Critical Analysis of Papers

Supplementary Data S1: Seventy-seven cases of primary signet ring cell adenocarcinoma of the bladder, identified from a systematic review of PubMed, EMBASE, and Medline databases.

Source	Age + Sex	Clinical Presentation	Investigations (Bloods)	Cystoscopy findings	Radiological findings/GI workup	Stage	Histology + Immuno/histochemical stains	Management	Outcome (months)
Bouhajja 2019 (2)	53 M	Gross haematuria	PSA 1.2 ng/mL	Cystoscopy showed an inflammatory bullous lesion on the right side of the face and bottom that suggest carcinoma in situ or chronic cystitis.	Abdo USS: thickened bladder wall (8 mm) CT: Bladder wall thickening of >15 mm with irregular surface and perivesical fat infiltration. Performed – negative.	NR	Mass measuring 21 x 15 x 15 mm. Primary bladder carcinoma composed of mucinous and signet ring cell components. Nests of columnar and signet-ring cells. Columnar cells contained pleomorphic hyperchromatic nuclei. Signet ring cells – intracytoplasmic mucin. Muscular invasion, but no evidence of lymphovascular or perineural invasion. Immunohistochemistry – positive for cytokeratin 7 and 20, as well as CDX2 and beta-catenin.	Endoscopic resection of the lesion.	Alive at 24 months, with no mention of recurrence.
Jayaraja 2017	71 F	Intermittent episodes of painless haematuria with clots, of 2 months duration. No FHx malignancies.	Haemoglobin 8.6 g/dl.	Cystoscopy revealed an exophytic solid tumour measuring 1.5 × 2.0 cm arising from the anterior fundal wall covered with slough.	Abdominal ultrasound – localised polypoidal vesical growth (2.9 x 2.5 x 2.4 cm) arising from the bladder dome.	T2	Mass measuring 21 x 15 x 15 mm. Primary bladder carcinoma composed of mucinous and signet ring cell components. Nests of columnar and signet-ring cells. Columnar cells contained pleomorphic hyperchromatic nuclei. Signet ring cells – intracytoplasmic mucin. Muscular invasion, but no	Deep transurethral resection, followed by partial cystectomy.	Alive at 12 months, with no evidence (USS/cystoscopy) of recurrence.

					Full endoscopic GI workup completed		evidence of lymphovascular or perineural invasion. Immunohistochemistry – positive for cytokeratin 7 and 20, as well as CDX2 and beta-catenin.		
Thomas 2008									
1	57 M	NR	NR	NR	NR Performed for all (including colonoscopy and upper endoscopy).	NR	5% signet ring cells. No IHC given.	Surgery – partial cystectomy. Article mentions some received adjuvant chemo, but not which cases	Dead at 100 months.
5	60 M	NR	NR	NR	NR	NR	60% signet ring cells. Non-urachal origin.	Surgery – radical cystectomy. Developed liver mets.	Dead of disease 51 months
6	60 F	NR	NR	NR	NR	NR	20% signet ring cells. Non-urachal origin.	Surgery – radical cystectomy.	Alive without disease 21 months.
7	51 F	NR	NR	NR	NR	NR	40% signet ring cells. Non-urachal origin.	Surgery – radical cystectomy.	Dead of disease 10 months.
8	55 M	NR	NR	NR	NR	NR	95% signet ring cells. Non-urachal origin.	Surgery – radical cystectomy.	Dead of disease 6 months.
9	73 M	NR	NR	NR	NR	NR	100% signet ring cells. Non-urachal origin.	Surgery – radical cystectomy.	Dead of disease 4 months.
10	49 M	NR	NR	NR	NR	NR	80% signet ring cells. Non-urachal origin.	Surgery – radical cystectomy. Developed liver + spinal mets.	Dead of disease 70 months.

11	78 F	NR	NR	NR	NR	NR	100% signet ring cells. Non-urachal origin.	Surgery – radical cystectomy Developed liver mets.	Dead of disease 2 months.
12	63 M	NR	NR	NR	NR	NR	100% signet ring cells. Non-urachal origin.	Surgery – radical cystectomy.	Dead of disease 7 months.
13	69 M	NR	NR	NR	NR	NR	100% signet ring cells. Non-urachal origin.	Surgery – radical cystectomy.	Dead of disease 9 months.
14	73 M	NR	NR	NR	NR	NR	100% signet ring cells. Non-urachal origin.	Surgery – radical cystectomy. Developed spine mets.	Dead of disease 24 months.
15	60 M	NR	NR	NR	NR	NR	100% signet ring cells. Non-urachal origin.	Surgery – unresectable.	Dead of disease 24 months.
16	37 M	NR	NR	NR	NR	NR	80% signet ring cells. Non-urachal origin.	Surgery – unresectable.	Dead of disease 2 months.
17	60 M	NR	NR	NR	NR	NR	100% signet ring cells. Non-urachal origin.	Surgery – unresectable.	Dead of disease 9 months.
18	64 F	NR	NR	NR	NR	NR	100% signet ring cells. Non-urachal origin.	Surgery – unresectable. Developed omental mets.	Dead of disease 7 months.
19	65 M	NR	NR	NR	NR	NR	100% signet ring cells. Non-urachal origin.	Surgery – unresectable. Developed spinal mets.	Dead of disease 12 months.
El Ammari 2013	51 M	Three months of intermittent, painless gross haematuria,	Tumour markers mentioned – nil values provided.	Cystoscopic examinations revealed nonpapillary sessile	Ultrasound – grade II left hydronephrosis and circumferential	pT3b N1M 0	Via transurethral resection: adenocarcinoma composed of signet ring cells with abundant mucin pool.	Radical cystectomy with ileal conduit and bilateral pelvic lymphadenopathy.	Passed away 22 after diagnosis. Presented at 18 months with

