INDEX

INTRODUCTION

Pancreatic endocrine tumours

Pancreatic endocrine tumours (PETs) are relatively uncommon tumours that account for 1% to 2% of all pancreatic neoplasms. They typically occur in adults, with a peak incidence from age 30 to 60 years even if cases have been described at all ages. These tumours likely originate from the hypothetical multipotent ductular stem cells,[1,2] and recently non-islet origin of these tumours was demonstrated in patients with multiple endocrine neoplasia type 1.[3]

Endocrine tumours are divided into functional and non-functional tumours. Functional tumours are classified based upon the hormones they produce and the associated endocrine syndrome. The more common functional tumors include insulinomas, glucagonomas, somatostatinomas, gastrinomas, and vasoactive intestinal polypeptide tumors. Non-functioning tumours are either an incidental finding or are associated with an expanding mass rather than a hormonal syndrome. However, serologic or immunohistochemical evidence for elevated hormones may be identified.[1]

Pancreatic endocrine tumours can be sporadic or associated with a genetic syndrome. Genetic syndromes associated with endocrine tumours include multiple endocrine neoplasia type 1, Von Hippel-Lindau disease, Von Recklinghausen disease, and tuberous sclerosis.[4 5]

Pathological findings

Endocrine tumours in the pancreas are usually solitary and well demarcated. Their size ranges from less than 1 cm to greater than 15 cm, and the colour varies depending on the stroma or the presence of amyloid, haemorrhage or necrosis. The growth pattern can be solid, nested, trabecular, ribbon-like, tubulo-acinar or glandular being mixed patterns common in the same tumor. Less commonly the hystological architecture of PETs can be characterized by an angiomatoid pattern while cystic change is felt to represent a degenerative alteration within the tumour. In most cases, the histological pattern is not distinctive to determine the functional status of the tumours even if amyloid deposition is frequently seen in insulinomas and glandular structures with psammoma bodies are common with somatostatin-producing tumours of the periampullary duodenum. The cells are round or polygonal and usually fairly uniform in size and shape. The nuclei are typically round to oval with finely stippled chromatin, and the cytoplasm varies from pale to moderately eosinophilic. Uncommon cytologic features include rhabdoid, oncocytic, clear, and fusiform cells.[1,6] The differential diagnosis for PETs includes chronic pancreatitis with islet aggregation, ductal adenocarcinoma, solid pseudopapillary tumour, acinar cell carcinoma, and pancreatoblastoma. Immunohistochemical stains for specific cell types seen in normal islets may be useful as the characteristic Immunoexpression of synaptophysin and chromogranin. Moreover, the clinical history and findings in the background pancreas can be useful to obtain a right diagnosis.[1, 6, 7]

Grading and Prognosis

No staging system is commonly used for PETs and the grading system remains controversial. Many studies have explored different clinico-pathological features able to predict the behaviour including metastasis, tumour size, hyperfunctional syndromes, mitotic count, proliferative index, vascular and perineural invasion, necrosis, and tumour grade.[7, 8]

Some multiparametric approaches have been suggested as most useful to predict prognosis.[7-9] The Capella classification is the most promising system including as parameters the tumour size and differentiation, vascular invasion and functional lineage, classifying tumours into benign, borderline, low-grade malignant, and high-grade malignant categories.[7] Heymann et al validated the usefulness of the Capella classification on a series of 82 PETs.[8]

The inclusion of the Ki-67 rate (an immunolabeling representing index of proliferation of the neoplastic cells) increased the value of the Capella classification generating an efficient modified classification system.[9]

The recent classification of the tumors of the endocrine organs of the World Health Organization (WHO) in 2004 proposed to classify PETs in four categories with specific prognostic value.[1] First of all PETs have been defined tumors or carcinomas according to the absence or the presence of local invasion or metastasis respectively. Well-differentiated tumours are then divided into those with *benign behaviour* and those with *uncertain behaviour*. The tumours with *benign behaviour* include those confined to the

pancreas that are non-angioinvasive, without perineural invasion, less than 2 cm in diameter, with fewer than 2 mitotic figures per 10 high-power fields and less than 2% Ki-67–positive cells. When an endocrine tumor is greater or equal to 2 cm in diameter or shows one or more of the features including 2 to 10 mitoses per 10 high-power fields, more than 2% of Ki-67– positive cells, angioinvasion, and perineural invasion is defined PET with *uncertain behaviour*. Neoplasms showing local invasion or metastasis are defined *well-differentiated carcinomas* or *poorly-differentiated carcinomas* according to the mitotic rate less or more than 10 mitotic figures per 10 high-power fields respectively.

Though WHO classification, PETs behaviour still remain difficult to predict basing on their histologic features. Recent studies lighted the role of some immunohistochemical markers as CK19,[10-12] and CD99[13] as prognostic marker in PET. Other studies proposed a system based on mitotic rate and necrosis dividing tumors into *low* and *intermediate* groups.

Because of the difficulty in determining which PETs are malignant, many pathologists use the term carcinoma for all PETs. Others use the 3-tier grading system commonly used in the lung, including carcinoid, atypical carcinoid, and poorly-differentiated neuroendocrine carcinoma.

Whichever system is chosen, it is clear that almost all of these tumours have the potential to metastasize, even after many years. The grading remains controversial and only clear signs of malignancy as metastasis and local invasion are able to predict the prognosis.

Treatment

The surgical management of patients with PET continues to evolve and remains controversial. In large surgical series, the best outcomes have been observed in patients with benign-appearing functional tumours and completely resected malignant tumors. Predictive factors that have been associated with long-term survival include definitive surgical resection, absence of liver metastasis, and aggressive treatment of liver metastasis when present.[15] Long-term survival has been commonly seen in patients with advanced disease, causing many to advocate for an aggressive surgical approach. The best hope for long-term survival remains a surgical approach with a curative intention.

