Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2025.354298.3806 Volume 31, Issue 4, April. 2025
Manuscript ID:**ZUMJ-2501-3806**
DOI:**10.21608/zumj.2025.354298.3806**

ORIGINAL ARTICLE

Efficacy and Safety of Quadrivalent Human Papillomavirus Vaccine (Gardasil) Versus 5-Fluorouracil in the Treatment of Basal Cell Carcinoma

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Submit Date: 20-01-2025
Revise Date: 10-04-2025
Accept Date: 09-02-2025

ABSTRACT:

BACKGROUND: The most recent studies indicate that Human papillomavirus (HPV) vaccination could potentially treat squamous cell cancer, basal cell carcinoma, and genital and cutaneous warts. We aimed to assess the efficacy and safety of the quadrivalent HPV vaccine (GARDASIL) versus 5-fluorouracil in treating basal cell carcinoma (BCC).

METHODS: This clinical trial was performed on 20 patients with a confirmed diagnosis of BCC; they were subdivided into two equal groups (n=10 for each). Group I was treated with intralesional injections of Gardasil (0.2 - 0.5 ml) based on the size of the lesions. The injections were administered every two weeks for a total of five sessions; Group II was treated with intralesional injections of 0.3 ml 5-fluorouracil (50 mg/ml) using an insulin syringe every two weeks for a total of five sessions. Therapeutic response and adverse events were assessed at the end of treatment.

RESULTS: The treatment response observed in the studied cohorts revealed a statistically significant improvement, with a higher proportion of marked and complete responses in the 5-Fluorouracil group compared to the Gardasil HPV vaccine group ($p = 0.004$). This highlights the effectiveness of 5-Fluorouracil in achieving higher response rates among participants. Pain during injection was common in both groups, and it was (mild and tolerable). Mild headache was the most common constitutional manifestation associated with the Gardasil vaccine.

CONCLUSIONS: Intralesional 5-fluorouracil is a promising therapeutic option for BCC, particularly for patients seeking less invasive treatments. At the same time, GARDASIL showed limited effectiveness in treating BCC.

KEYWORDS: Basal Cell Carcinoma; Quadrivalent; Human Papillomavirus Vaccine.

INTRODUCTION

Human papillomavirus is a widespread virus that colonizes the skin and mucous membranes. Anogenital and oropharyngeal carcinomas have been associated with a subset of the more than 200 HPV types, some of which are highly carcinogenic. Some estimates put the percentage of human malignant tumors caused by HPV at 5% or lower [1].

Multiple investigations have established a connection between the β-genus of HPV (c-HPV) and the development of keratinocyte carcinomas. The presence of β-HPV types 5, 8, 15, 17, 20, 24, 36, and 38 is associated with an elevated risk of developing cutaneous SCC, and this risk is even higher in individuals who test

positive for numerous β-HPV subtypes [2]. The keratinocyte carcinomas of 90% of immunocompromised patients and 50% of immunocompetent patients can be found to have β-HPV DNA, primarily subtypes 5 and 8 [3].

HPV is thought to play a role in developing keratinocyte carcinomas in several ways. One such mechanism is the production of oncoproteins E6 and E7; these proteins can deregulate gene expression and promote the proliferation of keratinocytes. In the presence of UV damage, this creates an ideal setting for viral multiplication. It was discovered that in immunocompetent individuals, vaccination against HPV can also prevent the development of SCCs and BCCs [4].

BCCs are epidermal skin tumors that are slow-growing, locally invasive, and primarily affect individuals with white skin. Basal cell carcinoma can destroy skin and adjacent tissues, especially on the face, causing substantial cosmetic deformity [5].

Patients who are poor surgical candidates, have numerous lesions, or prefer to delay surgery still have limited options for treating basal cell carcinoma (BCC), while surgery remains the gold standard. Since other vaccination types can induce immune responses that can eliminate tumor cells when administered directly into tumors, a combination of intramuscular and intratumoral HPV vaccines was administered to patients with SCC. There was a marked improvement in the patient's clinical status [6,7].

We conducted this study to assess the efficacy and safety of the quadrivalent HPV vaccine (GARDASIL) versus 5-fluorouracil in treating basal cell carcinoma.

