

Organoid models in bladder cancer: From bench to bedside?

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Abstract

Background: Bladder cancer (BC), one of the most prevalent and aggressive urological malignancies, poses significant challenges in diagnosis, treatment, and recurrence management. Patient-derived organoid provides new directions for the precision diagnosis and treatment of bladder cancer.

Objective: To make a comprehensive summary of the current bladder cancer organoid studies.

Methods: A comprehensive database search was conducted to provide an in-depth overview of the current state of bladder cancer organoid models, with a focus on their applications in basic research, clinical translation, and therapeutic discovery.

Results: We summarized the current bladder cancer organoid studies, highlighting their advantages, such as genetic fidelity and high-throughput drug screening capabilities. Additionally, we also address the challenges, including their limited representation of the tumour microenvironment and technical complexity. Finally, we discuss future directions, including the integration of immunotherapy, the development of co-culture systems, and the exploration of non-invasive sampling methods and organoid-on-chip systems.

Conclusions: Traditional pre-clinical models have inherent limitations in mimicking the complexity of human tumours. The emergence of organoid technology has offered a groundbreaking approach to address this challenge, providing an innovative tool for studying tumour biology, genetic alterations, drug screening, and personalized medicine in bladder cancer.

Keywords

bladder cancer, patient-derived organoid (PDO), personalized medicine, drug screening, immunotherapy, tumour microenvironment (TME)

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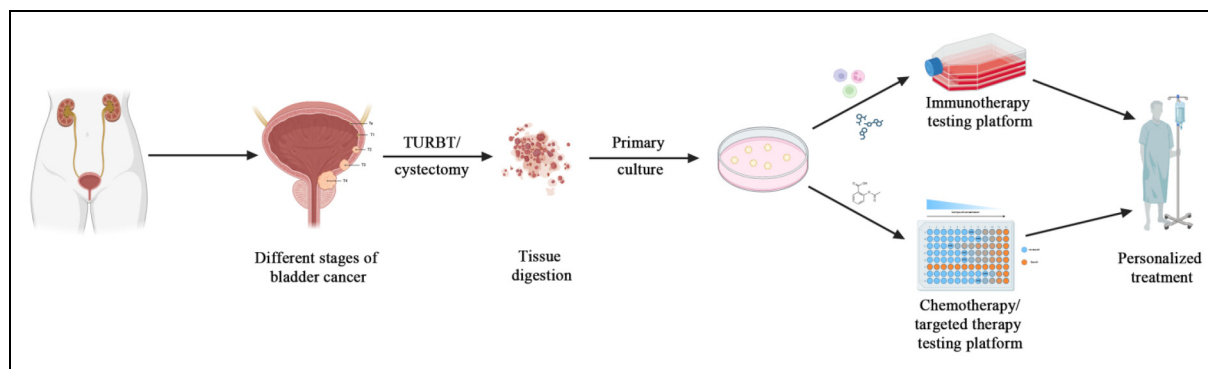


Figure 1. Schematic diagram demonstrating the application of organoids for personalized therapeutic discovery. (illustration created with BioRender.com).

Introduction

Bladder cancer (BC) remains a significant global public health issue, with high incidence and mortality rates.¹ Despite advancements in treatment options, BC is characterized by high recurrence rates, intrinsic resistance to chemotherapy, and a scarcity of effective therapeutic strategies, particularly in advanced stages.² While traditional research models such as 2D cell cultures have been instrumental in the initial stages of drug discovery, they fail to capture the tumour's true complexity, especially regarding tumour-microenvironment (TME) interactions and heterogeneity.³ Though valuable, patient-derived xenografts (PDXs) and animal models are time-consuming and costly.⁴ The development of organoid models has provided a breakthrough in this area, enabling the cultivation of 3D, self-organizing structures that more closely resemble the original tumours genetically and phenotypically.⁵ Organoids derived from bladder cancer tissues offer a novel platform for studying tumour biology, drug responses, and therapeutic efficacy in a manner that is more reflective of clinical realities.⁶⁻⁹

In this review, we will explore the current status of bladder cancer organoid models, their advantages over traditional models, the challenges encountered in their application, and their potential in clinical translation. Especially, we will discuss how organoids can contribute to the development of personalized treatment strategies and future research directions.

