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The Use of Desmocollin-2 and Cytokeratin-14 for Detection of Squamous Cell Carcinoma and Squamous Differentiation in Urothelial Carcinoma

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Abstract

Objective: To investigate Desmocollin-2 (DSC-2) compared to Cytokeratin-14 (CK-14) for detection of Squamous Cell Carcinoma (SCC) and squamous differentiation of Urothelial Carcinoma (UC) of the urinary bladder.

Methods: The study included 90 cases of radical cystectomy specimens (69 and 21) divided into 35 cases SCC, 38 cases UC, 13 cases undifferentiated carcinoma and 4 cases adenocarcinoma. The tissue blocks were examined for the expression of DSC-2 and CK-14 using the immunohistochemical technique.

Results: DSC-2 was expressed in 35.5% of UC, 100% of SCC and 54% of undifferentiated carcinoma, and is correlated with SCC Grade and clinical stage. CK-14 was expressed in 35.5% of UC, 100% of SCC and 69% ofundifferentiated carcinoma and its expression is correlated with SCC tumor stage. DSC-2 had a sensitivity of 85.7% and a specificity of 79.2% compared to a sensitivity of 100% and a specificity of 83.3% for CK-14 in detecting SCC and squamous differentiation of UC.

Conclusion: DSC-2 is a new marker for detection of SCC and squamous differentiation of UC of the urinary bladder.

Key Words: *DSC-2 – CK-14 – SCC – UC – Immunohistochemistry.*

Introduction

BLADDER cancer is still the most common malignant tumor among males in Egypt and some African and Middle East countries; however, the frequency rate of bladder cancer has declined significantly during the last 25 years. This drop is mainly due to the control of schistosomiasis **[1]**.

Urothelial carcinoma with squamous differentiation occurs in up to 40-60% of UC cases. It is often high-grade and high stage tumors that are thought to be associated with a poorer prognosis and response to both chemotherapy and radiotherapy compared to UC without squamous differentiation **[2]**.

Distinguishing invasive high grade UC from poorly differentiated SCC may be difficult. High grade UC may also demonstrate a squamous appearance and thus morphologically overlap with invasive UC **[3]**.

Much evidence now attests to the importance of desmosomes and their constituents in cancer. Alteration in the expression of the desmosomal components could contribute to the progression of the disease by modifying intracellular signal transduction pathways and/or by causing reduced cell adhesion. Loss of desmosomal adhesion is a prerequest for the epithelial-mesenchymal transition, implicated in the conversion of early stage tumors to invasive cancers **[4]**.

Desmocollin-2 (DSC-2), a trans-membrane glycoprotein belonging to the desmosomal cadherin family has been found to be differentially expressed in several types of cancer and to be involved in tumor progression. A reduction in the expression of DSC-2 has been reported in numerous types of carcinomas including colorectal, pancreatic, gastric, lung and urothelial cancer. It has been suggested that a reduction in the expression of DSC-2 may act as an independent biomarker for reduced survival **[5]**.

Cytokeratin is one of the three types of intermediate filaments that constituted the cytoskeleton of epithelial cells. At least, 20 different keratin genes located either on chromosome 12 or 17 have been described. Type I CKs are small, acidic and

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encoded by genes located on chromosome 17 whereas type II CKs are large, basic and encoded by genes on chromosome 12. CK-14 is consistently expressed in basal cells of multilayered epithelia, myoepithelial cells of the breast, salivary and sweat glands, Hassall's corpuscles of the thymus, parathyroid glands, hair follicle's outer root sheath, sebaceous glands and mesothelial cells [6].

Immunostaining for cytokeratin-14 identifies an early phenotypic switch from urothelial to squamous epithelium in bladder mucosa. CK-14 immunostaining is sufficiently sensitive to identify early squamous metaplasia which is not yetevident on examination of routine H & E stained sections [7].

Aim of the work: To investigate Desmocollin-2 (DSC-2) compared to Cytokeratin-14 (CK-14) for detection of Squamous Cell Carcinoma (SCC) and squamous differentiation of Urothelial Carcinoma (UC) of the urinary bladder.

Material and Methods

A total number of 90 cases of radical cystectomyfor cancer bladder werereceived from the Urology Department. The clinical data including age, sex, size of the tumor, and tumor clinical stage were obtained from the patients' medical records sheets. The specimens were collected at the Pathology Department during the period from January 2011 to October 2013.

