The predication of AgNOR value in reflection of environmental pollution carcinogenesis

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Abstract

The value of Nuclear organization region(AgNOR) count and polymorphism in association with carcinogens has not been clearly explained yet. The aim of study was to assess the value of mAgNOR, pAgNOR and pleomorphic analysis in bladder cancer for prediction of possibility of war pollution carcinogens in the causation of increase rates of cancer in Iraq.

A retrospective study was carried out on 100 TCC Iraqi patients classified into groups; A: include 50 cases diagnosed at 2005-2006 and B: 50 cases diagnosed at 2012-2013, and 30 cystitis as control group. After sliver staining paraffin's sections, mAgNOR and pAgNOR, and both pleomorphic and single dots were counted and analyzed.

The result shown that total mean of mAgNOR and pAgNOR for A, B and C groups were 2.6, 3.4, 1.68 and 12.4, 22.5, 1.6 respectively, with significantly increase in B group in comparisons with others (p≤0.05). mAgNOR was significantly higher in low grades and stage of B group in comparison with A group (p≤0.05), while pAgNOR was observed more frequently in both low and high grade and stage in this group rather than the other patient group (p≤0.05). overall mean of AgNOR was not significantly increased in B group in comparison with others, but AgNOR pleomorphism was significantly larger in low grade and stage in B group than in another malignant group(A) (p≤0.05)., and significantly associated with high grade and stage of this group only (p≤0.05).

mAgNOR and pAgNOR counts with along AgNOR pleomorphism can be useful markers of cellular kinetic to predict the effect of war pollution carcinogens. pAgNOR and AgNOR pleomorphism cellular proliferation markers have more predicative value in characterizing cell kinetic. Further large study will be needed to confirm these results.

Physiology Classification QP1-345

tumor suppressor proteins, modulating important changes in the pathway of cellular carcinogenesis [7]. Many Iraqi studies were established aiming to detect the role of environmental war hazards (e.g. depleted uranium) in an inactivation of genes causing tumors [8, 9, 10].

Nucleolar organizer regions (NORs) represent the loops of DNA actively transcribe to ribosomal RNA and are situated on short arms of the acrocentric chromosomes 13, 14, 15, 21 and 22. Silver staining technique was used to visualize the acidic, argyrophilic non-histonic NORs associated proteins in the metaphase and interphase as black dots that called AgNORs [11,12]. It is found that interphase AgNORs are the reflection the spetial arrangement of AgNOR-bearing chromosomes in metaphase [11]. The number of NORs reflects the transcriptional activity of cells, and is related to cell cycle stage, giving rise to increase in the quantity of interphase NORs in cycling cells from the early G1 phase to the late S phase. The NOR value is closely related to both the percentage of cycling and S-phase cells in cancer tissues [13]. The biologic properties of cells represented in metabolic activity, DNA content, histological grade of differentiation, and, specially, the rapidity of cellular proliferation is found to be associated

Introduction

The incidence of most types of cancer (including bladder cancer) among Iraqi population has increased sharply in the last years due to exposure to Gulf war's pollution, attributing these increase rates of cancer mainly to Deplete Uranium (DU) pollution [1,2,3]. It was found that at least 350 sites in Iraq as being contaminated with DU and Currently, Iraqis are facing about 140,000 cases of cancer with 7000 to 8000 new ones registered each year [3].

DU has potentially both chemical and radiological toxicity, targeting organs such as the kidneys and lungs. Damage depends on both the physical and chemical nature of the DU to which the individual is exposed, and the period of exposure [4]. Epidemiological studies indicate a correlation between uranium mining and milling and incidence of DNA damaging effects resulting in carcinogenesis in human, which dependent on both dose and period of exposure [5, 6]. However, it well demonstrated that carcinogens can cause genetic and epigenetic changes at the genomic level and post-translational modifications at the protein level. At both levels, changes elicited affect either the stability or the activity of key regulatory proteins, including oncoproteins and

