

Therapeutic strategy for ductal carcinoma in situ patients according to Van Nuys Prognostic Index



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AIM: Evaluation of therapeutic strategy for Ductal Carcinoma In Situ (DCIS) patients at our Breast Cancer Centre and analysis of our pattern of treatment with respect to Van Nuys Prognostic Index (VNPI) categories.

MATERIAL OF STUDY: Our study population is the result of a selection of 85 DCIS patients classified according to the VNPI risk of Local Recurrence (LR). A comparison was made between treatment effectively performed and therapy suggested by VNPI protocols.

RESULTS: Out of 53 DCIS women (62%) at low local recurrence risk, 5 patients underwent Breast Conserving Surgery (BCS) alone, 7 were treated with mastectomy and 41 underwent BCS followed by radiotherapy (RT). Out of 31 patients (37%) belonging to VNPI intermediate risk group, 25 cases received BCS+RT and 6 cases received mastectomy. Only one patient (1%) belonged to VNPI high risk group and underwent mastectomy.

DISCUSSION: Only 31 patients (36,5%) had their definitive treatment according to recommended VNPI criteria, but none of the other 54 cases (63,5%) was undertreated. Performing mastectomy instead of BCS or adding adjuvant radiotherapy at BCS alone were not considered overtreatment because the therapeutic strategy was the result of a multidisciplinary discussion.

CONCLUSION: As DCIS is a heterogeneous disease the one-size-fits-all approach to treatment seems inappropriate. The VNPI was developed in order to help treatment choices, but therapeutic strategies can't be based only on local recurrence risk and need a multidisciplinary approach.

KEY WORDS: Breast cancer, Ductal carcinoma in situ, Van Nuys Prognostic Index

Introduction

Ductal Carcinoma In Situ (DCIS) is a non invasive breast cancer histologically characterized by the proliferation of malignant ductal epithelial cells confined within intact breast ducts ^{1,2}.

It includes a wide spectrum of disease ranging from low grade lesions, that are not life threatening, to high grade ones, that may harbor foci of invasive breast cancer ³. Genetic similarities between invasive breast cancer and poorly differentiated DCIS support the role of intraductal cancer as a precursor to invasive breast carcinoma ⁴. Until 1980, DCIS was very rarely diagnosed and represented less than 1% of all breast cancer cases. The incidence of DCIS increased dramatically with the widespread of screening mammography so, currently in the United States, DCIS amounts at 15-25% of all newly diagnosed breast cancer cases ⁵. DCIS is considered a precancerous lesion that, if left untreated, has the average risk of 30-50% of progression to an invasive carcinoma within 10 years ⁶.

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Even if large epidemiological studies and survival analysis are limited³, data show that patients with pure intraductal carcinoma have excellent prognosis: expected mortality rate of pure DCIS is 2%⁷.

However recurrence after surgery in DCIS patients is high and amounts at 16% at 5 years for women undergoing wide local excision alone⁸. Moreover, data clearly show that recurrent lesions are invasive in 50% of patients^{1,9-11}.

Considering DCIS patients' excellent prognosis, the main goal of treatment is local control with prevention of recurrence and its hypothetical progression to invasive disease^{1,12}. For DCIS patients treated with breast conserving surgery (BCS), the reduction of ipsilateral recurrence due to postoperative radiation therapy was demonstrated by NSABP B-17 trial⁹ and EORTC trial¹³, but the series failed to demonstrate any benefit on overall survival. Therefore treatment is carefully planned according to each patient own risk of local recurrence (LR)¹²: patients at low risk of recurrence can be considered for BCS alone or followed by radiation therapy (RT), patients at high risk of recurrence should be considered for mastectomy. Many studies attempted to identify risk factors for DCIS recurrence after wide local excision: extent of disease, pathological grade, presence of tumor necrosis^{2,14-6}, pathological status of resection margin and patients' age^{6,16-18} are all demonstrated to be independent predictors of local recurrence.

In order to help treatment choices in DCIS patients, the Van Nuys Prognostic Index (VNPI) was developed at the University of Southern California in the mid-1990s and then updated in 2001¹⁹. It combines different data items with predictive utility for LR after BCS (patient's age, tumor's size, surgical margin width, nuclear grade and the presence or absence of comedonecrosis) and allows stratification of patients according to their own risk of recurrence. Patients are, therefore, divided into three groups corresponding to low, intermediate or high risk of local recurrence. Published data demonstrate that there is a recurrence-free survival benefit from adding breast radiation therapy to breast conservative surgery for patients with VNPI intermediate risk and from mastectomy for VNPI high risk patients^{6,9,16,19}. Thus, treatment is proposed with respect of VNPI groupings: BCS alone for low risk patients, BCS followed by external radiotherapy for intermediate risk patients and mastectomy for patients at high risk of local recurrence.

