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Significance of T1a and T1b Carcinoma Arising in Mucinous Cystic Neoplasm of Pancreas

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Abstract

Mucinous cystic neoplasm of pancreas (MCN) is one of the precursor lesions of pancreatic ductal adenocarcinoma (PDAC). The 5-year disease-specific survival for non-invasive MCNs was 100% and 20%-60% for those with PDAC arising in a MCN. However the significance of T1a (< 0.5 cm) and T1b (>0.5 cm and <1.0 cm) carcinoma arising in MCN as defined by the upcoming AJCC 8th edition is unclear. In this study, we examined 3 cases of MCN with T1a or T1b carcinoma and compared their clinicopathological characteristics and survival to 46 cases of MCN with low-grade dysplasia (MCN-LGD), 7 cases of MCN with high-grade dysplasia (MCN-HGD), and 7 cases of MCN with advanced invasive carcinoma (MCN-AIC, T2 or higher T stage). The tumors from all three cases were submitted in their entirety in 123, 296, and 200 blocks respectively. All three patients were alive with no recurrence during the follow up of 20.0, 113.8, and 137.2 months, respectively. Similarly, none of the patients who had MCN with either LGD or HGD had recurrence or died of disease. In contrast, 5 of 7 patients who had MCN-AIC had recurrence and later died of disease with a median survival of 22.9 months ($p<0.001$). Our study showed that MCN with T1a and T1b carcinoma had an excellent prognosis similar to MCNs with LGD or HGD after complete tumor sampling for histologic examination. Our results along with the previous studies suggest that close follow up, rather than aggressive systemic therapy, may be a better approach for these patients.

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Introduction

Mucinous cystic neoplasm (MCN) is a rare cystic, mucin producing neoplasm of the pancreas. In 1978, Compagno and Oertel first proposed to separate cystic, mucin-producing pancreatic neoplasm from serous cystic neoplasm of the pancreas (1). In 1996, the World Health Organization (WHO) classified cystic, mucin-producing pancreatic neoplasm into mucinous cystic tumor and intraductal papillary mucinous tumor, which were later renamed as mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN) in the 2000 WHO Classification (2). Along with IPMN and pancreatic intraepithelial neoplasia (PanIN), MCN is now considered one of the well-established precursor lesions of pancreatic ductal adenocarcinoma (PDAC) (3). In contrast to IPMN and PanIN which may be multifocal, MCN is almost always solitary, with the majority located in the body and tail of the pancreas. MCN is characterized by the presence of ovarian-type stroma, and does not communicate with the pancreatic ductal system. The mean age at presentation is 44 years for patients with a noninvasive MCN and 55 years for patients with an MCN with associated PDAC (4).

A review of the literature shows that for patients who underwent surgical resection for MCN, the reported frequency of invasive PDAC arising in association with MCN ranges from 3.9% to 36% (3–12). Because of the malignant potential of MCN, the current guidelines recommend resection of MCN, irrespective of lesion size (5, 6). Complete surgical resection of a non-invasive MCN is curative with a 5-year disease-specific survival rate of 100% (10, 13). However, the 5-year disease-specific survival rate is 20%-60% for patients of MCN-AIC (4, 5, 9, 10, 12, 14, 15). Recently, it has been reported that minimally invasive carcinoma (< 0.5 cm) (11, 12) as well as invasive carcinomas arising from mucinous cystic neoplasm with invasion limited to ovarian-like stroma or intratumoral septa, have a good prognosis (10, 15, 16). In the new upcoming 8th American Joint Committee Cancer (AJCC) staging system for pancreatic cancer, T1 tumor is subclassified into: T1a - invasive carcinoma ≤ 0.5 cm; T1b - invasive carcinoma >0.5 cm and <1.0 cm; and T1c, invasive carcinoma size of 1-2 cm (17). However, the prognostic significance of the newly defined pancreatic T1a and T1b carcinoma arising from a MCN is unclear. Here we report the clinicopathological features and survival of three cases of MCNs with T1a or T1b carcinoma as compared to 53 cases of MCN with no invasive carcinoma and to 7 cases of MCN with advanced invasive carcinoma (MCN-AIC, T2 or higher T stage). Although the number of cases are limited, our results in conjunction with previously reported cases suggest that patients with T1a and T1b carcinoma arising from a MCN have a better prognosis than those with MCN-AIC.

