Ann Surg Oncol
DOI 10.1245/s10434-013-3416-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Effect of Margin Width on Local Recurrence in Triple-Negative Breast Cancer Patients Treated with Breast-Conserving Therapy

Melissa Pilewskie, MD[1], Alice Ho, MD[2], Emily Orell, BS[1], Michelle Stempel, MPH[1], Yu Chen, BS[3], Anne Eaton, MS[4], Sujata Patil, PhD[4], and Monica Morrow, MD[1]

[1]Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY; [2]Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY; [3]Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY; [4]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

ABSTRACT

Background. The effect of increasing negative margin width after breast-conserving therapy (BCT) on local recurrence (LR) is controversial. LR rates vary by subtype, with the highest rates seen in triple-negative breast cancer (TNBC). This study examined LR rates in relationship to margin width in TNBC treated with BCT.

Methods. Women with TNBC who underwent BCT between 1999 and 2009 were identified. Margins were defined as positive (ink on tumor), 0.1–2.0, and 2 mm. Patients with positive margins were excluded. Statistical comparisons were by *t* test, Fisher's exact test, and Wilcoxon rank sum test. Cumulative incidence of LR was compared by competing-risks methodology.

Results. Of 535 cancers, 71 had margins ≤2 mm and 464 had margins >2 mm. At a median follow-up of 84 months (range 8–165 months), there were 37 local, 18 regional, and 77 distant recurrences or deaths as first events. Ten patients had a locoregional recurrence before planned radiotherapy and were excluded from cumulative incidence analyses. The cumulative incidence of LR at 60 months for margins ≤2 mm was 4.7 % (95 % confidence interval 0–10.0) and for >2 mm was 3.7 % (1.8, 5.5) ($p = 0.11$). After controlling for chemotherapy and tumor size, there was no difference in LR between the two margin groups ($p = 0.06$). A difference in the risk of distant recurrence or death was not observed ($p = 0.53$).

Conclusions. Margin width of >2 mm was not associated with reduced LR rates. These data support a negative margin definition of no ink on tumor, even in this high-risk TNBC cohort.

Breast-conserving therapy (BCT) is a well-established treatment modality for breast cancer, with equivalent survival to mastectomy.[1] Although rates of local recurrence (LR) have decreased since the initial prospective randomized trials of BCT, significant controversy exists regarding the optimal negative margin width.[2] Positive margins, defined as ink on tumor, are definitively associated with increased rates of LR compared to negative margins, but the optimal amount of normal breast tissue which constitutes a negative margin remains uncertain.[3] Both surgeons and radiation oncologists use widely varying definitions of what margin width precludes the need for re-excision, in spite of the findings of a meta-analysis of 21 published studies which found no significant improvement in rates of LR with increasing negative margin width.[4–7] Recent data indicate that rates of LR vary by breast cancer subtype as approximated by estrogen receptor (ER), progesterone receptor (PR), and HER2/neu, with patients with triple-negative breast cancer (TNBC) having higher LR rates compared to the non-triple-negative subtypes.[8] Given the higher reported rates of LR in TNBC, we sought to examine the impact of margin status in this subgroup to

The findings presented in this manuscript were presented in part in a poster discussion session at the 2013 American Society of Clinical Oncology Annual Meeting, May 31–June 4, 2013. This study was also the recipient of the 2013 Conquer Cancer Foundation of ASCO Merit Award.

First Received: 11 September 2013

M. Morrow, MD
e-mail: morrowm@mskcc.org

Published online: 11 December 2013

determine whether margins >2 mm were associated with decreased rates of LR in this population.