The aim of this study is to evaluate the therapeutic strategy chosen for DCIS patients at our Breast Cancer Centre and to analyse our patterns of treatment with respect to Van Nuys Prognostic Index categories.

Material and Method

An analysis was conducted on the records of 896 breast cancer patients who underwent a surgical procedure from May 2004 to May 2012 at the Department of General Surgery of Trieste University.

Study population is the result of a selection of 88 (9,8%) consecutive patients who had their definitive diagnosis of pure DCIS based on surgical specimen analysis. A retrospective review was made on data extracted from patients charts, radiology and pathology reports. Patients with previous breast carcinoma who had already had a surgical procedure were excluded from the study group as well as patients with definitive diagnosis of DCIS with presence of associated invasive lesion.

Data was collected with reference to the following items:

- patient's age;
- breast surgical procedure performed (BCS or mastectomy);
- adjuvant radiation therapy eventually performed;
- pathological definition of nuclear grade in the surgical specimen;
- presence or absence of comedonecrosis demonstrated at pathological analysis;
- maximal extension of each DCIS lesion measured on the surgical specimen;
- margin status.

According to the published USC/VNPI (Table I), we ascribed a numeric score to each of these items, from 1 for lesions with the best prognosis, to 3 for lesions with the worst prognosis. The sum obtained was added to the score derived from patient's age and the VNPI was calculated.

Patients were divided into three groups corresponding to low risk (score 4, 5 or 6) intermediate risk (score 7, 8 or 9) or high risk of local recurrence (score 10, 11 or 12). According to VNPI and current recommendations, different groups of patients are supposed to be treated with either conservative surgery eventually followed by radiation therapy or mastectomy.

A comparison was made between treatment recommended with respect to VNPI groupings and treatment effectively performed.

TABLE I

	1 Points	2 Points	3 Points
Size score	15 mm or less	16-40 mm	41 mm or more
Margin score	10 mm or more	1-9 mm	Less than 1 mm
Grading/comedonecrosis	Non-high grade without comedonecrosis	Non-high grade with comedonecrosis	High grade
Age score	61 years or older	40-60 years	39 years or younger

Results

From a cohort of 896 patients who underwent a surgical procedure for breast cancer from May 2004 to May 2012 at Department of General Surgery of Trieste, 88 (9,8%) women had a diagnosis of DCIS. We excluded from the serie three patients who had already had a surgical treatment on the ipsilateral breast.

Fourteen DCIS patients were treated with mastectomy, while 71 patients underwent BCS, which was followed by radiation therapy in 66 cases (Table II).

According to VNPI criteria we divided our study population into three groups: 53 patients (62%) presented a score ranging from 4 to 6 and therefore were classified at low risk of recurrence and belonged to VNPI Group 1. Thirty-one patients (37%) were at intermediate risk with a score ranging from 7 to 9 (VNPI Group 2) and only one patient (1%) belonged to high risk VNPI Group 3 with a score of 11.

Patients included in VNPI Group 1 were treated with mastectomy in 7 cases (13%) and underwent BCS in 46 cases (87%); 41 patients (89%) received postoperative radiation therapy after BCS while 5 women (11%) didn't receive any adjuvant treatment.

Out of 31 patients belonging to intermediate risk VNPI Group 2, 6 patients (19%) underwent mastectomy and 25 patients (81%) underwent BCS followed by adjuvant RT. The patient at high risk of recurrence who was classified in VNPI Group 3 was treated by mastectomy (Table III).

A comparison was made between treatment effectively performed and the one suggested by VNPI current recommendation. Thirty-one women of our study population (36,5%) underwent their surgical treatment according to current recommendations and VNPI criteria: the patient at high risk of recurrence was treated with mastectomy, 25 patients out of 31 cases at intermediate risk underwent BCS followed by radiation therapy and 5 women out of 53 at low risk of recurrence were treated with BCS alone.

