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Prognostic Significance of Ki-67 Index in Prostatic Cancer in Sulaymaniyah Governorate

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Abstract
Objective: This study aimed to assess the rate of Ki-67 expression in prostate adenocarcinoma patients in the Sulaymaniyah governorate and assess the overall survival of prostate adenocarcinoma and its association with Ki-67 expression and other risk factors.
Methods: Ki-67 expression was measured in 102 paraffin blocks from patients diagnosed with prostate adenocarcinoma from 2013 to 2019. Paraffin blocks, pathology reports, and patient relatives' phone numbers were collected from Shorsh Hospital and some private laboratories, and overall survival was determined through phone calls to patient relatives.
Results: The total survival of patients in our study from the time of diagnosis was (57.9 ± 21.9 months). The study revealed a remarkable difference (*P* value <0.05) in survival using a Log-rank test across 10% ki-67 expression, age at the diagnosis, Gleason score, PSA level, extraprostatic extension, perineural invasion, lymphovascular invasion, and obesity, in multivariate analysis only Ki-67 index and age were independent prognostic factors affecting five-year overall survival.
Conclusion: These results revealed that the rate of Ki-67 expression is crucial in predicting overall survival of patients with prostate adenocarcinoma.
Keywords: Prostate adenocarcinoma, Ki-67 antigen, prognosis, survival rate, risk factors

Introduction

Prostate cancer occurs when cells in the prostate gland multiply excessively and uncontrollably these malignant cells can invade local structures and metastasize to distant organs that are not anatomically continuous with the prostate.[1] Globally, prostate malignant tumors are the second most frequent type of malignancy affecting men, after pulmonary malignancy, and the sixth leading cause of death from cancer in men all over the world.[2] The burden is also significant regionally. In Iraq, 4.5 out of every 100,000 men were diagnosed with prostate cancer in 2016.[3] In Sulaymaniyah, prostate malignancy is diagnosed in 3.5 men per 100000 of the population annually, and it is the fifth most prevalent cancer.[4]

Prostate adenocarcinoma typically arises from the secretory epithelium of the prostate gland. Anatomically the prostate is one of the organs in the men reproductive system that belongs to the accessory sexual organs and located on the pelvic floor, its weight is about 20 grams in healthy men aged between 20–50 years and about 30 grams in men aged 60 to 80 years.[5]

Among the essential functions of the prostate gland is the storage of a certain amount of seminal fluid and assistance during ejaculation in the presence of sexual activity. About one-quarter of seminal fluid is made by the prostate gland. This fluid is slightly alkaline, and it is vital for sperm motility and viability within the female reproductive tract.[6]

Similar to other forms of malignancy, the aggressiveness of prostate adenocarcinoma differs among individual patients, histopathological examination is used to diagnose prostate adenocarcinoma and differentiate it from benign lesions. The Gleason scoring is determined under a microscope for the individual patients and combined with other features to determine cancer stage.[7] However, the subjective nature of Gleason grading can lead to inter-observer variability and pose difficulties in differentiating between certain grades among pathologists.[8,9]

Ki-67, or MKI67, is a protein that indicates the rate of cell proliferation and it is widely recognized for its ability to reflect aggressiveness of different tumors including prostate.[10] Ki-67 can be visualized immunohistochemically under a microscope and is closely related to cell cycle stages. During interphase (the period between cell divisions), the Ki-67 antigen is located within the nucleus of the cell, while during mitosis (cell division), it shifts to the chromosome periphery.[11]

Despite the recognized utility of Ki-67 expression in prostate adenocarcinoma prognosis, a critical knowledge gap remains regarding its association with overall survival of prostate adenocarcinoma patients in the Sulaymaniyah Governorate. To the extent of our knowledge, no prior study in the Sulaymaniyah Governorate has investigated the association between immunohistochemical expression of Ki-67 and the overall survival in patients with prostate adenocarcinoma.

The primary objective of this research is to investigate the correlation between the Ki-67 index, established risk factors, and overall survival of prostate adenocarcinoma in the Sulaymaniyah Governorate, the findings of this research are likely to be of great significance, one of which is determining patients who have aggressive disease who may benefit from more intensive therapies or closer follow-up, also our research may open up new areas for further research including the exploration of other biomarkers and the principles of targeted therapy.

