

# P53 Expression in Prostatic Cancer: An Immunohistochemical Study

Wahda M. Al- Nuaimy,<sup>1</sup> Luma I. Al-Allaf,<sup>\*2</sup> Hatim A. Alnaimi<sup>3</sup>

## Abstract

**Background:** Prostate cancer is the most common malignancy in men and the second leading cause of cancer death in the Western world. P53 alterations are the most frequent genetic changes in human cancers. Mutation of the p53 gene has been implicated in the development of >50% of all human cancers.

**Objective:** The current study aims at evaluating the immuno-histochemical expression of p53 protein in patients with cancer of prostate, as prognostic parameter in correlation with other parameters including PSA receptors, and to correlate the results with those of other studies.

**Patients and Methods:** Fifty two cases of prostate carcinoma in which the PSA receptor status was previously tested by immuno-histochemical staining, were included in this retrospective study. The prostate carcinoma specimens include 16 cases were obtained from needle biopsies, 34 cases were from Transurethral Resection of the Prostate (TURP), and 2 were obtained from open prostatectomy specimens. The blocks of these cases were collected from Al-Jumhuri Teaching hospital in the western side of Mosul City, northern Iraq, and from some private laboratories, during the period extending from 7<sup>th</sup> April 2010 to 7<sup>th</sup> June 2010. Sections from formalin fixed paraffin embedded biopsy blocks were taken on clean slides and stained with H&E, then examined under light microscope. Grading of the cases was done according to Gleason grading system. The expression of p53 protein was evaluated immuno-histochemically; the findings were correlated with the age of the patients, Gleason score, tumor differentiation and the Prostatic Surface Antigen (PSA) receptor status.

**Results:** P53 expression was detected in 15 cases of prostate carcinoma (29%). The patients age ranged from 41 -90 years, (mean=68.05±2.1 years). Most of them were in the 6<sup>th</sup> decade, P53 expression has a statistically significant relationship with patients' age (P value < 0.05). A statistically significant direct relationship was found between p53 expression and different Gleason scores of prostate carcinoma (P value < 0.01). It was highest in Gleason scores 9 and 10 (60%, 80%), respectively, while Gleason scores 3 and 5 failed to demonstrate positivity (0%).

An inverse relationship was found between p53 expression and tumor differentiation, which was statistically significant (P value < 0.05). P53 had higher expression in poorly differentiated adenocarcinoma of prostate (48.2%). Positive expression of p53 was inversely significantly associated with positive monoclonal and polyclonal antibodies PSA receptors cases. Most of monoclonal and polyclonal antibodies PSA receptors positive cases of prostate carcinoma (90.4%, 96.1%), respectively failed to show p53 expression positivity (76.6%, 72%), respectively, (P <0.01, <0.05), respectively.

1. MBChB, MSc, FICMS (Path.), Department of Pathology, College of Medicine, University of Mosul, Mosul, Iraq.

2. MBChB, MSc, Department of Anatomy, Histology and Embryology, College of Medicine, University of Mosul, Mosul, Iraq.

3. MBChB, FICMS, EBP (Path.), Unit of Histopathological Examination, Laboratory of Al-Jumhuri Teaching Hospital, Ninawah, Health Office, Mosul, Iraq.

\* Correspondence should be addressed to:

Luma I. Al- Allaf

E- Mail: [Lumaallaf1971@yahoo.com](mailto:Lumaallaf1971@yahoo.com)

**Conclusions:** In conclusion, P53 expression has been found in 29% of prostate carcinoma in Mosul city. P53 expression is directly correlated with the age of the patients and Gleason score, while inversely correlated with tumor differentiation of prostate carcinoma. Also, this study revealed a significant inverse relationship between p53 expression and monoclonal and polyclonal antibodies PSA receptors status.

