

## **Chapter Two:**

### **Literature Reviews**

#### **2.1 Prostate Gland Anatomy:**

Prostate gland is a firm, partly glandular, partly fibro-muscular body surrounding the first inch of the male urethra and is about the size and the shape of a chest nut. It divided into three main zones:

- ▣ Central zone which is about 25% of prostatic volume.
- ▣ Peripheral zone which is about 65% of prostatic volume.
- ▣ Transitional zone which is about 10% of prostatic volume.

It is lie at a low level of lesser pelvis, behind the inferior border of the symphysis pubis arch and anterior to rectal ampulla through which is palpated.

#### **2.2 Clinical Uses of PSA:**

**Hudson et al. (1989)**, evaluated the clinical use of PSA in staging and monitoring response to therapy in prostatic cancer patients, about 168 men with benign prostatic hyperplasia and 231 men with prostate cancer. On 44% of the men with proved prostate cancer. Preoperative prostate specific antigen levels increased with higher clinical stages of prostate cancer but there was substantial overlap among stages. After radical prostatectomy serum prostate specific antigen values decreased to undetectable levels (less than 0.6 ng per ml.) in 89% of the patients

with organ-confined disease, in 87% of those with microscopically positive margins only but in only 34% with seminal vesicles or lymph node involvement. Failure of the prostate specific antigen levels to decrease to the undetectable range after radical prostatectomy was associated with a greater likelihood of subsequent tumor recurrence. Only 3 of 18 patients (17%) treated with definitive radiation therapy had post-irradiation prostate specific antigen values of less than 0.6 ng. per ml, while in 39% the prostate specific antigens values remained greater than 4 ng. per ml. and in 4 of 18 (22%) the values were greater than 10 ng. per ml.

**(Nilsson et al. 2004),** Adopted a systematic review of radiation therapy trials in prostate cancer which had been performed according to principles adopted by the Swedish Council of Technology Assessment in Health Care (SBU).A 30 randomized trials, many dealing with hormonal therapy, 55 prospective trials, and 210 retrospective studies. Totally the studies included 152,614 patients. There is a lack of properly controlled clinical trials in most important aspects of radiation therapy in prostate cancer. However, with the advent of widely accepted prognostic markers for prostate cancer (pre-treatment PSA, Gleason score, and T-stage), such comparisons have been made possible. There is substantial documentation from large single-institutional and multi-institutional series on patients with this disease category (PSA < 10, GS < or = 6, < or = T2b) showing that the outcome of external beam radiotherapy and brachytherapy is similar to those of surgery. There is fairly

strong evidence that patients with localized, intermediate risk, and high risk (pre-treatment PSA  $\geq$  10 and/or GS  $\geq$  7 and/or  $\geq$  T2) disease, i.e. patients normally not suited for surgery, benefit from higher than conventional total dose. No overall survival benefit has yet been shown. There is some evidence that postoperative external beam radiotherapy after radical prostatectomy in patients with pT3 disease prolongs biochemical disease-free survival and that the likelihood of achieving long-term DFS is higher when treatment is given in an adjuvant rather than a salvage setting. A breakpoint seems to exist around a PSA level of 1.0 ng/mL, above which the likelihood for eradication of the recurrence of cancer diminishes.

**Nevertheless , Nguyen et al. (2005)**, were worked on determining whether a delay in initiating external beam radiation therapy (RT) following diagnosis could impact prostate-specific antigen (PSA) outcome for patients with localized prostate cancer, 460 patients, who received 3D conformal RT to a median dose of 70.4 Gy for clinically localized prostate cancer. The primary endpoint was PSA failure (American Society for Therapeutic Radiology and Oncology definition). This Estimation of PSA control was made using the Kaplan-Meier method. Delay was defined as the time between diagnosis and the start of RT. Risk groups were defined based on known predictors of PSA outcome, namely, baseline PSA level, clinical T-category, Gleason score, and percentage of biopsy cores positive for

tumor. They found that Treatment delay independently predicted time to PSA failure following diagnosis for high-risk (Adjusted Hazard Ratio = 1.08 per month;  $P = 0.029$ ) but not low-risk patients ( $P = 0.31$ ). Patients with high-risk disease ( $n = 240$ ) had 5-year estimates of PSA failure-free survival of 55% versus 39% (Plog-rank = 0.014) for those with delay  $< 2.5$  months versus  $> \text{ or } = 2.5$  months respectively. The median delay was 2.5 months.