Current Status of bladder cancer organoid

In 2018, Yoshida and colleagues highlighted the pivotal role of 3D organoid cultures in the study of bladder cancer, demonstrating how the culturing environment influences the sensitivity of cancer cells to therapeutics and underscoring the value of 3D models in *in vitro* drug screening.¹⁰ Building on this, Lee and Mullenders and their teams created biobanks of patient-derived organoid lines from bladder cancer, capturing the disease's histopathological and molecular diversity and advancing our understanding

of its pathogenesis.¹¹ These organoids are instrumental for drug screening and personalized medicine (Figure 1), with their drug response profiles remaining consistent despite phenotypic shifts between luminal and basal subtypes. Garioni et al. observed analogous phenotypic and genomic changes in sarcomatoid urothelial carcinoma organoids, with later passages more accurately reflecting the aggressive phenotype, aligning with previous findings.^{12,13}

The establishment of bladder cancer organoids typically involves several key steps. Various tissue sources, including surgical resection specimens (TURBT and radical cystectomy), biopsies, and urine samples, are used, though surgical specimens generally yield optimal results due to high cellularity and microenvironmental preservation.¹⁴ Immediately following collection, tissues are placed in a cold collection medium to maintain viability. Subsequent processing involves tissue washing, mincing, enzymatic digestion (often using collagenase), filtration, and centrifugation to isolate single cells or small cell clusters. These are then embedded in a 3D matrix, most commonly Matrigel, to recreate the *in vivo* microenvironment and promote cell-matrix interactions (Table 1). However, Matrigel's undefined composition and batch variability pose reproducibility challenges.¹⁵ Therefore, synthetic scaffolds, offering defined extracellular matrix (ECM) compositions, growth factor-free conditions, and customization to specific tissue environments, are increasingly employed as alternatives for high-throughput applications.¹⁶ Their consistent composition ensures uniform experimental conditions, crucial for reproducibility and clinical translation. However, scaffold-based methods may extend the organoid generation and drug screening timeline, potentially impacting clinical applicability.

In response to these challenges, Minoli et al. introduced a novel platform for culturing bladder cancer patient-derived organoids in a growth factor-rich medium devoid of ECM support.⁶ This approach aims to minimize biological variability, curb stromal cell overgrowth, enhance drug delivery, and abbreviate culture time, thereby enhancing the clinical relevance of

Table 1. Summary of published bladder cancer organoid studies.