		frequency and urgency. Unremarkable family history.		tumours occupying almost the whole of the bladder wall and the left side of the trigone, obstructing the left ureteral meatus.	thickening of the urinary bladder wall. CT – diffuse neoplasm of the urinary bladder with no lymph node enlargement or distal metastasis. Performed – no extravesical primary tumour found.		Invading perivesical adipose tissue and one lymph node. Stage: pT3bN1M0. Nil IHC.	Adjuvant chemo performed – four cycles of cisplatin and gemcitabine.	pelvic and back pain, with multiple mets to spine, lung and pelvis noted. Died four months later due to respiratory distress.
Fiter 1993 (2)	55 M	Episode of gross, painless haematuria.	Blood analysis, urine culture, urine cytology negative.	Bullous edema and necrotic mucosa of right lateral wall.	Cytology – malignant cells. IVP – irregularity of right lateral bladder wall with normal kidneys and ureters. US – low compliance, thick-walled bladder. Gastroscopy and barium enema negative.	NR	Histology – SRCC mucinous adenocarcinoma.	Cystoscopy + bladder biopsy.	Dead 0 months from azotaemia and sepsis.
Erdogru 1995									

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1	55 M	One episode of gross haematuria, lasting 2 days. Unremarkable physical examination except for minimal suprapubic tenderness. No palpable masses.	FBC, coags, LFT, electrolytes – no abnormalities. UA – red cells. Negative culture.	Cystoscopy - papillosolid 5 x 5 cm mass surrounded by erythematous bullous oedema.	IVP + pelvis USS revealed L side bladder wall filling defect. CT (post TURBT) – tumoural mass extending to the perivesical fatty tissue on left side of bladder. GI – radiographic studies + endoscopy and colonoscopy.	pT3a (grade 3)	Tumour invasion deep muscular wall of bladder (PT3a grade 3). Signet ring cell appearance. Abundance mucin. Positive for PAS and mucicarmine.	TURBT (resection of 3x3 papillosolid tumour). Exploratory laparotomy – normal stomach, colon and gallbladder. Radical cystectomy planned, but not carried out due to positive frozen sections of bilateral iliac, obturator and mesenteric lymph nodes. L ureter stented.	Alive with severe irritative voiding symptoms and stable disease for 8 months (conclusion).
Ivanov 2022	63 F	Presented with episodes of macroscopic haematuria (with clots) accompanied by unintentional weight loss.	FBC and serum biochemistry NAD.	Papillary tumour formation with diameter of 1.5 cm, involving the fundus of the bladder.	Abdo USS – no pathological abnormalities in the kidneys. Hetero-echoic formation on the bladder fundus of size 1.5 cm. Negative upper and lower endoscopy.	T1N0 M0	Poorly differentiated mucinous adenocarcinoma with signet ring features without presence of urothelial carcinoma or any other subtypes. At higher magnification, the foamy cytoplasm of the cells and the nuclei pushed into the periphery (arrows) can be seen, creating the illusion that there is a ring (cell membrane) with the ring facing inwards (the nucleus).	TURBT + intra-cavitary chemotherapy (ongoing).	Two negative cystoscopies at 12-month follow-up.

							IHC – positive for cytokeratin 7 and 20.		
Pugashetti 2015	71 M	Presented with haematuria and clot retention.	NR	Friable bladder mass along prostatic urethra, bladder neck and right ureteral orifice.	PET – mildly hypermetabolic paraesophageal LN, no other findings. Preoperative magnetic resonance imaging (MRI) of the abdomen and pelvis revealed that the mass invaded into the prostate gland but did not extend into the rectum. CT and endoscopies to rule out primaries.	T4aN 2Mx	SRCC CK7+, CK20+, CDX2+, PSA-, PAX2-, PAX8- Lymph nodes positive in external and internal iliac lymph nodes bilaterally, positive margin left apical prostate.	Radical cystoprostatectomy with ileal conduit and bilateral pelvic lymph node dissection. Restaging MRI 3 months post-op – 9 mm right iliac lymph node, 8 mm pericaval lymph node, and an 11 mm enhancing lesion in the L1 vertebral body. PET 4 months post-op – FDG PET/CT imaging again reported the osseous lesion in L1. Chemotherapy FOLFOX-6 3 months post-op → resolution of osseous lesions in lumbar spine and stable lymphadenopathy.	Alive 12 months, nodal disease at operation.

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Allen 1997	67 M white	Gross painless haematuria.	NR	Large sessile bladder tumour on the right hemitrigone and right lateral bladder wall.	Intravenous pyelogram – large mass in bladder with partial obstruction of right ureteral orifice. CT-AP – perivesical extension on the right side. CXR, bone scan and barium enema negative.	T3N0 M1	TURBT – SRCC with foci of TCC. Final pathology – positive margins right side.	Pelvic lymph node dissection with radical cystectomy and urinary diversion + adjuvant methotrexate, vincristine, adriamycin, and cisplatin. 3 weeks after surgery, metastatic TCC to penis diagnosed. Methotrexate, vincristine, adriamycin, and cisplatin were begun 1 week after the penile biopsy and continued through two cycles.	Dead 3 months. Pulmonary metastases. Left corpora metastasis.
Allameh 2017	18 M Afghan	1-year hx painless haematuria with clots. Hx of cystolithotomy seven years ago.	NR	White, calcified sessile tumour extending from the left bladder wall to the dome and obstructing the left ureteral orifice.	USKUB – bilateral hydronephrosis. CT – bilateral hydronephrosis with multiple bladder filling defects. Endoscopy, colonoscopy and	T2N0 M0	TURBT – SRCC. TB negative. CK7+, CK20+, CDX-2+, PSA-, CKD34-, Vimentin- Serum CA19.9 - Serum CA125 – Final pathology – ill-defined ulcerative and necrotic tumour mass with soft and gelatinous consistency filling the whole bladder cavity	Radical cystectomy with prostate and seminal vesicle sparing technique and orthotopic diversion with “W” ileum pouch made for him, pelvic lymphadenectomy.	Alive 6 months. No recurrence/metastases.

