

Overtreatment in surgery – does it concern also the patients with ductal breast carcinoma in situ

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ABSTRACT:

Overtreatment means treatment that goes beyond current standards, and patients with any disease can be overtreated. Overtreatment is also given to patients with cancer, including those who need surgery. Overtreatment is closely related to the problem of overdiagnosis.

In patients with cancer, unnecessary surgery may cause complications and generates unnecessary costs. The size of the problem of unnecessary surgery in patients with cancer can best be shown among patients with the most common cancers, which dedicated screening programs. Breast cancer patients, particularly those with pre-invasive types of the tumor, who typically have ductal carcinoma in situ (80%), are likely to undergo unnecessary surgery. We describe the most common clinical problems caused by overtreating patients with ductal carcinoma in situ.

KEYWORDS:

overtreatment, overdiagnosis, surgical treatment, breast cancer, ductal carcinoma in situ

The problem mentioned in the title of the study that means excessive treatment (treatment beyond therapeutic standards) may concern any form of healthcare. This phenomenon also occurs in oncology including patients with malignancies requiring surgical treatment.

Overtreatment is directly connected with overdiagnosis. The second term means diagnosing a disease which would not result in symptoms (including especially patient's death) if it remained undetected. Thus, according to the definition of „overdiagnosis”, „overtreatment” includes all the cases of treatment administered as a result of overdiagnosis.

Except for an important economic aspect (generation of significant expenses), a potentially avoidable surgery also results in conditions that are caused by adverse effects of operations. Therefore, the problem of overtreatment is analyzed more and more often [1].

The scale of this problem can be presented in those cancer patients who underwent surgery, by analyzing the morbidity of malignant neoplasms that are included in screening programs. It mostly refers to breast cancer patients and especially those with preinvasive carcinomas. Ductal carcinoma in situ (DCIS) accounts for around 80% thereof [2].

CAUSES AND SCALE OF OVERTREATMENT

Introduction of National Breast Cancer Early Detection Programs is believed to be the most important cause of overdiagnosis (and therefore also overtreatment) of DCIS. Before these programs were implemented, DCIS constituted 3-5% of all breast cancer cases. Popularization of screening mammography increased the percentage to 20-30% of all detected types of breast cancer (Europe, North America) [2-4].

An increase in overall morbidity of breast cancer also contributed to the rise in the number of DCIS cases. According to the epide-

miological data, between 1988 and 2010, it was observed that in the United Kingdom the standardized morbidity index of ductal carcinoma in situ significantly increased from 3.6 to 16.2 per 100 000. In invasive cancer, the difference was not so pronounced (90.9/100 000 vs. 126.2/100 000) [5]. In the same time period, a similar tendency in DCIS morbidity was observed also in Holland (increase from 4.9 to 22.3/100 000) [6] and Germany (the incidence of DCIS increased 7 times) [7].

More frequent detection, especially of tumors of small size, was also facilitated by technological progress in the parameters of diagnostic tests (introduction of digital mammography and devices with tomosynthesis mode, and popularization of magnetic resonance mammography) [8].

Ductal carcinoma in situ is a disease characterized by different grades [9]. According to the observations of the authors from Harvard Medical School, lesion of DCIS may develop in two different ways. Progress of the disease may lead to occurrence of high-risk DCIS (extensive pure ductal carcinoma in situ). It requires similar therapeutic approach as invasive breast cancer. Low-risk DCIS (indolent disease, low-grade DCIS) is the second option [10]. This type is only rarely a source of invasive high-grade cancer (G3). Invasive G3 cancer in a patient previously diagnosed with low-risk DCIS may be considered an entirely new, primary malignant breast neoplasm [11]. These conclusions are also confirmed by other authors [12, 13].

Among the above mentioned causes, administration of treatment in patients with low-risk ductal carcinomas is considered overtreatment. It mostly concerns surgical procedures of the axillary fossa (sentinel node resection, lymphadenectomy) and overly high rate of mastectomy [14]. Therefore, according to some publications, estimated percentage of overtreatment may be as high as 52% of all DCIS cases [15-18].

