Review Article

The dysregulation of Cyclin-Dependent Kinase Regulators Role in SV40 Related renal cell Carcinoma

Abstract:

This research used PCR and immunohistochemical techniques to evaluate the assistance of SV40 polyomavirus infection to the progression of renal cell carcinoma in patients from the province of Al Najaf.

This presentstudy was planned as a cross-section study to detect SV40 with renal cell carcinoma and includes 75 (45 males and 30 females, whose ages ranged from 22 to 70 years) paraffin impeding block tissues of renal cell carcinoma from archives of AL-Sader Medical City and some archives of private histopathology laboratories in Najaf governorate. The data are from January 2016 to December of the same year by using Polymers Chain Reaction (P.C.R) for the detection of DNA SV40 and immunohistochemistrytechnique (IHC) for detectingthe expression state of Cyclin-Dependent Kinase Regulators (KAP orcyclin-dependent kinase inhibitor 3(CDKN3)& Cyclin E1 markers), using Hematoxylin and Eosin stain for diagnosis of RCC.

An increased positive percentage for KAP or CDKN3 marker and a decreased positive percentage of Cyclin E1 marker were seen in the results of the Immunohistochemistry technique (IHC).Also, it found that clear cell type was higher with **42 (56%),** grade I was higher with 31 (41.3%), and tumor stage type I was higher (25). The positive results of PCR techniques in RCC patients showed that 20 (26.7% out of 75 cases) block tissues. The associationof RCC with SV40 is mostly caused by the dysregulation of Cyclin-Dependent Kinase regulators (CDK). It is clear from this study that the Simian Virus 40 (SV40), in particular its Large T Antigen (Tag), affects CDK regulators and upsets the delicate equilibrium of cell cycle regulation systems. There may be a connection between renal cell carcinoma development and the SV40 polyomavirus. Renal cell carcinoma patients are thought to undergo routine testing for detection using PCR and IHC methods.

OR [Suggested writeup for Abstract]

The purpose of this study was to explore the possible involvement of SV40 polyomavirus in the development of renal cell carcinoma (RCC) in patients from the province of Al-Najaf. The study analyzed 75 paraffin-embedded block tissues of RCC, collected from archives of AL-Sader Medical City, and some private histopathology laboratories in Najaf governorate. The patients included 45 males and 30 females, aged between 22 and 70 years. The study used advanced scientific techniques, including Polymerase Chain Reaction (PCR) and immunohistochemistry (IHC), to detect the presence of SV40 and evaluate the expression state of Cyclin-Dependent Kinase Regulators (KAP or cyclin-dependent kinase inhibitor 3 (CDKN3) & Cyclin E1 markers). Hematoxylin and Eosin staining was used for diagnosing RCC. The study found that RCC is associated with the dysregulation of Cyclin-Dependent Kinase regulators (CDK), caused by the SV40 polyomavirus. The results of the IHC analysis showed an increased positive percentage for KAP or CDKN3 marker and a decreased positive percentage of

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Cyclin E1 marker. Additionally, the clear cell type was found to be the most common, accounting for 56% of the cases, while grade I was the most prevalent, representing 41.3% of the cases. Tumor stage type I was found to be higher, with 25 cases. PCR detected the presence of SV40 in 20 cases, accounting for 26.7% of the total cases studied. The study concluded that the Simian Virus 40 (SV40), particularly its Large T Antigen (Tag), affects CDK regulators and disrupts the delicate equilibrium of cell cycle regulation systems. Therefore, the study suggests a possible link between the development of renal cell carcinoma and the SV40 polyomavirus. The study recommends routine testing for the detection of RCC using PCR and IHC methods.
Keywords: SV40, Renal cell carcinoma, Immunohistochemistry, PCR

Introduction:

Polyomaviruses (PyV) is recognized as small, non-enveloped, double-stranded deoxyribonucleic acid, icosahedral symmetry with 5 kbp genomes, belonging to the *polyomaviridae*family. The term polyomavirus (PyV) comes from Greek origin, where poly- indicatesnumerously and -omadenotes tumors,belongs to *Papovaviridae*family, an abbreviationsuggestedvia Melnick,as well asgainedviacombing the names of the following virusesrepresented by'*Pa*pilloma', *'Po*lyoma', and *'Vac*uolating' (Dalianis and Hirsch, 2013).

