

# Recurrent Tumours in Orthotopic Neobladder Using Isolated Gut Segment Post Radical Cystectomy for Urothelial Carcinoma: a Systematic Review

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**Citation:** Arya Bahadori, Gerard Bray (2023) Recurrent tumours in orthotopic neobladder using isolated gut segment post radical cystectomy for urothelial Carcinoma: A systematic review. J Surg Oper Care 7(2): 101

## Abstract

**Background:** Urothelial carcinoma recurrence of an orthotopic neobladder created from bowel segment is a rare occurrence. The growing usage of bowel segments to create neobladder following cystectomy for urinary diversion is growing yet there still remains a large gap in the literature about recurrence in neobladder. We carry out the first systematic review to outline current details of urothelial cancer recurrences in a neobladder, diagnostic approach, management and long term prognosis.

**Method:** We carried out a systematic review searching databases Pubmed (MEDLINE), Scopus and Web of Science. Only studies reporting on urothelial carcinoma recurrence of the neobladder with or without multi-focal disease were reported. All studies were case reports including one patient each. A quality assessment tool was utilised to ensure all studies met quality standards.

**Results:** Fifteen studies were included in the systematic review meeting inclusion criteria. Fourteen of these studies were cases in men where pT3 disease was the most prevalent (29%). The most common symptomology was macroscopic haematuria seen in 8 patients (53.33%). Management varied among cases and including adjuvant chemotherapy regimens and surgical interventions consisting of endoscopic resection to robotic neocystectomy and nephroureterectomy. Follow up period for these patients was up to 38 months and 55% of patients did not see a recurrence.

**Conclusion:** The nature of recurrence is hypothesised to be due to seeding of urothelial cells into the non-urothelial surfaces compatible for both implantation and growth. We present the first systematic review to report on recurrence rates and details of diagnosis and outcomes of various management regimes for urothelial carcinoma of the neobladder.

**Keywords:** Urothelial carcinoma; neobladder; recurrence; orthotopic

## Introduction

Urothelial carcinoma (UC) of the bladder accounts for an estimated 200 000 deaths worldwide annually. One third of UCs are invasive on initial diagnosis which require multi-modal and invasive major surgery. The remaining non-invasive subtypes require chronic surveillance and investigations that can place a burden on the health care system [1].

Unfortunately, even with optimal management, UCs are well known for being multifocal with 70% chance of cancer recurrence. Radical cystectomy and urinary diversion is the preferred method for management of muscle invasive urothelial carcinoma. In urinary diversion using small or large bowel, secondary malignancies such as adenocarcinomas from irritation of the intestinal mucosa from contact with urine is not uncommon. These rates have been reported up to 25% and 0.5% for colon segments and ileal segments respectively [2].

Urethral, upper urinary tract and ureteroenteric anastomotic recurrences are common and have been widely reported. The prevalence of upper urinary tract recurrence after cystectomy ranges from 0.75% to 6.4%. Urethral recurrence occurs in 4.4-7% of cases. Since the 1980s, continent urinary diversion as a catheterisable pouch or as an orthotopic neobladder substitution with various techniques has become popular due to the favourable functional outcomes and better quality of life. [3] However, despite this growing demand for orthotopic neobladder formation due to cystectomy, there is still no current systematic review on UC recurrence rates or the ideal approaches to managing them.

The current systematic review aims to fill a large gap in the literature by critically reviewing the cases of UC recurrence of orthotopic neobladders following cystectomy. Herein, we outline recurrence rates, commonly presenting symptoms, ideal investigations and ideal management for these cases.

## Methods and Materials

We carried out a systematic review using the databases Pubmed (MEDLINE), Scopus and Web of Science. This systematic review was conducted in accordance with the preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The published study protocol was registered in the PROSPERO database (420660).

### Search Strategy

The systematic review search process was undertaken independently by two authors A.B. and G.B. Databases Pubmed (MEDLINE), Scopus and Web of Science were utilised including the following key words; “urothelial carcinoma” or “transitional cell carcinoma” or “cancer” or “recurrence” and “neobladder” or “orthotopic neobladder” or “ileum” or “colon” were used to extract relevant papers. Timeframe was from database conception to January 2023. The included articles’ reference list were also examined for additional relevant papers.

