Schultz *Surgical and Experimental Pathology* (2018) 1:10
https://doi.org/10.1186/s42047-018-0023-6

Surgical and Experimental Pathology

REVIEW Open Access

The papilla as a biomarker in the molecular era of bladder oncology

Luciana Schultz[1,2]

Abstract

Background: Conventional optical microscopy has been fundamental in the diagnosis of cancer for over a century. Tumor morphology has prognostic value and impact on treatment choice, but integration with molecular knowledge can enhance the correlation with clinical behavior. A papillary structure implies that the proliferating epithelium has been able to interact with its microenvironment to conceive a fibrovascular core, suggesting a fair degree of differentiation.

Main body: In the bladder, a papillary architecture carries a favorable outcome and its presence is uniform in all non-invasive urothelial lesions, except for carcinoma in situ. Despite the increase in bladder cancer incidence, mortality has remained fairly stable for the last three decades, raising concern for overdiagnosis. Therefore, bladder cancer nomenclature has evolved to better communicate with the clinical scenario, including clinicians and patients. During this time, the need to incorporate new tools into morphology has raised a search for molecular biomarkers that grew exponentially with technology and scientific foment. Activating mutations in oncogenes like *HRAS*, *PIK3* and *FGFR3* are a hallmark of non-invasive papillary neoplasms, and their detection in advanced carcinomas is a favorable predictor of outcome. These alterations result in sustained proliferative stimuli and independent control of metabolism. Through the amplified interface of a papillary axis, the *lamina propria* can continue to supply nutrients, oxygen, hormones and other vital cellular needs to an increasing population of urothelial cells. mTOR regulates processes that require a substantial amount of matter and energy and alterations in this pathway are among the most frequent in urothelial tumors. Recent genomic landscape studies have provided data for molecularly subtyping urothelial cancers as luminal and basal. Within the luminal subtype, a p53-like signature is associated with chemoresistance. Luminal tumors, which phenotype is reminiscent of mature differentiated superficial cells, are enriched for papillary morphology and downregulation of miRNA involved in mTOR pathway regulation.

Conclusion: Because the papillary structure is the result of a transcriptional program and its post-transcriptional modifications, it is likely that its presence will be maintained in classification schemes as a powerful tool for clinical translation.

Keywords: Urothelial; bladder cancer, Papillary, Morphology, Molecular subtype, Microenvironment

Background

The relationship between the clinical behavior of a tumor and its morphology is well known. The first attempts to translate it to clinical practice were based on observations of atypia, anaplasia and abnormal mitotic Figures (Hansemann, 1890), as well as architectural features that reflect the degree of cell differentiation (Broders, 1922). They were proposed as early as the nineteenth century but only adopted in practice in the 1970s, when therapeutic complexity reached a need for better patient stratification. Today, in many instances, tumor gross and microscopic morphology has prognostic value and impact on treatment choice, but integration with molecular knowledge can enhance the correlation with clinical behavior.

Because a papillary structure implies that the proliferating epithelium has been able to interact with its microenvironment to conceive a fibrovascular core, it suggests

Correspondence: lschultz@iapat.com.br
[1]Instituto de Anatomia Patológica, Rua General Câmara, 1136, 5° andar, Santa Bárbara d'Oeste CEP 13450-029, Brazil
[2]Patologia D'Or, São Paulo, Brazil

a fair degree of differentiation. In the bladder, not only a papillary lesion has a more favorable outcome compared to lesions devoid of papillary architecture, but its presence also defines distinct entities. In the current WHO classification, carcinoma in situ is the only non-papillary entity in the section of non-invasive urothelial tumors (Humphrey et al., 2016). This stratification into flat and papillary is anchored in differing genetic alterations: activating mutations in oncogenes like HRAS, PIK3 and FGFR3 are a hallmark of papillary lesions, whereas inactivating mutations of major tumor suppressor genes like TP53 and RB1 are frequent in non-papillary tumors (Eich et al., 2017).

