International Journal of Sciences: Basic and Applied Research (IJSBAR)

ISSN 2307-4531
(Print & Online)

http://gssrr.org/index.php?journal=JournalOfBasicAndApplied

---

# Relation between Insulin-like Growth Factor Type 1 Receptor Expression and Histopathological of Prostate Adenocarcinoma

Hermien[a*], Muhammad Husni Cangara[b], Djumadi Achmad[c], Mahmud Ghaznawie[d], Andi Alfian Zainuddin[e], Muhammad Naufal Zuhair[f], Upik Anderiani Miskad[g]

[a,b,c,d,g]*Department of Anatomical Pathology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

[e]*Department of Public Health and Community, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

[f]*Medical Education Study Program, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia*

[g]*Email: emhyajix@gmail.com, upik.miskad@gmail.com*

**Abstract**

Prostate cancer is one of the most common cancer worldwide, where South Sulawesi is included in four provinces with the highest prevalence of prostate cancer in Indonesia. Laboratorium Sentra Patologia Makassar (SDPM) stated that prostate cancer cases continue to rise each year. Insulin-like growth factor system (IGF) has a central role in growth regulation, apoptosis resistance, and malignant invasion in humans. Increasing expression and IGF-1R activity are known to contribute to several aspects of cancer progression, including carcinogenesis, tumorigenesis, metastasis, chemotherapy resistance, and transformation. These inventions show that IGF-1R could be a potential target for cancer treatment. However, until now, no data shows relative levels of IGF-1R expression in prostate cancer and there's no consensus about IGF-1R roles in metastasis. This study is purposed to know IGF-1R expression in adenocarcinoma prostate grading.

---

* Corresponding author.

The type of this research is an observational analytical study with cross-sectional methods. Samples are taken based on consecutive sampling of as many as 46 respondents. There is no significant difference between IGF-1R expression score and histopathological feature of prostate adenocarcinoma WHO Grup Grade (p score=0,088 p>0,05). In conclusion, there is no correlation between IGF-1R and WHO Grup Grade.

***Keywords:*** Insulin-like growth factor 1 receptor (IGF-1R); prostate adenocarcinoma; WHO Grup Grade.

## 1. Introduction

Prostate cancer is the most common type of cancer worldwide after lung, breast and colorectal cancer [1]. The incidence of prostate carcinoma has increased significantly after the age of 60 years. The highest percentage occurred in the 60-70 year age group, which was 64%. Approximately 85-90% of the total prostate cancer is adenocarcinoma. Prostate adenocarcinoma is an invasive prostate epithelial malignant tumor consisting of secretory cells [2]. Based on data from Globocan, International Agency for Research on Cancer 2018, of all cancer cases in men, about 1.3 million cases (7.1%) were prostate cancer cases with 359 thousand deaths (3.8%). This puts prostate cancer as the most common type of cancer in men after lung cancer [1]. Currently, the determination of the degree of prostate malignancy uses a new scoring system that is simpler and more accurate, through histopathologic features of the prostate malignancy. This system has been recommended by the World Health Organization (WHO) in 2016, that the degree of prostate malignancy uses Groups grading. Based on the International Society of Urological Pathology Consensus, the Groups grading uses Gleason scoring system with the latest modification in 2014 [3]. The insulin-like growth factor (IGF) system plays an important role in the regulation of growth, resistance to apoptosis, and invasion in various malignancies in humans. The IGF system consists of two ligands, IGF-1 and IGF-2; two receptors, the IGF-1 receptor (IGF-1R) and the IGF-2 receptor (IGF-2R); and six high-affinity IGF-binding proteins (IGFBP 1 to 6) [4]. Insulin-like growth factor type 1 receptor (IGF-1R) is the primary receptor that carries out the IGF hormone and generates intracellular signals which resulting the growth and cell proliferation. Various studies have shown the evidence of IGF role in prostate cancer. First, epidemiological and clinical studies have shown that elevated serum levels of IGF-IR are associated with the increased risk of prostate cancer. Second, IGF-IR increases proliferation of prostate cancer cells in vitroly, while the inhibition of IGF-1 receptor (IGF-1R) expression in vivoly suppresses tumor growth and prevents cancer cell invasiveness. Third, in human prostate cancer cell xenografts, several experimental models have shown progression to androgen-independent forms in association with IGF-IR and IGF-I [4,5]. Increased expression and activity of IGF-1R has been contributed to various aspects of cancer progression, including carcinogenesis, tumorigenesis, metastasis, chemotherapy resistance and transformation. These findings show that IGF-1R can be a potential target for cancer treatment [6,7]. IGF-1R was detected in prostate stroma and epithelial cells. However, until now there are no data showing the relative levels of IGF-1R expression in prostate cancer and there is no consensus on the role of IGF-1R in metastasis. IGF-1R is overexpressed in several tumors such as colorectal cancer, breast cancer, and melanoma. Over-expression of IGF-1R induces cell growth, neoplastic transformation, and tumorigenesis. There are some evidences that the interaction between IGF-1R and its ligands plays a role in prostate cancer progression [4] . Therefore, it is important to conduct research to look at IGF-IR expression in various prostate cancer grading groups as a prognostic value. Androgen ablation therapy has been the main therapy of prostate cancer for many years. This

