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Prospective comparison of contrast-enhanced ultrasound and magnetic resonance imaging to computer tomography for the evaluation of complex cystic renal lesions

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Key words: CEUS; Complex renal cysts; Comparative imaging studies; MRI

Authors' contributions:

Study concept and design: SA

Acquisition of data: JTH, DWTV, SA, KB, BK, FB

Data processing: JTH, DWTV, SA, KB, DU.

Statistical analyses: MM, DU

Drafting of the manuscript: SA, KB, DWTV, JTH, MM,

Review of the manuscript: MM, SA, DU

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Abstract

Objective: To prospectively evaluate the diagnostic accuracy of contrast enhanced ultrasound (CEUS) and MRI compared to computed tomography (CT) as the current gold standard for the characterization of cystic renal lesions using the Bosniak classification.

Methods:

Between July 2014 and October 2017 we prospectively enrolled patients with cystic renal lesions. Based on the Bosniak classification of complex renal lesions (≥BII-F) we evaluated the accuracy of observed agreement by Cohen's Kappa coefficient and calculated sensitivity, specificity, positive and negative predictive values (PPV/NPV) between the three imaging modalities CT, MRI and CEUS.

Results: We evaluated 65 cystic renal lesions in 48 patients (median age 63 years, range 36-91 years; 18 females, 30 males). According to CT 29 (47%) of the cystic renal lesions were classified as complex. The agreement between CEUS and CT in the classification of complex cystic lesions was fair (agreement 50.8%, Kappa 0.31), and was excellent between MRI and CT (agreement 93.9%, Kappa 0.88).

Compared to CT, CEUS and MRI had a sensitivity of 100% and 96.6%, a specificity of 33.3% and 91.7%, a PPV of 54.7% and 90.3%, and a NPV of 100% and 97.1% with an accuracy of 63.1% and 93.8% respectively.

Conclusion: CEUS has an excellent sensitivity and NPV and represents a promising non-invasive screening tool for renal cystic lesions. The classification of complex renal cysts based on MRI and CT scans correlated closely.

Introduction

The widespread availability of abdominal diagnostic ultrasound and computed tomography (CT) has led to increased incidental detection of cystic renal lesions [1, 2]. This often leads to a diagnostic dilemma since differentiating between malignant and benign complex renal cysts remains challenging [3, 4]. The gold standard for establishing the need for surgical treatment is the classification of renal masses according to Bosniak, which was originally based on conventional contrast-enhanced CT imaging [5-7]. Whereas Bosniak I and II cysts are benign lesions not requiring any treatment or follow-up, Bosniak IIF-V cystic renal lesions are considered to be complex lesions requiring further action. Whereas Bosniak IIF cystic lesions are likely to be benign but require follow up, Bosniak III-V lesions have an increasing potential to be malignant, thus often requiring surgical treatment [8].

For decades contrast enhanced CT has been the gold standard for evaluation of cystic renal lesions. The main drawbacks of CT, however, are its ionizing radiation, the need for nephrotoxic iodinated contrast medium, and the potential for allergic reactions. Recently, magnetic resonance imaging (MRI) and contrast-enhanced ultrasound (CEUS) have been increasingly used for assessment of complex renal cysts. Patients with renal function impairment in particular would benefit greatly from imaging modalities that do not entail exposure to nephrotoxic contrast agents. The ideal diagnostic imaging modality, however, has yet to be determined.

Prospective, direct comparison of CT with CEUS and MRI with regard to accuracy of renal cystic lesion classification is lacking. Only a few clinical studies – most of them retrospective – have investigated and compared the classification of complex renal

cystic lesions using all three imaging modalities [3, 8-11]. The primary aim of this prospective study therefore was to compare the diagnostic accuracy, and sensitivity and specificity of CEUS and MRI with those of CT as the gold standard for grading of complex renal lesions based on the Bosniak classification

Materials and Methods

Study population

Between July 2014 and October 2017, 52 patients were prospectively enrolled in this study. Of these patients, 48 underwent all three imaging modalities (CT, CEUS, MRI) on a total of 65 renal cystic lesions with a transverse diameter of at least 1 cm and thus were included in this study. In patients with an initial CEUS evaluation for study recruitment, some complex cysts (Bosniak II-F) were later downgraded to Bosniak <II-F based on the CT evaluation, but all were included in our analysis.

