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Preoperative axillary nodal staging of invasive lobular breast cancer with ultrasound guided fine needle aspiration in patients with suspicious ultrasound findings versus aspiration in all patients – A retrospective single institutional analysis

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ABSTRACT

Introduction: – At present, surgical strategies for breast cancer patients with >2 lymph nodes (LN) involved differ from those with no or lower degree of nodal involvement. Preoperative assessment of the axilla is less sensitive in patients with lobular carcinoma (ILC) than patients with other histological tumour types.
Materials and methods: – A retrospective analysis of axillary staging by palpation, axillary ultrasound (AXUS) and AXUS-guided fine-needle aspiration cytology (FNAC) of 153 patients with ILC diagnosed and operated on between January 2013 and December 2020 was performed. Patients had either sentinel node biopsy or axillary lymph node dissection according to current practice. In period 1, patients had FNAC only when AXUS suggested nodal involvement (n = 106), and in period 2, all ILC patients had axillary FNAC (n = 47).
Results: – Of the factors associated with >2LNs involvement, logistic regression suggested only AXUS/FNAC based staging as independent variable for all patients. Patients with AXUS-guided FNAC had a significantly higher proportion of true negative and lower proportion of true positive cases in the P2 period (0 vs 55% and 72% vs 11% for >2 LNs involvement, respectively; both $p < 0.0001$).
Conclusions: – AXUS-guided FNAC of all ILC patients did not result in improved preoperative identification of patients with >2 metastatic LNs but increased the false-negative rate of the assessment by producing false-negative results in patients who would not have undergone a biopsy due to negative AXUS findings.

1. Introduction

Invasive lobular carcinomas (ILC) of the breast differ from other special type and no special type breast carcinomas in many aspects, including their propensity to cause architectural distortion or remain occult rather than forming masses on mammography, being composed of noncohesive cells due to their lack of functional E-cadherin, giving a different metastatic pattern … etc [1]. Sometimes massive axillary nodal involvement is found without prior clinical or imaging evidence of such involvement.

It is common practice to use ultrasonography (US) for the evaluation of the axilla during the preoperative evaluation of early breast cancers. This has also been the recommendation of 3 consecutive versions of the Hungarian diagnostic guidelines since 2010 [2]. Patients with no palpable lymphadenopathy and a

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Abbreviations

1-2 LN+	category of 1 or 2 metastatic lymph nodes
>2 LN+	category with more than 2 metastatic lymph nodes
ACOSOG	American College of Surgeons Oncology Group
ALND	axillary lymph node dissection
AXUS	axillary ultrasound
CNB	core needle biopsy
ER	oestrogen receptor
FNAC	fine-needle aspiration cytology
FN	false-negative
FNR	false-negative rate
FP	false-positive
HE	haematoxylin and eosin
HER2	human epidermal growth factor receptor-2
ILC	invasive lobular carcinoma
LN	lymph node
NSP	no special type (invasive breast cancer)
PR	progesterone receptor
SLNB	sentinel lymph node biopsy
TN	true negative
TP	true positive
US	Ultrasound

negative axillary US (AXUS-) are considered clinically node negative (cN0), and are candidates for axillary sentinel lymph node biopsy (SLNB), whereas those who are judged to have suspicious or positive lymph nodes (LNs) (AXUS+) are subjected to a sampling of at least one LN. This may be a fine needle aspirate for cytological assessment (FNAC) or a core needle biopsy (CNB) for histology. Negative microscopic findings (i.e., the lack of evidence for metastatic involvement) also result in a cN0 preoperative staging and an indication for axillary SLNB as a surgical staging procedure. Patients with positive findings (FNAC+ or CNB+) are considered clinically node positive (cN+) and underwent ALND earlier, but are more and more commonly offered neoadjuvant systemic treatment. AXUS has been reported to be of lower sensitivity for ILC than invasive breast carcinoma of no special type (NST) [3].

Patients with a cN+ status diagnosed preoperatively are about three times more likely than cN0 patients to have substantial nodal involvement, at least pN2 disease with >3 LNs involved [4], as suggested by our previous findings and a meta-analysis [5,6].

As concerns ILC, it seems that cytokeratin immunohistochemistry (IHC) of sentinel LNs (SLNs) may disclose nodal involvement in SLNs deemed negative on HE staining more often than in case of other histological types of breast carcinoma, the yield may be as high as 24% [7], with smaller macrometastases being also discovered with IHC only. Although the routine use of IHC for SLN assessment has declined, this method was and may still be more often used in cases of ILC [8], and some guidelines also support(ed) this approach [9,10].

