Evaluation of distant sequelae of breast cancer treatment among patients after breast-conserving surgery depending on the type of intervention in the axillary fossa

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Aim of the study: The goal of this work was to assess upper-limb sequelae among patients undergoing breast-conserving therapy (BCT) for breast cancer 5–6 years after the surgical procedure.

Material and methods: A controlled clinical study was conducted on 128 patients who had undergone surgery 5–6 years prior. BCT + ALND (axillary lymph node dissection) was performed in 58 patients and 69 underwent BCT + SLND (sentinel lymph node dissection). Patients declared active participation in physiotherapy. The following parameters were assessed in studied subjects: range of motion in the shoulder joint, superficial sensation, upper limb circumference, skin sensation, and presence of winged scapula sign.

Results: Five to six years after BCT, patients who had undergone BCT + ALND presented with significantly poorer outcomes concerning upper limb range of motion on the operated side compared to the BCT + SLND group with regard to the following features: flexion (p = 0.00004), external rotation (p = 0.0292), and internal rotation (p = 0.0448). However, no statistically significant differences were noted between compared groups with regard to upper limb circumference and sensation disturbances. Statistically significant differences between limb on the operated side (operated limb – OL) vs. contralateral limb (healthy limb – HL) were noted in the BCT + SLND group with regard to the range of motion in extension (p = 0.0004), external rotation (p = 0.0055), and internal rotation (p < 0.0001), as well as the occurrence of winged scapula sign (p < 0.0001) and sensation disturbances (p < 0.0001).

Conclusions: Our study demonstrated that both procedures are not free of distant sequelae, although the BCT + ALND group is more frequently affected.

Key words: breast conserving therapy, breast cancer, adverse effects, axillary lymphadenectomy, sentinel lymph node procedure

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Introduction

Breast cancer is the most common malignancy in women. Breast-conserving therapy (BCT) constitutes an alternative to mastectomy in early stages of breast cancer. Currently, the majority of surgical procedures in breast cancer patients are conducted using breast-conserving techniques. BCT is offered to patients with early stages of breast cancer (T1M0N0, T1N1M0, T2N0M0, T2N1M0; T-tumour, N-node, M-metastasis) [1–3]. Surgical intervention within the axillary fossa is necessary in all cases of conserving treatment involving invasive carcinoma of the breast. Sentinel lymph node biopsy (SLND) allows identification of the particular lymph node (or a group of lymph nodes) requiring histopathological verification. In the absence of sentinel lymph node metastases there is no need for removal of the entire lymphatic system of the axillary fossa (SLND) [1–3]. Excision of the entire contents of the axillary fossa (axillary lymph node dissection – ALND) is indicated if there are contraindications to SLND or when metastases (exceeding 2 mm in size – macrometastases) are identified [1–3]. Surgery does not conclude treatment in patients treated with BCT. Patients receive adjuvant treatments with radiotherapy, chemotherapy, and hormone therapy [4, 5].

Both surgical as well as adjuvant treatment may lead to development of sequelae unrelated to the neoplastic process itself. Complications of breast cancer treatment include: upper limb oedema, post-breast surgery pain syndrome, irritation of the brachial plexus, skin and subcutaneous tissue fibrosis, impairment of upper limb function on the operated side, change in posture, scapular protrusion, and foot disorders [6–10].

Numerous authors attempted to perform comparative analysis of long-term therapeutic effects of SLND and total axillary lymphadenectomy for the subsequent functioning of patients [11–16]. The majority of those studies are based on questionnaires [14–16] assessing patients' subjective feelings or evaluating functioning of patients up to three years after the procedure. Other authors point to the necessity of conducting thorough research based on objective parameters [17].

The goal of this study was to evaluate the range of motion in the upper limb and to assess the presence of lymphedema, sensation disturbances, or

wing scapula sign in females treated for breast cancer with BCT 5–6 years after surgery.

Material and methods

This controlled, non-randomised clinical study was conducted with the consent of the Bioethical Committee at the *Collegium Medicum* in Bydgoszcz (document no. KB 666/2016). It took place from June to December 2017 and included patients who had undergone surgery for breast cancer 5–6 years prior.