The study was approved by the Ethics Committee of Canton Bern, Switzerland (Cantonal Ethics Committee Bern, CH KEK: Nr. 084/14, ClinicalTrials.gov Identifier: NCT02371551).

Patient recruitment and eligibility criteria

We prospectively evaluated consecutive patients from the Departments of Urology and Nephrology who underwent either CT or CEUS after an initial diagnosis of a cystic renal lesion. Inclusion criterial were: 1) 18 years of age or older, 2) written informed consent, 3) suspected complex renal lesion (Bosniak classification ≥II-F, 4), lesion with a

transverse diameter of least 1 cm, 5) stable renal function during the last 3 months defined as an estimated GFR >30mL/min (according to the CKD-EPI formula).

Exclusion criteria were: 1) pregnancy, 2) history of allergic reaction to CT, MRI or CEUS contrast agents, 3) acute pyelonephritis and acute kidney injury (AKIN score ≥1), 4) vulnerable adults, and 5) non-adherence to follow-up.

After study inclusion, each patient was evaluated with CT, CEUS and MRI. If the CT Bosniak grade was ≥II-F, the treatment modalities (i.e. conservative or surgery) and follow-up intervals were determined by the urologist in consultation with the patient. Histopathological diagnoses for the complex cystic lesions were obtained in every patient who underwent surgery. The follow-up period for all patients who were primarily observed and did not undergo surgery was at least 12 months. For this study, all three imaging modalities were performed only at baseline. First follow up was performed with both CEUS and MRI, later follow up with MRI.

Imaging modalities and techniques

CT

The CT scanner used for this study was a Philips Brilliance CT 64. Contrast injection was mandatory for lesion enhancement, and a minimum of two phases were required to differentiate between cysts with high protein content and lesion enhancement.

The standard CT protocol for evaluation of suspected renal cell carcinoma includes a non-enhanced scan, an arterial scan at 15 seconds and a nephrographic phase at 85 seconds. The contrast agent used for CT was XeneticR 350 (Guerbet AG) which has a recommended dose of 1-2ml/kg body weight.

Ultrasound and CEUS

Ultrasound of the kidney was performed on an Accuson 3000 Siemens ultrasound device (Siemens, Erlangen, Germany) with a C6® MHz probe by two nephrologists (SA, KB) with more than 10 years' experience in sonography and CEUS of the kidney. SonoVue® (Bracco, Milan, Italy) was used as contrast agent, first dissolved in 10 mL 0.9% NaCl and then infused via a peripheral vein using a dedicated syringe pump (VueJect®, Bracco Research, Geneva, Switzerland). Low mechanical index (MI=0.06) ultrasound of the kidney was performed. Once adequate images of the kidney and cyst were obtained, the SonoVue® infusion was started at a test dose of 0.5 mL/min for 1 min, and then titrated in 0.5mL/min steps up to 2mL/min. Image depth, focus, gain, and frame rate were optimized at the beginning of each study and were held constant during the study. At least three consecutive destruction-refilling sequences were obtained.

MRI

MRI was performed using a 3 Tesla MRI (Skyra, Siemens, Erlangen, Germany). Conventional MRI sequences included T1 and T2-weighted sequences in the axial and coronal planes before and after injection of 0.2 mL/kg bodyweight Multihance (Bracco, Milano, Italy). Diffusion weighted imaging with 8 b values (0, 50, 100, 150, 200, 300, 500, 800) and dynamic contrast-enhanced MRI were also performed. Injection rate was 2.5 mL/s followed by a flush with 25 mL normal saline. A series of 10 scans was performed with a scan duration of 16 seconds and 15-second breaks between scans. The scan parameters are included in the Supplementary Table S1.

Image analysis

Image analysis for CT and MRI was performed on a PACS system Sectra Workstation IDS7 Version 18.2.18 by two radiologists with 15 (JTH) and 22 years' experience (DWT). CEUS was performed or supervised by a single skilled nephrologist (SA) with more than 20 years of clinical experience in renal ultrasound and more than 10 years CEUS experience in transplanted or native kidneys; images were also reviewed for the detection and characterization of cystic renal lesions.