**Keywords:** Prostate Cancer, P53 Protein, PSA Receptors.

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## Introduction

Prostate cancer is the most common extra-cutaneous malignancy and the second leading cause of cancer-related deaths in men in the Western world.<sup>1-3</sup> The accuracy of the pathologic diagnosis of this malignant tumor is critical for optimal patient care. Even though the diagnosis can usually be made on morphologic features such as growth pattern, nuclear atypia and the absence of basal cells, it is sometimes difficult to reach a firm diagnosis by routine histological study, in particular for small foci of cancer in needle biopsies.<sup>4</sup> Not only is no single morphologic feature cancer specific, but many benign conditions can mimic prostate cancer. Therefore, the application of immunohistochemistry to distinguish prostate cancer from benign mimickers and to confirm the diagnosis becomes helpful and necessary, especially in equivocal cases. In addition determination of certain tumor markers of cancer of the prostate as prostatic specific antigen and p53 can be used.<sup>5,6</sup>

Beyond functional characterization, immunohistochemistry may have other applications and may also afford diagnostic and prognostic information.<sup>7</sup>

Mutations of the p53 tumour suppressor gene can result in uninhibited cellular growth and have been implicated in numerous malignancies, and in most human cancers, increased immunohistochemical expression is associated with point mutations in one allele of p53 gene and loss in the other.

Several studies concluded that mutations of p53 gene, which have long half-life, are involved in carcinogenesis of prostate cancer, and that p53 reactivity marks an aggressive subset of prostate cancer.<sup>8,9</sup>

Scherr et al. (1999) evaluated the expression of P53 as one of the key regulators of apoptosis by immunohistochemical staining and it has been found that biopsies with positive p53 expression were associated with treatment failure after external beam radiation therapy.<sup>10</sup>

Although prostate cancer is very prevalent among men, relatively little is known about the molecular mechanisms involved in the development and progression of the disease.<sup>11,12</sup>

The current study aims at evaluating the immunohistochemical expression of p53 protein in patients with cancer of prostate, as prognostic parameter in correlation with other parameters including PSA receptors, and to correlate the results with those of other studies in order to highlight the histological, some cell biological and molecular features which help the clinicians to create practical prognostic models that can also potentially help in individualization of the treatment.

## Patients and Methods

Fifty two cases of prostate carcinoma in which the PSA receptor status was previously detected by immuno-histochemical staining, were included in this retrospective study. Samples were collected from Al-Jumhuri Teaching Hospital in

the western side of Mosul City, northern Iraq, and from some private laboratories through the period of two months starting 7<sup>th</sup> April 2010 to 7<sup>th</sup> June 2010. This study enrolled 16 samples which were obtained from needle biopsies, 34 were from transurethral prostatic resection, and 2 were from open prostatectomy. Multiple sections were taken from formalin fixed paraffin embedded biopsy blocks and stained with Hematoxylin and Eosin (H&E). Light microscopic examination was performed and the cases were classified according to Gleason score of grading system.<sup>13-15</sup>

Expression of p53 antigen by immunohistochemical staining was studied and compared in relation to different parameters including age of the patients, Gleason score, tumor differentiation. In addition, the relation of p53 status to both monoclonal and polyclonal antibodies of PSA receptors status was evaluated. P53 expression was assessed immunohistochemically on formalin-fixed paraffin-embedded sections of the tumor, using mouse monoclonal antibody (clone DO-7), RTU (DAKO, Carpinteria, Ca, USA) and permanent red Envision system K535511\_2.

Positive and negative control slides were involved in each run of staining. Positive expression of p53 gives clear cut nuclear staining of brown color. Positive cells were determined by counting 1000 tumor cells.<sup>16, 17</sup> All significantly stained cells were considered positive and divided by 10 to acquire the percentage (p53 index); at least 10 high power fields were measured for each case for the purpose of scoring. The extent of p53 immunostaining was assessed as follows:

- Negative: when p53 index was <50%.
- Positive: when p53 index was ≥50%.<sup>16</sup>

### **Statistical Analysis**

The relationship between p53 expression and the age of the patients, Gleason score, tumor differentiation and PSA receptor status was analyzed by chi-square test  $\chi^2$ . The results were considered statistically significant if the p value was ≤ 0.05.<sup>18</sup>

### **Results**

The present study revealed that the mean age was 68.05±2.1 years (range 41-90). Most of whom were in the 6<sup>th</sup> decade (Table 1).