**Yousif and Omer (2013)**, worked on determining the reference prostate specific antigen (PSA) range for different types prostatic disease patients in Sudanese men, A total of 50 patients, age ranged from 46-96 years with various types of prostatic disorders were enrolled into this study. The analyses included patients referred to RIA lab at RICK ,a biopsy was taken in those to exclude prostate cancer. The collected data included: PSA amount, diagnosis, habits, Age, residence and Races (tribe). The collected data analyzed using EXCELL software and statistical package for social science SPSS in forms of 3D clustered column and curves. Out of the results enumeration for this study which deals with assessment of prostate specific antigen (PSA) level among prostatic disease patients The common type of prostatic disorders was the adeno-carcinoma (84%), state which had a high incidence of prostatic disorders was the north state 42%, habit associated with prostatic disorders patients was the smoke (42% ), age group with high PSA level was (56-66) years with relative level 80.7 ng/ml, histopathological had a high mean of PSA level was adenocarcinoma with relative level 56.1 ng/ml. These results indicated the possible use of PSA to determine the reference prostate specific antigen (PSA) range for different type's prostatic disease patients in Sudanese men,

**Eggeneretal.(2005)**,evaluated possibility of subsequent prostate cancer in men with a prostate specific antigen of 2.6 to 4.0 ng/ml and an initially negative biopsy in order to decide whether and when repetition of taking a biopsy is challenging. They determined if patient specific variables might identify men at increased risk for the subsequent cancer. They analyzed the records of 24,893 men from a community based prostate cancer screening study. Which was consisting of 1,202 men with PSA 2.6 to 4.0 ng/ml and a previously negative prostate biopsy. . Mean follow up +/- SD in men without prostate cancer was (72 +/- 36 months). Prostate cancer was subsequently diagnosed in 35% of men with high grade prostatic intraepithelial neoplasia (HGPIN) on initial biopsy ( $p < 0.0001$ ), in 18% with abnormal or suspicious digital rectal examination (DRE) ( $p = 0.02$ ) and 16% with an annual PSA velocity of 0 ng/ml ( $p = 0.002$ ). Multivariate analysis identified HGPIN, initial PSA 3.6 to 4.0 ng/ml, abnormal DRE, family history of prostate cancer and annual PSA velocity 0 ng/ml as predictors of prostate cancer. Which means that Men with a PSA of 2.6 to 4.0 ng/ml and negative biopsy should be advised to undergo repeat biopsy if they have HGPIN, initial PSA 3.6 to 4.0 ng/ml, abnormal DRE, a family history of prostate cancer or a PSA velocity of 0 ng/ml or greater.

### **2.3 PSA, Radiotherapy & Surgery Relationship:**

**Carter et al.(1989)**,noted that no patient within undetectable PSA level after radical prostatectomy had a clinical evidence of active prostate cancer. Also he noted that all patients with clinically distance recurrences had elevated PSA.

**Stamey et al.(1987)**,added to these findings by noting that no patient who failed to normalized serum PSA within 3weeks of radical prostatectomy had a subsequent decreased in PSA levels to undetectable range without adjuvant therapy.

**Lange et al. (1990)**,measured PSA level three to six months after radical prostatectomy and correlated the result within the clinical outcome : in men with PSA level 0.2ng/ml , only 11% recurred ; for those who had PSA >0.4ng/ml , 100% recurred. Those 86 patients who had undetectable PSA level after radical prostatectomy , seven (8.1%)had a subsequent rise in PSA levels to a mean of 70.6 ng/ml .

Moreover, **Stein et al. (1992)**, reported that in all cases of a group of 230 patients with pathological stage T1-T2, non-metastatic diseased followed for a mean of 48 months after radical retropubicprostatectomy ; elevations of serum PSA preceded the clinical recurrence of disease, however , in 41 out of 175 patients with detectable PSA values and no clinical evidence of recurrent prostate cancer,

elevated serum PSA suggested a recurrence. The 5 – and 10-years clinical disease - free survival were 82% and 72% respectively.

In addition,(**Steven et al.1996**), assessed the outcome of patients who received radiotherapy for isolated elevation of serum prostate specific antigen (PSA) levels following radical retropubic prostatectomy. 64 patients were initially treated for localized prostate cancer with radical retropubic prostatectomy following negative pelvic lymphadenectomy. These patients had detectable serum PSA 6 or more months postoperatively. No patient had other clinical evidence of recurrent disease as determined by history, physical examination, bone scan, computerized tomography of the abdomen and pelvis, chest radiographs, complete blood cell counts and serum chemistry profiles. The patients received prostate bed irradiation using 10 MV. x-rays and a 4-field approach. Doses ranged from 60.0 to 67.0 Gy. in 1.8 to 2.0 Gy. fractions. Freedom from failure after radiotherapy was defined as maintaining a PSA of 0.3 ng./ml. or less without hormonal intervention. In 27 of the 46 patients (59 %) PSA had decreased to 0.3 ng./ml. or less at last measurement without hormonal intervention. Patients receiving radiation doses of 64 Gy. or more had more favorable response rates than those receiving lesser doses.