Recent genomic landscape studies (The Cancer Genome Atlas Research Network, 2014; The Cancer Genome Atlas Research Network, 2017; Aine et al., 2015; Choi et al., 2014a) have provided data for molecularly subtyping urothelial cancers as luminal and basal. Luminal tumors are characterized by expression of markers of intermediate and terminally differentiated cells in normal urothelium. As one would expect from being phenotypically reminiscent of well differentiated urothelium, luminal tumors frequently show papillary morphology. Therefore, this morphologic feature that arose in the earliest virchowian descriptions of bladder cancers, has endured through the genomic era. This exemplifies how a histological pattern may reflect the combination of the transcriptional program and its post-transcriptional modifications, making it a powerful tool for clinical translation.

Nomenclature and reporting of papillary urothelial features

Before Rudolf Virchow, all papillary lesions were termed *papillomata*, regardless of their nature. In his lecture about "Form and nature of pathological new-formations", delivered at the Pathological Institute of Berlin, on April of 1858 (Virchow, 1858), he acknowledges that not all lesions that present in the same form behave in the same fashion. This distinction still remains a difficult task and nomenclature of papillary urothelial lesions has evolved to cover the wide spectrum of biological behavior. Based on his microscopic observations, Virchow defined the papillary structure as a combination of proliferating cells and matrix and acknowledged differences in outcome between papillary and non-papillary lesions:

> "The papillae consist of connective tissue upon which they [cancerous cells] are seated; within the papillae therefore a cancerous mass may develop itself out of the connective tissue. Moreover, it cannot be denied that this peculiarity of superficial formation very frequently explain some peculiarities in the course of the disease, whereby a papillary tumor is strikingly distinguished from the same kind of tumor when not papillary."

Kakizoe et al. (Kakizoe et al., 1987; Kakizoe et al., 1988) explored the coexistence of papillary and nodular tumors in the bladder, developing the idea that nodular carcinomas may arise de novo or progress from a previous papillary lesion. Since then, others have reported on the prognostic significance of bladder cancer gross morphology (Portillo Martín et al., 1991; Park et al., 2009), underpinning its incorporation into the report. College of American Pathologists (CAP) cancer protocols are detailed checklists based on the American Joint Committee on Cancer (AJCC) UICC/TNM staging, oriented to capture gross and microscopic information that are clinically important. The current edition (Amin et al., 2012) on bladder standardizes the gross terminology as Flat, Papillary, Solid, Ulcerated and Indeterminate, but considers reporting it optional. In cystectomy specimens, papillary tumors are frequently non ulcerated and larger than non-papillary lesions, with favorable staging, suggesting that a proportion of more indolent bladder cancers tend to grow in size rather than invade and metastasize (Schultz et al., 2016; Xie et al., 2012). Likewise, colorectal tumors devoid of an adenomatous component are often ulcerated and invade at a smaller size, but with worst outcomes than those arising in polypoid adenomas (Nasir et al., 2004).

Non-papillary urothelial lesions encompass carcinoma in situ and invasive urothelial carcinoma, which have high cytological grade by definition and in the majority of cases, respectively (Tian & Epstein, 2015). Therefore, cytological grade is more informative in the context of non-invasive papillary lesions, where benign cytology corresponds to papilloma and presence of atypia defines a neoplasm that should be graded. In this scenario, identification of high grade cells increases the chance of recurrence and progression, although the cut-off of such proportion is still a subject of debate (Reis et al., 2016).

Among the various grading schemes proposed overtime, the World Health Organization (WHO)/1973 had been the most widely accepted, with a three-tiered system proportionate to the degree of atypia (Siegel et al., 2017). In 1998, the WHO and the International Society of Urological Pathology (ISUP) proposed a new consensus (Mostofi et al., 1973) intended to provide more specific morphological criteria for grading and avoid naming as carcinoma tumors with a low probability of progression and recurrence. Thus, the diagnostic category of papillary urothelial neoplasm of low malignant potential (PUNLMP) was created, referring to a papillary lesions with minimal to absent cytologic atypia but an increased cellular proliferation, and a two-tiered (low and high) grading scheme for urothelial carcinomas.

