procenio rizik od lokalnog recidiva i odredila optimalna strategija lečenja [29]. *DCIS nomogram* uključuje deset kliničko-patoloških faktora za preciznu procenu individualnog rizika od recidiva i donošenja odluka o radioterapiji, hormonskoj terapiji i adekvatnosti hirurških margina [30].

Sa napretkom molekularne onkologije, genomski testovi sve više nalaze primenu u kliničkoj praksi. *Oncotype DX DCIS Score* kvantifikuje desetogodišnji rizik od recidiva nakon BCS bez radioterapije, a na osnovu ekspresije 12 gena, i time pomaže u odlučivanju o potrebi za zračenjem [31]. Slično tome, test *DCISionRT* integriše molekularne biomarkere (npr. *HER2*, progesteronski receptori, *Ki-67*, *p16*) sa kliničkim podacima kako bi se procenila potencijalna korist od adjuvantne radioterapije. Prema nekim studijama, ovaj test menja terapijski plan kod više od 30% pacijentkinja. Navedeni alati dopunjuju tradicionalne kliničko-patološke parametre i imaju potencijal da unaprede personalizaciju lečenja, naročito u smislu izbegavanja prekomernog lečenja kod niskorizičnih slučajeva [32].

Prema smernicama NCCN, osnovni modaliteti lečenja DCIS-a su [6]:

1) mastektomija,
2) BCS (sa ili bez adjuvantne *WBRT* – engl. *whole-breast radiotherapy*),
3) adjuvantna hormonska terapija.

quadrant) [6]. In such cases, SLNB should be considered during the initial surgery, as it cannot be performed after mastectomy. The gold standard for this procedure is the dual-modality method with radioactive isotope and blue-dye method [24].

THERAPY

In recent years, there has been growing interest in less invasive therapeutic approaches for DCIS. Clinical trials such as *LORIS*, *LORD*, and *COMET* are investigating active surveillance as an alternative to surgery for carefully selected patients with low-risk forms of the disease [25–27]. Early results from these studies suggest comparable therapeutic outcomes to conventional treatments, at least in the short term. However, approximately 20% of patients initially diagnosed with low-risk DCIS are found to have IDC upon surgical excision [28]. Therefore, active surveillance requires strict patient selection criteria and consistent follow-up.

To better individualize treatment, various prognostic tools have been developed to support risk stratification and therapeutic decision-making. Among the traditional models, the *Van Nuys Prognostic Index* combines tumor size, margin width, nuclear grade, and the presence of comedo necrosis to assess the risk of local recurrence and determine optimal treatment strategies [29]. The *DCIS nomogram* incorporates ten clinicopathological factors to provide a precise estimate of individual recurrence risk and to guide decisions regarding radiation therapy, hormonal therapy, and surgical margin adequacy [30].

With advancements in molecular oncology, genomic tests are increasingly entering clinical practice. The *Oncotype DX DCIS Score* quantifies the ten-year risk of recurrence following BCS without radiotherapy, based on the expression of 12 genes, thereby assisting in decisions regarding the need for radiation [31]. Similarly, *DCISionRT* integrates molecular biomarkers (e.g., *HER2*, progesterone receptors, *Ki-67*, *p16*) with clinical data to assess the potential benefit of adjuvant radiotherapy. According to some studies, this test modifies the therapeutic plan in more than 30% of patients. These tools complement traditional clinicopathological parameters and have the potential to enhance treatment personalization, particularly by helping to avoid overtreatment in low-risk cases [32].

According to NCCN guidelines, the primary treatment modalities for DCIS are [6]:

1) mastectomy,
2) BCS (with or without adjuvant whole-breast radiotherapy - WBRT), and
3) adjuvant hormonal therapy.

Mastektomija

Studije ukazuju da se oko 95% pacijentkinja sa DCIS-om podvrgava hirurškom lečenju, pri čemu se kod jedne trećine sprovodi mastektomija [33]. Dugoročni rizik od lokalnog recidiva nakon mastektomije je veoma nizak i iznosi 1–2%, u poređenju sa 3–10% kod žena lečenih kombinacijom BCS i WBRT [6]. Važno je napomenuti da ova razlika u riziku od recidiva ne utiče na dugoročno preživljavanje (nakon 20 godina), koje ostaje visoko u obe grupe (97–99%) [34,35].