In the other 54 patients (63,5%) the treatment performed did not conform to the therapy suggested by VNPI in accordance with the patient's individual prognostic group: 48 patients in VNPI Group 1 received both mastectomy (7 cases) and BCS followed by RT (41 cases), while 6 patients belonging to VNPI Group 2 received mastectomy instead of BCS in association with RT. No patient was undertreated.

Discussion

DCIS is a proliferative condition probably associated with the development of an invasive breast cancer. Nowadays DCIS accounts for almost 15-25% of newly diagnosed breast cancers^{1-3,5,7,16,20,21} and shows an excellent prognosis.

In our population we observed an incidence of DCIS of 9,8%, which is significantly lower than data presented in other studies, probably due to the lack of screening programs before 2006.

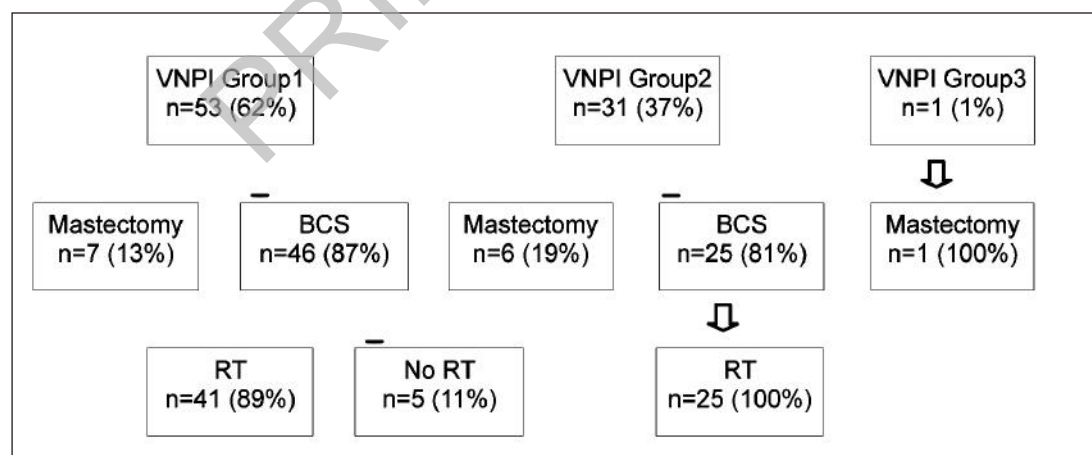
While DCIS is seldom life threatening, its management remains a dilemma²². Given that intraductal carcinoma is a heterogeneous disease, the one-size-fits-all approach to treatment seems inappropriate²³; stratification of patients according to VNPI allows individualized care according to independent risk factors^{6,9,16,19}.

In our experience, therapeutic choices did not conform to the recommended treatment proposed by VNPI prog-

TABLE II

	VNPI Group 1	VNPI Group 2	VNPI Group 3	TOTAL
BCS ALONE	5	—	—	5
BCS + RT	41	25	—	66
MASTECTOMY	7	6	1	14

TABLE III



nostic score in 54 cases (63,5%) who received a more extended treatment (mastectomy or BCS followed by radiotherapy instead of BCS alone). Mastectomy was performed in 7 patients belonging to low risk VNPI Group 1 and in 6 patients belonging to intermediate risk VNPI Group 2. Even if the data could support the idea of an extended surgical treatment performed instead of BCS in a large proportion of patients, in contrast with current clinical practice recommendations, it should be remembered that therapeutical choices and surgical decision making are more complex. Planning a mastectomy instead of BCS is a treatment decision affected by different factors²⁴. Selecting an appropriate treatment strategy must reflect not only patient's and tumor's characteristics but also the patient's preference. Small cross sectional studies have suggested that women with DCIS may overestimate their risk of future breast cancer events and, an inaccurate risk perception, may have an effect on decision making^{21,25-27}. The patient will be offered mastectomy also if breast size, in relation to lesion size, does not allow for cosmetically or surgically acceptable wide local excision^{1,28}. The recent introduction of pre-operative DCIS staging with breast MRI affects the decision making because of its high sensitivity in detecting DCIS and providing more accurate information on tumor size and extent of the lesion^{12,29-31}. MRI, with its ability in delineate soft tissue features and in providing precise estimation of tumor characteristics³², may lead to wider excision, unilateral mastectomy and/or treatment of the contralateral breast^{4,29}. Moreover, recent improvements in reconstructive surgery outcomes probably had increased the proportion of DCIS patients asking for an extended, radical surgical procedure in order to prevent any recurrence.

