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ORIGINAL ARTICLE

Prognostic and Clinic-Pathological Significances of SCF and COX-2 Expression in Inflammatory and Malignant Prostatic Lesions

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Abstract

The initiation of prostatic malignancy has been linked to chronic inflammation. Stem cell factor (SCF) is an inflammatory cytokine that is specific to the c-KIT receptor which is type III receptor tyrosine kinase (RTK). Cyclooxygenases (COXs) are the main enzymes which are responsible for prostaglandins production from arachidonic acid. COX2 is an enzyme which is produced under different pathological conditions. The aim of our study; is to investigate the clinicopathological and the prognostic significance of SCF and COX-2 expression in prostatic adenocarcinoma (PC), chronic prostatitis and nodular prostatic hyperplasia (NPH) in a trial to clarify the role of inflammation as a risk factor for prostatic carcinogenesis and cancer progression. SCF and COX-2 tissue protein expression were evaluated in 50 cases of PC, 20 cases of chronic prostatitis and 10 cases of NPH using immunohistochemistry, patients were followed up for 5 years. The relationship between their levels of expressions, clinicopathological, and prognostic criteria were studied. SCF expression in PC was positively correlated with advanced patient age (p = <0.001), high level of PSA ($p = 0.010$), higher Gleason score ($p = 0.011$). COX-2 expression in PC was positively correlated with advanced patient age (p = <0.001), high level of PSA ($p = 0.016$), advanced D'Amico risk group ($p = 0.038$). High levels of expression of both SCF& COX-2 are associated with higher incidence of tumor relapse, worse disease overall survival and free survival ($p < 0.001$). SCF and COX-2 are associated with PC progression and associated with poor prognosis in PC patients.

Keywords SCF · COX-2 · Prostatic adenocarcinoma · Immunohistochemistry · Prognosis

Introduction

Prostatic cancer became the most common cancer among men worldwide also it is considered the second leading cause of cancer-related deaths [1]. Since the 1940s hormonal therapy was the primary treatment for advanced prostate cancer. However, a lot of resistant prostate cancer cases keep growing and progress to castration-resistant prostate cancer (CRPC) after androgen deprivation therapy, so the need for new specific agents or target therapy became a must [2]. The initiation of prostate cancer was linked with many factors such as age, diet race, environment, heredity, in addition to, persistent

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inflammation, that initiates carcinogenesis through causing DNA damage, secreting many factors that could stimulate proteases, cellular proliferation, angiogenesis and apoptosis [3].

Chronic prostatitis is a very common prostate disease in men below the age of 50 years and accounts for 8%–14% of the visits to the urology clinics [4]. The prostate gland was divided into three zones; central, peripheral and transitional zones, it was found that prostate cancer and prostatitis occur mainly in the peripheral zone. It was found that the prevalence of chronic prostatitis in prostatic specimens (cancerous or noncancerous) was high and it was associated with what is called proliferative inflammatory atrophy (PIA). Recently, it has been suggested that chronic prostatic inflammation associated with PIA is considered a precursor of prostate carcinogenesis via prostatic intraepithelial neoplasia [3].

Stem cell factor (SCF) is an inflammatory cytokine that is specific to type III tyrosine kinase receptor after their interaction they trigger several signal transduction pathways that regulate fundamental biological processes, such as apoptosis, cell proliferation, differentiation, and migration.[5].

SCF is considered a major mast cell activator and growth factor that triggers signaling of c-Kit pathway for the migration, differentiation, maturation and survival of mast cells, which by its turn an important regulator of inflammation [6]. Mast cell activation changes the tumor's microenvironment by increasing immunosuppression and inflammation. This produces a new insight into SCF role in tumors through its effect on immunosuppression and inflammation [7]. Cyclooxygenases (COXs) are the key enzymes responsible for prostaglandins production from arachidonic acid. COXs are existing in two isoforms: COX1 and COX2. COX2 is not founded in the normal human tissues, but it is induced by tumor promoters and cytokines which are arising during different pathological conditions [8]. Many studies have explained the important role of SCF and COX-2 in the pathophysiology of inflammation and carcinogenesis as they have important roles in the pathogenesis of different types of malignancies [9]. But the results are still conflicting.

Up to our knowledge, the combined prognostic and clinicopathological role of SCF and COX-2 expression in PC carcinogenesis, inflamed and benign prostatic tissues is not clarified yet, so we aimed at our study; to investigate the prognostic and clinic-pathological significance of SCF and COX-2 expression in PC, chronic prostatitis and nodular prostatic hyperplasia in a trial to clarify the role of inflammation as a risk factor for prostatic carcinogenesis and cancer progression.

Patients and Methods

This is a prospective cohort study where we have included 50 patients with PC, 20 patients with chronic prostatitis and 10 cases of NPH, all cases were admitted to the department of General surgery Department, Oncology Unit and Department of Urology, faculty of medicine, Zagazig University, Radical dissection or core biopsy of the tumor was done, and sent to the Pathology department, where they processed for routine H&E staining, diagnosed as PC of different sub-types, chronic prostatitis and nodular prostatic hyperplasia, Gleason scoring system was used for pathological grading of PC. Sections from eighty paraffin blocks which were retrieved from all patients are stained with both SCF and COX-2 using immunohistochemistry, Expression of both markers in all tissue samples was assessed, analyzed and correlations between clinical and pathological parameters with the levels of expression was done e.g. pathological subtype, stage, grade, lymph node and distant metastases, other clinical parameters such as age of the patient, follow up and prognostic parameters as survival, recurrence, and therapeutic response. All patients were followed up till death or till the last known alive data for 5 years from October 2012 to October 2017 in Medical Oncology Department and in Clinical Oncology and Nuclear Medicine Department, Faculty of medicine, Zagazig University.

Ethical approval was obtained from the institutional review board (IRB) committee of faculty of medicine, Zagazig University for performing the study.

Immunohistochemical Staining

Streptavidin-biotin method was used for Immunohistochemistry [10], 4-μm thick sections were cut from the 80 included paraffin blocks, fixed on positively charged slides, incubated for 30 min at 65 °C, Xylene used for deparaffinization of all sections, then rehydration was done, we merged sections into EDTA buffer. For antigen retrieval; we put the slides in the microwave, adding hydrogen peroxide in methanol to antagonize the activity of endogenous peroxidase, then incubation with 1% bovine serum albumin was done. We incubated sections with primary mouse monoclonal; anti-human SCF (G-3) antibody (Alexa Fluor®, Inc., Oregon, USA) and with primary rabbit monoclonal anti-COX-2 antibody (BIOCARE MEDICAL, USA), diluted at 1:50 in phosphate buffered saline (PBS) overnight at 4 °C. Sections were washed, then were incubated with secondary anti-rabbit antibody (Abcam), followed by a streptavidin-horseradish peroxidase complex (Abcam) then finally counterstained by using 10% Mayer's hematoxylin followed by dehydration of the slides and mounted them in crystal mount. We used sections from the smooth muscle cells and lung carcinoma as positive controls for SCF and COX2 respectively; we have omitted the primary antibodies and replaced them with PBS for negative control. All stained slides were evaluated for the degree reactivity of SCF and COX2 by 2 senior pathologists who were blind to the clinical data of the included patients. Scores of extent and intensity were averaged.