Materials and Methods

Study population and patient follow up

This study was approved by the institutional review board. Sixty-three MCN patients with or without an associated PDAC, who underwent surgical resection with curative intent from January 1, 1991 to June 30, 2016 were identified from a database that is prospectively maintained by the Department of Surgical Oncology and the pathology database in the Department of Pathology at the University of Texas MD Anderson Cancer Center. There

were 3 male and 60 female patients with a mean age of 53.6 years (range: 21.8-79.4 years) at the time of surgery. Radiologic features of patients diagnosed with MCN with T1a or T1b carcinoma are reviewed by a radiologist (E.P.T.). The clinical and follow-up information, such as patient age, gender, date of diagnosis, tumor site, type of surgery, prior or concurrent lesions in other sites/organs, date and site(s) of recurrence was verified by reviewing patients' medical records. The date and cause of death when applicable was determined by the documented clinical follow-up information and the U.S. Social Security Index. The duration of follow-up ranged from 1 month to 196 months (mean: 49.1 months). Two cases of MCN with T1a or T1b carcinoma in this study were included in Lewis study (cases 1 and 2 corresponding to cases 11 and 10 respectively) (16). In current study, however, we provided much more detailed clinical, radiographic and pathologic characterization of both cases. In addition, we have followed both patients for additional more than 5 years.

Pathologic examination of pancreatectomy specimens

For all cases, if no invasive carcinoma was identified after careful gross examination, the entire tumor was submitted for histologic examination according to our institutional protocol. The diagnosis of MCN was defined as a mucin-producing cystic lesion of the pancreas with distinctive ovarian stroma and no connection to the pancreatic ductal system. The cases were further stratified into MCN with low-grade dysplasia (MCN-LGD); MCN with high-grade dysplasia (MCN-HGD); MCN with T1a or T1b carcinoma (<1.0 cm invasion) and MCN with advanced invasive carcinoma (MCN-AIC, T2 or higher T stage) based on the WHO criteria and AJCC Cancer Stage, 8th edition (17). There was no MCN with T1c carcinoma identified in our database. All the cases were reviewed by two gastrointestinal pathologists (L.H. and H.W.) who were blinded about the clinical and follow up data.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences software for Windows (Version 22, SPSS, Inc., Chicago, IL). Chi-square or Fisher's analyses were used to compare categorical data, and analysis of variance (ANOVA) was used to compare continuous variables. Survival curves were constructed using the Kaplan-Meier method, and the log-rank test was used to evaluate the statistical significance of differences. Overall survival (OS) was calculated from the date of diagnosis to the date of death or the date of last follow-up if death did not occur. A 2-sided significance level of 0.05 was used for all statistical analyses.

Results

The clinical features of 63 MCNs are summarized in Table 1. The tumor sizes ranged from 0.80 cm to 22.0 cm. Fifty-six patients underwent distal pancreatectomy and 7 patients had pancreaticoduodenectomy. The resection margins were negative in all cases. Among the 63 patients, 46 (73.0%) were MCN-LGD, 7 (11.1%) were MCN-HGD, 3 (4.8%) were MCN with T1a or T1b carcinoma, and 7 (11.1%) were MCN-AIC. There was no MCN with T1c carcinoma identified in our database. The mean ages for patients with MCN-LGD, MCN-HGD, MCN with T1a or T1b carcinoma and MCN-AIC were 52.9 ± 14.1 years, 42.2 ± 10.5

