JSMO 14th Annual meeting
6 Mar 2025

Expression of tumor-associated mucin 1 in bladder and upper urinary tract cancers

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Conflict of Interest disclosure slide for representative speakers or investigators

Research fund	☑ scientific research fund □contract □donation □other （ ） □N/A	Sponsor	Daiichi Sankyo Co. Ltd.

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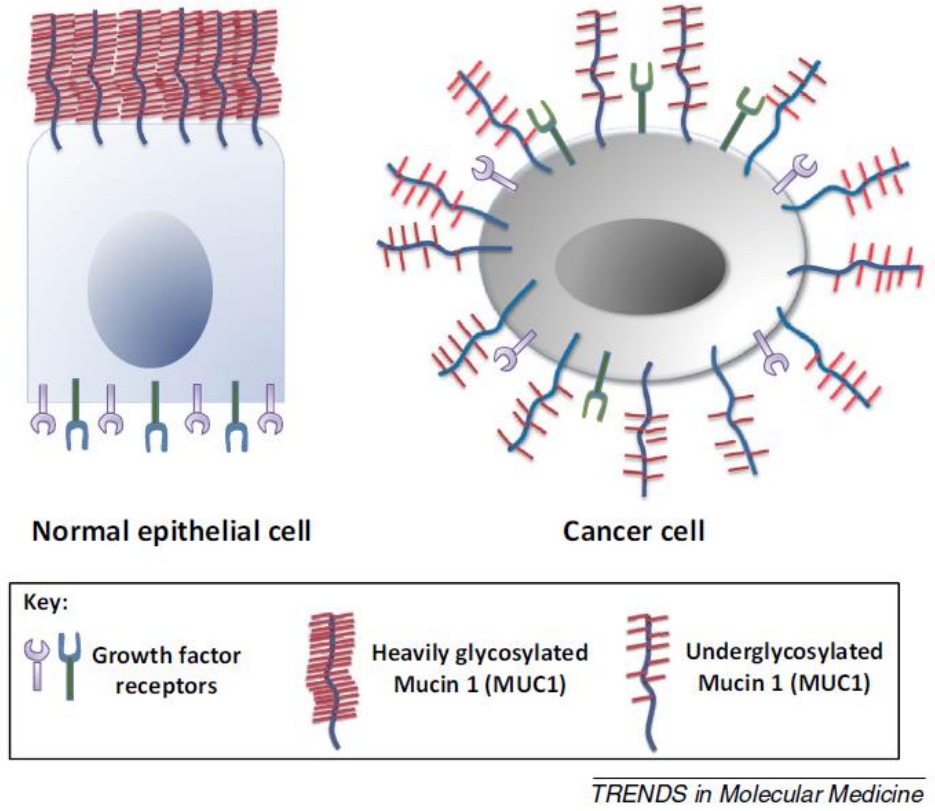
Background

- Mucin 1 (MUC1) is a transmembrane glycoprotein, an important structure in normal epithelial cells that forms a mucus barrier against external stimuli.

- Compared to normal cells, MUC1 expressed in tumor cells is characterized by less glycosylation of the glycoprotein and its expression lacks polarity[1]. It is called tumor associated (TA)-MUC1 and is a potential therapeutic target.

- In head and neck cancer, the higher the tumor grade, the higher the positivity rate (Grade1 29%, Grade2/3 64%), while normal tissue is negative[2].

The relationship between TA-MUC1 expression and prognosis in urothelial cancer has not been clarified yet.



1. Nath S, et al. Trends Mol Med. 2014;20:332-42.
2. Wiest I, et al. Antican Res 2016;36:3179.

Objectives

1. To evaluate TA-MUC1 expression levels immunohistochemically at the time of diagnosis of bladder or upper urinary tract cancer, at the time of bladder resection before or after chemotherapy, and in metastases.