Evaluation of SCF and COX2 Staining

We considered brown cytoplasmic expression as positive for both SCF and COX2 and the results of staining were analyzed semi quantitatively by the detection of both the percentage and the intensity of stained cells; the percentage of the positive cells and a staining intensity were evaluated as follow: staining percentage was scored as 0 if there is no staining, was scored as 1 if 1–10% of cells were stained, scored as 2 if 11–50% of cells were stained, was scored as 3 if 51–80% were stained, and was scored as 4 if 81–100% of cells were stained. Staining intensity was scored as 0 is if there was no staining, as 1 if there was a weak staining, as 2 if there is a moderate staining and as 3 if there is a strong staining. Both values of the intensity and the percentage scores were multiplied to give the final score from 0 to 12. A final staining score considered 0 as negative, 1–4 as weak, 5–8 as moderate and 9–12 was considered strong immunoreactivity [9]. We used the cut point of five above which was considered a high expression and below which is considered low expression.

Statistical Analysis

MedCalc windows (MedCalc Software BVBA 13, Ostend, Belgium) and SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA were used in performing all statistics. Shapiro-Wilk test was used to check the continuous variables. Comparing the two groups of non-normally distributed variables was checked using the Mann Whitney U test. Comparison between more than two groups of non-normally distributed variables was checked using the Kruskal Wallis H test. Pearson's Chi-square test or Fisher's exact test was used for Percent of comparing categorical variables. Strength of relationship between SCF & Cox-2 and clinicopathological features were determined by computing appropriate correlations coefficient. Calculation of Disease Free Survival (DFS) as the time from start of treatment to date of distant metastasis or local recurrence was detected or most recent follow-up in which local recurrence or distant metastasis was not detected. We calculated the Overall Survival (OS) from diagnosis to the recent follow-up contact (censored) or death. We have stratified OS and DFS according to immunohistochemical markers and clinicopathological features. Estimation of time-to-death distributions was done using the Kaplan-Meier plot. *P* value <0.05 was considered significant.

Results

Patient Clinicopathological Data; (Table 1)

The detailed clinic-pathological data of our patients were fully illustrated in Table 1.

Table 1 Comparison between prostatic adenocarcinoma, chronic prostatitis, and benign prostatic hyperplasia

	Prostatic adenocarcinoma (*N* = 50) No.(%)	Chronic prostatitis (*N* = 20) No.(%)	Benign prostatic hyperplasia (*N* = 10) No.(%)	p value
Age (years)				
Mean ± SD	65.60 ± 4.70	57.70 ± 7.39	49.80 ± 7.28	<0.001•
Median (Range)	67(50–70)	55(45–70)	48.50(40–61)	
< 65 years	14(28%)	15(75%)	10(100%)	<0.001‡
> 65 years	36(72%)	5(25%)	0(0%)	
Previous chronic prostatitis				
Absent	25(50%)	0(0%)	10(100%)	<0.001‡
Present	25(50%)	20(100%)	0(0%)	
PSA				
< 10 ng/dl	8(16%)	17(85%)	10(100%)	<0.001‡
10–20 ng/dl	14(28%)	3(15%)	0(0%)	
> 20 ng/dl	28(56%)	0(0%)	0(0%)	
Type of spécimen				
Radical prostatectomy	9(18%)	8(40%)	6(60%)	0.012‡
Core biopsy	41(82%)	12(60%)	4(40%)	
SCF IHC Staining				
Low	22(44%)	11(55%)	9(90%)	0.028‡
High	28(56%)	9(45%)	1(10%)	
Cox-2 IHC Staining				
Low	18(36%)	10(50%)	8(80%)	0.034‡
High	32(64%)	10(50%)	2(20%)	
SCF/Cox-2 IHC Staining				
Low/Low	13(26%)	9(45%)	8(80%)	0.069‡
Low/High	9(18%)	2(10%)	1(10%)	
High/Low	5(10%)	1(5%)	0(0%)	
High/High	23(46%)	8(40%)	1(10%)	

Categorical variables were expressed as number (percentage)

• Mann Whitney U test; ‡ Chi-square test; $p < 0.05$ is significant

Table 2 Relation between SCF, Cox-2 IHC staining and clinicopathological parameters in 50 prostatic carcinoma patients

Parameters	Prostatic adenocarcinoma (N = 50)	SCF IHC staining		p value	Cox-2 IHC staining		p value
		Low (*N* = 22)	High (*N* = 28)		Low (*N* = 18)	High (*N* = 32)	
	No. (%)	No. (%)	No. (%)		No. (%)	No. (%)	
Age (years)							
Mean ± SD	65.60 ± 4.70	63.72 ± 5.96	67.07 ± 2.72	0.076•	63.55 ± 5.55	66.75 ± 3.77	0.080•
Median (Range)	67(50–70)	65(50–70)	67.50(60–70)		64(54–70)	67.50(50–70)	
< 65 years	14(28%)	11(78.6%)	3(21.4%)	0.002‡	10(71.4%)	4(28.6%)	0.001‡
> 65 years	36(72%)	11(30.6%)	25(69.4%)		8(22.2%)	28(77.8%)	
Previous chronic prostatitis							
Absent	25(50%)	8(32%)	17(68%)	0.087‡	6(24%)	19(76%)	0.077‡
Present	25(50%)	14(56%)	11(44%)		12(48%)	13(52%)	
PSA							
< 10 ng/dl	8(16%)	6(75%)	2(25%)	0.010§	5(62.5%)	3(37.5%)	0.016§
10–20 ng/dl	14(28%)	8(57.1%)	6(42.9%)		7(50%)	7(50%)	
> 20 ng/dl	28(56%)	8(28.6%)	20(71.4%)		6(21.4%)	22(78.6%)	
Gleason score							
Mean ± SD	7.90 ± 1.51	7.31 ± 1.52	8.35 ± 1.36	0.011•	7.16 ± 1.79	8.31 ± 1.17	0.022•
Median (Range)	8(4–10)	7(4–9)	9(4–10)		7(4–10)	9(6–10)	
< 7	8(16%)	6(75%)	2(25%)	0.022§	5(62.5%)	3(37.5%)	0.041§
7	11(22%)	6(54.5%)	5(45.5%)		5(45.5%)	6(54.5%)	
> 7	31(62%)	10(32.3%)	21(67.7%)		8(25.8%)	23(74.2%)	
Type of specimen							
Radical prostatectomy	9(18%)	2(22.2%)	7(77.8%)	0.266‡	2(22.2%)	7(77.8%)	0.459‡
Core biopsy	41(82%)	20(48.8%)	21(51.2%)		16(39%)	25(61%)	
Perineural invasion							
Absent	26(52%)	15(57.7%)	11(42.3%)	0.042‡	13(50%)	13(50%)	0.032‡
Present	24(48%)	7(29.2%)	17(70.8%)		5(20.8%)	19(79.2%)	
Capsular invasion							
Absent	19(38%)	12(63.2%)	7(36.8%)	0.033‡	10(52.6%)	9(47.4%)	0.055‡
Present	31(62%)	10(32.3%)	21(67.7%)		8(25.8%)	23(74.2%)	
Seminal vesicle invasion							
Absent	26(52%)	15(57.7%)	11(42.3%)	0.042‡	13(50%)	13(50%)	0.032‡
Present	24(48%)	7(29.2%)	17(70.8%)		5(20.8%)	19(79.2%)	
T							
T1	8(16%)	6(75%)	2(25%)	0.005§	5(62.5%)	3(37.5%)	0.019§
T2	11(22%)	6(54.5%)	5(45.5%)		5(45.5%)	6(54.5%)	
T3	17(34%)	8(47.1%)	9(52.9%)		6(35.3%)	11(64.7%)	
T4	14(28%)	2(14.3%)	12(85.7%)		2(14.3%)	12(85.7%)	
N							
N0	33(66%)	20(60.6%)	13(39.4%)	0.001‡	16(48.5%)	17(51.5%)	0.010‡
N1	17(34%)	2(11.8%)	15(88.2%)		2(11.8%)	15(88.2%)	
M							
M0	40(80%)	20(50%)	20(50%)	0.154‡	16(40%)	24(60%)	0.295‡
M1	10(20%)	2(20%)	8(80%)		2(20%)	8(80%)	
D'Amico risk group							
Low risk	8(16%)	6(75%)	2(25%)	0.019§	5(62.5%)	3(37.5%)	0.038§
Internediate risk	11(22%)	6(54.5%)	5(45.5%)		5(45.5%)	6(54.5%)	
High risk	6(12%)	2(33.3%)	4(66.7%)		2(33.3%)	4(66.7%)	
Locally advanced	15(30%)	6(40%)	9(60%)		4(26.7%)	11(73.3%)	
Metastatic	10(20%)	2(20%)	8(80%)		2(20%)	8(80%)	
SCF IHC Staining							
Low	22(44%)				13(59.1%)	9(40.9%)	0.003‡
High	28(56%)				5(17.9%)	23(82.1%)	
Cox-2 IHC Staining							
Low	18(36%)	13(72.2%)	5(27.8%)	0.003‡			
High	32(64%)	9(28.1%)	23(71.9%)				