METHODS

After approval by the institutional review board at Memorial Sloan-Kettering Cancer Center, a prospectively maintained database was used to identify women with TNBC who underwent BCT at our institution between 1999 and 2009. TNBC was defined as ER and PR positivity of <1 %, and HER2/neu negativity (0, 1 + staining) by immunohistochemistry and/or no amplification by fluorescence in situ hybridization. All patients underwent lumpectomy and had planned whole-breast radiotherapy (RT). Patients receiving partial-breast RT and patients not undergoing whole-breast RT (as a result of refusal or medical recommendation) were excluded. Because the population of interest comprised women who completed standard treatment (i.e., lumpectomy and RT), women who experienced recurrence before RT were also excluded from estimates and comparisons of cumulative incidence of LR, regional recurrence, distant metastasis, and death. Margin status was defined as positive (ink on tumor), 0.1–2.0, or >2.0 mm. Forty-six patients with positive margins were excluded from analysis. One woman had a contralateral TNBC 3 years after her initial diagnosis; these cancers were treated as independent for all analyses. Data on patient, tumor, and treatment characteristics were collected: age at surgery; tumor size; lymphovascular invasion (present or absent); ER and PR status; HER2/neu status; receipt of adjuvant whole-breast RT, including a boost to the tumor bed or regional nodal irradiation; and receipt of adjuvant chemotherapy. Patient charts were reviewed for date of last follow-up, status at last follow-up (no evidence of disease; alive with disease; died of disease; died other cause; or died unknown cause). Recurrence events and dates were captured for local (ipsilateral breast), regional (ipsilateral axillary, internal mammary, or supraclavicular nodal basins), or distant metastasis.

Group characteristics were compared by *t* tests and Wilcoxon rank-sum tests for age and tumor size, respectively, and Fisher's exact test for categorical covariates. Time to first event (LR, regional recurrence, distant metastasis/death, or end of follow-up) was calculated from date of definitive surgery, and competing risks methodology was used to estimate the cumulative incidence of LR, regional recurrence, and distant recurrence/death. Nine women had a bilateral prophylactic mastectomy during follow-up and were censored at the time of the procedure. Gray's test, and Fine and Gray regression were used to test associations between clinical factors and LR in univariate and multivariate settings, respectively. Multivariate models were built to investigate the effect of margin status after adjusting for covariates with $p < 0.15$ for either margin status or LR on univariate analysis; RT was not included in these models because patients who experienced recurrence before RT were excluded.

All statistical analysis was performed by SAS 9.2 (SAS Institute, Cary, NC, USA) or R 2.3.1 (R Foundation for Statistical Computing, Vienna, Austria), and the *cmprsk* package was used. *p* values of <0.05 were considered significant.

RESULTS

A total of 535 TNBCs treated with BCT during the study period were identified in 534 women. Of the 535 cancers, 464 had margins >2 mm and 71 had margins ≤2 mm. The mean age of the study population was 55.4 years. The median tumor size was 1.6 cm (range 0.1–7.3 cm), 29 % were node positive, and 24 % had lymphovascular invasion identified. 84 % of the patients received adjuvant chemotherapy, 94 % had a radiation boost to the lumpectomy bed, and 11 % received regional nodal RT. Patient, tumor, and treatment characteristics by margin status are shown in Table 1. No significant differences in age, tumor size, nodal status, presence of lymphovascular invasion, or receipt of RT between the

TABLE 1 Patient and treatment variable by margin status

Variable	Margin of		*p* value
	≤2 mm ($n = 71$)	>2 mm ($n = 464$)	
Age at surgery (mean ± standard deviation)	56.7 ± 12.2	55.2 ± 12.2	0.30
Age >50 years	53 (75 %)	312 (67 %)	0.27
Tumor size, median (IQR)	1.5 (1–2.2)	1.6 (1.1–2.3)	0.27
Tumor size >2 cm	22/69 (32 %)	165/457 (36 %)	0.59
Lymphovascular invasion present	19 (27 %)	110 (24 %)	0.55
Nodal status positive	25/71 (35 %)	130/463 (28 %)	0.26
Chemotherapy	54 (76 %)	398 (86 %)	0.05
Whole-breast RT[a]	68 (96 %)	457 (98 %)	0.14
Tumor bed boost[b]	59/63 (94 %)	380/405 (94 %)	1.00
Regional RT[b]	10/62 (16 %)	41/404 (10 %)	0.19

Denominators are included in cases where not all patients could be included as a result of missing data

IQR interquartile range, *RT* radiotherapy

[a] The only patients who did not receive RT were those who experienced recurrence before planned RT

[b] Within the subset of patients treated with RT

≤2 and >2 mm margin groups were noted. There was a trend toward increased use of chemotherapy in the >2 mm margin group ($p = 0.05$).