2. To investigate the association between TA-MUC1 expression levels and prognosis and treatment efficacy.

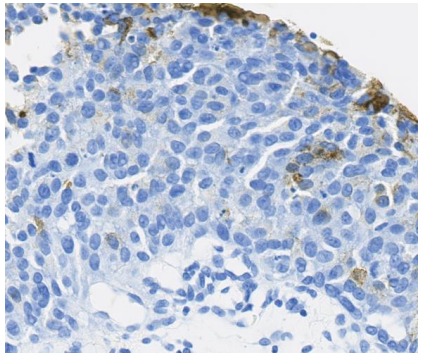
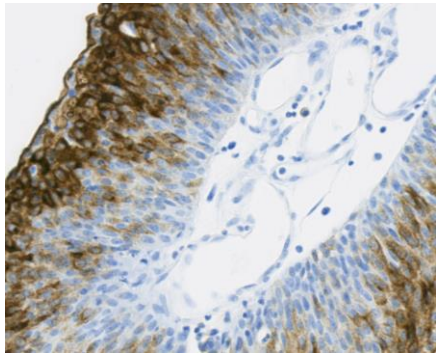
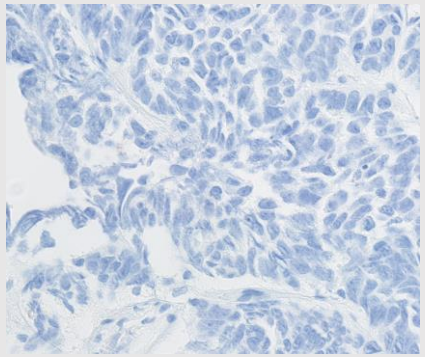
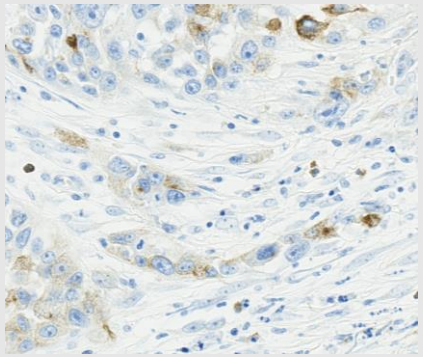
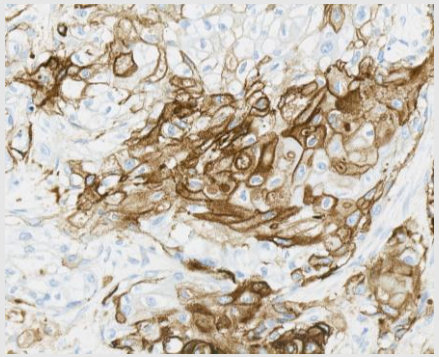
Methods

Patients with bladder or upper urinary tract cancer treated in our institution with non-muscle invasive cancer (NMIC), muscle invasive cancer (MIC), and metastatic cancer (MC) cases with histopathology samples were included.
All patients with MIC and MC were treated with chemotherapy.

This study was designed as a joint research project between the Department of Medical Oncology, Urology, Pathology and Laboratory Medicine, and Division of Cancer Immunology in our institution and Daiichi Sankyo Company, Limited. It was approved by an in-house ethical review based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects (Research Project No. 2021-103).

TA-MUC1 evaluation

FFPE sliced at 5μm, stained with HE and anti TA-MUC1 mAb derived from PankoMab antibody, Daiichisankyo Co., Ltd. Provided.

Score	0	1	2	3
NMIC	None	None		
MIC		None		

Abbreviations: TA-MUC1, tumor-associated mucin 1; FFPE, formalin fixed paraffin embedded; HE, hematoxylin and eosin; mAb, monoclonal antibody; NMIC, non-muscle invasive cancer; MIC, muscle invasive cancer

RNAseq analysis

Total RNA was extracted from 5 um x 5 slides per sample.
RNA-Seq libraries were generated using the SMART-seq standards kit (Takarabio). These libraries were sequenced using the Illumina NextSeq S4. The read sequences were analyzed using the DRAGEN Bio-IT Platform. Mapping was performed to the reference genome sequence (GRCh38), and transcripts per million(TPM) values of genes including MUC1 were calculated.

Caution: TA-MUC1 might not be predicted by MUC1 mRNA since TA-MUC1 is generated by glycosyl modification after transcription of MUC1 protein.

Statistics

- Spearman’s rank correlation coefficient was used to assess the association between MUC1 mRNA and TA-MUC1 immunohistochemistry (IHC) scores.