Materials and Methods

Study Design and Sampling

A cross-sectional retrospective study was performed in Sulaymaniyah governorate, the study was conducted on 102 paraffin blocks of prostate adenocarcinoma, the specimens types

included transurethral resection of the prostate (TURP), trucut biopsy, and open prostatectomy, the paraffin blocks were collected from Shorsh hospital and some private laboratories in Sulaymaniyah city in November of 2024, included patients who were diagnosed as prostate adenocarcinoma between 2013–2019, in addition to tissue blocks relevant pathology reports and mobile numbers that were given by the patient relatives were collected.

Data Collection

Patient data such as age prostate prostate-specific antigen (PSA) level along with Gleason score, perineural invasion, extraprostatic extension, and lymphovascular invasion were collected from pathology reports and compared to our findings when hematoxylin and eosin-stained slides reviewed under the microscope.

To collect patient information, telephone numbers of patient relatives that provided to Shorsh hospital and private laboratories were used, we conducts calls following a standardized script designed and asked about whether patient is still alive or not and the exact date of death if the patient died, presence, and absence of obesity in patients and whether there is prostate adenocarcinoma in their families or not, A maximum of three attempts were made to contact each identified relative on different days at various times.

Ki-67 Immunohistochemical Staining

The immunohistochemical staining procedure was performed in Anwar Shekha Private Hospital in Sulaymaniyah City using Bio-SB Ki-67 rabbit monoclonal antibody RM360, Staining was done using procedures recommended by the manufacturer and established in laboratory practices. Ki-67 expression was evaluated under a microscope, cells with brown color of nuclei were considered positive. An area with the highest fraction of Ki-67 was determined, at least 1000 malignant cells were examined, and the percentage was calculated.

Study Population

The study comprised men who were diagnosed and managed as prostate adenocarcinoma by urologists and oncologists, Additional inclusion criteria were the preservation of their paraffin blocks and the availability of their clinical data and phone numbers.

Patients who lacked any of the required records (age, PSA level) were excluded, and patients who did not respond to our phone calls after three attempts or had the wrong phone number in their records were excluded, patients with other malignancies or who died due to traumatic injury (like road traffic accidents) or who died from emergency situations (such as myocardial infarction) were excluded.

Statistical Analysis

We used IBM SPSS Statistics 30 to analyze the data. This included calculating descriptive statistics like means and percentages, Chi-square tests specifically used to examine the association between different categorical variables, Kaplan-Mier curve used to determine overall survival and to mark the linkage between different risk factors and overall survival Log-Rank test was used, univariate and multivariate cox regression analysis was used to determine effect of variables on five-year survival rate, probability (P) value under 0.05 were considered as significant, and participants were divided depending on the 10% expression level of Ki-67 into two groups, We chose a Ki-67 index cutoff of 10% based on its widespread use in the literature and its established prognostic significance in identifying more aggressive prostate cancer phenotypes.[10,11]

Results

Results indicated that the overall survival of patients in our study from the time of diagnosis was (57.9 ± 21.9 months). The study observed a range of survival times. When overall survival is investigated using Kaplan-Meier curves, it is observed that 97.1% of patients were alive after 1 year of diagnosis with prostate adenocarcinoma, which decreased to 87.3% after three years, and 40% after five years. (Figure 1).

Ki-67 positivity was identified as brown color in the nucleus of malignant cells, the minimum was 0.5% and the maximum was 48%, the ki-67 index mean in prostate adenocarcinoma patients was (15 ± 13), our study observed that men with a ki-67 index of <10% were 52 cases (Figure 2), and those with > 10% comprised 50 cases in the study (Figure 3).

The study demonstrated a significant disparity in overall survival using a Log-rank test (Figure 4) across 10% ki-67 expression (P <0.001), age at the diagnosis (P <0.001) (Figure 5), gleason score (P <0.001) (Figure 6), PSA level (P <0.001), extraprostatic extension (P <0.001), perineural invasion (P = 0.02), lymphovascular invasion (P <0.001), and obesity (P <0.001) (Table 1).

Results of the research showed that the rate of Ki-67 expression is significantly related to age, PSA level, gleason score, and body weight (Table 2).