Glavne indikacije za mastektomiju kod DCIS-a uključuju: (I) multifokalnost i/ili opsežnu rasprostranjenost lezije (u dva ili više kvadranata dojke), (II) visok nuklearni gradus, (III) nemogućnost postizanja čistih hirurških margina nakon BCS, (IV) starost ispod 40 godina, (V) prethodno zračenje dojke, i (VI) kontraindikacije za radioterapiju [6].

Savremena hirurgija dojke razvila se u pravcu estetski prihvatljivih pristupa, koji čuvaju estetski integritet dojke uz poštovanje onkoloških principa. Tehnike kao što su *mastektomija sa očuvanjem kože* i *mastektomija sa očuvanjem bradavice* zadovoljavaju ove kriterijume i danas predstavljaju zlatni standard kada je potrebna radikalna, ali tkivo-poštedna intervencija [6].

Uloga postmastektomijske radioterapije (engl. *postmastectomy radiation therapy – PMRT*) kod DCIS-a do danas ostaje kontroverzna i ograničena, jer ni u jednoj specifičnoj grupi pacijentkinja nije dokazan jasan klinički benefit. Samo mali broj visokorizičnih pacijentkinja (npr. sa opsežnom bolešću, tumorima visokog gradusa ili pozitivnim marginama) mogu biti podvrgnute PMRT [36].

BCS sa ili bez adjuvantne WBRT

Trenutno se oko 60–75% novodijagnostikovanih slučajeva DCIS-a leči BCS-om, sa ili bez WBRT [1,33]. Prema smernicama NCCN-a, BCS je odgovarajući izbor kod unifokalnih lezija (ograničenih na jedan kvadrant dojke), kada se mogu postići negativne hirurške margine od najmanje 2 mm. Smernice takođe preporučuju adjuvantnu WBRT kada god je to izvodljivo. U određenim slučajevima, kao što su male (≤ 2,5 cm), niskogradusne lezije sa negativnim marginama (obično ≥ 2 mm), ili kada postoji kontraindikacija za radioterapiju, može se razmatrati samo BCS bez radioterapije [6].

Kombinacija BCS i WBRT je detaljno proučavana, a brojne kliničke studije su potvrdile njenu efikasnost i superiornost u odnosu na BCS bez WBRT. Tabela 1. prikazuje rezultate šest prospektivnih, randomizovanih studija koja su upoređivale stopu recidiva DCIS-a i IDC-a kod pacijentkinja lečenih isključivo BCS (kontrolna grupa) u odnosu na one koje su lečene BCS uz adjuvantnu WBRT (eksperimentalna grupa) [37–42].

Mastectomy

Studies indicate that approximately 95% of patients with DCIS undergo surgical excision, with one-third of them receiving a mastectomy [33]. The long-term risk of local recurrence after mastectomy is very low, ranging from 1–2%, compared to 3–10% among women treated with BCS and WBRT [6]. Notably, this difference in recurrence risk does not affect long-term survival (after 20 years), which remains high in both groups (97–99%) [34,35].

The main indications for mastectomy in DCIS include: (I) multifocality and/or extensive lesion distribution (in two or more breast quadrants), (II) high nuclear grade, (III) inability to achieve clear surgical margins after BCS, (IV) age under 40 years, (V) prior breast irradiation, and (VI) contraindications to radiotherapy [6].

Modern breast surgery has evolved towards aesthetic approaches that preserve aesthetic integrity while adhering to oncological principles. Techniques such as *skin-sparing* mastectomy and *nipple-sparing* mastectomy meet these criteria and are now the gold standard when a radical, tissue-preserving intervention is required [6].

The role of post-mastectomy radiation therapy (PMRT) in DCIS remains controversial and limited, as no specific patient group has demonstrated consistent clinical benefit. Only a small subset of high-risk patients (e.g., those with extensive disease, high-grade tumors, or positive margins) may be considered for PMRT [36].

BCS with or without WBRT

Currently, approximately 60–75% of newly diagnosed DCIS cases are treated with BCS, with or without WBRT [1,33]. According to NCCN guidelines, BCS is appropriate for unifocal lesions (limited to a single breast quadrant) when negative surgical margins of at least 2 mm can be achieved. The guidelines also recommend adjuvant WBRT whenever feasible. In some instances, such as small (≤ 2.5 cm), low-grade lesions with negative margins (usually ≥ 2 mm), or when radiation is contraindicated, BCS alone may be considered [6].