Authors	Organoids features and applications	PDOs no.	Media	Supplementarys
Merrill et al. (2024) ⁸	Short-term PDOs represent the tumor molecular characteristics. Integration of multiomic profiling and ex vivo drug screening data identifies potential predictive biomarkers, including a novel signature of gemcitabine response.	65/106	DMEM	CS-FBS, B-27, anti-anti, gentamicin, EGF, Heregulin β -1, FGF-7, FGF-10, Noggin, RSPO1
Zhao (2024) ¹⁷	They developed a patient-derived, T-cell-retaining tumor organoid model, and use it to test the synergistic response of metallodrugs and ICIs.	8/NA	Advanced DMEM/F12	B27, A83-01, N-acetylcysteine, nicotinamide, FGF10, FGF7, FGF2, Y-27632, IL-2
Viergever (2024) ¹⁸	Urinoids provide a unique opportunity to culture sequential follow-up samples from bladder cancer patients during their treatment.	12/22	Advanced DMEM/F12	FGF10, FGF7, FGF2, B27, A83-01, N-acetylcysteine, nicotinamide
Hodara (2023) ¹⁹	Organoids were used to validate the role of SLC7A11 in bladder cancer chemoresistance	1/1	Advanced DMEM/F12	HEPES, GlutaMax, L-WRN conditioned media, N acetylcysteine, nicotinamide, B27, N2, Y-27632, FGF10, FGF7, FGF2, A83-01
Jiang (2023) ²⁰	Organoids were used as a drug-screening platform to reveal characteristics of different drug sensitivities	9/11	Advanced DMEM/F12	HEPES, GlutaMax, EGF, FGF10, FGF7, FGF2, B27 supplement minus vitamin A, A83-01, N-acetylcysteine, nicotinamide
Garioni (2023) ¹²	SarBC-01 represented the first fully characterized long-term organoid model derived from a sarcomatoid urothelial bladder cancer patient.	1/NA	Advanced DMEM/F12	WNT3A, R-Spondin1, EGF, N-acetyl-L-cysteine, Noggin, TGF β inhibitor, N2, B27, Y-27632
Hong (2023) ²¹	Organoids were used to evaluate the effect of RC48-ADC with different HER2 expression levels.	6/6	Advanced DMEM/F12	GlutaMax, HEPES, B27, N-acetylcysteine, nicotinamide, A83-01, R-spondin1, Noggin, FGF10, FGF2, EGF
Xiao (2023) ²²	Organoids proved that cephalomannine could inhibit the growth and metastasis of tumor cells.	4/4	Advanced DMEM/F12	GlutaMax, HEPES, B27, N-acetylcysteine, nicotinamide, A83-01, R-spondin1, Noggin, FGF10, FGF2, EGF
Minoli (2023) ⁶	Organoids from different BCa stages and grades were established by using ultra-low attachment method. The drug screening pipeline is implemented using organoids, testing standard-of-care and FDA-approved compounds for other tumors.	40/49	Advanced DMEM/F12	GlutaMax, HEPES, FBS, B27, nicotinamide, R-Spondin, N acetylcysteine, SB202190, Noggin, Wnt3a, HGF, A83-01, EGF, FGF10, Y-27632
Rangsitratkul (2022) ²³	Virus-mediated anti-tumor immunity was recapitulated in BCa PDOs.	2/2	Advanced DMEM/F12	FGF10, FGF7, FGF2, B27 supplement, A83-01, N acetylcysteine, nicotinamide
Yu (2021) ²⁴	Co-culture of BCa PDOs with CAR-T cells.	3/3	Advanced DMEM/F12	GlutaMax, HEPES, B27, N-acetylcysteine, nicotinamide, SB202190, A83-01, R-spondin1, Noggin, FGF10, FGF2, EGF
Mullenders (2019) ⁹	Human urothelial organoids cultured with around 50% efficiency and long-term propagation (>1 year). And organoids were used to do limited drug testing.	77/133	Advanced DMEM/F12	FGF10, FGF7, FGF2, A83-01, B27, N-acetylcysteine, nicotinamide
Lee (2018) ¹¹	Organoid lines frequently preserve the heterogeneity of the parental tumor and display a spectrum of genomic changes	22/18	Hepatocyte media	GlutaMax, CS-FBS, EGF, Y-27632

(continued)

Table 1. Continued.

Authors	Organoids features and applications	PDOs no.	Media	Supplementarys
Gheibi (2017) ²⁵	consistent with tumor evolution in culture. Analyses of drug response using bladder tumor organoids show partial correlations with mutational profiles, as well as changes associated with treatment resistance. PDX-derived ellipsoids in microchambers retained patterns of drug responsiveness and resistance observed in PDX mice and also exhibited <i>in vivo</i> -like heterogeneity of tumor responses.	6/6	RPMI	B27, EGF, bFGF

CAR-T cells = chimeric antigen receptor T-cells; PDX = patient-derived xenograft.

organoid models. By maintaining short-term culturing, particularly by the second passage, this method has preserved the key phenotypic, histological, and genomic traits of the original tissue, including both luminal and basal cells. This is in contrast to long-term Matrigel cultures, which have been noted for phenotypic plasticity and difficulties in maintaining luminal-subtype organoids, affecting their clinical utility.^{11,12}

Function of organoid in basic bladder cancer research

The use of organoid technology in bladder cancer research has opened up new avenues for understanding the molecular mechanisms driving tumorigenesis and for testing novel therapeutic strategies. Organoids derived from tumour tissues maintain the genetic and phenotypic characteristics of the original tumours, including the preservation of tumour-ECM interactions, which are crucial for modeling the complexity of the TME.^{26,27}