Categorical variables were expressed as number (percentage), continuous variables were expressed as mean ± SD & median (range)

• Mann Whitney U test; ‡ Chi-square test; § Chi-square test for trend; $p < 0.05$ is significant

The included 50 patients in our study that were diagnosed to have PC, 20 patients with chronic prostatitis and 10 cases of NPH mean age of patients with PC is 65.60 ± 4.70 median ages of PC, chronic prostatitis & NPH are 67, 55& 48.50 respectively.25 (25%) of patients with PC that has a previous history of chronic prostatitis.

The Assessed Immunohistochemical Results; (Tables 2 and 3)

SCF& COX-2 expression was more found in PC than in chronic prostatitis and NPH ($p = 0.28$& 0.034 respectively). (Figs. 1, 2, 3, 4, and 5).

Table 3 Relation between SCF/Cox-2 IHC staining and clinicopathological parameters in 50 prostatic carcinoma patients

Parameters	Prostatic adenocarcinoma (N = 50)	SCF /Cox-2 IHC staining				p value
		Low/Low (*N* = 13)	Low/High (*N* = 9)	High/Low (N = 5)	High/High (*N* = 23)	
	No.(%)	No.(%)	No.(%)	No.(%)	No.(%)	
Age (years)						
Mean ± SD	65.60 ± 4.70	62.92 ± 5.85	64.88 ± 6.27	65.20 ± 4.86	67.47 ± 1.95	0.225•
Median (Range)	67(50–70)	64(54–70)	66(50–70)	67(60–70)	68(61–70)	
< 65 years	14(28%)	8(57.1%)	3(21.4%)	2(14.3%)	1(7.1%)	0.003‡
> 65 years	36(72%)	5(13.9%)	6(16.7%)	3(8.3%)	22(61.1%)	
Previous chronic prostatitis						
Absent	25(50%)	4(16%)	4(16%)	2(8%)	15(60%)	0.225‡
Present	25(50%)	9(36%)	5(20%)	3(12%)	8(32%)	
PSA						
< 10 ng/dl	8(16%)	4(50%)	2(25%)	1(12.5%)	1(12.5%)	0.004§
10–20 ng/dl	14(28%)	5(35.7%)	3(21.4%)	2(14.3%)	4(28.6%)	
> 20 ng/dl	28(56%)	4(14.3%)	4(14.3%)	2(7.1%)	18(64.3%)	
Gleason score						
Mean ± SD	7.90 ± 1.51	7 ± 1.63	7.77 ± 1.30	7.60 ± 2.30	8.52 ± 1.08	0.042
Median (Range)	8(4–10)	7(4–9)	8(6–9)	8(4–10)	9(6–10)	
< 7	8(16%)	4(50%)	2(25%)	1(12.5%)	1(12.5%)	0.011§
7	11(22%)	4(36.4%)	2(18.2%)	1(9.1%)	4(36.4%)	
> 7	31(62%)	5(16.1%)	5(16.1%)	3(9.7%)	18(58.1%)	
Type of specimen						
Radical prostatectomy	9(18%)	0(0%)	2(22.2%)	2(22.2%)	5(55.6%)	0.185‡
Core biopsy	41(82%)	13(31.7%)	7(17.1%)	3(7.3%)	18(43.9%)	
Perineural invasion						
Absent	26(52%)	10(38.5%)	5(19.2%)	3(11.5%)	8(30.8%)	0.105‡
Present	24(48%)	3(12.5%)	4(16.7%)	2(8.3%)	15(62.5%)	
Capsular invasion						
Absent	19(38%)	8(42.1%)	4(21.1%)	2(10.5%)	5(26.3%)	0.121‡
Present	31(62%)	5(16.1%)	5(16.1%)	3(9.7%)	18(58.1%)	
Seminal vesicle invasion						
Absent	26(52%)	10(38.5%)	5(19.2%)	3(11.5%)	8(30.8%)	0.105‡
Present	24(48%)	3(12.5%)	4(16.7%)	2(8.3%)	15(62.5%)	
T						
T1	8(16%)	4(50%)	2(25%)	1(12.5%)	1(12.5%)	0.002§
T2	11(22%)	4(36.4%)	2(18.2%)	1(9.1%)	4(36.4%)	
T3	17(34%)	5(29.4%)	3(17.6%)	1(5.9%)	8(47.1%)	
T4	14(28%)	0(0%)	2(14.3%)	2(14.3%)	10(71.4%)	
N						
N0	33(66%)	13(39.4%)	7(21.2%)	3(9.1%)	10(30.3%)	0.006‡
N1	17(34%)	0(0%)	2(11.8%)	2(11.8%)	13(76.5%)	
M						
M0	40(80%)	13(32.5%)	7(17.5%)	3(7.5%)	17(42.5%)	0.167‡
M1	10(20%)	0(0%)	2(20%)	2(20%)	6(60%)	
D'Amico risk group						
Low risk	8(16%)	4(50%)	2(25%)	1(12.5%)	1(12.5%)	0.009§
Internediate risk	11(22%)	4(36.4%)	2(18.2%)	1(9.1%)	4(36.4%)	
High risk	6(12%)	1(16.7%)	1(16.7%)	1(16.7%)	3(50%)	
Locally advanced	15(30%)	4(26.7%)	2(13.3%)	0(0%)	9(60%)	
Metastatic	10(20%)	0(0%)	2(20%)	2(20%)	6(60%)	

Categorical variables were expressed as number (percentage), continuous variables were expressed as mean ± SD & median (range)

• Kraskall Wallis H test; ‡ Chi-square test; § Chi-square test for trend; $p < 0.05$ is significant

SCF Expression. (Fig. 2)

SCF expression in PC was positively correlated with older patient age ($p = 0.002$), high level of PSA ($p = 0.022$), higher Gleason score ($p = 0.011$), capsular invasion ($p = 0.033$), seminal vesicles invasion & perineural invasion ($p = 0.042$),, T staging ($p = 0.005$), N stage ($p = 0.001$), advanced D'Amico risk group ($p = 0.019$) recurrence of the tumor after successful therapy, overall survival and disease-free survival ($p < 0.001$).