					CT to rule out other primaries.		measuring 2.5 cm in maximal thickness. Microscopically, the bladder wall was infiltrated into deep muscularis propria (outer half) by a necrotic neoplasm composed of lakes of mucins containing floating nests or cords of epithelioid cells and many signet ring cells.		
Torenbeek 1996									
1	82 M	Frequency, retention 3 weeks.	NA	Non-exophytic, edema.	CT to rule out other primaries.	T4	75%, dysplasia of adjacent urothelium. Ker+ Cam5.2+ EMA+ CEA+ PSA- 115D8+.	Radiotherapy.	Dead 11.
2	75 M	Haematuria, frequency 3 weeks.	NA	Superficial tumour, central necrosis.	CT to rule out other primaries.	T2	30%, CIS of adjacent urothelium, TCC additional component. Ker+ Cam5.2+ EMA- CEA(ND) PSA- 115D8+.	Radiotherapy, intravesical radium.	Alive, no recurrence 87.
3	78 M	Frequency 11 months.	NA	Oedema.	CT to rule out other primaries.	T2	25%, CIS of adjacent urothelium. Ker+ Cam5.2+ EMA++ CEA+ PSA- 115D8+.	Radiotherapy.	Dead 15.
4	79 M	Haematuria 3 weeks.	NA	Polypous, massive.	CT to rule out other primaries.	T3	90%, normal. Ker+ Cam5.2+ EMA+ CEA+ PSA- 115D8+.	Radiotherapy.	Dead 12.
5	78 F	Haematuria 12 weeks.	NA	Exophytic.	CT to rule out other primaries.	T4	40%, TCC additional component.	Radiotherapy.	Dead 16.

							Ker+ Cam5.2+ EMA+ CEA+ PSA- 115D8+.		
6	74 M	Haematuria 5 days.	NA	Massive, spheric.	CT to rule out other primaries.	T4	100%. Ker(ND) Cam5.2+ EMA- CEA+ PSA- 115D8-.	Partial cystectomy, intravesical caesium.	Dead 48.
7	51 M	Frequency 2 weeks.	NA	Hyperaemia, oedema.	CT to rule out other primaries.	T3	70%, normal adjacent urothelium. Ker+ Cam5.2- EMA++ CEA+ PSA- 115D8+.	Radiotherapy.	Alive, no recurrence 67.
8	44 M	Haematuria 2 weeks.	NA	Polypous.	CT to rule out other primaries.	T3	100%. Ker+ Cam5.2+ EMA++ CEA+ PSA- 115D8+.	Radical cystectomy, Radiotherapy.	Dead 20.
9	62 M	Haematuria 2 days.	NA	Focal granular.	CT to rule out other primaries.	T2	75%. Ker++ Cam5.2++ EMA+ CEA+ PSA- 115D8+.	Radical cystectomy.	Alive, no recurrence 28.
10	76 F	Haematuria 6 weeks.	NA	Exophytic.	CT to rule out other primaries.	T3	80%, CIS of adjacent urothelium. Ker+ Cam5.2+ EMA++ CEA+ PSA- 115D8++.	Radiotherapy.	Dead 36.
11	83 M	Frequency, incontinence 7 months.	NA	Exophytic.	CT to rule out other primaries.	T3	15%, CIS of adjacent urothelium, small cell undifferentiated carcinoma additional component. Ker+ Cam5.2++ EMA++ CEA- PSA- 115D8+.	TURBT.	Dead 9.
12	59 M	Haematuria, retention, flank pain 8 weeks.	NA	Cobblestone, oedema.	CT to rule out other primaries.	T2	60%, TCC additional component.	Radical cystectomy, Radiotherapy.	Dead 24.

							Ker+ Cam5.2+ EMA+ CEA- PSA- 115D8 +.		
13	71 M	Dysuria, frequency 8 weeks.	NA	Large tumour, rigid wall.	CT to rule out other primaries.	T4	60%, dysplasia of adjacent urothelium. Ker+ Cam5.2- EMA++ CEA- PSA- 115D8+.	TURBT.	Dead 8.
Ohtsuki 2010	64 M	Haematuria.	Urine cytology negative.	Right anterolateral wall papillary tumour.	CT and endoscopies to rule out primaries.	T1	20%, TCC additional component. AE1/AE3+ CAM5.2+ EMA+ CEA+ CK7+ CK20+ B-catenin+.	TURBT, intravesical epirubicin hydrochloride.	Alive 4.
Burnett 1991									
1	45 M	Abdominal mass absent.	Urinalysis.	Trigone mass.	CT and endoscopies to rule out primaries.	TX	Well-differentiated SRCC with cystitis glandularis.	Radical cystoprostatectomy + ileal loop.	Alive 99 months. No evidence of disease.
2	73 F	Abdominal mass present.	Urinalysis.	Trigone mass.	CT and endoscopies to rule out primaries.	TX	Poorly differentiated SRCC. Positive left ovary metastasis.	Cystectomy, urethrectomy, bilateral pelvic lymph node dissection.	Dead 94 months. Carcinomatous meningitis.
3	62 M	Abdominal mass absent.	Urinalysis.	Trigone mass.	CT and endoscopies to rule out primaries.		Poorly differentiated SRCC. Positive lymph nodes.	Radiotherapy. Inoperable at exploratory laparotomy.	Alive 20 months. No evidence of disease.
4	74 M	Abdominal mass absent.	Urinalysis.	Trigone mass.	CT and endoscopies to rule out primaries.	TXN1	Poorly differentiated SRCC. Positive lymph nodes.	Radical cystoprostatectomy , ileal loop.	Alive 11 months. No evidence of disease.