The combination of BCS and WBRT has been extensively studied, and numerous clinical trials have confirmed its efficacy and superiority over BCS alone. Table 1 presents results from six prospective randomized trials comparing DCIS and IDC recurrence rates in patients treated with BCS alone (control group) vs. BCS with adjuvant WBRT (experimental group) [37–42]. The results consistently demonstrate that the combined approach leads to significantly lower recurrence rates, ranging from 3.0–9.3%, compared to 7.0–19.2% in the control groups.

Tabela 1. Tabelarni prikaz prospektivnih studija koje su upoređivale efikasnost BCS i WBRT (eksperimentalna grupa) naspram BCS bez WBRT (kontrolna grupa) [37–42]

Table 1. Tabular presentation of prospective studies comparing the efficacy of BCS and WBRT (experimental group) versus BCS without WBRT (control group) [37–42]

Studija / *Study*	**Dizajn / *Design***	**Medijana praćenja / *Median follow-up***	**Recidiv DCIS-a / *DCIS recurrence***	
			Exp. gr. / *Exp. gr.*	**Kont. gr / *Cont. gr.***
UKCCCR (37)	prospektivna / randomizirana / *prospective, randomized*	4.5 godina / years	3%	7%
EORTC 10853 (38)	prospektivna / randomizirana / *prospective, randomized*	10 godina / years	7%	14%
SweDCIS (39)	prospektivna / randomizirana / *prospective, randomized*	7 godina / years	9.3%	19.2%
UK/ANZ DCIS (40)	prospektivna / randomizirana / *prospective, randomized*	10 godina / years	5%	16%
NSABP B-17 (41)	prospektivna / randomizirana / *prospective, randomized*	15 godina / years	8.8%	15.7%
NRG/RTOG 980 * (42)	prospektivna / randomizirana / *prospective, randomized*	13.9 godina / years	7.1%	15.1%

Legenda: * DCIS I IDC zajedno

Legend: * DCIS and IDC together.

Rezultati dosledno pokazuju da kombinovani pristup vodi ka značajno nižim stopama recidiva, koje su u rasponu od 3,0–9,3%, naspram 7,0–19,2% u kontrolnim grupama.

Neke studije su takođe ispitivale i dugoročno preživljavanje pacijentkinja sa DCIS-om koje su lečene isključivo BCS-om naspram onih koje su lečene BCS uz WBRT. Stope preživljavanja ostale su veoma visoke u obe grupe (97–99%) bez značajnih razlika između istih [41,42]. Dakle, iako adjuvantna WBRT smanjuje rizik od lokalnog recidiva, ona ne utiče na samo preživljavanje, koje ostaje podjednako visoko u oba slučaja.

Hirurške margine

Hirurške margine se naširoko smatraju najvažnijim aspektom patohistološke analize tkivnih uzoraka nakon hirurške ekscizije DCIS-a. Do sada nije postignut profesionalni konsenzus po ovom pitanju, verovatno zbog kontradiktornih rezultata različitih studija. Retrospektivna studija koja je obuhvatila 445 pacijentkinja podvrgnutih BCS zbog čistog DCIS-a potvrdila je da širina hirurških margina ostaje najznačajniji nezavisni prediktor pojave lokalnog recidiva [43]. Meta-analiza koju su objavili Dunne i sar. 2009. godine potvrdila je da su pacijentkinje sa negativnim hirurškim marginama (nakon BCS i adjuvantne WBRT) imale za 64% manji rizik od pojave recidiva u poređenju sa onima sa pozitivnim marginama [44]. Ista studija je takođe pokazala da su margine < 2 mm povezane sa značajno većim rizikom od recidiva nego margine > 2 mm, iako nije utvrđena statistički značajna razlika u stopama recidiva između margina ≤ 5 mm i onih od tačno 2 mm [44]. Aktuelne smerinice koje su zajednički objavili Udruže-

Some studies have also examined long-term survival among DCIS patients treated with BCS alone vs. BCS with WBRT. Survival rates remained very high (97–99%) and did not differ significantly between the two groups [41,42]. Therefore, while adjuvant WBRT reduces the risk of local recurrence, it does not impact overall survival, which remains equally high in both treatment strategies.