therapy initially shows a good response, but the frequent recurrence of tumors makes this therapy less effective. Metastatic of prostate cancer most commonly involves bone and initially is androgen dependent. There is a progression to androgen independent after androgen therapy within 12-18 months. Thus, an approach is needed to identify other parameters, namely IGF-IR expression as a target for prostate cancer therapy [8]. This research aims to detect the expression of IGF-IR in prostate cancer using immunohistochemical staining. By knowing IGF-IR expression in prostate adenocarcinoma based on the WHO Group grading system, we hope can contribute to determining the prognosis and target of therapy for prostate malignancy.

## 2. Research Methods

This study is an analytical observational study with cross-sectional methods to determine IGF-1R expression in adenocarcinoma prostate grading. This research was conducted at the anatomical pathology laboratory of Universitas Hasanuddin Hospital Makassar from August to October 2020.Research sample was selected with a consecutive sample method that fulfill inclusion and exclusion criteria. The estimated sample is around 48 samples and the research population is resection tissue from prostate that was sent to the anatomical pathology RSUP Dr. Wahidin, RS Unhas, and Sentra Diagnostik Patologia Makassar from January to June 2020, which diagnosed as adenocarcinoma prostate with a grading determined by the Modified Gleason Grading System (WHO/International Society of Urological Pathology 2016) or referred as WHO Grade Group I, II, III, IV, and V in hematoxylin eosin staining. The Sample then stained with immunohistochemical staining and interpreted. The collected data samples were grouped based on purpose and the type of data that are not normally distributed. The statistical method used is univariate analysis to describe general characteristics obtained and bivariate analysis using the Kruskal-Wallis test to compare between IGF-1R expression score and WHO Grup Grade. Samples were continued with the Mann-Whitney Test to assess the mean difference between 2 test groups in WHO Grup Grade based on IGF-1R expression score.

## 3. Result

### *3.1. Sample Characteristic*

Samples that met the inclusion criteria were re-evaluated by two Pathology Anatomy specialists. Then proceeded with immunohistochemical staining to observe the expression of IGF-1R and AR in the sample by combining two parameters, which are the intensity and percentage of stained area. The percentage of stained area and the intensity was assessed on the cell membrane for IGF1R (figure 1) which was then calculated using the Histological score (H-score) formula.

This research was conducted from August to October 2020 with a total sample of 77 people. The age distribution of the sample is about 93.5% of the total patients at the age of ≥50 years old (Table 1), the distribution of histopathological features based on WHO Grade Group in this sample was equally distributed. In the sample of WHO Grade Group I there were at least 14 cases (18.2%), while the number of WHO Grade Groups III, IV, and V were 20 cases (20.8%) in each grade. Based on the results of this study, the highest expression of IGF-1R that was found very strongly expressed are 40 samples (51.9%), followed by moderate

expression by 33 samples (42.9%), weak expressed IGF-1R are found on 3 samples. (3.9%), and there were no unstained samples.

**Table 1:** Sample Characteristic based on age, histopathological features based on WHO Grade Group, score and expression of IGF-1R (n = 77).

| Characteristic | | n | % |
|---|---|---|---|
| **Age** | <50 years old | 5 | 6,5 |
| | ≥50 years old | 72 | 93,5 |
| **WHO Grade Group** | I | 14 | 18,2 |
| | II | 15 | 19,5 |
| | III | 16 | 20,8 |
| | IV | 16 | 20,8 |
| | V | 16 | 20,8 |
| **IGFR1 Expression** | Not Stained | 0 | 0 |
| | Weak | 3 | 3,9 |
| | Moderate | 24 | 31,2 |
| | Strong | 50 | 64,9 |

Note: n= number, IGF-1R= Insuline growth factor 1 receptor.