Cytokeratins

Cytokeratins (CK) represent the firs and the second type of intermediate filaments (IF) that are one group of the cytoskeleton components represented by six different types.

In comparison with the other types of IF (i.e. desmin, vimentin, glial fibrous acidic protein (GFAP) and neurofilament), CK are the most complex. A number of two-dimensional gel electrophoresis experiments on CKs subunits extracted from various epithelial tissues have shown a total of 20 different subunits in any mammalian species, with molecular weights varying within the range 40–70 kDa. Moll et al.(QUOTE MOLL ET AL) categorized a total of 19 human epithelial CKs identifying the additional CK 20. The CKs can be divided into low and high molecular forms based on molecular weight, and

divided into acidic and basic forms based on iso-electric point. In general, most low molecular weight CKs will pair with a specific high molecular weight CK and most basic CKs will pair with an acidic CK, as defined by co-expression.

At present, more than 20 different CKs are known and are divided into types I and II based on sequence homology . CKs 1–8 constitute the type II group (53–68 kDa, neutral to basic protein components), while cytokeratins 9–20 constitute the type I group (40–56 kDa, acidic proteins).[16]

The CKs are encoded by a large multigene family of approximately 50 different members. Aminoacid sequence analysis of the encoded individual filament proteins reveals a relatively weak relationship between the CKs and the other IF proteins. But as for all other IF proteins, the CKs exhibit a characteristic structure harboring three major domains: a non-helical N-terminal region, a predominantly-helical central-rod, and a non-helical C-terminal segment. The helical rod-like domain (mostly of alpha-helical structure) constitutes a conserved sequence of about 300–320 aminoacid residues and can be subdivided into four different domains: coil 1A, 1B, 2A, and 2B. The aminoacid composition of the helical domains appears to be almost constant in size and contains repeated sequences of aminoacid residues with a similar distribution of a polar aminoacids and alternating charged aminoacid residues. The helical segments are separated by significantly less conserved short linker regions, named L1, L1-2, and L2.

The end-domain sequences of type I and II CK chains contain in both sides of the rod domain the subdomains V1 and V2, which have variable size and sequence. The type II also presents the conserved subdomains H1 and

H2, encompassing 36 and 20 residues respectively. The subdomains V1 and V2 contain residues enriched by glycines and/or serines, the former providing the CK chain a strong insoluble character and facilitating the interaction with other molecules. These terminal domains are also important in defining the function of the CK chain characteristic of a particular epithelial cell type. Two dimers of CK group into a CK tetramer by anti-parallel binding. This CK tetramer is considered to be the main building block of the CK chain. By head-to-tail linking of the CK tetramers, the protofilaments are originated, which in turn intertwine in pairs to form protofibrils. Four protofibrils give place to one CK filament.[16]

In the cytoplasm, the CK filaments conform a complex network which extends from the surface of the nucleus to the cell membrane. Numerous accessory proteins are involved in the genesis and maintenance of such structure. The association between the plasma membrane and the nuclear surface rapresented by CKs filaments provides important implications for the organization of the cytoplasma and cellular communication mechanisms.

Apart from the relatively static functions provided in terms of supporting the nucleus and providing tensile strength to the cell, the CK networks undergo rapid phospate-exchanges-mediated depolymerization, with important implications in the more dynamic cellular processes such as mitosis and post-mitotic period, cell movement and differentiation. CKs interact with desmosomes and hemidesmosomes, thus collaborating to cell-cell adhesion and basal cell-underlying connective tissue connection.[16]

Not all CKs are synthesized simultaneously: different subsets of CKs are expressed during the course of terminal differentiation, in different stages of cellular development, as well as in different epithelial cell type. Thus, all epithelia (simple and complex) can be classified based upon CK protein expression. CKs expression is remarkably tissue specific, suggesting that the type of CKs present in the cell is related to their biological functions . Different epithelial tissue express specific setting of CKs, and the consequent profile is used in common diagnostic process to identify the origin, differentiation status and behaviour of neoplasia. Otherwise some neoplasia can acquire during the carcinogenetic process the expression of different CKs, usually not present in the normal tissue of origin and in many cases the acquired expression is sign of malignancy or index of poor prognosis.[17]

Moreover, CKs also have a clinical value because the determination of soluble CK protein fragments in body fluids (TPA, TPS and CYFRA), cn be a tool to monitor the recurrence and the fast assessment of the efficacy of therapy response in carcinomas.[18]

Tissue Array

The introduction of tissue microarray (TMA) technology by Kononen *et al* in 1998[19] has greatly facilitated the retrospective study of large sets of formalin-fixed, paraffin-embedded tissues. With this high-throughput technology, hundreds of samples can be arrayed in a single paraffin block that can then be analyzed with a variety of techniques, including immunohistochemical analysis and fluorescence *in situ* hybridization. In

contrast to traditional methods, which require processing hundreds of slides, TMA technology allows large numbers of specimens to be processed under identical conditions, which greatly reduces the time, cost and amount of archival tissue required for analysis.

TMAs are produced by a method of re-locating tissue from conventional histological paraffin blocks so that tissue from multiple patients or blocks can be seen on the same slide. This is done by using a needle to biopsy the tissue in a standard paraffin block and placing the core into an array on a recipient paraffin block.[20]

In order to fully exploit TMAs and to maximize the chances of a successful study outcome, proper consideration must be given to the array source. Some researchers construct their own array block, this requiring a high level of technical expertise and resources. Construction requires tissue acquisition and pathological review, as well as preparation of the slides.