Surgical Margins

Assessment of surgical margins is widely regarded as the most critical aspect of the pathological evaluation of tissue specimens following surgical excision of DCIS. To date, no professional consensus has been established on this matter, likely due to conflicting findings across various studies.

A retrospective study involving 445 patients who underwent BCS for pure DCIS demonstrated that margin width is the most significant independent predictor of local recurrence [43]. A meta-analysis published by Dunne *et al.* in 2009 confirmed that patients with negative surgical margins (following BCS and adjuvant WBRT) had a 64% lower risk of recurrence compared to those with positive margins [44]. The same study also found that margins < 2 mm were associated with a significantly higher risk of recurrence than margins > 2 mm, although no statistically significant difference in recurrence rates was observed between margins ≤ 5 mm and those measuring exactly 2 mm [44]. Current guidelines from the *Society of Surgical Oncology* (SSO), *American Society for Radiation Oncology* (ASTRO), and *American Society of Clinical Oncology* (ASCO) recommend excision with at least 2 mm margins followed by

nje onkoloških hirurga (engl. *Society of Surgical Oncology – SSO*), Američko udruženje radijacionih onkologa (engl. *American Society for Radiation Oncology – ASTRO*) i Američko udruženje kliničkih onkologa (engl. *American Society of Clinical Oncology – ASCO*) preporučuju eksciziju DCIS-a sa marginama od minimum 2 mm, uz adjuvantnu WBRT radi minimizacije rizika od nastanka lokalnog recidiva [45].

Ubrzana parcijalna iradijacija dojke (engl. accelerated partial breast irradiation – APBI)

APBI predstavlja skraćeni oblik radioterapije koji cilja samo deo dojke gde se nalazila tumorska lezija. Ovaj pristup smanjuje izloženost zdravog tkiva zračenju, skraćuje trajanje terapije i može doprineti očuvanju kvaliteta života pacijentkinje bez ugrožavanja onkološke bezbednosti [6].

Prema ASTRO smernicama, kandidatkinje za APBI su pacijentkinje sa DCIS-om otkrivenim skriningom, veličine tumora ≤ 2,5 cm, gradusa I–II, sa hirurškim marginama ≥ 3 mm [45].

Četiri prospektivne studije su pokazale da je APBI efikasan kao i WBRT u postizanju lokalne kontrole bolesti, uz isti profil toksičnosti, ali povoljniji kozmetički ishod [46–49].

Radioterapijski "boost"

Radioterapijski "boost" predstavlja dodatnu, lokalizovanu dozu zračenja koja se primenjuje na mesto tumora nakon WBRT [50]. Ovaj pristup se preporučuje pacijentkinjama sa negativnim hirurškim marginama i povećanim biološkim rizikom (tumori visokog gradusa, prisustvo komedo nekroze, ili mlađa životna dob). Studije su pokazale da ovaj pristup može da dovede do značajnog smanjenja rizika od lokalnog recidiva – i do 27% [50].

Hormonska terapija

Adjuvantna hormonska terapija je indikovana kod pacijentkinja sa DCIS-om pozitivnim na estrogenske i/ili progesteronske receptore, a nakon široke lokalne ekscizije tumora, sa ili bez primene adjuvantne radioterapije.

Za ovu svrhu koriste se dve glavne grupe lekova [6]:
1) selektivni modulatori estrogenskih receptora (tamoksifen),
2) inhibitori aromataze (anastrozol).

Tamoksifen je selektivni modulator estrogenskih receptora koji se primenjuje u standardnoj dozi od 20 mg dnevno tokom pet godina. Deluje tako što blokira estrogenske receptore u tkivu dojke, sprečavajući hormonski stimulisanu proliferaciju tumorskih ćelija [51]. Njegova

adjuvant WBRT as the optimal strategy for minimizing local recurrence rates [45].

Accelerated Partial Breast Irradiation (APBI)

APBI is a shortened form of radiotherapy that targets only the portion of the breast where the lesion was located. This approach reduces radiation exposure to healthy tissue, shortens the duration of therapy, and may help preserve patient quality of life without compromising oncologic safety [6].

According to ASTRO guidelines, candidates for APBI include patients with screen-detected DCIS measuring ≤ 2.5 cm, grade I–II, and with surgical margins ≥ 3 mm [45].