The classification of cases according to Gleason score system was shown in Table (2), while the tumor differentiation of these cases was revealed in Table (3).

Nuclear staining for p53 immunoreactivity was observed in 15(29%) out of 52 cases (Figures 1&2), while the remaining 37(71%) failed to demonstrate p53 positive immunoreactivity (Figure 3).

A statistically significant relationship between the expression of p53 and the patients' age (P value < 0.05). The highest percentage of positive p53 expression were observed in patients with the age groups 71-80 & 81-90 years, respectively (Table 1).

On the other hand, a significant direct relationship was found between p53 expression and different Gleason scores of prostate carcinoma (P < 0.05). It was highest in Gleason scores 9 and 10, respectively, while Gleason scores 3 and 5 failed to demonstrate positivity (Table 2).

An inverse relationship has been found between p53 expression and tumor differentiation, which was statistically significant (P < 0.05). P53 had higher expression in poorly differentiated adenocarcinoma of prostate (Table 3).

The positive expression of p53 was inversely associated with positive monoclonal and polyclonal antibodies PSA receptors cases (P < 0.05). Most of the monoclonal and polyclonal antibodies PSA receptors positive cases of prostate carcinoma (90.4%, 96.1%) failed to show p53 expression positivity (76.6%, 72%), respectively, (P < 0.05) (Figures 4&5).

**Table (1):**The expression of p53 according to the age of patients with cancer of prostate.

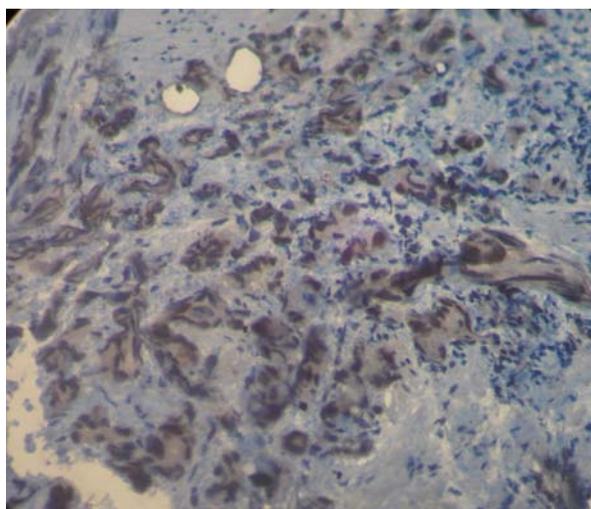
<u>Age</u>	<u>P53 expression</u>		<u>Total</u>	<u>P-Value</u>
	<u>Positive</u>	<u>Negative</u>		
41-50	0 (0%)	2 (100%)	2	P≤0.05
51-60	1 (12.5%)	7 (87.5%)	8	
61-70	5 (18.5%)	22 (81.5%)	27	
71-80	6 (54.5%)	5 (45.5%)	11	
81-90	3 (75%)	1 (25%)	4	
<b>Total</b>	15 (29%)	37 (71%)	52	

**Table (2):** The relationship between p53 expression & Gleason scores distribution of patients with cancer of prostate.

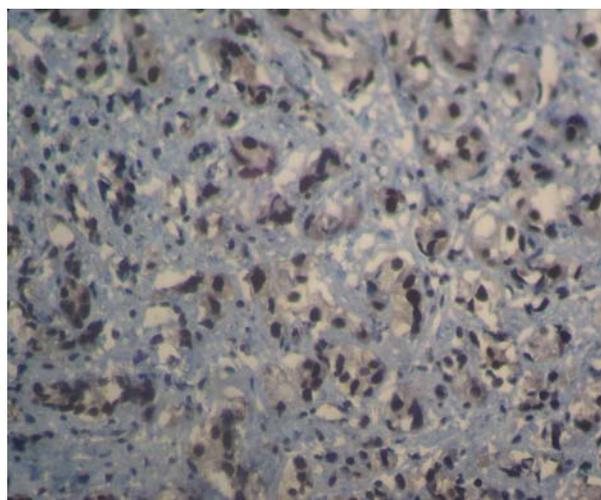
<u>Gleason Scores</u>	<u>P53 expression</u>		<u>Total</u>	<u>P-Value</u>
	<u>Positive</u>	<u>Negative</u>		
3	0(0%)	1(100%)	1(100%)	P≤0.05
5	0(0%)	3(100%)	3(100%)	
6	1(11.2%)	8(88.8%)	9(100%)	
7	1(8.3%)	11(91.7%)	12(100%)	
8	2(16.7%)	10(83.3%)	12(100%)	
9	3(60%)	2(40%)	5(100%)	
10	8(80%)	2(20%)	10(100%)	
<b>Total</b>	15(29%)	37(71%)	52(100%)	