Last but not least, some of our patients could have chosen mastectomy in order to avoid the possible need for radiotherapy after BCS⁸.

Although definitive results in terms of outcomes of mastectomy or BCS or BCS plus RT are not already available from prespective randomized trials, there are some data coming from several observational studies which support the idea that women undergoing mastectomy are less likely to experience local recurrence than women undergoing BCS followed or not by RT, even if there seems to be no difference in terms of overall survival^{3,28,33-35}.

Therapeutical choices are the result of a multidisciplinary discussion: each DCIS case is evaluated by a medical board including pathologists, oncologists, radiotherapists and surgeons who plan together the adjuvant therapies.

In our serie we performed radiation therapy after BCS in 41 low risk VNPI Group 1 patients (48,2%), even though current VNPI recommendations indicate that excision alone is probably sufficient. Our therapeutic choice is based on the idea, coming from published studies, that there is a benefit in terms of local control due

to the addition of RT at BCS if compared with lumpectomy alone. As a matter of fact, several randomized controlled trials demonstrated the benefit of adjuvant RT, in terms of significantly reduced risk of LR in patients who undergo BCS^{1,4,6,9,11,36}; in NSABP-17 (National Surgical Breast and Bowel Project) and EORTC 10853 (European Organization for Research and Treatment of Cancer) clinical trials, whole breast RT following BCS was associated with a reduction of local DCIS or invasive carcinoma recurrence of approximately between 45% (NSABP-17) and 55% (EORTC). Despite of the reduction of recurrence, the application of RT had no impact on breast cancer mortality^{1,3,11}. Similar results were obtained by the UK/ANZ DCIS and SweDCIS randomized clinical trials that showed a significant reduction of LR after RT. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) and other published review³⁶ of the four previously cited randomized trials stressed that the 10-year rate of local failure (invasive carcinoma plus DCIS) was decreased by 15,2% with the addition of radiation treatment after lumpectomy with no differences in 10-year rates of overall survival, mortality without recurrence or cardiac mortality.

A Cochrane review^{1,11} published in 2009 confirmed the benefit of radiotherapy in effectively preventing local recurrence after BCS, even in patients grouped according to age, presence or absence of comedonecrosis and tumor size greater than 10mm.

So, published data seems to support the use of postoperative radiation in DCIS patients management, even if the VNPI criteria, based on retrospective studies, suggests that a subset of patients with low risk DCIS may be treated with surgery alone^{10,28}.

Conclusions

The study shows that the therapeutic approach to DCIS patients proposed at our institution is often different from the treatment proposed by VNPI protocols. Such a discordance is mostly due to the more extensive application of mastectomy or of postoperative radiotherapy after BCS. Even if VNPI seems to be a useful tool in order to calculate the patients' own risk of recurrence after BCS, allowing precise individualized prognostic estimation, we stress the importance of multidisciplinary discussion in order to make therapeutic decision considering also other variables different from VNPI and the patients' preferences.

Riassunto

L'attuale strategia terapeutica per il trattamento del CDIS è oggetto di ampia discussione poichè esiste ancora oggi una conoscenza solamente parziale della storia naturale che caratterizza questa lesione neoplastica. L'incidenza di

malattia è in costante aumento in relazione alla diffusione su larga scala dei programmi di screening mammografico. Appurato che il rischio di mortalità legato a questa patologia è molto basso, intorno al 2%, il rischio di recidiva locale (RL) dopo terapia chirurgica rappresenta la questione più importante da affrontare. L'Indice Prognostico di Van Nuys (IPVN) elaborato dall'University of Southern California permette di identificare pazienti ad alto, intermedio e basso rischio di recidiva locale dopo terapia chirurgica proponendo per ogni categoria un trattamento adeguato.

A partire da 896 pazienti operate per carcinoma mammario da maggio 2004 a maggio 2012 nell'ambito del dipartimento di Chirurgia Generale dell'AOU "Ospedali Riuniti" di Trieste, sono state selezionate 85 pazienti con diagnosi postoperatoria di DCIS.