PUNLMP was adopted in the following year by the WHO/ISUP/1999 system, but it was not until WHO/2004 that grade was adopted as a dichotomous variable. In this edition, if PUNLMP cytologic features were seen in a thickened lesion devoid of true branching papillae, it was termed papillary hyperplasia. In the current WHO/2016, this contradictory terminology has been re-named urothelial proliferation of uncertain malignant potential (UPUMP), since it can only progress to non-invasive neoplasms.

The evolution of terminology towards descriptive terms regarding malignant potential was motivated by the need to establish a nomenclature that better communicated with the clinical scenario, including clinicians and patients. Although there is no established screening for bladder cancer, access and safety of cystoscopy has increased the diagnosis of early non-invasive carcinomas, including some that seldom progress to fatal disease, raising concern of over-diagnosis and overtreatment. In fact, despite the increase in bladder cancer incidence, mortality has remained fairly stable for the last three decades (Epstein et al., 1998). During this time, the need to incorporate new tools into morphology has raised a search for molecular biomarkers that grew exponentially with technology and scientific foment. As a result, luminal and basal molecular subtypes are now well established and, in many instances, morphology correlates with this layout.

The subgroup of lesions with a molecular signature reminiscent of more differentiated luminal urothelial cells are enriched for papillary morphology, while the subgroup more similar to urothelial basal cells are enriched for the presence of a squamous component (The Cancer Genome Atlas Research Network, 2014). Squamous differentiation occurs in around 20% of invasive bladder cancers and this phenomenon is associated with a worse prognosis (Antunes et al., 2007).

Papillary morphology is characteristic of well differentiated urothelial lesions

Within the normal urothelium, basally located cells are immature and gain differentiation as they advance towards the lumen. Mature luminal cells are able to interact with the external compartment, including maintenance of physical integrity, permeability and defense mechanisms (Lazzeri, 2006). The basal layer has a higher turn-over because it harbors urothelial stem cells with a pivotal role in homeostasis and regeneration of the epithelial compartment. Bellow, the *lamina propria* is composed of a network of connective tissue (such as collagen and elastin), blood and lymphatic vessels, myofibroblasts, immunologically competent cells and nerve endings.

Traditionally, the *lamina propria* has been suggested to operate as the capacitance layer of the bladder, determining bladder compliance and enabling adaptive changes to increasing volumes. More recently (Andersson & McKloskey, 2014), other possible functions are being better understood, such as its integrative role in transduction of thermal, mechanical and chemical stimuli to the central nervous system and communication between the urothelium and the bladder wall, contributing to detrusor muscle contraction. In addition, the *lamina propria* may serve as a source for production of important bioactive substances that are contained within the matrix, such as growth factors, adhesion molecules, and modulators of coagulation and fibrinolysis, that enhance cell viability and tissue regeneration.

The *lamina propria* may project itself towards the lumen when there is inflammation and edema, leading to follicular and/or polypoid cystitis (Fig. 1). However, when the projection carries a fibrovascular core, it implies an organization meant to last. A papillary urothelial structure is formed by a projected axis of *lamina propria* carrying a fibrovascular core, in order to accommodate a larger population of epithelial cells (Fig. 2). Activating mutations in oncogenes like *HRAS*, *PIK3* and *FGFR3* are a hallmark of non-invasive papillary lesions, and result in sustained proliferative stimuli that increase the population of urothelial cells. Through the amplified interface of a papillary axis, the lamina propria can continue to supply nutrients, oxygen, hormones and other vital cellular needs. Other anatomic structures that share this composition – a small protuberance formed by a nurturing axis – are also called papilla, such as in gustatory papillae, renal papillae, the nipple or the papillar dermis.

Papillary phenotype in advanced urothelial lesions confers better prognosis

Advanced urothelial carcinomas are associated with inactivating mutations of major tumor suppressor genes like *TP53* and *RB1*. These alterations may arise de novo in a flat lesion (carcinoma in situ) or they can represent progression from an earlier non-invasive papillary tumor. Upon an advanced urothelial lesion, would it be clinically relevant to define from which oncogenic pathway it has evolved?

