

## ORIGINAL ARTICLE

# Ipsilateral in-breast tumor recurrence after breast conserving therapy: true recurrence versus new primary tumor

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## Summary

**Purpose:** To classify ipsilateral in-breast cancer recurrences (IBCR) in patients treated with conservative surgery and radiation therapy, either as new primary tumor (NP) or true recurrence (TR) and to assess the prognostic and therapeutic importance of this classification.

**Methods:** The records of 107 patients treated for local tumor recurrence after breast-conserving therapy (BCT) at the National Cancer Center, Sofia, between March 1999 and May 2011 were retrospectively analysed. The patients' primary tumors were up to 2 cm in size. For their primary tumors all patients underwent quadrantectomy, axillary lymph node dissection and postoperative radiotherapy (RT) up to 50Gy. In cases with nodal metastasis additional RT has been used. Adjuvant chemotherapy and hormonotherapy have been used according to the clinical indications and depending of the patient's condition. Every attempt was made to define a tumor as a TR or NP, based on the changes in location and histology. <sup>99m</sup>Tc-MIBI SPECT-CT was used to localize the site of recurrence.

**Results:** Forty-four (41.1%) of the relapses were TR and 63 (58.9%) NPs. Out of 63 relapses defined as NPs, 54 (85.7%)

changed the location and 49 (68.3%) had a different histology. The age of patients with TR and with NP did not differ significantly at the time of diagnosis of the primary tumor (TR 48.8±10.45 years vs NP 50.8 ±10.56;  $p<0.330$ ), but those who developed TR were significantly younger than those with NP at the time of recurrence (TR 53 years, 66±11.1 vs NP 58,15±10.6;  $p<0.05$ ) Recurrences defined as NPs, developed after a significantly longer period of time in comparison to the TRs (7.4±2.6 years vs 4.8±2.2 years;  $p<0.0001$ ). Five-year overall survival of patients with TR was significantly lower compared to patients with NP (31.8% vs 96.7%;  $p=0.0001$ ).

**Conclusions:** Recurrences developing after BCT represent different clinical events, having different origin, prognosis and, therefore, requiring different type of treatment. It seems that a significant part of the recurrences that develop in the residual parenchyma, following BCT, are new carcinomas.

**Key words:** breast cancer, breast conserving therapy, local recurrence

## Introduction

The optimal treatment of patients with local tumor recurrences after BCT is not well established. Do all these patients need chemotherapy? Studies have shown that local recurrences after BCT are an independent predictor for developing distant metastases. An analysis of the results from the National Surgical Adjuvant Breast and Bowel Project B06 (NSBPP) found 3.14 higher risk for distant disease in patients with local recurrence [1]. Likewise, Botteri et al. [2] reported

that local recurrence has significant impact on the occurrence of distant metastases (HR 2.5, 95% CI 1.1-5.8). Fortin et al. [3] reported 2.8 times higher risk for systemic progression in patients with local recurrences after BCT.

Numerous studies have reported that the 5-year survival, following local in-breast recurrence, ranges from 59 to 90% [4-7].

Despite this data it is not clear if all recurrences in the breast are equal in terms of predict-

ing a poor prognosis. Several studies have suggested that the importance of local recurrence is exaggerated. Numerous investigators believe that there are subgroups of patients with favorable prognosis after in-breast local recurrence.

A hypothesis exists that relapses may represent two different types of disease. This distinction was described first by Veronesi et al. [8], who determined TR "as cases consistent with the re-growth of malignant cells not removed by surgery or not killed by RT", while NPs were defined as "de novo cases of malignancies arising from mammary epithelial cells of the residual breast tissue".

The purpose of this study was to classify IBTR in patients treated with conservative surgery and RT, either as NP or TR and to assess the prognostic and therapeutic importance of this classification.

## Methods

We retrospectively analyzed the medical records of 107 patients, treated for local breast recurrence after BCT at the National Cancer Centre in Sofia between March 1999 and May 2011. The primary tumor size of these patients was up to 2 cm. For their primary tumors all patients underwent quadrantectomy, axillary lymph node dissection and postoperative RT up to a total dose of 50Gy. Additional RT was used to the regional lymph nodes in cases with nodal metastasis.

Adjuvant chemotherapy and adjuvant hormone therapy were administered according to clinical indications and depending on the patient's condition. Amongst all patients experiencing local recurrences, 58 (54.2%) had received adjuvant chemotherapy and 76 (71%) had received adjuvant hormonal therapy with tamoxifen for their primary tumors. The patients were routinely checked on a 6-month basis.

