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Original Article

Changes in breast cancer grade from biopsy to excision following surgery or primary chemotherapy

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Summary

Objective. To compare histological grade (G) of breast cancer and its components (scores for tubule formation - T, nuclear pleomorphism - P and mitotic counts - M) in core needle biopsies (CNBs) and surgical excision specimens (EXC) in patients treated with primary surgery (CHIR) or primary chemotherapy (PST).

Methods. Grade of matched pairs of carcinomas in CNB and EXC was assessed according to the Nottingham grading system.

Results. PST cases tended to have higher pretreatment G. Concordance rates in the CHIR (n = 760) and PST (n = 148) groups for T, P, M and G were 79%, 70%, 75%, 71% and 77%, 70%, 50%, 62%, respectively; differences in concordance rates were significant in M ($p < 0.0001$) and G ($p = 0.024$). For discordant cases in the CHIR group, CNBs tended to overestimate T and underestimate P, M and G, whereas in the PST group, the same trends were identified for T and P, but there was a significant tendency for M and G to be lower in EXC specimens.

Conclusions. The reversal of M and G underestimation in CNB to "overestimation" in the PST group can only be explained with the effect of mitosis reduction following chemotherapy. Whether the posttreatment decrease in G reflects any prognostic value remains to be elucidated.

Key words: Breast cancer, histological grade, core needle biopsy, excision, neoadjuvant chemotherapy

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Introduction

Histological grade of invasive breast carcinomas, as modified by Elston and Ellis, i.e., the so-called Nottingham grade is a prognostic factor of proven value [1], and has become a standard part of histology reporting of breast cancer, including the International Collaboration on Cancer Reporting (ICCR) dataset recommendations [2]. As all pathologists know, this is a combined grading system that incorporates lumen (tubule, gland) formation, nuclear pleomorphism and area adjusted mitotic rate, all of which are scored on a three-tiered ordinal scale, and give a sum that is used to determine the grade, which is itself an ordinal variable in prognostication. The prognostic impact was first established on the basis of patients treated by primary surgery, therefore surgical specimens were used for grading, and form the gold standard [1].

A criticism of histological grading is that all of its elements are subjectively evaluated, and are influenced by the grader's experience and skills. The interobserver consistency, reproducibility of this parameter is generally considered moderate [3,4]. Nevertheless, its prognostic impact

is unquestionable even in the era of gene expression profiling, as reflected by its added value to genomic markers of prognosis [5,6].

Grade of breast cancers is also assessed in core needle biopsies (CNBs). In some cancers, this is the only tumour sample allowing the assessment of prognostic and predictive markers, as patients do not have residual tumour following primary systemic treatment, or there is no further specimen to assess after some novel/experimental forms of local treatment such as cryoablation [7], radiofrequency ablation [8] or high-intensity ultrasound ablation [9]. As one or a few tissue cores are only a limited representation of the tumour, their representative value has been tested in some studies and has been found to increase with the number of tissue cores obtained [10]. Overall, histological grade, as assessed on CNB, seems a moderate reflection of tumour differentiation established on the basis of excision specimens with 71% (95% confidence interval (CI): 69-73%) pooled agreement between the two, and a pooled estimate of Cohen's kappa of 0.54 (95%CI: 0.50-0.58) [11].

The ICCR also recommends to determine histological grade in the post-neoadjuvant setting, although the impact of grade on prognosis is based on less evidence in this context [12].

In the present study, we aimed to compare the grade and its components as determined in paired CNB and surgical excision (EXC) specimens in patients who were treated by primary surgery (CHIR) and those who received neoadjuvant chemotherapy (PST) and had residual cancer to grade.

Materials and methods

Invasive breast cancers diagnosed at the Bács-Kiskun County Teaching Hospital between 2010 and 2022 with available preoperative CNB and EXC specimens were selected for this study. All CNB samples were gained by image-guided (generally ultrasound-guided) 14G gun biopsies with the aim of obtaining 3 tissue cores. Of the cases with this dual specimen representation at the Department of Pathology, the following were excluded: i) multifocal tumours where the histological grade of the foci was different, and it could not be decided which focus was sampled preoperatively (cases with identical histological grade of the multiple foci sampled were not excluded); ii) the CNB specimen was crushed or had limited diagnostic value, preventing adequate assessment of grade – e.g., tumour dimension smaller than 10 high power fields (2 mm^2) or uncertain nuclear pleomorphism or lumen formation due to crush artefacts; iii) the CNB diagnosis was that of an in situ carcinoma; iv) neoadjuvant endocrine therapy was given; v) pathological complete regression was achieved or the residual disease was not suitable for grading.

In all included cases, the histological grade and subscores for its components were extracted from the histology reports. All data were recorded in Microsoft Excel spreadsheets.