During the study period, the use of chemotherapy regimens changed. In the initial year of the study (1999), cyclophosphamide, methotrexate, and fluorouracil was the most frequent regimen used, with 44 % of patients receiving this regimen. Between 2000 and 2009, an anthracycline with or without a taxane was increasingly used, and an anthracycline with a taxane became the most frequently used regimen by 2009 (75 %). Among women who completed standard treatment, there was no difference in the rate of LR by year of surgery during the study period ($p = 0.240$) or when comparing patients treated during the first 5 years (1999–2003) to those treated in the last 5 years (2004–2009) ($p = 0.25$).

For the entire population, at median follow-up of 84 months (range 8–165 months), there were 37 LR, 18 regional recurrences, and 77 distant recurrences or deaths as first events. Ten patients had an early locoregional recurrence (LRR) after lumpectomy but before planned RT (9 local, 1 regional). 4 % (3 of 71) of patients with ≤2 mm margins experienced LRR before planned RT, compared to 1.5 % (7 of 464) of patients with margins >2 mm ($p = 0.14$). All ten patients with an LRR before planned RT developed distant metastasis, and at date of last follow-up, eight had died. The ten patients with an LRR before planned RT were not included in analyses of cumulative incidence of LR, regional recurrence, and distant metastasis/death.

Among the remaining 525 patients who completed RT, the cumulative incidence of LR at 60 months for patients with margins ≤2 mm was 4.7 % (95 % confidence interval [CI] 0–10.0) and 3.7 % (1.8–5.5) for those with margins >2 mm ($p = 0.11$) (Table 2; Fig. 1). After controlling for the use of adjuvant chemotherapy and tumor size, there remained no significant difference in LR between the margin groups ($p = 0.06$, subdistribution hazard ratio 2.23 for margins ≤2 mm or less compared to >2 mm with 95 % CI 0.97–5.14). No significant differences in incidence of LR were observed on the basis of age, tumor size, lymphovascular invasion, nodal status, chemotherapy, or radiation boost. There were no observed differences in the risk of regional recurrence ($p = 0.58$) or distant recurrence/death ($p = 0.53$) between the margin groups (Fig. 2).

DISCUSSION

Our study does not support the idea that wider surgical margins improve LR rates in patients with TNBCs. These data add to the growing literature that obtaining a margin more widely clear than no ink on tumor in BCT for invasive breast cancer does not impact local control.[7,9,10] A meta-analysis by Houssami et al. of 14,571 women found no significant decrease in LR with increasing negative margin distance, although positive margins were highly correlated with LR.[7] However, this meta-analysis did not examine the relationship between breast cancer subtype and margins because hormone receptor status and HER2/neu status were not reported in a majority of the included studies. Although it may seem counterintuitive that more widely clear margins do not reduce LR, an emerging body of literature supports the idea that biology and the use of effective systemic therapy are the major determinants of

TABLE 2 Univariate analysis of patient and treatment factors, and risk of LR

Factor	Cumulative incidence of LR at 60 mo (95 % confidence interval)	*p* value
Margin status ≤2 mm	4.7 % (0–10.0)	0.11
Margin status >2 mm	3.7 % (1.8–5.5)	
Age at surgery >50 years	3.8 % (1.7–5.8)	0.60
Age at surgery ≤50 years	3.9 % (0.8–7.0)	
Tumor size >2 cm	6.4 % (2.5–10.3)	0.11
Tumor size ≤2 cm	2.6 % (0.8–4.3)	
LVI present	4.3 % (0.6–8.1)	0.79
LVI absent	3.6 % (1.7–5.6)	
Nodal status positive	5.3 % (1.4–9.2)	0.65
Nodal status negative	3.2 % (1.3–5.1)	
Chemotherapy	4.0 % (2.1–5.9)	0.83
No chemotherapy	2.7 % (0–6.3)	
Boost	4.3 % (2.3–6.4)	0.48
No boost	3.4 % (0–10.2)	