polymorphism [21,22,23,**20**]. Morphometry of AgNOR has been proven to be of value in the detection of incipient cellular alterations of radiation lesion in squamous epithelium [21]. It found that the pleomorphic AgNOR dots are related to the HPV infection [20]. Others revealed that AgNOR count is increased in oral buccal mucosa of smokers as compared to non-smokers [22]. Also, it well demonstrated that the variations in AgNOR and epithelial vascularization would be practical biomarkers to evaluate changes underlying the augmented risk of cancerization in oral mucosa of alcoholic and smoking patients [23]. It is imperative in view of the findings of that bladder cancer (TCC) represents one of the first tumors that have been associated with environmental risk factors that produce genetic alterations [24,25]. We thought it interesting to assess the value of mAgNOR, pAgNOR and pleomorphic analysis in bladder cancer for prediction of possibility of war pollution carcinogens in the causation of increase rates of cancer in Iraq.

Materials and Methods

This retrospective study was carried out in Medical Genetics laboratory, Middle Euphrates Unit for Cancer Research, College of Medicine, Kufa University,

with AgNORs expression [14]. Furthermore, predictive AgNOR value in regarding the differentiated between malignant and benign tumors, and with other certain clinical parameters has also been widely described in many cancers included bladder carcinoma [15,**16**, 17,13, **18**].

Various studies has been established that interphase AgNORs are more a reflection of cell kinetics [13], and the AgNORs value has been confirmed as proliferation markers in many cancers [**11,13,17,19**]. Interphase AgNORs was found to be correlated with ploidy and / or proliferative activity and the distinction between them based on mAgNOR and pAgNOR counts. mAgNOR is the mean number of AgNORs per nucleus correlated with ploidy and the proliferative activity index (pAgNOR) is the percentage of nuclei exhibiting five or more AgNORs per nucleus [**11,13**]. Moreover, it was shown that polymorphism of AgNOR is potential marker of proliferative activity in process of cervical carcinogenesis and progression of squamous cell carcinoma (SCC) [16, 20].

Since, several studies have been conducted to evaluate the association of some carcinogens and the possibility of finding out the tumour marker potential of the variation in AgNOR counts and

AgNOR Count (mAgNOR), Proliferative AgNOR (pAgNOR) and AgNORs polymorphism:

The counting sections were examined under the light microscope with 100x objective using oil immersion. One hundred cells were selected randomly from each specimen, avoiding any non-tumorous or necrotic area. The nuclei stained light yellow and the AgNOR were visualized as brown-black discrete dots of variable sizes within the nuclei.

The mean AgNOR count (mAgNOR) is the mean number of AgNOR dots counted in 100 nuclei. The mAgNOR count of 2.4 or more is indicated aneuploidy. The AgNOR proliferative index (pAgNOR) is percentage of cells with 5 or more AgNOR dots, and pAgNORs more than 8% were considered to display high proliferative activity [11,13]. All the pleomorphic and single small dots were counted individually, and the mean number of AgNORs, both pleomorphic and single, per nucleus was calculated for each section [16].

Statistical Analysis

The F test and T test were calculated by using the Statistical Package of Social Science program (SPSS for windows,

during the period from July 2013 to June 2014. A total of 130 cases (23 females and107 males), 100 of them was TCC bladder obtained by transurethral resection and diagnosed during 2005-2013 and 30 cases was cystitis, which selected from Al-Sadr Teaching Hospital and Assad Al-Janabi Private laboratory in Najaf Province were included in the present study. These cases were classified in the following groups:

Group A diagnosed during 2005-2006, group B diagnosed during 2012-2013, as well as thirty cases of cystitis were regarded as control group (C) diagnosed during 2005-2013.

AgNOR Silver Staining: five μ-tissue paraffin embedded section was subjected to silver nitrate staining according to the procedure proposed by Ploton *et al* in 1986 (26). The sections were deparaffinized in xylene and hydrated through graded ethanol into deionized water. AgNOR staining was done using a solution consisting of one volume of 2% gelatin in 1% formic acid and two volumes of 50% aqueous sliver nitrate solution. The sections were kept in the dark at 37 °C for 15-20 min and then washed with deionized water, hydrated in graded ethanol, cleared in xylene and mounted without being counterstained.