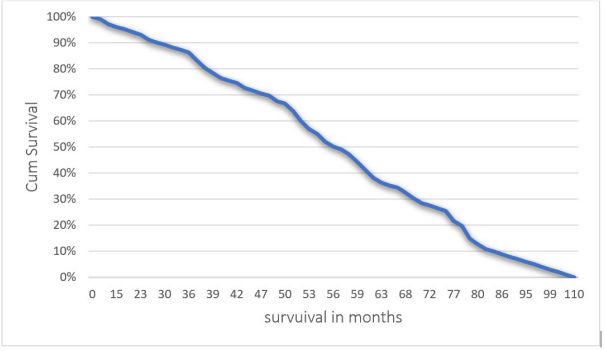

Fig. 1 **Overall survival using Kaplan-Meier curve of prostate adenocarcinoma patients in Sulaymaniyah governorate.**

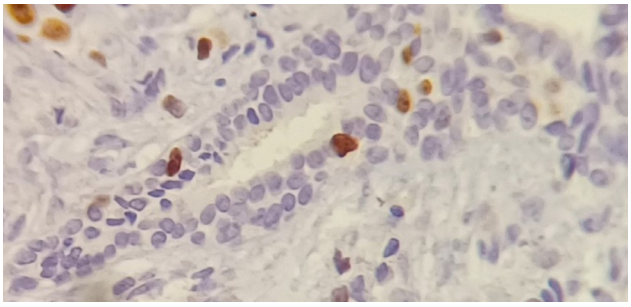

Fig. 2 **Prostate adenocarcinoma with low Ki-67 index <10%, at 40x magnification.**

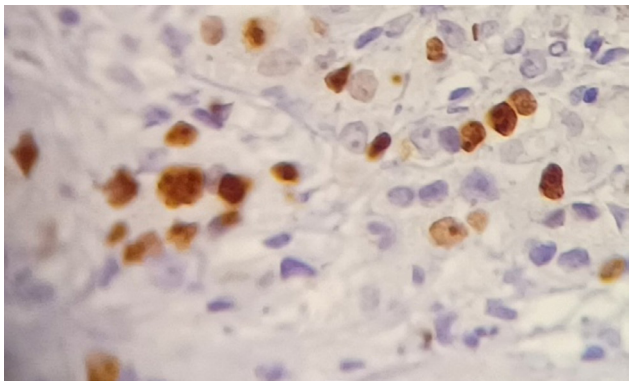

Fig. 3 **Prostate adenocarcinoma with high Ki-67 index >10%, at 40x magnification.**

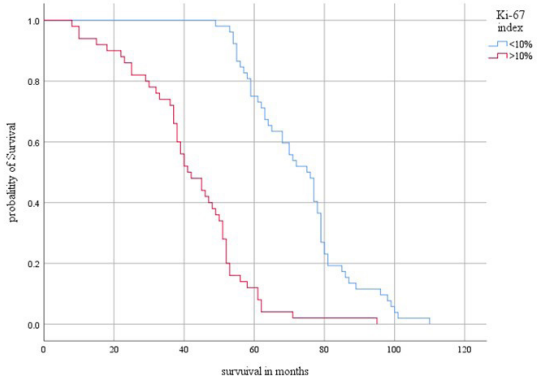

Fig. 4 **Kaplan-Meier curves comparing survival of prostate adenocarcinoma patients with low (blue line) and high (red line) Ki-67 index.**

When the effect of different risk factors was investigated on five-year survival using cox regression, In univariate analysis, Ki-67 expression, age, Gleason score, extraprostatic extension, and obesity were identified as statistically significant predictors of five-year overall survival, Specifically, high Ki-67 expression (>10%) was associated with a greater than two-fold increased hazard of death (HR = 2.19; 95% CI: 1.4–3.3 ; *P* <0.001) compared to low expression (<10%), patients aged 71–80 years (HR = 3.4; 95% CI: 1.7–6.9; *P* <0.001) and those >80 years (HR = 3.9; 95% CI: 1.8–8.3; *P* <0.001) exhibited substantially increased hazards of death compared to patients aged <60 years, Furthermore, a Gleason score of ≥9 conferred a 2.2-fold increased hazard of death (HR = 2.2; 95% CI: 1.2–4.2; *P* = 0.01) relative to Gleason score ≤6. And Extraprostatic extension (HR = 1.5; 95% CI: 1–2.4; *P* = 0.035) and obesity (HR = 1.5; 95% CI: 1–2.3; *P* = 0.04) were also significantly associated with increased hazards.

