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Gene of the month: GATA3

Zekai Qiang[1], Ibrahim Jubber[1], Kirsty Lloyd[2], Marcus Cumberbatch[1], Jon Griffin[1,2,*]

[1.] Academic Urology Unit, University of Sheffield, Sheffield, UK; Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

[2.] Histopathology Department, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

[*]Corresponding author: jonathan.griffin@sheffield.ac.uk

Abstract

GATA3 is a zinc-finger pioneer transcription factor involved in diverse processes. GATA3 regulates gene expression through binding nucleosomal DNA and facilitating chromatin remodelling. Post-translational modifications modulate its activity. During development, GATA3 plays a key role in cell differentiation. Mutations in *GATA3* are linked to breast and bladder cancer. GATA3 expression is a feature of the luminal subtype of bladder cancer and has implications for immune status and therapeutic response. It also has clinical relevance in SCCs and soft tissue sarcomas. This paper reviews the structure and function of GATA3, its role in cancer and its use and pitfalls as an immunohistochemical marker.

Word count: 2116

Structure of GATA3

The GATA binding protein 3 (GATA3), consisting of 444 amino acids, is part of a six-member zinc-finger transcription factor family[1]. It specifically recognises the consensus DNA sequence A/T GATA A/G and is encoded by the six-exon *GATA3* gene on the chromosome 10p14[2]. Structurally, it encompasses two transactivation domains positioned at the N-terminus, as well as two highly conserved zinc-fingers towards the C-terminus, each immediately adjacent to a basic region[3] (figure 1)

Mechanism of action of GATA3

Two distinct modes of DNA binding contribute to GATA3's essential physiological functions[4]. Firstly, the zinc-finger located at amino acids 318-342 binds to the GATA site on DNA. Simultaneously, the second zinc-finger (amino acids 264-288) strengthens this interaction by engaging with the C-terminal basic tail, resulting in a "wrapped" structure. Secondly, the linker region between the N- and C-fingers exhibits remarkable conformational flexibility, enabling the binding of both zinc fingers to target sites on DNA molecules with different orientations. This mechanism is central to GATA3 acting as a pioneer factor by binding to promoters and enhancers with nucleosomal or 'closed' chromatin and increasing chromatin accessibility at these site[5]. Cryo-electron microscopy of reconstituted DNA, histones and GATA3 showed that GATA3 preferentially binds its consensus motif in the major groove of nucleosomal DNA. Furthermore, the specific engagement of tandem GATA motifs was predicted to promote histone removal thereby promoting open chromatin; more likely to bind additional transcription factors. These processes are influenced by various factors, such as local DNA sequence, chromatin architecture, and the presence of transactivation domain-dependent cofactors[6] (figure 1).

Regulation of GATA3 gene transcription and activity – lessons from T-cell differentiation

Physiologically, GATA3 is involved in many aspects of the immune response and T helper 2 (Th2) cells have been used as a model to study the gene's regulation. Many post-translational modifications play crucial roles in regulating the physiological and pathophysiological functions of GATA3 (figure 1). GATA3 is essential for T helper 2 (Th2) cell differentiation and binding of cytokine gene promoter regions, requiring interaction with the transporter importin-α in a process involving p38 mitogen-activated protein kinase-mediated phosphorylation of GATA3 serine residues[7]. Furthermore, the transcription of interleukin-5 (IL5), a key Th2 cytokine gene implicated in eosinophilic inflammation, required

demethylation of arginine residues in the N-terminal zinc finger of GATA3 and subsequent dissociation of heat shock protein 60[8]. In a third example of post-translational modification, AKT1 was identified as the kinase responsible for GATA3 phosphorylation at serine/threonine residues on the C-terminal zinc finger, resulting in the dissociation of histone deacetylase 2 (HDAC2) and subsequent derepression of T-box transcription factor 21 (TBX21) and interferon gamma (IFN-γ) expression in interferon-γ producing memory Th2 cells[9].The latter is involved in neutrophilic inflammation and eosinophil infiltrations and is possibly implicated in the pathogenesis of allergic asthma[10]. GATA3 activity in Th2 cells may also be controlled at the gene expression/ mRNA transcription level. A divergent antisense long non-cording RNA (GATA3-AS1) in the *GATA3* promoter was necessary to maintain an open chromatin structure at this location. Knockdown of the lncRNA was sufficient to reduce GATA3 expression in Th2 cells. Interestingly, this control was exerted through the formation of DNA:RNA hybrids (R-loops), co-transcriptional non-canonical nucleic acid structures with roles in DNA damage and regulation of gene expression[11,12].