A common concern in the use of TMAs is related to the ability of a small tissue core to accurately reflect data about large tumor specimens. It should be evident that a 1.0-2.0 mm tissue sample will not uniformly reveal all data from tumours. This is especially true in tumours which can be highly heterogeneous. However, it must be noted that there is an essential difference with respect to the applications of TMAs and their low density counterparts. While generally desirable to use large tissue sections for the purpose of clinical diagnosis, the strength of the TMA lies not in its usage for diagnostics, but as a research tool with the ability to provide statistically

significant, population-level data faster and more economically then other methodologies.[21,22]

Another common concern questions the concordance of TMA data with clinically significant findings obtained from large sections. Several studies demonstrating clinical and molecular associations between ER, PR, p53, and HER2 with breast cancer, bladder cancer, and kidney cancer have been confirmed using TMAs.[23-25] Further, the authors mentioned a study in which clinco-pathological associations were made in TMAs, but not in large sections, which further strengthens the position of TMAs as a powerful research tool.

AIM

Recent studies highlighted the role of the immunohistochemical marker CK 19 as a prognostic marker in pancreatic endocrine tumors.[10-13] We studied the immunohistochemical expression of this CK in a series of 149 endocrine neoplasms to assess its prognostic role in the largest series analyzed to date.

MATERIALS and METHODS

Patients

Our study included the analysis of 149 cases of endocrine tumour obtained from patients undergoing surgical intervention at Surgical Department of University of Verona. All patients were treated by radical surgical removal with resection margins free of microscopic disease and did not receive pre- or post-operative chemo- or radio-therapy. Follow-up data were available and histological classification was according to Capella and to WHO 2004 classification.

Tissue array construction

Six TMA blocks were previously constructed using 1 mm cylinders from selected areas of standard paraffin-embedded tissue samples; each tissue array represented about 30 cases. Three tissue cores were arrayed for each case using a tissue microarrayer from Beecher Instruments (Sun Prairie, WI, USA). Each block contained an internal control consisting of normal pancreas.

Immunohistochemistry

For immunohistochemical evaluation, 6-µm sections were cut from each block of TMA. Tissue sections were deparaffinized in xylene and rehydrated in a series of graded ethanol. Slides were immersed in citrate buffer (10 mM pH 6.0) and boiled in a microwave oven at 600 W, 3 times

for 5 minutes each to enhance antigen retrieval. Endogenous peroxidase activity was blocked with 0.3% hydrogen peroxidase in methanol for 30 minutes and non-specific binding sites were blocked using Protein block serum-free (Dako, Carpinteria, CA, USA). Subsequently, slides were incubated with an anti-CK19 (BA17 clone Dako Laboratories, USA). The primary antibody was not included in negative controls. After incubation with an appropriate biotinylated antiserum, slides were incubated with streptavidin horseradish peroxidase (Dako). Antibody localization was detected using diaminobenzidine as a chromogen substrate and haematoxylin as a counter stain. Protein expression was evaluated by three independent observers (BE, BS, SA); in cases in which the evaluation led to different results, a consensus interpretation was reached after examination.

Cases were considered negative if none of the tissue cores showed cytoplasmic staining for the protein; the expression of CK 19 was scored positive when at least 10% of neoplastic cells were positively stained. Tthe evidence of cytoplasmic staining of adjacent ductal pancreatic cells served as internal positive controls.

RESULTS

The expression of CK 19 was evaluated in a total of 184 samples, corresponding to 149 primitive samples and 35 matched metastases. The staining of CK 19 were prevalently localized to the cytoplasm although in rare cases the membrane was also strongly stained.

The presence of CK 19 was detected in a total of 100/149 primitive tumours (67.1%) and 26/35 (74.2%) metastases both in lymph node and in other sites. The difference between the prevalence of CK 19 in metastasis and primitive tumours was not significant. There was a strong correlation between presence of CK 19 in the primitive and its matched metastasis (Fisher's test; $P = 0.0012$) (see Table 1). In fact, In 30 cases CK 19 was positive in both the primitive tumor and the matched metastases, in 3 cases the presence of CK 19 was detected in the primitive samples only and in two cases CK 19 resulted to be expressed only in the metastasis.

We investigated the correlation between CK 19 expression and clinical features in 149 primitive samples. Expression of CK 19 was significantly correlated with tumour dimension ($p=0.020$), lymph node status ($p=0.070$), presence of metastasis ($p=0.023$), 5 years survival ($p<0.002$), and with the subgroups of WHO 2004 classification that have a worse prognosis (well-differentiated endocrine carcinomas and poorly-differentiated endocrine carcinomas).

A multivariate Cox's model was fit to assess the prognostic value of CK 19, independent of other clinical pathological features. When the WHO

parameter was added to the model, CK 19 was no longer significantly associated with survival. Furthermore, CK 19 expression was not significantly associated with survival when evaluated in single WHO subgroups.

DISCUSSION

Recent studies highlighted the role of some immunohistochemical markers as CK 19 as prognostic marker.[26]

The first promising report was a study on 54 cases of PETs performed by Deshpande et al. suggesting CK 19 as a powerful predictor of survival of PET and its expression correlated with mitoses, necrosis, solid pattern, vascular invasion, perineural invasion and Ki-67 index; both univariate and multivariate analyses demonstrate that CK 19 is an independent prognostic factor.[10] These results were partially confirmed by Abdullah et al. on a series of 54 PETs and two liver metastases. They found an association of CK 19 expression and lymph node spread, liver metastasis, lymph vascular and perineural invasion, mitotic count and MIB1 index. The relatively short follow-up period for the majority of patients in this study does not allow a meaningful comment regarding patient survival and CK 19 staining. They also studied the role of CD99 with no significant results.[13]