**Table (3):** The relationship between p53 expression & different tumor differentiation distribution according to Gleason score.

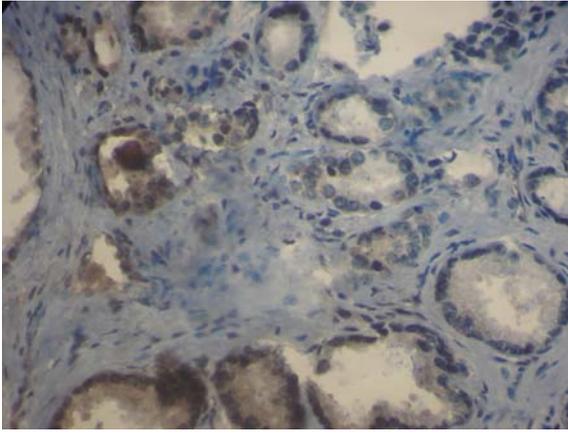
<u>Differentiation</u>	<u>Gleason Scores</u>	<u>P53 expression</u>		<u>Total</u>	<u>P-Value</u>
		<u>Positive</u>	<u>Negative</u>		
Well Differentiated	2-4	0 (0%)	1 (100%)	1 (100%)	P≤0.05
Moderately Differentiated	5-7	2 (8.3%)	22 (91.7%)	24 (100%)	
Poorly Differentiated	8-10	13 (48.2%)	14 (51.8%)	27 (100%)	
<b>Total</b>		15 (29%)	37 (71%)	52 (100%)	



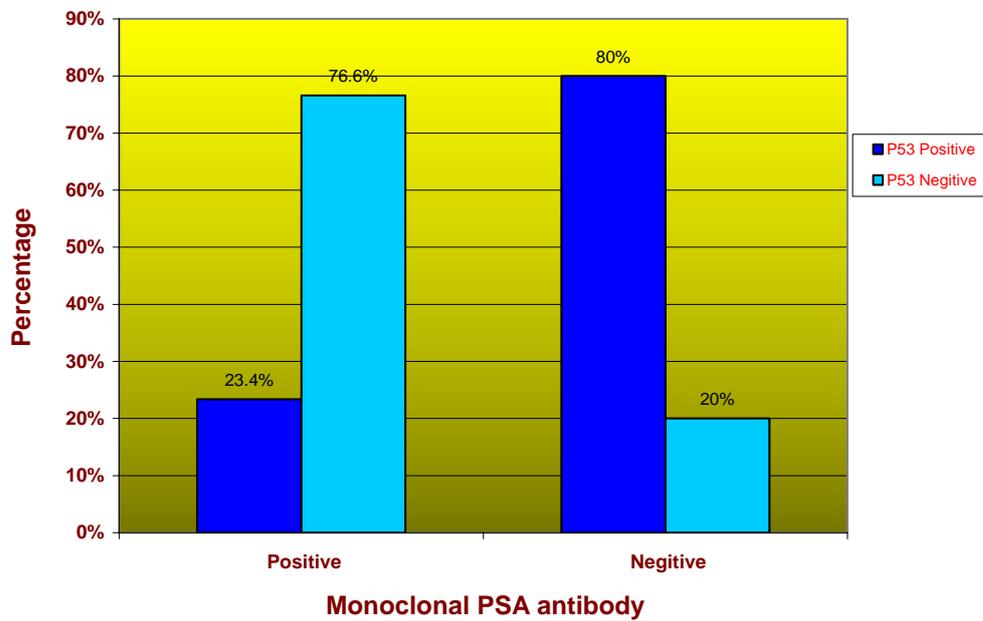
**Figure (1):** A photomicrograph of moderately differentiated prostate cancer with positive P53 expression (x 600).