METHODS

This clinical trial was performed on 20 patients with a confirmed diagnosis of Nodular BCC. All the patients were recruited from the Outpatient Clinic of Dermatology, Venereology, and Andrology Department at Zagazig University Hospitals from April 2022 to October 2024. Written informed consent was obtained from all participants; the research ethical committee of the Faculty of Medicine, Zagazig University, approved the study (ZU-IRB#10103/4-12-2022).

Twenty patients, aged 18 years and older, from both sexes, with histologically confirmed Nodular BCC tumors, were recruited and willing to participate in the study.

Cases with the following characteristics were excluded: patients with a history of active or being treated for other cancers, patients using antiviral medications, steroids, or immunization within 14 days before the study, and Pregnant or lactating women.

All patients were evaluated through thorough history taking, current history duration, history of systemic or other dermatological illnesses, current drug usage, and any other relevant medical conditions. A complete general examination was done to exclude any associated medical problems. Dermatological examination: Proper dermatological examination for characteristics of the BCC lesions, including site and size, was done at the start of the study and each follow-up visit.

Material Preparation

1- Gardasil: Gardasil from (Merck & Co., Inc. – USA) is a quadrivalent human papillomavirus (type 6, 11, 16, 18) recombinant vaccine. It was supplied in the form of vials, Single-dose 0.5 ml.

2-5-fluorouracil: 5-fluorouracil from (Hikma Specialized Pharmaceuticals - Egypt) was supplied as vials under the tutorial 500mg/10ml.

Preparation of the treatment area: Normal saline and betadine solution were used to clean the skin properly. Topical lidocaine was applied to the treated area 30 minutes before injection.

The study included 20 cases with BCC. They were assigned into two groups. **Group (I):** Consisted of 10 patients with (BCC) who were treated with intralesional injections of Gardasil (0.2 - 0.5 ml) based on the size of the lesions. The injections were administered every two weeks for a total of five sessions. **Group (II):** Consisted of 10 patients with BCC who were treated with intralesional injections of 0.3 ml 5-

fluorouracil (50 mg/ml) using an insulin syringe every two weeks for a total of five sessions.

Assessment of therapeutic response: The response to the treatment was classified into three categories: Complete response, showing full improvement of the visible/palpable lesion; Marked response, showing more than 75% reduction in tumor size; Moderate response, showing between 50% and 75% reduction in tumor size; and No response, showing less than 50% reduction in tumor size.

Adverse effects: All patients were followed up for 6 months after the last session.

Statistical analysis

We utilized IBM SPSS Statistics version 23.0 for Windows (SPSS Inc., Chicago, IL, USA) for data entry, checking, and analysis. Mean, median ± SD and range represent quantitative data, whereas number and percentage were used to describe qualitative data. We use Fisher's exact and Chi-square tests to search for correlations between qualitative variables. We use the independent t-test and the Mann-Whitney U test to determine how the two groups' quantitative variables are related. We utilized the Kruskal-Wallis test or analysis of variance (ANOVA) to learn more about the link between several sets of quantitative data. Statistical significance is defined as a p-value greater than 0.05, while insignificance, as a p-value of 0.05 or less, is used to describe the same thing.

RESULTS

Twenty patients were included in the study and divided into two groups, with a mean age of 73 years and a gender distribution of 45% males and 55% females. Comparing the two groups' demographic and tumor data showed no statistically significant differences (Table 1).

The response to treatment among the studied groups demonstrated a better therapeutic response.

To 5-Fluorouracil than Gardasil. The treatment response observed in the studied cohorts revealed a statistically significant improvement, with a higher proportion of marked and complete responses in the 5-Fluorouracil group compared to the Gardasil HPV vaccine group ($p = 0.004$). The response rates indicated a significant increase in cases with more than 75% and 100% response in the 5-Fluorouracil group as compared to the Gardasil HPV vaccine group (p=0.004) (Table 2) (Figure 1,2).

In the studied groups, Pain during injection was common in both groups, and it was (mild and tolerable); constitutional manifestations (Headache, Nausea, and Fatigue) were more prevalent in the vaccine group. Mild headache was the most common constitutional manifestation associated with the Gardasil vaccine ($p<0.001$) (Table 3).

In Groups I and II, analysis revealed no significant relation between the therapeutic response and the site or size of BCC (Tables 4 and 5).