Modeling tumour evolution and genetic alterations

Bladder cancer is a genetically heterogeneous disease, with several mutations driving the progression from superficial tumours to muscle-invasive bladder cancer (MIBC), and ultimately metastatic disease.^{28,29} Studies have shown that organoids derived from bladder cancer tissues preserve key genetic alterations found in clinical bladder tumours.^{6,11} For instance, mutations in the tumour suppressor gene TP53, commonly observed in high-grade invasive bladder cancer, are faithfully recapitulated in bladder cancer organoids. Similarly, FGFR3 mutations, prevalent in non-muscle invasive bladder cancers (NMIBC), have been modeled in organoid systems, providing insights into the molecular mechanisms driving tumour growth and resistance to therapy.³⁰

Organoids also provide a valuable platform for modeling tumour evolution.¹¹ Recent studies have shown that bladder cancer organoids can evolve over time in culture, reflecting

the evolutionary dynamics seen *in vivo*. This allows researchers to track the acquisition of additional mutations that promote tumour progression, helping to identify key driver mutations involved in the transition from NMIBC to MIBC. In addition, the acquisition of mutations in genes involved in DNA damage repair (such as mutations in ATM, BRCA1/2, or MRE11) may decrease the tumour's resistance to conventional chemotherapies, such as cisplatin.³¹ The ability to model these mutations in organoids allows for more accurate predictions of therapeutic responses and provides insights into the mechanisms of drug resistance.

High-Throughput drug screening

One of the major advantages of using bladder cancer organoids is their potential for high-throughput drug screening (Table 1). Since organoids maintain the genetic and phenotypic complexity of the original tumour, they offer a more representative model of tumour biology compared to traditional 2D models.³² High-throughput screening using organoid models enables the identification of novel therapeutic agents and allows researchers to test the efficacy of various drugs in a personalized manner.³³ This is especially important in bladder cancer, where treatment responses can vary significantly between patients due to the genetic diversity of the disease.³⁴

A key advantage of using organoid models for drug screening is their ability to simulate *in vivo* drug responses more accurately than 2D cultures. For instance, organoid models have been shown to predict patient responses to cisplatin-based chemotherapy, one of the standard treatments for bladder cancer, as well as to novel targeted therapies such as FGFR inhibitors.⁶ Organoids can also be used to assess drug resistance mechanisms, a critical aspect in the treatment of advanced bladder cancer.

The predictive power of organoid-based drug screening has been demonstrated in several studies, where responses to chemotherapy, immunotherapy, and targeted therapies were shown to correlate with patient outcomes.^{32,35,36}

However, there have not yet been large-scale studies focusing on bladder cancer that combine clinical responses with organoid predictions. This underscores the potential value of using organoids to guide personalized treatment strategies in the context of bladder cancer.

Clinical translation of organoid

The successful translation of organoid models from the research laboratory to clinical practice is a critical step in realizing their full potential for personalized medicine.³⁷ Organoids derived from patient biopsies are now being investigated as a way to predict drug responses and guide treatment decisions.³⁷ This section explores the progress made in translating organoid-based approaches into the clinic, highlighting key achievements, and their potential impact on the management of bladder cancer.

Organoids provide an exciting avenue for personalized medicine, as they allow clinicians to test a wide range of therapies on patient-derived tumour models. This approach holds significant potential for improving treatment outcomes, particularly in bladder cancer, where tumour heterogeneity can result in vastly different responses to treatment.^{6,38} By using organoids to predict how a patient's tumour will respond to chemotherapy, targeted therapies, or immunotherapies, clinicians can develop more effective, individualized treatment regimens.^{5,37}

Challenges and limitations

While organoids have proven to be a powerful tool in bladder cancer research and have significant clinical potential, there are several challenges that remain, both in the development of organoid models and in their clinical applications.

Challenges in organoid model development

1. Incomplete TME

Despite their ability to replicate many aspects of tumour biology, organoid models are still limited by their inability to fully recapitulate the TME.³⁹ Organoids often lack important components such as blood vessels, lymphatics, and ECM, which play key roles in tumour growth, invasion, and metastasis. Additionally, the immune microenvironment is often underrepresented in organoid cultures, which limits their utility in studying immune evasion and response to immunotherapy.

Although co-culture systems are being developed to include stromal cells, fibroblasts, endothelial cells, and immune cells, these models still fall short of fully mimicking the complexity of the *in vivo* environment.⁴⁰ The absence of a fully functional vasculature, for example, can affect the delivery of therapeutics, particularly those targeting blood vessels or those that rely on drug diffusion through tumour tissues.