While several factors were significant in univariate analysis, only age and Ki-67 expression were independent prognostic factors in multivariate analysis, patients with high Ki-67 expression showed 72% increased risk of death within five year after diagnosis, for age, the increased hazard remained significant for those aged 71–80 compare to those aged less than 60 years, other factors (Gleason, extraprostatic extension, obesity, and age >80) lost thier significance in multivariate model (Table 3).

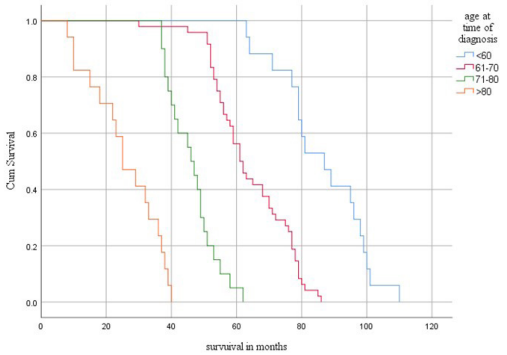

Fig. 5 **Demonstrating how age is related to overall survival in prostate adenocarcinoma.**

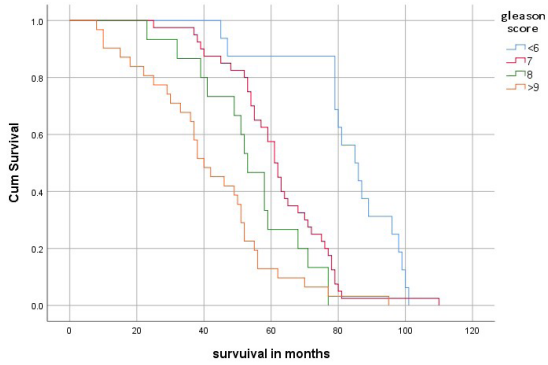

Fig. 6 **Demonstrating overall survival across different gleason scores.**

Discussion

This study aimed to investigate the prognostic significance of the Ki-67 index in prostate adenocarcinoma patients in Sulaymaniyah Governorate.

When comparing our overall survival rates with other studies, we observed that a study from Kurdistan province in Iran reported similar five-year survival at 40%, but their one- and three-year rates were lower at 93% and 64%, respectively.[12] Other regional data indicate varying outcomes, for instance, a study from Turkey involving over 1,000 patients reported a seven-year survival rate of 76.9%.[13] Meanwhile, five-year rates were 49% in Saudi Arabia,[14] and 48% in China[15] Notably, survival rates in South Korea appear considerably higher, at 96%.[16]

The difference in survival between our country and other countries may stem from several factors prevalent in our region, a significant contributing factor is lack of widespread prostate cancer screening program which is done by measuring PSA levels, other causes are late diagnosis of prostate adenocarcinoma due to late appearance of symptoms, furthermore, cultural stigma associated with cancer in our community can result in patients seeking medical help at advanced stages, finally patient reluctant to take treatment due to fear from side effects and financial constraints affects adherence and overall prognosis.

Our study provides compelling evidence for the prognostic importance of Ki-67 expression in prostate adenocarcinoma patients from Sulaymaniyah, as there was a significant

Table 1. **Pathological and clinical characteristics of patients and their association with overall survival using the Kaplan-Meier method**