5	69 M	Abdominal mass absent.	Urinalysis.	Lateral posterior wall mass.	CT and endoscopies to rule out primaries.	TXN1	SRCC with cystitis glandularis. Positive lymph nodes.	Radical cystoprostatectomy, ileal loop.	Dead 24 months. Dead of disease.
6	66 M	Abdominal mass absent.	Urinalysis.	Bladder neck mass.	CT and endoscopies to rule out primaries.	TXN1	Poorly differentiated SRCC. Positive lymph nodes.	Radical cystoprostatectomy, ileal loop + radiotherapy.	Dead 14 months. Dead of disease.
7	71 M	Abdominal mass absent.	Urinalysis.	Diverticulum.	CT and endoscopies to rule out primaries.	TX	Well-differentiated SRCC.	Diverticulectomy.	Dead 11 months. Dead of disease.
Morelli 2006	60 M	Haematuria.	CEA 21.7 ng/mL.	White sessile tumour anterior bladder wall, incomplete obstruction of left ureteral orifice.	USKUB – left hydronephrosis. CT-IVP – left hydro, non-functioning left kidney, left bladder wall defect. CT and endoscopies to rule out primaries.	T3b	PAS+.	Radical cystectomy, left nephrectomy, BPLND. Chemotherapy to treat recurrence (5-FU, oxaliplatin and folinic acid).	Dead 41. Recurrence in stomach, colon and rectum @ 18 months post-op. Recurrence 12 months post-chemo → death.
DeFillipo 1987	67 M	Urgency, dysuria, frequency, haematuria.	NA	Tumour with finger projections along right lateral wall and	CT and endoscopies to rule out primaries.	T4N0 M1	Infiltrative signet cell carcinoma in subepithelial connective tissue.	Radical cystectomy, ileal conduit. Radiotherapy.	Dead 4. Metastasis to lungs, bone and pelvis.

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				ulceration lesion in dome.					
Boukettaya 2014									
1	72 M	Haematuria, urgency, pollakiuria.	NA	Solid mass in left side wall.	CT and US – bilateral hydroureteronephrosis with thickening of urinary bladder wall. CT and endoscopies to rule out primaries.	pT3N0M0	40%; Round-cell aspect of signet ring, colloid component, invasive, extending into perivesical fat with carcinomatous lymphangitis and nerve sheath involvement. CK7+ CK20-.	Radical cystoprostatectomy. Radiotherapy @ 16 months.	Alive 36. Recurrence in anterior urethra @ 16 months.
2	64 M	Haematuria.	NA	Pseudopolypoid mass on left posterolateral wall.	US – left hydronureterone phrosis and infiltrating mass in posterolateral wall. CT – peritoneal effusion, no peritoneal carcinomatosis. CT and endoscopies to rule out primaries.	T4	Poorly differentiated invasive signet ring cell. Ascitic fluid cytology – neoplastic cells.	TURBT. Palliation.	Dead 5.
Manassero 2009	65 M	Microhaematuria.	Annual sonography of kidneys,	Hyperaemic area on	CT – irregular bladder wall.	T1	Signet ring cell with marked proliferative activity.	TURBT.	Alive 24.

		Concurrent diagnosis of penile SCC requiring partial penectomy. Post-kidney transplant for chronic pyelonephritis, ex-smoker.	bladder and prostate PSA UA urine cytology.	posterior bladder wall.	CT and endoscopies to rule out primaries.		PAS+ PAS-D+.	Intravesical chemotherapy – mytomicin C for 6 weeks then 11 months.	
Kim 2009	43 F	Haematuria. OE: bilateral inguinal lymphadenopathy, abdominal and gynaecological exam NAD.	Hb 89 CEA 42.8 ng/mL CA-125 38.8 U/mL.	Multiple floating tissues, large mass in anterior and posterior wall.	CT-IVP – diffuse lobulated wall thickening and enhancement of bladder, pericystic fat plane infiltration, bilateral hydronephrosis. CT-AP – multiple necrotizing common iliac, external iliac, internal iliac and bilateral inguinal lymph nodes; 4 mm enhancing nodule in hepatic dome. CT and endoscopies to rule out primaries.	T4N1 M0	Signet ring cells, round and hyperchromatic cells with prominent nucleoli with variable cytoplasm and pools of mucin. PAS + CK7+ CK20+.	TURBT Systemic chemotherapy – cisplatin, mitomycin C and etoposide. Bilateral nephrostomies.	Dead 4 months.

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Yamamoto 2001	56 M	Oliguria/retention. Right nephrostomy due to obstructive uropathy.	CEA 19.2 ng/mL, Cr 6.0 mg/dL.	White-coloured, non-papillary tumour extending from trigone to neck of urinary bladder and incompletely obstructing ureteral orifices.	CT-AP confirmed cystoscopy findings, no LN involvement. CT and endoscopies to rule out primaries.	pT3b, pN2, pMx	Diffuse infiltration of tumour cells with signet ring cells invading deeper layers. CEA+ PAS+.	Radical cystectomy and ileal conduit. Refused chemotherapy.	Dead 8 month.
Blute 1989									
1	65 F	4 months urgency and frequency.	Urine cytology negative.	Bullous erythematous edema, left posterior wall.	Mass on CT-IVP. CT and endoscopies to rule out primaries.	TxN1 M1	Linitis plastica, grade 4 signet ring cell adenocarcinoma.	Cystectomy, palliative diversion and radiotherapy 5000 cGy.	Dead 27 months. Bowel obstruction from metastatic deposits.
2	81 M	4 months urgency and frequency.	Urine cytology positive.	Punctate haemorrhagic area right lateral wall, bullous edema.	Mass on CT-IVP. CT and endoscopies to rule out primaries.	TxN1 M1	Grade 4 signet ring cell adenocarcinoma.	Chemotherapy, radiotherapy 5000 cGy.	LTF 9 months.
3	61 M	3 months urgency, frequency and suprapubic pain.	Urine cytology negative.	Irregular erythematous mucosa with bullous edema, right lateral wall.	Mass on CT-IVP. CT and endoscopies to rule out primaries.	TxN1 M1	Grade 4 signet ring cell adenocarcinoma.	Anterior exenteration, chemotherapy.	Alive 11 months with recurrence.