Table (1): Demographic, tumor data, and Number of sessions among the studied groups:

Variable		**Group I (Gardasil HPV vaccine) (n=10)**		**Group II (5-Flourouracil) (*n*=10)**		**t**	**P**
Age: (years)	*Mean ± Sd* *Range*	73±11.83 50-85		60±17.98 19-80		1.91	0.07 NS
Variable		**No**	**%**	**No**	**%**	χ^2	**P**
Sex:	*Female* *Male*	5 5	50 50	6 4	60 40	0.20	0.65 NS

Tumor data							
Variable		**Group I (Gardasil HPV vaccine) (n=10)**		**Group II (5-Flourouracil) (*n*=10)**		**χ^2**	**P**
		No	**%**	**No**	**%**		
Site:	*Forehead*	3	30	4	40		
	Nose	1	10	5	50	6.6	0.09
	Under eye	4	40	1	10	1	NS
	Chin	2	20	0	0		
Number:	*1*	10	100	9	90	1.0	0.31
	2	0	0	1	10	5	NS
Size: (cm)	*Mean ± Sd*	2.35±1.16		1.7±0.92		M	
	Median	1.75		1.25		W	0.06
	Range	1.5-4		1-3		1.8	NS
						8	

Number of sessions					
Variable		**Group I (Gardasil HPV vaccine) (n=10)**	**Group II (5-Flourouracil) (*n*=10)**	**t**	**P**
Sessions:	*Mean ± Sd*	4.3±1.49	3.9±0.88	0.	0.48
	Range	2-6	3-5	73	NS

SD: Standard deviation t: Independent t test, MW: Mann Whitney test χ^2:Chi square test NS: Non-significant (P>0.05)

Table (2): Therapeutic Response to treatment among the studied groups:

Variable		**Group I (Gardasil HPV vaccine) (n=10)**		**Group II (5-Flourouracil) (*n*=10)**		**χ^2**	**P**
		No	**%**	**No**	**%**		
Response:	*No response*	6	60	1	10		
	Moderate response	4	40	1	10	**13.37**	**0.004***
	Marked response	0	0	5	50		
	Complete response	0	0	3	30		

χ^2:Chi square test *: Significant (P<0.05)

Table (3): Side effect among the studied groups:

Side effect	Group I (Gardasil HPV vaccine) (n=10)		Group II (5-Flourouracil) (*n*=10)		χ^2	P
	No	%	No	%		
Pain during injection	10	100	8	80	2.22	0.14 NS
Burning during injection	0	0	2	20	2.22	0.14 NS
Constitutional manifestation (Headache, Nausea, and Fatigue)	10	100	0	0	20	<0.001**

χ^2:Chi square test NS: Non-significant (P>0.05) **: Highly significant (P<0.001)

Table (4): Relation between therapeutic response and tumor data and number of sessions among Group I:

Variable		No response (n=6)		Moderate (*n*=4)		χ^2	P
		No	%	No	%		
Site:	*Forehead*	2	66.7	1	33.3		
	Nose	0	0	1	100	7.22	0.07
	Under eye	4	100	0	0		NS
	Chin	0	0	2	100		
Size: (cm)	*Mean ± Sd*	2.13±0.20		3.5±1		MW	
	Median	2.05		4		1.67	0.10
	Range	2 – 2.5		2-4			NS

SD: Standard deviation **t: Independent t test** MW: Mann Whitney test χ^2:Chi square test
NS: Non-significant (P>0.05) *: Significant (P<0.05)

Table (5): Relation between therapeutic response and tumor data and number of sessions among Group II:

Variable		No or moderate (n=2)		Marked (*n*=5)		Complete (n=3)		χ^2	P
		No	%	No	%	No	%		
Site:	*Forehead*	0	0	3	75	1	25		
	Nose	1	20	2	40	2	40	5.6	0.23
	Under eye	1	100	0	0	0	0		NS
Size: (cm)	*Mean ± Sd*	2.25±0.35		3±1		2.2±0.26		KW	
	Median	2.25		3		2.1		0.96	0.62
	Range	2-2.5		2-4		2-2.5			NS

SD: Standard deviation **F: ANOVA test** KW: Kruskal Wallis test χ^2:Chi square test
NS: Non-significant (P>0.05)