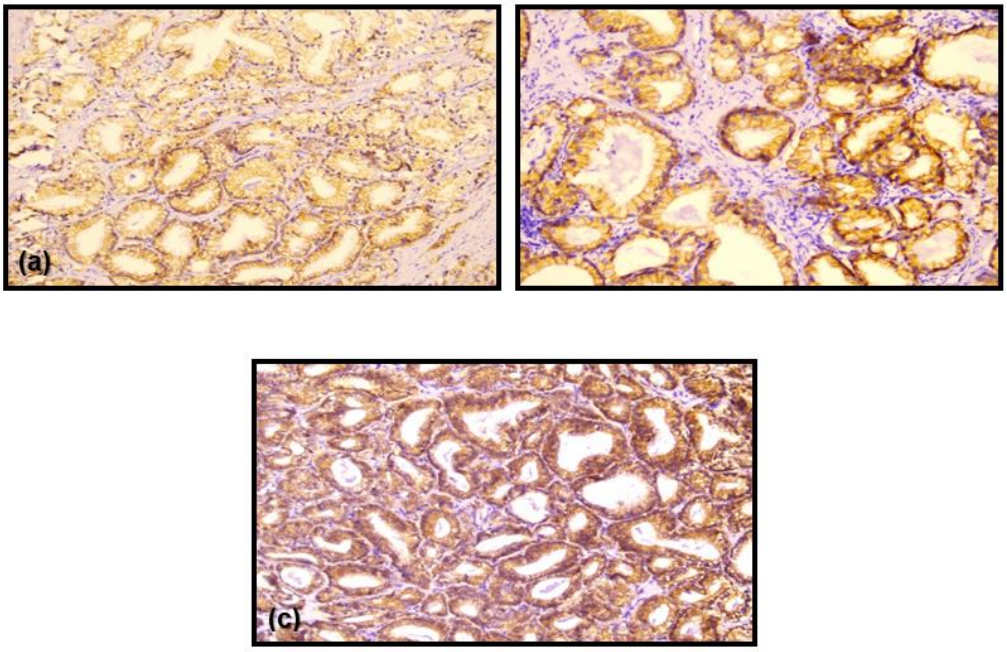


**Figure 1:** Positive IGF1R expression in prostate adenocarcinoma. (a) Weak Positive (b) Moderate Positive (c) Strong Positive. (Objective 20x)

### *3.2. Analysis of The Relationship between IGF-1R Expression Scores with histopathological features in prostate adenocarcinoma based on WHO Grade Group*

Based on the analysis of the relationship between IGF-1R expression scores and histopathological features, the mean expression scores of prostate adenocarcinoma were almost the same in each WHO Group Grade

respectively 2.74±1.04; 3.41±3.60; 3.43±3.60; 3.27 ±3.60; and 2.69 ± 2.40 (Table 2), and from the results of the Kruskal Wallis test, the p value are 0.088 (p>0.05). Which shows that there is no significant relationship between the IGF-1R H-Score value with histopathological features of adenocarcinoma based on WHO Grade Group.

**Table 2:** Analysis of the relationship between IGF-1R expression scores and histopathological features of prostate adenocarcinoma based on WHO Grade Group with Kruskal Wallis Test.

| WHO Grade Group | IGF-1R Expression Score | | | P value |
|---|---|---|---|---|
| | Mean±SD | Min | Max | |
| I | 2,74±1,04 | 0,80 | 4 | |
| II | 3,41±0,41 | 2,40 | 4 | |
| III | 3,43±0,50 | 1,80 | 4 | 0,088 |
| IV | 3,27±0,68 | 2,10 | 4 | |
| V | 2,69±0,93 | 1,00 | 4 | |

Note : Kruskal Wallis Test p=0,088 (p>0,05)

### *3.3. The Relationship of IGF-1R expression between two prostate adenocarcinoma WHO Grade Groups*

After knowing that there is no significant relationship between IGF-1R expression scores and histopathological grading of prostate adenocarcinoma based on WHO Grade Group, it is necessary to conduct further analysis of the relationship between each of the WHO Grade Group. The analysis are done by comparing nominal variables between two unpaired groups using the Mann-Whitney test. Comparative analysis of the H-Score value of IGF1R expression on each histopathological features of prostate adenocarcinoma based on WHO Grade Group showed insignificant results based on the Kruskall-Wallis test with p value = 0.088. The comparison between groups using the Mann-Whitney test showed a significant difference in IGF1R scores between WHO Grade Group II vs V and WHO Grade Group III vs V with p values each * 0.041 and * 0.043 (graph 1), but overall between the five groups there is no significant differences.