- Fisher’s exact test was used to evaluate the association between clinical and histological subgroups and TA-MUC1 expression.

- Disease-free survival (DFS) or overall survival (OS) were evaluated in each stages. Survival was evaluated by the Kaplan-Meyer method and log-rank test. Dur to sample size limitation, only MIC treated with perioperative chemotherapy was shown here.

- Statistical analyses were performed using SPSS software (v29, IBM Corp.), with a significance level set at $p < 0.05$.

Patient characteristics 1

		NMIC	MIC	MC
N		60	58	19
Age	Median (range)	68.0 (47-89)	68.0 (38-87)	71.0 (57-84)
Gender	Male	54 (90)	40 (69)	13 (68)
	Female	6 (10)	18 (31)	6 (32)
Primary site	Upper urinary tract	0 (0)	17 (29)	8 (42)
	Bladder	60 (100)	41 (71)	11 (58)
Histology	Pure UC	59 (98)	47 (81)	16 (84)
	UC with variant/ non-UC	1 (2)	11 (19)	3 (16)
Tumor grade	Low Grade1-2	53 (88)	21 (36)	9 (47)
	High Grade 3	7 (12)	37 (64)	10 (53)
Site of sample collection	Original site	60 (100)	57 (98)	15 (79)
	Metastatic site	0 (0)	1 (2)	4 (21)
Method of sample collection	Surgery	1 (2)	23 (40)	7 (37)
	Biopsy	59 (98)	35 (60)	12 (63)

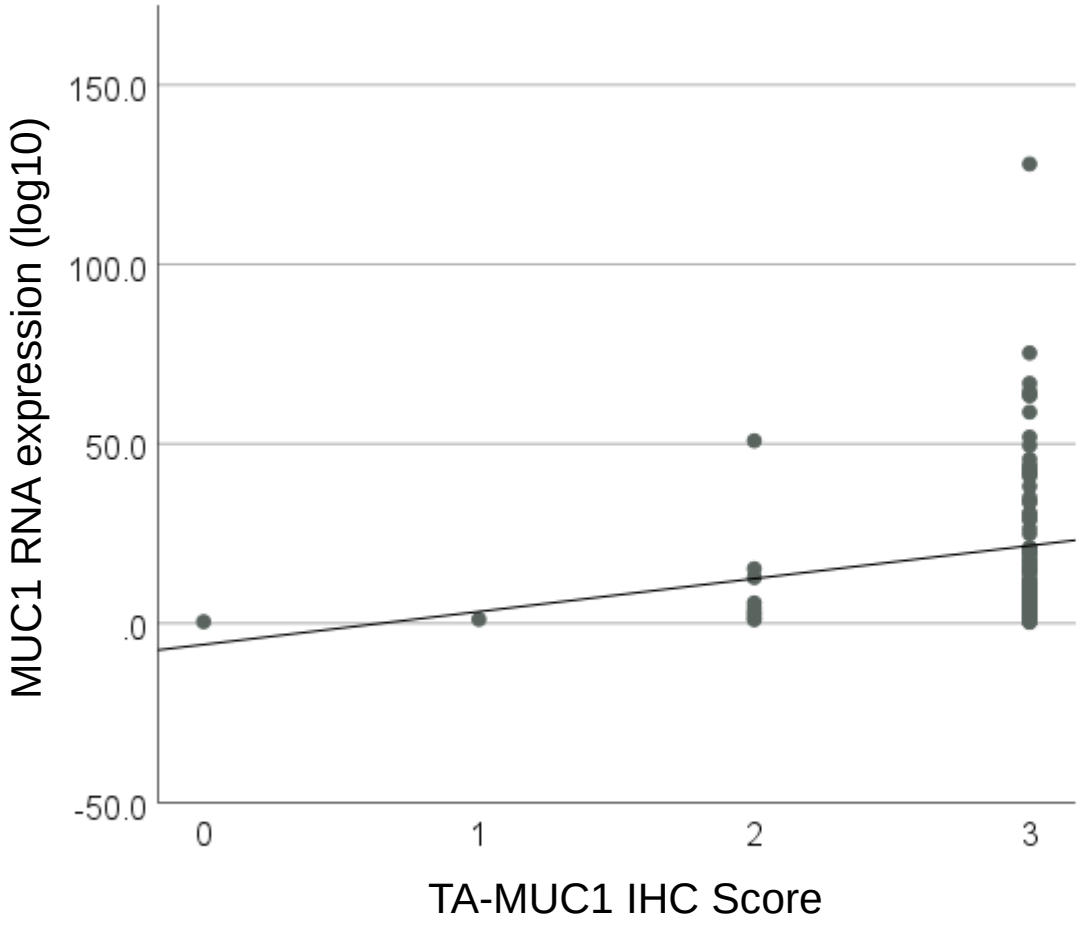
Abbreviations: UC, urothelial carcinoma; NMIC, non-muscle invasive cancer; MIC, muscle invasive cancer; MC, metastatic cancer