No significant statistical correlations were found between SCF expression with the presence of distant metastases, type of specimen or previous history of CP.

Survival Analysis: (Tables 4 and 5)

- After a median follow-up time of 43.22 months, 21 (42%) of our PC patients have died.
- The 5-year overall survival (OS) rate was 46% (95% CI; 38.04–48.40 months).

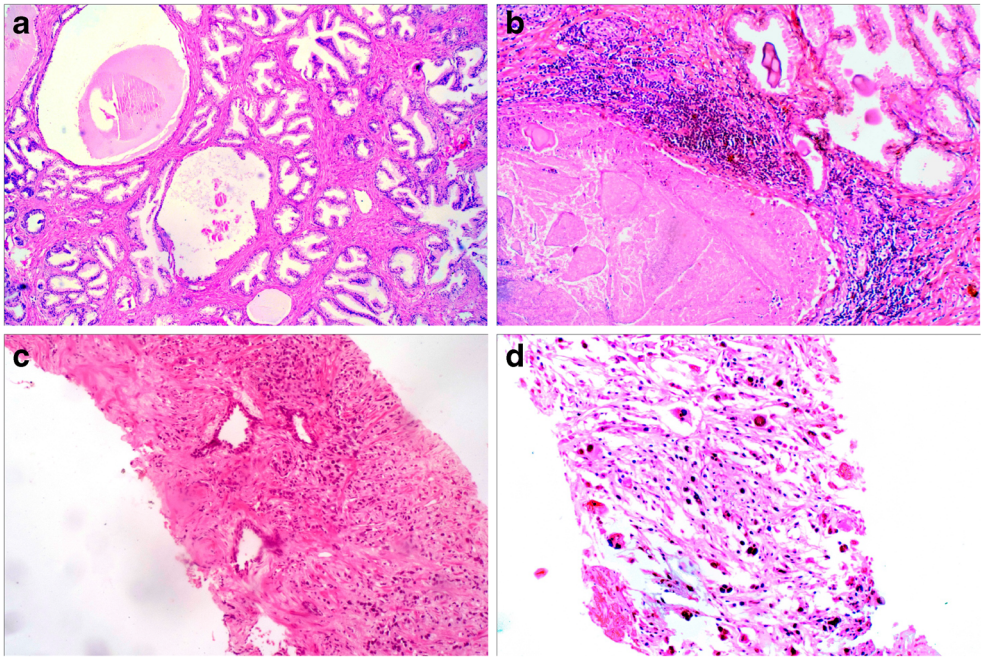

Fig. 1 Different Prostatic lesions stained with routine hematoxylin and eosin stained sections (**a**) Nodular prostatic hyperplasia ×100. (**b**) Chronic prostatitis ×100. (**c**) Low grade prostatic carcinoma Gleason 4 × 100 (**d**) High grade prostatic adenocarcinoma Gleason 9 × 100

- The 3-year disease-free survival (DFS) rate was 41.8% (95% CI; 33.44–44.72 months).
- At the end of follow up period, there was a 24 (55.8%) patients developed disease relapse.

Progression, Relapse, Response to Therapy and Survival Results in Relation to SCF Expression (Table 6)

- High SCF expressing cases were more liable to cancer progression and a higher incidence of relapse after therapy ($p < 0.001$).
- High SCF expressing patients had poor DFS and 5 year OS rates ($p < 0.001$).

COX-2 Expression

COX-2 expression in PC was positively correlated with older patient age ($p = 0.001$), high level of PSA ($p = 0.016$), higher Gleason score ($p = 0.041$), perineural & seminal vesicles invasion ($p = 0.032$), T staging ($p = 0.019$), N stage ($p = 0.01$), advanced D'Amico risk group ($p = 0.038$) higher incidence of tumor relapse, worse disease free survival and overall survival ($p < 0.001$).

No significant correlations between expression of COX-2 with capsular invasion, distant metastases, type of specimen or previous history of CP was found.

- SCF and COX-2 were positively correlated with each other correlation coefficient $r = +0.426$.

Progression, Relapse, Response to Therapy and Survival Results in Relation to COX-2 Expression (Table 6)

- High COX-2 expressing cases were more liable to cancer progression and a higher incidence of relapse after therapy ($p < 0.001$).
- High COX-2 expressing patients had poor DFS and 5 year OS rates ($p < 0.001$).

Discussion

SCF which is a potent c-KIT legend growth factor is known as steel factor or mast cell growth factor. It has been shown that the SCF overexpression leads to the growth and progression of different types of human malignancies which have placed the SCF/c-KIT system on the road of the anticancer therapy [5].

In the present study, we have correlated SCF expression in PC, chronic prostatitis and BPH with clinic-pathological and follow up criteria and we found that SCF expression in PC was associated with poor clinic-pathological criteria as higher grade and advanced stage. That was similar to [Siddique et al. [11] who have found that SCF was secreted by tumor cells in PC and it proportionate positively with the progression of its stage and grade.

