Review

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Current role of radiomics and radiogenomics in predicting oncological outcomes in bladder cancer

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Abstract

Background: Radiomics refers to the conversion of medical images into high-throughput, quantifiable data to analyze disease patterns, aid decision-making, and predict prognosis. Radiogenomics is an extension of radiomics and involves a combination of conventional radiomics techniques with molecular analysis in the form of genomic and transcriptomic data. In the field of bladder cancer, studies have investigated the development, implementation, and efficacy of radiomic and radiogenomic nomograms in predicting tumor grade, gene expression, and oncological outcomes, with variable results. We aimed to perform a systematic review of the current literature to investigate the development of a radiomics-based nomogram to predict oncological outcomes in bladder cancer.

Materials and methods: The Medline, EMBASE, and Web of Science databases were searched up to February 17, 2023. Gray literature was also searched to further identify other suitable publications. Quality assessment of the included studies was performed using the Quality Assessment of Diagnostic Accuracy Studies 2 and Radiomics Quality Score.

Results: Radiogenomic nomograms generally had good performance in predicting the primary outcome across the included studies. The median area under the curve, sensitivity, and specificity across the included studies were 0.83 (0.63–0.973), 0.813, and 0.815, respectively, in the training set and 0.75 (0.702–0.838), 0.723, and 0.652, respectively, in the validation set.

Conclusions: Several studies have demonstrated the predictive potential of radiomic and radiogenomic models in advanced pelvic oncology. Further large-scale studies in a prospective setting are required to further validate results and allow generalized use in modern medicine.

Keywords: Radiomics; Radiogenomics; Oncology; Bladder cancer; Survival; Recurrence; Treatment response

1. Introduction

Radiomics refers to the conversion of medical images into high-throughput, quantifiable data to analyze disease patterns, aid decision-making, and predict prognosis.[1,2] Since its inception in 2012, data have been extracted and analyzed from various imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography to determine prognosis and predict patient outcomes, particularly in the field of surgical oncology.[1,3] Radiogenomics is an extension of radiomics and involves a combination of conventional radiomics techniques with molecular analysis in the form of genomic and transcriptomic data.[4] This particular field of medicine offers a noninvasive alternative to traditional genetic testing via the development of imaging surrogates that can predict genetic aberrations from raw radiological imaging alone.[5] In brief, parameters derived from advanced image processing and analysis can be used to identify specific phenotypic and genotypic characteristics of the tumor without requiring costly genetic testing.[6]

Despite thorough research into this novel field of medicine, many studies are limited by lack of reproducibility and external validation.[7,8] In the field of bladder cancer, studies have investigated the efficacy of radiomic and radiogenomic nomograms in predicting tumor grade, gene expression, and oncological outcomes, with variable results.[9–11] Neoadjuvant chemotherapy (NAC) and radical cystectomy remain the gold standard treatment combination for patients with muscle-invasive bladder cancer (MIBC).[12] Despite this, patients with pathological residual disease treated with NAC have inferior survival outcomes than those treated with radical cystectomy alone.[13] Predicting response to NAC in this cohort of patients using radiomic or radiogenomic techniques will allow for stratification of patients and optimization of outcomes.[14] Similarly, in the era of precision medicine, the ability to predict recurrence, survival, and disease progression will undoubtedly assist in our treatment decisions, perhaps avoiding highly morbid interventions altogether in those deemed as high risk by radiomic and radiogenomic nomograms.[15] We aimed to perform an up-to-date analysis of the current literature on the use of radiomics and radiogenomics to predict survival, recurrence, and treatment response in patients with MIBC.

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2. Materials and methods

2.1. Study design and reporting guidelines

This study is a systematic review of randomized and nonrandomized trials and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines.

2.2. Search strategy

The Medline, EMBASE, and Web of Science databases were searched. The systematic search processes with detailed search terms are outlined in Supplementary Material S1, http://links.lww.com/CURRUROL/A50. The last date of search was February 17, 2023, and gray literature was also searched to further identify other suitable publications.

2.3. Inclusion criteria

Studies in English were assessed for eligibility based on strict inclusion criteria. Randomized controlled trials and cohort studies investigating the development of radiomics- or radiogenomics-based models to predict outcomes in bladder cancer were included in our analysis. Case reports and conference abstracts were excluded.

i. Study design:
   a. Randomized controlled trials
   b. Cohort studies
ii. Participants:
   a. Patients with bladder cancer
iii. Intervention:
   a. Radiomic or radiogenomic signature development
iv. Outcomes:
   a. Oncological outcomes: recurrence, disease-free survival, overall survival, pathological complete response

2.4. Study selection, data extraction, and critical appraisal

A database was created using the reference managing software EndNote X9 (Clarivate, London, United Kingdom). Two researchers (NOS and HCT) reviewed outputs from the searches independently of each other.