years, 53.5 ± 8.2 years, and 54.3 ± 12.0 years respectively. There were no significant differences in patient mean ages among different groups ($p > 0.05$). The mean tumor sizes for MCN-LGD, MCN-HGD, MCN with T1a or T1b carcinoma, and MCN-AIC were 4.8 ± 4.0 cm, 9.7 ± 7.7 cm, 13.0 ± 3.0 cm, and 7.5 ± 3.5 cm respectively. The mean tumor size of MCN-LGD was smaller than those of MCN-HGD ($p = 0.01$) and those with T1a or T1b carcinoma ($p = 0.001$). Among 7 patients who had MCN-AIC, five had moderately differentiated adenocarcinoma, one had poorly differentiated adenocarcinoma and one had adenosquamous carcinoma. Nine patients with MCN-LGD had no lymph nodes submitted. For the remaining cases, the number of lymph nodes examined ranged from 1 to 59 with a median of 11. None of the patients with MCN-LGD, MCN-HGD, or MCN with T1a or T1b carcinoma had positive lymph nodes. In contrast, 4 of 7 MCN-AIC (57.1%) had lymph node metastasis at the time of surgery [3 with N1 disease (1-3 positive lymph nodes) and one with N2 disease (4 positive lymph nodes)] (Table 1). One patient of MCN-AIC had a metastasis to the right ovary (stage IV disease) at the time of surgery.

All 3 patients who had MCN with T1a or T1b carcinoma had stage IA disease at the time of surgery based on the AJCC Stage Manual, 8th edition. Patient #1 was a 60-year old female, who had a long history of irritable bowel syndrome, presented with intermittent epigastric pain. She underwent abdominal ultrasound followed by CT scan. CT scan showed an 8.3×5.7 cm complex cystic mass in the tail of pancreas with irregular and enhancing internal septations, foci of calcification, and one internal nodule (Figure 1A and 1B). She underwent distal pancreatectomy and splenectomy. Grossly, there was a multiloculated $10.0 \times 7.0 \times 5.0$ cm cyst tumor filled with mucinous fluid with areas of calcification in the tail of pancreas. Maximal cyst wall thickness was 1.5 cm. There was no communication with the pancreatic ducts and no solid mass lesion identified grossly. The tumor was submitted in its entirety in 123 blocks. Histopathologic examination showed a MCN with LGD, focal HGD, and six separate foci of poorly differentiated PDAC measuring up to 0.6 cm in size and 43 negative lymph nodes (0/43). All foci of invasive adenocarcinoma were identified in the superficial layer of the cyst wall in the ovarian stroma. There were no complex intraluminal nodules identified (Figure 1C–1F). The pancreatic margin is negative for tumor. The patient received close follow up with no further treatment. There was no recurrence during the follow-up of 137.2 months.

Patient #2 was a 57-year old female who was in her usual state of health and found to have large abdominal mass during a regular checkup. She underwent a CT scan of abdomen and pelvis with contrast, which showed a 16×15 cm cystic mass with an irregularly thickened wall, and nodular foci of mural enhancement in the tail of the pancreas (Figure 2A and 2B). There were no lesions identified in other organs and no pancreatic or biliary ductal dilatation. She underwent distal pancreatectomy, splenectomy, and celiac lymphadenectomy. Grossly, there was a large unilocular cystic tumor ($16.0 \times 16.0 \times 14.5$ cm) in the pancreas containing tan-brown clear fluid with a fibrotic wall measuring up to 2.0 cm in thickness. Along the cyst wall were four delicate papillary excrescences ($1.5 \times 1.5 \times 0.3$ cm up to $3.5 \times 2.5 \times 0.3$ cm), which did not invade the cyst wall. The rest inner surface of the cyst was smooth. There was no solid mass lesion identified grossly. The tumor was submitted in its entirety in 296 blocks. Histopathologic examination showed a MCN, mostly denuded, with LGD, HGD, carcinoma in situ, and three foci of moderately differentiated PDAC measuring

up to 0.3 cm in size invading the wall of MCN. All three foci of PDAC were identified in the superficial layer of hyalinized stroma of the cyst wall, not in the papillary excrescences (Figure 3). Twenty-eight regional negative lymph nodes were negative for carcinoma (0/28). The pancreatic margin is negative for tumor. The patient received close follow up, but no further treatment. She had no recurrence during the follow-up of 113.8 months.