LR local recurrence, *LVI* lymphovascular invasion

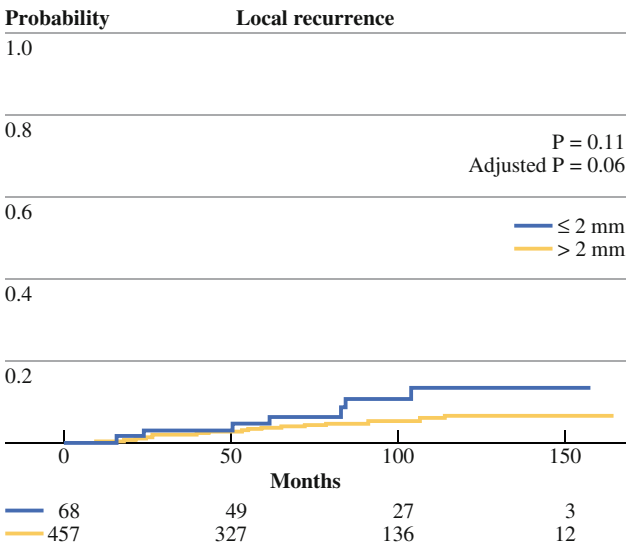

FIG. 1 Cumulative incidence of local recurrence

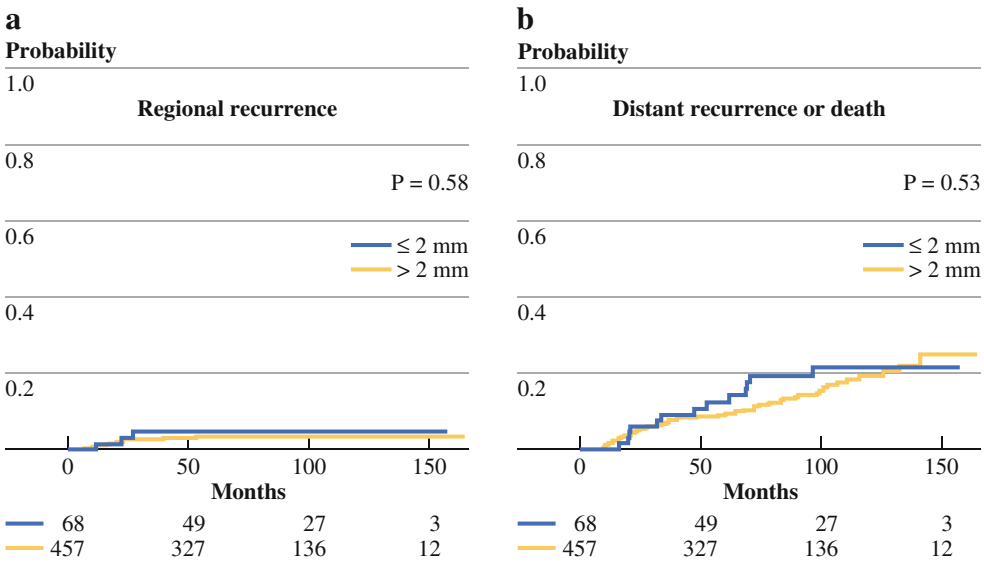

FIG. 2 Cumulative incidence curves for **a** regional recurrence, **b** distant recurrence, or death

local control. Rates of both local and distant recurrence vary by breast cancer subtype.[8,11–13] A meta-analysis by Lowery et al.[8] examined LRR rates by subtype in 7,174 patients undergoing BCT. At a median follow-up of 57 months, patients with a non-TNBC (ER, PR positive or HER2/neu overexpressing) had lower rates of LRR than the triple-negative subtype (relative risk [RR], 0.49; 95 % CI 0.33–0.73). A similar pattern was seen in 5,416 women treated with mastectomy where patients with non-TNBC were significantly less likely to develop an LRR after mastectomy then the triple-negative cohort (RR 0.66; 95 % CI 0.53–0.83). In a more recent study, Russo et al. examined the impact on LR of margin widths of ≥2 mm to margins <2 mm in 906 women undergoing BCT between 1998 and 2006, controlling for tumor subtype.[14] The 5-year rate of LR was 0 % for margins <2 mm and 2.3 % for ≥2 mm margins. On multivariate analysis, margin width was not associated with LR, but triple-negative subtype was a highly significant predictor of LR with an adjusted hazard ratio of 3.7 (95 % CI 1.6–8.8; $p = 0.003$).