In fact, detection of *HRAS* and *FGFR3* mutations in advanced lesions are favorable predictors of outcome (Wu, 2005). Initial studies by Lindgren et al. (Lindgren et al., 2010; Lindgren et al., 2012) combined molecular and pathologic data to assign molecular subtypes for different stages of bladder cancer. Two molecular signatures were proposed based on whole genome array-CGH analysis and mutation analyses of *FGFR3*, *PIK3CA*, *KRAS*, *HRAS*, *NRAS*, *TP53*, *CDKN2A*, and

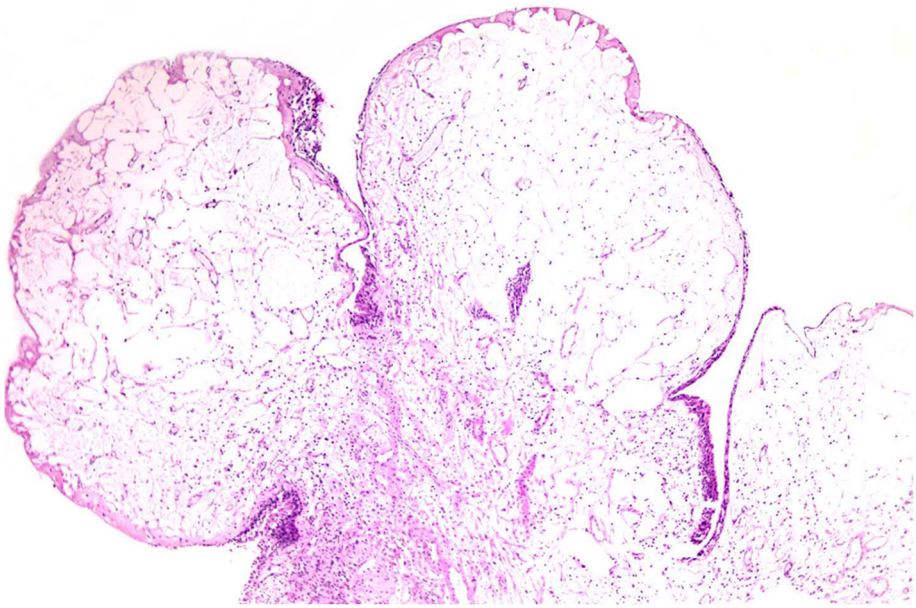

Fig. 1 Polypoid cystitis (H&E; 40x). The inflamed *lamina propria* is projected towards the lumen. It lacks a fibrovascular core and the epithelial compartment is not proliferated, therefore this is a reactive condition and not a papillary lesion

TSC1. They found that genomic instability was the most distinguishing feature of advanced tumors, independent on *TP53* alterations. This signature was absent in non-invasive papillary lesions (pTa), while superficially invasive carcinomas (pT1) exhibited an intermediate profile.

Later, genomic studies detailed these phenotypes and set off the nomenclature of Luminal and Basal subtypes (The Cancer Genome Atlas Research Network, 2014; The Cancer Genome Atlas Research Network, 2017; Aine et al., 2015; Choi et al., 2014a). Luminal bladder cancers were further subdivided into "p53-like" and "luminal", distinguished from