H & E staining: Five microns thickness tissue sections were prepared from the formalin-fixed paraffin-embedded tissue blocks. Deparaffinized in xylol and rehydrated through down-graded concentrations of ethanol, the slides were stained with Hematoxyline for 2-5min and Eosin for 3-7min. The slides were dehydrated in up-graded concentrations of ethanol, cleared in xylol and mounted with DPX. Each slide was examined by three pathologists and a full report was written for every case including the histopathological diagnosis. The UC were graded according to WHO/ISUP [8] and were classified according to The American Joint Committee on Cancer (AJCC) staging system. SCC was classified according to WHO/ISUP grading criteria [9]. Pathological staging of the tumors (depth of invasion and lymph node status) were done according to (AJCC) [10].

Immunohistochemical staining of DSC-2 and CK-14:

Three slides from each case block were prepared and five-micron thickness tissue sections were deparaffinized, rehydrated and incubated with hydrogen peroxide for 10min before washing in Phosphate Buffer Saline (PBS) to block endogenous peroxidase activity. The tissue sections were incubated with proteinase K enzyme for 5min at room temperature and the slide were placed in 1 0mmol sodium citrate buffer solution pH 6 in the microwave oven for 15min divided into three, 5min each then the sided were allowed to cool at room temperature, rinsed in distilled water and placed in PBS form 5min. Nonspecific protein binding was blocked by exposure to 10% normal goat serum for 1 0min. Few drops of DSC-2 (Rabbit polyclonal AB against DSC-2, catalog # D3221-49-US Biological, Life science, USA) at dilution 1/100 were added for 2h in a humid chamber. CK-14 was added at a dilution 1/400 overnight in a humid chamber (Mouse monoclonal AB against human CK-14, catalog # MS-115-P0, LAB Vision Corporation, Fremont, USA). The slides were rinsed in PBS, then two drops of biotinylated goat serum polyvalent was applied to each section for 10min, then the slides were rinsed with PBS. Streptavidin peroxidase was added to each slide and incubated for 10min at room temperature before washing in PBS. DAB chromogen then added to eachslide, incubated for 10min at room temperature then washed in distilled water. Normal skin was the positive control for both DSC-2 and CK-14. The slides were counterstained with Mayer's hematoxyline for 1min before washing in distilled water and mounted with DPX with coverslips.

Evaluation of immunostained slides:

DSC-2 immunostain appeared as membranous brown stainand CK-14 appeared as cytoplasmic brown stain. Immunostain Reactive Score (IRS) was calculated by multiplying the staining intensity and quantity as followed according to [11].

Percentage of positivecells. Intensityof staining. IRS (0-12).

0=No positive cells.	0=No color reaction.	0-1=Negative.
1=(>10%) positive cells.	1=Mild reaction.	2-3=Mild.
2=(10-50%) positive cells.	2=Moderate reaction.	4-8=Moderate.
3=(51-80%) positive cells.	3=Intense reaction.	9-12=Strong.
4=(<80%) positive.		

The results were statistically analyzed using SPSS (16) for Windows. Pearson's correlation coefficient was used according to [12], and Chi-square tests were used to evaluate statistical significance of various parameters with p-value less than 0.05 was considered significant [13].

Results

DSC-2 was expressed in all 30 cases of squamous metaplasia, in 6/7 cases of invasive UC with foci of squamous differentiation in addition to other 5/24 (20.8%) of cases of invasive pure UC. DSC-2 was expressed in all cases of SCC and in 7/13 (53.8%) of cases of undifferentiated carcinoma [(Table 2) & Fig. (3)]. No cases of adenocarcinoma showed DSC-2 immunostaining. DSC-2 immunostaining in UC was correlated with tumor stage (p=0.01) and the presence of squamous differentiation in UC (p=0.02). DSC-2 expression in SCC was correlated to tumor grade (DSC-2 immunostaining was higher in Grade I and II than in Grade III) with (p=0.001) and LN metastasis (p=0.018). DSC-2 had a sensitivity of (85.7%), a specificity of (79.2%) and a positive predictive value of (54.5%) for areas of squamous differentiation in UC and a negative predictive value of (95%) for pure UC (Table 4).