The impact of biology on LR is mitigated by effective systemic therapy. In the National Adjuvant Breast and Bowel Project (NSABP) B14 trial of tamoxifen versus placebo in ER-positive women, the use of tamoxifen reduced LR to 4.3 % compared to 14.7 % in the placebo group.[15] A similar reduction in LR was seen with the addition of chemotherapy in ER-negative women from 13.4 to 2.6 % in NSABP B13.[16] However, the experience with HER2-overexpressing patients indicates that even greater reductions in LR can be obtained with the addition of targeted therapy to chemotherapy.[13,17,18] A meta-analysis of randomized trials comparing adjuvant chemotherapy with or without trastuzumab for HER2/neu-positive breast cancer showed significant reductions in LR in the trastuzumab-treated patients (RR 0.58; 95 % CI 0.43–0.77, $p = 0.0002$).[18]

At this time, there is no targeted therapy for TNBC, so it could be postulated that more extensive surgery might improve LR for the triple-negative subtype. A mastectomy represents the widest margin that can be obtained in breast cancer surgery, and three studies have examined the effect of surgery type (BCT compared to mastectomy without RT) on LR in TNBCs. Patients treated with mastectomy had larger tumors and higher risk features; however, on multivariate analysis, type of surgery was not a predictor of LRR in this patient population.[19–21]

To our knowledge, our study is the first to directly address the question of margin width in BCT in TNBC. In addition to finding no impact of margins >2 mm on LR, it is noteworthy that rates of local control were high in this patient cohort, with only 5 % of those with margins of 2 mm or less and 4 % of those with margins >2 mm experiencing LR. The non-significant reported hazard ratio for LR after controlling for chemotherapy and tumor size, coupled with the studies showing no difference in outcome for TNBC patients treated with BCT and mastectomy, strongly suggests that bad biology is unlikely to be overcome with larger surgical procedures. This finding has implications for clinical practice because significant controversy currently exists among surgeons and radiation oncologists regarding the acceptable margin width in BCT for invasive breast cancer, with only 11–40 % of surveyed surgeons comfortable with a negative margin definition of no ink on tumor.[4–6] However, acceptance of this negative margin definition has the potential to benefit a significant number of women, as recent data show that 25 % of all women treated with BCT undergo a re-excision, and approximately half of re-excisions are performed to

achieve wider negative margins.[22–24] Minimizing the need for re-excision decreases the risk of poorer cosmetic outcome associated with the resection of larger amounts of breast tissue, delayed time to adjuvant therapy, additional operating room costs, and the possible psychological impact of reoperation on patients.[24]

Strengths of this study include a large cohort of contemporarily treated TNBC patients at a single institution, with detailed information available on margin and treatment data. Furthermore, because TNBCs recur early, with peaks of LR seen in the first 3 years, we have likely captured the majority of LR events with a median follow-up of 84 months.[25,26] However, this study is a retrospective analysis with known potential limitations. There was a trend toward decreased chemotherapy utilization in the $\leq$2 mm margin group. During the time period of this study, there was no consensus on the use of chemotherapy for tumors <1 cm in size, and this difference likely represents chance variation. On univariate analysis, factors such as age, lymphovascular invasion, use of chemotherapy, nodal status, tumor size, and use of a boost were not found to be significant predictors of LR, which may be the result of insufficient power to detect a difference based on our population size. However, the numerically low rates of LR in both groups in our study suggest that even if a larger sample size resulted in a statistically significant difference, the magnitude of difference is unlikely to be clinically meaningful.

In conclusion, although patients with TNBCs have higher reported rates of LR than other breast cancer subtypes, it does not appear that more extensive surgery improves outcome. Our current data continue to support the definition of a negative margin as no ink on tumor, even in this high-risk breast cancer subset.

ACKNOWLEDGMENT This study was funded in part through NIH/NCI Cancer Center Support grant P30 CA008748.