**The Stanford group (1989)** followed 183 patients after completion of radiation therapy (most of whom had localized disease) for a mean of 61 months. Serum PSA

was reduced to undetectable level in 11% of the patients; 25% of patient had a decrease in serum PSA values to the normal levels persisted in 65% of patients.

Radiation therapy during the first year caused reduction after the first year of therapy occurred in only 8% of patients. PSA values rose in 51% of the patients.

**Kabalin et al. (1989)**, Assessed trans-rectal US-guided sextant biopsies on 27 men 18 months after external beam Radiotherapy. Persistent prostate carcinoma was detected in 25 of the 27 patients including 20 of 22 men in whom it was also detectable with normal digital rectal examination. All four patients with normal PSA levels (<2.5ng/ml pros-check), including one patient with undetectable PSA levels after radiotherapy.

**Gilbertetal. (2009)** commented on Prostate Cancer Diagnosis and Treatment after the Introduction of Prostate-Specific Antigen Screening: 1986–2005, Although there is uncertainty about the effect of prostate-specific antigen (PSA) screening on the rate of prostate cancer death, there is little uncertainty about its effect on the rate of prostate cancer diagnosis. Systematic estimates of the number of men affected, however, to our knowledge, do not exist. By obtaining data on age-specific incidence and initial course of therapy from the National Cancer Institute's Surveillance, Epidemiology, and End Results program. They then used age-specific male population estimates from the US Census to determine the excess (or deficit) in the number of men diagnosed and treated in each year after 1986—the



year before PSA screening was introduced. Overall incidence, however, obscured distinct age-specific patterns: The relative incidence rate (2005 relative to 1986) was (0.56) in men aged 80 years and older, (1.09) in men aged 70–79 years, (1.91) in men aged 60–69 years, (3.64) in men aged 50–59 years, and (7.23) in men younger than 50 years.

**Steven et al. (1996)**, evaluated the use of Radiotherapy for Patients with Isolated Elevation of Serum Prostate Specific Antigen Following Radical Prostatectomy. To assess the outcome of patients who received radiotherapy for isolated elevation of serum prostate specific antigen (PSA) levels following radical retropubic prostatectomy, 46 patients were initially treated for localized prostate cancer with radical retropubic prostatectomy following negative pelvic lymphadenectomy. These patients had detectable serum PSA 6 or more months postoperatively. The patients received prostate bed irradiation using 10 MV. x-rays and a 4-field approach. Doses ranged from 60.0 to 67.0 Gy. in 1.8 to 2.0 Gy. fractions. Freedom from failure after radiotherapy was defined as maintaining a PSA of 0.3 ng./ml. or less without hormonal intervention. The result showed about 27 of the 46 patients (59 percent) PSA had decreased to 0.3 ng./ml. or less at last measurement without hormonal intervention. The freedom from failure rate was 50 percent at 3 and 5 years. More favorable responses to salvage radiotherapy occurred in patients with low grade tumors and serum PSA 1.1 ng./ml. or less initiation of radiotherapy.

Patients receiving radiation doses of 64 Gy.or more had more favorable response rates than those receiving lesser doses.Isolated elevations of serum PSA following prostatectomy reflect residual disease. This shows that Radiotherapy administration to the prostate bed effectively decreased serum PSA in approximately half of the cases.This effect appears to be accomplished by eradicating tumor cells in the prostate bed.

**Rafi et al.(2014)**, mentioned that in order to evaluate the prognostic value of prostate-specific antigen (PSA) decline during salvage radiation therapy (SRT) after prostatectomy by reviewing all prostate cancer patients who treated with SRT between years 2003-2010 who had at least 1 PSA measurement during their SRT course, and had no history of androgen deprivation therapy use prior to or during SRT. Then PSA response during SRT was defined as a PSA decline of at least 0.2 ng/mL compared with the pretreatment PSA level. Bivariate and multivariate analyses using Cox proportional hazards modeling were used.They found that 64 patients met eligibility criteria for this analysis. Median PSA before SRT was 0.63 ng/mL (interquartile range: 0.42-1.00). With a median follow-up time of 70 months after SRT, 5-year actuarial rates for biochemical control and metastasis-free survival were 61% (95% confidence interval [CI], 48%-75%) and 88% (95% CI, 79%-97%), respectively. The median number of PSA measurements per patient during SRT was 3 (range, 1-5). On bivariate analysis, PSA response during SRT

and positive surgical margins were significantly associated with a decreased risk of biochemical recurrence (BR), with hazard ratios of 0.160 (95% CI, 0.059-0.431,  $P < .001$ ) and 0.396 (95% CI, 0.168-0.935,  $P = .035$ ). On multivariate analysis, PSA response during SRT and positive surgical margin were independent, favorable predictors for BR, with hazard ratios of 0.171 (95% CI, 0.063-0.463,  $P < .001$ ) and 0.411 (95% CI, 0.177-0.956,  $P = .039$ ). The 5-year biochemical control rate for PSA responders was 81%, compared with 37% for non responders ( $P < .001$ ). Which means that Prostate-specific antigen decline during SRT may be a valuable prognostic factor for subsequent clinical outcomes.