There was no statistically significant correlation between DSC-2 expression and the age of the patient, sex, tumor size, or the presence of bilharziasis, in either SCC or UC.

CK-14 was expressed in 7/7 cases of invasive UC with squamous differentiation, in addition to 4/24 (16.7%) of cases of pure UC, in all cases of SCC (35 cases), in 9/13 (69.2%) of cases of undifferentiated carcinoma [(Table 3) & Fig. (4)]. There was a statistically significant correlation between CK-14 expression in UC and tumor stage (p=0.015) and squamous differentiation in invasive UC (p= 0.02). There was a highly statistically significant correlation between CK-14 expression and UC with squamous differentiation and pure UC and between SCC, invasive UC with squamous differentiation and pure invasive UC (p=0.000). CK-14 had a sensitivity of (100%), a specificity of (83.3%), a positive predictive value of (63.6%) for areas of squamous differentiation and a negative predictive value of (100%) for pure invasive UC (Table 4).

CK-14 immunostaining was not correlated with age, sex, tumor size, tumor grade, LN metastasis, or the presence of bilharsiasis in both SCC and UC.

There was positive correlation between DSC-2 and CK-14 expression in UC and SCC (Pearson's coefficient = 0.8 1, p-value=0.000 and 0.42, and p=0.011) respectively. There was a highly statistically significant difference in expression of DSC-2 (p=0.000) and CK-14 (p=0.000) among different types of bladder carcinomas (SCC, UC and adenocarcinoma).

Table (1): Different histopathological types in the study.

Histological diagnosis	No. of cases	GI	GII	GIII	Bilharz	Squadifferen
Invasive UC	31	4		27	9	7
Non invasive UC	7					
SCC	35	9	12	14	26 (74.3%)	
Undifferen	13			13		
Adeno	4	4				
Total	90				35 (39%)	7

Table (2): DSC-2 expression in different histopathological cases.

Histological diagnosis	No	GI	GII	GIII	DSC-2			No	p-value
					+	++	+++		
Noninvasive UC	7		–						
Invasive UC	31	4	–	27	3	6	2	11 (35.5%)	
SCC	35	9	12	14	3	13	19	35 (100%)	0.001
Undifferentiated C	13	–	–	–	2	–	5	7 (53.8%)	
Adenocarcinoma	4	–	–	–	–	–	–		

Table (3): CK14 expression in the study groups.

Histopathology	No.	CK-14+			GI	GII	GIII	No	*p*-value
		+	++	+++					
Invasive UC	31	5					5	5 (16.1%)	0.001
Non invasive UC	7								
UC and Sq Diff	7	6			–	–	6	6	
SCC	35	1133			9	12	14	35 (100%)	
Undifferentiated	13	225			–	–	9	9 (69.2%)	
Adenocarcinoma	4								

Table (4): Comparison between DSC-2 and CK-14 statistical results.

Parameter	DSC-2	CK-14
Sensitivity	85.7%	100%
Specificity	79.2%	83.3%
Positive predictive value	54.5%	63.6%
Negative predictive value	95%	100%

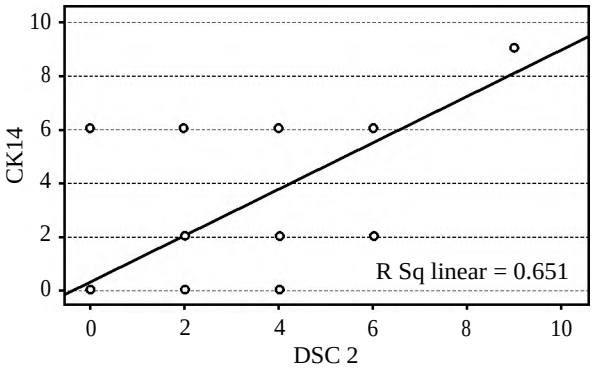

Fig. (1): Pearson's correlation coefficient (*r*) of DSC-2 expression with CK-14 in invasive UC.