However, according to many authors, overtreatment should be

detected when any type of surgical treatment was administered to the patient with low-risk DCIS. Based on US epidemiological data, within the last 30 years, around 1.5 million cases of early breast cancer have been diagnosed due to screening mammography (mostly DCIS) and approximately 1.3 million of patients may have been overtreated [19,20].

Due to popularization of screening for early detection of breast cancer, the main goal was achieved - the number of deaths caused by this disease was decreased. However, as the analyses show, in every „saved life” there are three to four cases of „overtreatment”, with accompanying adverse results of treatment [9,21]. According to other estimations, only one in fifteen patients diagnosed with DCIS by screening mammography benefits from the administered treatment. However, in other cases the existence of „overdiagnosing” and its consequences should be recognized [22].

WHAT CONFIRMS HIGH OVERTREATMENT RATE IN DCIS

Due to its histological presentation (as per definition: unaffected basilar membrane of the ductal epithelium, resulting in no infiltration of the stroma), ductal carcinoma in situ shows a favorable prognosis. The death risk in this cancer amounts to 3.3% in 20 years. Whereby, it is only twice as high as the risk estimated for the general population [23]. According to the observations by Morrow and Katz, regardless of the surgical procedure applied, the 10-year survival rate in patients with DCIS exceeds 98% [24].

Approximately 40% of patients diagnosed with ductal breast cancer at the age of 70 years or more later die of diseases affecting blood circulation. Whereas, only 5.4% of patients die as a result of this cancer [25].

The possibility of a benign or even asymptomatic course of this disease was also confirmed in other studies. Almost 80% of patients diagnosed with DCIS using mammography screening present no clinical symptoms [2]. Previously undiagnosed ductal carcinoma in situ is detected during autopsy in 10-39% of women who died not because of breast cancer [26].

The observation of patients with DCIS proved that approximately in 50-85% of cases ductal carcinoma will never develop into invasive cancer [27].

WHAT CONTRADICTS THE PROBLEM OF „OVERTREATMENT” OF PATIENTS WITH DCIS

In 6-41% of DCIS diagnosed after core-needle biopsy, histopathological examination of the biopsy specimen reveals also the presence of an invasive component [28-30]. The factors that increase the risk of incidence of both types of cancer have been determined. They include young age (below 35 years), large size of DCIS (over 4 cm), intermediate or high grade (G2-3), presence of comedo necrosis, lack of steroid receptors, palpable lesion and the evidence of „mass” in mammography of the tumor [23,29-31]. The change in pathological evaluation of the tumor to another diagnosis results in an obligation to perform another operation - sentinel node resection. Therefore, it is considered necessary to evaluate the sentinel lymph node simultaneously, when the abovementio-

ned „bad prognostic factors” are identified.

The invasive component in the lesion initially diagnosed as ductal carcinoma in situ may also concern low-grade and medium-grade DCIS. Clinical data analyzed by Brenn et al. indicated that almost 20% of DCIS patients with G1 or G2 tumor show this invasive component [32].

The risk of progression to invasive cancer suggests that it is necessary to perform surgery when DCIS is diagnosed. It was shown that 20-53% of patients with this type of cancer who received conservative treatment (as a result of primary false-negative diagnosis of a benign lesion based on core-needle biopsy) will develop invasive cancer in the next 10 years [27,33].

Histopathological examination of the lymph nodes resected during SLNB in DCIS patients reveals metastases in 11-15% of patients [30,34]. It proves that it is possible to omit foci of microinvasion or invasive cancer coexisting with carcinoma in situ. This may also accrue in the course of postoperative pathological evaluation of DCIS after radical surgery.