Capella et al. studied 145 PETs with two different CK 19 clones (Ba17 and RCK108) on traditional slides. They obtained different staining: in particular, more intense and widespread CK 19 positivity was elicited with the BA17 clone than with the RCK108 antibody, in both control tissues and tumours. They found a correlation with survival only in univariate analysis and only when the RCK108 clone was used; CK 19 expression did not correlate with survival when it was detected with the BA17 antibody.[11] Schmitt et al. studied and classified according WHO 2004 the histology of 216 PETs,

constructing TMAs for immunohistochemical staining. They studied the expression of CK 19, COX2, p27, and CD99 and the prognostic value of these markers was tested in 93 patients. They conclude that 2004 WHO classification with 4 risk groups is very reliable for predicting both disease-free survival and the time span until tumour-specific death. CK 19 staining is a potential additional prognostic marker independent from the WHO criteria for pancreatic endocrine tumours.[12]

The present study evaluates the expression of CK 19 in a total of 184 samples corresponding to 149 primitive samples and 35 matched metastases. CK 19 was found in 67.1% of PETs and 74.2% metastases both in lymph node and in other sites.

We confirm the association previously reported with CK 19 expression and tumour dimension, lymph node status, presence of metastasis, 5-years survival ($p<0.002$), and with the subgroups of WHO 2004 classification that have a worse prognosis (well-differentiated endocrine carcinomas and poorly-differentiated endocrine carcinomas). Multivariate analysis do not show the role of CK 19 as an indipendent prognostic marker. So we can conclude that CK 19 can be used as a malignancy marker and index but they are not an independent prognostic markers.

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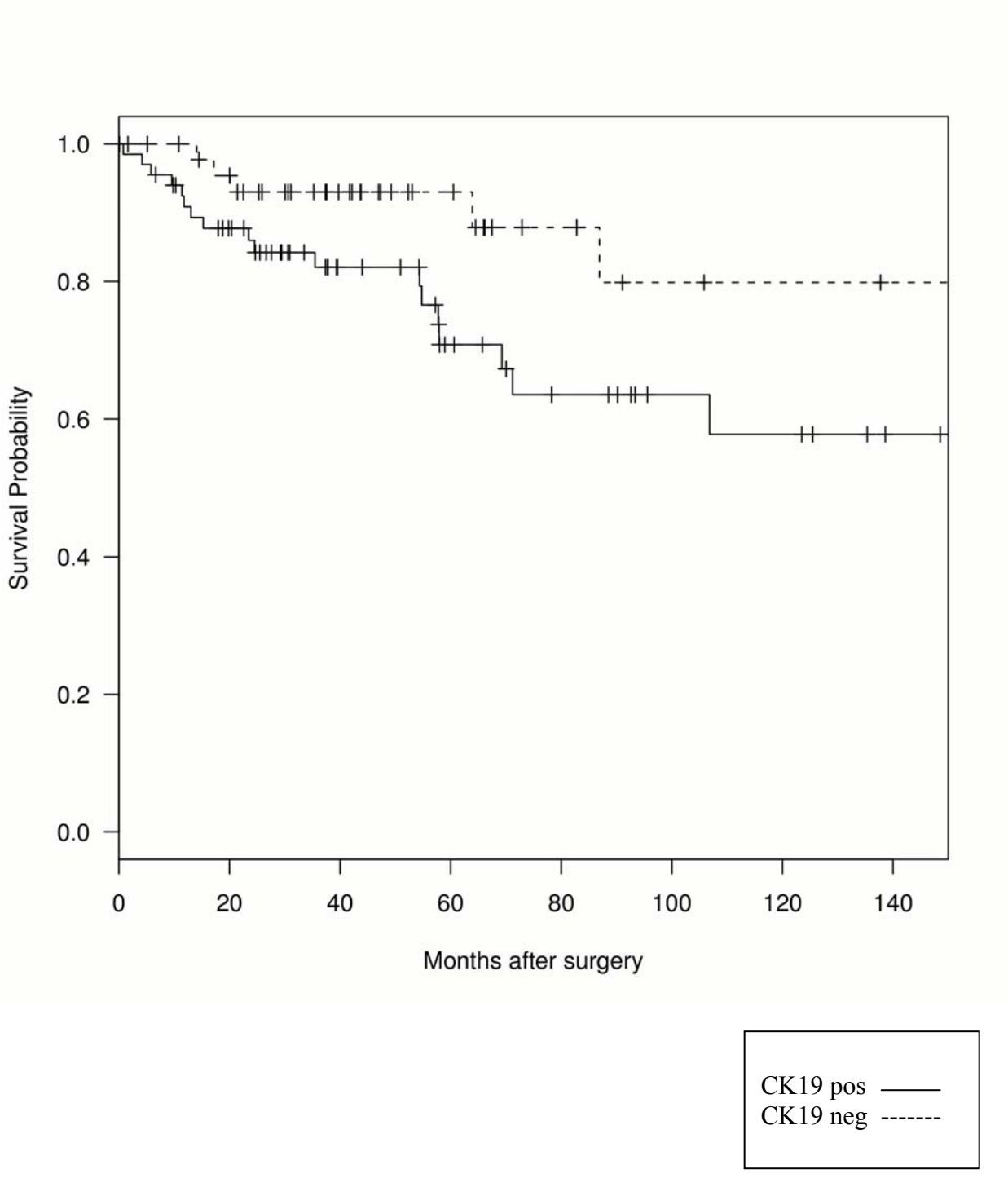
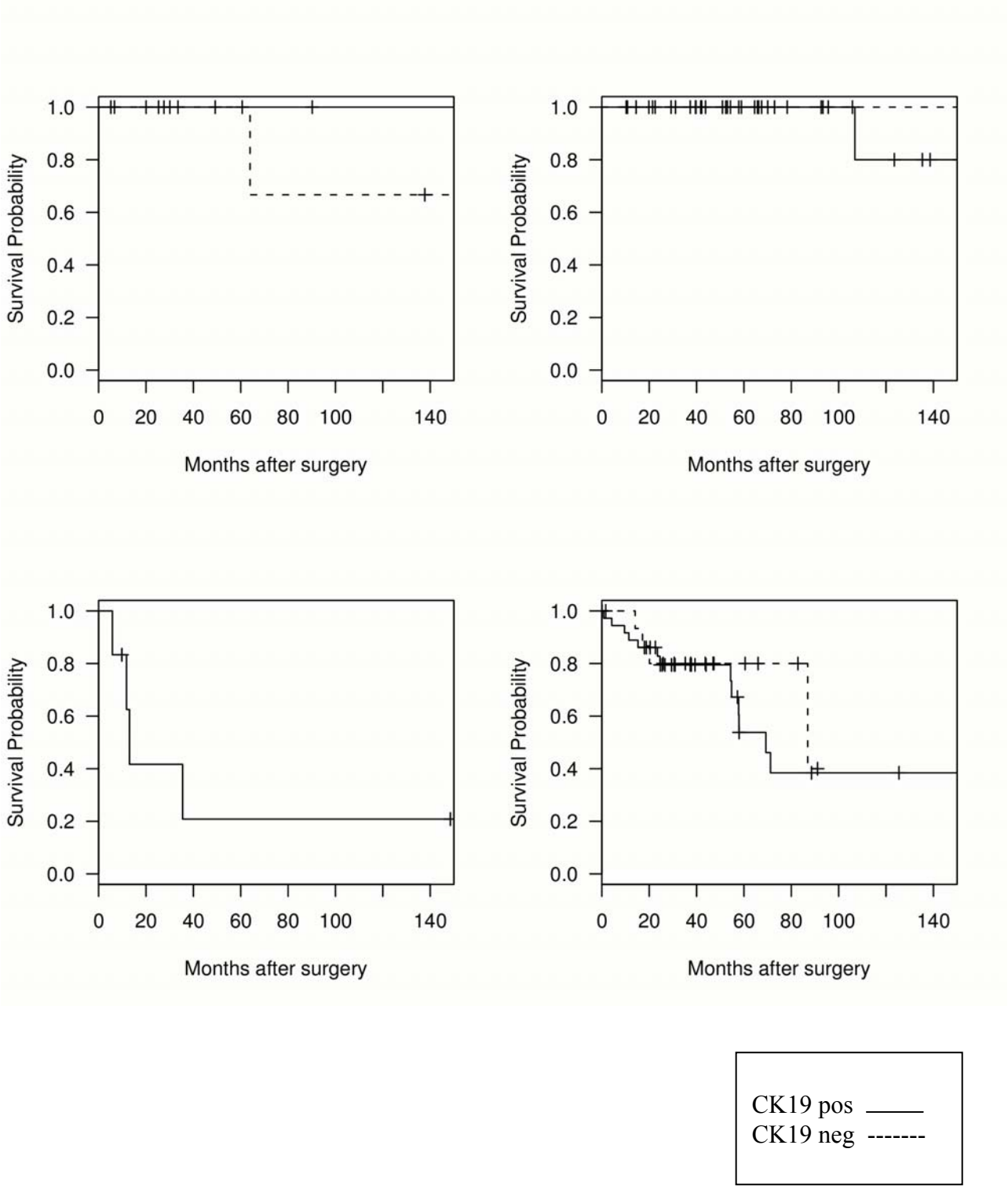
GRAPHICS