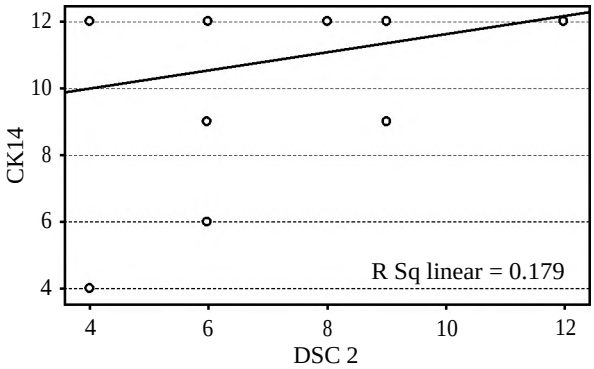

Fig. (2): Pearson's correlation coefficient (*r*) of DSC-2 expression with CK-14 in SCC.

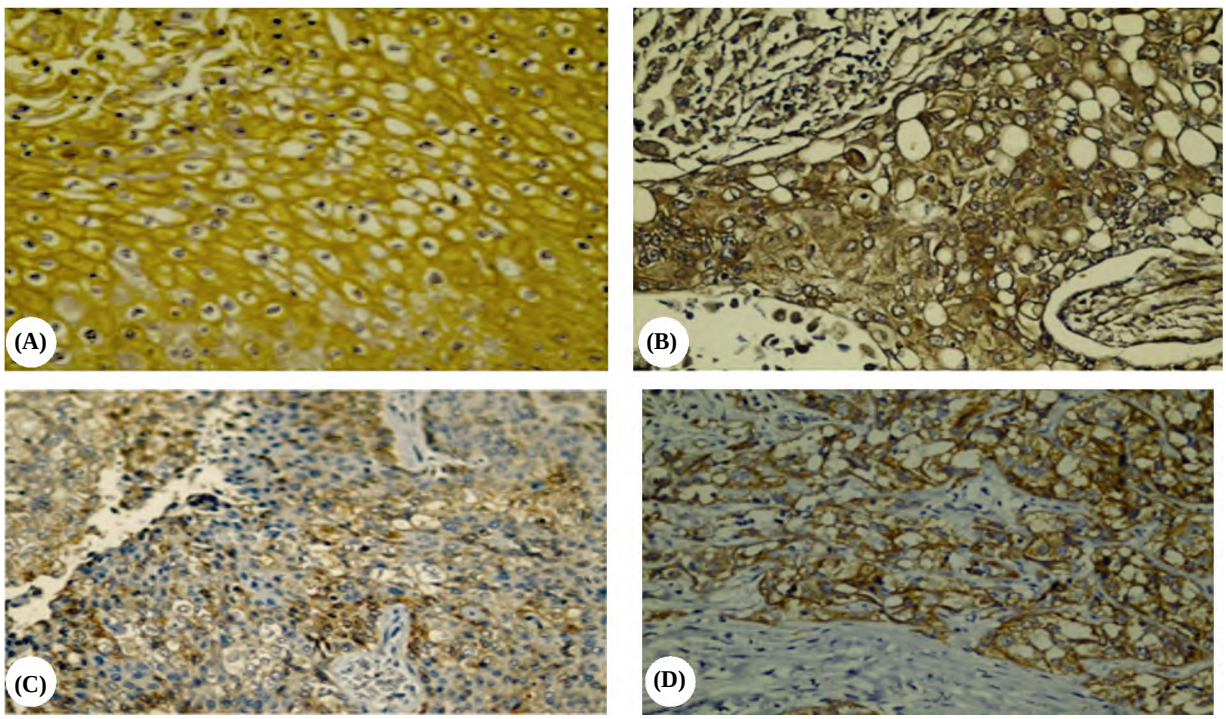

Fig. (3): (A) Grade II, (B) III Squamous cell carcinoma showed strong DSC-2 expression. (C) Urothelial carcinoma with foci of squamous differentiation showed DSC-2 expression. (D) Undifferentiated carcinoma with DSC-2 expression.