GATA3 in cancer

Breast cancer

GATA3 is the most abundantly expressed transcription factor in the mammary luminal epithelium, and functions to maintain its differentiated state. Studies in transgenic mouse embryos with conditional knock down of *GATA3* revealed disrupted growth of terminal end buds, leading to failed invasion of the ductal epithelium into the fatty stroma, highlighting GATA3's involvement in mammary branching morphogenesis. Additionally, acute loss of GATA3 in adult mammary glands was shown to cause proliferation of undifferentiated luminal cells, suggesting its engagement in cell-cycle control and the maintenance of differentiated, quiescent cellular states[13].

In The Cancer Genome Atlas (TCGA) breast cancer cohort *GATA3* was one of the most frequently mutated genes with mutations in ~10% of cancers. Common mutations cluster in

the zinc finger domains and most mutations arise in the second zinc finger region, involving splice site deletions and frameshift mutations, affecting GATA3's DNA binding properties and lead to altered transcriptomic networks in breast cancer cells[14–16]. GATA3 co-operates with another pioneer factor FOXA1 in oestrogen receptor signalling. The two factors pre-mark chromatin to increase accessibility for the hormone-bound oestrogen receptor. Loss of function mutations in GATA3 are associated with reduced hormone receptor signalling. In turn, there is upregulation of genes involved in epithelial to mesenchymal transition (EMT) and a subsequent increase tumour growth and invasion. This translates to a worse prognosis for patient with mutations in the second zinc finger domain. However, breast cancer patients with any GATA3 mutation have a better overall survival implying that some GATA3 mutation are gain of function and may drive luminal differentiation. In a morpho-molecular study using TCGA data[17], GATA3 mutations were more common in Luminal-A and Luminal-B type tumours as well as rarer histological subtypes such as mucinous and luminal papillary. Conversely p53 mutations were more prevalent in basal and triple-negative subtypes including metaplastic carcinoma.

GATA3 is an important factor in breast cancer development and establishment of different molecular subtypes with different clinical trajectories. The apparent contradictions of the association between GATA3 mutations and outcomes are likely to reflect the effects of different types of mutation, specifically the difference between partial and total loss of the zinc finger domains. In support of this, knockdown of GATA3 by siRNA led to an upregulation of bone metastasis-associated trefoil factor genes TFF1 and TFF3[18]. Intriguingly, these oestrogen regulated genes were more upregulated in the absence of GATA implying that GATA3 may also play a chromatin-licensing role and that the redistribution of ER binding sites seen with GATA3 loss can upregulate pathways associated with poor outcomes. Overall, the combination of GATA3 mutation type and the context of ER activity and other mutations create a complex association between GATA3 mutations and clinical outcomes.

Bladder cancer

GATA3 is part of a network including p63, FOXA1 and PPAR-γ that determines differentiation of the urothelium[19]. Urothelial basal cells differentiate into luminal/ umbrella cells through PPAR-γ signalling. FOXA1 and GATA3 co-operate to drive this differentiation however p63 can repress this process, maintaining cells in a basal state[20]. Concordantly, in the molecular classification of muscle invasive bladder cancer, GATA3 mRNA expression is upregulated in luminal and luminal papillary subtype tumours compared to basal subtype tumours. Whilst this may be reflected in the morphological appearances of MIBC, there is not a perfect correlation between morphology and molecular classification[21]. As in breast cancer, the activity of GATA3 drives a chromatin state associated with expression of luminal differentiation genes including CK19, FGFR3 and GPX2. Luminal subtype cancers have shown resistance to cisplatin and immunotherapy[22]. Interestingly a recent study established a link between GATA3 and protease-activated receptor 1 which induced cisplatin resistance in neuroblastoma cell lines[23]. A similar link has not yet been investigated in bladder cancer.