Four prospective studies have demonstrated that APBI is effective as WBRT in achieving local disease control, with a comparable toxicity profile and improved cosmetic outcomes [46–49].

Radiotherapy Boost

A radiotherapy boost refers to an additional, localized dose of radiation delivered to the tumor bed, following WBRT [50]. This approach is recommended for patients with negative surgical margins but elevated biological risk factors, such as high-grade tumors, the presence of comedo necrosis, or young age. Studies have demonstrated a significant reduction in local recurrence risk by up to 27% [50].

Hormonal Therapy

Adjuvant hormonal therapy is indicated for patients with estrogen and/or progesterone-receptor-positive DCIS following wide local excision, with or without radiotherapy.

Two main classes of drugs are used for this purpose [6]:
1) selective estrogen receptor modulators (tamoxifen), and
2) aromatase inhibitors (anastrozole).

Tamoxifen is a selective estrogen receptor modulator administered at a standard dose of 20 mg per day for five years. It works by blocking estrogen receptors in breast tissue, thereby preventing hormone-induced stimulation of tumor cell proliferation [51]. Its efficacy in reducing the risk of local recurrence has been evaluated in several major clinical trials (Table 2) [37,40,41]. The *NSABP B-24* study showed that tamoxifen, compared to placebo, reduced the 10-year DCIS recurrence rate from 7.2% to 5.6% [41]. Overall survival did not differ significantly between the groups. Similar results have been reported in other studies addressing this topic [37,40].

Anastrozole, an aromatase inhibitor, reduces systemic estrogen levels by inhibiting the conversion of

Tabela 2. Tabelarni prikaz prospektivnih studija koje su upoređivale efikasnost BCS, WBRT i tamoksifena (eksperimentalna grupa) naspram BCS, WBRT i placebo (kontrolna grupa) [37,40,41]

Table 2. Tabular presentation of prospective studies comparing the efficacy of BCS with WBRT, and tamoxifen (experimental group) versus BCS with WBRT, and placebo (control group) [37,40,41]

Studija / *Study*	**Dizajn / *Design***	**Medijana praćenja / *Median follow-up***	**Recidiv DCIS-a / *DCIS recurrence***	
			Exp. gr. / *Exp. gr.*	**Kont. gr / *Cont. gr.***
UKCCCR (37)	prospektivna / randomizirana / *prospective, randomize*	4.5 godina / years	1%	1%
UK/ANZ DCIS (40)	prospektivna / randomizirana / *prospective, randomize*	10 godina / years	3%	5%
NSABP B-24 (41)	prospektivna / randomizirana / *prospective, randomize*	10 godina / years	5.6%	7.2%

Tabela 3. Tabelarni prikaz prospektivnih studija koje su upoređivale efikasnost BCS, WBRT i anastrozola (eksperimentalna grupa) naspram BCS, WBRT i tamoksifena (kontrolna grupa) [51,52]

Table 3. Tabular presentation of prospective studies comparing the efficacy of BCS with WBRT, and anastrozole (experimental group) versus BCS with WBRT, and tamoxifen (control group) [51,52]

Studija / *Study*	**Dizajn / *Design***	**Medijana praćenja / *Median follow-up***	**Recidiv DCIS-a / *DCIS recurrence***	
			Exp. gr. / *Exp. gr.*	**Kont. gr / *Cont. gr.***
NSABP B-35 (51)	prospektivna / randomizirana / *prospective, randomize*	10 godina / years	0.9%	1.1%
IBIS-II DCIS (52)	prospektivna / randomizirana / *prospective, randomize*	7.5 godina / years	1%	2%

efikasnost u smanjenju rizika od lokalnog recidiva ispitivana je u nekoliko velikih kliničkih studija (Tabela 2) [37,40,41]. Studija *NSABP B-24* je pokazala da je tamoksifen, u poređenju sa placebom, smanjio stopu recidiva DCIS-a u periodu od 10 godina sa 7,2% na 5,6% [41]. Ukupno preživljavanje nije se značajno razlikovalo između grupa. Slični rezultati prijavljeni su i u drugim studijama koje su se bavile ovom problematikom [37,40].

Anastrozol, inhibitor aromataze, smanjuje nivoe sistemskog estrogena inhibirajući konverziju androgena u estradiol. Obično se propisuje u dozi od 1 mg dnevno tokom pet godina [51].