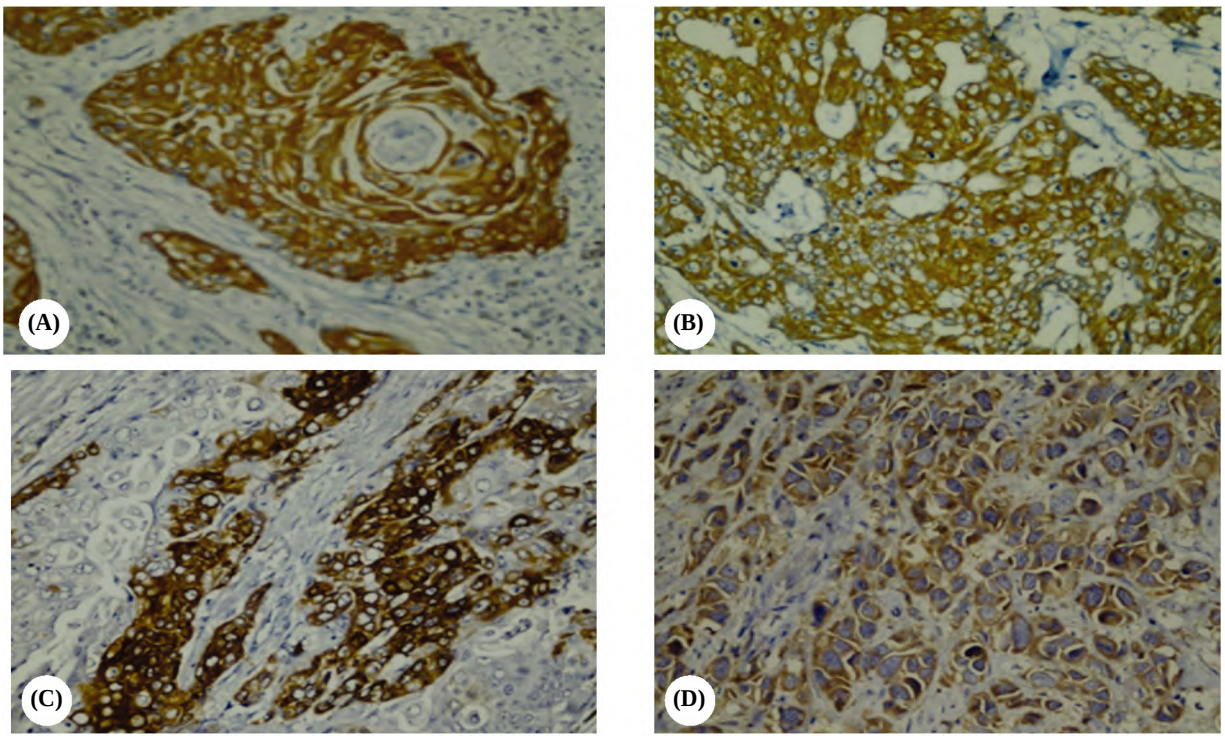

Fig. (4): Squamous cell carcinoma Grade I (A) & II (B) with strong CK14 expression. (C) Urothelial carcinoma with CK14 expression. (D) Undifferentiated carcinoma with CK14 immunostaining.

Discussion

An estimated 386, 300 new cases and 150, 200 deaths from bladder cancer occurred in 2008 worldwide. The majority of bladder cancer occurs in males and there is a 14-fold variation in incidence internationally. Egyptian males have the highest mortality rate (16.3/100000). Smoking and occupational exposures are the major risk factors in Western countries whereas chronic infection with schistosoma Hematobium in developing countries, particularly in Africa and the Middle East; accounts for 50% of the total burden **[14]**.

A majority of bladder cancers associated with Schistosomiasis are squamous cell carcinoma, while those associated with smoking are transitional cell carcinoma. Bladder cancer continues to be the most common cancer among males in Egypt despite the large decreases in schistosoma-associated bladder cancer. This is likely the result of a reduction in schistosoma-related bladder cancer being offset by an increase in tobacco-related bladder cancer **[15]**.

Squamous differentiation of urothelial carcinoma showed disease recurrence after radical cystectomy in 64% of patients compared to 34% in patients with pure UC. Squamous differentiation of UC was an independent prognostic factor for cancer-specific survival in patients treated with radical cystectomy together with pathological stage, tumor size and LN involvement in multivariate analysis **[16-17]**.

The patients' ages in our study ranged between 34-85 years with mean age 55.5 years and the highest age incidence was 46-55 years and male to female ratio was 2.5:1. Gouda et al., demonstrated an increase in median age of patients from 47.4 to 60.5 years with an increase in urothelial carcinoma from 16% to 65.8% and a decrease in SCC from 75.9% to 28.4% **[18]**. In Salem and Mahfouz study the mean age incidence was 41 ± 11.2-52±8.6 years and the male to female ratio was 4.2:1 with an increased in TCC from 20% to 66% and a decrease in SCC from 73% to 25% **[19]**, while another study documented that the highest age incidence was 55-65 years for SCC and 65-75 years for UC and male to female ratio was 4.3:1 **[20]**.