After identification of local recurrence, we reviewed all patients' data, including operative protocols, hospital reports, pathologic reports and mammograms obtained from other hospitals. The majority of the cases of primary tumors were re-reviewed by two independent pathologists. The clinical and pathological characteristics of all patients, who experienced an IBTR, are presented in Table 1.

An attempt was made to define each relapse as TR or NP, based on the changes in location and histology. This attempt was made after a review of all available clinical and histological data. If one or both categories of the relapse changed, the recurrence was classified as a NP. The difference in the histological type between the primary tumor and the recurrence, as well as the change from invasive to less invasive cancer, were the histological characteristic of the NP. For example, the changes from invasive ductal (IDC) to medullary or tubular cancer, as well as the changes from IDC to intraductal carcinoma are considered as characteristics of

**Table 1.** Clinical and pathological characteristics of 107 patients with IBTR

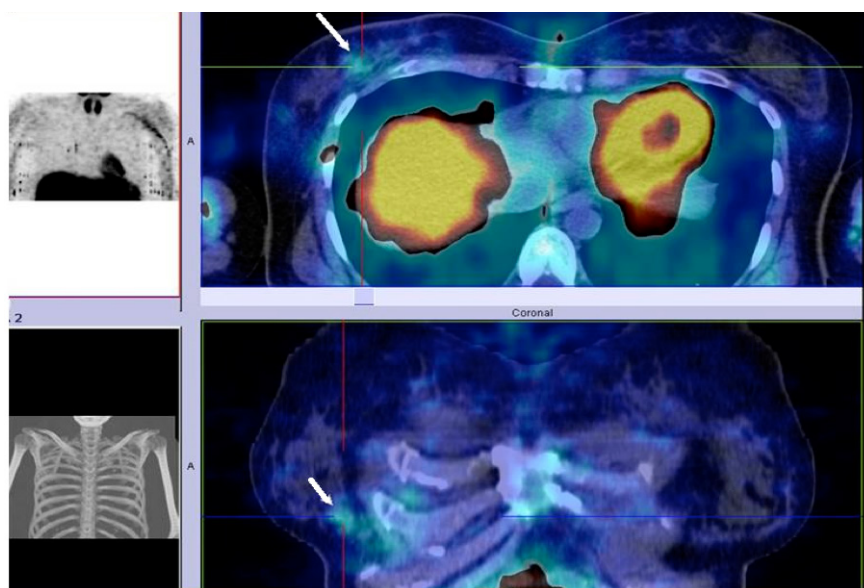
Characteristics	No. of patients (N=107) N	%
Age at diagnosis (mean = 49.8 years)		
<35	20	18.7
36-49	40	37.4
>50	47	43.9
Histology original/relapse		
Infiltrating ductal	61/57	57/53
Intraductal	12/20	11.2/18.7
Invasive lobular	26/23	24.3/22.5
Others*	8/7	7.5/6.7
Nodal status at primary presentation		
Negative / Positive	71/36	66.3/33.4
Estrogen receptor		
Positive/ Negative	67/40	62.6/37.4
Progesterone receptor		
Positive/ Negative	76/31	71/29
Adjuvant chemotherapy		
Yes/No	58/49	54.2/45.8
Adjuvant hormone therapy		
Yes/No	76/31	71/29

\*Gelatinous, papillary and tubular carcinoma, IBTR: in-breast tumor recurrence

NP. In cases when histology was identical with that of the primary tumor, the recurrence was classified as a NP if it was located away from the site of the primary tumor. It is important to acknowledge that we introduced a limitation to our scheme. The recurrences were defined as TR if they were located in an area up to 3 cm away from the primary tumor and had identical histology with the primary tumor.

<sup>99m</sup>Tc-MIBI SPECT-CT was used to localize the site of recurrence. SPECT-CT studies with <sup>99m</sup>Tc-MIBI of the neck and chest were performed 20 min after the i.v. injection of 740 MBq (mean activity dosage). SPECT-CT gamma camera Symbia T2, Siemens, was used to obtain topographic localization and morphological substratum of "hot" abnormal foci. Low dose CT scanning (130 KeV, 30mA; Symbia T2, Siemens, Germany) was carried out in the helical mode. Our results were interpreted, based on all other clinical and radiological data (Figure 1).