1.6 (1%-3%) for group A, B and C, respectively, giving high significant difference (p< 0.05) (Table 1). The total mean cell counts of both pleomorphic and single dots in the different groups revealed significantly increasing of numbers (p< 0.05), while the pleomorphic dots revealed increasing number but not significant difference (Table 1) (Figure 1).

On the other hand, our study showed that mAgNOR in low grades and stage of malignant groups (A and B) were 2.92 (2.42-3.93) and 3.40 (2.6-4.8), respectively, with significantly in difference (p< 0.05). No significant was found between groups of high grade and stage (Table 2). Whereas there is significantly associated with high grade and stage within only A group (p< 0.05). The mean pAgNOR of low grade and stage was 12.18 (2%-36%) of A group and 22.1 (2%-58%) of B group, while for high grade and stage were 22.1 (14%-40%) and 40.2 (21%-62%) for group A and B, respectively. Both comparisons were significant in differences (p< 0.05) (Table 2). Comparing mean cell counts of pleomorphic vs single dots between and within the malignant groups, the mean of pleomorphic dots was significantly larger in low grade and stage in B group than in another (p< 0.05)

version 10.0) in order to analyze the data of current study. The significant differences between groups were considered as statistically significant at P-value ≤0.05.

Results

The patients of each group A, B and C who included in the present study were matched of both age and sex. The patient's ages varied between 40 and 80 years with median age of 67 years. Male and females patients of group A and B were 41 (82%) and 9 (18%), respectively, with a ratio of 1:4.6. Cystitis males and females were 25 (83%) and 5 (17%) with a ratio of 1:5, respectively.

For A group, 24 (48%) were classified histologically and staging as Low grade (grade I and II) and low stage (superficial TCC Ta and T1), and 26 (52%) as high grade (grade III) and high stage (invasive T2). While group B, the low grade and low stage were 30 (60 %), and high grade and high stage were 20 (40%) cases.

The total mean mAgNOR of group A, B and C were 2.6 (range of 2.18-3.14), 3.4 (range of 2.24-5.5), and 1.68 (range of 1.4-2.12), respectively. The difference was significant. The total mean pAgNOR was 12.4 (4%-60%), 22.5 (4%-64%) and

in comparison with A group. The differences in single dots within groups were significantly higher in high grade and stage compared with low grade and stage (p< 0.05) (Figure 1).

(Table 2). Whereas there is increase significant of pleomorphic dots in high grade and stage of B group only. In the table 2, the present findings showed that mean count of single dots was identified higher in high grade and stage of B group

Table (1). Comparison of overall Mean AgNOR Count, p AgNOR proliferative index, and pleomorphic and single dots between presented groups

| Parameter	Total No (%)	Overall M of mAgNOR	Overall M of pAgNOR	Overall M of single	Overall M of pleomorphic
Group	130 (100)				
A group	50 (38.5%)	2.6 b	12.4 b	0.55 b	2.5 a
B group	50 (38.5%)	3.4 a	22.5 a	0.93 a	2.68 a
C group	30 (23%)	1.6 c	1.6 c	0.43 c	0.87 b
LSD		0.45	4.56	0.12	0.67

*Different Letters indicted to present difference between groups.

Table (2). Comparasion of mAgNOR , p AgNOR proliferative index, and pleomorphic and single dots with grade and stage of TCC Patients.

Parameter		M of mAgNOR		M of pAgNOR		M of single		M of pleomorphic	
Groups	No (%)	A	B	A	B	A	B	A	B
Low grade (I&II) Low stage (Ta&T1)	64 64%	2.92* a	3.40 b	12.18* a	22.2* b	0.52* a	0.81* a	2.38 a	2.74* b
High grade (III) High stage (T)	46 36%	3.38 a	3.6 a	22.1 a	40.2 b	0.56 a	1.05 b	2.57 a	3.00 a

*Different Letters indicted to present difference between groups.