Patient #3 was a 44-year old female who presented with abdominal pain, nausea and vomiting. She underwent CT scan, which showed a 15.2×12.6 cm cystic mass in the tail of the pancreas protruding into the left retroperitoneum with internal nodule, mural calcification, and septations with enhancement/vessels (Figure 2C and 2D). She underwent distal pancreatectomy and splenectomy. Grossly, there was a well-circumscribed, cystic lesion in the tail of the pancreas ($13 \times 12 \times 8.5$ cm) with smooth outer surface. The cystic had a smooth inner lining and filled with clear straw colored fluid. Focal areas of cysts showed multi-septation and calcifications, but no solid mass lesion identified. The tumor did not involve the pancreatic duct. The tumor was submitted in its entirety in 200 blocks. Histopathologic examination showed a MCN with LGD and HGD with two foci of moderately differentiated PDAC measuring 0.3 cm and 0.7 cm in size in ovarian stroma of the superficial layer of cyst wall (Figure 4A–4D), and one focus of undifferentiated carcinomas with osteoclast-like giant cells (0.3 cm) in the septum of the cyst (Figure 4E–4F). There was no the complex intraluminal nodules. Fifty-one regional negative lymph nodes were negative for carcinoma (0/51). The pancreatic margin was negative for tumor. Given her young age, the patient was treated postoperatively with Gemzar for four months. There was no recurrence during the follow-up of 20 months.

The median follow-up period for the cases of MCN-LGD, MCN-HGD, and MCN-AIC were 52.3 months, 73.4 months and 24.0 months respectively. During the follow up period, none of the patients who had MCN with either LGD or HGD had recurrence or died of disease. In comparison, 5 of 7 patients who had MCN-AIC had recurrence and died of disease with a median survival of 22.9 months ($p=0.0001$) and of these five patients, three developed liver metastasis; one had peritoneal metastasis; and one had local recurrence and cervical lymph node metastasis. The Kaplan-Meier survival curves for disease-specific overall survival are shown in Figure 5. Patients of MCNs with T1a or T1b carcinoma had a good prognosis similar to patients with MCN-LGD and MCN-HGD ($p>0.05$). Compared to the other three MCN groups, patients who had MCN-AIC had significantly shorter survival ($p<0.001$).

Discussion

In this study, 11.1% of patients had invasive carcinoma arising in association with a MCN. This is in keeping with the reported 3.9% - 36% prevalence of invasive carcinoma in MCN patients (3–12). There is very limited reported data on the relationship between the extent of invasion and the biologic behavior of MCN. Yamao K et al. (11) and Suzuki Y et al. (12) reported that minimally invasive carcinomas (defined as invasive carcinoma <0.5 cm) have an excellent prognosis with a 5-year survival of 100% after surgical resection. The definition of minimally invasive carcinoma used in these studies was, however, not widely accepted by other pathologists. Other studies found that patients with early invasive carcinoma limited to ovarian-like stroma or intratumoral septa of a MCN also have an excellent prognosis (10,

15). Recently, Lewis et al (16) examined 16 patients with minimally invasive carcinoma confined to the ovarian stroma of MCNs with a mean follow-up of 48.6 months and found that only one patient, whose tumor was only sampled representatively for histologic examination, recurred and died of disease in their study. However, the sizes and numbers of foci of minimally invasive carcinoma were not provided in their study. Jang et al reported 17 cases of MCN with early invasion (13 with pT1a, 3 with pT1b and one with pT1c disease). Interestingly, three patients with multifocal pT1a invasion died of disease at 13, 29, and 64 months (18). Similar to the case who died of disease in the study published by Lewis et al (16), the tumors of these three cases was not entirely submitted for microscopic evaluation (18). Since the tumors of these four patients were not completely submitted for histologic examination in these two studies, the possibility of more advanced invasion or a larger focus of invasive carcinoma could not be excluded. In this study, we examined the clinicopathologic features and survival of three well-documented MCN patients with T1a or T1b invasive carcinoma. None of these patients had grossly identifiable area of invasive PDAC. The tumors of all three patients were submitted in their entirety for histologic examination in 123, 200, and 296 blocks respectively. In all three cases, the invasive carcinomas were found by histology in ovarian stroma or hyalinized stroma in the superficial layer of cyst walls or the septum of the cyst. It is interesting that 23 of 29 invasive carcinomas arising from MCNs reported by Jang et al. have intracystic papillary nodules of 1.0 cm (18). None of our cases had invasive carcinoma in the intracystic papillary nodule. During follow-up, none of our patients had recurrence or died from disease during follow up even though two of our patients received no adjuvant therapy after surgery. Our results are consistent with the above-mentioned studies and showed that patients with T1a or T1b carcinoma invading into the ovarian stroma of MCN have an excellent prognosis similar to those who had a MCN with no invasive carcinoma (16, 18). Currently, there are no guidelines for the management of patients with T1a and T1b carcinoma arising in association with a MCN. Although the number of patients examined in this study is small, our results along with those from the previously mentioned studies suggest that these patients should be followed up closely. However aggressive adjuvant therapy, which could lead to severe side effects and unnecessary medical expense, should be avoided if the tumors have been submitted in their entirety for histologic examination. Since we did not found any T1c carcinoma in our database and only one case of MCN with pT1c carcinoma was reported by Jang et al (18), it remains whether MCN patients with T1cN0M0 carcinoma would have a good prognosis similar to those MCN patients with T1aN0M0 or T1bN0M0 disease or have a clinically aggressive course similar to those with MCN-AIC. Future studies are needed to address this important question.