In a small number of cases it was not possible to establish the location of the recurrence because the tumor encompassed the entire breast. In these cases the recurrences were classified as TRs, based on the same



**Figure 1.** A patient with breast cancer on the right after breast conserving surgery. SPECT-CT with  $^{99m}\text{Tc}$ -MIBI was positive for local recurrence in the region between the lower quadrants (arrows).

**Table 2.** Clinical characteristics and management of both types of in-breast cancer recurrence

Characteristics	True recurrence (N=44) N (%)	New primary (N=63) N (%)	p value
Mean age at diagnosis (years)	48.8±10.45	50.8±10.56	0.330
Mean age at relapse (years)	53.66±11.1	58.15±10.6	0.035
Mean interval to relapse (years)	4.8±2.2	7.4± 2.6	p<0.0001
Recurrent site			
Same site	39 (88.6)	7 (11.1)	0.0001
Different site	2 (4.60)	54 (85.7)	0.0001
Unclear	3 (6.8)	2 (3.2)	
Histology of relapse			
Same to primary tumor	41 (86.4)	12 (19)	0.0001
Different from primary	3 (6.8)	55 (81)	0.0001
Surgery for IBCR			
Mastectomy	36 (88.1)	56 (88.9)	NS
Wide local excision	4 (9)	6 (9.5)	NS
No surgery	4 (9)	1 (1.6)	NS

IBCR: in-breast cancer recurrence, NS: nonsignificant

histology (Table 2).

The IBTR were determined as a NP if they occurred elsewhere in the breast and had a distinct histological type. In addition, changes in histology from IDC to DCIS were considered as characteristic of a NP because this change is in line with the natural progression of breast cancer.

#### Statistics

Comparisons between the numerical variables were performed using the Mann-Whitney U test. Chi-square test or Fisher's Exact test were used whenever

appropriate for comparison between categorical variables. To calculate the time to recurrence and overall survival, the Kaplan-Meier method was used [4]. Comparisons of clinical and pathological characteristics and overall survival between NP vs TR were carried out using the log-rank test. A p value <0.05 was considered as statistically significant.

#### Results

The average time of follow-up of the patients with local recurrence was 12.2±3.6 years, start-

**Table 3.** Comparison between the morphological characteristics of true recurrences and new primary tumors

Characteristics	True recurrences (N=44) N (%)	New primary tumors (N=63) N (%)	p value
Mean age at diagnosis (years)	48.8±10.45	50.8±10.56	0.330
<35	11 (25)	9 (14.3)	0.3265
36-49	15 (34)	25 (39.7)	0.7104
>50	18 (41)	29 (46)	0.8587
Histology of primary/relapse			
Infiltrating ductal	29 (65.9) / 27 (61.4)	32 (50.8) / 30 (47.6)	0.4244 / 0.5088
Intraductal	2 (4.5) / 3 (6.8)	10(15.9%) / 17(27)	0.1254 / 0.0413
Invasive lobular	10(22.7) / 12(27.3)	16(25.4) / 11(17.5)	1.0000 / 0.3606
Others*	3 (6.8) / 2 (4.5)	5 (7.9) / 5 (7.9)	1.0000 / 0.6996
Nodal status at primary			
Positive	33 (75)	38 (60.3)	0.5376
Negative	11 (25)	25 (39.7)	0.0088
ER-primary/relapse			
Positive	31 (70.4) / 7 (61.4)	45 (71.4) / 42 (66.7)	1.0000 / 0.8752
Negative	13 (29.6) / 17 (38.6)	18 (22.2) / 21 (33.3)	1.0000 / 0.7065
Adjuvant chemotherapy			
Yes/No	26 (59) / 18 (41)	32 (50.8) / 31 (49.2)	0.7417 / 0.7248
Adjuvant hormone therapy			
Yes/No	33 (75) / 11(25)	43(68.2) / 20(31.8)	0.7636 / 0.6784

\*Gelatinous, papillary and tubular carcinoma

ing with the diagnosis of recurrence until the last check up in December 2012. The average patient age during the period of diagnosis was 49.8±10.5 years. Applying the scheme described above, 44 (41.1%) of the relapses were classified as TRs and 63 (58.9%) as NPs.

Of 63 relapses defined as NPs, 54 (85.7%) changed the location and 49 (68.3%) had a different histology. The patient average age with TRs and with NPs did not differ significantly at the time of diagnosis of the primary tumor (TR 48.8±10.45 years vs NP 50.8±10.56;  $p < 0.330$ ) (Tables 2 and 3). Patients, who developed TRs were significantly younger than those with NPs at the time of recurrence (TR 53.66±11.1 years vs NP 58.15±10.6;  $p < 0.05$ ) (Tables 2 and 3).