The detection of Simian virus 40 SV40, was reported in 1960 when millions of population in Africa, Europe, Canada, Asia,and North and South America were inoculatedfrom both in-activated and live polio vaccines, initiate to be infected by Simian virus 40 (Sweet and Hilleman, 1960).

SV40genome is circular ds DNA,whichencodes for 6 proteins: threestructural proteins (including VP-1; VP-2, and VP-3, which are structural proteins that allowgenetic material to be accumulated in SV40 virion (Kawano *et al*., 2015), 2 proteinsimportant for the life cycle, thatinducereplicationofSV40, gene-expression, in addition tothe entry of S phase and DNA synthesis, by this meansinducing cycle development(large "T" antigen plus small "t" antigen oncoproteins)(Sullivan and Pipas, 2002; Qi *et al*., 2011) and 2 small proteins of unidentified function (the apoprotein, which rules the perinuclear localize of "VP-1"throughout virion constructionafter thatinduceassemblage ofthe virion (Saribas *et al*., 2018), and17kT, which participatethe majority of amino acid sequence withN terminal domain ofT-ag, encouragethe progression ofthe cell cycle in the existence of t-Ag, as well astumorigenic formation(Comerford*et al*., 2012).

Simian virus 40 returns to Polyomaviridae, genus Betapolyomavirus, which is stronglycorrelated toother types of polyomavirusesincluding JCPyV and BKPyV(Calvignac-Spencer et al.,2016). SV40 is capable ofbeing transmitted bydiversewayslikethe sexual course and fecal-oralwaysthat are accountable for horizontal virusinfection in people (Vanchiere*et al*., 2005).

The infection of the cell begins by attachment of the capsidof SV40 to the cell surfaceby binding among VP-1, cell surface receptor ganglioside GM1,and the major histocompatibility complex class-I(MHC-I), whichfunction as coreceptors (Campanero-Rhodes*et al*., 2007).

This virus in nature infects specific species of Asian macaques, especially rhesus monkeys. Sequences of SV40 were detected in samples of urine and stool as well as in both children and adults, representing that the sexual and Oro-fecal ways of spreadthatpossiblyaccountable for horizontalSV40 infection in individuals (Academies, 2003; Vanchiere*et al*., 2005).

On the other hand, the liberation of SV40 with notexhibit a cytopathic effect (CPE) found in particulartypes ofcells, for instance, humanepithelial, fibroblasts, mesothelial,and embryonic renalcells which points that kidney tissue can function asa reservoir for SV40 in humans (Cacciotti *et al*., 2001).

Expression of bothT-Ag and t-Ag can cause elevated cell transformation professionally. In reality, Tag prohibits the actions of numerousdiverse cellular factors concernedwithdifferentiation, cell growth,and the cell cycle, for instance, p130, p300, and p400. Also, T-Ag and t-Ag was prohibitedthe activity of pRb and p53. These interconnections are obligatorytoaccomplishcomplete cell transformation in humans(Khalili*et al*., 2008).

The oncogenic role ofpolyomavirus was formerlyrelatedto a widearray of tumor types, for instance, malignant pleural mesothelioma (MPM) and bone (Thanh*etal*., 2016), brain (Wang*et al*., 2017), lung (Ramaeland Nagels, 1999), thyroid (Vivaldi *et al*., 2003), pituitary (Woloschak*et al*., 1995), and urothelial (Loghaviand Bose, 2011) tumors, pleomorphic adenomas of parotid glands (Martinelli*et al*., 2002), ependymomas choroid and plexus tumors in youth (Bergsagel*et al*., 1992). Additionally, footprints from the DNA of SV40 have been reported in breast (Hachana*et al*., 2009) and colon carcinoma (Campello*et al*., 2010).

Also,the Tag of SV40 possibly causes transformation by stimulating mutations to the genome of cellular or numerical/structural variation of chromosomes, like gaps, breaks, ring and dicentric chromosomes, chromatid exchanges, translocations, duplications,and deletions (Tognon*et al*., 1996). The majorfunction of tag in transformation is to linkboth subunits,catalytic (36 kDa) and regulatory (63 kDa) of protein phosphatase 2A (PP2A), in-activating role (Garceaand Imperiale, 2003).