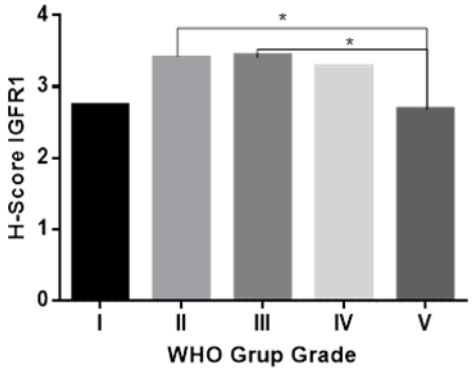


**Figure 2:** Comparison of IGF-1R Expression Scores by Prostate Adenocarcinoma WHO Grade Groups

The results of the comparative analysis of IGF1R H-score between groups of prostate adenocarcinoma WHO grade groups where most of the WHO grade group pairs were not significantly different, between I vs II; I vs III; I vs IV; I vs. V; II vs III, II vs IV; III vs. IV; and IV vs V with p value > 0.05 (Table 3). There were only two pairs of WHO grade groups that showed significant differences in IGF1R H-Score, which are II vs V and III vs V. These data generally showed no significant relationship between IGF1R expression and prostate adenocarcinoma grading.

**Table 3:** Analysis of the Relationship between IGF1R Expression Scores between two groups of WHO group grade adenocarcinoma prostate with the Mann-Whitney Test.

| No | Prostate Adenocarcinoma WHO Grade Groups | Mann-Whitney Test (P value) | Kruskal Wallis Test (P value) |
|---|---|---|---|
| 1 | I vs II | 0,146 | |
| 2 | I vs III | 0,093 | |
| 3 | I vs IV | 0,179 | |
| 4 | I vs V | 0,822 | |
| 5 | II vs III | 0,520 | P=0,088 |
| 6 | II vs IV | 0,953 | |
| 7 | II vs V | 0,041 | |
| 8 | III vs IV | 0,696 | |
| 9 | III vs V | 0,043 | |
| 10 | IV vs V | 0,086 | |

## 4. Discussion

Based on the characteristics of the research sample, it shows that the number of patients with prostate adenocarcinoma is dominant at the age over 50 years old (93.5% samples), compared to under 50 years old patients (6.5% samples). This proves the result of the previous research which found that cases of prostate adenocarcinoma were rare in people under 50 years of age and often found in people over 50 years of age [9]. By using Kruskal-Wallis test to analyze the associations between IGR-1R expression and histopathological features of prostate adenocarcinoma based on WHO Group grade, we found out that there are no significant associations between IGF-1R and WHO Grup grade. This may be due to the presence of an alternative activation pathway that is stronger in influencing the grade of prostate adenocarcinoma. Another thing that may also play a role is complex molecular interactions at the epigenetic level that can affect the IGF1R signaling pathway. Besides that, the heterogeneity of IGF1R expression in various paraffin block samples and fresh tissue was also suspected to have a role in determining IGF1R expression in prostate adenocarcinoma tissue. These findings were supported by the research conducted by Ahearn on 2018 which founds that there are no significant associations between IGF-1R and WHO Grup grade [10]. The insulin-like growth factor (IGF) system plays an important role in the process of growth regulation, resistance to apoptosis and invasion in various malignancies in humans. The role of IGF1R in the process of carcinogenesis through 2 pathways, the main pathway in cell

survival is PI3K/Akt. Phosphorylation of PI3K activates the Akt pathway and inhibition of PI3K will stop the cell cycle, causing apoptosis or differentiation. Akt is a kinase activation molecule that causes the induction of anti-apoptotic proteins. In addition, Akt also plays a role in blocking the process of apoptosis through phosphorylation. The pathway associated with IGF-IR activation is linked to the Ras/Raf/MEK/MAPK pathway. The cascade involves activation of the G protein Ras followed by activation of the protein serine kinase Raf, which then activates the MEK/MAPK pathway. The result of the activation of this pathway is the modulation of cell proliferation and cell differentiation through mitogenic signal transduction by activating transcription factors. The MAPK pathway also plays a role in cell transformation induced by Ras, Raf, and other oncoproteins. However, in this study, the expression of IGF-1R which is the problem is that IGF-1R is not only stained in malignant cells but also stained in normal epithelial cells and benign prostate hyperplasia. In low-grade acinar adenocarcinoma of the prostate, especially grades I and II, it is difficult to distinguish it from benign prostatic hyperplasia, this can be misinterpreted or minimized by looking at the presence of basal cells and basement membranes that are still present in normal epithelium and benign lesions. Apart from these problems, there is no relationship between prostate adenocarcinoma grading and IGF1R expression has also been proven in a previous study by Giles O Hellawel in 2002, but his research provides evidence that even though benign lesions also express IGF1R, its expression is weak compared to adenocarcinoma, but does not provide differences by WHO Group grade of prostate adenocarcinoma are thought to be due to differences in PTEN expression among WHO group grades. So the expression of IGF1R may depend on the PTEN mutation[8]. There are many pathways related to IGF1R, one of which is related to the androgen pathway. This research has several limitations such as only examined 1 type of IGF-1R expression pathway, so it did not have comparative data for each pathway. Other confounding factors of the sample were not investigated especially PTEN expression.

