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# Should local treatment of breast ductal carcinoma *in situ* be the same as the treatment of early invasive breast cancer

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Heterogenicity of breast ductal carcinoma in situ gives rise to opposing proposals concerning its treatment — ranging from attempts to recommend the *watch and wait* strategy in low risk forms ending with the currently binding standards of treatment of DCIS in the way identical as early invasive cancer in the high risk. Arguments for the treatment of ductal carcinoma in situ in the same way as patients with early invasive cancer have been presented. These arguments comprise: unknown natural history of untreated DCIS, high risk of undervaluation of the invasive component in the core-needle biopsy, the increase of recurrence risk with the progress of time, lack of verified separators of the groups with the risk of adverse course of the disease, the results of the clinical studies confirming the justification of combined local treatment and the proof that the clinical course of DCIS is the same as early invasive breast cancer, and, first and foremost, the fact that there are no clinical studies which could justify a limitation of the treatment scope.

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**Key words:** DCIS — breast ductal carcinoma *in situ*, cancer heterogenicity, local treatment, watch and wait strategy, clinical studies

Breast ductal carcinoma *in situ* (DCIS) is characterised with a malignant transformation of the epithelium of the ducts, which is limited to the epithelia and myoepithelial layers without crossing the basal cell membrane. This type of cancer is regarded as a transitional stage between the normal breast tissue and invasive cancer. It is characterised with a significant diversity of the morphological, immunochemical, molecular and clinical picture [1]. Depending on the tissue architecture, DCIS can be defined as solid, cribriform, papillary and micropapillary; whilst depending on the malignancy grade, as: poorly-, moderately- and highly differentiated and — depending on the presence of the *comedo* type necrosis — as comedo type carcinoma (with a more aggressive clinical course) and non-comedo type carcinoma. Intraductal spread of the disease in connection with an irregular routing of the ducts and difficulties in macroscopic evaluation of the scope of the lesions illustrates well the deceptive character of the disease and the widely understood heterogenicity of the DICS requires some significant evaluation of the therapeutic management [2]. The risk of development of an invasive form of cancer, which — depending on the subtype of DCIS — is 20–30% within 10 years and is 15 times greater than the average risk of breast cancer morbidity in the general population [3] of key importance for the choice of the scope of treatment.

The scale of the problem can be illustrated with the fact that since the 1970s there has been a continued increase in diagnoses of ductal carcinoma *in situ* due to the popularisation of screening examinations and more advanced diagnostic techniques. Currently DCIS makes up about 20–25% of breast cancers in the Western countries and in Poland 7–10% of new diagnoses per year [4]. In spite of the increasing number of DCIS diagnoses and early invasive cancers, the number of diagnoses of advanced breast cancer have not dropped, which remains a paradox [5].

Diagnosis of ductal breast carcinoma *in situ* is made in 90% of cases during a screening mammography, whilst, in a clinical examination such diagnosis is made much more

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rarely, usually only when a tumour in the breast or an exudation from a papilla is found. DCIS comprises a vast range of symptoms, from some slight low-risk lesions to eventually the involvement of extensive breast areas with lesions of high malignancy potential. The most frequent symptom of the disease consists in lesions, visible in mammography as accumulations of malignant micro-calcifications, which can be uni- or bilateral, frequently multifocal. The MRI mammography, useful in particular for the evaluation of the multifocality of neoplastic lesions and a more accurate estimation of the tumour size, is more sensitive than classical mammography. A microscopic diagnosis is usually made from the specimen collected in a mammotomy biopsy or — less frequently — in the surgical specimen, in which DICS may occur independently or co-exist with an invasive carcinoma.

The primary objective in the DCIS treatment is to reduce the number of recurrences and to decrease the number of recurrences with an invasive component. The determination of the groups with the risk of an adverse course of the disease is of essential importance for the choice of optimum therapeutic management. The DCIS heterogenicity thus gives rise to opposing proposals concerning its treatment — from attempts to recommend the watch and wait strategy in low risk forms to currently binding standards of treatment of DCIS in the same way as early invasive cancer in the high risk group [6].

The scope of treatment of DCIS ranges from the resection of the neoplastic lesion, through an excision with an adjuvant hormonotherapy, excision with the sentinel node biopsy and adjuvant radiotherapy, excision with the sentinel node biopsy and adjuvant radiotherapy with hormonotherapy, simple mastectomy, simple mastectomy with the sentinel node biopsy, subcutaneous mastectomy with the sentinel node biopsy and immediate reconstruction to end with the subcutaneous mastectomy with the sentinel node biopsy and immediate reconstruction and adjuvant hormonotherapy. The choice of the optimum scope of locoregional treatment is usually assisted with the assessment of the prognostic value of the Van Nuys Prognostic Index (VNPI), worked out in 2002 or VNPI/SCI, corrected in 2009 [7]. Amongst the tools recommended for a more specific prediction of the course of the disease, are also genetic tests, including Oncotype DX and the examination of the *BRCA1* and *BRCA2* gene mutation [8, 9].