### Quality Assessment

This systematic review utilised the Joanna Briggs Institute (JBI) critical appraisal tool for case reports in systematic reviews. The tool utilizes an eight point checklist to create an overall appraisal of each case report. [4] This was undertaken by author A.B. during data collection as well as a random sample being cross checked by G.B. Only case reports which had an overall high-quality appraisal were included in the systematic review.

### Inclusion/Exclusion Criteria

Two authors independently extracted the data into Microsoft Excel. Studies were included if they reported on a case of UC recur-

rence in an orthotopic neobladder consisting of small or large bowel. Neobladder formation must be due to prior cystectomy for muscle invasive UC (pathological stage T2 or greater). Papers in language other than English were excluded. Non-urothelial recurrences such as Adenocarcinomas or Neuroendocrine carcinoids were excluded. PRISMA flow diagram can be seen in figure 1.

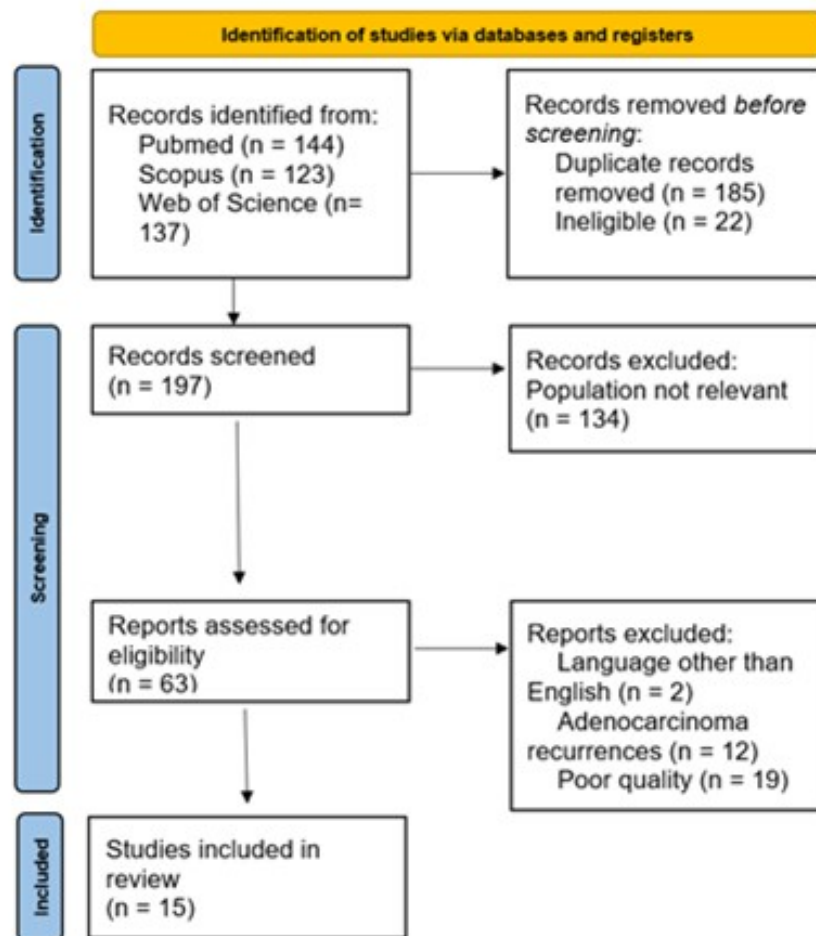


Figure 1: PRISMA flow diagram

## Outcomes

Primary endpoints were recurrences of UC in an orthotopic neobladder of the included studies. Secondary end points were patient characteristics (age, sex, ethnicity), symptoms, laboratory findings, imaging modalities, image findings including any lesions, initial and definitive management, follow up and clinical outcomes were extracted. Meta-analysis was not conducted due to heterogeneity of papers.

## Results

A total of 15 articles were eligible for inclusion in the analysis. All articles were case reports including one patient each, of high quality and met inclusion criteria. Studies are summarized in table 1. The earliest reported case was published in 1985 whilst the most recent case was in 2010. All 15 articles reported cases of UC recurrence in the orthotopic neobladder with or without upper tract and/or urethral involvement.

## Patient Demographics

Out of 15 patients 14 were male while only 1 patient was a female. Patients receiving orthotopic neobladder were between 40 to 78 years old with the mean age of 64.1 years. Europe had the most reported cases with 7 (46.6%), followed by Asia with 4 cases, North America with 3 cases and only 1 reported case in Africa as seen in table 1.