Histological grade was assessed according to the Nottingham scheme also recommended by the most recent World Health Organization (WHO) Classification of breast tumours by one of two pathologists with experience in breast pathology [13]. For each pair of samples, the three-tiered values of the histological grade (G) and its subscores for tubule/gland formation (T), nuclear pleomorphism (P) and standardised mitotic rate (M) were recorded for the CNB specimen first, and these were coupled with the corresponding values from the EXC specimen as a second measurement of the same parameters.

The distributions of each value for the T, P and M subscores and histological grade in the CHIR and PST groups as well as the concordance rates in the two groups were compared by means of the Chi-square test for both CNB and EXC specimens.

To assess the changes in values of T, P and M subscores and G from CNB to EXC in the CHIR and the PST groups, the nonparametric Wilcoxon signed rank test was used as this accounts for positive and negative changes of the variables, and helps to check whether the changes seen are random or show any tendency. The calculations were done in the Microsoft Excel's Real Statistics Resource Pack add-in, with the corrections recommended by the creator and author of the add-in [14,15]. For the statistical tests, a significance level of $p < 0.05$ was used.

The study was approved by the Human Investigation Review Board, University of Szeged (approval number 90/2021-SZTE-RKEB).

Results

A total of 1257 pairs of invasive breast cancer CNBs and EXC specimens were identified, from which 908 were left after the exclusions. Of these, 760 did not receive neoadjuvant chemotherapy (CHIR group), whereas 148 patients received such a preoperative treatment (PST group). The primary systemic therapy in the latter group often included a taxane which was part of the treatment in 132/148 (89.2%) cases, and was generally administered consecutively with anthracyclines (most commonly epirubicin) or a platinum derivative. Anti-HER2 treatment was also included for

HER2 positive (overexpressing or amplified) tumours. The distribution of grading subscores and histological grades in the various groups are shown in Table I, and Figure 1.

Comparing the distributions of the grading subscores and the grades of the CHIR and PST groups, there were significant differences in all parameters in CNB specimens (T, P, M and G, all $p < 0.001$), whereas only T ($p < 0.05$), P ($p < 0.001$) and Grade ($p < 0.001$) showed significant differences in EXCs; the M subscore was not statistically different ($p = 0.544$).

The PST/CHIR ratio of relative frequencies observed in each subscore and grade is represented in Figure 2. I is remarkable for the CNB specimens, that at the time of planning therapy, the PST group shows greater proportions of poorly differentiated (G3) carcinomas, and higher rather than lower mitotic count based-scores. These excesses are no longer seen in the EXC specimens, whereas the higher relative prevalence of P score 3 in the PST group did not change from CNB to EXC.

The changes in grading subscores (T, P and M) and G from CNB to EXC for the CHIR and PST groups are shown in Figure 3. It is apparent that the subscores and grades of the two types of specimens were concordant in the majority of the cases in the CHIR group (T: 78.9%, P: 68.9%, M: 74.6%, G: 71.2%) and the PST group (T: 77%, P: 70.3%, M: 50%, G: 61.5%), and whenever there was discordance, the changes were most commonly of one score. The unchanged parameters are detailed in Table II. Despite the majority of the cases being concordant for the variables assessed in CNB and EXC in both groups, there were significant differences between the concordance rates of the CHIR and the PST samples in G ($p = 0.024$) and its M subscores ($p < 0.0001$), whereas there was no such difference in the T ($p = 0.68$) and P subscores ($p = 0.82$).

For discordant cases, the following trends could be identified. Gland formation (T subscore) changes were predominated by a change from a low CNB tubule formation, i.e. high score (< 10%; T: score 3) to a higher tubule formation tendency, i.e. a lower subscore (10-75%; T: score 2) EXC value in both the CHIR and the PST groups. In the CHIR group, the most common change in both nuclear pleomorphism (P) and mitotic rate (M) was a single point increase (1→2 or 2→3), however in case of M, 2-point-increases were also noted. In the PST group, one of the most common changes was the P: 2→3 increase in pleomorphism, however a single point or a 2-point-reduction of M was the dominant change observed. As a result of these changes in subscores, the histological grade more commonly increased in the CHIR (71.2%, 95% CI: 64.7-77.0%) and decreased in the PST (63.2%, 95%CI: 50.2%-74.5%) groups.

The Wilcoxon signed rank test indicated that there was a statistically significant change (from CNB to EXC) in all the parameters evaluated and in both groups (CHIR group: T, P, M and G, all $p < 0.001$; PST group: T, $p < 0.001$; P, M and G, $p < 0.05$).

Table I. Case numbers, (percentages and [95% confidence interval limits]) of tubule formation, nuclear pleomorphism and mitotic activity subscores and histological grades in the two types of specimens in the two groups investigated.