Despite their cisplatin resistance, luminal-subtype tumours have a better prognosis overall, however, this is not driven solely by GATA3. A recent study of more than 500 patients who had radical cystectomy for MIBC found that GATA3 protein expression was not predictive of survival[24]. However, in a separate study which defined a ‘double negative’ group as tumours with combined with loss of CK5/6 and GATA3, these patients did have a significantly worse prognosis[25]. The bladder cancer TCGA study identified the set of genes regulated by GATA3 (the GATA3 ‘regulon’) as having increased activity in patients with longer survival[21]. This group was enriched for patients with luminal type tumours. In contrast to breast cancer, *GATA3* was not commonly affected by missense or truncating mutations in the bladder cancer TCGA cohort. Instead, it was commonly amplified, which

may explain the substantial proportion of patients with upregulated GATA3 activity. Interestingly, copy number alterations of GATA3 did not cluster with common mutation events such as p53 or ARID1A mutations.

Several studies aimed to characterise immunotherapy-responsive and non-responsive bladder cancers based on their molecular phenotype for improved treatment selection. GATA3-rich tissues displayed downregulation of immunomodulators such as programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and reduced dendritic cell, CD4 and CD8 T-cell infiltration[26]. Using the IMvigor 210 cohort to validate these findings confirmed globally reduced immune infiltration in the tumour microenvironment of GATA3 expressing tumours, and reaffirmed that the basal subtype, characterised by low GATA3 enrichment, may respond better to checkpoint blockade.

Other cancers

GATA3 is also expressed in squamous cell carcinomas (SCC) of different anatomical sites and confers varied clinical significance. In oesophageal SCC (OSCC), GATA3 expression is typically low, and strongly positive immunohistochemical staining serves as a prognostic marker for poor survival[27]. Interestingly, in vitro studies of OSCC have revealed cooperation between GATA3 and androgen receptor, with subsequently suppressed transcription of genes DUSP4 and FOSB[28]. Lower expression of these genes has been linked to unfavourable clinical outcomes. Similar observations have been made in soft tissue sarcomas, lung adenocarcinoma, cholangiocarcinoma, head and neck SCC, where GATA3 enhances cancer invasiveness through hypoxia-inducible factor 1α stabilisation, and anorectal SCC, where its co-expression with ER renders it reminiscent of breast cancer[29–31]. GATA3 is expressed in 81% of skin SCCs, but its prognostic value remains uncertain.

GATA3 in diagnostic histopathology practice – uses and pitfalls

GATA3 immunohistochemistry is a useful marker in routine histopathology practice[32]. In a study of more than 2000 developmental and tumour tissues, GATA3 was highly expressed in urothelial carcinoma and both ductal and lobular breast cancer[31]. Less consistent expression was seen in a variety of other epithelial and mesenchymal neoplasia including germ cell tumours, mesothelioma, pancreatic ductal adenocarcinoma and squamous cell carcinoma of skin, lung, larynx and cervix. GATA3 can be a useful immunohistochemical marker in resolving differential diagnoses in a range of scenarios[32]. Distinguishing urothelial carcinoma from high grade prostate cancer and delineating metastatic breast[33] or urothelial cancer are two common uses of GATA3 immunohistochemistry. We have also used GATA3 in recognising a collision tumour of high-grade urothelial carcinoma of the renal pelvis and conventional high-grade clear cell renal cell carcinoma[34]. In addition, other tumours that feature in differential diagnosis scenarios have also been described. These include eosinophilic renal cell tumours (figure 2)[35–37], juxtaglomerular cell tumour[38], distinguishing differentiated vulvar intra epithelial neoplasia from non-neoplastic dermatoses as part of a panel including p16 and p53[39], parathyroid tumours[40], some salivary gland tumours[41] and choriocarcinoma[42,43] (summarised in table 1).