The readers were blinded to clinical information. CT images were evaluated by both radiologists to locate and then grade the lesion. The parameters of the lesions evaluated by CEUS, CT and MRI were size, location, presence and septal thickness, presence and size of calcification, enhancement characteristics, and presence of solid areas. The presence of any diffusion restriction on MRI was also assessed. The Bosniak system was used to classify the lesions [12] for each modality separately based on the presence and nature of calcification, septation, wall-thickening, signal characteristics, solid components and enhancement, and diffusion restriction with enhancing tissue.

Data analysis and statistical analysis

Stata 13.1 (StataCorp, College Station, Texas, USA) was used for statistical analysis. Medians with ranges or the total number in a category with its proportion were used to describe continuous or categorical variables.

The present analysis was performed to compare the Bosniak classification grades based on CT as the gold standard versus those of MRI and CEUS**.** The Bosniak classifications were first displayed as a modified scatter plot, then grouped as pathological/complex (at least Bosniak II-F) or non-pathological (Bosniak I and II). Based on contingency tables (CT pathological vs. MRI or CEUS pathological), the following parameters were

calculated to determine the diagnostic accuracy of CEUS and MRI compared to CT: prevalence, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. All parameters were determined with 95% confidence intervals (CI). For both steps, Cohen's Kappa was calculated to determine the inter-modality agreement and its standard error (SE). The following definitions for strength of agreement for the values of Kappa were used: <0.20 poor, >0.20-0.40 fair, >0.40-0.60 moderate, >0.60-0.80 good, >0.80 excellent. We calculated Pearson's correlation coefficient for correlations between MRI, CEUS and CT. The results were bootstrapped to obtain 95% CI.

Results

The 48 patients (30 [62.5%] male, 18 [37.5%) female) had a total of 65 cystic renal lesions (5 BI, 31 BII, 7 BII-F, 5 BIII, and 17 BIV as scored by CT) that were analyzed. The Bosniak classifications of MRI and CEUS compared to the classification obtained by CT are shown in Figure 1 and Tables 2 and S2. Lesion size ranged from 1 cm to 11 cm; 33 (51%) lesions were located in the right kidney, 32 (49%) in the left kidney.

The median age of the study cohort was 63 years (range 36–91 years). The median interval between CT and CEUS (and vice versa) was 2 weeks (range 0–4 weeks), between CEUS/CT and MRI 4 weeks (range 0–20 weeks**)**. Table S2 provides an overview of the study group.

Comparison of CT and CEUS

In 51% (33/65) of cystic renal lesions, the CEUS Bosniak classification was the same as CT Bosniak score (Kappa 0.389, SE 0.056), in 43% (28/65) the CEUS score was higher than the CT score, and in 6% (4/65) CEUS score was lower than CT score (Fig. 1). Pearson's correlation coefficient r was 0.78 (95% CI: 0.71-0.86) between CT and CEUS.

At CT scan, 44.6% (n=29/65) of cystic renal lesions were classified as complex cysts compared to 63.1% (41/65) using CEUS (Kappa 0.31, SE 0.09) (Table 1a). For CEUS this resulted in an accuracy of 63.1% (95% CI: 50.5-74.1), a sensitivity of 100.0% (95% CI: 88.1-100.0), a specificity of 33.3% (95% CI: 18.6-51.0), a PPV of 54.7% (95% CI: 40.4-68.4), and a NPV of 100% (95% CI: 73.5-100.0).

Comparison of CT and MRI

In 80% (52/65) of renal cystic lesions the MRI Bosniak score was the same as the CT Bosniak score (Kappa 0.708, SE 0.071) (Fig 1), in 12% (8/65) the MRI score was higher the CT score (example shown in Fig. 2), and in 8% (5/65) MRI score was lower than the CT score (Supp. Fig. 1). Pearson's correlation coefficient r was 0.95 (95% CI: 0.92-0.97) between CT and MRI.

At CT scan, 44.6% (n=29/65) of renal cystic lesions were classified as complex cysts (mentioned above) compared to 48% (n=31/65) using MRI, amounting to an agreement between CT and MRI in 93.9% of lesions (61/65) (Kappa 0.88, SD 0.12) (Table 1b). For MRI this resulted in an accuracy of 93.8% (95% CI: 84.3-97.7), a sensitivity of 96.6% (95% CI: 82.2-99.9), a specificity of 91.7% (95% CI: 77.5-98.2), a PPV of 90.3% (95% CI: 74.2-98.0), and a NPV of 97.1% (95% CI: 84.7-99.9).