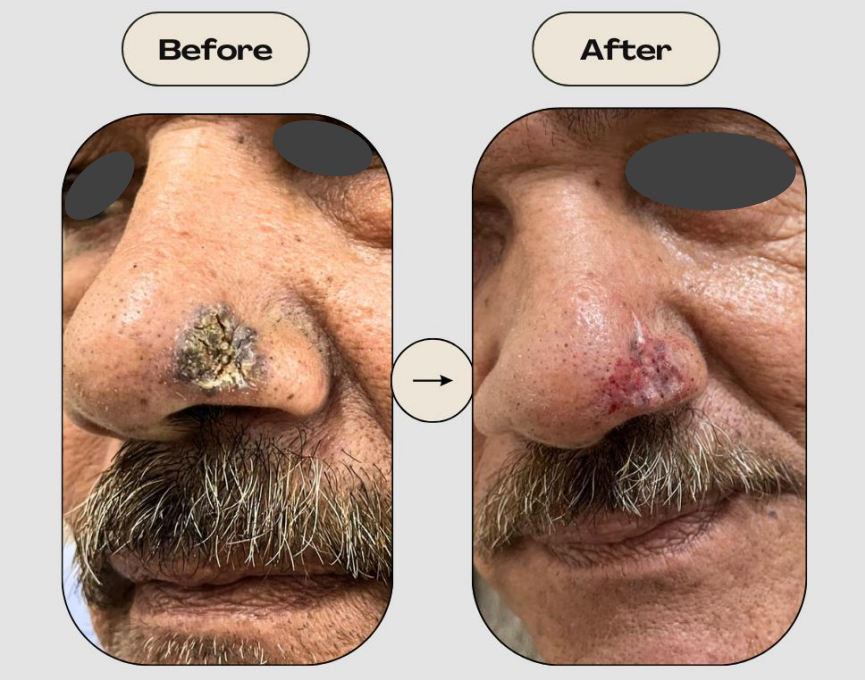

Figure 1: (A) a case of BCC before treatment by GARDASIL injected intratumoral. (B) Moderate response after treatment every 2 weeks for 5 sessions

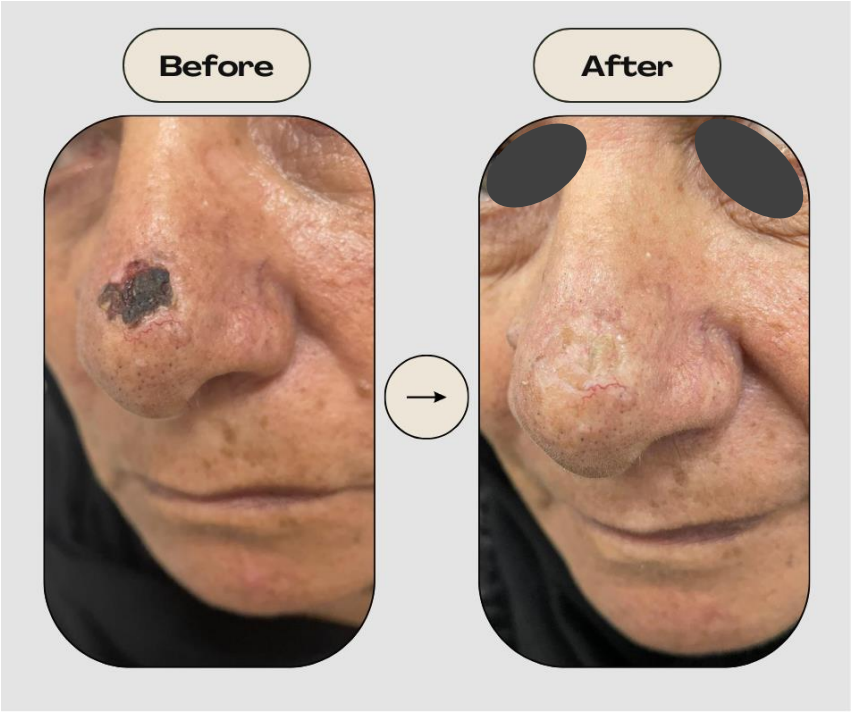

Figure (2): (A) a case of BCC before treatment by 5-fluorouracil injected intratumoral. (B) Showing Marked response after treatment every 2 weeks for 5 sessions

DISCUSSION

Exposure to ultraviolet radiation is the primary environmental risk factor linked to the causation of BCC. Fair skin, advanced age, a family history of skin cancer, immunosuppression, and inherited conditions like xeroderma pigmentosum and nevoid basal cell carcinoma syndrome are among the other risk factors listed [9].