We retrospectively analysed a series of ILCs in order to look for the factors associated with nodal positivity in >2 LNs, and looked at how AXUS-guided FNAC of LNs in all ILC patients compares with FNAC restricted to patients with AXUS+.

2. Materials and methods

Consecutive primary ILCs or carcinomas with a lobular component diagnosed by core needle biopsy as such and surgically treated at the Bács-Kiskun County Teaching Hospital between January 2013 and June 2018 (period 1, P1) were retrospectively collected from the archives of the Pathology Department. Recurrent cases and cases with missing data on staging were excluded.

From July 2018 to December 2020 (P2), patients with a preoperative diagnosis of ILC and an AXUS- status were re-assessed by AXUS (Philips HD5, 3–12 MHz), and sampling at least one LN (generally the largest LN visualized) was attempted. During the P2 period, 10 patients with an ILC diagnosis had no FNAC of their ipsilateral axilla due to core needle biopsy misdiagnosis as non-lobular carcinoma (n = 1), no AXUS identifiable LNs (n = 2), initiation of primary endocrine therapy because of old age or presence of metastatic disease or COVID19 pandemic and a limited access to surgery (n = 5) and no obvious reasons (n = 2), these could not be analysed further, and were therefore excluded. Six patients with either positive or inconclusive FNAC results were not operated either because of death from unrelated cause (n = 1), distant metastases, locally advanced tumour and/or primary endocrine treatment (n = 5), and were therefore staged as pNx; they were also excluded from the final analysis.

The preoperative assessment of the axilla in the patients reported followed the steps delineated in the introduction. The sampling procedure used for AXUS+ patients was FNAC, its results were interpreted as positive (metastatic), negative (only lymphoid tissue sampled without evidence of metastasis) or inconclusive (not diagnostic: neither tumour cells nor lymphocytes present). For P1, only standard staining (haematoxylin and eosin – HE and Giemsa) was used for evaluation, but from July 2018, cytokeratin immunohistochemistry was added in cases where the FNAC sample contained sufficient cells and was negative for metastasis by conventional staining. The smears were stained with AE1/AE3 (Biogenex, San Ramon, CA; 1:200 dilution, 20 min incubation at room temperature, citrate buffer). SLNB was generally performed with dual tracer administration with slight modification of the previously described method [11]. The radiocolloid (60–90 MBq 99mTc-labelled 40–80 nm particle size Nanoalbumon, Medi-Radiopharma Kft., Érd, Hungary; or similarly sized Nanocoll, Gipharma, Saluggia, Italy) was given under US-guidance into the breast parenchyma (intra- and/or peritumorally) for non-palpable or uncertainly palpable tumours to allow radioguided occult lesion localisation [12], whereas it was given superficially (periareolarly) for palpable lesions the day before surgery. Patent blue dye was given most commonly subareolarly 10–15 min before surgery. During a brief period in Spring 2020, the Nuclear Medicine department was shut down due to the COVID19 pandemic, and dual labelling was solved by indocyanine green (Verdye™ (Diagnostic Green GmbH, Aschheim-Dornach, Germany) given instead of the radiocolloid. This was detected by means of a Visionsense VS Iridium system (EleVision™ IR Platform, Medtronic PLC, New Haven, CT, USA) [13].

As part of changing practice, patients with positive SLNs generally underwent a level I + II ALND, but from 2016, the Hungarian National Guidelines allowed skipping ALND for patients operated on with breast conserving surgery and limited nodal involvement (up to 2 macrometastases) in conditions matching the American College of Surgeons Oncology Group trial (ACOSOG) Z-0011 [14–16].

The SLNs were assessed with gross slicing at about 2 mm intervals and HE staining of the initial cuts and two additional levels separated by 250 μm from each other (limited step-sectioning). When negative, cytokeratin (AE1/AE3) immunohistochemistry was also applied to one level for ILC cases, i.e., the reported cases. Two levels of cytokeratin staining were generally used for all SLNs

till December 2014. Lymph nodes involved by isolated tumour cells were considered as negative for the purpose of the study [4].