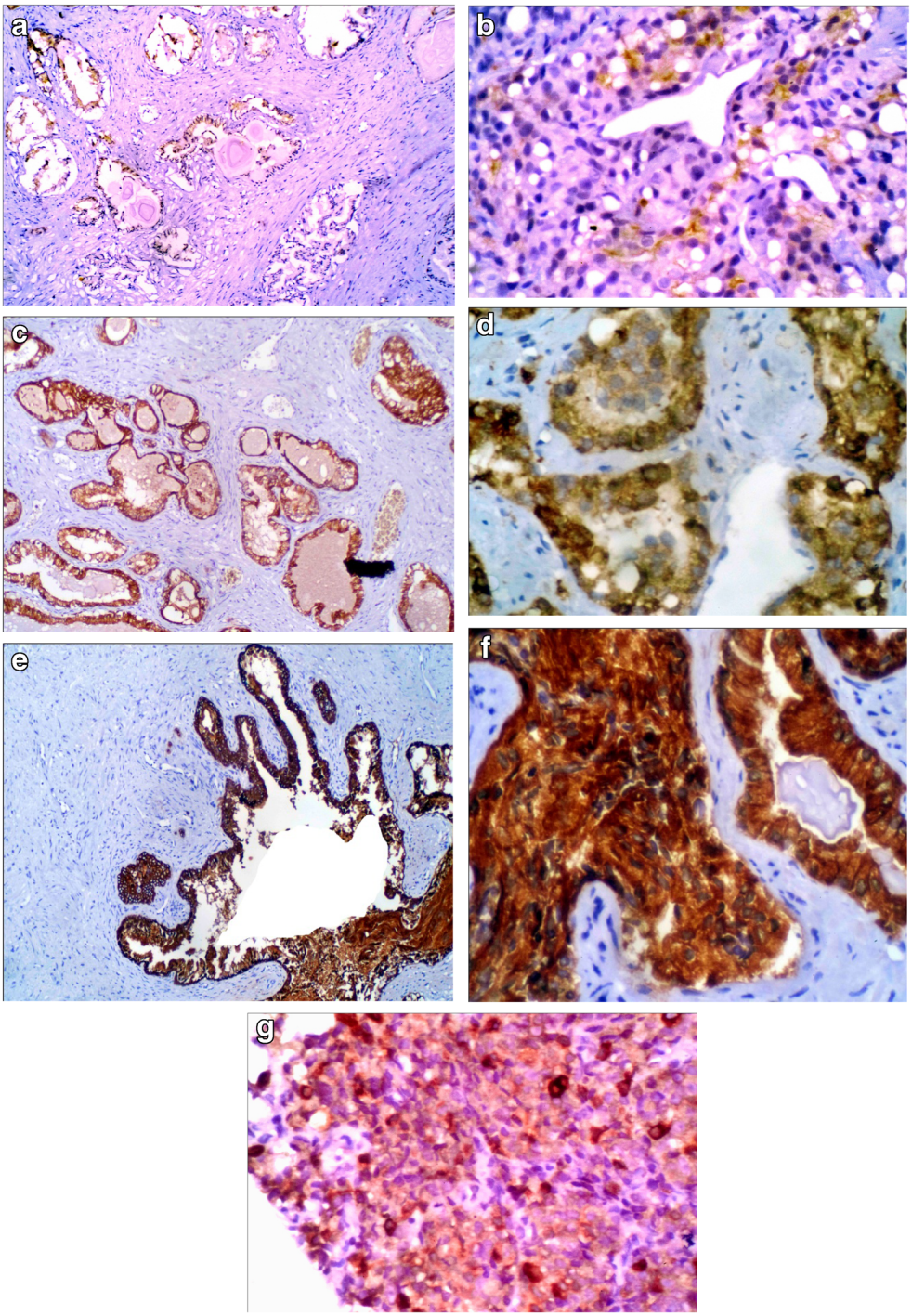

Fig. 2 Immunohistochemical expression of SCF in Prostatic lesions: **a** Low expression in the cytoplasm of NPH ×100. **b** Low expression in the cytoplasm of chronic prostatitis ×400. **c** Low expression in the cytoplasm of low grade prostatic carcinoma Gleason 3 × 100 **d** Moderate expression in the cytoplasm of low grade prostatic carcinoma, Gleason 4 × 400 **e** high expression in the cytoplasm of high grade prostatic carcinoma Gleason 7 × 100. **f** high expression in the cytoplasm of high grade prostatic carcinoma Gleason 8 × 400. **g** High expression in the cytoplasm of high grade prostatic carcinoma Gleason 9 × 100

As we proved that high SCF expression was correlated with poor outcomes of PC patients as advanced D'Amico risk group, recurrence of the tumor after successful therapy, worse DFS and OS rates, similarly [Wang et al. [12]] reported that higher expression of SCF in HCC patients is linked to worse prognosis of these patients and showed a shorter time to recurrence, moreover similar results were proved by [Wang et al. [13]] that higher SCF expression in patients with hepatocellular carcinoma was related to poor prognosis and latent metastasis. Also, [Bellone et al.] [14] who found that SCF

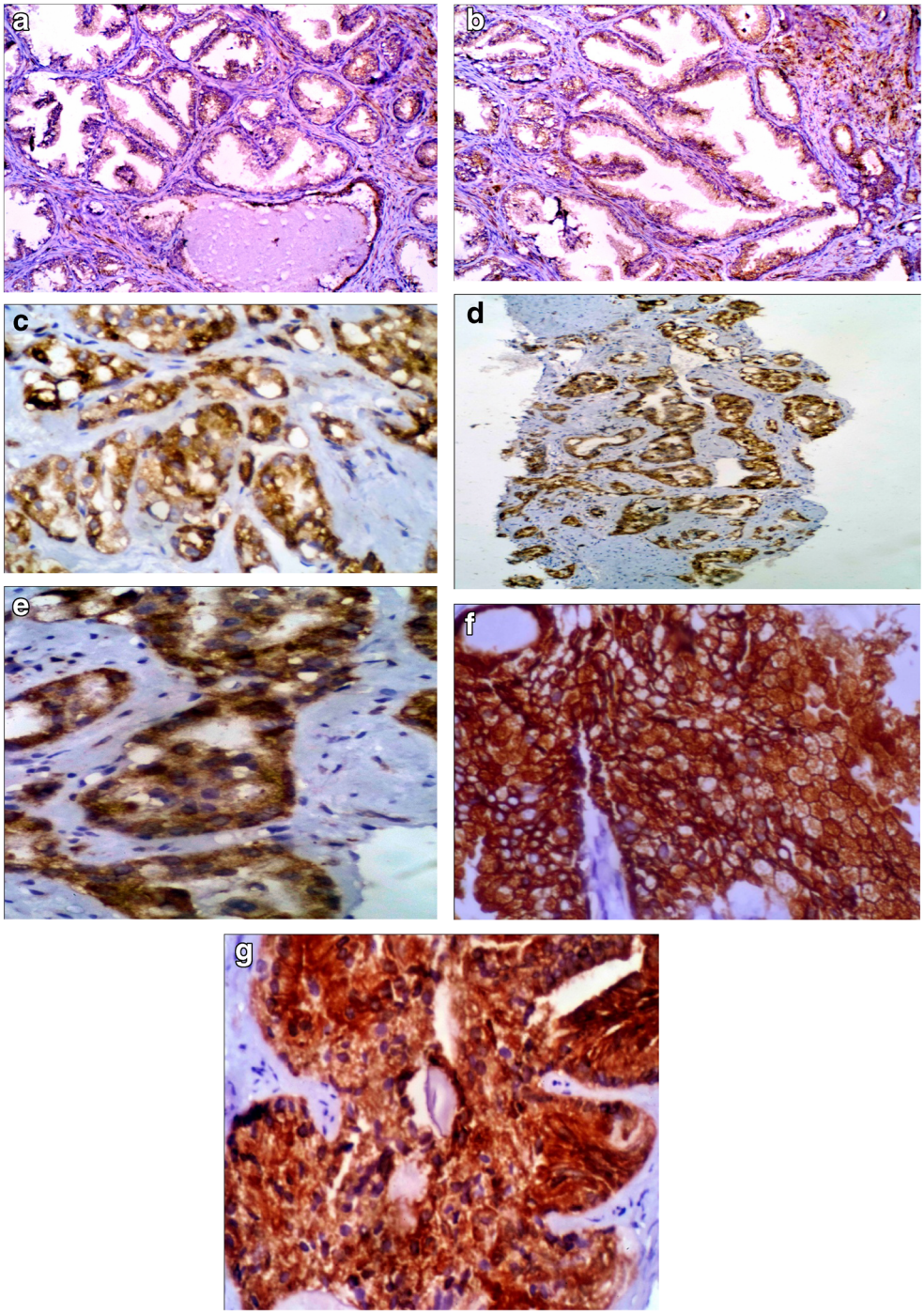

Fig. 3 Immunohistochemical expression of Cox-2 in Prostatic lesions: **a** Low expression in the cytoplasm of NPH ×100. **b** Low expression in the cytoplasm of chronic prostatitis ×100. **c** Low expression in the cytoplasm of low grade prostatic carcinoma Gleason 3 × 400 **d** Moderate expression in the cytoplasm of low grade prostatic carcinoma, Gleason 4 × 100 **e** high expression in the cytoplasm of high grade prostatic carcinoma Gleason 5 × 400. **f** High expression in the cytoplasm of high grade prostatic carcinoma Gleason 8 × 400. **g** High expression in the cytoplasm of high grade prostatic carcinoma Gleason 9 × 400

expression was correlated positively with advanced Dukes' stages in colorectal adenocarcinoma, and the SCF expression is progressively increased towards advanced stages. Additionally, [Gao et al.] [15] have found near results in pancreatic ductal adenocarcinoma, where they stated that SCF could enhance the proliferation and invasion of pancreatic cancer cells and SCF expression is increased by hypoxia that leads to accelerates the progression of the malignant pancreatic cells. Near to our results; [Yasuda et al.] [16] stated that increased activation of SCF-KIT signals increases the proliferation and invasiveness in cancer cell lines with positive SCF-KIT expression.