Characteristic	Category	Number of cases	Median survival (95% CI) (months)	Mean survival ± std dev (month)	*P* value
Ki-67 expression	<10%	52	75 (68–81)	73 ± 2	<0.001
	>10%	50	41 (34–47)	42 ± 2.3	
Age	<60	17	87 (74–99)	86 ± 3	<0.001
	61–70	48	61 (56–65)	64 ± 1.7	
	71–80	20	46 (41–50)	46 ± 1.6	
	>80	17	25 (16–33)	25 ± 2.6	
PSA level	<10 ng/dl	6	79 (45–112)	73 ± 8	<0.001
	11–20 ng/dl	24	78 (75–80)	79 ± 3	
	>20 ng/dl	72	52 (48–55)	49 ± 2	
Gleason score	≤6	16	85 (75–94)	83 ± 4	<0.001
	7	40	61 (57–64)	61 ± 2	
	8	15	53 (46–59)	53 ± 4	
	≥9	31	40 (30–49)	41 ± 3	
Extraprostate extension	Yes	34	40 (26–53)	43 ± 3	<0.001
	No	68	63 (50–75)	63 ± 2	
Perineural invasion	Yes	63	56 (49–62)	54 ± 2	0.021
	No	39	59 (43–74)	63 ± 3	
Lymphovascular invasion	Yes	34	52 (47–56)	47 ± 3	<0.001
	No	68	62 (54–69)	63 ± 2	
Family history	Yes	29	50 (39–60)	51 ± 4	0.76
	No	73	58 (52–63)	60 ± 2	
Obesity	Yes	33	46 (36–56)	44 ± 3	<0.001
	No	69	62 (57–66)	64 ± 2	

CI: Confidence interval, std dev: Standard deviation, *P*: Probability.

Table 2. **Showing Ki-67 expression and its association with other variables**

Variable		Ki-67 index <10%	Ki-67 index >10%	Total	*P* value
Age (years)		62.5 ± 5.5	73 ± 9	68 ± 9.3	<0.001
PSA level (ng/dl)		20 ± 8	53 ± 30	36.6 ± 27.2	<0.001
Gleason score		7.05 ± 1	8.2 ± 1	7.6 ± 1.1	<0.001
Obesity	Yes	9	24	33	0.001
	No	43	26	69	
Family history	Yes	11	18	29	0.097
	No	41	32	73	
Perineural invasion	Yes	29	34	63	0.2
	No	23	16	39	
Lymphovascular invasion	Yes	15	19	34	0.32
	No	37	31	68	
Extraprostatic extension	Yes	14	20	34	0.16
	No	38	30	68	

P value: Probability value.

Table 3. **Cox regression analysis of five-year survival (univariate and multivariate)**

Variable	Category	Univariate analysis HR (95 % CI)	*P* value	Multivariate analysis HR (95 % CI)	*P* value
Ki-67 expression	<10%	1	<0.001	1	0.04
	>10%	2.19 (1.4–3.3)		1.72 (1.0–2.8)	
Age	<60	1		1	
	61–70	1.4 (0.8–2.5)	0.16	1.3 (0.6–2.7)	0.43
	71–80	3.4 (1.7–6.9)	0.001	2.4 (1–5.8)	0.04
	>80	3.9 (1.8–8.3)	<0.001	1.9 (0.6–5.4)	0.21
PSA level	<10				
	11–20	0.8 (0.3–2)	0.66	0.7 (0.2–2.1)	0.62
	>20	1.5 (0.6–3.5)	0.3	0.9 (0.3–2.9)	0.9
Gleason score	≤6	1		1	
	7	1.2 (0.7–2.3)	0.3	0.93 (0.4–2)	0.8
	8	1.8 (0.8–3.7)	0.09	1.05 (0.4–2.6)	0.9
	≥9	2.2 (1.2–4.2)	0.01	1.15 (0.4–2.7)	0.7
Extraprostate extension	No	1		1	
	Yes	1.5 (1.–2.4)	0.03	1.17 (0.6–2)	0.5
Lymohovascular invasion	No	1		1	
	Yes	1.4 (0.9–2.1)	0.1	1.2 (0.7–1.9)	0.3
Perineural invasion	No	1		1	
	Yes	1.017 (0.7–1.6)	0.7	0.8 (0.5–1.2)	0.3
Obesity	No	1		1	
	Yes	1.5 (1–2.3)	0.04	1.1 (0.7–1.8)	0.5
Family history	No	1		1	
	Yes	1.09 (0.7–1.6)	0.6	0.9 (0.5–1.4)	0.7

HR: Hazard ratio, CI: Confidence interval, *P*: Probability.

difference in overall survival across 10% Ki-67 expression (*P* value <0.001).