Although there was a report of undifferentiated carcinomas with osteoclast giant cells of the pancreas follow an aggressive course (19), others have found that presence of undifferentiated carcinoma with osteoclast-like giant cells in PDAC patients did not make a difference in prognosis (15, 20, 21). There is also report that 61% of undifferentiated Carcinoma with osteoclast-like giant cells show prominent intraductal/intracystic growth and had better clinical outcome (22). In this study, we reported the first case of a T1a (0.3 cm) undifferentiated carcinomas with osteoclast-like giant cells in the septum of an MCN. There was no conventional ductal/tubular adenocarcinoma associated with this focus of

undifferentiated carcinomas with osteoclast-like giant cells. However this patient has two separate foci of moderately differentiated PDAC measuring 0.3 cm and 0.7 cm in size. Given the young age of this patient, she received gemcitabine-based adjuvant chemotherapy and was disease-free at 20 month of follow up.

In this study, none of the 53 patients with MCN-LGD or MCN-HGD had recurrence or died from the disease after resection with a mean follow-up of 59.9 months or 74.3 months respectively. Our findings are consistent with previous studies which showed that patients who undergo resection for non-invasive MCNs have excellent prognosis with a 5-year survival rate of 100% (4, 6). The reported 5-year survival rates for patients who had MCN-AIC ranges from 20% to 60% (5, 10, 14). Consistent with these studies, 5 of 7 patients in our study, who had MCN-AIC (pT2 or higher stage of invasive carcinoma) died of disease. In our study, 2 of 7 patients who had MCN-AIC were men, which could represent a referral bias in our patient population. MCN in men, although rare, does exist (11, 12, 23–26). We also noted that MCN-AIC was more likely located in the head of pancreas (4 out of 7 patients) compared to other MCN groups. It has been reported that MCN in the head of the pancreas is more likely to have invasive PDAC than those in the tail or body of pancreas (10).

Currently, there are no reliable clinical, imaging or cystic fluid biomarkers that can accurately predict the malignant potential of a MCN (5, 27). As demonstrated in our cases, it is almost impossible to rule out a T1a or T1b invasive carcinoma without careful examination of the entire MCN by histopathology. Notably, only MCN with low-grade and high-grade dysplasia was identified in the initial twenty representative sections from the tumor of patient #3. All three foci of T1a/T1b invasive carcinoma in this case were identified in the subsequently submitted sections from the rest of the MCN. Similarly only rare microscopic foci of T1a or T1b carcinoma were identified in the 133 and 296 blocks respectively in the other two cases in our study, which could have been easily missed by representative sampling. Our study highlights the importance of complete assessment of a MCN if no invasive carcinoma is identified grossly as suggested by Wilentz et al (10). The previously reported malignant behavior of non-invasive MCN (7, 11, 16, 28), could have been secondary to insufficient sampling of the original tumors (10). In addition, these studies were published before the requirement of ovarian-type stroma for the diagnosis of MCN per the WHO 2010 criteria and may contain cases that would now be classified as intraductal papillary mucinous neoplasm (IPMN). One limitation of our analysis is the limited number of cases. However, since we submitted the entire specimen for microscopic examination, we would be the first one offered detailed information on true microscopic invasion of MCNs as far as we can determine.