[Esposito et al. [17] have found different results for us as they did not find a significant relationship between tumor grading or staging and high SCF expression in pancreatic ductal adenocarcinoma.

By contrast to our results, another study has reported that the c-kit/SCF pathway has a significant role in the normal

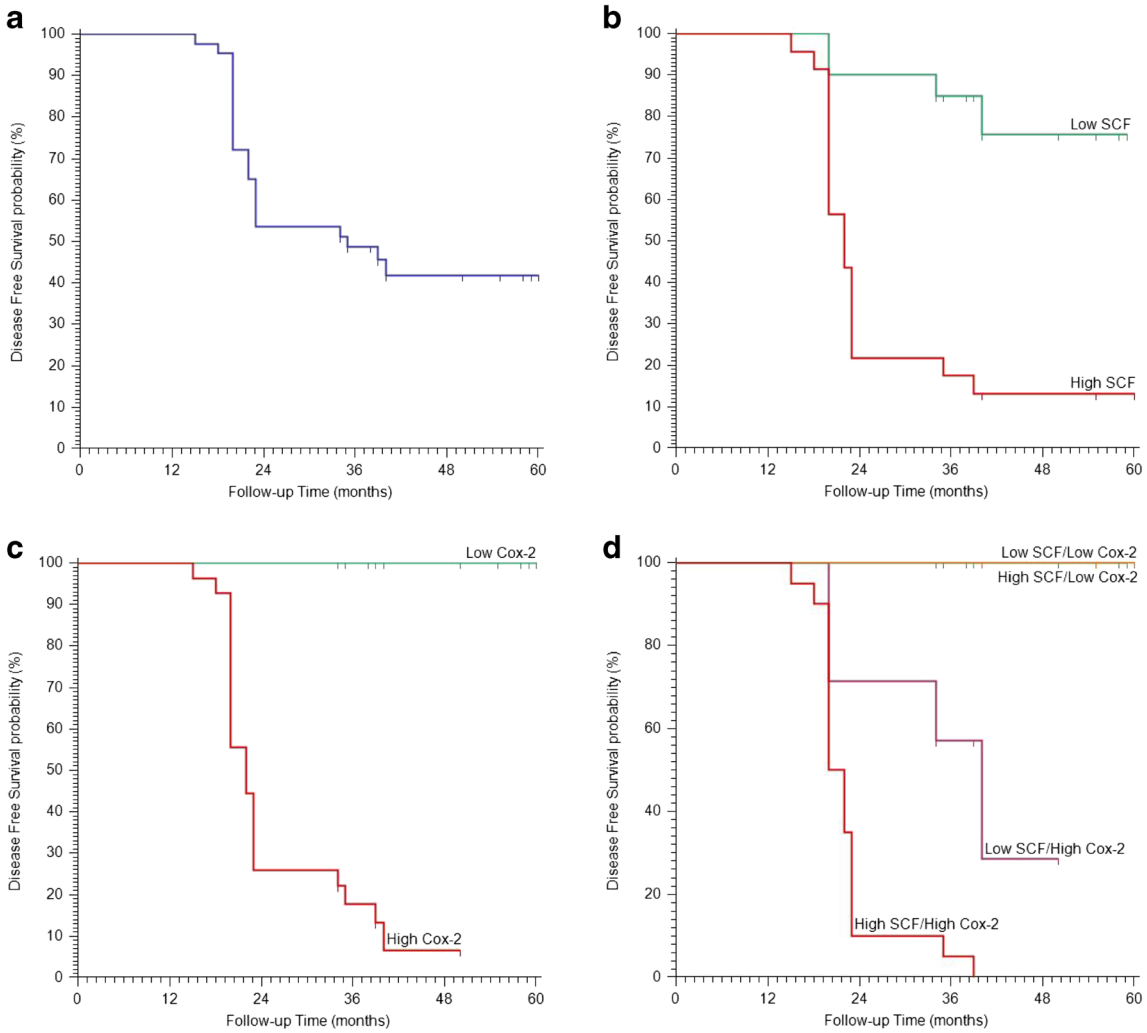

Fig. 4 **a** Kaplan-Meier plot of Disease Free Survival (DFS) of All prostatic adenocarcinoma patients **b** DFS of All prostatic adenocarcinoma patients stratified according to SCF IHC staining, **c** DFS of All prostatic adenocarcinoma patients Stratified according to Cox-2 IHC staining and **d** DFS of All prostatic adenocarcinoma patients Stratified according to SCF/Cox-2 IHC staining

growth of the glandular epithelium of the mammary gland and the malignant transformation of these cells is associated with progressive loss of these signals [18]. Different results may be due to different organs or may attribute to different methodologies and morphological approaches defining the cellular source of SCF expression or a different method of marker interpretation.

Our results can be explained by that SCF has an important function in healthy tissues through activation of c-KIT pathway, SCF overexpression leads to over-activation of SCF/c-Kit pathway in tumors and in pre-cancerous lesions that leads to increased cancer progression, cancer cell proliferation, migration and cancer stemness [19], additionally SCF overexpression lead to loss of control of apoptosis and cell differentiation that allows neoplastic transformation and tumor progression [5]. Moreover, tumor cell-released SCF lead to the initiation of tumor microenvironment remodeling that has an essential role in cancer progression [7]. All such findings pointed to that targeting of SCF/c-Kit pathway by the tyrosine kinase inhibitor like Imatinib was considered an optimal tool for a tumor-specific targeted therapy for PC novel management, Imatinib was used to treat leukemia and GIST-tumors but in recent years also for other solid tumors [19]. Our results and results of these studies suggest that the prognosis of patients with PC may be assessed by evaluation of the expression of SCF.

COX-2 is an inflammatory active mediator that plays an important role in several degenerative, inflammatory, autoimmune and different types of cancers, that draws an attention to the development of COX-2 inhibitors as a therapeutic method for such diseases [20].

In the current study we proved that expression of COX2 in PC was significantly positively correlated with poor clinical and pathological criteria as older patient age, high level of PSA, higher Gleason score, perineural invasion, seminal vesicles invasion, and advanced stage.