When the patients were separated according to age, it was established that 25% of those with TRs were under the age of 35. This finding was in accordance with the younger age of those patients at the time of recurrence. As expected, the location of TR and NP was significantly different ( $p < 0.0001$ ) (Table 2).

TRs were located more often at the site of the primary tumor (at the exact same place 88.6%; 38.5% in the upper-lateral quadrant; 25.6% in the

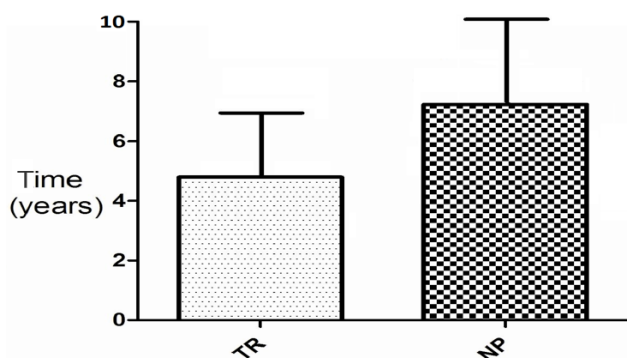
lower-lateral quadrant; 12.8% in the central zones; 23% in the upper-medial quadrant). On the other hand, the NPs were located at different sites, primarily distant from the primary tumor (various locations 85.7%; 33.3% in the upper-lateral quadrant; 24% in the lower-lateral quadrant; 22.2% in the central zones; 20.5% in the upper-medial quadrant).

On rare occasions, when clinical and  $^{99m}\text{Tc}$ -MI-BI SPECT-CT data showed that recurrences were positioned close, but not exactly, in the zone of up to 3 cm around the primary tumor, they could be classified as TRs, based on the same histology and other characteristics.

The status of the axillary lymph nodes, the positivity of the progesterone receptors and the adjuvant therapy did not differ significantly between patients with TRs and patients with NPs (Table 3).

The histological type of the primary tumors in patients from both categories did not differ significantly, either. IDCs were most common in TRs (65.9 vs 50.8%,  $p = 0.4244$ ). At the same time, the frequency of intra-ductal cancer was significantly higher in NPs (27 vs 6.8%,  $p = 0.0413$ ) (Table 3).

The majority of TRs (86.4%) had the same



**Figure 2.** Comparison of the mean time to appearance of NP and TR ( $p < 0.0001$ ). NP: new primary, TR: true recurrence.

histological structure with the primary tumor, as opposed to only 9.5% of NPs ( $p = 0.0001$ ).

Based on the change of the histological characteristics, 6.3% of the local recurrences were identified as NPs regardless of the fact that they were located in the area of the damaged quadrant.

Some other recurrences (6.5%) were identified as NPs. This was based on the changes of the histology from non-invasive to invasive cancer (ductal or lobular), which corresponds to the natural history of breast cancer.

Recurrences that were defined as NPs begun to develop after a significantly longer period of time in comparison to the TRs ( $7.4 \pm 2.6$  years vs  $4.8 \pm 2.2$ ,  $p < 0.0001$ ) (Figure 2).

Twenty-two (50%) of the patients with TRs developed distant metastases, against only 11 (19%) of patients with NPs ( $p < 0.05$ ).

The overall 5-year survival rate of patients with TR was significantly lower compared to patients with NP (31.8 vs 96.7%;  $p = 0.0001$ ) (Figure 3).

The majority of the patients (13 patients) with TR passed away as a result of disease progression till the end of the 3<sup>rd</sup> year after their treatment. The remaining 9 passed away after 40 months.

Of the patients with NPs 2, passed away on the 26<sup>th</sup> and 32<sup>nd</sup> month.

## Discussion

With this research we have tried to classify

107 in-breast recurrences as TRs or NPs and to evaluate the clinical importance of this classification.

Using the accepted scheme for classification, the majority of the recurrences were identified as NPs (TR 41.1 vs NP 58.9%).

Similar results between the two types of local recurrences (TR 22 vs NP 55%) were reported by Kurtz et al. [10], Smith et al. [11] (TR 44 vs NP 51%) and by researchers at MD Anderson Cancer Centre (38 vs 62%, respectively) [12].