Despite these uses GATA3 is also associated with some potential pitfalls:

- A high-grade tumour in the prostate which could be Gleason pattern 5 prostate cancer or direct invasion by high-grade urothelial cell carcinoma (UCC). Here GATA3 expression can help delineate UCC however a potential pitfall is GATA3 expression by atypical prostate glands following radiation therapy[44] (figure 3)
- Determination of urothelial origin for a tumour with unusual differentiation in the bladder. In this scenario paraganglioma presents a pitfall as it can mimic UCC morphologically and expresses GATA3 with the potential for a misdiagnosis with important clinical consequences[45] (figure 4). Pathologists should also be mindful that expression of GATA3 is variable between cases of UCC and varies by molecular subtype[46–48]

- Nephrogenic adenoma can mimic urothelial carcinoma in-situ (CIS) or invasive cancer and 40% of cases express GATA3. This emphasises the importance of using GATA3 as part of a panel including PAX8 in this diagnostic scenario.
- GATA3 can be used as part of a panel when attempting to identify the primary site of a metastasis. In isolation GATA3 expression could indicate a breast or urothelial primary site. However, background lymphocytes will also express GATA3 and these need to be discounted in the histological assessment. In addition, areas of squamous differentiation in bladder cancer may express GATA3. The morphology, clinical context and presence of convetional urothelial carcinoma are therefore important.
- A recently described pitfall is the expression of GATA3 in pulmonary mucinous adenocarcinoma[49]. This case report also described lack of TTF1 and Napsin expression. These features have the potential for misleading the pathologist to errantly be diagnose the tumour as a mucinous breast cancer metastasis. A KRAS G12A mutation was found in the tumour consistent with lung origin. We have also seen this situation with GATA3 expression in a primary pulmonary mucinous adenocarcinoma (figure 5).

Conclusion and take-home points

- GATA3 is a pioneer transcription factor with roles in development, homeostasis, and disease.
- GATA3 acts through chromatin interaction via its zinc finger domains to control gene transcription in many different contexts including T-cell differentiation, bladder and breast cancer.
- Multiple post translational modifications are involved in the regulation of GATA3 activity.
- GATA3 is a useful immunohistochemical marker in breast and urological pathology with emerging use in other differential diagnosis scenarios.

- Potential immunohistochemistry pitfalls include expression of GATA3 in: Post-radiation prostate glands, bladder paraganglioma, lymphocytes, and pulmonary mucinous adenocarcinoma.

Statements

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Competing interests

None

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QZ, JG: Literature review

KL, IJ, JG: Figures and histopathology images

QZ, IJ, KL, MC, JG: Manuscript design and writing/editing of critical intellectual content

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Table 1 – GATA3 expression in common diagnostic scenarios

Diagnostic scenario	**% of cases expressing GATA3**
Identification of urothelial carcinoma	Depends on molecular subtype [46–48]: Basal: <10% Luminal: 60-75% Intra-tumour heterogeneity of GATA3 expression
Identification of breast carcinoma	60-90% of invasive ductal carcinoma [33] ~40% of triple negative breast cancer GATA3 expressed is often retained in metastases
Differential diagnosis of salivary gland tumours	Expressed in 100% of: • Mammary analogue secretory carcinoma • Salivary duct carcinoma • Warthin tumour • Oncocytoma Less frequent expression in acinic cell carcinoma (10%), adenoid cystic carcinoma (22%), mucoepidermoid carcinoma (41%) and epithelial-myoepithelial carcinoma (82%) [41]
Differential diagnosis of renal cell tumours	Low-grade oncocytic tumour (LOT): 100% [35] Papillary renal cell neoplasm with reverse polarity: 100% [36] Clear cell papillary renal cell tumour: 76% [37]
Differential diagnosis of differentiated vulval intraepithelial neoplasia (dVIN)	GATA3 expressed in 90% of dVIN vs. <10% of benign vulval dermatoses [39]
Juxtaglomerular cell tumour vs. renal glomus tumour	78% of juxtaglomerular cell tumours expressed GATA3 vs. 0% of renal glomus tumours [38]