In conclusion, our study suggests that T1a and T1b carcinoma arising in association with a MCN has an excellent prognosis similar to those with MCN-LGD or MCN-HGD. Careful histologic examination of the entire tumor is critical to identify microscopic invasion (T1a and T1b carcinoma) if no invasive carcinoma is grossly identified. Our results suggest that close follow up rather than aggressive systemic therapy may be a better approach to manage the patients with T1a and T1b carcinoma arising in a MCN after complete sampling of the tumor.

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Figure 1.

A–B: CT images of large complex cystic mass in the tail of pancreas (A and B, arrowheads) with internal septations (A, thick arrow), focal calcifications (A and B, curved arrows), and on internal nodule (B, arrow). C–F, Representative micrographs showing mucinous cystic neoplasm with ovarian stroma and low-grade dysplasia (C, H & E stain, magnification: 200×); a microscopic focus of invasive poorly differentiated adenocarcinoma invading ovarian stroma (D and E, H & E stain, magnification: D, 100×; E, 200×); and a separate focus of invasive poorly differentiated adenocarcinoma (F, H & E stain, magnification: 200×). All foci of invasive carcinoma are located in ovarian stroma in the superficial layer of cyst wall.

Figure 2.

A–B: CT images of large cystic mass in the tail of pancreas in case #2 (A and B, white arrowheads) shows an irregularly thickened wall (A, white arrow), and nodular foci of mural enhancement (B, thick white arrows). C–D: CT images of large complex cystic mass in the tail of pancreas in case #3 (C and D, white arrowsheads) with internal nodule (C, white arrow), and septations with enhancement/vessels (D, big thick arrow).

Figure 3.

Representative micrographs showing mucinous cystic neoplasm with ovarian stroma, low-grade and high-grade dysplasia (A) and three separate foci of invasive moderately differentiated adenocarcinoma invading the wall of MCN in case #2 (B–F). B represents one focus of PDAC; C and D represent the second focus of PDAC; E and F represent the third focus of PDAC. All three foci of invasive carcinoma are located in hyalinized stroma in the superficial layer of cyst wall. H & E stain; magnification: A, B and D, 200×; C, 100×; E 40×; F, 400×

Figure 4.

Representative micrographs showing mucinous cystic neoplasm with ovarian stroma, low-grade and high-grade dysplasia, and three separate foci of invasive carcinoma in case #3. A and B represent MCN with high-grade dysplasia and one focus of PDAC; C and D represent the second focus of PDAC; E and F represent the focus of undifferentiated carcinoma with osteoclast-like giant cells arising in MCN with low- and high-grade dysplasia. All three foci of invasive carcinoma are located in ovarian stroma in the superficial layer of cyst wall (A–D) or in the septum of the cyst (E, F). H & E stain; magnification: A, 100×; B and D, 200×; C and E, 40×; F, 400×).

Figure 5.

Kaplan-Meier curves of overall survival in different groups of MCN patients. Patients of MCN-AIC have significantly shorter survival compared to those with MCN-LGD, MCN-HGD and MCN with T1a and T1b carcinoma ($p=0.001$, log-rank test). However there is no difference in survival among the other three groups ($p=1.00$, log-rank test).

Table 1

Clinicopathological features of study population

MCN Groups	MCN-LGD	MCN-HGD	MCN with T1a or T1b carcinoma	MCN with PDAC
Number of cases (%)	46 (73%)	7 (11.1%)	3 (4.8%)	7 (11.1%)
Mean Age $\pm$ S.D. (years)	52.9 $\pm$ 14.1	42.2 $\pm$ 10.5	53.5 $\pm$ 8.2	54.3 $\pm$ 12.0
Tumor size $\pm$ S.D. (cm)	4.8 $\pm$ 4.0	9.7 $\pm$ 7.7	13.0 $\pm$ 3.0	7.5 $\pm$ 3.5
Gender (female: male)	45:1	7:0	3:0	5:2
Type of surgery	43	7	3	3
Distal pancreatectomy				
Pancreaticoduodenectomy	3	0	0	4
Tumor location (head: body and tail)	3:43	0:7	0:3	4:3
AJCC stage (8 th edition)	N/A	N/A	IA (3)	IB (1), IIA (1), IIB (4), IV (1)
Lymph node metastasis	0/37	0/7	0/3	4/7 (N0,3; N1,3; N2, 1)