The data collected included tumour size, histological type, grade, oestrogen receptor (ER) status, progesterone receptor (PR) status, HER2 (human epidermal growth factor receptor-2) status, focality, mammographic morphology; the number of LNs assessed and positive for metastasis, extracapsular extension of nodal metastases, data on the axillary status gained by palpation, AXUS and FNAC, and type of axillary surgery (SLNB vs ALND). Results of FNAC were classified as positive of metastasis vs negative, and this latter category also included inconclusive results.

For nodal positivity (as outcome value), the two categories of pN0 and limited nodal involvement (cases with 1–2 lymph nodes involved) versus more extensive nodal involvement (>2 LNs metastatic) were selected. This was done in order to follow the ACOSOG Z-0011 trial inclusion criteria and the practice of omitting further axillary surgery in cN0 patients with 1–2 metastatic SLNs.

Statistical analysis was performed with the SPSS Statistics software (IBM, SSPS 23.0, Armonk, NY USA) and Vassarstats [17] on the basis of Microsoft Excel stored data. For univariate analysis, the chi-square test or the Fisher exact test was used for categorical variables and the Mann-Whitney *U* test for continuous variables, whereas for the multivariable analysis of the factors influencing greater nodal involvement, a forward binary logistic regression was performed. True positive (TP), true negative (TN), false positive (FP) and false negative (FN) results of AXUS and FNAC were calculated for both P1 and P2 periods to allow comparison of the two diagnostic approaches. Comparisons of these rates and sensitivity or specificity for P1 and P2 were done with the binomial test with results of P1 used as standard. The significance level was $p < 0.05$ for all statistical tests.

This retrospective analysis was approved by the Regional Ethical Committee of the University of Szeged as part of a larger clinicopathological analysis of ILCs.

3. Results

In the retrospective analysis involving P1 between January 2013 and June 2018, 106 ILC cases from 104 female patients were included. The main characteristics of the tumours are summarized in Table 1. The median age of the patients was 65 years. Of the tumours, 59 were left sided, whereas 47 were right sided; at least 6 patients had bilateral tumours, including metachronous cases falling outside of the studied period. Axillary surgery was ALND in 37 cases (9 of these following SLNB) and SLNB in the remaining 69 (14 patients with limited nodal involvement and 55 with a pN0 status, including 7 pN0(i+) cases). Of the 106 ILCs analysed, 28 (26%) had more than 2 LNs involved by metastasis.

During the P2 period, 47 patients with AXUS-guided FNAC were operated on, and the results are summarized in Table 1.

In P1, all cases that were deemed node-positive by palpation ($n = 8$, 8/106), and all those which were thought suspicious on AXUS and had FNAC sampling, proved to be node-positive on final histology. Of the cases with positive palpation findings in the axilla, 7 were proven to be positive by preoperative FNAC. All cases positive by palpation (8/8) and 20/25 (0.8; 95% confidence interval (CI): 0.61–0.91) positive/suspicious by AXUS and having an FNAC had >2 metastatic LNs. All cases with positive physical examination findings also had abnormal AXUS. (In a logistic regression model inclusive of all P1 cases and preoperatively available factors, AXUS/FNAC based staging was the only independent predictor of more than 2 involved LNs: $p < 0.0001$; OR 7.15, 95%CI: 2.47–20.79).

Of the P1 cases which were cN0 by palpation and AXUS negative or AXUS positive but FNAC negative ($n = 81$), 27 had axillary metastasis, and 8 had more than 2 LNs involved (Supplementary Table 1). For these, the univariable analyses suggested that the factors being significantly associated with >2 LNs involved include age, the pT category, pathological tumour size, (lympho-)vascular invasion, the ER status, extracapsular extension of the metastasis, whether only SLN biopsy or ALND had been performed and whether or not primary systemic treatment was given or not. Of these parameters, only the presence of extracapsular extension ($p < 0.001$; OR = 77.02 95%CI:7.49–791.9) and lymphovascular invasion ($p = 0.045$; OR = 13.87 95%CI:1.01–189.1) remained significant independent predictors, neither of which is available preoperatively. Taking into account only factors available preoperatively, only age remained a significant predictor ($p = 0.038$, OR = 0.89 95% CI: 0.81–0.99), suggesting that with increasing age, the frequency of massive nodal involvement tends to decrease.