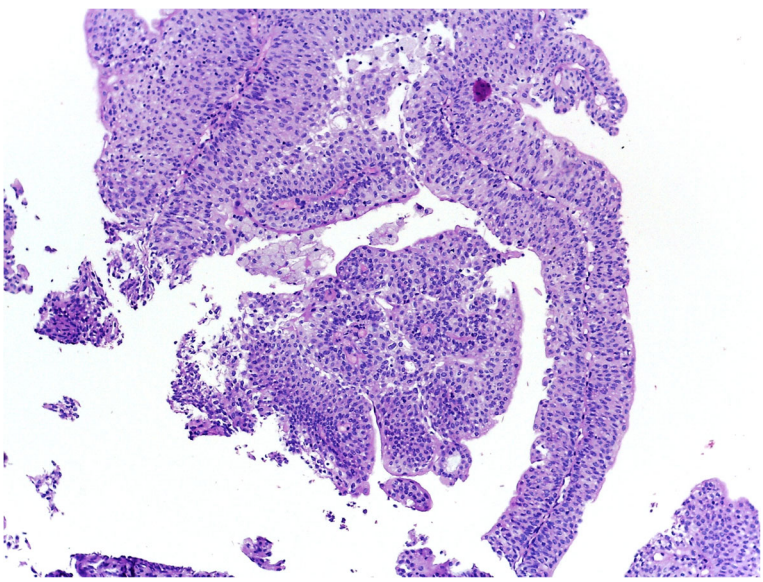

Fig. 2 Papillary urothelial lesion (H&E; 10x). It is defined by the presence of a fibrovascular core, which is depicted transversally in the center of the figure, and longitudinally in the right side. It is a low grade well differentiated lesion, with relatively uniform cytology and maintenance of polarity towards the basement membrane

one another by different levels of biomarkers associated with stromal infiltration, cell cycle progression, and proliferation. The p53-like luminal are so called because they express an active p53-associated gene expression signature, although they do not carry *TP53* mutations. Importantly, although the luminal subtypes are not as intrinsically aggressive as basal cancers, p53-like tumors are resistant to chemotherapy (Choi et al., 2014b).

Differentiation and metabolism regulation in papillary urothelial lesions

Another interesting difference between Luminal and Basal tumors that came out of such studies regards to microRNA (miRNA) status. Of note, their targets are important components in the regulatory networks that maintain cell phenotype and control cell differentiation. The seminal study by The Cancer Genome Atlas (TCGA) (The Cancer Genome Atlas Research Network, 2014) showed that basal tumors are enriched for squamous differentiation, cytokeratin 5/6 expression and mir-200a-3p and mir-200b-3p downregulation. The miR-200 family of miRNA are expressed in all epithelial cells, acting as enforcers of the epithelial phenotype, since their expression must be turned off to allow for epithelial to mesenchymal transition (Park et al., 2008). Interestingly, while Luminal tumors were enriched for papillary morphology and GATA3 expression, the p53-like subset showed downregulation of mir-99a-5p and mir-100-5p. These are members of the miR-99 family that regulate cell proliferation, cell migration, and mechanistic target of rapamycin (mTOR) pathway signaling (Jin et al., 2013).

mTOR pathway regulates processes that require a substantial amount of matter and energy, such as cell metabolism, proliferation and differentiation. The metabolic needs of a cell are greatly altered when it commits to growth and proliferation. While quiescent cells optimize for high ATP yield, doubling cellular mass requires acquisition of an anabolic phenotype, which increases the uptake of nutrients, reprogramed for glycolysis and macromolecular synthesis (Palm & Thompson, 2017). Downstream of growth factor activation, *PI3K* and *HRAS* promote independent control of metabolism, increasing nutrient uptake and biosynthetic enzymes activity. Therefore, gene overexpression sets the order of magnitude of proteins, but a combination of post transcriptional, translational and degradative regulation, acting through miRNA or other mechanisms, then fine tune protein abundances to the cell's preferred level. Indeed, miRNA have been found to fine-regulate protein expression levels, rather than to cause large expression changes (Vogel & Marcotte, 2012; Fraser et al., 2004).