Our findings were similar to other studies, even when different cutoff levels of Ki-67 expression were used, such as 1% by Aaltomaa (1997), 5% Aaltomaa et al (2006), 7.1% Li et al (2004), and 15% Siddiqui (2024).[17–20]

Consequently, determining the Ki-67 expression is crucial in patients diagnosed with prostate adenocarcinoma, as men with a high Ki-67 expression usually have a more aggressive disease and poorer outcome. Because of that, individuals with a higher level of Ki-67 may need more attention and a different management regime.

In our study, the rate of Ki-67 expression was significantly related to several factors, including PSA level, Gleason score, age, and obesity (*P* <0.05), and these results were similar to previous studies in the field such as Aaltomaa et al (1997), Rasheed (2016), Wu et al (2023) and Rubio et al (2025).[17,21–23]

In our research, the average age at which patients were diagnosed was 68 years, which was a significant factor affecting overall survival and an independent prognostic factor in multivariate analysis.

This aligns with results from a study in the Kurdistan province in Iran, in which the average age at diagnosis was 68.3 ± 8.2 years, and a Turkish study in which the average age of participants was 69 years at diagnosis, and age significantly impacted overall survival.[12,24] Conversely, in Saudi Arabia, the average age at diagnosis was 71.1 ± 10.8 years, and age was not significant in affecting overall survival reflecting potential regional differences.[25]

In our study gleason score was significant in predicting overall survival, with the majority of patients showed a gleason score of 7, our results were similar to the previous studies in the area regarding the importance of the gleason score in predicting overall survival, such as the studies by Rasouli et al (2021) and Song et al (2024).[12,22,26]

The average PSA level of our study was 36 ± 27 ng/dl, and it was a crucial factor in predicting overall survival, this finding is consistent with previous research in the field, including studies by Yilmaz (2020) and Wu et al. (2023).[22,24,27]

In the multivariate Cox regression analysis of five-year survival in our study, only the rate of Ki-67 expression and age were identified as independent prognostic factors. These

results agreed with previous studies regarding the significance of Ki-67 expression in multivariate analysis and showed a *P* value <0.05 even when specific patient groups were used, such as those who received radiation therapy and hormone therapy,[28] patients with localized prostate cancer,[29] and those with distant metastasis.[30]

Specifically, our multivariate analysis showed high Ki-67 expression (HR = 1.72) and age 71–80 years (HR = 2.4) were independent predictors of reduced survival. The magnitude of these hazard ratios indicates a substantially increased risk of death, suggesting their critical role in patient prognosis beyond other standard clinical factors.

Gleason score and PSA level were significant in univariate analyses, however, their significance was not maintained in the multivariate analysis. This is mostly caused by multicollinearity, since these factors are related to each other and affected by other strong factors (Ki-67 index and age) in our study. This suggests that the comprehensive multivariate model captured their prognostic value, underscoring the interplay of multiple factors in prostate adenocarcinoma survival.

This study is the first to explore the predictive value of Ki-67 in prostate adenocarcinoma within Sulaymaniyah Governorate, offering crucial local insights. However, it's important to acknowledge some limitations. Because this was a retrospective study, there's an inherent risk of recall bias and incomplete data. While the sample size was sufficient for identifying primary associations, a larger sample would allow for more in-depth subgroup analyses. Additionally, relying on patient relatives for follow-up information on factors like obesity and family history could potentially introduce inaccuracies.

Conclusion

While there has been many studies in the western countries investigating relationship between Ki-67 expression and prostate adenocarcinoma, this study contributed to a better understanding of overall survival in the Sulaymaniyah Governorate, by integrating the Ki-67 index into clinical practice and promoting further research, we can strive to improve patient outcomes and advance the fight against prostate adenocarcinoma in the region.

Depending on the findings and limitations of our study, we suggest conducting further research on the prognostic importance of the Ki-67 expression in prostate adenocarcinoma, particularly its association with outcomes following different treatment modalities, Future studies should incorporate more patients and involve more than one governorate, additionally investigate the relationship between the Ki-67 index and other molecular markers relevant to prostate adenocarcinoma, such as Gleason score, androgen receptor status, and circulating tumor DNA, could further refine risk stratification and improve treatment decisions.

Ethical Approval

The study was approved by the ethics committee of the College of Medicine of the University of Sulaimani (No. 316 on September 25, 2024).

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Conflicts of Interest

The Authors announce that they have no conflicts of interest.

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