Grading Renal Cell Carcinoma:

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EXPLANATION WITH EACH FIGURE. Try to draw
these tables

Patients are distributed according grading of The World Health Organization(WHO)/InternationaSociety of Urological Pathology

Table 1: The World Heath Organization/International Society of urological pathology grading system for clear cell and papillary renal carcinoma

Grade 1	Tumour cell nucleoli absent or inconspicuous and basophilic at 400× magnification
Grade 2	Tumour cell nucleoli conspicuous and eosinophilic at 400× magnification and visible but not prominent at 100× magnification
Grade 3	Tumour cell nucleoli conspicuous and eosinophilic at 100× magnification
Grade 4	Tumuors showing extreme nuclear pleomorphism, tumour giant cells and/or the presence of any proportion of tumour showing sarcomatoid and/or rhabdoid dedifferentiation

Result:

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-Clinicopathological analysis:

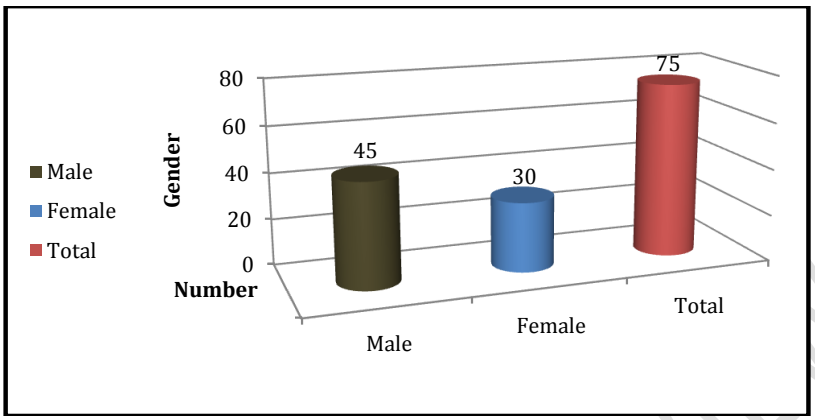

Fig 1:Distribution of RCC Patients according to Gender

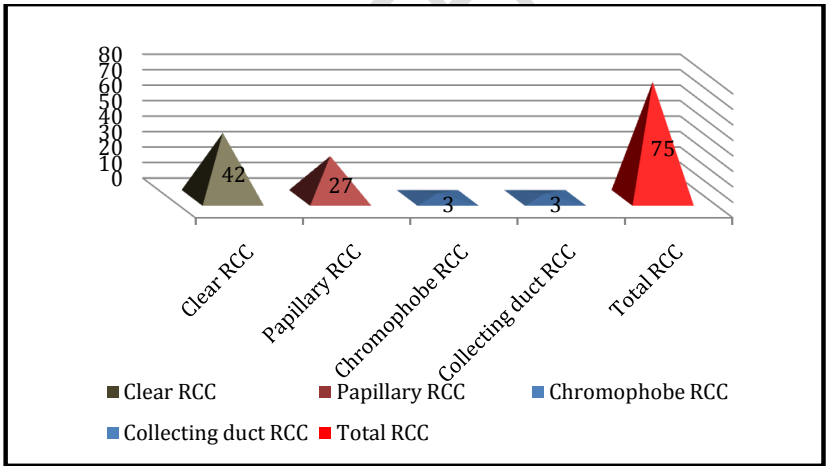

Fig 2:Distribution of RCC Patients according to histological types.

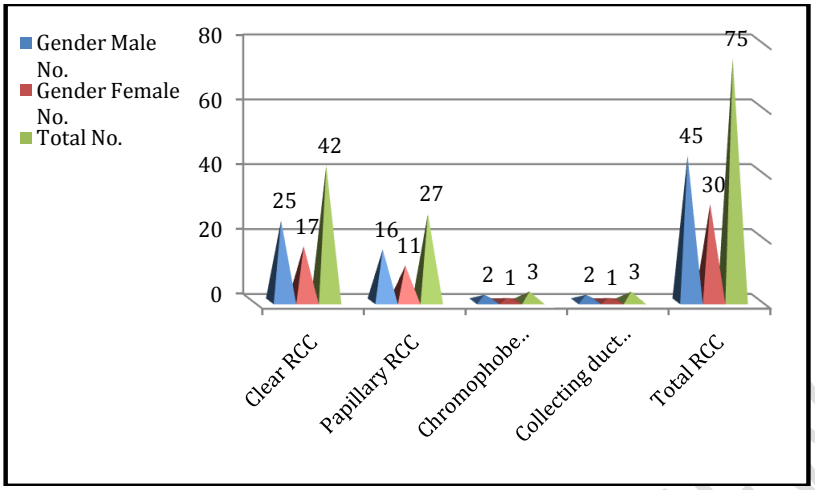

Fig 3:Distribution of RCC patients according to their Histopathological types and Gender