CHIR (n = 760)				PST (n = 148)			
CNB	1	2	3	CNB	1	2	3
T	60 (7.9% [6.2-10.0])	187 (24.6% [21.7-27.8])	513 (67.5% [64.1-70.7])	T	2 (1.4% [0.4-4.8])	20 (13.5% [8.9-20.0])	126 (85.1% [78.5-90.0])
P	127 (16.7% [14.2-19.5])	372 (49.0% [45.4-52.5])	261 (34.3% [32.0-37.8])	P	8 (5.4% [2.8-10.3])	45 (30.4% [23.6-38.2])	95 (64.2% [56.2-71.5])
M	553 (72.8% [69.5-75.8])	94 (12.4% [10.2-14.9])	113 (14.9% [12.5-17.6])	M	59 (39.9% [32.3-47.9])	43 (29.1% [22.3-36.8])	46 (31.1% [24.2-38.9])
G	233 (30.7% [27.5-34.0])	376 (49.5% [45.9-53.0])	151 (19.9% [17.2-22.9])	G	14 (9.5% [5.7-15.3])	63 (42.6% [34.9-50.6])	71 (48.0% [40.1-56.0])
EXC				EXC			
T	68 (9.0% [7.1- 11.2])	238 (31.3% [28.1-34.7]	454 (59.7% [56.2-63.2])	T	4 (2.7% [1.1- 6.7])	43 (29.1% [22.3-36.8])	101 (68.2% [60.4-75.2])
P	60 (7.9% [6.2- 10.0])	386 (50.8% [47.2-54.3])	314 (41.3% [37.9-44.9])	P	4 (2.7% [1.1- 6.7])	31 (21.0% [15.2-28.2])	113 (76.4% [68.9-82.5])
M	461 (60.7% [57.1-64.1])	129 (17.0% [14.5-20.0])	170 (22.4% [19.6-25.5])	M	88 (59.5% [51.4-67.0])	16 (10.8% [6.8-16.8])	44 (29.7% [23.0- 37.5])
G	186 (24.5% [21.6-27.7])	371 (48.8% [45.3-52.4])	203 (26.7% [23.7-30.0])	G	13 (8.8% [5.2-14.5])	81 (54.7% [46.7, 62.5])	54 (36.5% [29.2- 44.5])

CHIR: the group treated with primary surgery, CNB: core needle biopsy, EXC: excision specimens, G: histological grade, M: mitotic activity, P: nuclear pleomorphism, PST: the group treated with primary chemotherapy before surgery, T: tubule (gland) formation.