*stars indicted to present difference within groups
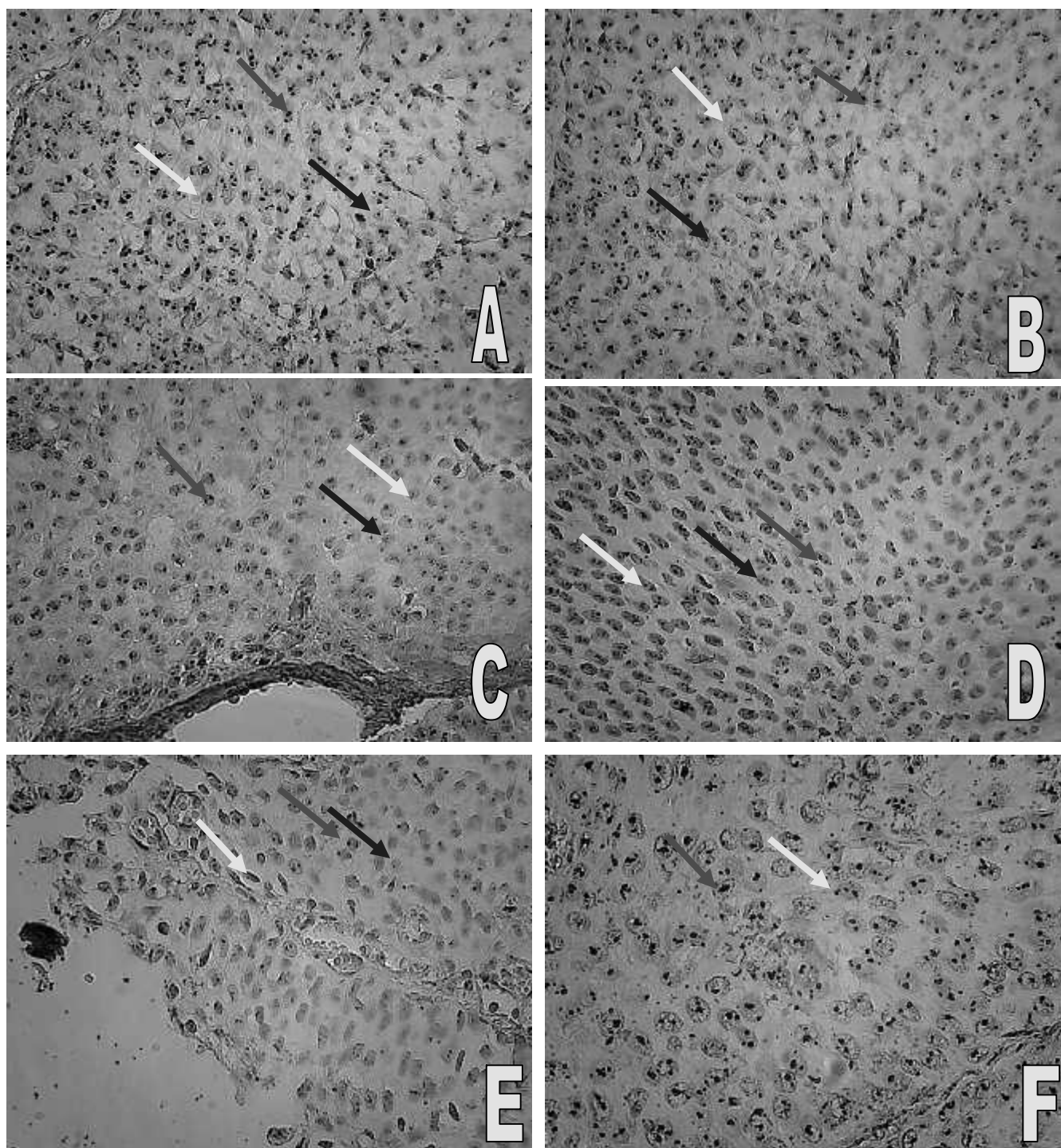
Figure(1). Cystitis and malignant bladder tissues staining by the sliver colloid method. A and B showing number AgNOR in the nuclei of malignant bladder tissues (low grade and high grade respectively) in A Group. C and D showing number AgNOR in the nuclei of malignant bladder tissues (low grade and high grade respectively) in B Group. E and F showing number AgNOR in Cystitis and malignant bladder tissues respectively. Yellow arrows indicted AgNOR staining and red and blue arrows indicted pleomorphic and single dots respectively.