Follow-up of complex renal cystic lesions and histopathological examination

Six cystic renal lesions classified as Bosniak II-F were followed up with MRI for 12-36 months and showed no change of classification during follow up. Two patients were lost to follow up after 12 months.

One cystic renal lesion classified as Bosniak BII-F by CT was upgraded to a complex lesion Bosniak III by CEUS and MRI; subsequent histopathological examination showed it was a papillary renal cell carcinoma (RCC).

In 19 patients, a total of 22 high-grade complex cystic renal lesions ≥ Bosniak III (Bosniak III [n=5], Bosniak IV [n=17]) where identified using CT. All told (including the patient with Bosniak IIF on CT upgraded to Bosniak III on CEUS and MRI), 11 patients underwent surgery (Table S2). Histopathological examination showed malignancy in

91% (10/11) of these complex cystic renal lesions: three papillary RCC, five clear cell RCC, one multilocular RCC, and one oncocytic RCC. In one patient with a complex renal cystic lesion classified as Bosniak III, a benign multilocular cyst was diagnosed on histopathology. Nine patients did not undergo surgery, two refused surgery, and the remaining seven were managed conservatively due to advanced age and comorbidities.

Discussion

An increasing number of cystic renal lesions are detected incidentally as part of various different abdominal imaging modalities. However, not every renal cystic lesion is necessarily a malignant tumor potentially requiring surgical treatment. Precise differentiation between harmless and malignant renal cystic lesions is of utmost importance. The primary aim of this study, therefore, was to compare the diagnostic accuracy and Bosniak scoring of two diagnostic modalities not using ionized radiation -- MRI and CEUS -- to the current diagnostic gold standard, CT.

CEUS showed 100% sensitivity in classification of complex cysts in comparison to CT but low specificity and thus low accuracy. MRI, on the other hand, showed excellent sensitivity (90%) and specificity (91%), with an accuracy of 94% compared to CT.

Our results show that there was a fair agreement regarding complex cyst classification between CEUS and CT and a good agreement between MRI and CT.

Since CEUS allows for an excellent visualization of septum-walls and perfusion within the cystic lesions, even in small cystic renal masses, it resulted in upstaging to a higher Bosniak category in almost half of the renal complex cystic lesions (Bosniak ≥2F). Our findings are in line with previously published studies showing that CEUS tends to result in higher grading for such lesions. In a study comparing CEUS with contrast-enhanced CT, Xue et al. found that CEUS was superior to CT in visualizing the number of septums, wall thickness and the presence of solid cystic components, which resulted in identification of more malignant lesions compared to contrast-enhanced CT [13]. Additionally, as shown by others, complex renal cystic lesions are assigned higher

grades based on CEUS in 20% to 40% of cases when compared to CT [14-17]. Nevertheless, in contrast to our own findings some authors report high concordance between CEUS and CT for complex renal cysts. However, the retrospective nature of these studies, different patient selection criteria, and study-specific definitions of cystic lesions do not allow direct comparison with our findings [17,18].

Due to its high sensitivity, CEUS evaluation of renal cystic lesions may help to exclude complex/pathologic renal lesions thus lowering the need for examination and follow-up with cross-sectional modalities such as CT or MRI after the initial screening with CEUS. Despite the high sensitivity of CEUS, however, caution is needed when making surgical indications for partial or total nephrectomies based solely on CEUS because it has a low specificity.

The high concordance we found between MRI and CT in classifying renal cystic lesions ~~,~~ are in line with most previous studies, showing that the two modalities result in very similar classification grades for cystic renal lesions in most cases. MRI has higher contrast resolution compared to CT and, in addition to having classic CT signal characteristics, it allows for a better evaluation of cystic content, such as hemorrhage or mucus [19, 20]. Although detection of calcifications is not as precise with MRI as with CT, MRI is more sensitive in capturing enhancement of internal septation, resulting in assignment of higher grades for such lesions [21]. The presence of calcifications is not as important as the accompanying soft tissues in the detection of tumors and MRI can detect enhancing soft tissues very well. We therefore think that missing small calcifications without soft tissue components is not relevant in the detection of tumors [22]. We also performed diffusion-weighted MRI sequences and found diffusion impediment in solid tumor parts and in hemorrhagic cysts. Diffusion impediment alone,

however, is not sufficient for diagnosis of malignancy since it may also be present in abscesses and hematomas.