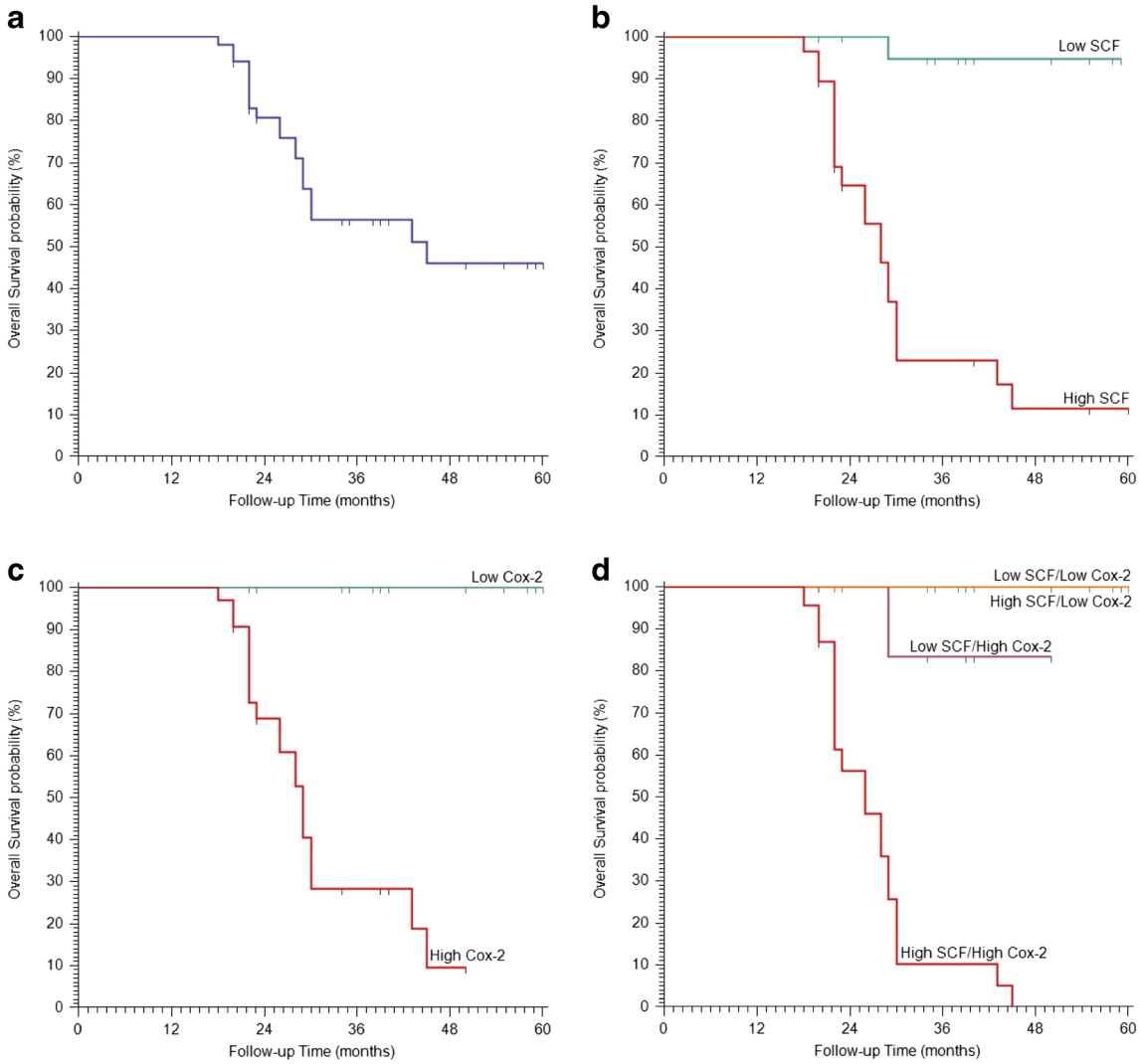

Fig. 5 **a** Kaplan-Meier plot of Overall Survival (OS) of all prostatic adenocarcinoma patients **b** OS of All prostatic adenocarcinoma patients Stratified according to SCF IHC staining, **c** OS of All prostatic adenocarcinoma patients Stratified according to Cox-2 IHC staining and **d** OS of All prostatic adenocarcinoma patients stratified according to SCF/Cox-2 IHC staining

That was similar to results of [Wang et al. [21], who linked the higher expression of COX-2 in prostatic cancer with poor clinicopathological parameters (age, PSA level, Gleason score and tumor amount), additionally, the result of [Hu et al.][22] who found that COX-2 overexpression was significantly associated with distant metastasis, the depth of invasion and TNM staging of esophageal cancer was similar to us, and similarly, [Xu et al. [22], who found a proportional relation of higher COX-2 expression with clinicopathological features such as large size and LN metastasis of breast cancer.

Different from our results [Zha et al. [23] have found that overexpression of COX-2 did not correlate with poor clinical-pathological parameters as (staging or Gleason scoring).

[Malaysiana et al.] [24], have proved that the over-expression of COX-2 has a significant association with prostate cancer and higher grade tumor.

Although did not correlate significantly with clinicopathological indices as age, tumor size and PSA.

In our results, the expression COX2 in PC was significantly positively correlated with poor clinical, pathological criteria and dismal patients' outcome such as advanced D'Amico risk group, higher incidence of tumor relapse, worse disease-free survival and overall survival.

Our results were similar to [Khor et al. [25] who have considered COX-2 staining intensity was significantly associated with therapeutic failure, distant metastasis, and PC cells irradiation resistance. Near to that [Richardsen et al. [26] found that COX-2 overexpression was associated significantly in metastases and death from PC, also [Hu et al. [22] who explained the proportional correlation between higher COX-2 expression and the prognostic survival rate in esophageal cancer patients, also [Xu et al. [27] demonstrated that the increased expression of

Table 4 Relation between SCF, Cox-2 IHC staining and outcome in 50 prostatic carcinoma patients

Outcome	Prostatic adenocarcinoma	SCF IHC staining		p value	Cox-2 IHC staining		p value
	No.(%)	Low No.(%)	High No.(%)		Low No.(%)	High No.(%)	
Relapse	(*N* = 43)	(N = 20)	(N = 23)	<0.001§	(*N* = 16)	(*N* = 27)	<0.001§
Absent	19(44.2%)	16(80%)	3(13%)		16(100%)	3(11.1%)	
Present	24(55.8%)	4(20%)	20(87%)		0(0%)	24(88.9%)	
DFS							
Mean (months) (95%CI)	39.08 months (33.44–44.72)	52.06 months (45.92–58.19)	27.30 months (21.75–32.86)	<0.001†	60 months	25.88 months (22.26–29.50)	<0.001†
Median DFS	35 months	NR	22 months		NR	22 months	
1-year DFS	100%	100%	100%		100%	100%	
2-year DFS	53.5%	90%	21.7%		100%	25.9%	
3-year DFS	48.9%	85%	17.4%		100%	17.8%	
4-year DFS	41.8%	75.6%	13%		100%	6.7%	
5-year DFS	41.8%	75.6%	13%		100%	–	
Mortality	(N = 50)	(N = 22)	(N = 28)	<0.001§	(N = 18)	(N = 32)	<0.001§
Alive	29(58%)	21(95.5%)	8(28.6%)		18(100%)	11(34.4%)	
Died	21(42%)	1(4.5%)	20(71.4%)		0(0%)	21(65.6%)	
OS							
Mean (months) (95%CI)	43.22 months (38.04–48.40)	57.42 months (54.41–60.43)	31.37 months (26.21–36.52)	<0.001†	60 months	31.23 months (27.36–35.09)	<0.001†
Median OS	45 months	NR	28 months		NR	29 months	
1 year OS	100%	100%	100%		100%	100%	
2 year OS	80.8%	100%	64.7%		100%	68.9%	
3 year OS	56.3%	94.7%	23.1%		100%	28.4%	
4 year OS	46.1%	94.7%	11.6%		100%	9.5%	
5 year OS	46.1%	94.7%	11.6%		100%	–	

Categorical variables were expressed as number (percentage); continuous variables were expressed as mean (95%CI); 95%CI: 95% confidence interval; § Chi-square test; † Log rank test; $p < 0.05$ is significant

Table 5 Relation between SCF/Cox-2 IHC staining and outcome in 50 prostatic carcinoma patients