4	56 F	3 months urgency and frequency.	Urine cytology negative.	Erythematous bullous edema, right bladder wall.	Mass on CT-IVP. CT and endoscopies to rule out primaries.	TxN1 M1	Linitis plastica, grade 4 signet ring cell adenocarcinoma.	Anterior exenteration.	Dead 5 months. Bowel obstruction from metastatic deposits.
5	56 M	6 months urgency, frequency, suprapubic pain, left flank pain, 4.5 kg weight loss, difficulty in defecation.	Urine cytology negative.	Erythematous irregular left bladder wall.	Mass on CT-IVP. CT and endoscopies to rule out primaries.	TxN1 M1	Colon serosal infiltration (bladder linitis plastica by inspection), grade 4 signet ring cell adenocarcinoma.	Palliative right hemicolectomy with colostomy, radiotherapy 5000 cGy, interferon.	Alive 9 months with disease.
Tanaka 1987	62 M Japanese	3-month hx intermittent, painless macrohaematuria.	UA – red cells, white cells and bacteria. Bladder washing/urine cytology positive signet ring cells.	Papillary tumour near right ureteral orifice.	CT-IVP – bladder filling defect. CT and endoscopies to rule out primaries.	T2N1 M0	Reddish and finely granular mucosal surface around right UO. Signet-ring neoplastic cells. Infiltrated beneath the urothelium, involving entire thickness of bladder. Metastasis in 1/3 left inguinal lymph nodes. PAS+.	Radical cystectomy, ureterostomy and bilateral ureterocutaneostomy, chemotherapy (adriamycin, 5-FU, mitomycin C and OK-432). 17 months after surgery, chemotherapy (mitomycin C, PEP, oncobin, endoxan: 6 cure), radiotherapy.	Recurrence at 17 months – left inguinal lymphadenopathy. Alive 23 months.
Ponz 1985	65 M Caucasian	1-year low abdominal pain, urgency, severe	Urine cytology NAD.	Small bladder capacity (40–50 ml).	CT-IVP – bilateral hydroureteronep	T4N1 M1	Signet ring cell carcinoma. No malignant transformation in prostate gland. Diffuse	Attempted radical cystectomy (unable due to fixed	Dead 11 months.

		frequency and nocturia. No haematuria. 2-month hx of constipation. OE: mildly enlarged, uniformly hard and non-tender prostate, discrete bilateral flank tenderness. BG: Billroth's II partial gastrectomy for perforated duodenal ulcer 30 years ago.		Mamelonated mucosa and entire base and trigone irregular and oedematous.	hrosis, bladder uniformly thickened, infiltration of seminal vesicles. Metastatic diagnostic study NAD. CT and endoscopies to rule out primaries. AUTOPSY – metastatic deposits in adrenals, pancreas, stomach, prostate, seminal vesicles, rectum.		infiltration of submucosa and muscular layer. PAS+ Mucicarmine stains.	bladder to surrounding tissues). Diverting colostomy with colo-uretero anastomosis.	Readmitted with bilateral pneumonia and died.
Rosas-Uribe 1969 (1)	65 M Cauc asian	1-year low abdominal pain, urgency, severe frequency and nocturia. No haematuria. 2-month hx of constipation. OE: mildly enlarged, uniformly hard and non-tender	Urine cytology NAD.	Small bladder capacity (40–50 ml). Mamelonated mucosa and entire base and trigone irregular and oedematous.	CT-IVP – bilateral hydroureteronep hrosis, bladder uniformly thickened, infiltration of seminal vesicles. Metastatic diagnostic study NAD.	T4N1 M1	Signet ring cell carcinoma. No malignant transformation in prostate gland. Diffuse infiltration of submucosa and muscular layer. PAS+ mucicarmine stains.	Attempted radical cystectomy (unable due to fixed bladder to surrounding tissues). Diverting colostomy with colo-uretero anastomosis.	Dead 11 months. Readmitted with bilateral pneumonia and died.

		prostate, discrete bilateral flank tenderness. BG: Billroth's II partial gastrectomy for perforated duodenal ulcer 30 years ago.			CT and endoscopies to rule out primaries. AUTOPSY – metastatic deposits in adrenals, pancreas, stomach, prostate, seminal vesicles, rectum.				
Kume 2000	72 M	Asymptomatic haematuria.	NAD	5 cm pedunculated tumour, nodular surface on left lateral wall.	CT abdomen NAD. CT and endoscopies to rule out primaries.	T1N0 M0	TURBT – poorly differentiated adenocarcinoma mainly composed of SRCs with some TCC. Final – nodular, pedunculated and infiltration of submucosal layer with predominantly SRCs. Ureteral component was TCC with no adenocarcinoma.	Radical cystoprostatectomy with right nephrouretectomy (1 cm mass palpated mid ureter intraoperatively). Ileal neobladder.	Alive 78 months. No recurrence.
Braun 1981	45 M	Evaluation of recurrent haemorrhagic cystitis of 8 months. Exam NAD. BG: T3 SCI.	Urine MCS – pseudomonas and e. coli. Hb 11 g/dL.	Diffuse mucosal edema with hypertrophy of mucosal folds and intense hyperaemia in trigone.	CT-IVP NAD. "complete diagnostic workup to rule out extravesical neoplasms was negative".	T2Nx Mx	Bladder biopsy – SR cells diffusely infiltrating subepithelial stroma. Repeat biopsy @ 2 weeks – new ulcerated lesion with infiltrating carcinoma. Final path – contracted and irregular in contour.	Radical cystectomy with ileal conduit.	Alive 36 months. No recurrence or metastasis.