REFERENCES

1. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet.* 2005;366(9503):2087–106.
2. Bouganim N, Tsvetkova E, Clemons M, et al. Evolution of sites of recurrence after early breast cancer over the last 20 years: implications for patient care and future research. *Breast Cancer Res Treat.* 2013;139:603–6.
3. Singletary SE. Surgical margins in patients with early-stage breast cancer treated with breast conservation therapy. *Am J Surg.* 2002;184:383–93.
4. Azu M, Abrahamse P, Katz SJ, et al. What is an adequate margin for breast-conserving surgery? Surgeon attitudes and correlates. *Ann Surg Oncol.* 2010;17:558–63.
5. Lovrics PJ, Gordon M, Cornacchi SD, et al. Practice patterns and perceptions of margin status for breast conserving surgery for breast carcinoma: National Survey of Canadian General Surgeons. *Breast.* 2012;21:730–4.
6. Hassani A, Griffith C, Harvey J. Size does matter: High volume breast surgeons accept smaller excision margins for wide local excision—a national survey of the surgical management of wide local excision margins in UK breast cancer patients. *Breast.* 2013;22:718–22.
7. Houssami N, Macaskill P, Marinovich ML, et al. Meta-analysis of the impact of surgical margins on local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy. *Eur J Cancer.* 2010;46:3219–32.
8. Lowery AJ, Kell MR, Glynn RW, et al. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. *Breast Cancer Res Treat.* 2012;133:831–41.
9. Groot G, Rees H, Pahwa P, et al. Predicting local recurrence following breast-conserving therapy for early stage breast cancer: the significance of a narrow (</=2 mm) surgical resection margin. *J Surg Oncol.* 2011;103:212–6.
10. Chen W, Stroom J, Sonke JJ, et al. Impact of negative margin width on local recurrence in breast conserving therapy. *Radiother Oncol.* 2012;104:148–54.
11. Hattangadi-Gluth JA, Wo JY, Nguyen PL, et al. Basal subtype of invasive breast cancer is associated with a higher risk of true recurrence after conventional breast-conserving therapy. *Int J Radiat Oncol Biol Phys.* 2012;82:1185–91.
12. Panoff JE, Hurley J, Takita C, et al. Risk of locoregional recurrence by receptor status in breast cancer patients receiving modern systemic therapy and post-mastectomy radiation. *Breast Cancer Res Treat.* 2011;128:899–906.
13. Kim MM, Dawood S, Allen P, et al. Hormone receptor status influences the locoregional benefit of trastuzumab in patients with nonmetastatic breast cancer. *Cancer.* 2012;118:4936–43.
14. Russo AL, Arvold ND, Niemierko A, et al. Margin status and the risk of local recurrence in patients with early-stage breast cancer treated with breast-conserving therapy. *Breast Cancer Res Treat.* 2013;140:353–61.
15. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst.* 1996;88:1529–42.
16. Fisher B, Dignam J, Mamounas EP, et al. Sequential methotrexate and fluorouracil for the treatment of node-negative breast cancer patients with estrogen receptor–negative tumors: eight-year results from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 and first report of findings from NSABP B-19 comparing methotrexate and fluorouracil with conventional cyclophosphamide, methotrexate, and fluorouracil. *J Clin Oncol.* 1996;14:1982–92.
17. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.* 2005;353:1673–84.
18. Dahabreh IJ, Linardou H, Siannis F, et al. Trastuzumab in the adjuvant treatment of early-stage breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Oncologist.* 2008;13:620–30.
19. Adkins FC, Gonzalez-Angulo AM, Lei X, et al. Triple-negative breast cancer is not a contraindication for breast conservation. *Ann Surg Oncol.* 2011;18:3164–73.
20. Parker CC, Ampil F, Burton G, et al. Is breast conservation therapy a viable option for patients with triple-receptor negative breast cancer? *Surgery.* 2010;148:386–91.
21. Zumsteg ZS, Morrow M, Arnold B, et al. Breast-conserving therapy achieves locoregional outcomes comparable to mastectomy in women with T1–2N0 triple-negative breast cancer. *Ann Surg Oncol.* 2013;20:3469–76.

22. Morrow M, Jagsi R, Alderman AK, et al. Surgeon recommendations and receipt of mastectomy for treatment of breast cancer. *JAMA*. 2009;302:1551–6.
23. McCahill LE, Single RM, Aiello Bowles EJ, et al. Variability in reexcision following breast conservation surgery. *JAMA*. 2012; 307:467–75.
24. Al-Ghazal SK, Blamey RW, Stewart J, et al. The cosmetic outcome in early breast cancer treated with breast conservation. *Eur J Surg Oncol.* 1999;25:566–70.
25. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res.* 2007;13(15 Pt 1):4429–34.
26. Pogoda K, Niwinska A, Murawska M, et al. Analysis of pattern, time and risk factors influencing recurrence in triple-negative breast cancer patients. *Med Oncol.* 2013;30:388.