increased proliferative activity other than the first. This is may be reflected the effect of both accumulated high dose and long periodof exposure to DU resulting from Gulf war's pollution. In fact, previous studies found that bladder cancer (TCC) represents one of the first tumors that have been associated with environmental risk factors that produce genetic alterations [24,25]. Some research(30,31) reported the increased incidence of bladder cancer in the radio-contaminated area in, Ukraine and Belarus respectively, compared with pre-Chernobyl station accident[30,31]. It was demonstrated that exposure to more stable isotopes, Cesium-137 (137Cs) was the mainly source of radiation risk for people living in these radio-contaminated areas (32), and the presence of low levels but persistent pollution in the soil and especially in food by 137Cs which is known to be concentrated and excreted in urine that could be responsible for the increase in bladder cancer [33]. Al-Kashwan et al 2012 [8] suggested that specific-mutational patterns in bladder carcinoma among the Iraqi patients may explicitly indicate a distinct molecular pathway responsible for the development of bladder cancer due to exposure to environmental hazards (e.g. depleted uranium). Unfortunately, there are few studies that related AgNOR count

Discussion

Recently, much attention has been given to potential value of variation in AgNOR counts and polymorphism in association with some carcinogens [20,21,22,23,]. In Iraq, at least 350 sites was found to being contaminated with DU and thirteen of them regarded as major sites severely contaminated included An Najaf Al-Ashraf governorate [3], indicating these increase the rates of cancer in the last years due to exposure to Gulf war's pollution [1,2, 3].

It has been established that AgNOR technique was found to be alternative technique of cell kinetics analysis other than flow cytometry as a method; demonstrating mAgNOR and pAgNOR reflected the total chromosome or ploidy and S-phase fraction, respectively [27, 28]. Further findings confirmed that pAgNOR counts was reflected the cellular proliferation when correlated with proliferating markers Ki-67 and bromodeoxyuridine [18, 29].

The present study revealed that mAgNOR and pAgNOR were significantly higher in TCC patients diagnosed at 2012-2013 than in other diagnosed at 2005-2006, with two-fold increase of pAgNOR count (p≤0.05) (Table 1), suggesting this group has higher incidence of aneuploidy and

significantly increased in patient group diagnosed at 2012-2013 in comparison with other group (p≤0.05) (Table 1), but AgNOR pleomorphism was significantly larger in low grade and stage of this group patients than in another malignant group (p≤0.05)., and significantly associated with high grade and stage of this group only (p≤0.05) (Table 2). This is indicated that AgNOR pleomorphism may be rise due to the cellular proliferation activity increased by the effect of severe environmental pollution. The important finding was found by Alarcón-Romero *et al* (2009) [20] that during the progression of the lesion HPV induces a progressive increase in cellular proliferation, appearing the presence of atypical AgNOR dots product of cellular alterations that are clearly related not only to viral integration with the infected cell's DNA but also to the progression of the lesion .

In conclusion, the compound study of mAgNOR and pAgNOR counts with along AgNOR pleomorphism can be useful markers of cellular kinetic to predict the effect of war pollution carcinogens in increase rate of cancers. Our study also concludes that cell kinetic analysis is very important to evaluate the environmental pollution, and both pAgNOR and AgNOR pleomorphism cellular proliferation markers have a

variation with certain carcinogens. AgNOR count was found to be increased in oral buccal mucosa of smokers [22], and variations in AgNOR was regarded as practical biomarkers to evaluate changes underlying the augmented risk of cancerization in oral mucosa of alcoholic and smoking patients [23].