2. Technical Challenges in Culturing Organoids

Organoids are complex, three-dimensional structures that require specialized culture conditions, and the process of culturing and expanding organoids is resource-intensive. This complexity can make it difficult to scale up organoid culture for large-scale drug screening or for routine clinical use.^{34,41} Standardization of culture protocols remains an ongoing challenge, with different labs often using different methods, leading to variability in results. Furthermore, growing organoids from patient samples requires fresh tissue and may be limited by patient-specific factors, such as tumour type or genetic profile, that affect the success of culture initiation.

3. Genetic homogeneity of organoids

Although organoids maintain the genetic fidelity of the original tumour, they are often monoclonal in nature.^{41,42} This genetic homogeneity can limit their ability to fully represent the heterogeneity of the original tumour, particularly in cases where genetic diversity plays a critical role in drug resistance or metastasis. To address this, efforts are being made to incorporate additional cell types or induce genetic diversity within organoid cultures, but this remains an ongoing challenge.

4. Long-Term culture and stability

While organoids are often stable for several passages, long-term culture can result in genetic drift or changes in their molecular profile over time.¹¹ This is particularly concerning for their use in drug screening, as alterations in tumour biology that occur during prolonged culture may affect drug responses. Developing methods to maintain the stability and reproducibility of organoids over extended periods is crucial for their use in clinical settings.

Challenges in clinical applications

1. Standardization and regulatory hurdles

To integrate organoids into clinical practice, it is imperative to develop standardized protocols that ensure reproducibility and consistency across various laboratories and clinical settings. Variations in organoid culture, manipulation, and analysis can yield inconsistent results, complicating their validation as clinical tools.⁴³ Additionally, the regulatory landscape for organoid-based diagnostics and therapies is evolving, necessitating further efforts to align organoid models with standards for clinical trials and patient care.^{37,44}

2. Clinical integration and cost

The integration of organoids into routine clinical practice faces logistical and financial challenges.^{37,44} The processes of culturing organoids, conducting drug screenings, and

devising personalized treatment plans require specialized equipment, expertise, and time, potentially limiting their widespread adoption, especially in resource-limited settings or hospitals with limited access to advanced technologies. Moreover, the cost of generating and maintaining organoid models could be prohibitive for some healthcare systems, particularly in low-income regions

3. Patient selection and cohort size

In clinical trials, patient selection is a critical issue. Not all patients will have tumour tissues that can be successfully cultured into organoids, and the success rate may vary depending on individual tumour molecular characteristics or responses to standard culture conditions.⁴³ Smaller cohort sizes in clinical trials could diminish the statistical power of studies, hindering the ability to draw meaningful conclusions from organoid-based drug screening or therapeutic predictions. Larger, multi-center trials that encompass diverse patient populations will be essential to validate the clinical utility of organoids.^{37,44}

Future directions

Despite these challenges, the future of organoid research in bladder cancer is promising. Several exciting developments in organoid technology and its integration with other emerging research tools have the potential to enhance our understanding of bladder cancer biology and improve patient outcomes.

Integration with immunotherapy

Immunotherapy has revolutionized cancer treatment, with bladder cancer being one of the leading areas where immunotherapies like immune checkpoint inhibitors have shown promise. However, only a subset of patients responds to these therapies, and the mechanisms of resistance remain poorly understood. Organoids could serve as a critical tool in elucidating the tumour-immune system interactions that underlie responses to immunotherapy.

The development of organoid models that incorporate immune cells offers the opportunity to study the immune microenvironment in bladder cancer. These co-culture models can help identify biomarkers of response and resistance to immunotherapy, which are crucial for selecting the right candidates for treatment. Additionally, organoids can be used to test the effectiveness of combination therapies that combine immune checkpoint inhibitors with other agents to overcome resistance.

Co-Culture systems and TME

As discussed earlier, current organoid models lack a full representation of the TME. The development of advanced co-culture systems, where organoids are grown alongside additional cell types, will enhance the predictive power of

organoid models. These systems will be crucial for studying complex interactions such as immune evasion, tumour angiogenesis, and metastasis. Efforts to replicate the tumour's vasculature and ECM will improve the accuracy of drug response predictions and provide more clinically relevant models for testing new therapies.