Alterations in the mTOR pathway are among the most frequent in urothelial tumors and, in fact, expression of the mTOR effector phosphorylated (Ser240/244) S6 protein has shown prognostic significance. Its expression is higher in non-muscle invasive and papillary tumors (Chaux et al., 2013) and maintenance in advanced invasive lesions is a protective factor for disease-specific survival (Schultz et al., 2010) (Fig. 3). This is a counter-intuitive finding, since mTOR activation is classically associated with growth and proliferation. It is also potentially therapeutically relevant, since mTOR is amenable to pharmacological inhibition. A gradual decrease of mTOR protein expression has been shown in the malignant transformation of other organs and reports of a less accentuated loss in well differentiated adenocarcinomas of the stomach, lung, biliary tract and prostate, have been associated with a favorable prognosis (Afonso et al., 2014; Xiao et al., 2009; Shah et al., 2005; Lee et al., 2012; Anagnostou et al., 2009; Müller et al., 2013). Therefore, it is possible that constitutive expression of mTOR is necessary for normal metabolic activity in urothelium and other epithelia (Gibbons et al., 2009), and maintenance of its activation, even if partially, could confer favorable prognosis in certain tumors, in a tissue-specific manner.

Interaction between the matrix and the urothelium is optimized by a papillary architecture

The various signaling pathways interact directly or indirectly in different ways, including feedback mechanisms, often times redundantly. Therefore, in order to achieve invasive and metastatic potential, a neoplastic clone must acquire a collection of mutations that allows for multiple advantages, which have been called the hallmarks of cancer by Hanahan & Weinberg (Hanahan & Weinberg, 2000; Hanahan & Weinberg, 2011). They acknowledge that invasion is preceded by the cell's acquisition of an aggressive phenotype, resultant from a driver mutation(s) and genomic instability, but its conclusion depends on abilities related to its interaction with the microenvironment. These include loss of cell adhesion and polarity, with cell motility, proteolysis of basement membrane and extracellular matrix, epithelial to mesenchymal transition, and angiogenesis (Fig. 4). Therefore, it is thought that the neoplastic cell and its environment evolve together towards progression. While the papillary structure preserves a certain degree of cell-matrix interaction, it also provides a larger interface for metabolic interplay and contributes for continuous proliferation. A papillary lesion, then, has the optimized architecture for the oncogenic progression.

Away from microscopic dimensions, the construction of Port-Grimaud, in France, provides a good analogy to this phenomenon. In a panoramic view (Fig. 5), it shows a papillary architecture, where the land extensions, with its supportive roads, represent the *lamina*