Paper	M/F	Age	Year	Study origin
Pardalasis et al [5]	M	56	2008	Europe
Cherbanyk et al [6]	M	66	2004	Europe
Doshi et al [7]	M	71	NA	North America
Groen et al [8]	M	65	2004	Europe
Cakmak et al [9]	M	40	2002	Europe
Kawamoto et al [10]	M	61	NA	Asia
Ide et al [11]	M	73	1993	Asia
Moore et al [12]	M	62	NA	North America
Sanchez et al [13]	M	57	1991	Europe
Hadzi-Djokic [14]	M	65	1985	Europe
Moeen [15]	F	59	2010	Africa
Yamashita et al [16]	M	66	2005	Asia
Hara et al [17]	M	67	1994	Asia
Herawi et al [18]	M	60	NA	North America
Dadikhi et al [19]	M	78	2009	Europe

**Table 1:** Summary of fifteen articles included in systematic review

## Initial UC Staging Characteristics

General data and pathological characteristics are summarized in the table 2 below. The most common stage of UC diagnosed in males was pT3 (four cases). Nodal status was not always recorded but of the three reported; only one had N1 staging. The staging of UC in the only female article was pT1 with no nodal involvement.

Variable	Male (n=14)	Female (n=1)
Age, years	62.7 (40-73)	59 (59)
Pathological stage of bladder cancer		
PTis	1	
pTa		
pT1	2	1
pT2	3	
pT3	4	
pT4	1	
Data unavailable		

Pathological nodal status		
N0	8	1
N1	1	
N2	1	
N3		
NX	1	
Unknown	3	0

**Table 2:** Pathological staging of initial UC diagnosis by gender.

## Initial Management

All cases included, initially underwent radical cystectomy and neobladder formation. Only 1 case was robotically assisted while the other 14 cases were open procedures. 3 patients had extended bilateral lymphadenectomy. In the majority (80%) of cases an Ileal segment was used for formation of the neobladder however in 2 patient an Ileocolonic segment was used while 1 patient received Sigmoid Colon segment. 1 patient received adjuvant chemotherapy with 3 courses of Cisplatin and Gemcitabine and 1 patient received Methotrexate, Vinblastine, Doxorubicin, and Cisplatin however this was stopped after 2 cycles due to side effects. The median time of follow up was 108 months (1-132 months). The surveillance information was generally not well reported however in some cases it was mentioned that patients were followed up with Computersied Tomography (CT) IVP, Urine Cytology and Flexible cystoscopy at regular intervals.

Paper	Histology	Neoadjuvant chemotherapy	Cystectomy and Neobladder procedure	TNM
Pardalasis et al [5]	HGT1	None	Robotic Cystoprosatatectomy, bilateral extended lymphadenectomy, ileal neobladder	PT1N0M0
Cherbanyk et al [6]	Grade II- III UC	None	Radical Cystoprostectomy with ileal neobladder	pT3aN1M0
Doshi et al [7]	HG UC+CIS	None	Radical Cystoprostectomy, extended lymphadenectomy with ileal neobladder	pT3aN0Mx
Groen et al [8]	MIBC	four cycles Gemcitabine / Cisplatinum/ Taxol	Radical Cystoprostectomy, extended lymphadenectomy with ileal neobladder	pT4aN2M1
Cakmak et al [9]	HGT1	None	Radical Cystoprostectomy with ileal neobladder	pT1N0M0
Kawamoto et al [10]	MIBC	None	Radical cystoprostectomy, struder ileal neobladder	pTisN0M0
Ide et al [11]	NA	None	Radical Cystectomy and ileal neobladder	pT1N0M0
Moore et al [12]	MIBC	None	Radical Cystoprostectomy with ileal neobladder	pT3N0M0
Sanchez et al [13]	MIBC	None	NA	NA
Hadzi-Djokic [14]	MIBC	None	Radical Cystoprostectomy with ileal neobladder	T2N0M0