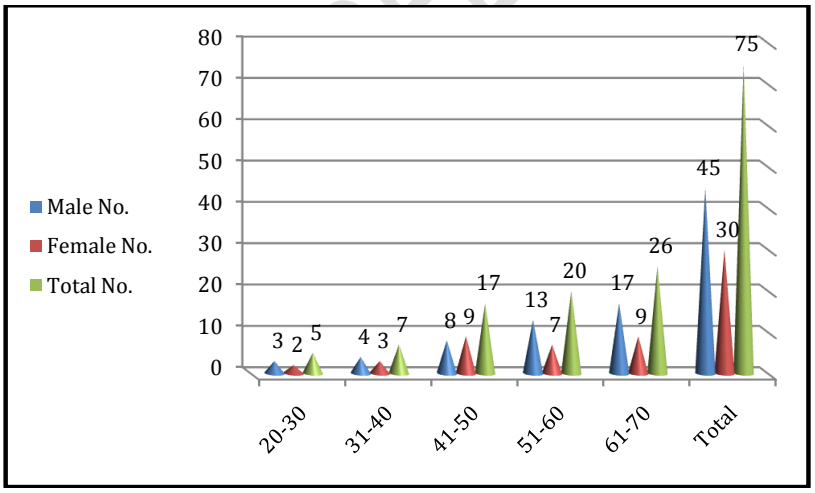

Fig 4:Distribution of RCC patients according to their Gender and Age

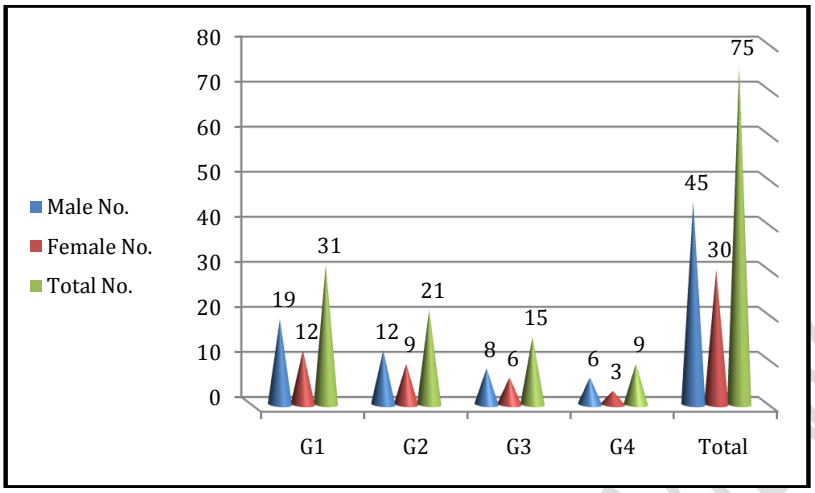

Fig 5:Distribution of RCC patients according to their Gender and Grading Systems

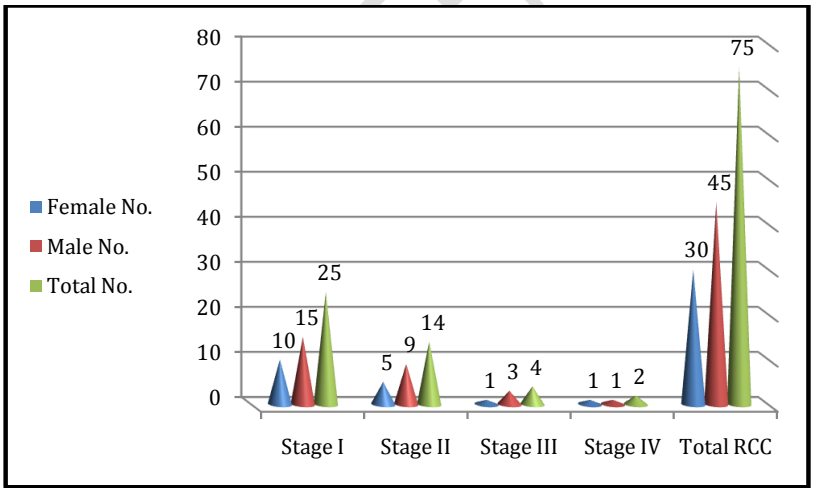

Fig 6: Distribution of RCC patients according to their Gender and Pathological Tumor Stage