By incorporating more components of the TME, including immune and stromal cells, organoids can better investigate mechanisms of drug resistance and metastasis. These advances could allow for more precise modeling of bladder cancer biology and lead to the identification of new therapeutic targets.

Non-Invasive sampling techniques

Another exciting area of future research involves the development of non-invasive sampling techniques, such as urine-derived organoids. Bladder cancer is one of the few cancers that can be accessed non-invasively through urine, making it an ideal candidate for this approach. Recent studies have demonstrated that organoids can be generated from urine samples, providing a less invasive method for modeling bladder cancer and monitoring treatment responses.¹⁸

Urine-derived organoids could offer a convenient and accessible platform for studying bladder cancer, particularly in clinical settings where repeated biopsies are not feasible. This approach could also provide a valuable tool for early diagnosis, allowing clinicians to detect tumours at an earlier stage and monitor disease progression more effectively.

Additionally, the ability to create organoids from liquid biopsies could provide a dynamic model to track real-time changes in tumour behavior and therapeutic responses without the need for invasive tissue biopsies. This would represent a major breakthrough in bladder cancer monitoring, making it easier for patients to undergo routine checks and enabling more personalized and frequent monitoring of treatment efficacy.

Organoid-on-chip system

While organoid technology has made significant strides in modelling bladder cancer, the integration of chip technology remains an untapped frontier with enormous potential. Organoid-on-chip systems, which combine the advantages of organoids with microfluidic devices, offer a novel approach to studying tumour in a more physiologically relevant microenvironment.¹⁴ These systems have the potential to recreate the complexity of tumour-microenvironment, drug penetration, and metabolic gradients, which are critical for understanding tumour biology and responses to therapy.

The future direction of bladder cancer organoids may involve the development of organoid-on-chip models that more accurately mimic the *in vivo* TME. These models could be used to study the heterogeneity of BC, test the efficacy of new drugs, and personalize treatment strategies based on individual patient's tumour characteristics.

Automatization

Automation plays a crucial role in improving the accuracy, efficiency, and economic viability of experimental procedures, as well as in maintaining data uniformity. However, the automation of biomanufacturing processes for bladder cancer patient-derived organoids is challenged by several factors, such as the heterogeneity of organoids, complex structures of organoids, and the necessity for human intervention in experimental protocols. To address these challenges, Schuster et al. developed an automated microfluidic platform that not only generates morphogen gradients and promotes the growth of organoids but also monitors their development and biochemical attributes in real time.⁴⁵ This technological advancement has made a significant contribution to the standardization and refinement of organoid cultivation techniques.

Conclusion

Organoid technology has made significant strides in bladder cancer research, offering valuable insights into tumour biology and drug responses. They represent a promising platform for understanding the molecular underpinnings of bladder cancer and simulating the TME. Organoids also present an exciting opportunity for personalized medicine, enabling clinicians to predict how individual patients will respond to various therapies and tailor treatments accordingly.

However, significant challenges remain, including the need for more comprehensive TME models, standardization of culture methods, and overcoming the technical complexities of organoid culture. While these hurdles pose a challenge to the widespread clinical adoption of organoid models, continued research and technological advancements are likely to address these issues, bringing organoid-based therapies closer to routine clinical use.

As the field of organoid research advances, future studies should focus on integrating immunotherapy, improving co-culture systems, exploring non-invasive sampling techniques, developing organoid-on-chip systems and automatization to further enhance the clinical relevance and predictive power of organoid models. With these advancements, organoids have the potential to revolutionize bladder cancer research and treatment, offering new hope for more effective, personalized therapies.

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Statements and declarations

Author contributions/CRediT

H.Z conducted the review of the literature and wrote the first draft of the manuscript. C.FN, D.W, J. YCT supervised the process of the study and revised the manuscript. All authors contributed to the conception and interpretation of data. All authors approved the final version of the manuscript.

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Conflict of interest

Jeremy. Y.C. Teoh is an Editorial Board Member of this journal, but was not involved in the peer-review process nor had access to any information regarding its peer-review.

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