Graphic 1. PET overall survival and CK19



Graphic 2- WHO 2004 groups, survival and CK19

TABLES

Clinicopathologic Classification of Endocrine Tumors of the Pancreas
Well-differentiated endocrine tumor
Benign behavior: confined to pancreas, nonangioinvasive, <2 cm in size, ≤2 mitoses ≤2% Ki-67 positive cells/10 HPF
Functioning: insulinoma
Nonfunctioning
Uncertain behavior: confined to pancreas, ≥2 cm in size, >2 mitoses/ 10 HPF, >2% Ki-67 cells positive/10 HPF or angioinvasive
Functioning: gastrinoma, insulinoma, vipoma, glucagonoma, somatostatinoma, or other tumors*
Nonfunctioning
Well-differentiated endocrine carcinoma
Low-grade malignant with gross local invasion and/or metastases
Functioning: gastrinoma, insulinoma, glucagonoma, vipoma, somatostatinoma, or other tumors*
Nonfunctioning
Poorly differentiated endocrine carcinoma
High-grade malignant (small to intermediate cell) carcinoma
*Cushing (ACTH), acromegaly or gigantism (GRH), etc.

Table 1. WHO2004 Endocrine tumour classification applied to PET

Parameter	Categories	ck19-	ck19+	OR (95% C.I.)	P Value
pT	t1	20 (58.8%)	14 (41.2%)	1	0,020
	t2	22 (50.0%)	22 (50.0%)	1.4 (0.6 - 3.6)	
	t3	7 (35.0%)	13 (65.0%)	2.7 (0.9 - 8.7)	
	t4	9 (25.0%)	27 (75.0%)	4.3 (1.6 - 12.3)	
pN	N0	44 (51.8%)	41 (48.2%)	1	0,007
	N1	12 (27.3%)	32 (72.7%)	2.9 (1.3 - 6.5)	
pM	M0	50 (47.2%)	56 (52.8%)	1	0,023
	M1	8 (25.0%)	24 (75.0%)	2.7 (1.1 - 6.9)	
WHO 2004	WDET	13 (54.2%)	11 (45.8%)	1	0,002
	WDET-u	27 (55.1%)	22 (44.9%)	1.0 (0.4 - 2.6)	
	WDEC	20 (30.3%)	46 (69.7%)	2.7 (1.0 - 7.2)	
	PDEC	0 (0.0%)	6 (100.0%)	Inf	
Vascular invasion	1	34 (53.1%)	30 (46.9%)	1	0,060
	2	21 (36.2%)	37 (63.8%)	2.0 (1.0 - 4.2)	
Perineural infiltration	1	32 (48.5%)	34 (51.5%)	1	0,148
	2	16 (34.8%)	30 (65.2%)	1.8 (0.8 - 3.9)	
Gender	F	31 (37.8%)	51 (62.2%)	1	0,390
	M	30 (44.8%)	37 (55.2%)	0.7 (0.4 - 1.4)	
Proliferative index (ki67)	<2	14 (45.2%)	17 (54.8%)	1	0,7249
	>= 2	42 (41.6%)	59 (58.4%)	1.2 (0.5 - 2.6)	
Survival (5 years)		93,00%	70,80%	3.05 (1.11 - 8.27)	0,022
Functional status		19 (55.9%)	15 (44.1%)	1	0,04847
		40 (36.4%)	70 (63.6%)	2.2 (0.94 -5.2)	

Table 2. Correlation of clinical pathological features of 149 pancreatic endocrine cancer patient