**Figure (2):** A photomicrograph of poorly differentiated prostate cancer with positive P53 expression (x 600).

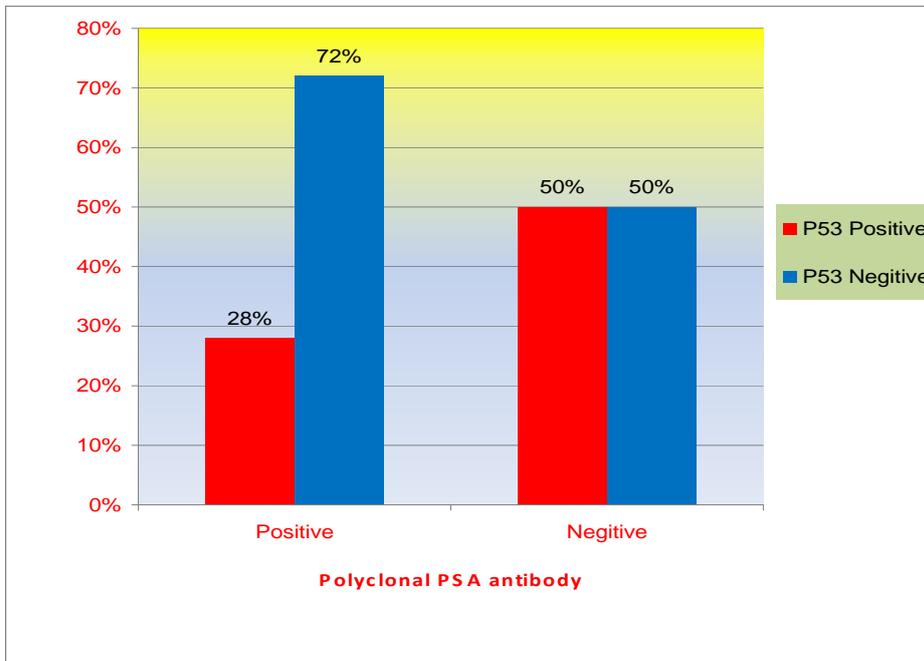


**Figure (3):** A photomicrograph of well differentiated prostate cancer with negative P53 expression (x 600).



**Fig1:** The relationship between P53 expression and monoclonal PSA antibody in cancer of prostate

**Figure (4):** The relationship between p53 expression and monoclonal PSA antibody in cancer of Prostate.



**Figure (5):** The relationship between p53 expression and polyclonal PSA antibody in cancer of Prostate.

### Discussion

Pathologists play an important role in preoperative diagnosis and in the postoperative evaluation of prostate cancer. Prostate tumors, although they are slower growing than most other tumors, vary widely in their aggressiveness.<sup>19</sup> The challenges of deciding which patients require immediate treatment,<sup>20</sup> various types of clinical and pathological information may contribute in building decision making systems or tools for this purpose.<sup>21, 22</sup> Clinicians treating prostate cancer patients may potentially use these tools.<sup>21</sup> The biological heterogeneity that characterizes this disease causes decision issues unique to prostate cancer so the biological distinction of such patients should have a high priority in continuing research.<sup>21</sup> Several studies have shown that p53 mutations are frequent in prostate cancer and are associated with advanced disease & reflected poor prognosis.<sup>8, 21</sup> It seems that p53 expression has the potential to become a dominant prognosticator in clinical practice.<sup>9, 21, 23, 24</sup> The determination of p53 expression in pre- treatment stage may be helpful for predicting response to definitive radiotherapy.<sup>10</sup> P53 expression acts as a tumor

biopotential marker, whereas a PSA provides diagnostic information.<sup>25</sup>

This study revealed that the age of most of the patients with prostate cancer was above 60 years, these finding are in agreement with those of Miller (1996); Kirby et al. (2001) and Al-Nuaimy et al. (2009),<sup>26- 28</sup> who reported that the prostate cancer is more common among older men, and it is expected to increase as the population ages.