Our method of classification possibly leads to lower frequency of TRs. Due to lack of universal criteria or a standard method for classification of recurrences, the majority of the researchers uses localization and histology for differentiating recurrences [4,13,14]. This is also due to the unavailability of modern molecular methods in everyday practice [15,16].

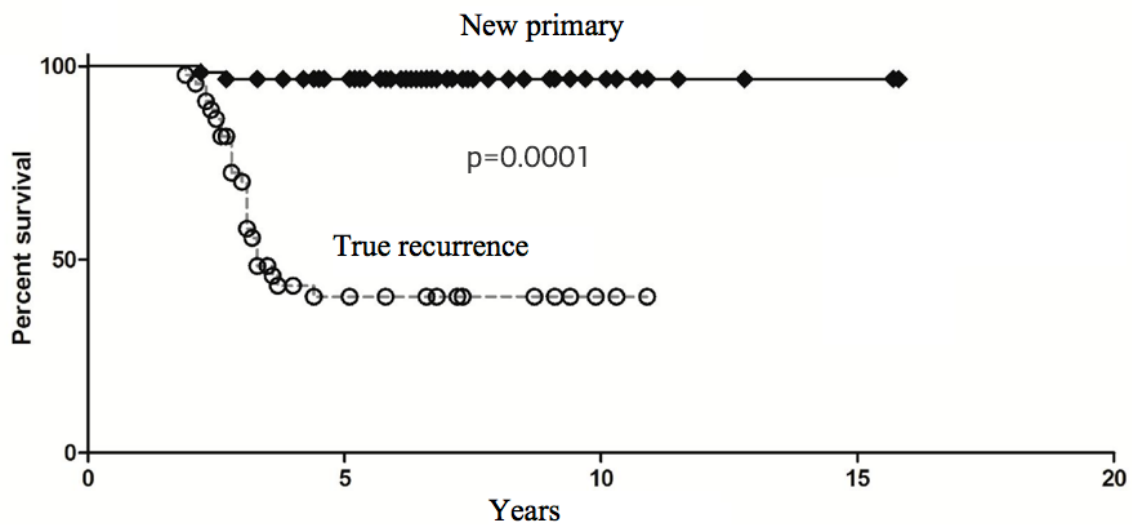
In the analysis presented we used the same criteria for differentiating the recurrences, supported by data from  $^{99m}\text{Tc}$ -MIBI SPECT-CT.

We have chosen this simple scheme, accessible to the clinicians, since local recurrences are in essence "recurrence of the illness on the spot". The restrictive classification, which we accepted for the TR and the use of data from  $^{99m}\text{Tc}$ -MIBI SPECT-CT support the precise description of the locality of the recurrences and, in this way, the relationship between TRs and the NPs.

It is well-known that working on a retrospective analysis like the present one, it is difficult to assess the distance based on the medical records because on the one hand, it is a linear measure, while, on the other hand, the distance within the breast is a spherical distance. This often leads to imprecision in defining local recurrences and to unrealistic overestimation of the TRs. In order to eliminate these uncertainties, we used  $^{99m}\text{Tc}$ -MIBI SPECT-CT, which provides objective information about the localization of the recurrence within the breast parenchyma and increases the accuracy and the importance of the classification scheme for prognosis.

Using this scheme, we have detected a significant difference in the localization of the two kinds of recurrences ( $p = 0.001$ ): 86.4% of TRs were located closely to the site of the initial tumor, and 85.7% of the NPs were located outside the treated quadrant. The same significant difference in the localization has also been detected by Hassan et al. ( $p = 0.002$ ) [17].

These results coincide with those by Smitt et al. [11], who reported that 90% of the NPs were lo-



**Figure 3.** Overall survival.

cated outside the affected quadrant, and with Fowble et al.[4], who analyzed 65 local recurrences in the remaining parenchyma and discovered that 54% of the NPs were located outside the affected quadrant.

The significance of the histological data, as a second method for classification has been proven in previous studies [7,8,13], especially convincingly, by Smitt et al. [11] who have found that if recurrences were classified only according to localization, the NPs were 37%, instead of the reported 51%.

Our analysis confirms the significance of the histological data for the classification of recurrences, demonstrating that 88.6% of TRs have similar histological type with the primary tumor, while 87.3% of the NPs have different histological structure.

In comparison to our data, Veronezi et al. [18] discovered that 60% of TRs have a similar histological structure with the primary tumor, and in our study 84.5% of the local recurrences had the same histological structure.