FIGURES

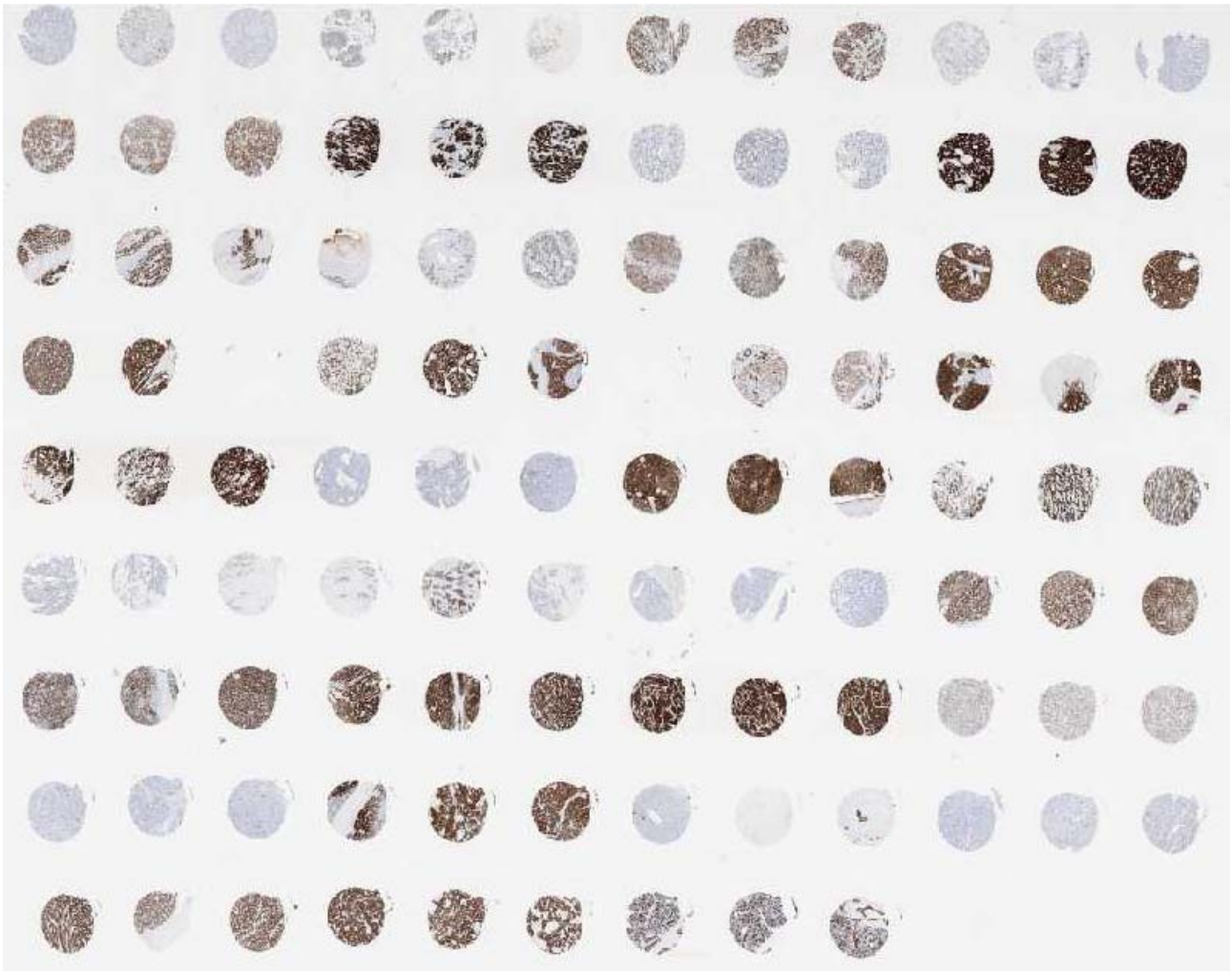


Figure 1. Tissue Array stained wit for CK19 immunohistochemestry