Studije koje su upoređivale efikasnost tamoksifena i anastrozola, uključujući *NSABP B-35* i *IBIS-II* studiju, pokazale su sličnu efikasnost u prevenciji recidiva (Tabela 3) [51,52]. Iako je ukupna učestalost neželjenih efekata bila slična, njihovi profili neželjenih efekata su se razlikovali – frakture su bile češće kod anastrozola, dok su vazomotorni simptomi i troboze bile češće kod tamoksifena.

Zaključno, i tamoksifen i anastrozol imaju značajnu ulogu u prevenciji recidiva DCIS-a. Izbor samog agensa treba individualizovati u skladu sa karakteristikama pacijentkinje, uključujući njen menopauzalni status i podnošljivost potencijalnih neželjenih efekata. Tamoksifen je terapijski izbor kod premenopauzalnih žena, dok se primena anastrozola može razmotriti kod postmenopauzalnih žena, s obzirom na sličnu efikasnost, ali drugačiji profil toksičnosti.

androgens to estradiol. It is typically prescribed at a dose of 1 mg daily for five years [51].

Comparative studies between tamoxifen and anastrozole, including *NSABP B-35* and *IBIS-II,* have shown similar effectiveness in recurrence prevention (Table 3) [51,52]. Although the overall rate of adverse events was comparable, the side effect profiles differed - fractures were more common with anastrozole. In contrast, vasomotor symptoms and thrombotic events were more frequent with tamoxifen.

In conclusion, both tamoxifen and anastrozole play a significant role in preventing DCIS recurrence. The choice of agent should be individualized based on patient characteristics, including menopausal status and tolerance to potential side effects. Tamoxifen is the preferred option for premenopausal women, while anastrozole may be considered for postmenopausal women due to similar efficacy and a different toxicity profile.

CONCLUSION

Despite its generally favorable prognosis, DCIS requires a careful and well-considered diagnostic and therapeutic approach. The combination of BCS and adjuvant WBRT remains the most reliable strategy for reducing the risk of local recurrence, while the addition of hormonal therapy and radiotherapy boost can further improve outcomes, particularly among younger patients. In carefully selected low-risk cases, APBI may

ZAKLJUČAK

Uprkos generalno povoljnoj prognozi, DCIS zahteva pažljiv i promišljen dijagnostički i terapijski pristup. Kombinacija BCS i adjuvantne WBRT ostaje najpouzdanija strategija za smanjenje rizika od nastanka lokalnog recidiva, dok dodatak hormonske terapije i radioterapijskog "boosta" može dodatno poboljšati ishod lečenja, naročito kod mlađih pacijentkinja. Kod pažljivo odabranih pacijentkinja sa niskim rizikom, APBI se može razmatrati kao efikasna alternativa WBRT, pružajući uporedivu onkološku sigurnost uz povoljniji estetski rezultat.

Iako aktivni nadzor još uvek nije deo standardne kliničke prakse, ohrabrujući rezultati nedavnih studija ukazuju na njegov mogući značaj u zbrinjavanju pažljivo selektovanih pacijentkinja, pod uslovom da su primenjeni strogi kriterijumi selekcije.

Lečenje DCIS-a treba biti individualizovano i vođeno kombinacijom kliničkih, radioloških i patoloških faktora, uz aktivno učešće pacijentkinje u procesu zajedničkog donošenja odluka.

Buduća istraživanja treba da budu usmerena na validaciju molekularnih markera koji mogu pouzdano razlikovati indolentne od agresivnih oblika DCIS-a, čime bi se popravilo personalizovano lečenje, uz očuvanje kvaliteta života.

Sukob interesa: Nije prijavljen.

be considered an effective alternative to WBRT, offering comparable oncologic control with superior cosmetic results.

Although active surveillance has not yet been incorporated into standard clinical practice, encouraging findings from recent studies suggest that it may have a role in the management of carefully selected patients, provided that strict selection criteria are applied.

Treatment of DCIS should be individualized and guided by a combination of clinical, radiological, and pathological factors, with active patient involvement in shared decision-making.

Future research should aim to validate molecular markers that can reliably distinguish indolent from aggressive forms of DCIS, thereby enabling truly personalized treatment while preserving quality of life.

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