Tali pazienti sono state classificate secondo il personale rischio di RL in base all'IPVN, e la terapia effettivamente eseguita è stata confrontata con quella proposta sulla base del IPVN. Da tale confronto sono emerse alcune divergenze: nel 63,5% dei casi il trattamento eseguito non era in linea con quanto proposto sulla base dell'IPVN. In particolare 13 pazienti appartenenti al primo e secondo gruppo IPVN sono state sottoposte a mastectomia e 41 pazienti, appartenenti al primo gruppo IPVN hanno ricevuto radioterapia postoperatoria piuttosto che la sola chirurgia conservativa. Queste scelte terapeutiche non possono però essere considerate come overtreatment, in quanto, nella pratica clinica è necessario tenere conto non solo del rischio di recidiva locale, ma anche di ulteriori parametri, quali le dimensioni della lesione rapportate al volume mammario, la possibilità di ottenere margini chirurgici adeguati a fronte di un risultato estetico soddisfacente ed i desideri della paziente. Inoltre, nonostante le attuali indicazioni basate sull'IPVN consiglino l'astensione da un'eventuale radioterapia adiuvante in pazienti selezionate, numerose evidenze in letteratura (NSABP-17, EORTC 10853) descrivono come anche le pazienti a basso rischio di recidiva possano in realtà beneficiare della radioterapia postoperatoria, sebbene non in termini di sopravvivenza, ma solo in termini di controllo locale di malattia.

Risulta importante sottolineare quindi come per una strategia terapeutica adeguata non ci si possa basare solo sulla stratificazione del rischio di ripresa di malattia, ma su differenti aspetti: l'iter terapeutico richiede pertanto necessariamente un approccio più ampio improntato su una discussione multidisciplinare.

References

1. Barnes NLP, Ooi LJ, Yarnold RJ: *Ductal carcinoma in situ of the breast*. BMJ, 2012; 344:e797.
2. Inder S, et al: *Ducatal carcinoma in situ (DCIS): Pathological features, differential diagnosis, prognostic factors and specimen evaluation*. Modern Pathology, 2010; 23: s8-13.
3. Virnig BA, Tuttle TM, Shamliyan T, Kane RL: *Ductal carcinoma in situ of the breast: A systematic review of incidence, treatment, and outcomes*. J Natl Cancer Inst, 2012; 102:170-78.
4. Schmale I, Liu S, Rayhanabad J, et al.: *Ductal carcinoma in situ (DCIS) of the breast: Perspective on biology and controversies in current management*. J Surg Oncol, 2012; 105:212-20.
5. Polyak K: *Molecular markers for the diagnosis and management of ducatal carcinoma in situ*. J Natl Cancer Inst Monogr, 2010; 41: 210-13.
6. Maass N, Alcasí Ö, Bauer M: *Actual management of ductal carcinoma in situ of the breast*. Arch Gynecol Obstet, 2009; 280:699-05.
7. Ansari B, Ogston SA, Purdie CA, et al.: *Meta-analysis of sentinel node biopsy in ductal carcinoma in situ of the breast*. Br J Surg, 2008; 95:547-54.
8. Whitfield R, Kollias J, De Silva P, et al.: *Management of ductal carcinoma in situ according to Van Nuys Prognostic Index in Australia and New Zeland*. ANZ J Surg, 2012; 82:518-23.
9. Estevez LG, Alvarez I, Segui MA, et al.: *Current perspectives of treatment of ductal carcinoma in situ*. Cancer treatment Reviews, 2010; 36:507-17.
10. Roses ER, Arun BK, Lari AS, et al.: *Ductal carcinoma-in-situ of the breast with subsequent distant metastasis and death*. Ann Surg Oncol, 2011; 18:2873-78.
11. Patani N, Khaled Y, Reefy AS, et al.: *Ductal carcinoma in-situ: an update for clinical practice*. Surg Oncol, 2011; 20:e23-31.
12. Kuerer H, Albarracin CT, Yang WT, et al.: *Ductal carcinoma in situ: state of the science and roadmap to advance the field*. J Clin Oncol, 2008; 27:279-88.
13. Bijker N, Meijnen P, Peterse JL, et al.: *Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: Ten-year results of European Organization for Research and Treatment of Cancer randomized phase III trial 10853. A study by the EORTC radiotherapy group*. J Clin Oncol, 2006; 24:3381-387.
14. Lagios MD, Margolin FR, Westdahl PR, et al.: *Mammographically detected duct carcinoma in situ. Frequency of local recurrence following tylectomy and prognostic effect of nuclear grade on local recurrence*. Cancer, 1989; 63:618-24.
15. Solin LJ, Yeh IT, Kurz J, et al.: *Ductal carcinoma in situ (intraductal carcinoma) of the breast treated with breast conserving surgery and definitive irradiation. Correlation with pathologic parameters with outcomes of treatment*. Cancer, 1993; 71:2532-542.
16. MacAusland GS, Hepel JT, Chog FK, et al.: *An attempt to independently verify the utility of the Van Nuys Prognostic Index for ductal carcinoma in situ*. Cancer, 2007; 110:2648-653.9
17. Gage I, Schnitt SJ, Nixon AJ, et al.: *Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving surgery*. Cancer, 1996; 78:1921-928.
18. Vicinif A, Kestin LL, Goldstein NS, et al.: *Impact of young age on outcome in patients with ductal carcinoma-in-situ treated with breast conserving therapy*. J Clin Oncol, 2000; 18:296-06.
19. Silverstein MJ, Lagios MD, et al.: *Choosing treatment for patients with ductal carcinoma in situ: Fine tuning the University of Southern California/Van Nuys Prognostic Index*. J Natl Cancer Monogr, 2010; 41:193-96.