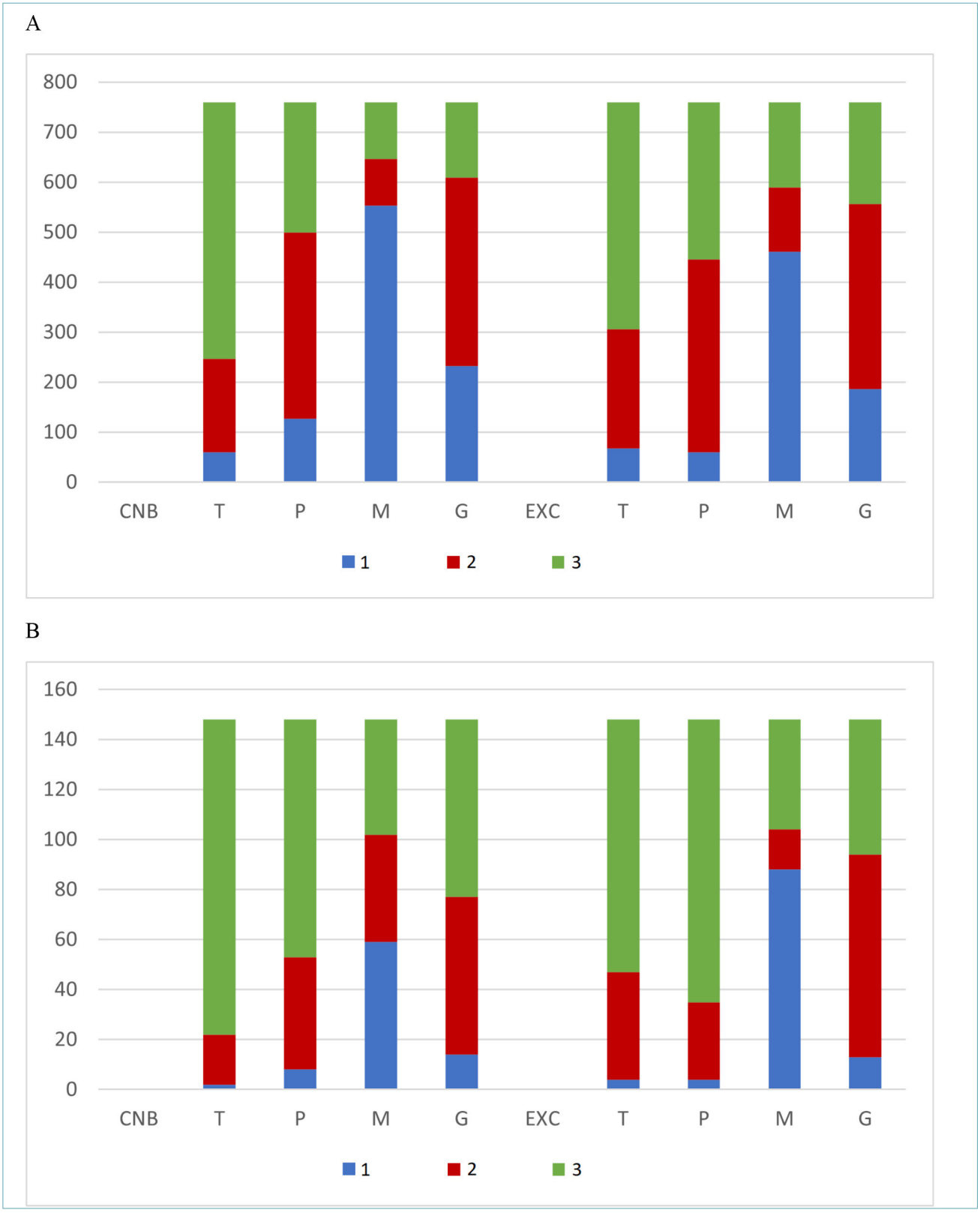

Figure 1. Distributions of case numbers for each grading subscore (T, P and M) and grade (G) in the group treated with A: primary surgery (CHIR) or B: primary chemotherapy (PST). CNB: core needle biopsy, EXC: excision specimen. *CHIR: the group treated with primary surgery, CNB: core needle biopsy, EXC: excision specimens, G: histological grade, M: mitotic activity, P: nuclear pleomorphism, PST: the group treated with primary chemotherapy before surgery, T: tubule (gland) formation.*

Table II. Unchanged parameters from core needle biopsies to excision in the two groups investigated.

CNB to EXC:	1-1	2-2	3-3	All
T (CHIR)	46 (7.7%)	134 (22.3%)	420 (70%)	600
P (CHIR)	43 (8.2%)	265 (50.6%)	216 (41.2%)	524
M (CHIR)	435 (76.7%)	38 (6.7%)	94 (16.6%)	567
G (CHIR)	148 (27.4%)	267 (49.4%)	126 (23.3%)	541
T (PST)	0 (0%)	16 (14%)	98 (86%)	114
P (PST)	2 (1.9%)	17 (16.3%)	85 (81.7%)	104
M (PST)	46 (62.2%)	4 (5.4%)	24 (32.4%)	74
G (PST)	7 (7.7%)	45 (49.5%)	40 (44%)	91

CHIR: the group treated with primary surgery, CNB: core needle biopsy, EXC: excision specimens, G: histological grade, M: mitotic activity, P: nuclear pleomorphism, PST: the group treated with primary chemotherapy before surgery, T: tubule (gland) formation.