Immunohistochemical Analysis (Cyclin E1 & CDKN3)

In this study, the results of IHC by utilizing EnVision™ FLEX stain revealed a brownish discoloration of nucleus or nucleoplasm for Cyclin E1 whereas in CDKN3 was staining the cytosol or cytoplasm, as shown in figures (7&8&9).

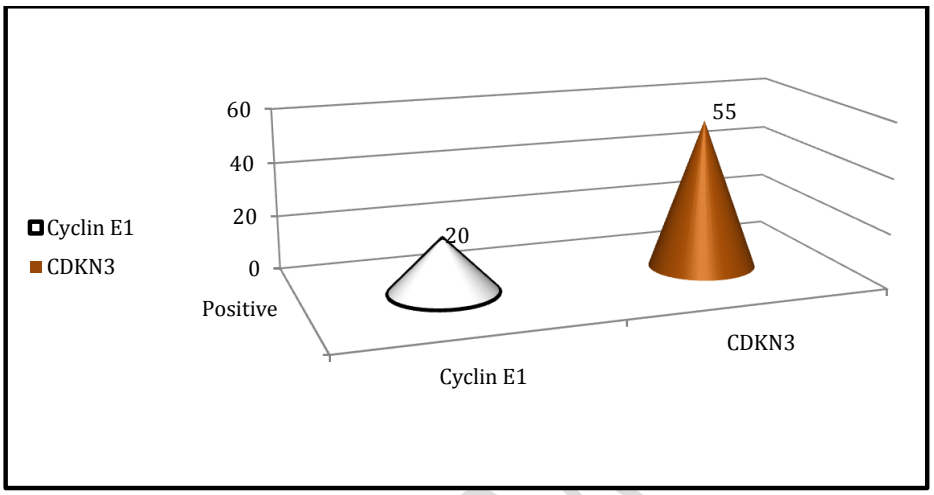

Fig 7:Circulation of Cyclin E1 and CDKN3 by using IHC.