## 5. Conclusion

There is no significant relationship between IGF-1R and WHO Group grade.

## Acknowledgements

The author would like to thank all of the clinical colleagues and laboratory teams at Anatomical Pathology Laboratory of Wahidin Sudirohusodo Hospital for their assistance and discussions throughout this work. The author also acknowledge Hasanuddin University Hospital, Sentra Diagnostik Pathology Makassar, and Wahidin Sudirohusodo Hospital for providing clinical sampling for this research.

## 6. Conflict of Interest

The author declares that she has no conflict of interest.

## References

[1]. Ferlay, J. (2018). “Estimating the global cancer incidence and mortality in 2018 : GLOBOCAN sources and methods.” *International Journal of Cancer*, 1–13. https://doi.org/10.1002/ijc.31937

[2]. Humphrey, P. A., Amin, M. B., Berney, D. M., Billis, A., Cao D., Cheng L., … Van der Kwast, T. (2016). Acinar adenocarcinoma. In J. M. Eble, G. Sauter, J. I. Epstein, & I. A. Sesterhenn (Eds.), *WHO classification of tumours of the urinary system and male genital organs* (pp. 138–162). Lyon: IARC Press.

[3]. Humphrey PA, Amin MB, Berney DM, Billis A, Cao D, Cheng L, et al. (2016). WHO CLASSIFICATION OF TUMOURS OF THE PROSTATE WHO Blue Books : History TUMOURS OF THE PROSTATE. In *Acinar adenocarcinoma* (4th editio, pp. 135–183). Lyon Cedex 08, France: International Agency for Research on Cancer (IARC).

[4]. S. K. Denduluri et al. (2015). "Insulin-like growth factor (IGF) signaling in tumorigenesis and the development of cancer drug resistance," Genes Dis, vol. 2, no. 1, pp. 13–25, Mar. 2015, doi: 10.1016/j.gendis.2014.10.004.

[5]. A. Philippou, A. Armakolas, and M. Koutsilieris. (2013). "Evidence for the Possible Biological Significance of the igf-1 Gene Alternative Splicing in Prostate Cancer," Front Endocrinol (Lausanne), vol. 4, p. 31, Mar. 2013, doi: 10.3389/fendo.2013.00031.

[6]. A. Arcaro. (2013). "Targeting the insulin-like growth factor-1 receptor in human cancer," Front Pharmacol, vol. 4, p. 30, 2013, doi: 10.3389/fphar.2013.00030.

[7]. J. Wu and E. Yu. (2014). "Insulin-like growth factor receptor-1 (IGF-IR) as a target for prostate cancer therapy," Cancer Metastasis Rev, vol. 33, no. 0, pp. 607–617, Sep. 2014, doi: 10.1007/s10555-013-9482-0.

[8]. Hellawell, G. O., Turner, G. D. H., Davies, D. R., Poulsom, R., Brewster, S. F., & Macaulay, V. M. (2002). Expression of the type 1 insulin-like growth factor receptor is up-regulated in primary prostate cancer and commonly persists in metastatic disease. *Cancer Research*, *62*(10), 2942–2950.

[9]. Epstein, J. I., & Lotan, T. L. (2015). The lower urinary tract and male genital system. In V. Kumar, A. K. Abbas, & J. C. Aster (Eds.), Robbins and Cotran pathologic basis of disease (Ninth, pp. 980–990). Philadelphia: Elsevier Saunders.

[10]. Ahearn, T. U., Peisch, S., Pettersson, A., Ebot, E. M., Zhou, K., Graff, R. E., … Edward, L. (2018). Expression of IGF/insulin receptor in prostate cancer tissue and progression to lethal disease. Carcinogenesis, 39(12), 1–18. https://doi.org/10.1093/carcin/bgy112/5079148