One of the risk factors for mucocutaneous cancer is infection with specific forms of cutaneous HPV, specifically papillomavirus beta-types. This may occur because the virus prevents DNA repair or apoptosis in response to UV light. In vitro research has shown that specific kinds of beta-HPV mitigated the apoptotic responses to UV irradiation in human keratinocytes, suggesting that these viruses may amplify the skin cancer-causing effects of UV radiation [10].

Only vaccines targeting alpha-HPV infection have been approved for use in preventing HPV infection. Diseases connected to α-HPV can be prevented by using one of three licensed HPV vaccines now available: Cervarix®, Gardasil®, or Gardasil-9®. This vaccination targets specific alpha HPV strains in mucosal types, specifically the viral capsid L1. On the other hand, the immunogenic L1 and L2 capsid proteins of alpha- and beta-HPV are very similar [11].

Acknowledging risk factors and quickly obtaining a diagnosis and treatment, especially in vulnerable populations, are the cornerstones of basal cell carcinoma prevention and treatment [12].

The most effective method for treating basal cell carcinoma is surgical excision. This method is conditional on the tumor's stage, histological subtype, location, and the patient's other medical conditions [13].

Radiotherapy is an effective treatment for primary and recurrent BCC, especially in elderly patients or when surgery is contraindicated; however, it is generally not recommended for specific sites due to the risks of poor cosmetic outcomes. Laser treatments, such as pulsed dye and CO2 lasers, have shown promise in treating low-risk BCCs with minimal scarring, though they remain less common than other modalities. Each treatment option presents unique advantages and challenges, highlighting the necessity for a tailored approach to optimize outcomes for individuals with BCC [14,15].

This study evaluated the efficacy and safety of quadrivalent HPV vaccine (GARDASIL) versus intralesional 5-fluorouracil in treating BCC.

Twenty individuals diagnosed with BCC were randomly assigned to one of two groups. Both groups were given intralesional injections of the following: Group I got 0.2 – 0.5 ml of the quadrivalent HPV vaccine (Gardasil) every two weeks for five sessions, and Group II got 0.3 ml of 5-fluorouracil (50 mg/ml) every two weeks for five sessions as well. Nine males and eleven females, aged nineteen to eighty-five, comprised the patient group.

The study found that basal cell carcinoma (BCC) was prevalent in 45% of males and 55% of females. These findings align with previous research by Christenson et al. [16], as they reported that hormonal factors might play a role in the discrepancy. Additionally, Lukowiak et al. [17] noted that female patients often present with BCC at a younger age than males, suggesting differing risk profiles that warrant further investigation.

In contrast, several studies have indicated that basal cell carcinoma (BCC) exhibits a higher prevalence in males compared to females. For instance, research by Khalil et al. [18] found that BCC rates were significantly elevated in males, accounting for approximately 60% of cases in their sample population. This male predominance may be attributed to various factors, including increased sun exposure and outdoor occupations commonly associated with men. Furthermore, Adams et al. [19] highlighted that men are often less vigilant about sun protection measures, which could further contribute to the higher incidence of BCC.

Our study found that the most significant risk factors for basal cell carcinoma (BCC) were sun exposure and advanced age. Chronic sun exposure is a well-established cause of DNA damage in skin cells, which promotes carcinogenesis and increases the risk of BCC development. Additionally, aging may play a critical role, as the cumulative effect of sun exposure over a lifetime significantly contributes to the likelihood of skin damage and tumor formation. The mean age of studied patients in our study was 73 and 60 years in Groups I and II, respectively. These results align with those reported in the studies conducted by Lear and Smith [20] and Naik and Desai [21], who also identified sun exposure and older age as significant risk factors for BCC.

Our study also highlights those two immunocompromised patients, organ transplant recipients in the 5-fluorouracil group, who may have an increased risk of developing BCC. Studies by Fortina et al. [22] and Wu et al. [23] have

similarly reported a significantly higher incidence of skin cancers among organ transplant recipients.