The study methodology was as follows: patient medical records were analysed with respect to the inclusion and exclusion criteria. Subsequently, selected patients who had undergone surgery between June 2011 and June 2012 using BCT + SLNB and BCT + ALND techniques were invited by phone to participate in free, voluntary visits assessing the range of motion in shoulder joints, presence of lymphoedema, skin sensation, and scapular winging. There were 424 patients treated with the above-described techniques at the Department of Breast Cancer and Reconstructive Surgery of the Oncology Centre in Bydgoszcz between June 2011 and June 2012. A total of 297 patients were referred for breast-conserving therapy (quadrantectomy) with simultaneous SLNB, while 124 patients qualified for BCT + ALND. As many as 128 patients fulfilled the inclusion criteria for the study: 59 patients undergoing BCT + ALND and 69 patients who had BCT + SLND performed.

Study inclusion criteria were as follows:

- patients referred for breast-conserving therapy: BCT + SLND or BCT + ALND,
- patients who gave informed consent to participate in the study,
- patients who declared willingness to participate in physiotherapy and anti-oedematous prophylaxis of the upper limb on the operated side,
- patients who responded to the invitation to participate in the study and reported to visit.

Study exclusion criteria were as follows:

- patients who required escalation of the extent of surgery to total excision of the axillary fossa or breast amputation within 5–6 years of the primary surgery,
- patients with other neoplastic processes or cancer metastases,
- patients who underwent surgical procedure on the contralateral breast,
- patients after reconstructive surgery of the breast,
- previous trauma to the upper limbs/shoulder girdle,
- lack of consent to participate in the study.

The following examinations were performed order to determine the presence and severity of adverse effects of surgical and adjuvant breast cancer treatment among qualified patients:

- Body mass measurements were performed using medical scales; patients were examined without footwear with measurement accuracy reaching 0.5 kg.
- Height.
- Body mass index (BMI) was calculated for each patient based on body mass height.
- Superficial sensation was examined with the monofilament test, which is commonly used in the diagnostics of neuropathy. The instrument used for this test consists of a handle and an attached filament. The filament bends as the pressure reaches 10 g. The test was performed on the upper limb (arm, forearm), in the axillary fossa, on the thorax and around the scapula.
- Mobility in the shoulder joint – the following angular measurements of the range of motion in the shoulder joint were performed: extension, flexion, external rotation, internal rotation, and abduction (examination was performed on the operated as well as the non-operated side). Measurements were taken using a gonimeter in accordance with the standard norms, and the result was recorded in degrees.
- The degree of scapular protrusion was assessed in order to verify the presence of winged scapula. All patients underwent scapula winging test – deviation of the medial margin of the scapula from the thoracic wall during upper limb flexion indicates dysfunction of the anterior serratus muscle innervated by the long thoracic nerve.
- Upper limb circumference was measured with a tape measure at three levels: metacarpal region (excluding the thumb), 10 cm below lateral epicondyle of humerus, and 10 cm above the lateral epicondyle of humerus. In accordance with the current standards, three grades of severity of oedema were distinguished depending on the difference between limb circumference on the operated vs. non-operated side:
  - mild oedema – difference in limb circumference 2–3 cm,
  - moderate oedema – difference in limb circumference 3–5 cm,
  - severe oedema – difference in limb circumference above 5 cm.

Statistical methods

Statistical analysis was performed using PQStat software v. 1.6.4.122.

Age, body mass, height, and BMI were compared between the study groups using Student's t-test. The number of removed nodes and affected nodes was compared between the study groups using Mann-Whitney's *U* test. Qualitative scale results depending on the study group were compared using χ^2 test of independence.

Results of scapular winging test and skin sensation test depending on the study group were compared using χ^2 test of independence and McNemar's test depending on the operated side. Results of limb mobility and circumference depending on the study group were compared using Mann-Whitney *U* test or Wilcoxon test depending on the operated side.

The level of probability was considered significant at $p < 0.05$, while the probability was considered highly significant with $p < 0.01$.