All cases with positive axillary palpation findings in P2 were also deemed positive by AXUS and proven to be metastatic by FNAC. Of the physically negative cases 10 were positive by AXUS, and all but three cases (including one with non-diagnostic cytology sample, and no subsequent operation) had metastatic lymph nodes; the 5 FNAC-positive cases had >2 (range: 5–17) involved LNs, whereas only one of the 4 FNAC-negative cases fell into this category (with 10/10 involved LNs). Of the 39 AXUS-negative cases 11 had minimal nodal involvement and 4 patients with non-diagnostic/inconclusive FNAC results had >2 metastatic LNs (with 3/12, 9/18, 5/10 and 15/16 involved LNs, respectively) (Supplementary Table 2).

The true and false negative and positive values for AXUS and FNAC for both P1 and P2 are reported in Table 2. The proportion of FPs for FNAC was 0% in both periods, and that of AXUS was also nil to low. There were no significant differences in the P1 and P2 proportions of TNs, TPs, FNs and FPs for AXUS, neither in the setting of node negative versus node positive cases, nor in that of ≤2LNs involved versus >2LNs involved. For FNAC, obvious differences are seen in the proportions of TNs (0 vs 55%) and TPs (76 vs 15% for nodal involvement, and 72% vs 11% for >2LN+ involvement) of P1 versus P2 (all $p < 0.0001$); the FN and FP proportions were not statistically different between P1 and P2. In other comparisons, the FN rate (FNR=FN/(FN + TP) of identifying >2LN+ cases was significantly higher in P2 than P1 (0.5 vs 0.1, $p < 0.001$) whereas the sensitivity to identify >2LN+ was lower (0.5 vs 0.9, $p < 0.001$). The data reported clearly indicate that doing FNAC in all patients (P2 period) did not improve the preoperative staging in a clinically relevant way.

4. Discussion

Despite the improvement of diagnostic methods, ILCs of the breast may still lead to frustrating diagnostic experiences. Not only can they manifest as occult carcinomas [18], or carcinomas with more foci than expected [19], but they may also have massive nodal involvement without prior notice. Indeed, a clinically node negative status may hide multiple metastatic lymph nodes, as this happened in 14/153 (9%) of this overall cohort.

In keeping with current knowledge, axillary palpation had a low sensitivity to disclose significant axillary LN involvement. On the basis of systematic reviews, AXUS is said to identify every second case with metastasis to the axilla, but one of four cases with an AXUS- status harbours metastasis in the LNs [20,21]. The Z-0011 trial completely changed the policy of preoperative nodal staging, and it is not sufficient to identify node-positive breast cancers, but involvement with higher nodal burden needs to be identified. On the basis of a report on 577 cases, it seems that a negative AXUS can predict for the lack of massive (pN2-pN3) nodal involvement in the majority of cases (negative predictive value: 95.5%), but an

Table 1
Clinical and pathological factors in the two periods assessed.

	P1 (n = 106)	P2 (n = 47)	p values or all cases
Median age in years (range)	65 (38–88)	63 (35–83)	p = 0.96
pN category			p = 0.96
pN0	55 (52%)	26 (55%)	81
pN1	24 (23%)	11 (23%)	35
	(1–2 LN+: 23)	(1-2LN+: 11)	
pN2	11 (10%)	4 (9%)	15
pN3	16 (15%)	6 (13%)	22
Nodal status of interest		(n = 47)	p = 0.79
pN0	55 (52%)	26 (55%)	81
1-2LN+	23 (22%)	11 (23%)	34
>2LN+	28 (26%)	10 (21%)	38
pT category			p = 0.66
pT1	50 (47%)	22 (42%)	72
pT2	32 (30%)	18 (34%)	50
pT3	21 (20%)	7 (13%)	28
pT4	1 (1%)	0	1
pTx, pT0[a]	2 (2%)	0	2
(Lympho)vascular invasion			p = 0.27
Present	12 (11%)	2 (4%)	
Absent	94 (89%)	45 (96%)	
Histological grade (on CNB)			p = 0.03
G1	4 (4%)	0	
G2	91 (86%)	47 (100%)	
G3	11 (10%)	0	
Histological type			p = 0.20
pure ILC	96 (91%)	46 (98%)	
mixed ILC and NST	10 (9%)	1 (2%)	
ER status			p = 1.0
ER+	102 (96%)	46 (98%)	
ER-	4 (4%)	1 (2%)	
PR status			p = 0.38
PR+	93 (88%)	38 (79%)	
PR-	13 (12%)	9 (21%)	
HER2 status			p = 0.34
HER2+	2 (2%)	3 (6%)	
HER2-	104 (98%)	44 (94%)	
Palpation of the axilla			p = 0.12
node-negative	97 (91%)	47 (100%)	
node-positive	8 (8%)	0	
Unknown	1 (1%)	0	
AXUS and FNAC[b]			p = 0.33
AXUS negative	81 (76%)	38 (81%)	
FNAC negative or not diagnostic	5 (5%)	4 (9%)	
FNAC positive	20 (19%)	5 (11%)	
Extracapsular extension			p = 0.79
Present	28 (26%)	10 (21%)	
Absent	23 (22%)	11 (55%)	
Not applicable	55 (52%)	26 (23%)	
Neoadjuvant therapy given			p = 0.35
Yes	11 (10%)	2 (4%)	
No	95 (90%)	45 (96%)	
SLNB only or ALND			p = 0.89
SLNB only	68 (64%)	30 (64%)	
ALND	38 (36%)	17 (36%)	