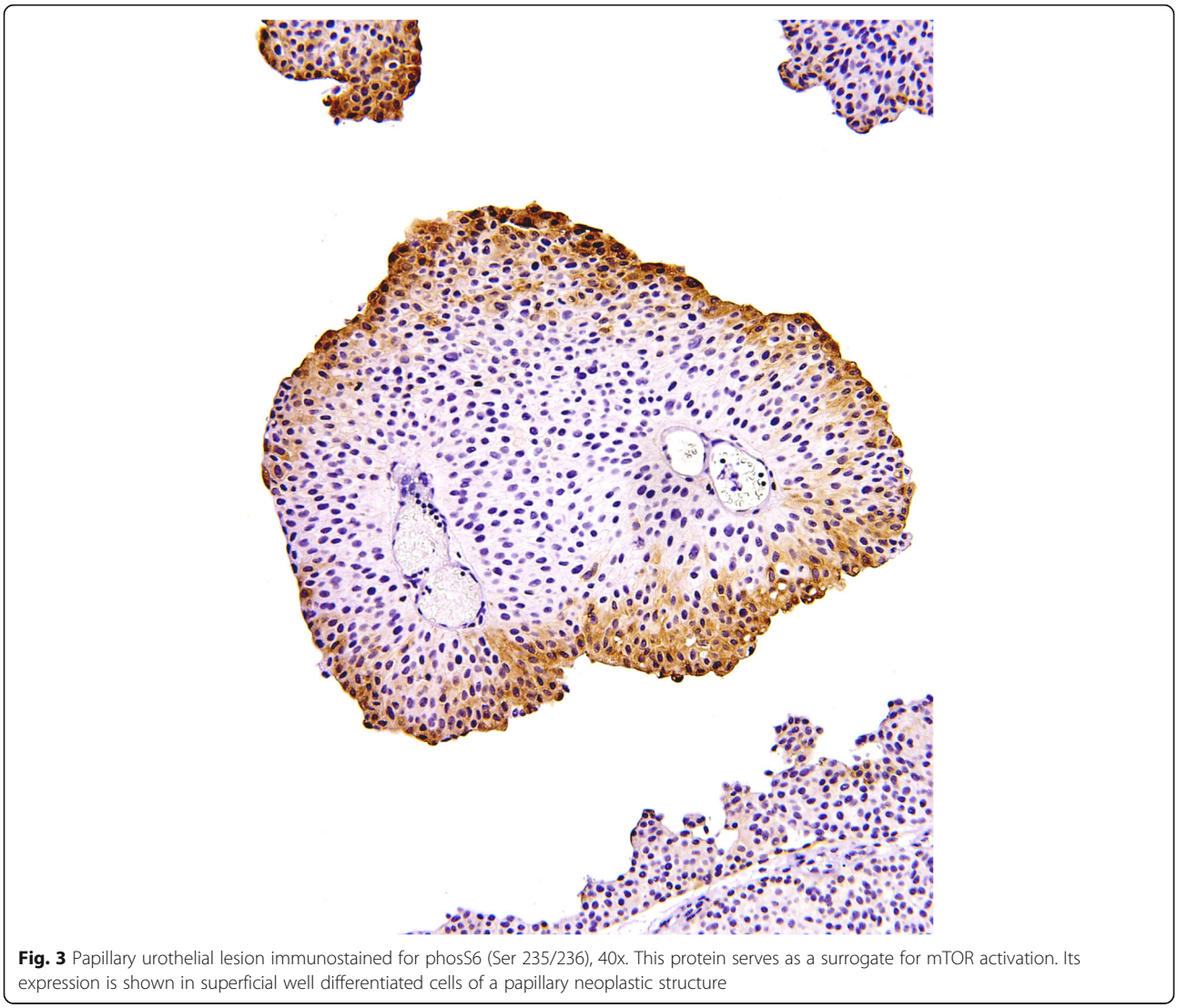

Fig. 3 Papillary urothelial lesion immunostained for phosS6 (Ser 235/236), 40x. This protein serves as a surrogate for mTOR activation. Its expression is shown in superficial well differentiated cells of a papillary neoplastic structure