One limitation to the present study is the fact that after the initial, blinded cystic lesion classification by each imaging modality, an unblinded re-evaluation of all cysts was performed to ensure that the same lesion was being evaluated by the three different modalities.

Another limitation of our study is that histopathology was available for only a small subgroup of cystic renal lesions (11/65), thus we could not assess enhancement patterns for different tumors. Follow up for two of the six lesions classified as Bosniak IIF was only available for 12 months as the patients were lost to follow up. However, in one patient initially classified on CT as having a Bosniak IIF renal cystic lesion the classification was upgraded on CEUS and MRI to a Bosniak III complex renal cystic lesion; indeed the histopathological examinations finally disclosed a malignant papillary RCC.

Although the numbers are small, we found an excellent correlation between histopathological findings and CEUS and MRI findings, while none of the complex lesions showed changes that necessitated reclassification or further diagnostic workup.

The use of CEUS and MRI allows the detection and evaluation of complex cystic lesions without CT, thereby avoiding ionizing radiation and the risks of contrast material reactions and nephropathy [8]. This is especially important in younger patients and those with kidney insufficiency or a history of allergic reactions. Furthermore, for repeated imaging during the course of follow up, imaging modalities not using ionizing radiation are especially useful. Another patient cohort of particular interest for imaging with CEUS are patients with chronic kidney impairment since the majority of these patients have

multiple cystic lesions. Due to their chronic kidney failure, CT and MRI with contrast agents are used reluctantly, making CEUS for these patients a highly valuable diagnostic tool.

Based on our findings and previous studies, there is growing evidence that the majority of complex renal lesions can be reliably characterized with CEUS [23]. As a consequence, we propose an imaging algorithm that places a high value on CEUS in the classification of complex renal lesions (Supp. Fig 2).

In this study, CEUS had a sensitivity of 100% and a NPV of 100 %, but it has the limitation that the results are dependent on the observer's previous CEUS experience [24-27]. Since standardized and specific molecular imaging-related criteria for CEUS are lacking, the reproducibly of the Bosniak classification using this technique is dependent on the experience and criteria applied by the on-site ultrasonographer [28]. In the present study, renal CEUS examinations were performed or supervised by a single skilled nephrologist (SA) with more than 20 years of clinical experience in renal ultrasound and more than 10 years CEUS experience in transplanted or native kidneys. This is possible in a CEUS-specific study but not in everyday clinical practice. Also, the derivation of standardized Bosniak grades using CEUS findings results in higher false-positive rates.

As proposed by other studies and by the EFSUMB Expert Task Force, the current CT-based classification scheme needs modification, while CEUS-based renal cystic criteria require validation, including histopathological correlation, in large prospective studies as a way to improve CEUS specificity and overall diagnostic performance [23, 24, 29].

Conclusion

The cross-sectional imaging modalities MRI and CT show a high degree of concordance in classifying cystic renal lesions applying the Bosniak system; MRI might therefore be widely used for this purpose, especially in cases where ionizing radiation or CT contrast media are contraindicated. For its part, CEUS is highly sensitive and has an excellent NPV in the evaluation of cystic renal lesions. Its specificity, however**,** is lower making it less suitable as the sole imaging modality for cystic renal lesions. But because it is readily available and easily performed, it can be used for first-line investigations and for subsequent follow-up studies after initial CT or MRI-based grading, especially in persons with impaired kidney function.