ALND: axillary lymph node dissection, AXUS: axillary ultrasound, CNB: core needle biopsy, ER: oestrogen receptor, FNAC: fine needle aspiration cytology, G: grade, HER2: human epidermal growth factor receptor-2, ILC: invasive lobular carcinoma, NST: no special type, PR: progesterone receptor, SLNB: sentinel lymph node biopsy.

[a] The pT0 refers to an occult carcinoma with pN3 nodal involvement.

[b] For P2 these are virtual categories matching P1 settings, e.g. FNAC positive cases of AXUS negative patients are listed under AXUS negative, and not under FNAC positive, to allow comparison. Therefore, "AXUS negative" refers to cases that were negative by axillary ultrasound, "FNAC negative or not diagnostic" refer to cases with suspicious axillary ultrasound findings in which FNAC could not prove nodal involvement, and finally "FNAC positive" refers to cases with suspicious axillary ultrasound and positive cytology.

AXUS+ status cannot really distinguish between pN1 vs pN2-pN3 cases [4,22]. In this respect, AXUS is not worse than standard or dedicated MRI assessment of the axilla [23,24]. Most of the time, greater nodal burden is reflected by pN2 and pN3 categories, only a few studies have concentrated on a definition of >2LNs involved (i.e. inclusive of the upper pN1 category) matching the evidence of the Z0011 trial and the American Society of Clinical Oncology recommendations [25]. A meta-analysis of these studies (with results of 4271 patients reviewed) reported that 79% of AXUS- patients have low nodal burden (0–2 involved LNs) vs AXUS+ patients having only 43% with similar low nodal burden [26].

An AXUS-guided biopsy, when positive is much more likely to reflect greater degree of nodal involvement among node-positive cases than a negative needle biopsy (FNAC or CNB) [5,6,21], and the false-positive rate of FNAC or CNB is negligible, no false-positive cases occurred in this series.

Table 2
Distribution of true and false negative and positive results per pathological nodal categories of surgically staged cases for AXUS and preoperative FNAC results in periods P1 & P2

	AXUS					
Surgical pathological staging	P1 negative	P1 positive	All	P2 negative	P2 positive	All
negative	TN: 55 (52%)	FP: 0	55	TN: 24 (51%)	FP: 2 (4%)	26
positive, >2LN+	FN: 26 (25%), FN: 8 (8%)	TP: 25 (24%), TP: 20 (19%)	51, 28	FN: 14 (30%), FN: 4 (9%)	TP: 7 (15%), TP: 6 (13%)	21, 10
	FNAC					
Surgical pathological staging	P1 non-positive	P1 positive	All	P2 non-positive	P2 positive	All
negative	TN: 0	FP: 0	0	TN: 26 (55%)	FP: 0	26
positive, >2LN+	FN: 6 (24%), FN: 2 (8%)	TP: 19 (76%), TP: 18 (72%)	25, 20	FN: 14 (30%), FN: 5 (11%)	TP: 7 (15%), TP: 5 (11%)	21, 10

AXUS: Axillary ultrasound, FNAC: fine-needle aspiration cytology; FN: false-negative, FP: false-positive, TN: true negative, TP: true positive, >2LN+: more than 2 lymph nodes involved by metastasis; non-positive refers to negative and inconclusive together (inconclusive results occurring only in P2). Note: the calculations of FN and TP for >2LN+ used categories >2LN+ versus ≤2LN+ (i.e. 2, 1 or 0 LN+).