The most popular locoregional management is organ sparing treatment, consisting of the resection of the neoplastic lesion with an adjuvant radiotherapy. The indications for the sentinel node biopsy are limited to patients with a high risk of the presence of a malignant component, (large areas of malignant calcifications, location in the tail of Spence, planned mastectomy) [10]. In spite of the predominance of breast sparing treatment, the published data points to significant differentiation of treatment choices resulting from the attitudes of the patients and the experience of the therapeutic team [11, 12]. In the USA, after the period of a decrease in the number of mastectomies in 1998–2004 (from 36 to 28%), since 2011 a further growth in the number of breast amputations, following the diagnose of DCIS has been observed, correlating additionally with the increase of the contralateral breast amputation. This concerns mostly younger patients, *BRCA1* gene carriers, in particular, in families with a family history burdened with ovarian cancer [9]. An additional argument for this option is the reluctance for revision surgeries necessary to obtain a cancer-free margin, chimeric course of the disease in spite of a lack of any signs of invasion, the possibility to avoid radiotherapy and access to the procedures of immediate breast reconstruction [13–15]. This escalation of the scope of surgical treatment is one of the mechanisms driving the debate on the necessity to look for decision factors, allowing the optimisation of the treatment of breast ductal carcinoma *in situ*.

The basic arguments for the treatment of ductal carcinoma *in situ* in the same way as early invasive cancer comprise:

— unknown natural history of untreated DCIS [16];
— high risk of undervaluation of the invasive component in the core-needle biopsy [10, 16–18];
— increase of recurrence risk with the progress of time [3, 19–21];
— lack of verified separators of the groups with the risk of adverse course of the disease [1, 2, 20];
— the results of the clinical studies confirming the justification of combined local treatment [22–26];
— and the proof that the clinical course of DCIS is the same as early invasive breast cancer [27, 28];
— the lack of clinical studies which could justify a limitation of the treatment scope [28–30].

Given the fact that a large share of ductal carcinoma *in situ* is diagnosed as a small lesion seen only in a mammography image, and then treated with a mammotomy biopsy, a substantial part of DCIS is resected during this procedure. Thus, the natural history of untreated DCIS remains unknown [16].

According to the published data, in 10 to 50% patients with ductal carcinoma *in situ* diagnosed during a core-needle or mammotomy biopsy, there is a risk of the underestimation of the co-existence of an invasive component, which is illustrated by microscopic evaluation performed after the surgical resection of the lesion [2, 10, 17, 18]. In the opinion of the authors of this meta-analysis, which comprised 7350 subject with a diagnosis of DCIS established with a core-needle biopsy, a consequence of underestimation of the risk of the presence of an invasive component was the delay of the correct diagnosis and treatment in one out of five cases. The presence of invasive cancer was found in 1738 patients from the analysed group [18]. In the studies

in which an invasive component was diagnosed in 40% of patients, the following factors were regarded as a risk: the presence of tissue mass in the preoperative MRI mammography, the involvement of the nipple-areolar complex, a large heterogenicity of the lesion and HER2 overexpression [10, 17]. The recurrence risk increases with the progress of time and, given the unknown natural history of untreated DICS, the observations concerning disease recurrence are a source of knowledge of DICS biology and the effects on the therapy applied. In one-centre retrospective study comprising 200 patients, within an 8-year observation period, in 25 patients (12.5%) a disease recurrence was diagnosed, and the risk factors were the young age, tumour size and grade [3]. In a prospective multicentre trial, ECOG-ACRIN E5194 with an average observation period of 12.3 years, where the minimum cancer-free margin was more than 3 mm, special attention was paid to the group of patients with a potentially low recurrence risk low-grade DCIS. In this group, comprising 561 patients, also 14.4% of recurrence cases were found (*vs* 24.6% in the high-grade group), including 7.5% invasive recurrences (*vs* 13.4% in the high-grade group) [19]. In the group of patients with an almost 20-year observation period, after the treatment of asymptomatic DCIS, found in the mammographic picture, 16.3% of recurrences were found, ¾ of which were invasive and the independent risk factor was an age below 45 years [24].