Results

Fifty-nine females from the study group had BCT + ALND performed, while 69 women underwent BCT + SLND. There were no statistically significant differences between groups

Table 1. Analysis of clinical and sociodemographic features in the studied group of patients

Characteristic	BCT + SLNB *n* = 69 (%)	BCT + ALND *n* = 59 (%)	Value of calculated probability
Age	Mean = 63.62 Me = 65 SD = 8.47	Mean = 63.73 Me = 64 SD = 8.60	$t = 0.1370$ $p = 0.8912$
Body mass	Mean = 73.90 Me = 69 SD = 13.78	Mean = 73.97 Me = 72 SD = 11.62	$t = 0.0297$ $p = 0.9764$
Height	Mean = 1.63 Me = 1.64 SD = 0.05	Mean = 1.61 Me = 1.62 SD = 0.05	$t = -2.448$ $p = 0.0157$
BMI	Mean = 27.65 Me = 26.29 SD = 5.11	Mean = 28.46 Me = 28.26 SD = 4.58	$t = 0.9389$ $p = 0.3496$
Operated side L R	 35 (50.72) 34 (49.28)	 28 (47.46) 31 (52.54)	$\chi^2 = 0.1358$ $p = 0.7125$
OR (+) (–)	 60 (86.96) 9 (13.04)	 47 (79.66) 12 (20.34)	$\chi^2 = 1.2343$ $p = 0.2666$
PR (+) (–)	 53 (76.81) 16 (23.19)	 41 (69.49) 18 (30.51)	$\chi^2 = 0.8736$ $p = 0.3499$
HER2 (+1) (+2) (+3) (–)	 35 (50,72) 0 (0) 5 (7.25) 29 (42.03)	 25 (42,37) 2 (3.39) 9 (15.25) 23 (38.98)	$\chi^2 = 4.8074$ $p = 0.3076$
Clinical staging of the disease (cTNM) T1 N0 M0 T1 N1 M0 T2 N0 M0 T2 N1 M0	 51 (73.913) 0 (0) 14 (20.29) 4 (5.797)	 43 (72.88) 1 (1.69) 11 (18.64) 4 (6.78)	$\chi^2 = 1.2673$ $p = 0.7369$
Degree of clinical advancement IA IIA IIB	 51 (73.913) 14 (20.29) 4 (5.797)	 43 (72.88) 12 (20.34) 4 (6.78)	$\chi^2 = 0.0538$ $p = 0.9735$
Number of removed lymph nodes	Mean = 6.07 Me = 3 SD = 7.79	Mean = 9.32 Me = 3 SD = 8.73	$Z = 2.1743$ $p = 0.0297$
Number of involved lymph nodes	Mean = 0.61 Me = 0 SD = 1.46	Mean = 1.86 Me = 0 SD = 4.47	$Z = 1.0737$ $p = 0.2829$
Adjuvant treatment CHTH CHTH + RTH RTH HTH	 2 (2.90) 25 (36.23) 40 (57.97) 2 (2.90)	 3 (5.08) 28 (47.46) 28 (47.46) 0 (0.00)	$\chi^2 = 3.7290$ $p = 0.2923$

M – arithmetic mean; SD – standard deviation; Me – median; BMI – body mass index; L – left; R – right; BCT + SLNB – breast-conserving therapy + sentinel lymph node biopsy; BCT + ALND – breast-conserving therapy + axillary lymph node dissection; OR – oestrogen receptor; PR – progesterone receptor; HER2 – human epidermal growth factor receptor 2; RTH – radiotherapy; CHTH – chemotherapy

with regard to: age, body mass, BMI, operated side, presence of oestrogen, progesterone, and HER2 (human epidermal growth factor receptor 2) receptors, tumour grading, number of involved lymph nodes, or adjuvant treatment. All patients testing positive for the presence of oestrogen receptors (ER+) were referred for hormone therapy. Statistically significant differences between study groups were noted with regard to patient height ($p = 0.0157$; women from the BCT + SLNB group were taller) and the number of removed lymph nodes ($p = 0.0297$; greater number of lymph nodes were removed in the BCT + ALND group). Table 1 presents exact study group characteristics and differences between groups (BCT + SLNB vs. BCT + ALND).