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Legends

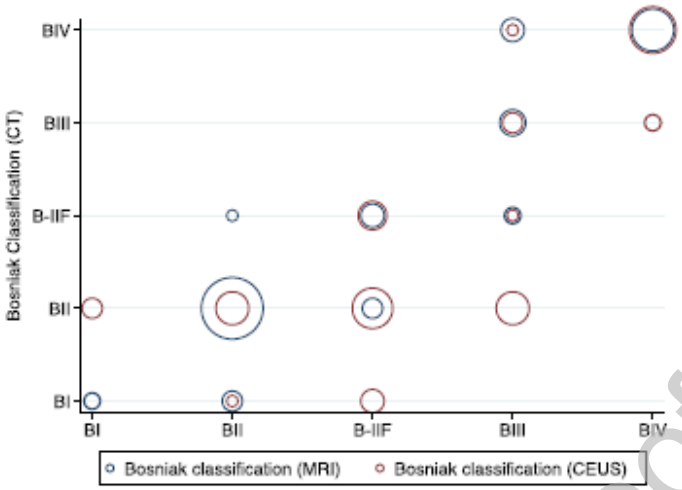

Figure 1. Bubble plot showing Bosniak classification of cysts based on the gold standard CT in comparison with CEUS and MRI.

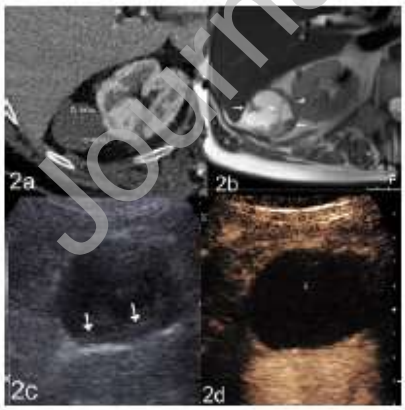

Figure 2. An 81-year-old male patient with von Willebrand disease. An axial-enhanced CT image (a) shows a heterodense lesion of the right kidney without enhancement with a prominent wall, classified as BII-F. An axial T2-weighted native MR image (b) shows the irregularly thickened wall, septation (arrowheads), and nodular internal thickening (arrows). Some diffusion restriction is seen, although no definite enhancement was evident after giving contrast medium (not shown); classified at MRI as BIII. A long axis US image (c) shows the cyst filled with hyperechogenic material (arrows) mimicking wall thickening, but the corresponding CEUS image (d) shows only an evident wall and no internal enhancement; classified as BII-F at CEUS.

Supplementary Figure 1: A 50-year-old male patient underwent CT scan for aortic aneurysm with incidental detection of a renal lesion. An axial native CT scan before (a) and after contrast medium (b) shows diffuse enhancement of the lesion in the upper pole of the right kidney; classified as BIV. An axial T1 weighted MRI scan before (c) and after contrast medium with fat saturation (d) shows multiple fine enhancing septation (arrows); classified as BIII.

Supplementary Figure 2: Flow chart for our proposed management plan placing a high value on CEUS in the classification of complex renal lesions in the imaging algorithm

Table 1. Comparison of the ratings of a) CEUS and b) MRI in detecting complex renal cysts compared to the gold standard of CT Bosniak classification.

a)

	Complex renal cyst	**Non-complex**	**Total**

		renal cyst	
CEUS positive test	29 (100%)	24 (67%)	53 (82%)
CEUS negative test	0 (0%)	12 (33%)	12 (18%)
Total	29 (100%)	36 (100%)	65 (100%)

b)

	Complex renal cyst	**Non-complex renal cyst**	**Total**
MRI positive test	28 (97%)	3 (8%)	31 (48%)
MRI negative test	1 (3%)	33 (92%)	34 (52%)
Total	29 (100%)	36 (100%)	65 (100%)

Table 2. Comparison of the Bosniak classification (BI-BIV) based on the gold standard CT compared to a) MRI and b) CEUS.

a)

		MRI					
		BI	**BII**	**BII-F**	**BIII**	**BIV**	**Total**
CT	**BI**	2	3	0	0	0	5
	BII	0	28	3	0	0	31
	BII-F	0	1	4	2	0	7
	BIII	0	0	0	5	0	5
	BIV	0	0	0	4	13	17
	Total	2	32	7	11	13	65

b)

		CEUS					
		BI	**BII**	**BII-F**	**BIII**	**BIV**	**Total**
CT	**BI**	0	1	4	0	0	5
	BII	3	8	12	8	0	31
	BII-F	0	0	6	1	0	7
	BIII	0	0	0	3	2	5
	BIV	0	0	0	1	16	17
	Total	3	9	22	13	18	65