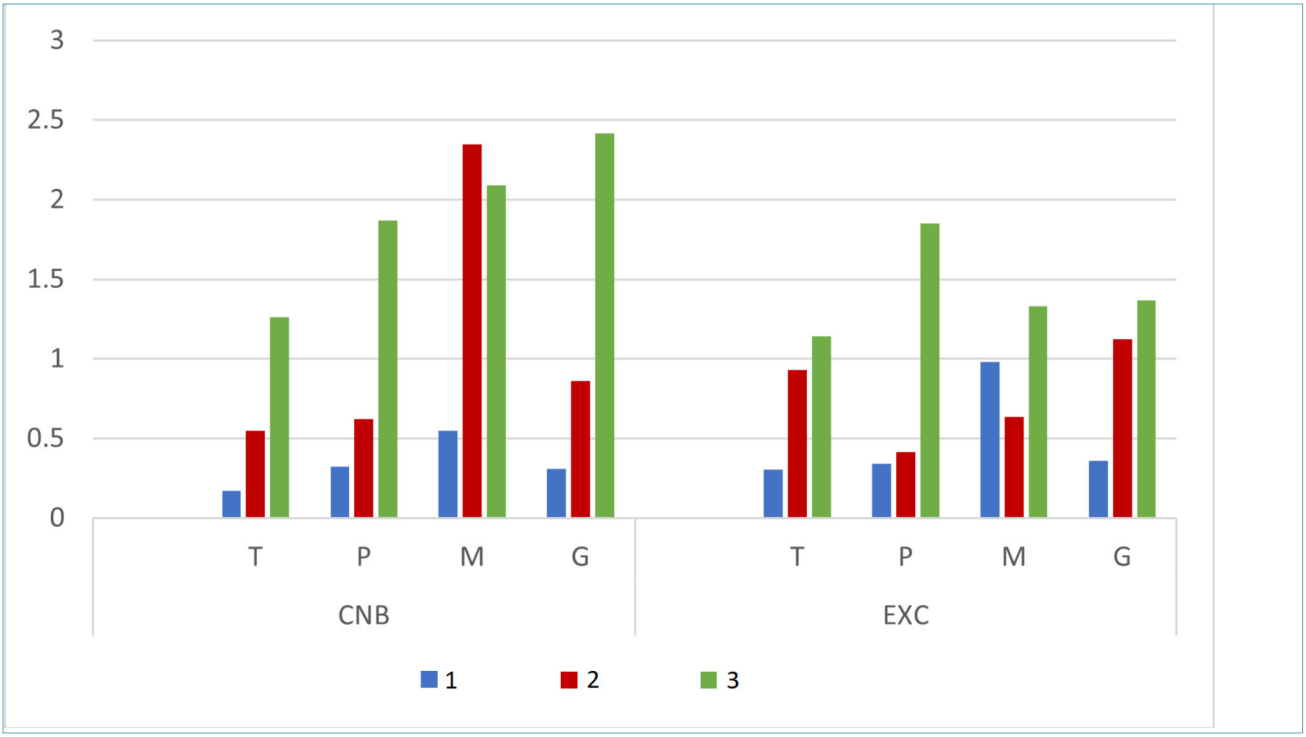

Figure 2. PST/CHIR ratio of relative frequencies per grading subscores (T, P and M) and grade (G). *Values above 1 (especially > 1.5) reflect greater incidence of a variable in the PST group. CHIR: the group treated with primary surgery, CNB: core needle biopsy, EXC: excision specimens, G: histological grade, M: mitotic activity, P: nuclear pleomorphism, PST: the group treated with primary chemotherapy before surgery, T: tubule (gland) formation.*

Discussion

The clinical value of some traditional prognostic factors of breast cancers, like histological type [16] or grade has been scaled back by the possibility to classify tumours according to biomarkers for targetable genetic or phenotypic alterations. Nevertheless, histological grade of breast cancer is a recognised prognosticator of this disease maintaining its utility even in the era of genomic tests of prognosis and despite reported interobserver variability. There have been studies comparing grading on CNB and EXC specimens, and it has been shown that despite being concordant in many cases, there are some trends in discordance. A meta-analysis of 33 studies (4980 patients) suggested that concordance in grade was seen in the major-

ity of cases (ranging from 59% to 94%, with a pooled estimate of 71%), but when the CNB grade was discordant from the EXC grade, underestimation was roughly twice as common (19%) than overestimation (9%) [11]. Some of the studies included in the cited meta-analysis also reported on grade components, and could be assessed for concordance and discordance: 1. concordance was predominant for all parameters, but when discordant, 2. tubule formation (T) was more frequently overscored than underscored (13% vs 9% on the basis of pooled percentages of 12 studies); 3. nuclear pleomorphism (P) was more often underestimated than overestimated (17% vs 10% on the basis of 14 studies); 4. finally, mitotic activity (M) was more commonly underestimated than overestimated (30% vs 8% on the basis of 13 studies) [11].

Our findings are in keeping with the pooled analysis in many respects. The concordance rate of grade between CNB and EXC specimens was 71%, practically identical with the pooled results, and this is a reliable record as even the study given the greatest weight [17] in the meta-analysis of Knuttel et al. [11] had only 300 cases, i.e. less than half of the cases included in the CHIR group of the present study. The tendencies to overestimate T and underestimate P, M and G are also consistently reinforced by our data; G being roughly twice as often underestimated than overestimated. Concerning the subscores on grade components, we also noted the highest concordance rate for T (79% vs 78%); but there was a minor discrepancy from the meta-analysis data; our second highest rate of concordance was seen in connection with M (75% vs 62%) and this was followed by P (69% vs 73%).

Discrepancies between grades established on CNB and corresponding EXC samples have generally been explained with undersampling by CNB and the ensuing underrepresentation. Indeed, some breast cancers show heterogeneous aspects in appearance. A typical example of this phenomenon may be illustrated by tubular mixed carcinomas, of which the one part, generally the central area, reflects a tubular carcinoma with plenty of tubules, whereas the periphery might not show tubule formation at all (Fig. 3A-C) [18]. Another recognised phenomenon present in many breast carcinomas is the zonation of proliferation, and the stemming recommendation to preferably count mitotic figures at the periphery of the tumours (Fig. 3D). Both of these examples can lead to discrepancies on the basis of radial versus tangential sampling by the needle, but obviously neither sampling passes of the needle will adequately reflect a full cut surface of an EXC specimen. The smaller size or crush artifacts of CNB samples may also lead to the unassessability of grade; e.g., due to the lack of 2 mm^2 tumour area (10 high power fields) for the proper determination of the mitotic score. These cases have been excluded from the present study, too (as grade X cases), though in real life conditions, these are given a likely grade or an approximation such as non-high grade on the basis of the available subscores, to allow the consideration of the limited prognostic information gained from the specimen. Differences in cold ischaemia time and fixation are also mentioned as a possible cause for the discrepancies. Although the EXC samples are considered the gold standard, CNBs may have more ideal tissue processing. Lehr and colleagues have rather confidently explained why larger specimen size, slower permeation by formalin, delayed fixation and the development of more easily identifiable mitotic figures may be the principal cause for the consistent underestimation of M in CNB samples, or more precisely an overestimation in EXC specimens [19]. It is unknown whether alternative fixatives, like acid-free glyoxal [20,21] would have the same effect on M scores, and this remains to be explored.