Parathyroid tumours	100% parathyroid adenomas and carcinomas express GATA3 [40]
Identification of trophoblast tissues	GATA3 stained 100% of testis choriocarcinoma [42] and normal trophoblastic tissue [43]

Figures

Figure 1: **GATA3 gene structure, function and post translational modifications**. A. Gene model illustration from USCS Genome Browser. B. Two conformations of GATA3 are shown demonstrating binding of a single or tandem GATA motifs. GATA3-DNA interaction model from Protein Data Bank (https://doi.org/10.2210/pdb4HC7/pdb) based on Chen et al[4]. Accessed 10/06/2023. C. GATA3 binds nucleosomal DNA, ejects histones and creates more accessible chromatin. This favours chromatin looping to bring enhancers and promoters into close proximity. Further cofactors and the transcription machinery assemble at gene promoters. Illustrations adapted from BioRender with permission. D. Post-translational modifications of GATA3 (retrieved from www.phosphositeplus.org). Colour key - Blue: Phosphorylation; Green: Acetylation; Orange: Methylation. The two green rectangles indicate the zinc-finger GATA binding regions of the protein.

Figure 2: **GATA3 expression in low grade oncocytic tumour of the kidney and clear cell papillary renal cell tumour.** Images reproduced from Williamson et al [35] and Mantilla et al [37] with permission. A and B: Low-grade oncocytic tumour of the kidney with solid and tubular morphology, eosinophilic cytoplasm and perinuclear haloes. C and D: clear cell papillary renal cell tumour with tubular and papillary structures lined by clear cell with luminal nuclear polarity.

Figure 3: **GATA3 pitfall 1: Expression in benign prostatic glands with radiation atypia**. Images reproduced from Tian et al [44] with permission.

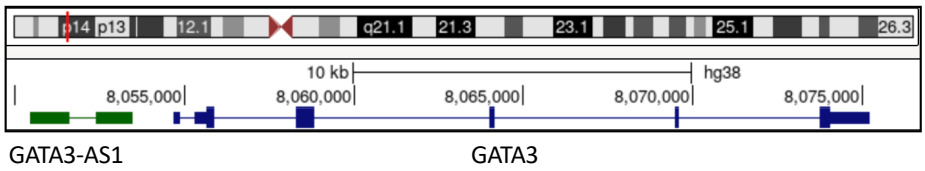
Figure 4. **GATA3 pitfall 2: Expression in paraganglioma of the bladder.** The nested appearance of epithelioid cells within the bladder wall can mimic invasive urothelial

carcinoma. Strong nuclear GATA3 expression is seen in this paraganglioma. Eighty-three per cent of paragangliomas will express GATA3. Images reproduced from So et al [45] with permission.

Figure 5. **GATA3 pitfall 3: Expression in pulmonary mucinous adenocarcinoma.** This patient had a PET-negative solitary lung nodule. A tumour composed of glands with goblet cells and extravasated mucin is seen adjacent to an airway lined by normal bronchial epithelium. Dotted outline indicates area of higher magnification showing separate clusters of tumour cells within intercellular mucin. The tumour cells expressed CK7, GATA3 and focally TTF1. No expression of ER, CDX2 or GCDFP-15 was present.