Patient characteristics 2

		NMIC	MIC	MC
N		60	58	19
T Stage at diagnosis	Ta	16 (27)	0 (0)	-
	T1	44 (73)	0 (0)	-
	T2	-	16 (28)	-
	T3	-	38 (65)	-
	T4	-	4 (7)	-
Clinical/ pathological stage at diagnosis	0a	15 (25)	-	-
	I	45 (75)	-	-
	II	-	14 (24)	-
	III	-	37 (64)	-
	IV	-	7 (12)	-
Perioperative chemotherapy	Neoadjuvant	-	35 (60)	-
	Adjuvant	-	23 (40)	-
	None	-	0 (0)	-

Abbreviations: NMIC, non-muscle invasive cancer; MIC, muscle invasive cancer; MC, metastatic cancer

Correlation between IHC score and mRNA expression levels



Spearman correlation analysis
R = 0.215
p = 0.019

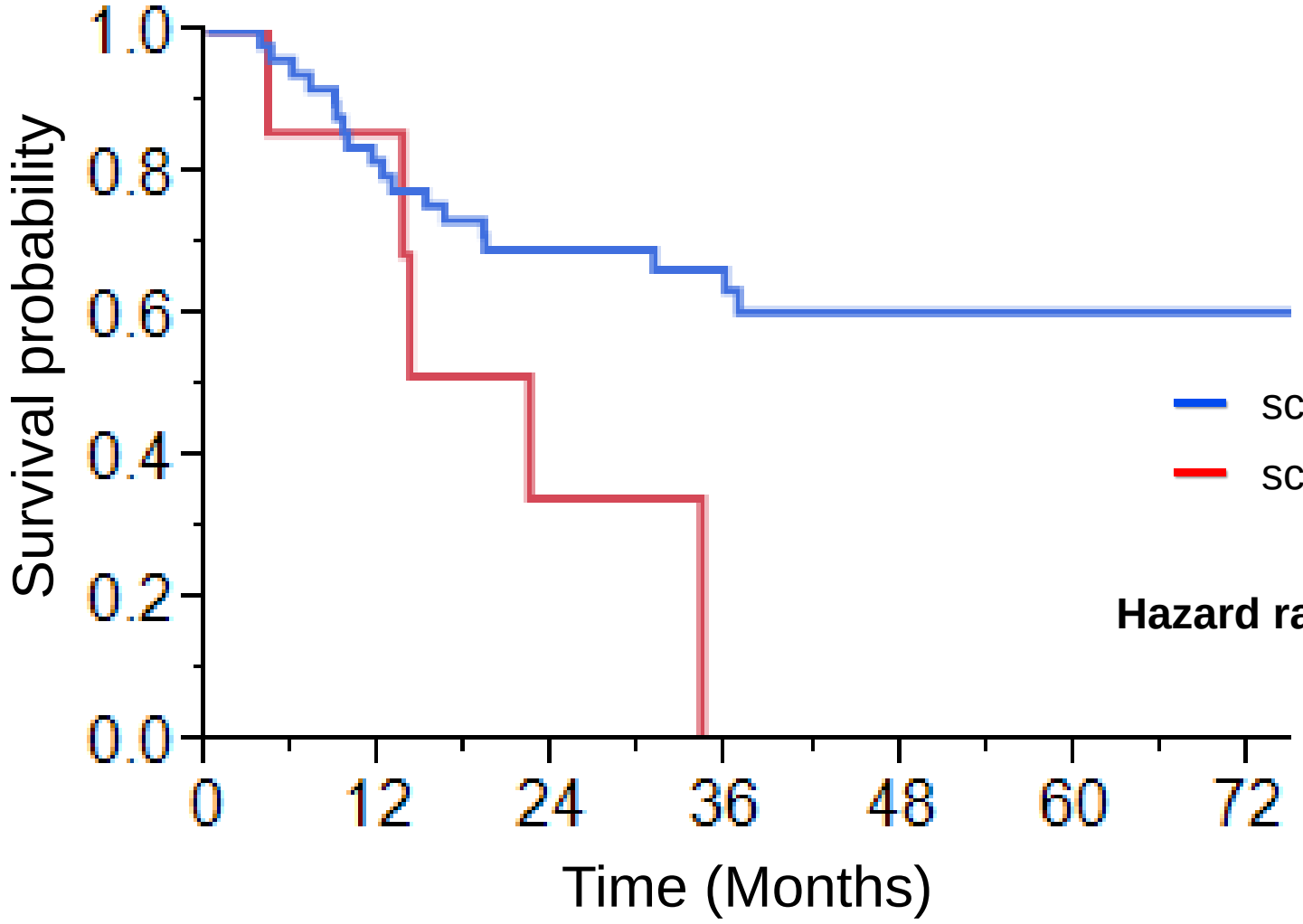
Clinicopathological evaluation and TA-MUC1 expression (IHC score)