In our study group we assessed the range of motion in the shoulder joint with respect to flexion, extension, internal and external rotation, as well as abduction. Results

Table 2. Assessment of movement in the shoulder joint between upper limb on the healthy side vs. operated side among patients operated using BCT + SLNB and BCT + ALND techniques as well as comparison between BCT + SLND vs. BCT + ALND groups

Movement in the shoulder joint	BCT + SLNB *n* = 69 (%)			BCT + ALND *n* = 59 (%)			Value of calculated probability
	OL	HL	Value of calculated probability	OL	HL	Value of calculated probability	
Flexion	M = 89.35 Me = 90 SD = 2.25	M = 88.84 Me = 90 SD = 3.75	$Z_3 = 0.3178$ $p_3 = 0.999$	M = 86.1017 Me = 90 SD = 6.3699	M = 89.8305 Me = 90 SD = 0.9126	$Z_4 = 3.8334$ $p_4 = 0.0001$	$Z_1 = 3.5123$ $p_1 = 0.0004$ $Z_2 = 1.7518$ $p_2 = 0.0798$
Extension	M = 33.19 Me = 35 SD = 4.02	M = 36.09 Me = 35 SD = 7.61	$Z_3 = 3.5672$ $p_3 = 0.0004$	M = 31.44 Me = 35 SD = 4.83	M = 36.10 Me = 35 SD = 3.36	$Z_4 = 4.9319$ $p_4 < 0.0001$	$Z_1 = 1.8302$ $p_1 = 0.0672$ $Z_2 = 0.9902$ $p_2 = 0.3221$
External rotation	M = 73.98 Me = 80 SD = 12.47	M = 78.33 Me = 80 SD = 8.12	$Z_3 = 2.7785$ $p_3 = 0.0055$	M = 71.69 Me = 75 SD = 12.13	M = 79.24 Me = 80 SD = 6.07	$Z_4 = 4.9193$ $p_4 < 0.0001$	$Z_1 = 2.1810$ $p_1 = 0.0292$ $Z_2 = 0.7524$ $p_2 = 0.4518$
Internal rotation	M = 51.38 Me = 45 SD = 12.57	M = 71.45 Me = 75 SD = 7.53	$Z_3 = 6.5317$ $p_3 < 0.0001$	M = 46.69 Me = 45 SD = 9.03	M = 69.41 Me = 75 SD = 11.45	$Z_4 = 6.2631$ $p_4 < 0.0001$	$Z_1 = 2.0063$ $p_1 = 0.0448$ $Z_2 = 0.5048$ $p_2 = 0.6137$
Abduction	M = 86.74 Me = 90 SD = 8.61	M = 88.84 Me = 90 SD = 5.23	$Z_3 = 1.8015$ $p_3 = 0.0716$	M = 84.75 Me = 90 SD = 9.58	M = 87.29 Me = 90 SD = 8.87	$Z_4 = 2.1839$ $p_4 = 0.0290$	$Z_1 = 1.6272$ $p_1 = 0.1037$ $Z_2 = 0.9530$ $p_2 = 0.3406$

M – arithmetic mean; SD – standard deviation; Me – median; BCT + SLND – breast-conserving therapy + sentinel lymph node biopsy; BCT + ALND – breast-conserving therapy + axillary lymph node dissection group; *n* – number of patients; OL – upper limb on the operated side; HL – upper limb contralateral to the operated one; *p* – value of calculated probability; Z_1, p_1 – value of calculated probability for upper limb parameters in the BCT + SLNB vs. BCT + ALND on the operated side; Z_2, p_2 – value of calculated probability for upper limb parameters in the BCT + SLNB vs. BCT + ALND on the healthy side; Z_3, p_3 – value of calculated probability for upper limb parameters in the BCT + SLNB group (OL vs. HL); Z_4, p_4 – value of calculated probability for upper limb parameters in the BCT + ALND group (OL vs. HL)

were compared for limbs on the operated side vs. contralateral side in both groups (BCT + ALND and BCT + SLNB). We also compared the results between those patient groups (BCT + ALND vs. BCT + SLNB). Results are presented in Table 2.

Statistically significant differences between the limb on the side of the operated breast (OL) vs. the limb on the healthy side (HL) were noted in the BCT + SLND group with respect to extension ($p = 0.0004$), external rotation ($p = 0.0055$), internal rotation ($p < 0.0001$), scapular winging ($p < 0.0001$), and sensation disturbances ($p < 0.0001$). In the BCT + ALND group statistically significant differences between OL and HL were found with regard to flexion ($p = 0.0001$), extension ($p = 0.0004$), external rotation ($p < 0.0001$), and internal rotation ($p < 0.0001$). Comparison between BCT + ALND and BCT + SLNB demonstrated significant differences with regard to flexion ($p = 0.0004$), external rotation ($p = 0.0292$), and internal rotation ($p = 0.0448$) of the limb on the operated side. Patients operated using the BCT + ALND technique presented with poorer results. There were no differences in mobility of the shoulder joint on the contralateral side.