In this study, p53 was expressed in 15(29%) of cases. These findings are in accordance with that of Shurbaji et al., (1995)<sup>23</sup> Grignon et al. (1997).<sup>17</sup> However, Stricker et al. (1996)<sup>8</sup> and Moul et al. (1996)<sup>29</sup> reported that p53 was expressed in 80%, 90%, respectively and that could be attributed with the number of cases examined, different immunohistochemical techniques used which include the type of antibody, as well as different scoring and cutoff values of p53 protein expression. Also, differences in population groups, diversity of risk habits and variation of genetic predisposition may contribute to this wide range of p53 expression reported.

The present study revealed that 48(92.0%) out of 52 cases were of high Gleason score ( $\geq 6$  scale). These findings are in accordance with that of Schere et al. (1999).<sup>10</sup>

On the other hand, 27(51.9%) were diagnosed as poorly differentiated and 24(46.1%) of moderately differentiated type and only one case (1.92%) of well differentiated type. These findings are similar to that of Al- Nuaimy et al. (2009).<sup>28</sup>

There is a statistically significant relationship between the expression of p53 and the patients' age (P value < 0.05). This finding is comparable with that reported by Neilsen and Nyholm (1994),<sup>30</sup> supporting the idea that the p53 mutation more frequently occurs in older patients.<sup>31</sup>

A significant direct relationship was found between p53 expression and different Gleason scores of prostate carcinoma (P < 0.05). It was highest in Gleason scores 9 and 10, respectively. These findings are similar to that of Thomas in Papadolopoulos in Moul in.<sup>9, 25, 29</sup>

On the other hand, an inverse relationship has been found between p53 expression and tumor differentiation, which was statistically significant (P < 0.05). P53 had higher expression in poorly differentiated adeno carcinoma of prostate. These findings are in agreement with that of Moul et al. (1996).<sup>29</sup>

The positive expression of p53 was inversely associated with positive monoclonal and polyclonal antibodies PSA receptors status (P < 0.05). Most of monoclonal and polyclonal antibodies PSA receptors positive cases of prostate carcinoma (90.4%, 96.1%) failed to show positive p53 expression (76.6%, 72%). Several studies reported that both monoclonal and polyclonal anti PSA displayed inverse correlation with Gleason score.<sup>31- 34</sup> In addition, monoclonal and polyclonal anti PSA were directly proportional to the tumor differentiation<sup>35- 37</sup> and that may be the cause of the inverse correlation between the positive expression of p53 and the positive monoclonal

and polyclonal antibodies PSA.

A recent study which was carried out by Nelson (2009) reported that the importance of any study is in linking molecular markers, as in the current work, and he suggested that the choice of particular markers is arguably less important than the demonstration of an association between markers obtained at prostate biopsy.<sup>38</sup>

## **Conclusion**

P53 expression has been found in 29% of prostate carcinoma in Mosul city. P53 expression is directly correlated with the age of the patients and Gleason score, while inversely correlated with tumor differentiation of prostate carcinoma. Also, this study revealed a significant inverse relationship between p53 expression and monoclonal and polyclonal antibodies PSA receptors status.

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## **Authors' Contributions**

All authors contributed in designing and conducting the present work, analyzing data, and drafting the manuscript. All authors read and approved the final manuscript.

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## التعبير عن بروتين ب 53 في حالات سرطان المثانة (البروستات): دراسة كيميائية نسيجية مناعية

وحدة النعيمي<sup>1</sup>، لمسى العلاف<sup>2</sup>، حاتم النعيمي<sup>3</sup>

1- فرع الأمراض، كلية الطب، جامعة الموصل، الموصل، العراق؛ 2- فرع التشريخ والأنسجة والأجنة، كلية الطب، جامعة

الموصل، الموصل، العراق؛ 3- وحدة الفحص النسيجي المختبري، المستشفى الجمهوري التعليمي، دائرة صحة نينوى، الموصل، العراق

### الملخص

**الخلفية:** إن سرطان المثانة أو البروستات هو من أكثر أنواع السرطانات شيوعاً في الذكور والمسبب الثاني للموت بينهم (من بين كل أنواع السرطانات) وخاصة في العالم الغربي. إن التحويرات في بروتين ب 53 من التغيرات الوراثية الشائعة في حالات السرطان في الإنسان. إن الطفرة في الجين الحامل لبروتين ب 53 ممكن أن يكون له التأثير في التطور الحاصل لأكثر من 50% من السرطانات المصيبة للإنسان.