Less than perfect interobserver variation has also been mentioned as a possible cause of discrepancies, since the reproducibility of histological grading of breast cancers has been found to be only moderate [3,4]. Reflecting our results on concordance of the grade components between CNB and EXC samples, T has been the most consistently and P the least consistently reported component of grade in a large review of the UK breast pathology external quality assessment scheme [22]. However, interobserver variability might have had little influence in the present dataset, as only 6.7% of the CNB/EXC pairs had been independently reported by two different pathologists. Intraobserver variability might have contributed to the discrepancy rates, but intraobserver agreement of grading has always been reported as better than interobserver agreement [23].

All the phenomena described above should play a similar role when assessing the grade of CNB specimens in the PST group, and divergences in the CNB-EXC pairs from trends seen in the CHIR group should either stem from differences in the two populations or the effect of systemic chemotherapy.

Although concordance between CNB- and EXC-assessed histological grade was also seen in the majority of the PST cases, this was significantly less common than in the CHIR group (71% vs 62%). In cases of discordance, the most notable change was that of a decrease in G (88%). Regarding the subscores of grade, T and P presented a substantial concordance between CNB and EXC samples, and both were nearly identical with the corresponding concordance rates observed in the CHIR group (T(PST): 77% vs T(CHIR):

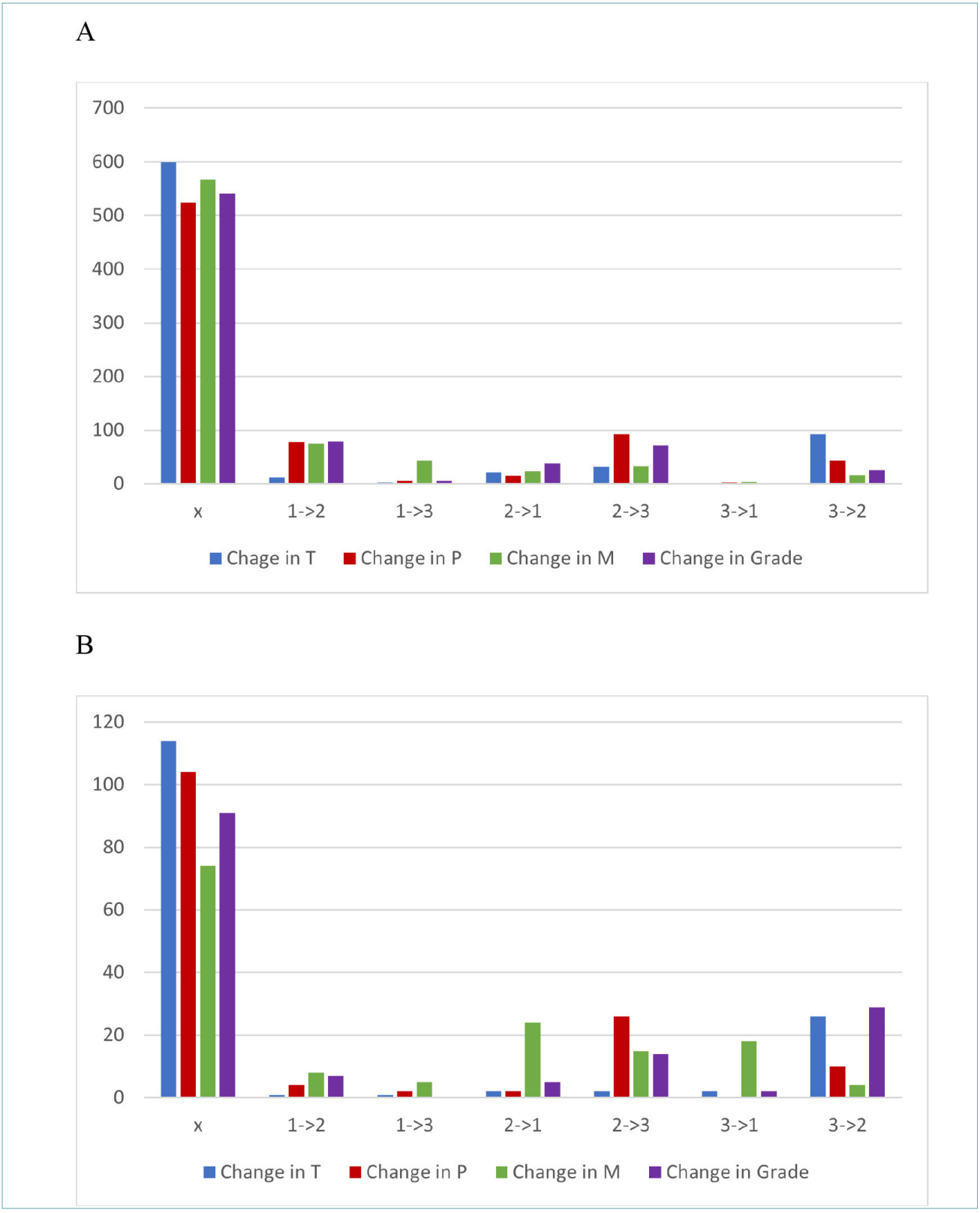

Figure 3. Changes in the values of T, P, M subscores and grade (G) from CNB to EXC in the two patient groups (A: CHIR and B: PST groups).
CHIR: the group treated with primary surgery, CNB: core needle biopsy, EXC: excision specimens, G: histological grade, M: mitotic activity, P: nuclear pleomorphism, PST: the group treated with primary chemotherapy before surgery, T: tubule (gland) formation, x: no change in the values.