Measurements of upper limb circumference were performed in the study group at several levels: in the metacarpal region (excluding the thumb), 10 cm below lateral epicondyle of humerus, and 10 cm above the lateral epicondyle of humerus. Patients were also examined for disturbances of sensation and winged scapula sign. Results are shown in Table 3. There were no statistically significant differences between BCT + SLND and BCT + ALND groups with respect to upper limb circumference, winged scapula sign, or sensation disturbances. Winged scapula sign was present in five patients from the BCT + SLNB group and four patients from the BCT + ALND group. Sensation disturbances occurred in 42 subjects from the BCT + SLND and 37 subjects from the BCT + ALND group.

Discussion

In this study we assessed the sequelae of breast cancer treatment 5–6 years after the BCT + SLNB and BCT + ALND procedures. Results of the study revealed that limitation in the range of motion of the shoulder joint, sensation disturbances, and winged scapula sign affected both groups of patients. However, patients treated with BCT + ALND technique presented with significantly poorer outcomes with regard to extension, external, and internal rotation.

Limitation of the upper limb movement on the operated side is a complication that adversely impacts the ability to perform everyday tasks, and thus affects patient's quality of life. Numerous authors describe limitation of shoulder mobility, particularly with regard to flexion and extension, in this group of patients [18–21]. In our study both groups presented with limitation in the range of motion. Limita-

Table 3. Comparison of upper limb circumference, winged scapula sign, and superficial sensation between the limb on the healthy side (HL) vs. operated side (OL) among patients treated with BCT+SLNB and BCT+ALND techniques as well as comparison between BCT+SLND vs. BCT+ALND groups.

Measurement of upper limb circumference (cm)		BCT + SLNB *n* = 69 (%)			BCT + ALND *n* = 59 (%)			Value of calculated probability
		OL	HL	Value of calculated probability	OL	HL	Value of calculated probability	
Circumference 1		Mean = 29.14 Me = 29 SD = 3.72	Mean = 29.17 Me = 29 SD = 3.92	$Z_3 = 0.1174$ $p_3 = 0.9065$	Mean = 29.17 Me = 29 SD = 3.74	Mean = 29.18 Me = 29 SD = 3.58	$Z_4 = 0.2399$ $p_4 = 0.8104$	$Z_1 = 0.0791$ $p_1 = 0.9369$ $Z_2 = 0.1152$ $p_2 = 0.9082$
Circumference 2		Mean = 24.64 Me = 24 SD = 2.98	Mean = 24.43 Me = 24 SD = 2.71	$Z_3 = 0.4451$ $p_3 = 0.6563$	Mean = 24.86 Me = 24.5 SD = 3.23	Mean = 24.60 Me = 24 SD = 3.08	$Z_4 = 0.5262$ $p_4 = 0.6338$	$Z_1 = 0.9200$ $p_1 = 0.3576$ $Z_2 = 0.1274$ $p_2 = 0.8986$
Circumference 3		Mean = 19.22 Me = 19 SD = 1.13	Mean = 19.54 Me = 19 SD = 1.32	$Z_3 = 1.4035$ $p_3 = 0.1605$	Mean = 19.80 Me = 19 SD = 2.03	Mean = 20.04 Me = 19.5 SD = 2.69	$Z_4 = 0.5908$ $p_4 = 0.5546$	$Z_1 = 1.4417$ $p_1 = 0.1494$ $Z_2 = 0.6379$ $p_2 = 0.5235$
Other undesirable sequelae								
Winged scapula sign, *n* (%)	No	64 (92.75)	69 (100)	$\chi^2 = 53.6351$ $p_3 < 0.0001$	55 (93.22)	59 (100)	$\chi^2 = 46.2857$ $p_4 < 0.0001$	$\chi^2 = 0.0106$ $p_1 = 0.9180$
	Yes	5 (7.25)	0 (0.00)		4 (6.78)	0 (0.00)		$\chi^2 =$ --- $p_2 =$ ---
Sensation disturbances, *n* (%)	No	27 (39.13)	69 (100)	$\chi^2 = 6.0901$ $p_3 = 0.0136$	22 (37.29)	59 (100)		$\chi^2 = 0.0457$ $p_1 = 0.8307$
	Yes	42 (60.87)	0 (0.00)		37 (62.71)	0 (0.00)		$\chi^2 =$ --- $p_2 =$ --- $\chi^2 = 6.0901$ $p_3 = 0.0136$