Initially, duplicates were removed. Study titles were then screened and assessed for potential relevance. The abstracts of selected potential studies were then read and assessed for eligibility for inclusion based on the inclusion/exclusion criteria detailed above. Rejected studies were grouped together in the database by their reason for exclusion. The full texts of the abstracts deemed eligible for inclusion were then further analyzed using the same criteria. Conflicts between the 2 reviewers (NOS and HCT) were resolved following an open discussion and final decision by the senior author (MK).

To extract and store data efficiently, the Cochrane Collaboration screening and data extraction tool, Covidence, was used.[16] Data were collected by 2 reviewers (NOS and HCT) independently using the following headings: study details, study design, population, intervention, comparison groups, and outcomes. Conflicts between the 2 reviewers were resolved following an open discussion and final decision by the senior author (MK).

A critical appraisal of the methodological quality and risk of bias of the included studies was performed. The critical appraisal was completed by 2 reviewers independently. Quality assessment of the included studies was performed according using Quality Assessment of Diagnostic Accuracy Studies 2 and radiomics quality score.[3,17]

2.5. Systematic review registration

This systematic review was registered on PROSPERO , with a registry number of CRD42023396249.

3. Results

3.1. Search results

The literature search described above yielded a total of 845 results (Supplementary Material S2, http://links.lww.com/CURRUROL/A50). After removing 370 duplicates, 475 studies were screened. After the initial screening, 117 abstracts were reviewed and assessed for eligibility, of which 22 were selected for full text review. From these 22 full texts, a total of 8 studies met the inclusion criteria and were included in our analysis.

3.2. Methodological characteristics and quality of studies

All 8 included studies were retrospective in design.[11,14,18–23] Table 1 summarizes the methodological characteristics of the included studies. Of the 8 included studies, 5 were single center,[11,14,19,20,22,23] 1 was multicenter,[21] and 2 did not specify.[11,18] Data quality, assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 tool, was generally satisfactory, and all studies were deemed as having low risk of bias. All included studies ranked poorly on the radiomics quality score, primarily due to lack of prospective setting and external validation in many studies. A detailed explanation of the tools and breakdown of the results can be found in Supplementary Material S3–S6, http://links.lww.com/CURRUROL/A50.

3.3. Participant characteristics

The total number of participants from the 8 included studies was 1051. Five studies included both training and validation sets within their studies,[11,14,20–22] whereas the remaining 3 studies included only a training cohort.[18,19,23] In studies including both the training and validation sets, 67.7% (n = 610) of patients were in the training set, and the remaining 32.3% (n = 290) were in the validation set. Among 1051 participants, 80% (n = 841) were male and 20% (n = 210) were female. Supplementary Material S7, http://links.lww.com/CURRUROL/A50, summarizes the baseline characteristics of participants. Tumor characteristics and treatment regimens of each study are presented in Supplementary Material S8, http://links.lww.com/CURRUROL/A50.

3.4. Acquisition parameters

Contrast-enhanced CT was the most commonly used modality, implemented in 5 studies. Multiparametric MRI was used in the remaining 3 studies. Table 2 illustrates the individual acquisition parameters of each study, including contrast phase, agent, and rate, as well as model of CT/MRI scanner and subsequent acquisition parameters.

3.5. Signature development

Exact feature extraction methods varied across studies; however, a relatively similar pathway was followed across the board. Regions of interest were first segmented manually by experienced radiologists in all included studies. Radiomic features were then extracted from these segments using various radiomics software applications. All 8 included studies incorporated radiomics features in the development of their prognostic signature.[11,14,18–23] In addition, Lin et al. integrated a radiogenomic component in their signature attempting to predict progression-free interval in their cohort of patients with bladder cancer.[18] Contrast-enhanced CT was the imaging modality of choice for 5 of the included studies, whereas the remaining 3 studies used multiparametric MRI. Table 3 presents a breakdown of individual signatures and overall findings as well as the area under the curve (AUC) of signatures for predicting primary outcomes. Precise feature reduction and selection methodology is also demonstrated in Table 4.

Table 1

Methodological characteristics of included studies.