**Thomas et al. (2002)**, examined the value of PSA Measurements at 30Gy, 50Gy and 6Gy for Dose Limitation in Patients with Radiotherapy for PSA Increase after Radical Prostatectomy. Examination had been done on about 41 patients with rising PSA level following prostatectomy received radiotherapy to the prostatic bed and were treated up to a median dose of 66.6 Gy. We evaluated serum PSA levels during radiotherapy at 30 Gy, 50 Gy and 60 Gy and compared them to the pre-radiotherapy PSA level and the outcome of radiotherapy. Thus After radiotherapy, 31 patients (76%) had either undetectable (n=15), or decreasing but still detectable PSA levels (n=16) and ten patients (24%) had rising PSA levels and did not respond. PSA evaluation at 30 Gy showed that 26% (8/31) of those patients who would respond to radiotherapy still had a rising PSA when compared

to pretreatment PSA. At 50 Gy and 60 Gy 93% (27/29) of these patients had decreasing PSA levels. In contrast, 75% (6/8) and 88% (7/8) of those patients in whom radiotherapy was not effective had rising PSA levels at 50 Gy and 60 Gy ( $p < 0.05$ ). By this way PSA measurements at 30 Gy, 50 Gy and 60 Gy for radiotherapy of PSA increase following radical prostatectomy without histologically proven local recurrence gives valuable information about the later tumor response. Therefore it possibly gives the opportunity to finish radiotherapy between 50 and 60 Gy, as almost all patients with continued PSA increase at 60 Gy do not stand to profit from radiotherapy.

**Thomas et al. (2009)**, compared Phase III Postoperative Adjuvant Radiotherapy After Radical Prostatectomy Compared With Radical Prostatectomy Alone in pT3 Prostate Cancer With Postoperative Undetectable Prostate-Specific Antigen: Two randomized trials demonstrated an advantage for adjuvant radiotherapy (RT) compared with a wait-and-see policy. They conducted a randomized, controlled clinical trial to compare RP followed by immediate RT with RP alone for patients with 192 men were randomly assigned to a wait-and-see policy, and 193 men were assigned to immediate postoperative RT. Eligible patients had pT3 pN0 tumors. Patients who did not achieve an undetectable PSA after RP were excluded from treatment according to random assignment ( $n = 78$ ; 20%). Of the remaining 307 patients, 34 patients on the RT arm did not receive RT and five patients on the

wait-and-see arm received RT. Therefore, 114 patients underwent RT and 154 patients were treated with a wait-and-see policy. The primary end point was biochemical progression-free survival. Thus found Biochemical progression-free survival after 5 years in patients with undetectable PSA after RP was significantly improved in the RT group (72%; 95% CI, 65% to 81%; v 54%, 95% CI, 45% to 63%; hazard ratio = 0.53; 95% CI, 0.37 to 0.79;  $P = .0015$ ). The rate of grade 3 to 4 late adverse effects was 0.3%.

**Stamey & Kabalin, (1989)** , Described Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. III. particularly in Radiation treated patients. By means of determination of serum PSA (Yang polyclonal radioimmunoassay) in 183 men after radiation therapy for adenocarcinoma of the prostate. Then found that a total of 163 men had received 7,000 rad external beam radiotherapy and 20 had been implanted with <sup>125</sup>Iodine seeds. Only 11 per cent of these 183 patients had undetectable prostate specific antigen levels at a mean interval of 5 years since completion of radiotherapy. Prostate specific antigen levels after radiotherapy were directly related to initial clinical stage and Gleason score before treatment. Multiple prostate specific antigen determinations were performed with time in 124 of 183 patients. During year 1 after radiotherapy prostate specific antigen levels were decreasing in 82 per cent of the patients but only 8 per cent continued to decrease

beyond year 1. Of 80 patients observed greater than 1 year after completion of radiotherapy 51 per cent had increasing values and 41 per cent had stable values. Total serum acid phosphatase levels were poorly related to prostate specific antigen levels, were less effective in discriminating patients with metastatic disease and provided no additional information beyond that provided by prostate specific antigen.