Moeen [15]	MIBC	None	Radical cystectomy with ileal neobladder	pT2N0M0
Yamashita et al [16]	MIBC	None	Radical Cystoprostatectomy with ileal neobladder	pT3aN0M0
Hara et al [17]	MIBC	None	Radical Cystectomy with sigmoid colon neobladder	NA
Herawi et al [18]	Recurrent LGTa	None	Radical Cystectomy with ileocolonic neobladder	NA
Dadikhi et al [19]	MIBC	None	Radical Cystoprostatectomy with ileal neobladder	pT2aN0M0

**Table 3:** Summary of multi-modal management received in each study

### Clinical Presentation

Most common presenting symptom was visible haematuria in 8 patients (53.33%), while 5 patients were asymptomatic and 1 patient presented with non specific abdominal pain. In one case the information of presenting symptom was unclear. In the 5 asymptomatic patients 3 of them had Atypical or Malignant Urine Cytology while 2 patients had concerning CT IVP or Renal Ultrasound (US) features which prompted a Cystoscopy.

### Imaging and Diagnosis

The most common imaging modality for investigation was CT IVP while 1 patient received renal ultrasound and Magnetic Resonance Imaging (MRI) abdomen and pelvis. 7 patients did not have any urethral or upper tract involvement while the other 8 patients had concurrent recurrence. After their presentation, all patients underwent either flexible or Rigid Cystoscopy. The earliest recurrence was 3 months post radical cystectomy and formation of neobladder and 12 years was the longest cancer free period.

### Site of Recurrence and Management

Site of recurrence as well as the management of recurrence is outlined in table 3. The majority of patients underwent Neobladder resection of their tumour. 3 patients had adjuvant chemotherapy post neocystectomy. Only 1 patient did not have any surgical intervention for their recurrence (patient refusal), they underwent chemotherapy with Carboplatin and Gemcitabine instead. The neobladder recurrence site and management is shown in Table 4 below.

### Outcomes

Patient outcomes are summarised in table 4. All patients were followed up following management of their recurrence between 3-48 months with no recurrence in majority of cases (53.33%). One patient who underwent chemotherapy alone had a recurrence in bladder as well as metastasis to the brain and underwent anterior bladder resection. Another patient died within a year from Laryngeal Carcinoma.

Paper	Recurrence (years)	Site of recurrence	Upper tract	Urethra	Treatment	Outcome
Pardalidis et al [5]	10	Neobladder	No	No	Robotic neocystectomy+ adjuvant chemotherapy x4	No recurrence at 1 year

Cherbanyk et al [6]	9	Neobladder	No	No	Carboplatin+ Gemcitabine -(Pt refused neocystectomy)	Recurrence bladder and brain - patient passed away
Doshi et al [7]	11	Neobladder	No	No	Neocystectomy with creation of ileal conduit	No recurrence at 3 months
Groen et al [8]	9	Neobladder, uretero-ileal anastomosis	yes	No	Neocystectomy + distal ureter with creation of ileal conduit	No recurrence at 24 months
Cakmak et al [9]	11	Neobladder	No	No	TUR - (patient refused neocystectomy)	No recurrence at 18months
Kawamoto et al [10]	9	Uretero-ileal anastomosis	Yes	No	Neocystectomy+ urethrectomy+ left nephU+ right ureterocutaneostomy - 9 courses of adjuvant chemotherapy (gemcitabine and carboplatin)	NA
Ide et al [11]	11	Uretero-ileal anastomosis, urethra-neobladder anastomosis	Yes	Yes	Left NephU, resection of neobladder, urethrectomy	No recurrence at 1 year
Moore et l [12]	1	Neobladder Urethro-neobladder anastomosis, urethra	No	Yes	resection of neobladder+ urethrectomy + creation of an ileal conduit +three cycles of gemcitabine and cisplatin	NA
Sanchez et al [13]	NA	Neobladder	Yes	No	Partial resection of neobladder, radiochemotherapy	NA
Hadzi-Djokic [14]	12	Uretero-ileal anastomosis	Yes	No	Right nephU +partial resection of the neobladder	Passed away withing 1 year- laryngeal Ca
Moeen [15]	1.5	Neobladder	No	No	TUR- (patient refusing neocystectomy)	No recurrence at 3 years
Yamashita et al [16]	6	Neobladder	No	No	TUR +BCG x7	No recurrence at 8 months

Hara et al [17]	8	Neobladder	Yes	No	Neobladder resection with ureterocutaneostomy	NA
Herawi et al [18]	3 months	Neobladder, uretero-ileal anastomosis	Yes	No	Neobladder resection	NA
Dadikhi et al [19]	10	Neobladder, uretero-ileal anastomosis	Yes	No	Neocystectomy+ ileal conduit	NA

**Table 4:** Patient outcomes following management for UC recurrence of the neobladder

## Discussion

We present, the first systematic review conducted to assess the diagnosis, management and outcomes relating to tumour recurrence in an orthotopic neobladder. Neobladder recurrences have only been described in case reports and no large studies or reviews have been carried out to date.