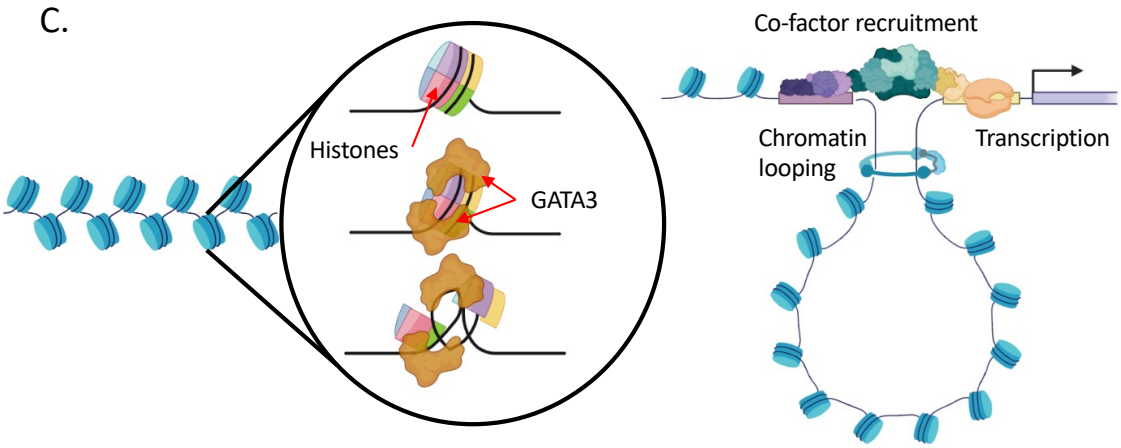
FIGURE 1

A.



B.

C.



D.