According to our study's results, the response rate to 5-fluorouracil was significantly higher than that of the Gardasil HPV vaccine. Patients treated with 5-fluorouracil had moderate to marked responses, while those treated with Gardasil showed no response.

Previous Studies have examined the effects of the HPV quadrivalent or nonavalent vaccine on patients diagnosed with SCC or BCC. They showed signs of a successful clinical regression after three doses of quadrivalent vaccine [24].

Nichols et al. [25] investigated the impact of the intramuscular quadrivalent, 9 Valent HPV vaccine on patients with a history of numerous keratinocyte carcinomas. Following treatment, new squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs) were lower in every patient than at the beginning of the study, with a decrease in the size and number of SCCs.

Our results regarding the efficacy of Gardasil in the treatment of BCC disagree with those of the previously mentioned studies [25, 24]. Most patients in our study showed no response to Gardasil, and no patients showed a complete response. This may stem from differences in the included population—immunosuppressed patients in Nichols et al. [25] study versus immunocompetent patients in our study. The carcinogenic effect of HPV may be more pronounced in immunosuppressed patients than in immunocompetent ones, so the HPV vaccine might have a more critical role in the treatment and prevention of BCC in immunosuppressed patients.

On the other hand, 5-FU is employed in the treatment of numerous solid tumors, such as those inside the gastrointestinal tract (e.g., esophageal, gastric, pancreatic, colorectal, anal, and hepatic malignancies), the breast, ovarian, and head and neck regions [26].

Consistent with earlier research, our results demonstrate that 5-FU effectively treats BCC. Maghfour et al. [27] found that intralesional fluorouracil (5-FU) is a better option than other chemotherapeutic drugs in NMSC, and our study supports this conclusion. With 91% of evaluable treated tumors achieving complete tumor remission, Miller et al. [28] proved that 5-FU treatment of BCC is safe and effective.

A facilitated transport pathway allows 5-fluorouracil to enter cells, where it is converted into FdUMP or fluorodeoxyuridine monophosphate. Afterward, FdUMP blocks the enzyme thymidylate synthase from making deoxythymidine monophosphate (dTMP) by forming complexes with it. Depletion of dTMP disrupts the normal equilibrium of nucleotides within cells, which triggers the production of double-stranded DNA breaks aided by the endonuclease enzyme [29].

In our study, pain during injection was common in both groups and was mild and tolerable. Mild headache was the most common constitutional manifestation associated with the Gardasil vaccine.

In Groups I and II, there was no significant relationship between treatment response and the site or size of basal cell carcinoma (BCC). Early diagnosis and treatment are critical due to BCC's tendency for local invasion, particularly in high-risk areas such as the head and neck, which can lead to significant cosmetic and functional complications [14,15].

Gardasil is primarily a preventive vaccine against diseases caused by human papillomavirus (HPV), and according to our results, it can only be used as an adjuvant treatment for BCC.

Limitations

Our study has some limitations that need to be mentioned. The first limitation is that our results may not apply to a broader population due to the small sample size (20 cases). Gardasil effectiveness in treating existing BCC lesions was limited in this study, with no patients achieving a complete response. To conduct further clinical trials and encourage more extensive clinical trials to assess the efficacy and safety of Gardasil specifically for treating BCC, as current data shows limited effectiveness. Improve Patient Education: Give clear information about the benefits and side effects of Gardasil and 5-fluorouracil.

CONCLUSIONS

Intralesional 5-fluorouracil is a viable, effective, and economical treatment option, particularly for patients seeking less invasive treatments. GARDASIL showed limited effectiveness in treating BCC, primarily as a preventive measure.

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Figure legend

Figure 1: (A) a case of BCC before treatment by GARDASIL injected intratumoral. (B) Moderate response after treatment every 2 weeks for 5 sessions

Figure (2): (A) a case of BCC before treatment by 5-fluorouracil injected intratumoral. (B) Showing Marked response after treatment every 2 weeks for 5sessions

Citation

Khater, M., Sayed Ahmed, A., Ibrahim, A. S. Efficacy and Safety of Quadrivalent Human Papillomavirus (Gardasil) Versus 5-Fluorouracil in the Treatment of Basal Cell Carcinoma. *Zagazig University Medical Journal*, 2025; (1711-1720): -. doi: 10.21608/zumj.2025.354298.3806