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							Markedly thickened. Infiltrative tumour dissecting through muscularis. Mucin-positive.		
Bodi 2004	60 M	2-week hx of headache and neck pain with nausea and vomiting. Exam: 10 kg weight loss.	All tumour markers negative apart from CA199 2616 kU/I.	TURBT 9 months earlier. No macroscopic description.	CXR, CT-chest and abdomen NAD.	T1N1 M1	TURBT – TCC G3PT1 but with SRCs. LP CSF – CAM5.2 +, EMA +, LCA -, CD68 -, HMB45 -. AUTOPSY – widespread carcinomatous meningitis. CAM5.2 +, PAS +, Alcian blue +. Many SRCs. Pelvic LNs SRCs with no TCC component.	TURBT 9 months prior to admission. Lumbar puncture to relieve raised ICP.	Dead 10 months from metastasis to brain.
Wong 1999	84 M	3-week hx of oliguria and LUTS. 3 months of anorexia, fatigue and constipation. Exam: DRE – flat prostate with marked induration of rectal wall circumferentially. Bilateral LL pitting edema. BG: HTN, MI, BPH (TURP)	Hb 114 g/L, Hematocrit 0.33, PSA 3.3 ug/L BUN 25.7 mmol/L, Cr 313 umol/L. CEA 12.8 ug/L. Urine cytology atypical cells.	No obvious mucosal lesions. Bullous edema on bladder floor and posterior wall. UOs not notified.	CXR NAD Bone scan NAD. Colonoscopy – external compression of rectum @ 10 cm. CT and endoscopies to rule out primaries.	T1Nx Mx	Biopsy bladder – diffuse infiltration of lamina propria with round to polygonal tumour cells. Eccentric nuclear positioning and presence of mucin. SRCs. PAS + AE1/AE3 + CEA + PSA – Biopsy rectum – poorly differentiated SRC with sparing of mucosa.	Right nephrostomy tube. Refused further treatment.	Dead 3 months.

Critical Analysis of Papers

Horne 1987	63 M White	2-month urinary frequency, urgency, urge incontinence. Exam: DRE hard rectal mass with rectal-shelf. No intrinsic lesion.	Cr 3.0 mg/dL anaemia.	Left trigonal papillary tumour and thickened oedematous posterior wall and dome.	Excretory IVP – bilateral hydronephrosis secondary to distal ureteric obstruction. CT-AP: no mass, incidental AAA. CT and endoscopies to rule out primaries.	T4Nx M1	TURBT – non-invasive grade II/III TCC and invasive SRC of dome, posterior bladder wall, left trigone and posterior bladder neck.	TURBT. Exploratory laparotomy – unresectable, rock-hard mass posterior bladder and anterior rectal wall, iliac vessels and small bowel mesentery. End-to-end transureterouretero stomy. Radiotherapy 3000 rad of Cobalt-60.	Dead 10 months. Recurrence of pain and left LL edema 2 months post-laparotomy requiring radiotherapy.
Hirano 2002	65 M	Gross haematuria.	Urine cytology class V.	White, sessile tumour extending from left bladder wall to trigone and incompletely obstructing left ureteric orifice.	US – left hydronephrosis. CT-IVP – invasive bladder tumour. MRI – invasive bladder tumour. CT and endoscopies to rule out primaries.	T3bN 0M0	Biopsy – mucin forming SRCs. With high grade TCC also. PAS +.	Refused total cystectomy. Arterial carboplatin (3 courses at 3-week intervals).	Alive 44 months. Complete remission on CT, MRI and cystoscopy, biopsy 1 month after chemo.
DeMay 1985	65 F	18 months painless haematuria.	Urine cytology malignant SR cells.	Large tumour on anterior bladder wall and	IVP – bladder filling defects.	T3N1 M0	SRC. Mucosal surface granular and red. Neoplastic infiltration submucosally and involved entire thickness of	Radical cystectomy with bilateral ureterosigmoidosto mies.	Alive 6 months. No recurrence.

		Smoked 1.5 packets per day for many years, previous hysterectomy.		sweeping down over dome and down posterior wall.	CT-AP – extension of neoplasm to abdominal wall vs. scarring from hysterectomy. CT and barium enema to rule out primaries.		bladder and extending into perivesical tissues. 1 of 3 left obturator LNs involved.		
DeTure 1975	62 M Black	8 months poor stream, hesitancy, straining and nocturia. Several weeks postprandial nausea and vomiting. RUQ pain with radiation to right renal angle Exam: 10-pound weight loss, hypertension, holosystolic murmur. Prostrate enlarged and rubbery. Right renal angle tenderness.	Hb 12.5 g/ml. BUN 138 mg, Cr 12.1 mg/ml. UA – microscopic haematuria, gross pyuria and proteinuria. Urine cytology negative. Stool guaiac negative.	Extensive, fungating, exophytic lesion on trigone, posterior wall and dome. Both ureteral orifices covered.	Upper GI series – pyloric narrowing. Gastroscopy – negative for tumour or ulcer. Small bowel XR, barium enema and sigmoidoscopy negative.	T2N0 M0	SRC of varying degrees of differentiation. Final: Two fungating papillary tumours from mucosa. One on trigone (5x5x1 cm, poorly differentiated with primitive mucin-producing glands lined by pleomorphic, poorly differentiated epithelium). and one on posterior wall (4x3x0.7 cm, better differentiated with malignant cells lined with basal nuclei and abundant apical, mucin-containing cytoplasm; muscle-invasive). Remaining mucosa was highly abnormal – translucent, grey and glistening. Metaplastic	Exploratory laparotomy. Bilateral end cutaneous ureterostomies. Radiotherapy 2000. Radical Cystoprostatectomy 4 days after. 14 months later, ileoconduit formed. 8 months later, left nephrostomy for left ureteroileal anastomosis obstruction.	Dead 30 months from myocardial infarction. Non-cancer related.