In spite of the probability of a different course of disease depending on the group with a low or high tumour grade, there are no verified and well documented risk separators. The knowledge of the molecular aspect of DCIS will allow for a better understanding of heterogenicity of this type of cancer and its significance for the clinical picture of a disease. For the time being the studies concentrate on the analysis of epigenetic modifications such as DNA methylation and the changes within miRNA, which play a significant role in genetic disorders. Additionally, the tumour increase and invasion are facilitated by a distorted tumour microenvironment, whose fibroblasts and macrophages excrete growth factors and angiogenesis stimulating factors [1]. Another group of molecular studies concern the relationships of the expression of selected biomarkers and the prognoses, where the triple-positive DCIS (p16, COX-2, Ki67) is significantly related to a higher risk of the occurrence of invasive breast cancer [31].

In the light of the recent studies whose results may in future foster the modification of clinical decisions, it must be concluded that the current state of knowledge, providing strong evidence justifying the local treatment of breast DCIS in the same way as early invasive form of this cancer [22]. With regards to the strength of the arguments from clinical studies, an identical standpoint is presented in the current recommendations of NCCN, AGO, ESMO or recommendations of the Polish Society of Surgical Oncology, currently prepared for publication [32–34]. The arguments for the positive answer were provided, among others, by the results of the NSABP studies: B-17 and B-24 in their section concerning DCIS. Within more than a 15-year observation period, 490 recurrences were observed, including 263 (53.7%) invasive cases, which were related to a higher risk of death. A significant reduction of recurrences was confirmed in the group of patients undergoing adjuvant radiotherapy (and also among those treated with tamoxifen). The share of contralateral breast cancer, within the period of 15 years was 10% in the studied groups, whilst it was reduced to 7.3% after the addition of tamoxifen to the therapy. It was proven that multiple year prognoses after surgical treatment is very good [23]. The recurrence risk factors were the young age of the patients and the lack of a tumour free margin [23, 35].

A definition of an adequate margin still remains under discussion. What is beyond all doubt, however, is the significance of the cancer-free margin as the strongest risk factor of local recurrence [36–39]. In accordance with the St. Gallen recommendations, a cancer free margin means the lack of cells of invasive or pre-invasive cancer in the excision line ("no ink on invasive tumour or DCIS") [40]. In the meta-analysis of 20 studies, published in August 2016 and concerning as many as 7883 patients with a mean observation period of 78.3 months, a definite standpoint of three opinion-forming American scientific societies (SSO, ASTRO, ASCO), that a standard in the treatment of DCIS is a margin not smaller than 2 mm in patients undergoing surgical intervention and a radical adjuvant radiotherapy (WBRT) [41].

The application of adjuvant radiotherapy in breast conserving surgery in the patients with DCIS has a proven significance for decreasing the recurrence risk [26]. The prospective clinical study, RTOG 9804, proved the benefit in adjuvant radiotherapy also in the group of patients with good prognoses (low and medium recurrence risk in the patients with negative surgical margin). During the mean observation period of 7.17 years in the group of patients without irradiation, there was 42% cases of disease recurrence, whilst the addition of radiotherapy resulted in a reduction of the recurrence risk from 6.7% to 0.9% [25]. The analysis of data coming from the SEER register (Surveillance, Epidemiology and End Results), concerning the population of 56968 people treated for DCIS with an average observation period of 91 months, confirmed the beneficial effect of adjuvant radiotherapy on the overall survival period throughout the entire study group, yet this effect was expressed in the strongest way in younger patients, without or with a low content of oestrogen receptors in the nuclei of the cancer cells [42].

Strong arguments for the treatment of DCIS in the same way as early invasive cancer are also presented in the publications in which the analysis of the data from the SEER register concerning 108 196 women with a diagnosis of DCIS confirms the fact that the clinical course of the disease in

both groups of patients is similar [27, 28]. One of the most essential contra-arguments against the reduction of local treatment, even in the group defined as *low risk* DCIS, is the lack of results of such randomised clinical studies as LORIS in Great Britain, which is a prospective study comparing surgical treatment (plus adjuvant radiotherapy or hormonotherapy) with an active observation, which was supposed to foster better understanding of the natural history of untreated DCIS [29]. In 2015 also, the LORD study was started (the third phase study EORTC-BCG 1401/BOOG 2014-04), in which in 1240 patients with a diagnosis of low risk DCIS, and with a 10 year follow-up period and active observation (watch and wait strategy) will be compared with treatment considered so far to be the standard [30].

In the light of the presented facts, the authors of this publication wish to sustain their standpoint that a local treatment of a patient with a ductal carcinoma *in situ* should be the same as the treatment of patients with early invasive cancer, as there is strong evidence for the effectiveness of the local treatment of DCIS, whilst the abandonment of surgical treatment and the treatment combined with radiotherapy remains premature without any data from the prospective clinical studies which could confirm the safety of such procedure.

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