An increase in the prevalence of smoking in Egypt is believed to have contributed to the shift towards urothelial carcinoma as that tumor type has a strong association with smoking **[18]**.

Cigarette smoking was associated with 2-6 times increased risk of urothelial carcinoma, while a history of schistosomiasis was associated with increased risk of both UC and SCC in women and men **[21]**.

DSC-2 is a calcium-dependent glycoprotein which is a major intercellular adhesive junction in squamous epithelium that is a member of the desmocollin subfamily of the cadherin superfamily. These are found primarily in epithelial cells where they constitute the adhesive proteins of the desmosomes cell-cell junction and are required for cell adhesion and desmosome formation. The desmosomal family members are arranged in two clusters on chromosome 18; occupying less than 650Kb combined [22].

In the present study DSC-2 was expressed in all cases of squamous metaplasia (30 cases), and SCC (35 cases) whileit was expressed in only 4/24 cases of UC and 7/13 cases of undifferentiated carcinoma in agreement with Hayashi et al., study where DSC-2 was detected in 24/25 patients of UC with squamous differentiation but none of 85 cases of pure UC. DSC-2 in their study offers a high sensitivity (96%) and a high specificity (100%) for the detection of squamous differentiation in UC. DSC-2+SCC had a worse prognosis than DSC-2-SCC cases and are correlated with higher stage and poor prognosis [22].

In our study DSC-2 had a sensitivity of (85.7%) and a specificity of (79.2%) and a positive predictive value of (54.5%) for the squamous differentiation in UC. There was a statistically significant correlation between DSC-2 expression and LN metastasis in SCC in agreement with two studies [5,22] who found that DSC-2 expression was correlated with LN metastasis in esophageal SCC. This finding was explained previously by Khan et al., as the significant reduction in DSC-2 expression reduces the adhesion between epithelial cells resulting in an increased propensity of the cells to proliferate, invade surrounding tissues and undergo metastasis [23].

In the current study, DSC-2 expression in SCC Grade I and II was higher than in Grade II (p= 0.001) in agreement with Fang et al., who found that DSC-2 expression was prominent in normal esophageal epithelium and well differentiated esophageal tumors with reduced expression in poorly differentiated tumors specimen [24]. These results indicated that down regulation of DSC-2 is involved in the transformation and development of SCC of the urinary bladder and that DSC-2 expression was correlated with poor differentiation and may serve as a predictor for prognosis and outcome in patients with SCC of the urinary bladder.

A recent study found in their study that DSC-2 showed increased expression in tumor cells in acantholytic SCC and conventional SCC. It might suggest an immature phenotype of neoplastic cells because DSC-2 is normally found in the basal layers accordingly, overexpression of DSC-2 may play an important role in cancer development [25].

Absolute negativity of DSC-2 in cases of adenocarcinoma of the urinary bladder that observed in our study is similar to the result found by Hayashi et al. This finding is valuable in the distinction of poorly differentiated adenocarcinoma from poorly differentiated SCC of the urinary bladder [22].

Cytokeratin can be divided into two types; basic, type II, CK1-CK8 and the acidic, type I, CK9-CK20. Cytokeratin profile tends to remain constant when epithelium undergoes malignant transformation. The main clinical implications is that the study of cytokeratin profile by immunohistochemistry technique is widely used for tumor diagnosis and characterization in surgical pathology [26].

In our study CK-14 was expressed in (100%) of squamous metaplasia in agreement with earlier studies found that all cases of squamous metaplasia showed positive cytoplasmic immunostaining for CK-14 [7,27]. Hammam et al., found in their study that CK14 was expressed in (58%) of UC with morphological areas of squamous differentiation while Gulmann et al., found that CK-14 was expressed in pure SCC in (100%), in pure UC in (27%) and urothelial carcinoma with squamous differentiation in (87%) of cases [28,29]. These results indicate that CK-14 is valuable in recognition of sites of squamous metaplasia of the surface urothelium of the bladder and its early management before SCC can occur.