**أهداف الدراسة:** تهدف الدراسة إلى تقييم التعبير النسيجي الكيميائي المناعي لبروتين ب 53 في مرضى سرطان البروستات وعلاقته لبقية المؤشرات المستقبلية من ضمنها المستضاد النوعي البروستاتي كما تهدف الدراسة إلى مقارنة النتائج مع مثيلاتها في الدراسات السابقة.

**طرق العمل:** تشمل الدراسة اثنتين وخمسين حالة شخصت كسرطان للبروستات والتي سبق وان تم تقييم المستضاد البروستاتي النوعي بطريقة التحليل النسيجي الكيميائي المناعي. تم اخذ النماذج من 16 حالة عن طريق اخذ الخزعة الابرية و 34 حالة من الاستئصال عن طريق الاحليل وحالتان من الاستئصال الجراحي عن طريق فتح البطن. وتم جمع البلوكات البارافينية خلال المدة المحصورة بين السابغ من نيسان من عام 2010 إلى السابغ من حزيران من نفس العام وذلك من وحدة الفحص النسيجي المختبري، مستشفى الجمهوري التعليمي الواقع في الجهة الغربية من مدينة الموصل شمالي العراق وكذلك من بعض المختبرات الخاصة. تم صبغ الشرائح البارافينية بصبغة الهيماتوكسيلين اوسين وإخضاعها للفحص بالمجهر الضوئي. تم تصنيف الحالات بنظام كليسون. إن التعبير عن بروتين ب 53 قد قيم بطريقة التحليل النسيجي الكيميائي المناعي وتم دراسة علاقته مع العمر ودرجات كليسون، درجات تمايز الورم، وكذلك مع حالة مستقبلات ضمنها المستضاد النوعي البروستاتي بنوعيه الاحادي والمتعدد السلالة.

**النتائج:** إن التعبير عن البروتين ب 53 ظهر واضحاً في 15 (29%) حالة من الذين يعانون من سرطان البروستات وكان عمر المرضى يتراوح ما بين 41-90 سنة (بمعدل 68.5 ± 1 سنة 2). كان هناك علاقة معنوية واضحة بين عمر المريض والتعبير عن بروتين ب 53. لوحظ وجود علاقة مباشرة وبفارق معنوي بين ب 53 ودرجات كليسون ( $p \geq 0.05$ ) وكانت أعلى نسبة للتعبير قد ظهرت في درجات كليسون 9 و 10 ونسبة 60% و 70% بالتعاقب في حين فشلت الشرائح العائدة لتلك التي لديها درجة ثلاثة أو خمسة في أن تظهر أي تعبير. لوحظ وجود علاقة عكسية وبفارق معنوي بين التعبير عن ب 53 ودرجة تمايز الورم ( $p \geq 0.05$ ) وكانت أعلى نسبة للتعبير قد ظهرت في الأورام الضعيفة التمايز، وكذلك مع درجة التعبير عن المستضاد النوعي البروستاتي بنوعيه الاحادي والمتعدد السلالة.

**الاستنتاجات:** إن التعبير عن البروتين ب 53 ظهر واضحاً في 15 (29%) حالة من الذين يعانون من سرطان البروستات في مدينة الموصل. كان هناك علاقة معنوية واضحة مباشرة بين عمر المريض. ودرجات كليسون والتعبير عن بروتين ب 53 بينما كان هناك علاقة عكسية بين التعبير بروتين ب 53 ودرجة تمايز الورم، وكذلك مع حالة مستقبلات ضمنها المستضاد النوعي البروستاتي.

**الكلمات الدالة:** سرطان المثانة أو البروستات، بروتين ب 53، المستضاد النوعي البروستاتي.