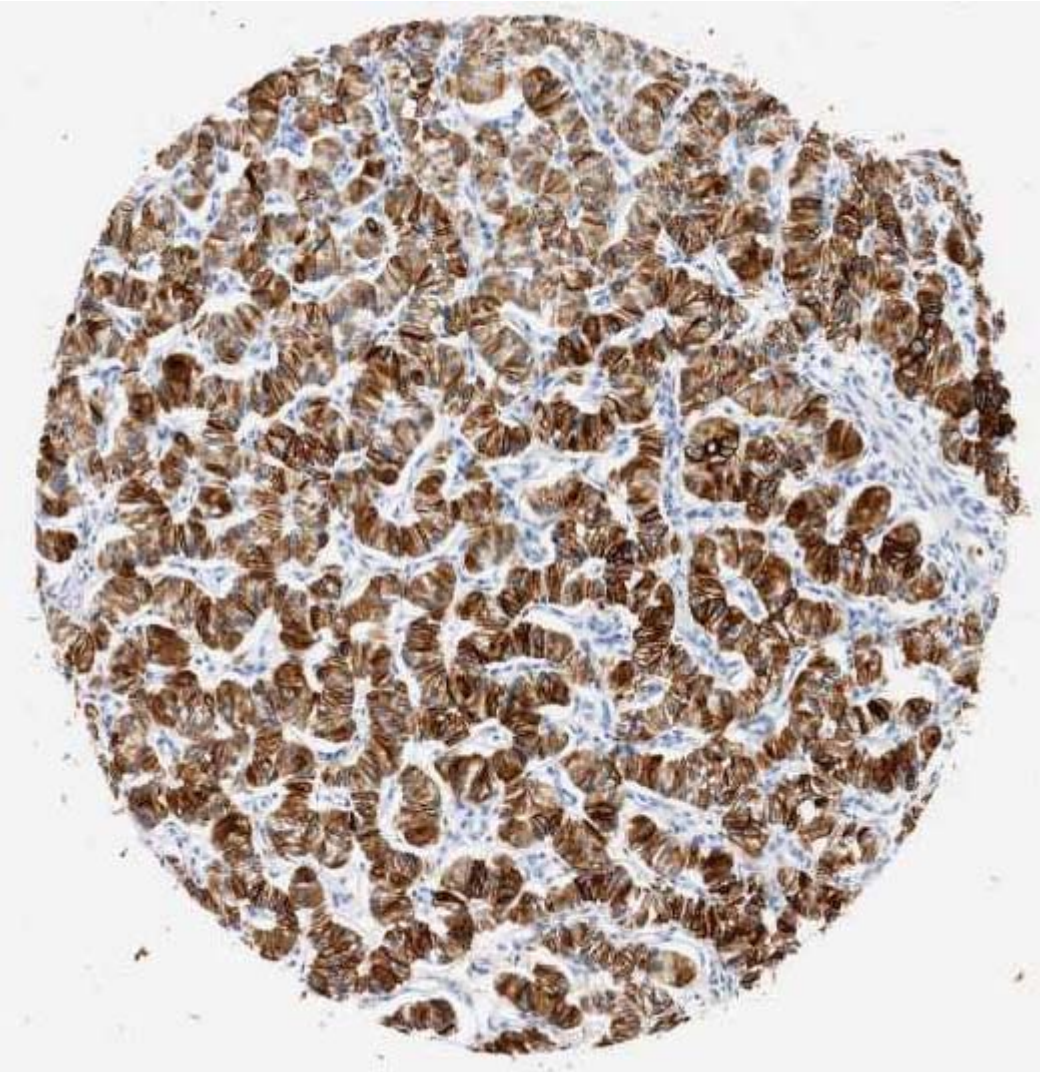


Figure 2. PET positive for CK19

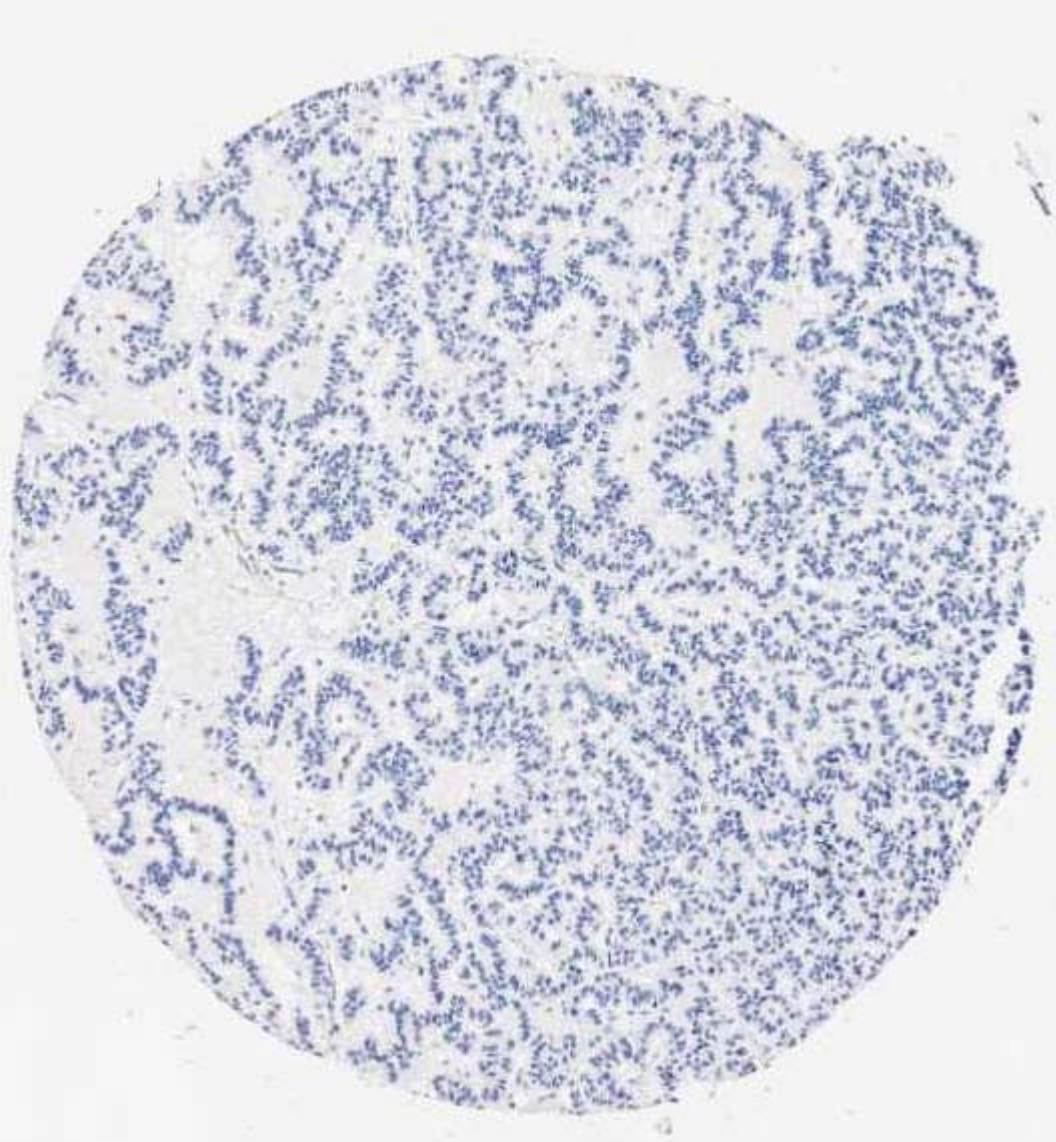