The above data were all derived from series with a mixture of breast cancer types. As concerns the problem with ILC, several authors have highlighted that the imaging assessment of nodal status in these tumours is less reliable. The FNR for identifying a massive nodal metastatic load (pN2-pN3) is higher for ILC than for NST invasive breast carcinomas (17% vs 4%) by AXUS [27]. AXUS-guided FNAC is also significantly worse in detecting nodal involvement (with sensitivities of 55% for ILC vs 76% for NST) [3]. These data are reflected by frustrating individual clinical experiences. Our series of 153 ILCs suggested that AXUS has an overall sensitivity of 68% (95%CI: 51–82%) for detecting >2LN involvement and the FNR is pretty high at 32% (95CI: 18–49%). These data reflect that lobular carcinomas are indeed different from NST breast cancers in the reliability of their nodal staging, and data derived from series without stratification by tumour type cannot be reliably extrapolated to ILCs.

Since AXUS-guided biopsy has better sensitivity than AXUS alone, as a policy, we introduced AXUS-guided FNAC for all ILCs, to increase the detection rate of higher nodal burden. On retrospect, this policy failed. A higher proportion of patients were sampled by FNAC as compared to the previous policy in P1 (53/63, 87% vs 25/106, 24%). The difference in sampling policy explains the differences in the TN rate of FNAC in P2 vs P1 (in P1: only suspicious LNs were sampled, therefore the likelihood of being negative was low) and has also led to significant decrease in the sensitivity of the test along with an increase in the FNR. These figures show that extending the sampling to all patients without abnormal AXUS finding does not improve the identification of patients with high nodal burden. Moreover, it also leads to the loss of the single factor that was found on multivariable analysis to be independently associated with >2 metastatic lymph nodes. Only half of the ten patients with a high nodal burden could be identified with this policy, whereas the remaining five had not only an AXUS- status, but also a negative (n = 1) or inconclusive (n = 4) FNAC result. The results have led to abandon this policy and limit AXUS-guided FNAC to patients with abnormal AXUS.

A possible refinement could be the extension of FNAC to patients with advanced T categories (T3, T4) as suggested by Morrow et al. on the basis of their multivariable analysis [3]. Indeed, these tumours were associated with a higher rate of >2LNs involved, but our multivariable analysis failed to reveal this variable as an independent one; of the factors available preoperatively, only traditional (P1-related) AXUS + FNAC (all patients) or age (only cN0 patients) remained significant in the multivariable analysis.

The limitations of the present work include the retrospective nature of the analysis. The periods (P1 and P2) compared had a different prevalence of patients with high nodal burden, and the case numbers are limited, despite the timescale of 7 years covered. Because of changing policy toward ALND, not all patients with positive SLNs had ALND, limiting the identification of greater nodal load. In fact, patients with cN0 status, including AXUS- and metastasis in 1 or 2 SLNs (n = 14 and 8 in P1 and P2, respectively) without ALND might have harboured more involved lymph nodes, but could not be identified. This policy is becoming more and more general, and the data gained must be accepted as the best that could be reached in a non-prospective data collection outside clinical trial; no better data with higher rates of ALND can be expected in the future considering the conservatism in axillary surgery.

5. Conclusions

Literature data suggest that preoperative nodal staging of ILC is less sensitive than that of NST carcinomas, a higher nodal burden (>2LNs involved) can more often remain hidden, but FNAC of the axilla of all AXUS-negative patients has not led to better identification of cases with high nodal burden.

CRediT authorship contribution statement

G. Cserni: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **É. Ambrózay:** Conceptualization, Investigation, Methodology, Resources, Visualization, Writing – review & editing. **P. Serényi:** Investigation, Methodology, Resources, Visualization, Writing – review & editing. **R. Bori:** Investigation, Resources, Visualization, Writing – review & editing. **I. Sejben:** Investigation, Methodology, Resources, Visualization, Writing – review & editing. **E. Csörgő:** Investigation, Resources, Visualization, Writing – review & editing. **O. Serfőző:** Investigation, Resources, Visualization, Writing – review & editing. **K. Lóránd:** Investigation, Resources, Visualization, Writing – review & editing. **L. Venczel:** Investigation, Resources, Visualization, Writing – review & editing. **R. Maráz:** Investigation, Resources, Visualization, Writing – review & editing. **M. Sinkó:** Investigation, Resources, Visualization, Writing – review & editing. **N. Szeleczki:** Investigation, Resources, Visualization, Writing – review & editing. **T. Nyári:** Data curation, Formal analysis, Validation, Visualization, Writing – review & editing. **T. Zombori:**

Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing.

Declaration of competing interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.11.130.

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