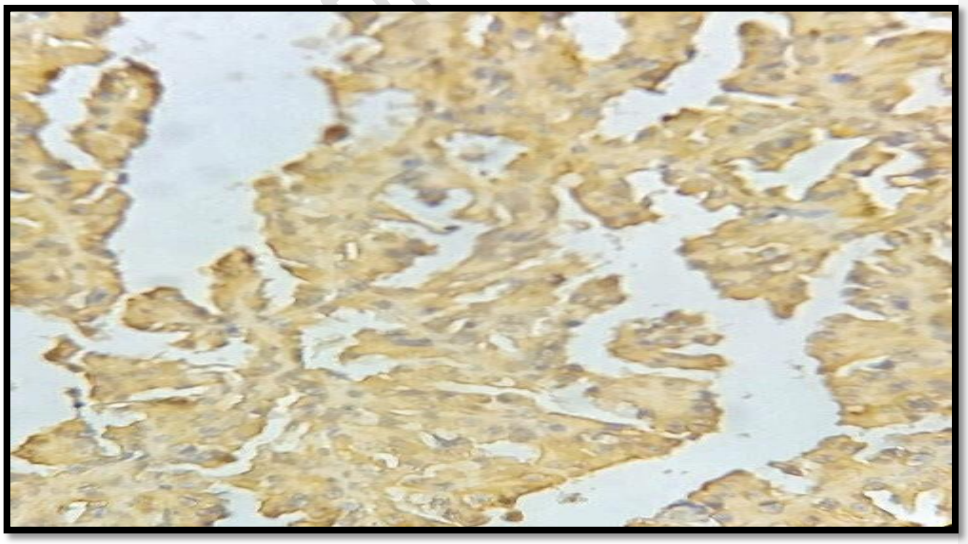

Fig8: Negative cyclineE1 stain ofpapillarytype of RCCpatients

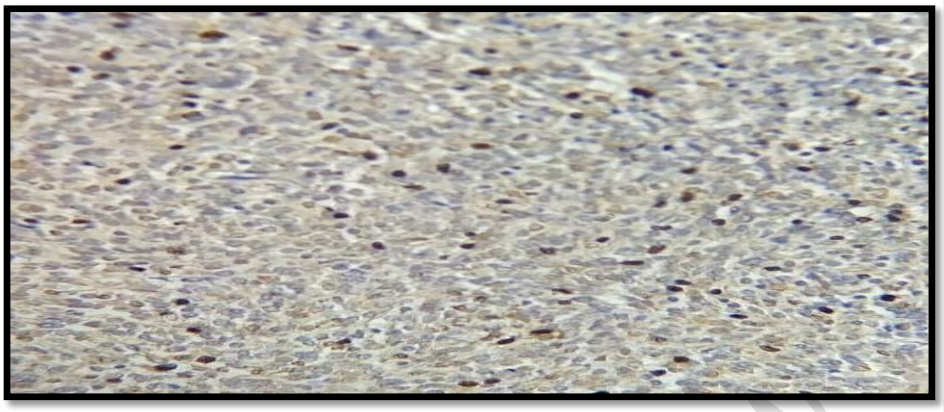

Fig9: Sarcomatoid carcinoma positive strong cyclineE1 stain score 2 (10 X40)

Discussion:

In this study, the existence of SV40 inblocked tissue takenfrom 75 patients suffering from RCC, uses molecular techniques involving PCR technique for detection of SV40 DNA united with immunohistochemistry technique (IHC)which are significant to verify the existence of Simian virus 40.
Simian virus 40 (SV40) is defined as a monkey virus thatby accidententeredman, in 1955-1963years,throughoutpolluted polio-virus vaccines that found the transforming and oncogenicityactionsof T-Ag and t-Ag of this virus, whichprovokedexaminationof SV40 in humancancer.Generally, it is thought that contamination ofpolio vaccines was considered the major cause of infection with SV40 in humans, nearly all researchers have defined exposure to SV40 founded on vaccination (Engels *et al*., 2003).

Most studiesdemonstrate that the kidney can function as a reservoir for SV40 in individuals. The sequence of this virus was reported in renal tissue and cells of urine sediments suffering from RCC (Li *et al*., 2002) like Garcea and Imperiale, (2003)who found that SV40 causes infection in renal cells somewheremightreactivation by immunosuppression. Also, Vanchiere*et al*., (2005) reported the discovery of SV40 in the renal tissueof humans which indicatesthat the kidneyrepresented a position of viral latency, similar to in the usualsimian host.

Bofill-Mas *et al*., (2000)doesnot discoverSV40 sequences in any tissueof RCC combined in diverse geographic regions of Europe and South Africa, while other types of polyomavirus's sequences were detected from the majority of these tissues. In contrast to Manfredi *et al*., (2005) whohave failed to discoverthe sequences of SV40 in these tumors.

In molecular technique involving PCR, it was found that only 20 of 75 paraffin-embedded block tissue yielded SV40 for the reason that only extremelysmall amounts of these tissueblocks were offered for investigation, it was inspiring that DNA of SV40 was

recognized from 75renal block tissue.The likelihood of occasional laboratory pollution of tissue blockwas excludeddue togenetic material (DNA)linkedwith cancer and DNA ofSV40 from laboratory progenydiverge sequences both within the viral regulatory area and at the carboxy terminus of T-Ag(Stewart *et al*., 1998).

Some reports have lackedproof that SV40 was causationsignificant in the progression of human cancerbut, Buteland Lednicky, (1999) reported that the presence of the DNA of SV40 will suggest that the opportunity of this virus in the genesis of some RCC in humans.

Bergsagel*et al*. (1992) have revealednegative SV40 outcomes in renal tumors possibly because ofthe utilization of few technical approaches.Also similarly, Leithner*et al*., (2002)and Priftakis*et al.,* (2002) haverecorded that never detected the sequences of SV40 in bothAustria andTurkey, as in Sweden.Thepredominanceof SV40 DNA that isrevealed in thesecancers was diversecountriesfor instance in Germany and Hungary (Heinsohn*et al*., 2009).