*p<0.05

		Score 0-2	(%)	Score 3	(%)	p (IHC 0-2/3)
Primary site	Upper urinary tract	2	(9)	21	(91)	1.000
	Bladder	10	(9)	102	(91)	
Site of Sample collection	Original site	11	(8)	119	(92)	0.377
	Metastatic site	1	(20)	4	(80)	
Histology	pure UC	9	(8)	111	(92)	0.132
	UC with variant/ non-UC	3	(20)	12	(80)	
Tumor grade	Low grade 1-2	2	(2)	79	(98)	0.003*
	High grade 3	10	(19)	44	(81)	
Stage	NMIC (0-I)	1	(2)	58	(98)	0.018*
	MIC (II-IVA)	7	(12)	50	(88)	
	MC (IVB)	4	(21)	15	(79)	

Abbreviations: TA-MUC1, tumor-associated mucin 1; IHC, immunohistochemistry; UC, urothelial carcinoma; NMIC, non-muscle invasive carcinoma; MIC, muscle invasive carcinoma; MC, metastatic carcinoma

DFS and TA-MUC1 expression in MIC

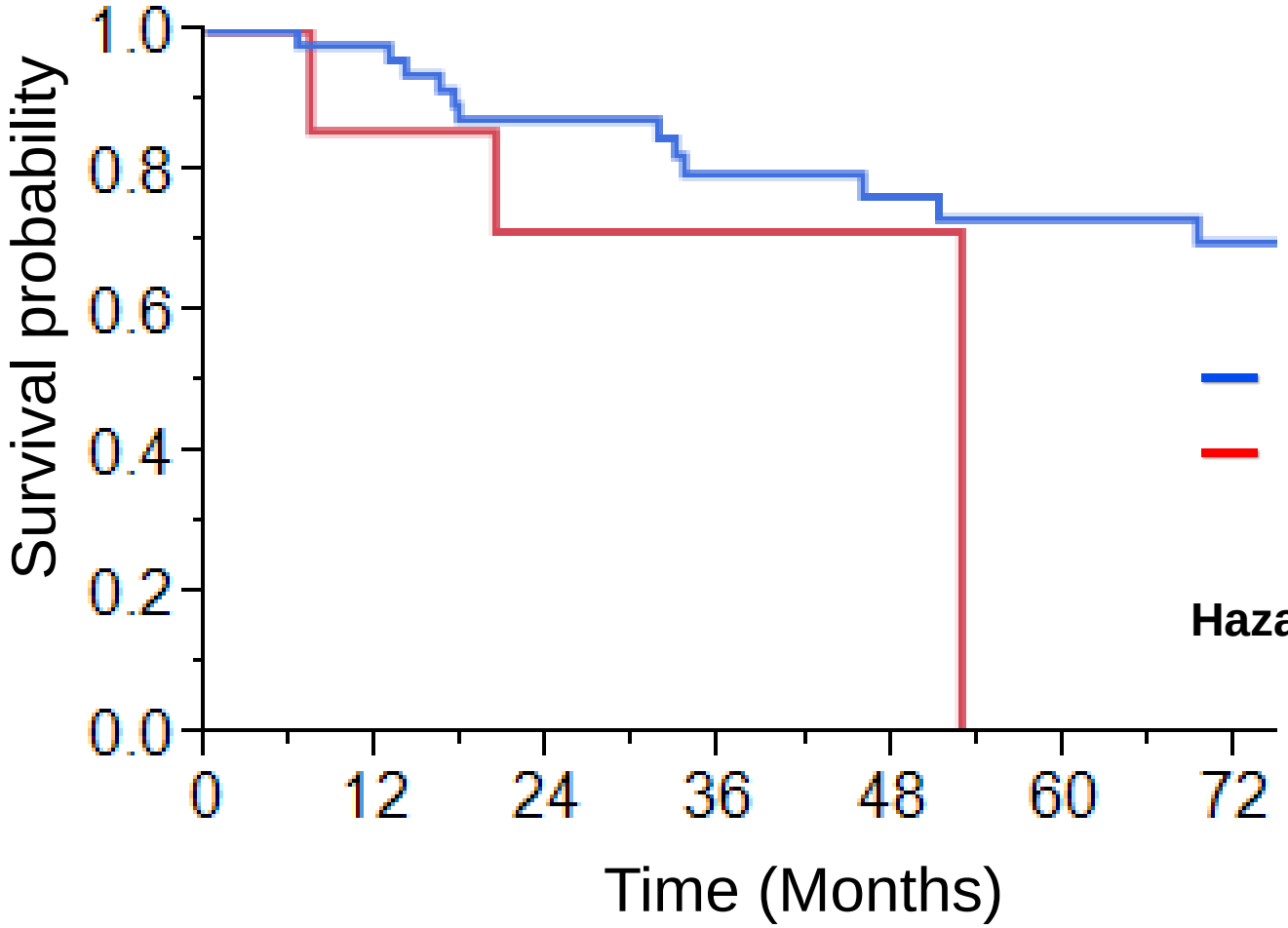


	Event/ Patient	Median (months)	95% CI
score 3	18/50	NR	35.8-NE
score 0-2	5/7	22.3	4.2-34.2

Hazard ratio 0.27 (95% CI, 0.10-0.71), p=0.008

Abbreviations: DFS, disease-free survival; TA-MUC1, tumor-associated mucin 1; MIC, muscle invasive carcinoma; CI, confidential interval; NR, not reached; NE, not evaluated

OS and TA-MUC1 expression in MIC



	Event/ Patient	Median (months)	95% CI
score 3	14/50	NR	76.3-NE
score 0-2	3/7	52.8	7.3-52.8

Hazard ratio 0.27 (95% CI, 0.07-1.10), p=0.067

Abbreviations: OS, overall survival; TA-MUC1, tumor-associated mucin 1; MIC, muscle invasive carcinoma; CI, confidential interval; NR, not reached; NE, not evaluated

Summary

- TA-MUC1 IHC score and MUC1 mRNA showed a statistically significant association, but it is also possible that the sample size was too small to fully analyze.
- TA-MUC1 was highly expressed over 90% of cases in the upper urinary tract and bladder, with the histological type being pure urothelial carcinoma.
- IHC score of TA-MUC1 tends to be slightly lower in high-grade tumors and advanced stages.
- In patients with MIC treated by perioperative chemotherapy, DFS and OS tended to have a worse prognosis with lower IHC score in TA-MUC1.

Conclusion

Although some low expression groups exist, TA-MUC1 is widely highly expressed in patients with bladder and upper urinary tract cancer, which suggests its potential as a future therapeutic target.