Study	Year	Country	Journal	Impact factor	Primary outcome
Choi et al.[14]	2021	Republic of Korea	*Clinical Radiology*	3.3	Pathological complete response
Lin et al.[18]	2019	China	*European Radiology*	7.0	Progression-free interval
Parmar et al.[19]	2021	Canada	*CUAJ*	1.8	Pathological complete response
Qian et al.[20]	2022	China	*Frontiers in Oncology*	6.2	Recurrence
Woźnicki et al.[21]	2022	Germany	*Cancers*	6.5	Overall survival
Xu et al.[22]	2019	China	*Journal of MRI*	5.1	Recurrence
Zhang et al.[11]	2020	China	*European Journal of Radiology*	3.5	Progression-free survival
Zhang et al.[23]	2022	China	*Frontiers in Oncology*	6.2	Pathological complete response

3.6. Signature performance

Model performance, estimated using the receiver operating characteristic curve and summarized as the AUC, ranged between studies. Median AUC, sensitivity, and specificity across included studies were 0.83 (0.63–0.973), 0.813, and 0.815, respectively, in the training set and 0.75 (0.702–0.838), 0.723, and 0.652, respectively, in the validation set. Table 3 illustrates the performance of each model in predicting their oncological outcome. All included studies had at least satisfactory performance in prediction of oncological outcome. Regarding pathologic complete response, model performance ranged from satisfactory to excellent in prediction of this outcome within their training cohorts (AUC range, 0.63–0.97). Signatures developed to predict disease-free survival or recurrence had good performance, with AUCs ranging from 0.74 to 0.96. Finally, the remaining signature predicted overall survival with good performance (AUC, 0.79) in this cohort of patients.

4. Discussion

Our review demonstrated the feasibility and efficacy of developing radiomic signatures to predict oncological outcomes for patients with MIBC from preoperative imaging. All signatures developed in included studies demonstrated at least modest accuracy in predicting their primary outcome. These results are hindered by several limitations, primarily driven by high levels of variability in imaging protocols and radiomic feature extraction. Although these are promising results, significant heterogeneity between studies makes further replication difficult. Standardization in the form of open-source scans, segmentations, and code will allow for controlled external validation across institutions, paving the way for eventual application within the clinical setting.[3,8] To the best of the authors' knowledge, this is the first systematic review to describe studies using radiomics and radiogenomics to develop signatures capable of predicting oncological outcomes in patients with MIBC.

Radical cystectomy remains a highly morbid procedure with an estimated 5-year survival of approximately 60%.[24–26] Despite radical treatment, a significant proportion of patients will experience either local or distant recurrence, with reported rates as high as 54% and 50%, respectively.[27] Similarly, early complication rates within 90 days of surgery are relatively common, with reports of 13% of patients having a severe complication (Clavien-Dindo ≥3). In contrast to parameters set out by clinical predictive models, usually only applicable after intervention, radiomic signatures provide a noninvasive prediction of oncological outcomes, which may avert the requirement for highly morbid treatments in patients unlikely to respond or having overall poor outcomes.[21] Quality of life should be at the forefront of patient care when considering radical treatment, and highly morbid treatment modalities should be avoided where possible in patients likely to respond poorly.[28]

Our analysis yielded similar results to those reported by Kozikowski et al. who reviewed the current role of radiomics in the prediction of muscle invasiveness in bladder cancer.[29] Their analysis of 8 studies showed an overall high diagnostic performance of radiomics-based signatures in predicting MIBC, with an area under hierarchical summary receiver operating characteristic, sensitivity, and specificity of 0.88, 0.82, and 0.81, respectively.[29] Similarly to our analysis, many studies included in their review lacked external validation and were entirely retrospective. None of the studies included in our review included a prospective phase. Ideally, a large-scale, multi-institutional study with both training and validation sets, and involving several

Table 2

The individual acquisition parameters of each study.

Study	Modality	Model	ST (s)	TR/TE (ms)	TV (kVp)	ATC (mA/s)	SLT (mm)	FOV (mm)	Contrast
Choi et al.[14]	ceCT	Siemens (Somatom Definition Flash/ Sensation 16)	-	-	120	240	-	-	100–140 mL nonionic IV iopromide 4 mL/s
Lin et al.[18]	ceCT	Toshiba, Philips, GE, Siemens	-	-	100–140	95–795	-	320–500	-
Parmar et al.[19]	ceCT	-	-	-	-	-	-	-	-
Qian et al.[20]	ceCT	Siemens (Definition Flash), Toshiba Aquilion ONE, Philips Ingenuity	-	-	100–120	-	5–6	500	Iohexol 350 mg I/mL 3 mL/s
Woźnicki et al.[21]	ceCT	Siemens, Toshiba, GE. Other	-	-	120	-	5	-	-
Xu et al.[22]	mpMRI	Siemens Magnetom Trio 3.0 T MR	223	3500–4500/91–131	-	-	4	200 × 200	0.2 mL/kg gadolinium at 2 mL/s
Zhang et al.[11]	mpMRI	Philips Ingenia 3.0-T MR	230	8216/67	-	-	3	-	-
Zhang et al.[23]	mpMRI	GE Discovery 750 3.0-T	146	5043/102	-	-	3	200 × 200	-