M – arithmetic mean; SD – standard deviation; Me – median; BCT + SLND – breast-conserving therapy + sentinel lymph node biopsy; BCT + ALND – breast-conserving therapy + axillary lymph node dissection group; n – number of patients; OL – upper limb on the operated side; HL – upper limb contralateral to the operated one; Z_1, p_1 – value of calculated probability for upper limb parameters in the BCT + SLNB vs. BCT + ALND on the operated side; Z_2, p_2 – value of calculated probability for upper limb parameters in the BCT + SLNB vs. BCT + ALND on the healthy side; Z_3, p_3 – value of calculated probability for upper limb parameters in the BCT + SLNB group (OL vs. HL); Z_4, p_4 – value of calculated probability for upper limb parameters in the BCT + ALND group (OL vs. HL); Circumference 1 – 10 cm above the lateral epicondyle of humerus; Circumference 2 – 10 cm below the lateral epicondyle of humerus; Circumference 3 – metacarpal region without the thumb

tion to flexion, as well as internal and external rotation movements on the operated side predominated in the group of subjects 5–6 years after BCT + SLND procedure. In the BCT+ALND group all examined limb movements in the shoulder joint on the operated side were limited.

Lymphoedema is a common adverse consequence of breast cancer treatment [22, 23]. It occurs more often in women after axillary lymphadenectomy [24, 25]. Prospective longitudinal study assessing the range of motion among patients operated for breast cancer demonstrated that the greatest increase in upper limb circumference occurred within the first six months of the procedure, while changes taking place between six months and five years after surgery were not statistically significant [26, 27]. Therefore, our study did not show statistically significant differences between BCT + SLNB and BCT + ALND groups. There were no statistically significant differences within BCT + SLNB and BCT + ALND groups between the upper limb on the operated side vs. the healthy side ($p > 0.05$).

There are numerous literature reports concerning sensation disturbances and associated symptoms among patients treated for breast cancer [28, 29]. Reitman *et al.* [11] describe a reduced number of complications after sentinel lymph node procedure compared with axillary lymphadenectomy [11], while according to Del Bianco *et al.*, as much as 22% of patients after sentinel lymph node procedure experience disorders of superficial sensation. These disturbances gradually withdrew with time, and 24 months later they were only observed in 8% of subjects [18].

In our study sensation disturbances were observed in the axillary region on the side of the operated breast in both groups. Sensation disorders were present in 42 patients from the BCT + SLND group and 37 patients from the BCT + ALND group. Results did not differ significantly between groups ($p > 0.05$).

Transient or complete nerve damage in the course of a surgical procedure may be associated with, among other things, presence of winged scapula (*scapula alata*). Damage to the long thoracic nerve may lead to reduced muscle power or total paresis of anterior serratus muscle, resulting in scapular instability – its medial position is disrupted, and the inferior angle of the scapula is rotated medially. In such a position the medial margin of the scapula protrudes from the thoracic wall [30]. The problem of winging scapula mainly concerns women who have undergone axillary lymphadenectomy. There are, however, reports of

such complication among patients who underwent SLND as an isolated intervention in the axillary fossa [31].

In our study the winged scapula sign on the operated side was observed in five patients treated with BCT + SLNB and in four patients treated using BCT + SLNB technique.

There are limitations to our study because the patient baseline status (before the procedure) was not assessed and the number of patients in specific subgroups was too low.

Conclusions

Our study demonstrated that both types of intervention in the axillary fossa in women, who declared participation in physiotherapy after 5–6 years from surgical procedure was associated with the risk of undesirable treatment sequelae. Comparison of those two surgical techniques, which are very different in terms of invasiveness, demonstrated superiority of the SLND procedure over axillary lymphadenectomy due to possible adverse effects, such as limitation of upper limb mobility.

The authors declare no conflict of interest.

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