		BG: 45 pack year hx. Worked as farmer and gardener all his life.					colonic-type mucosa with benign gland).		
Naeim 1972	52 M	1-day hx haematuria. 5-week hx nocturia, urgency, frequency and 2 episodes of haematuria.	UA – erythrocytes.	Pedunculated lesion of anterior wall to left of VUJ. Smaller sessile lesion on right bladder neck.	Bone survey, upper GI series, barium enema and gallbladder series negative.	TXN XM0	Biopsy – TCC with occasional SRCs. PAS +. Final – pedunculated, tan, rubbery polypoid tumour 5x5x10 mm on lower third of anterior wall. Tumour located in lamina propria.	Neoadjuvant radiotherapy followed by radical cystoprostatectomy and ileal conduit.	Alive on discharge. No follow-up.
Corwin 1971	56 F White	10 months frequency, nocturia, urgency and dribbling. Painless vaginal bleeding, progressive weight loss and anorexia. Exam: huge, semi-mobile, painful suprapubic mass. Pelvic exam revealed small uterus fixed to undersurface of pelvic mass.		Neoplastic mass invading dome, floor and right lateral wall.	"Search for metastasis were negative." Excretory urography – huge irregular intravesical filling defect and bilateral hydroureteronephrosis.	T4N0 M0	Biopsy – mucinous adenocarcinoma, signet ring cell variant. Final – large sessile mass in bladder occupying fundus, posterior and right lateral wall. Muscular wall completely replaced with extension to surrounding fatty tissue. Urothelium malignancy predominantly composed of signet ring cells. Abundant clear cytoplasm and deeply stained eccentric and semilunar nuclei in sheets and nests invading entire thickness of bladder wall.	Radical cystectomy and TABHSO with left cutaneous triangular flap ureteroureterostomy. Radiotherapy 3500 Rads to pelvis.	Alive 10 months with no metastasis or recurrence.

		BG: Heavy smoker and alcoholic.					Ovarian stroma and small vessels contained small neoplastic cells and signet ring cells.		
Choi 1984									
1	64 M	3-week hx urinary frequency, urgency, dysuria and suprapubic fullness. 2-day hx of painless haematuria. Exam – firm suprapubic mass.	UA – leucocytes, erythrocytes. Cr 459. CEA 130 ng/ml.	Diffuse bladder mucosal edema and irregularity of anterior wall and trigone.	CT-AP – thick-walled urinary bladder, more prominent on left side, bilateral hydronephrosis. GI primary ruled out via endoscopy and CT.	TXN XM1	Biopsy – SRCC infiltrating submucosa. Final – diffuse, marked thickening and stiffening of bladder wall. SRCC, full thickness, mucin-positive.	Percutaneous bilateral nephrostomies Radical cystoprostatectomy, pelvic lymph node dissection and ileal conduit.	Dead 0.5 months. 15 days post-op. Extensive peritoneal carcinomatosis on exploratory laparotomy.
2	83 M	Admitted for right inguinal hernia repair. 2-week hx of LUTS and haematuria. Exam – no masses.	UA – leucocytes, erythrocytes.	3 cm nodular mass right bladder.	GI primary ruled out via endoscopy and CT.	TXN XMX	Biopsy – SRCC, mucincarmine +.	Radiotherapy.	Dead 3 months, unknown cause.
Marino 2005	65 M	Haematuria, anuria and renal failure with bilateral hydronephrosis.	NA	Multiple non-papillary broad-based neoformations extending from trigone	CT – diffuse thickness of the bladder wall with suspected invasion of the	T4aN 2M0	Biopsy – SRC adenocarcinoma. Final – Grossly bladder substituted by granular, red-	Radical cystectomy, urethrectomy and urinary continent cutaneous diversion (ileal T pouch).	Alive 12 months No recurrence or metastases.

				to neck of black and obstructing the ureteral orifices.	anterior rectal wall. GI primary ruled out via endoscopy.		grey formation in infiltrating fashion (linitis plastica). Microscopic – SRC without TCC component. Isolated or small nests of cancer cells infiltrating as far as perivesical fat with prostatic extension and left ductus deferens invasion. TWO right iliac nodal metastases present. PAS + Pancytokeratins + PSA – Chromogranin – Kappa – Lambda –	Small tract of anterior rectal wall resected as suspected for infiltration.	
Ohnita 1998	85 F	Azotaemia and bilateral hydronephrosis.	CEA 10.7 ng/ml, CA50 223 units/ml, CA19.9 193.2 units/ml.	Nonpapillary mass on right wall and papillary tumour beside left ureteral orifice.	Autopsy – no digestive organ adenocarcinoma.	T2N2 M1	Autopsy – SRC diffusely spread in vesical mucosa and invaded muscle layer. Small metastatic tumours in left ureter, para-aortic lymph nodes and lung.	Nephrostomies (poor health excluded all surgical treatment).	Dead 3 months.
Azadeh 1989	46 M Filipino	1-month terminal haematuria, frequency and strangury. Passed 2 stones 1 week earlier.	UA – 100 RBCS/HPF. MSU NAD.	Large growth with necrotic areas anterior wall and dome. Rest of bladder normal.	IVU – normal upper tracts, irregularity anterior wall and large PVR.	T3N0 M0	Biopsy – SRC. Final – Diffusely infiltrated especially at dome. Linitis plastica appearance.	Total cystectomy and ileal conduit.	Dead 10 months. Returned to Philippines. Unknown cause of death.

		OE: NAD. prostate NAD.	Urine cytology – SRC.		Barium meal, barium enema and CXR NAD GI malignancy ruled out.		Pure SRCs infiltrating full wall thickness into perivesicular fat. Lakes of mucin. Prostate and SV free of tumour. PAS + Mucicarcmine + Cytokeratin + CEA +		
Romics 2008	45 F	Haematuria, frequency, abdominal pain and irritable voiding. PMH: caesarean section, iliac vein thrombosis postoperatively.	USKUB moderate dilatation of left renal pelvis and 2 cm thickening of left bladder wall.	Tumour with wide, necrotic surface.	GI malignancy ruled out with CT and gascolon.	T3bN 0M0	Biopsy – SRC. Final – T3b stage SRC infiltrating perivesical fat. No metastasis to regional lymph nodes or surrounding organs.	Total cystectomy. Adjuvant chemotherapy – 4 cycles cisplatin and fluorouracil.	Alive 60 months. PET @ 24 months – no evidence of malignancy.