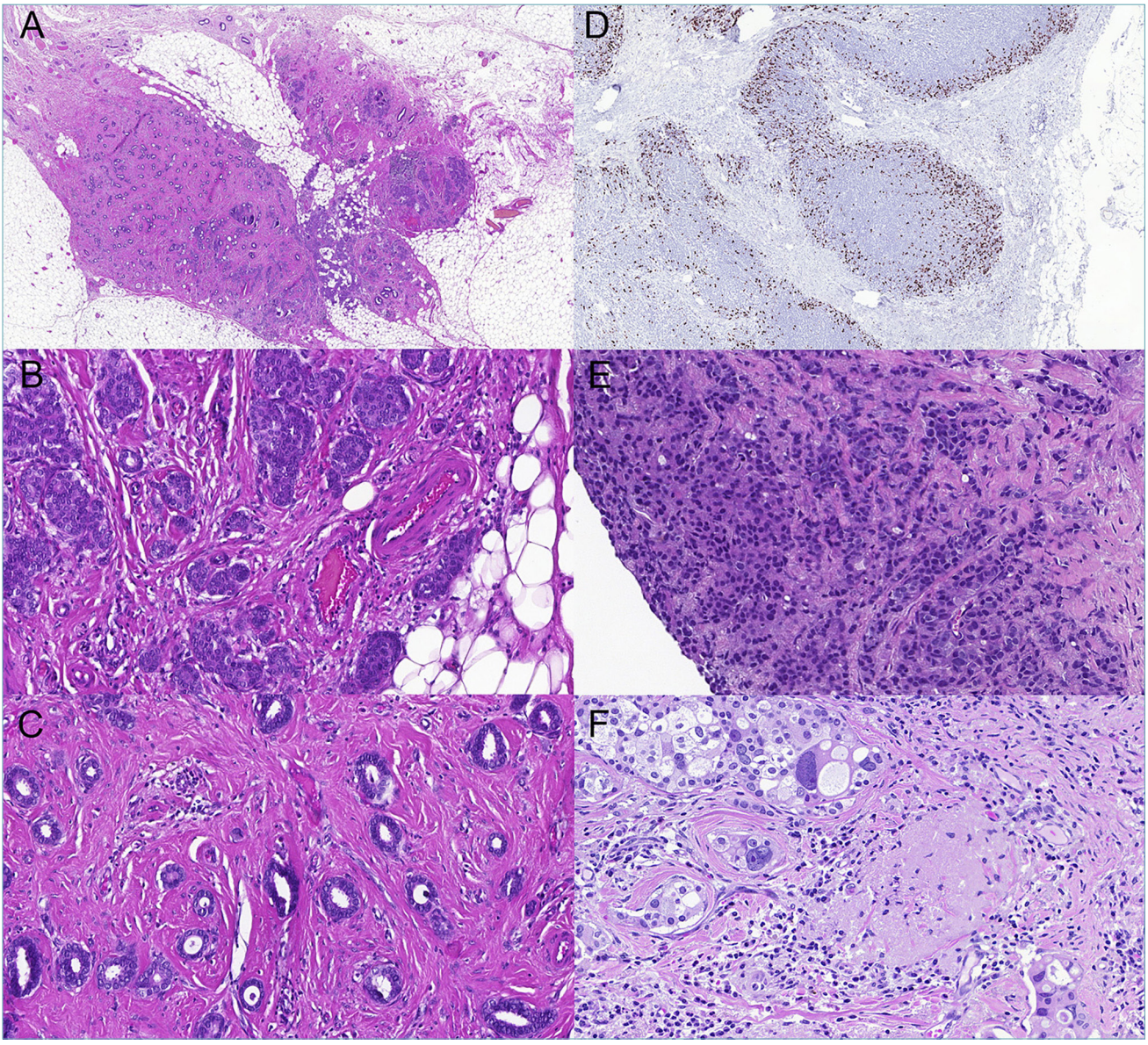

Figure 4. Histological variability that may account for differences in subscores and grades between core needle biopsies and excisions. (A-C): Mixed tubular carcinoma; A: x2, right side with less than 10% gland formation (B: x20) and left side with 100% tubule formation characteristic of tubular carcinoma (C: x20). D: A Ki-67 immunostain highlighting inhomogeneity and zonal distribution of the cells in the cell cycle, a zonation that may also characterise the distribution of mitotic figures (Ki67, x5). (E-F): The same tumour before chemotherapy in the core needle biopsy and after chemotherapy in the excision, with P scores 2 and 3, respectively (x30).

79% and P(PST): 70% vs P(PST): 69%). In contrast, the M subscores were concordant/discordant in half of the cases, and this meant a statistically significant difference from the 75% concordance rate in the CHIR group. For discordant cases, T and M scores more often decreased (in 88% and 62%, respectively), whereas an increase was seen more commonly for P (73%).

The fact that T and P scores showed nearly identical concordance rates in CHIR and PST cases, and discordant cases in the PST group showed overestimation of T and underestimation of P in CNBs similar to that seen in the CHIR cases, suggests the same underlying mechanisms, i.e., undersampling of heterogenous tumours. There is no data on neoadjuvant

treatment affecting gland formation in breast cancer, but there is observational evidence that taxane-containing chemotherapy used in most PST patients here, may lead to the formation of pleomorphic tumour giant cells (Fig. 3E-F) [24]. Taxanes distrupt microtubule function and mitotic spindle formation, leading to polyploidisation and the development of large nuclei with bizarre morphology, which increase pleomorphism [24,25]. However, as many of the tumours were originally of P score 3, such nuclear alterations, might have led to less effect in this population. Changes in the M scores were the most obvious, and these must be related to the mitotic activity blocking effect of the chemotherapy regimen, a desired effect of (neoadjuvant) systemic treatment.

As a combined result of the above-mentioned effects, and especially of the predominant decrease (rather than the increase seen in the CHIR group) of M scores in non-concordant CNB-EXC pairs, G tended to decrease rather than increase in EXC specimens, an effect that we must attribute to the effect of systemic treatment.

A previous study on 40 matched pairs of pretreatment and posttreatment grades also found a significant decrease in the mitotic count score, but not in grade [26].