Our result also showed that mAgNOR was significantly higher in in low grades and stage of group patients diagnosed at 2012-2013 (p≤0.05) (Table 2), while pAgNOR was observed more frequently in both low and high grade and stage in this group rather than the patient group at diagnosed at 2005-2006 (p≤0.05) (Table 2). This is consistent with our previous explanation, but present our result confirmed the more reflection of pAgNOR to predict the effect of environmental pollution that may be lead to tumor development. As elucidated well, the pAgNOR correlates with percent of cells in S-phase of the cell cycle or proliferative activity [**11,13**]; therefore, previous study suggest the DCIS cases not associated with invasion, which having high pAgNOR counts exhibit high proliferative activity would have progressed into invasive carcinoma if left untreated [**11**].

On the other hand, the present investigation revealed Both AgNOR pleomorphism and single dots were

needed to confirm these results.

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more predictive value to characterize this kinetic. Further large study will be

Acknowledgments:

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القيمة ألتنبؤيه لـAgNOR في عكس التلوث البيئي المسرطن

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الخلاصة

أن أهمية عدد والإشكال المتنوعة ل AgNOR لم يتم توضيحها بشكل كامل لحد الآن. وفي دراستنا الحالية هدفنا لتوضيح أهمية و قيمة mAgNOR و pAgNOR وتحليل الإشكال المتنوعة لها في سرطان المثانة وإمكانية استخدامها كعامل تنبؤي باحتمالية دور الملوثات المسرطنة للحروب في الزيادة حدوث سرطان المثانة في العراق.

شملت الدراسة الحالية على 100 عينة من سرطان المثانة من المرضى العراقيين. والتي صنفت الى :مجموعة A تضمن 50 عينة تم تشخيصها في الفترة من 2005-2006 , مجموعة B تضمنت 50 عينة تم تشخيصها في الفترة من 2012_2013 ومجموعة C والتي تضمنت 30 عينة (cystitis) استخدمت كمجموعة سيطرة. بعد أن تم تقطيع العينات وتحضير الشرائح وصبغها باستخدام صبغة sliver staining تم حساب mAgNOR وpAgNOR لكل من الأجسام المتعددة والأجسام المنفردة.

أشارت النتائج إلى ان المعدل لكلي لكل من mAgNOR وpAgNOR في مجموعة A, B و C كانت 2.3, 3.4 1.6, و 4 .12, 22.5 ,1.6 على التوالي مع وجود زيادة معنوية (p≤0.05) في مجموعة B مقارنة مع المجاميع الأخرى. mAgNOR كان ذو معنوية (p≤0.05) في الدرجة والمرحلة الواطئة من المرض في مجموعة B بينما pAgNOR كان أكثر تردد في كل درجة ومرحلة المرض العالي والواطئ في هذة المجموعة مقارنة بمجموعة A. من جانب أخر أن المعدل الكلي AgNOR و الإشكال المتنوعة كان ذو زيادة غير معنوية (p> 0.05) في مجموعة B مقارنتا مع المجاميع الأخرى .وكانت للاشكال المتنوعة أكثر معنوية في درجة ومرحلة المرض المنخفضة في مجموعة B منة في مجموعة A . وان الزيادة المعنوية لها علاقة مع درجة ومرحلة المرض العالي في هذة المجموعة.

أن حساب mAgNOR و pAgNOR للاشكال المتغايرة يعتبر معلم مفيد لفعالية ونشاط الخلية لغرض التنبؤ بتلوث الحرب المسرطن. وان معلم النشاط الخلوي pAgNOR و AgNOR يعتبر عامل تنبأ ذو قيمة لوصف نشاط الخلية وانقسامها ونحتاج إلى دراسات أخرى لتأكيد هذة النتيجة.

الكلمات المفتاحية:AgNOR, الملوثات البيئية المسرطنة.