Even though bladder cancer is not uncommon, secondary tumours in various forms of urinary diversion are rarely encountered. The mean latency period of secondary tumours according to published literature is between 4-34 years. [20] The risk of secondary neoplasm differs in various forms of urinary diversion with ileal conduit carrying the lowest risk. After urinary diversion, recurrences have been reported to occur in the urethra, ileal conduit at the ureteroenteric anastomosis and upper urinary tract as well as the colonic mucosa of ileocolonic neobladder. Urethra is the most common recurrence localisation after radical cystectomy with orthotopic neobladder formation. In large studies it has been reported to be around 0.7% and 18% depending on individual risk factors for recurrence. Risk factors for urethral recurrences include multifocality, associated carcinoma in situ, bladder neck on trigone involvement, and prior prostatic or upper tract involvement. As expected those with risk factors have a higher incidence of urethral recurrence and reported in 8-18% of those with prostatic urethral involvement at cystectomy or any time prior to cystectomy as opposed to 2.7% in those with no prior history of urethral involvement or prostatic urethral involvement at the time of cystectomy [21].

Secondary malignancies develop in 0.5% of patients 20 years after their surgery where an ileal segment is used. Excluding tumours secondary to ureterosigmoidostomies, adenomas and adenocarcinomas make up 72.6% of tumours secondary to urinary diversions using isolated gut segment. The rest (27.4%) are comprised of Transitional Cell Carcinoma, Squamous Cell Carcinoma, Signet Ring Cell Carcinoma, Small Cell Carcinoma and Leiomyosaromas [14].

A well-known characteristic of urothelial cell carcinoma is the development of recurrent solitary or multifocal tumours in the urinary tract. The mechanism of local recurrence in the mucosa of neobladder is not proven yet due to the scarcity of cases. However, there are two theories regarding the mechanism behind urothelial recurrence that can explain this phenomenon: 'field carcinogenesis' and 'seed and implantation'. [18] Field carcinogenesis states that tumour cells exist in normal urothelium where they independently and eventually may develop into tumours, this may explain recurrence at anastomosis sites or extra-neobladder recurrences however does not completely explain localised neobladder recurrences [22].

'Seed and implantation' theory states that papillary tumours in the upper urinary tract recur in the bladder in 15-50% of cases and has been proven that urothelial tumour cells originated from the renal pelvis which is the main source of this theory. Where intestinal mucosa is used for the formation neobladder the seed and implantation theory can explain the reason behind tumour recurrence. It is claimed that droplets of tubular cells find bladder and non-urothelial surfaces compatible for both implantation and growth. An important mechanism of metachronous TCC recurrence appears to be intraluminal tumour cell seeding therefore can be considered as one of the potential factors that contribute to multifocal recurrence of TCC in tissues other than the urothelium [23-24].



Long term follow-up post radical cystectomy and neobladder formation is required given the risk of malignant transformation in every form of urinary diversion. Patient's may present with visible haematuria, new onset hydronephrosis, abnormal cytology or suspicious finding on surveillance imaging such as CT IVP, renal US or MRI kidneys. In these cases, urgent cystoscopy should be performed to rule out recurrence of tumours. The analysis suggests that managing these recurrences with TURBT or neobladder resection might have the best outcome however longer term follow up is required.

## **Conclusion**

Surgical management of neobladder recurrences with transurethral resection of tumour or neobladder resection with alternate urinary diversion should be considered, taking into consideration the patient's wishes and surgical fitness. The endoscopic follow up of neobladder remains controversial partly due to unknown true incidence rate of secondary malignancies in neobladder however urine cytology can be considered as a minimally invasive and easily carried out test. The strength of these recommendations are low given the small number of cases reported worldwide. We also recommend long term follow up of these to assess the effectiveness of their management plan.

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