Little is known about the prognostic role of postneoadjuvant grade, although its determination is a core element of the ICCR recommendations for breast cancer reporting after primary systemic treatment. Physicians from the MD Andreson Cancer Center have reported that nuclear grade 3 has not only a value in predicting the response to neoadjuvant treatment, but also has an additive prognostic value for determining 5-year outcomes; however, the grade used was derived from the preoperative specimens [27]. A component of grade, posttreatment mitotic index was correlated with prognosis, with higher mitotic rate reflecting worse prognosis [28], meaning that lower mitotic counts must have been associated with better prognosis.

The present study has obvious limitations arising from its retrospective nature. Due to the relatively low case numbers in the PST group, there was no chance to analyse the data according to surrogate molecular types of breast cancers or according to the neoadjuvant therapy given, which was not uniform in the series, but generally included docetaxel or paclitaxel for 89% of all patients, and targeted anti-HER2 treatment for HER2 positive tumours.

Conclusions

This is a single-centre study with a large case number reinforcing previous reports on the predominant concordance of grade and its components between CNB and corresponding EXC samples, as well as the tendency to overestimate tubule (gland) formation and underestimate nuclear pleomorphism, mitotic rate and histological grade on CNBs when compared with EXC specimens in non-concordant cases. Many of these tendencies were also seen in cases with pretreatment CNBs and EXC specimens after primary chemotherapy, but importantly, concordance rates were lower; and mitotic scores and histologic grade in EXC specimens were more often lower than higher (in contrast to the primary surgery group). Whether the posttreatment decrease in grade reflects any prognostic value remains to be elucidated.

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Conflicts of interest

The authors have no potential conflicts of interest.

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The study received no funding.

Authors' contributions

ÁF managed the data, performed statistical analyses, drafted the manuscript. GC conceived the study, collected data, drafted and edited the manuscript. Both authors have read and approved the final version of the manuscript.

Ethical consideration

The study was approved by the Human Investigation Review Board, University of Szeged (approval number 90/2021-SZTE-RKEB). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. An exemption to obtain written informed consent from patients whose material was investigated was part of the ethical approval.

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