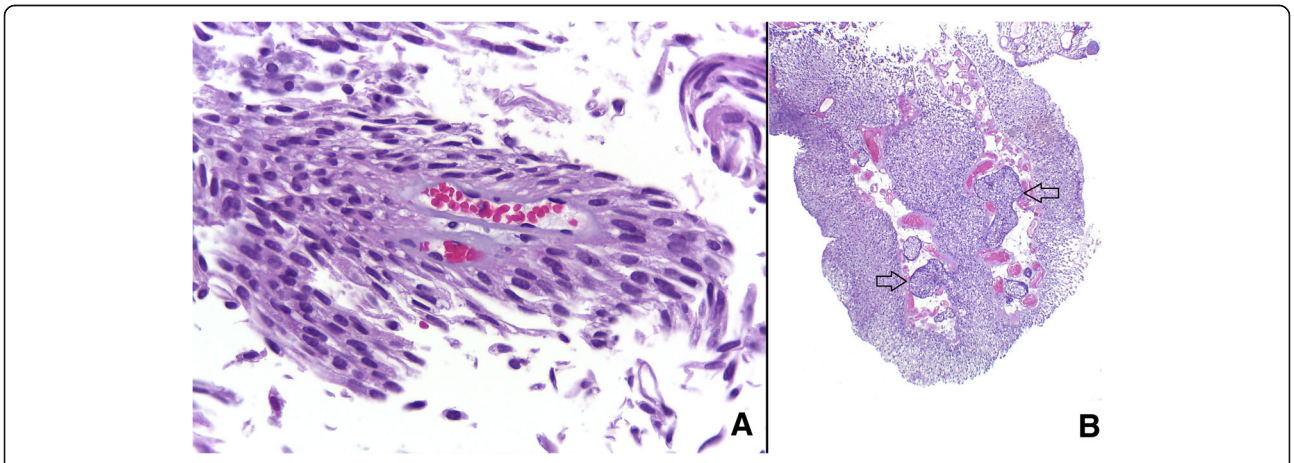

Fig. 4 High grade papillary urothelial lesion (H&E). There is loss of cell adhesion, with shedding of superficial cells (A; 40x). It is a high grade lesion, with hiperchromatic nuclei that have lost polarity. (B; 10x) The epithelial layer is densely cellular and thick and the fibrovascular core shows proliferated ectatic vessels, with foci of invasion through the basement membrane (arrow)

Fig. 5 Aerial view of Port-Grimaud, France. Google Earth: 43°16′08.0″N 6°34′55.3″E (https://www.google.com/earth/). The village was projected by François Spoerry to provide the best disposition where every docked boat would have direct access to mainland. It serves as an analogy to how the papillary architecture in the bladder is a non-physiological organization that optimizes the dynamics of proliferated *lamina propria* and urothelial cells

propria and the abundant docked boats represent the epithelial cells. Port-Grimaud was not formed by natural phenomena, but rather projected by François Spoerry (Spoerry, 1991) to provide the best disposition where every docked boat would have direct access to mainland. It started with the need to accommodate an increasing population of sailors. The French were flocking towards the seaside for their holidays and Côte d'Azur became highly urbanized. In this new composition, the road had to be indented from the land to avoid the need for bridges and also provide each boat easy access to the sea. Regardless of whether Spoerry ever saw a microscopic papilla, he calculated a composition able to optimize the dynamics of proliferated land and boats.

Conclusion

Conventional optical microscopy of H&E stained sections from formalin-fixed-paraffin-embedded tissue has been fundamental in the diagnosis of cancer for over a century. It is an efficient and reproducible method, with high predictive power and the ability to drive therapy decisions. Papillary and non-papillary lesions not only differ with regards to their form, but also their nature, impacting on prognosis, nomenclature and molecular profiles (Table 1).

Table 1 Differences between papillary and non-papillary urothelial lesions

	PAPILLARY	NON-PAPILLARY
Gross terminology	Papillary	Flat, Solid, Ulcerated
Histological classification	Papilloma, PUNLMP, Non-invasive urothelial carcinoma, Invasive urothelial carcinoma	Urothelial carcinoma in situ, Invasive urothelial carcinoma
Growth	Tends to grow in size before invasion and metastases	Invade and metastasize early
Clinical behavior	Benign, uncertain malignant potential, malignant	Malignant
Most frequent molecular alterations	Activating mutations in oncogenes	Inactivating mutations in tumor suppressor genes, genomic instability
Oncogenesis	De novo	De novo or progress from papillary carcinoma
Most frequent molecular subtype	Luminal	Luminal and basal
Squamous differentiation	Rare	Frequent
Relationship with extracellular matrix	Cooperation	Proteolysis

Today, there is an opportunity to increment the surgical pathology report with information about genes, proteins, and specific genomic alterations, enhancing the power to predict clinical behavior. Because the papillary structure is the result of a transcriptional program and its post-transcriptional modifications, its presence will likely be maintained in future classification schemes and perhaps contribute to delineate more effective individual-based therapy.

Acknowledgements
Not applicable

Funding
There was no funding source for this review.

Availability of data and materials
This review was based on references and does not add data sets.

Authors' contributions
This manuscript is the result of the author's sole work. The author read and approved the final manuscript

Authors' information
Luciana Schultz is a pathologist specialized in the genitourinary field, trained at Johns Hopkins by a combined Clinical and Research Fellowship. Her most prominent research line involves bladder cancer morphology with an interface on molecular biology, which was the focus of her Oncology PhD at AC Camargo Cancer Center. This translational profile is also reflected by an academic production combined with intense clinical practice as senior pathologist at Patologia D'Or and managing director of Instituto de Anatomia Patológica.

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

Received: 15 February 2018 Accepted: 20 April 2018
Published online: 19 December 2018

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