20. Dunne C, Burke JP, Morrow M, et al.: *Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ*. J Clin Oncol, 2009; 27:1615-620.
21. Partridge A, Adloff K, Blood E, et al.: *Risk perception and psychosocial outcomes of women with ductal carcinoma in situ: Longitudinal results from a cohort study*. J Natl Cancer Inst, 2008; 100:243-51.
22. Cappellani A, Di Vita M, Zanghi' A, et al.: *Ductal carcinoma in situ (DCIS) of the breast: Thirty-two consecutive cases under 50 yrs detected by mammography: treatment and results*. Ann Ital Chir, 2000; 71:477-82.
23. Wang S, Shamliyan T, Virnig BA, Kane R: *Tumor characteristics as predictors of local recurrence after treatment of ductal carcinoma in situ: A meta-analysis*. Breast Cancer Res Treat, 2011; 127: 1-14.
24. Newmann LA: *Local control of ductal carcinoma in situ based on tumor and patient characteristics: the surgeon's perspective*. J Natl Cancer Inst Monogr, 2010; 41:152-57.
25. Kennedy F, Harcourt D, Rumsey N, White P: *The psychosocial impact of ductal carcinoma in situ (DCIS): a longitudinal prospective study*. The Breast, 2010; 19:382-87.
26. Ganz PA: *Quality-of-life issues in patients with ductal carcinoma in situ*. J Natl Cancer Inst Monogr, 2010; 41:218-22.
27. Allegra CJ, Aberle DR, Ganschow P, et al.: *National Institutes of Health State-of-the-Science Conference Statement: Diagnosis and management of ductal carcinoma in situ september 22-24,2009*. J Natl Cancer Inst, 2010; 102:161-69.
28. Franceschini G, Terribile D, Magno S et al.: *Current controversies in the treatment of ductal carcinoma in situ of the breast*. Ann Ital Chir, 2008; 79:151-56.
29. Tuttle TM, Shamliyan T, Virnig BA, Kane R: *The impact of sentinel lymph node biopsy and magnetic resonance imaging on important outcomes among patients with ductal carcinoma in situ*. J Natl Cancer Inst Monogr, 2010; 41:117-20.
30. Scomersi S, Urbani M, Tonutti M, et al.: *Role of magnetic resonance in managing selected women with newly diagnosed breast cancer*. The breast, 2010; 19:115-19.
31. Lehman C: *Magnetic resonance imaging in the evaluation of ductal carcinoma in situ*. J Natl Cancer Inst Monogr, 2010; 41:150-51.
32. Petronella P, Scorzelli M, Ferretti M, et al.: *Our orientation regarding the ductal carcinoma in situ of the breast*. Ann Ital Chir, 2012; 83, 497-502.
33. Moran M, Bai HX, Harris EER, et al.: *ACR appropriateness criteria ductal carcinoma in situ*. The Breast J, 2012; 18:8-15.
34. Hwang SE: *The impact of surgery on ductal carcinoma in situ outcomes: the use of mastectomy*. J Natl Cancer Inst Monogr, 2010; 41:197-99.
35. Kane R, Virnig A, Shamliyan T, et al.: *The impact of surgery, radiation, and systemic treatment on outcomes in patients with ductal carcinoma in situ*. J Natl Cancer Inst Monogr, 2010; 41:130-33.
36. Solin L: *The impact of adding radiation treatment after breast conservation surgery for ductal carcinoma in situ of the breast*. J Natl Cancer Inst Monogr, 2010; 41:187-92.