In our study CK-14 was expressed in 7/7 cases of invasive UC with squamous differentiation with foci of squamous differentiation and focal positivity for CK-14 was also detected in 4/24 cases of pure UC with no morphological evidence of squamous differentiation suggesting that it is a probable foci of early squamous phenotypic switch. CK-14 had a sensitivity of (100%), a specificity of (83.3%), positive predictive value of (63.6%) for the area of squamous differentiation and a negative predictive value of (100%) for pure invasive UC. These results are in agreement with Mostafa et al., also found that CK-14 was expressed in 6/7 cases of UC with definite and probable foci of squamous differentiation, and CK-14 had a sensitivity of (85.7%), a specificity of (100%) and a positive predictive value of (100%) for the areas of squamous differentiation in pure UC and a negative

predictive value of (91%) for pure UC **[27]**. Gaisa et al., found that (57.1%) of cases of UC showed CK-14 positive expression while in our study it was (35.5%) of UC that showed CK-14 immunostaining **[30]**. These different findings can be explained by the fact that they used a different technique (tissue microarray) and a larger number of cases (89 SCC+UC) and (66 UC). They found in their study that CK-14 was expressed in (95.8%) of SCC cases which is similar to the current study finding (100%) in SCC) and Chu et al., also found that CK-14 was constantly expressed in SCC even in poorly differentiated SCC, regardless the organ in which they arise **[31]**.

Considering the high sensitivity and specificity of both DSC-2 and CK-14 in the detection of foci of squamous differentiation in cases of UC, DSC-2 and CK-14 are sensitive markers to identify early squamous differentiation which is not yet clear on routine H and E stained sections and the combination of these two markers may aid in distinguishing poorly differentiated SCC from high grade UC andpoorly differentiated adenocarcinoma.

Conclusion:

Desmocollin 2 (DSC-2) is a new immunohistochemical marker indicative of squamous differentiation in urothelial carcinoma. It can be used to separate UC with squamous differentiation from pure UC especially in high grade tumors.

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الملخص العربى

أهداف البحث: دراسة ظهور الديسموكولين-٢ بالمقارنة بالسيتوكيراتين-١٤ فى تحديد سرطان الخلايا الحرشفية والتغيرات الخلايا الحرشفية فى سرطان الخلايا الانتقالية بالمثانة البولية.

طريقة البحث: يتضمن البحث ٩٠ حالة استئصال كلى للمثانة منها ٦٩ رجل و٢١ سيده مقسمين الى: ٣٥ حالة سرطان الخلايا الحرشفية و٣٨ حالة سرطان الخلايا الانتقالية و١٣ حالة سرطان المثانة الغير متميز و٤ حالات سرطان الخلايا الغدية. يتم فى الدراسة فحص التعبير المناعى لكل من الديسموكولين-٢ والسيتوكيراتين-١٤ بعد الصبغة الروتينية.

نتائج البحث: تم تحديد الظهور المناعى للديسموكولين-٢ فى ٣٥.٥٪ من حالات سرطان الخلايا الانتقالية وفى ١٠٠٪ من حالات سرطان الخلايا الحرشفية وفى ٥٤٪ من حالات سرطان المثانة الغير متميز وكان الظهور المناعى له يرتبط احصائيا بالمرحلة الاكلينيكية للورم ومدى تميزه.

الظهور المناعى للسيتوكيراتين-١٤ تبين فى ٣٥.٥٪ من حالات سرطان الخلايا الانتقالية وفى ١٠٠٪ من حالات سرطان الخلايا الحرشفية وفى ٦٩٪ من حالات سرطان المثانة الغير متميز وكان الظهور المناعى له يرتبط احصائيا بالتطور الاكلينيكى للورم.

بلغت قيمه التخصص النوعى للديسموكولين حوالى ٧٩.٢٪ وحساسيتة لتحديد نوع الخلايا الحرشفية بالاورام ٨٥.٧٪ مقارنة بحساسية السيتوكيراتين التى بلغت حوالى ١٠٠٪ والتخصص النوعى له التى بلغت ٨٣.٣٪ فى تحديد الخلايا الحرشفية لسرطان الخلايا الانتقالية بالمثانة.

خلاصة البحث: يعتبرالديسموكولين-٢ من احدث دلالات الاورام لتحديد سرطان الخلايا الحرشفية والتغيرات الحرشفية لسرطان الخلايا الانتقالية بالمثانة البولية.