ATC = automatic tube current; ceCT = contrast-enhanced CT; FOV = field of view; IV = intravenous; kVp = kilovoltage peak; mA = milliampere; mm = millimeter; mpMRI = multiparametric magnetic resonance imaging; ms = milliseconds; s = seconds; SLT = slice thickness; ST = scanning time; TE = echo time; TR = repetition time; TV = tube voltage.

Table 3

Performance of each model in predicting their oncological outcome.

Study	Segmentation software	Radiomics software	Performance of signature (training) AUC	Sens	Spec	95% CI	Performance of signature (validation) AUC	Sens	Spec	95% CI	Outcome
Choi et al.[14]	MITK	AsanFEx	0.85	-	-	0.78–0.93	0.75	0.75	0.607	0.60–0.86	Pathological complete response
Lin et al.[18]	ITK-SNAP*	Ultrasomics	0.956	0.928	0.896	-	-	-	-	-	Progression-free interval
Parmar et al.[19]	3D Slicer v4.10.2	NIfTI	0.63	0.529	0.694	-	-	-	-	-	Pathological complete response
Qian et al.[20]	Deepwise	PyRadiomics 3.0.1	0.811	0.698	0.733	0.74–0.89	0.749	0.696	0.696	0.61–0.89	Recurrence
Woźnicki et al.[21]	MITK	AutoRadiomics	0.785	-	-	0.65–0.89	-	-	-	-	Overall survival
Xu et al.[22]	Custom in-house software	MatLab	0.915	-	-	-	0.838	-	-	-	Recurrence
Zhang et al.[11]	ITK-SNAP*	n/a	0.739	-	-	0.65–0.83	0.702	-	-	0.6–0.8	Progression-free survival
Zhang et al.[23]	ITK-SNAP*	Artificial Intelligence Kit v3.3.0	0.973	0.944	0.941	0.93–1	-	-	-	-	Pathological complete response

AUC = area under curve; CI = confidence interval; MITK = medical imaging interaction toolkit; NIfTI = neuroimaging informatics technology initiative; Sens = sensitivity; Spec = specificity.
*ITK-SNAP (http://itksnap.org) is a medical image segmentation tool.

different imaging modalities and acquisition parameters, will improve the confidence and performance of constructed signatures, allowing for a safe and evidence-based experience for participants.[30] Moreover, incorporation of genomic data into signatures could potentially improve the performance of future models, as demonstrated by Lin et al. in our review.[18] To further deepen clinical applications, standardization in the form of open-source scans, segmentations, and code will allow for controlled external validation in alternative institutions, paving the way for eventual applications within the clinical setting.[3,8]

Several other limitations affect the validity and reproducibility of signatures produced in this review. Radiomic features can be affected by multiple parameters, thus affecting the reproducibility and generalizability of studies from different scanners and institutions.[7,14] Features are highly dependent on image acquisition parameters, segmentation, and extraction methods.[31,32] For this reason, the selection of

Table 4

Feature processing and nomogram construction.