HOW CAN WE REDUCE THE PROBLEM OF OVERTREATMENT IN DCIS PATIENTS

According to the up-to-date guidelines on treatment of DCIS, surgical resection with negative surgical margins is considered a standard procedure [35-37]. In some cases it is necessary to perform simple breast amputation (in case of extensive or multiple DCIS). Whereas, only in some clinical situations (patients initially qualified for simple mastectomy and those with ductal carcinoma in situ and the aforementioned: “bad prognostic factors”) assessment of local condition of lymph drainage may be indicated, in this case, using sentinel lymph node biopsy.

It is possible to decrease the percentage of overtreatment by various means. The most frequently mentioned method is total elimination of elective lymphadenectomy in DCIS patients. It is also about decreasing the number of verification of lymph nodes in the axillary fossa with SLNB in patients undergoing local resection of in situ tumor (at present it happens in approximately 18% of all DCIS cases) [25]. According to the up-to-date guidelines of NCCN, application of sentinel lymph node biopsy was limited to only those patients who require mastectomy or local resection of DCIS located in the tail of Spence [35].

The propositions of further changes aim at defining cases of „high-risk” DCIS requiring a „standard” therapeutic approach. As it is probable that carcinoma in situ coexists with invasive cancer, evaluation should additionally include assessment of the regional lymph drainage system (SLNB). The identification of this group of patients is easier owing to the diagnosis of a „triple-positive” type of DCIS. For that purpose it is necessary to conduct immunohistochemical testing, which detects p16 overexpression, COX2 hyperactivity, and increased Ki-67 mitotic index. As it has been noticed, diagnosis of this cancer in situ correlates with a very high risk of invasive cancer in the future. Thus, elective simple mastectomy should be considered in these patients [38,39].

We should consider a change in present terminology concerning

histopathological diagnoses, as a supplementation of the aforementioned suggestions. According to the author, introduction of the term „borderline breast disease” as suggested by Masood instead of DCIS in some cases would decrease the number of cases requiring surgery [13].

WHAT SHOULD BE DONE NEXT WITH THE DISCUSSED PROBLEM?

The currently available studies presenting treatment options used in DCIS patients and the outcomes were mostly conducted on a small number of clinical materials. Therefore, they are not representative for the entire population with this problem.

The analysis of data from Cancer Data Base (USA) from the time period 2004–2014 including almost 219000 patients may help us to formulate conclusions on this topic. As many as 70.8% of patients underwent local resection. In the remaining cases simple mastectomy was performed. The percentage of sentinel lymph node biopsy in both groups of patients (BCT vs. mastectomy) amounted to 19.0% and 63.5% respectively. In 3.6% to 19.0% of treated patients, axillary lymphadenectomy was eventually performed [31].

The other authors also report on the surprisingly frequently performed axillary lymph node resection. In 2010, it was performed

in 15.3% of patients who underwent mastectomy. Axillary fossa lymphadenectomy was also performed in 2.8% of patients after local resection of ductal carcinoma [25].

Maybe the currently on-going studies (LORD, LORIS) will be a turning point in the present trends in the treatment of breast carcinoma in situ, including the possibility to reduce the problem of overtreatment. The goal of these studies is to evaluate the safety of conservative treatment („active supervision”) in selected patients with DCIS. According to the valid principles of randomization, it is planned to do a comparison of long-term treatment results in patients, who underwent breast conserving therapy and those who received conservative treatment [5,6].

The proper summary of the analysis of the problem presented in this paper would be a conclusion of Lagios and Silverstein, authors of novel solutions regarding diagnosis and treatment of DCIS: „(...) in the recent literature the problem of overdiagnosis and overtreatment in breast cancer is often addressed. We agree with most of the presented opinions. However, when the lesion diagnosed with medical imaging and biopsy contains DCIS, action must be undertaken. Resection with possibly the best aesthetic outcome, using oncoplastic techniques, is the considered treatment of choice. (...) In most cases of DCIS, VNPI result allows for surgical resection without radiotherapy. Mastectomy is our last choice” [1].

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