In addition, 6.3% of the local recurrences were defined as NPs only on the basis of the different histology, despite that they were located in the affected quadrant. Another 6.5% were defined as NPs on the basis of the change in the histology from non-invasive to invasive carcinoma (ductal or lobular). Despite the fact that we did not discover significant differences in the histology of the TRs and NPs, the higher incidence of intra-

ductal carcinomas in NPs in comparison with the incidence of these carcinomas in TRs (27 vs 6.8%, respectively), corresponded to our scheme of classification, in which the change from IDC towards intraductal histological type, has been accepted as a sign of the NPs, coinciding with the natural history of the carcinoma.

Our data are very close to the ones, reported by Smith et al. [11] (28 vs 8.3%, respectively) and by Hassan et al. (25 vs 9.5%, respectively) [17].

In this analysis we detected some differences in the profile of the risk factors of the patients who developed TRs and NPs.

The patients with TRs were considerably younger at the time of the appearance of the recurrence in comparison with those with NPs ( $53.66 \pm 11.1$  years vs  $58.15 \pm 10.60$  years, respectively;  $p=0.035$ ).

The same significant difference in the age of patients with TRs and those with NPs was reported by Dutch investigators, (48 vs 59 years, respectively;  $p<0.0001$ ) [19].

The younger age of the women in our study could be explained with some unfavorable histological features, relatively frequently encountered with tumors in young populations [18-20], which are signs of increased biological aggressiveness. The diffuse inflammatory forms of TRs, which were reported in patients under 35 years of age, are probably signs of this biological behavior (Figure 1).

The younger age of women with TRs in this

analysis is probably due to the fact, that young women, especially those under the age of 35, are not the subject of screening programs and are usually diagnosed with tumors which are larger in size [20,21].

TRs and NPs in this study demonstrated pathomorphological differences. Recurrences, classified as TR, appeared within a significantly shorter period of time following treatment, in comparison with the ones classified as NPs ( $4.8 \pm 2.2$  years vs  $7.4 \pm 2.6$  years;  $p < 0.0001$ ). Haffty et al. [13] reported a mean period to the appearance of TR of 3.2 vs 5.4 years, respectively; ( $p < 0.05$ ); Smith et al. [11] : 3.7 vs 7.3 years, respectively ( $p < 0.0001$ ); Nishimura et al. [22]: 37 vs 55 months, respectively ( $p = 0.031$ ); Komoike et al. [23] : 47 vs 62 months respectively ( $p = 0.025$ ); and Yoshuda et al. [24] : 30.6 months for TR and 57.4 months for NPs ( $p = 0.0197$ ).

Many studies, including the current one, have discovered quite different characteristics of TR and NPs.

For example, 5-year overall survival of the patients with TR in our study was significantly lower in comparison with the overall survival of the patients with NPs (31.8 vs 96.7%;  $p < 0.0001$ ) (Figure 3).

Our results are comparable with the results of many important studies, which have reported the same significant differences in the overall survival in both types of local recurrences. Komoike et al. [25] reported a 5-year overall survival in patients with TRs of 71% as compared with 94.7% in NPs ( $p = 0.0022$ ); Huang et al. [12] reported 36% 10-year overall survival in TRs and 87% in NPs. Data, which are particularly demonstrative for this relation, are those in the study of Yoshuda et

al. [24], which showed, that a 5-year overall survival of patients with TRs was 72.4% in comparison with 100% of those with NPs. Some studies reported controversial results about the survival after the two types of recurrences, and two studies did not find significant differences in the survival of TRs and NPs [4,26]. This is probably due to the different criteria used for classification and the different period of follow-up of the patients.

## Conclusions

In conclusion, it seems that a significant part of recurrences, which develop in the residual breast parenchyma following BCT, are new carcinomas.

Consequently, the recurrences developing after BCT represent different clinical events, having different origin, prognosis and therefore, requiring different treatment.

The short period of time till the appearance of TRs, their localization around the site of the primary tumor and the similar histology with the primary tumor, confirm the standpoint that they originate from residual cells of the primary tumor, "not eliminated during the resection and not destroyed by radiotherapy".

The long period till the appearance of the NPs, their localization in different parts of the residual breast parenchyma and the different histology, are major reasons to assume that they originate "*de novo*", without relation with the primary tumor.

The considerably lower 5-year overall survival of patients with TRs as a result of disease progression, defines these recurrences as a more aggressive and severe disease, requiring aggressive chemotherapy.

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