Figure 3. PET negative for CK19

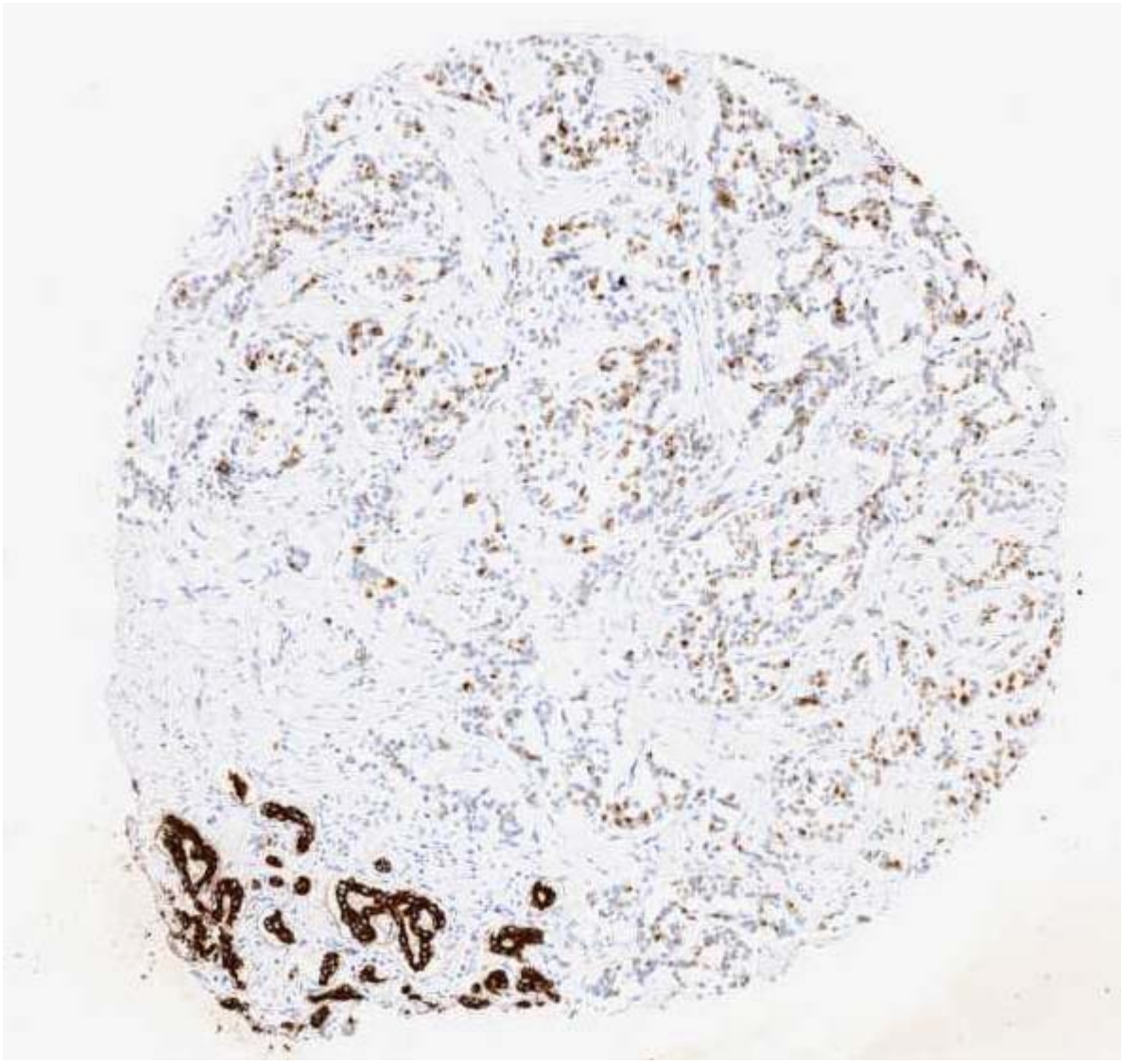


Figure 4. PET partially positive for CK19