Critical Analysis of Papers

Supplementary Data S2 – Critical analysis of the papers

Source	Review of Paper	Level of Evidence
Bouhajja 2019	Two case reports. First case report did not rule out GI primaries. Second case report included as had good clinical details, including clinical findings, treatment, and survival. Also ruled out GI primary.	4
Jayaraja 2017	Single case report. Good description of examination and radiological findings. In-depth histology, including sample images. Outlines treatment and follow-up duration, including monitoring for recurrence.	4
Thomas 2008	25 case reports, with most data compiled into a simple table detailing age + sex, % of signet ring cells, surgical management and outcome. Unfortunately, no details given on presentation, radiology or any immunohistochemical findings. GI screening (upper and lower endoscopy) was reported to be performed in all cases, as written during the article.	4
El Ammari 2013	Single case report. Good description of ethnicity, family history and presentation. Nil biochemical values given for tumour markers. Brief description of histology, with no immunohistochemistry reported. Thorough description of treatment and rationale.	4
Fiter 1993	Three case reports, one of which was not a primary urinary signet ring but a gastrointestinal metastasis. Very brief description of case reports – mostly lacking data on the histology and no mention of immunohistochemistry. Good description of imaging findings. Comprehensive lit review; however, little further detail on the three case reports.	4
Erdogru 1995	Two case reports, very similar presentations. Good description of presenting complaint and initial investigations, as well as subsequent imaging. Brief description of histology, but no histochemistry. Good description of initial surgery and treatment rationale, but no further follow-up/treatment described immediately post-surgery.	4
Ivanov 2022	Comprehensive case report (1 case) and discussion – including all relevant radiological and pathological data (including immunohistochemistry) and treatment (albeit limited detail given for chemotherapy regimen).	4
Pugashetti 2015	Case report. Minimal immunochemical examination. Detailed entry. GI primary ruled out.	4
Allen 1997	Case report. No immunochemical examination. Detailed entry. GI primary ruled out.	4
Allameh 2017	Case report. Minimal immunochemical examination. Detailed entry. GI primary ruled out.	4
Torenbeek 1996	Retrospective review of single institution records. Other primaries ruled out.	4
Ohtsuki 2010	Case report. 4-month follow-up only. GI primary ruled out.	4
Burnett 1991	Large retrospective review. 9 cases. GI workup completed. No immunochemical examination.	4
Morelli 2006	Case report. Did not include much on immunohistochemical staining. GI primary ruled out.	4
DeFillipo 1987	Case series. 3 cases. However, only 1 case fit inclusion criteria. GI primary ruled out.	4
Boukettaya 2014	Case series. 2 cases. No immunochemical examination. GI primary ruled out.	4
Manassero 2009	Case report. Good case. Detailed entry. Detailed immunochemical examination. GI primary ruled out.	4
Kim 2009	Case report. Good case. Detailed clinical history. Minimal immunochemical examination. GI primary ruled out.	4
Yamamoto 2001	Case report. Good case. Detailed clinical history. Minimal immunochemical examination. GI primary ruled out.	4
Blute 1989	5 cases. Good cases. Detailed clinical history. Minimal immunochemical examination. GI primary ruled out.	4
Tanaka 1987	Case report. Good case. Detailed clinical history. Minimal immunochemical examination. GI primary ruled out.	4
Ponz 1985	Case report. Good case. Detailed clinical history. Minimal immunochemical examination. GI primary ruled out.	4
Kume 2000	Case report. Good case. Detailed clinical history. Minimal immunochemical examination. GI primary ruled out.	4
Braun 1981	Case report. Good case. Detailed clinical history. Minimal immunochemical examination. GI primary ruled out.	4

Critical Analysis of Papers

Bodi 2004	Case report. Good case. Detailed clinical history. Minimal immunochemical examination. Did not rule out GI primary; however, was an autopsy, so primary GI malignancy ruled out post-mortem.	4
Wong 1999	Case report. Good case. Detailed clinical history. Moderately detailed immunochemical examination. GI primary ruled out.	4
Horne 1987	Case report. Good case. Detailed clinical history. No immunochemical examination. GI primary ruled out.	4
Hirano 2002	Case report. Good case. Detailed clinical history. Minimal immunochemical examination. GI primary ruled out.	4
DeMay 1985	Case report. Good case. Detailed clinical history. No immunochemical examination. GI primary ruled out.	4
DeTure 1975	Case report. Good case. Detailed clinical history. No immunochemical examination. GI primary ruled out.	4
Naeim 1972	Case report. Detailed clinical history. No immunochemical examination. GI primary ruled out.	4
Corwin 1971	Case report. Clinical history detailed. States ruled out GI primary but does not specify how. No immunochemical examination.	4
Choi 1984	3 cases. Only 2 fit inclusion criteria. No immunochemical examination. GI primary ruled out.	4
Marino 2005	Case report. Good case. Detailed clinical history. Minimal immunochemical examination. GI primary ruled out.	4
Ohnita 1998	Case report. Good case. Minimal clinical history. No immunochemical examination. Did not rule out GI primary; however, was an autopsy, thus primary GI malignancy ruled out post-mortem.	4
Rosas-Uribe 1969	1 of 2 cases fit inclusion criteria. Case report. Detailed clinical history. GI workup performed with radiography only. No endoscopy. However, GI malignancy ruled out post-mortem.	4
Azadeh 1989	Case report. Good case. Detailed clinical history. Minimal immunochemical examination. GI primary ruled out.	4
Romics 2008	Case report. Good case. Detailed clinical history. No immunochemical examination. GI primary ruled out.	4