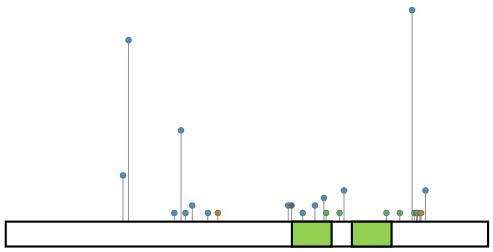


FIGURE 2

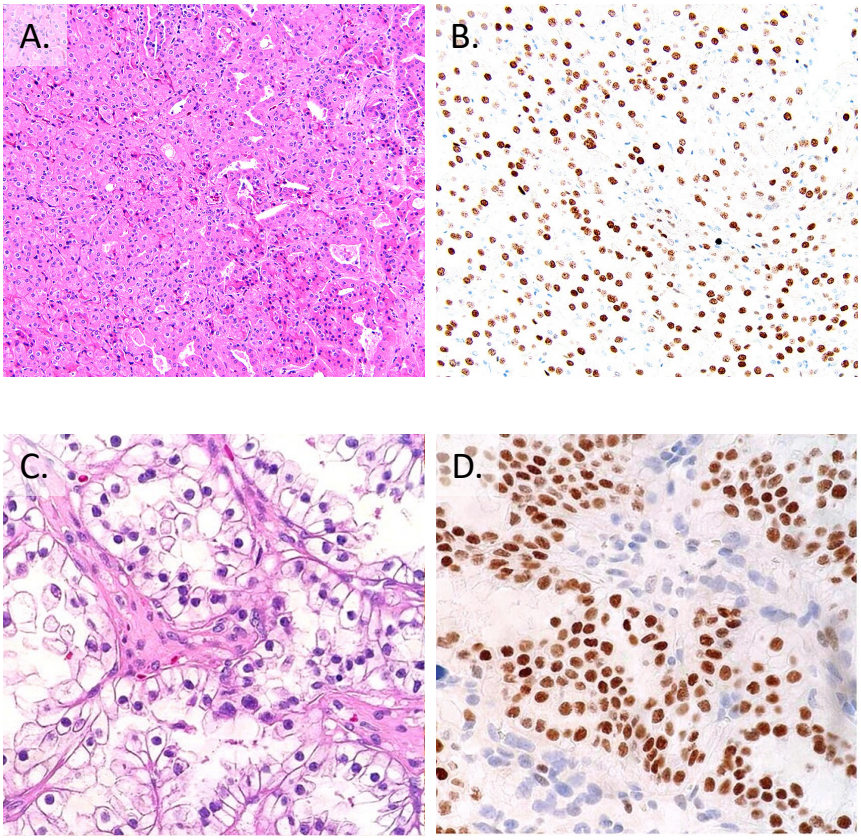


FIGURE 3

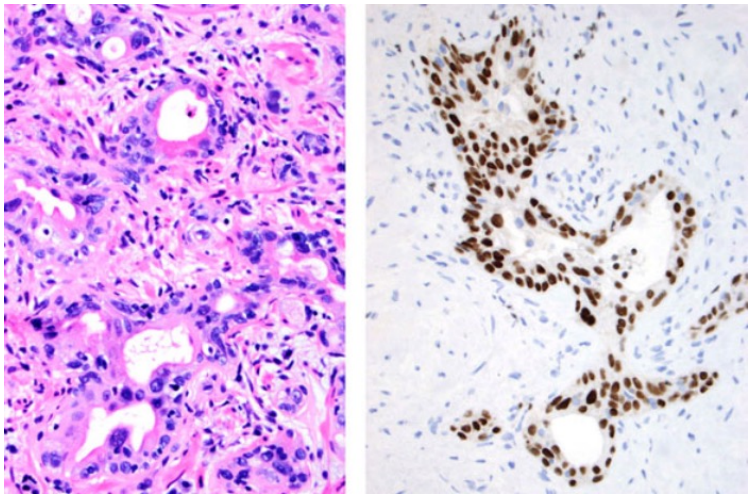


FIGURE 4

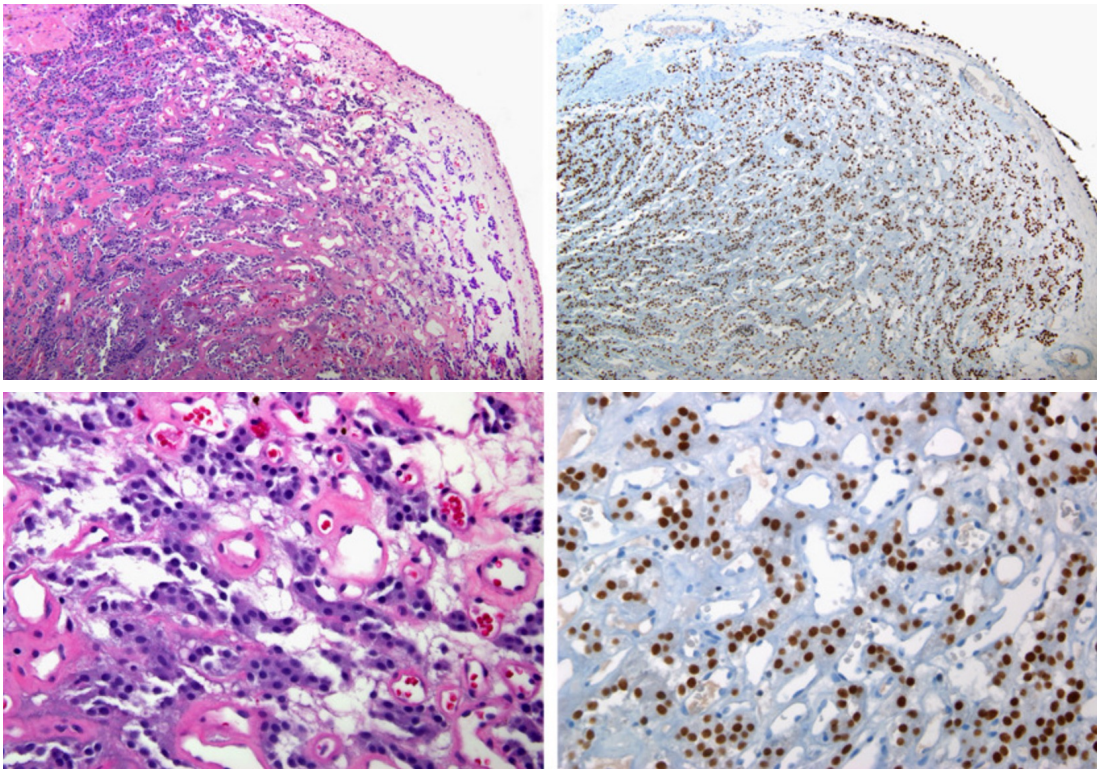


FIGURE 5