Outcome	Prostatic adenocarcinoma	SCF/Cox-2 IHC staining				*p* value
	No.(%)	Low/ Low No.(%)	Low/High No.(%)	High/ Low No.(%)	High/High No.(%)	
Relapse	(N = 43)	(N = 13)	(*N* = 7)	(N = 3)	(N = 20)	<0.001§
Absent	19(44.2%)	13(100%)	3(42.9%)	3(100%)	0(0%)	
Present	24(55.8%)	0(0%)	4(57.1%)	0(0%)	20(100%)	
DFS						
Mean (months) (95%CI)	39.08 months (33.44–44.72)	60 months	36.29 months (27.26–45.31)	60 months	22.40 months (20.03–24.77)	<0.001†
Median DFS	35 months	NR	40 months	NR	20 months	
1 year DFS	100%	100%	100%	100%	100%	
2 year DFS	53.5%	100%	71.4%	100%	10%	
3 year DFS	48.9%	100%	57.1%	100%	5%	
4 year DFS	41.8%	100%	28.6%	100%	0%	
5 year DFS	41.8%	100%	–	100%	0%	
Mortality	(N = 50)	(N = 13)	(N = 9)	(N = 5)	(N = 23)	<0.001§
Alive	29(58%)	13(100%)	8(88.9%)	5(100%)	3(13%)	
Died	21(42%)	0(0%)	1(11.1%)	0(0%)	20(87%)	
OS						
Mean (months) (95%CI)	43.22 months (38.04–48.40)	60 months	46.50 months (40.24–52.76)	60 months	26.92 months (23.86–29.98)	<0.001†
Median OS	45 months	NR	NR	NR		
1 year OS	100%	100%	100%	100%	100%	
2 year OS	80.8%	100%	100%	100%	56.3%	
3 year OS	56.3%	100%	83.3%	100%	10.2%	
4 year OS	46.1%	100%	83.3%	100%	0%	
5 year OS	46.1%	100%	–	100%	0%	

Categorical variables were expressed as number (percentage); continuous variables were expressed as mean (95%CI); 95%CI: 95% confidence interval; § Chi-square test for trend; † Log-rank test; $p < 0.05$ is significant

Table 6 Association & correleation between SCF, Cox-2 & SCF/Cox-2 and study parameters in 50 prostatic carcinoma patients

	SCF (Low, High)		Cox-2 (Low, High)		SCF/Cox-2 (L/L, L/H, H/L, H/H))	
	r	p value	r	p value	r	p value
Age (years)	+0.357	0.011	+0.329	0.020	+0.402	0.004
Age group (<65, >65)	+0.434	0.002	+0.460	0.001	+0.520	<0.001
PSA group (<10, 10–20, >20)	+0.369	0.008	+0.352	0.012	+0.360	0.001
Gleason score	+0.344	0.014	+0.367	0.009	+0.406	0.003
Gleason group (<7, 7, >7)	+0.323	0.022	+0.289	0.042	+0.293	0.006
Perineural invasion (absent, present)	+0.287	0.042	+0.304	0.032	+0.343	0.015
Capsular invasion (absent, present)	+0.302	0.033	+0.271	0.055	+0.340	0.016
Seminal vesicle invasion (absent, present)	+0.287	0.042	+0.304	0.032	+0.343	0.015
T (T1, T2, T3, T4)	+0.404	0.004	+0.335	0.017	+0.370	<0.001
N (N0, N1)	+0.466	0.001	+0.362	0.010	+0.489	<0.001
M (M0, M1)	+0.242	0.087	+0.167	0.239	+0.240	0.093
D'Amico risk group (Low, intermediate…..)	+0.332	0.018	+0.292	0.040	+0.293	0.002
SCF (Low, High)	–	–	+0.426	0.003	–	–
Cox-2 (Low, High)	+0.426	0.003	–	–	–	–
Relapse (absent, present)	+0.672	<0.001	+0.865	<0.001	+0.851	<0.001
Mortality (Alive, Died)	+0.673	<0.001	+0.638	<0.001	+0.786	<0.001

R correlation coefficient; $p < 0.05$ is significant

COX2 was significantly associated with both disease-free survival and the overall survival of patients.

Our results are explained by that overexpression of COX-2 enhances cellular proliferation, mutagens production, inhibits epithelial differentiation, apoptosis and immunological cells [9]. Also, COX-2 stimulates angiogenesis in PC by increasing the secretion of angiogenic factors as prostaglandins which in turn regulates VEGF production. Overexpression of COX-2 was positively associated with tumor mean microvessel density (MVD) as measured by CD31. This proved that using selective COX-2 inhibitors in treating selected cancers could decrease neovascularization and growth progression [28].

Several pieces of evidence suggest a correlation between chronic prostatitis and prostatic cancer as mutations in the regulatory genes of the inflammation have been connected to the risk of prostate cancer. Moreover, chronic prostatitis became a risk factor for the relapse following radical prostatectomy especially in patients with high-grade inflammation surrounding malignant glands [21].

In our results 50% of chronic prostatitis cases showed high expression of COX2, also 50% of our PC cases had a history of chronic prostatitis and showed chronic inflammatory cells around the malignant glands had shown higher expression of COX2, This was similar to [Wang et al. [21] results that found expression of COX-2 is increased focally in tumor areas which are surrounded by chronic inflammatory cells.

We found that COX2 expression was high only in 20% of BPH cases near to [Ceylan et al. [29] results reported that 24% of BPH cases showed high expression for COX2 also similar results were found by [Khodeir et al. [30] that found high expression of COX2 in BPH was in 23.5% of cases. Moreover, near to our results [Malaysiana et al. [24] have stated that higher expression was in 16% of BPH cases that was similar to [Kim et al.] [31], who found that high COX2 expression in 20.3% of BPH cases, additionally, results that were found by [Madaan et al. [32] that higher cytoplasmic expression was found in only 10% of BPH cases.

Regarding our SCF results concerning chronic prostatitis and BPH we found high expression in 45% of chronic prostatitis and 10% of BPH cases, SCF which is an inflammatory mediator that used by many previous studies as a diagnostic tool for different types of cancers including prostate cancer [14], we use it as a predictive marker of PC in high risk cases of chronic prostatitis and BPH that will advise early prostatectomy in these cases avoiding progression to prostate cancer and decrease risk of malignancy in such patients.

So we recommended further studies on a large number of cases with long-term follow up to better predict the behavior of SCF high expression cases and stand on the accurate neoplastic risk.

In conclusion, SCF that is the potent mast cell growth factor and COX2 that is an active mediator of the inflammatory response expression in PC were proved to be related to poor clinicopathological parameters, poor prognosis and in the mechanism of drug resistance.

Recommendations

Further studies are required to ensure the possibility of chronic prostatitis as a cause of prostatic cancer. And the use of target therapy as adjuvant treatment of prostatic adenocarcinoma positive for both legends, especially those with history of chronic prostatitis, use of selective anti COX-2 drugs in in

high COX-2 expression cases, to reduce neovascularization and tumor progression, As the SCF/c-Kit active pathway is very important in the remodeling of tumor microenvironment, it is a novel target therapy for such tumors [7].

Imatinib which is the most common tyrosine kinase inhibitor was targeting the SCF/c-Kit pathway considered to be an optimal tool for a tumor-specific treatment,

Compliance with Ethical Standards

Conflict of Interest Authors had declared no conflict of interest.

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