Various reports recordedby Lopez-Rios *et al*., (2004) show that positive sequences of SV40 DNA by PCR techniqueas well as Mayall*et al*., (2003) and Aoe *et al*., (2006) reportednegative resultsby using quantitative PCR assay.

In general,Iraq isconsidered one of the variouscountries in the Middle East regions that have special exciting torenal cell carcinoma which is regarded as the second mainlyfrequent urological malignancy (Ibrahim, 2013). As a result, it is found the elevatedproportionof males than females has in agreement with many studies finished by Vikram *et al*., (2016) and Mahasin*et al*., (2018).

Renal cell carcinoma is the majorityfrequent malignancy of the kidney, as well ascan classified into five types including ccRCC, pRCC, chRCC, cd RCC, and unclassified types. It is found in the presented study the most frequent type was clear cell RCC (42 of 75) whichconcordance with reportsaccomplished by Aiman *et al*., (2013) and Mahasin *et al*., (2018).

By using TNM classificationof malignant tumors of RCC relying on the American Joint Committee on Cancer (AJCC), Stafford *et al*., (2008)recorded that male patientshavehigher-stage tumors while femalepatients havelower-stage cancers, Thisis in concordance withour study.When anexamination of the Fuhrman nuclear grade,Mukhopadhyay*et al*., (2015) discoveryhigherfrequency of Grade 1 and a lower frequency of Grade 3 and Grade 4.

The most common age group in their study is 61-70 years followed by 51-60 years. These results conform with numerousreportssuch as Noroozinia*et al*., (2014) Khafaja*et al.,* (2015)and Hassan *et al*., (2017) whileunlikeness with Latif *et al.,* (2011) and Takure*et al*., (2013).

In the immunohistochemical technique, the immunohistochemical indicators are significant in identifying RCC patients that are investigatedby the EnVision System, this is in agreement with the report done by Lai *et al*., (2017) who have recorded that aelevated expression of CDKN3 in renal tissues whilstBisteau*et al*., (2014) have found that tough expression of cyclin E1 which is related with poor prognosis of patients.

Also, Brousset*et al*., (2005) have been unsuccessful in discoveringthe Tag of SV40 in this tumor by using immunohistochemistrytechnique with an extremely sensitive technique despiteactuality that recorded in experienced tissueshave DNA sequences of SV40.

The results of analysisof DNASV40 polyomavirus by PCR in patients with RCC are as; the total number of positive results of PCR is 20 (26.7%) whilst the negative results of PCR is 55 (73.3%).

Conclusion:

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Finally, the dysregulation of CDK regulators in renal cell carcinoma associated with SV40 highlights the complex molecular pathways involved in the etiology of cancer. In addition to expanding our knowledge of the condition, the findings of this study open the door for the creation of tailored treatments meant to counteract SV40-related renal cell carcinoma by reestablishing the equilibrium of cell cycle regulation.

Suggestion:

Renal cell carcinoma (RCC) is a complex and heterogeneous disease that is associated with a dysregulation of cyclin-dependent kinase (CDK) regulators. The CDK regulators play a crucial role in the regulation of the cell cycle, and any dysregulation can lead to the uncontrolled proliferation of cancer cells. Recent studies show that the Simian virus 40 (SV40) is responsible for the dysregulation of CDK regulators in RCC. SV40 has been identified as a potential oncogenic virus in humans, and its association with RCC has been established. The dysregulation of CDK regulators in RCC associated with SV40 is a complex molecular pathway that involves the interaction between the viral proteins and host cell pathways. The findings of this study have expanded our knowledge of the condition. It has been suggested that the creation of tailored treatments meant to counteract SV40-related RCC by reestablishing the equilibrium of cell cycle regulation is possible. These treatments could target the CDK regulators and the mechanisms by which the virus interacts with the host cell pathways, thus leading to the restoration of normal cellular function. In conclusion, this study has shed light on the complex molecular pathways involved in the

etiology of RCC associated with SV40. The findings have opened the door for the creation of targeted treatments meant to restore the equilibrium of cell cycle regulation and counteract the dysregulation caused by the virus. This has the potential to significantly improve the prognosis of patients with SV40-related RCC

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