Study	Preprocessing	Feature selection process	Selected features	Nomogram
Choi et al.[14]	ZSS	CCC >0.7, PCC >0.75, random forest classifier, MLR	Six features: Dependence count nonuniformity normalized, dependence count nonuniformity, low gray-level count emphasis, busyness, local intensity peak, large distance emphasis	Radiomics signature, tumor shape, T stage, tumor size
Lin et al.[18]	-	LASSO	Seven features: CoLIAGe2D_WindowSize9_firstorder_Minimum, wavelet-HHH_lbp-3D-k_firstorder_Median, wavelet-HHL_lbp-3D-m1_firstorder_Kurtosis, wavelet-HLH_lbp-3D-k_firstorder_Maximum, wavelet-HLH_lbp-3D-m1_firstorder_Median, wavelet-LHH_lbp-3D-k_firstorder_Kurtosis, wavelet-LLH_lbp-3D-m1_firstorder_	Radiomics score, transcriptomics score, age, gender, race, AJCC stage, T stage, N stage
Parmar et al.[19]	Gray-level normalization	-	142 features—not disclosed	Radiomics signature
Qian et al.[20]	ZSS	-	14 features: 2 first-order, 2 gray-level co-occurrence matrix, 4 gray-level dependence features, 3 gray-level size zone matrix, 1 gray-level run-length matrix, 2 neighborhood gray-level difference matrix	Radiomics signature, number of tumors, tumor grade
Woźnicki et al.[21]	-	-	firstorder_Range_peri_pt, firstorder_10Percentile_peri_ln, shape_SurfaceVolumeRatio_intra_pt, firstorder_Entropy_peri_pt, shape_VoxelVolume_intra_pt, shape_MeshVolume_intra_pt, firstorder_Maximum_peri_ln, shape_LeastAxisLength_peri_ln	Radiomics signature, age, sex, T stage, N stage, margin status, lymphovascular invasion status
Xu et al.[22]	Gray-level normalization	SVM-RFE, LASSO	32 features: 19 CM, 7 RLM.4 GLSZM, 1 histogram, 1 NGTDM.	Radiomics signature, age, gender, tumor grade, muscle invasion status, tumor size and number, surgery, stalk, submucosal linear enhancement
Zhang et al.[11]	-	ICC >0.85, C-index >0.6 or <0.4, LASSO	GLCM.Inverse Difference Moment Normalized, Maximum 3D Diameter, GLSZM. Large Area High Gray-Level Emphasis, GLCM.Informational Measure of Correlation 1, GLSZM.Large Area High Gray-Level Emphasis, GLSZM.Large Area Emphasis, GLSZM.Large Area Low Gray-Level Emphasis, GLCM.Correlation	Radiomics signature, gender, age, neoadjuvant therapy status, surgery, ki-67, N stage, T stage, CIS status
Zhang et al.[23]	-	ICC >0.75	log_sigma_3_0_mm_3D_NGTDM_Contrast, wavelet LowHighHigh_GLDM_DependenceVariance, wavelet_HHH_NGTDM, wavelet_LowHighHigh_GLCM_correlation, wavelet_LowHighHigh_firstorder_Entropy, wavelet_LowLowLow_GLCM_correlation, wavelet_HighLowLow_GLRLM_RunEntropy, wavelet_LowLowLow_firstorder_10Percentile, wavelet_LowLowHigh_GLCM_Differenceaverage	Radscore + T stage

AJCC = American Joint Committee on Cancer; C-index = univariate concordance index; CCC = concordance correlation coefficient; CIS = carcinoma in situ; CM = co-occurrence matrix; ICC = intraclass correlation coefficient; GLCM = gray-level co-occurrence matrix; GLRLM = gray-level run length matrix; GLSZM = gray-level size zone matrix; LASSO = least absolute shrinkage and selection operator; MLR = multivariate logistic regression; NGTDM = neighborhood gray-tone difference matrix; PCC = Pearson correlation coefficient; RFE = recursive feature elimination; RLM = run-length matrix; SVM = support vector machine; ZSS = Z-score standardization.

robust, stable, and reproducible features is imperative to develop signatures that can be applied across multiple centers and patient cohorts. Future studies should focus on the development of a sustainable signature, trialed in a large-scale prospective setting.

5. Conclusions

Several studies have demonstrated the predictive potential of radiomic and radiogenomic signatures in advanced pelvic oncology. Further large-scale studies in a prospective setting are required to further validate results and allow generalized use in modern medicine.

Take home message

1. Our review demonstrated the current evidence for the predictive potential of radiomics-based nomograms in bladder cancer. Developed signatures had good performance in predicting the primary outcome across included studies.
2. Many of these studies are limited by lack of external validation or prospective design.
3. Multicenter, large prospective trials are required to validate signatures and allow implementation into modern medicine.

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None.

Statement of ethics

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guideline and was registered on PROSPERO, with a registry number of CRD42023396249.

Conflict of interest statement

The authors report no conflict of interest.

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Author contributions

NOS, HT, AC, PL, JM, MK: Conceptualization;
NOS, HT, AC: Data curation;
NOS, HT: Formal analysis;
AC, PL, JM, MK: Supervision;
NOS, HT, AC, PL, JM, MK: Writing—original draft, writing—review and editing.

Data availability

The datasets generated during and/or analyzed during the current study are publicly available. Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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