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Research Article

Retrospective Study of Outcomes of Salvage RT with ADT in Patients of CA Prostate with Relapse

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Abstract

Despite the success of radical prostatectomy in many cases, a subset of patients experiences biochemical or structural relapse so, postoperative radiation therapy i.e., Salvage radiotherapy in combination with Androgen deprivation therapy (ADT) is one such treatment option for managing patients with prostate cancer recurrence. The primary objective of our study was to assess the overall survival postprostatectomy relapse patients treated using salvage RT along with ADT. The secondary objective was to assess if combining these therapies can enhance freedom from progression by maintaining PSA levels.

The sample size consists of 118 patients who were recruited over 6 years between October 2017 and December 2023. Survival probabilities were estimated using Kaplan-Meier and x^2 test based on the radiation dose.

Results: The overall survival rate was 80.52% and it was found that factors such as age ($x^2 = 5.801$, $p < 0.05$), PSA ($x^2 = 28.676$, $p < 0.05$), regional lymph node involvement ($x^2 = 0.473$, $p < 0.05$), were statistically significant, suggesting that more than one predictor variables are related to survival.

Keywords: Structural Relapse; Salvage Radiotherapy; Radical Prostatectomy; Survival; Prognostic Factors

Abbreviation

PSA: Prostate Specific Antigen; RT: Radiotherapy; SRT: Salvage Radiotherapy; ADT: Androgen Deprivation Therapy; BCR: Biochemical Recurrence; ECOG: Eastern Cooperative Oncology Group; CTCAE: Common Terminology Criteria for Adverse Events; AUA-SI: American Urology Association Symptom Index; Gy: Gray; PS: Performance Status

Introduction

Prostate cancer is one of the most prevalent malignancies affecting men worldwide and is also a leading cause of death in adult males around the world. In various epidemiological studies, the majority of patients in the world suffer from cases of prostate cancer posing a significant health burden and demanding constant research to enhance treatment strategies and improve patient outcomes.

A brief anatomical study is required to understand the positional and structural placement of the prostate in the bladder. The prostate gland plays a major role in the nourishment and transportation of the sperm. The prostate gland produces the fluid known as the seminal fluid.

The prostate also produces the antigen known as prostate-specific antigen, which plays an important role in liquefying the sperm for ejaculation and also plays an important role in breaking the cervical mucous in the cervix, for the proper entry of sperm into the vaginal cavity.

A change in the levels of PSA is commonly seen as the patient's age increases, this is genetic and can't be controlled. Hence an abnormal increase in the PSA levels can depict the presence of prostate cancer.

The body undergoes various hormonal changes when the cancer starts progressing in the bladder and spreads to the urethra, this causes urine inconsistency, abdominal pain, and also various other major symptoms [7].

Radical prostatectomy remains the primary curative treatment option for localized prostate cancer, offering a chance for long-term disease control and overall survival. However, despite the success of surgery in many cases, a subset of patients experiences biochemical or structural relapse, indicated by rising prostate-specific antigen (PSA) levels or evidence of disease recurrence on imaging studies [1].

Managing patients who experience relapse after initial surgery is a task. It becomes essential to explore salvage treatment options to achieve disease control and potentially extend the patient's life. One such option is salvage radiotherapy (SRT) with androgen deprivation therapy (ADT) which shows promising results, but uncertainties persist regarding the optimal treatment duration, toxicities, and outcomes in this specific patient cohort to address these issues we are conducting a retrospective study to assess the overall survival and quantify treatment-related outcomes [1-3].

Materials and Methods

A retrospective study was conducted from August 2023 to February 2024, in the oncology department at AIG Hospitals, Gachibowli, Hyderabad. The data of 118 patients meeting the inclusion criteria was recruited over the last 6 years between October 2017 and December 2023. The data is collected from the Oncology Departments nursing stations using case sheets of inpatients and outpatients, and electronic medical records of patients. The patients meeting inclusion criteria were selected for a retrospective study of outcomes in patients of CA prostate after surgery with structural or biochemical relapse treated with salvage RT along with ADT.

For the present study, we included

- Patients who have undergone radical prostatectomy as primary treatment.
- Patients showing lymph node-positive by pelvic lymphadenectomy.
- Patients with PSA of ≥0.1 and <2.0ng/mL for at least 6 weeks after prostatectomy.
- Patients with PT2 or PT3 disease with a positive prostatectomy surgical margin or not.
- Patients having a Gleason score of 9 or less.
- Patients showing Zubrod Performance Status of 0-1.
- The age group of 50-85 yrs.
- Patient undergoing salvage RT with ADT after prostatectomy.

Exclusion criteria were

- Patients on ADT before prostatectomy for > 6 months duration.
- Neoadjuvant chemotherapy before or after prostatectomy
- Patients underwent chemotherapy for any other disease condition within the last 5 years.
- Patients underwent prior cryosurgery or brachytherapy of the prostate.
- Patients with a history of previous invasive malignancy (except non-melanomatous skin cancer) or superficial bladder cancer unless disease-free for a period of 5 years (carcinoma in situ of the oral cavity is permissible).
- People with certain medical conditions or recent hospitalizations are not eligible for treatment. These conditions include inflammatory bowel disease, hepatitis B or C, unstable angina, recent heart failure, recent heart attack, severe bacterial or fungal infections requiring IV antibiotics, severe respiratory illnesses requiring hospitalization, or any condition that prevents participation in the study therapy.
- There are no distant metastases according to the following criteria:
- Physical examination, including digital rectal exam, conducted within 8 weeks before therapy.

- CT scan or MRI of the pelvis conducted within 120 days before therapy.
- A bone scan taken within 120 days before the treatment. If there is any suspicion of metastasis, a plain X-ray, MRI, or both must be done to confirm the absence of metastasis.

Clinical data Age at first diagnosis, age at surgery, age at relapse, PSA before surgery (baseline PSA), PSA at relapse, PSA post-surgery (NADIR PSA), margins, EPE, recurrence, total radiation dose, duration of treatment, involvement of lesions and lymph node data collected at each follow-up visit, ECOG performance status, prescribed ADT drugs, and survival status and date of death were among the prognostic variables that were determined and studied [4-6].

Statistical analysis

- This data was analyzed using version 20 of SPSS software.
- Kaplan-Meier test was used for survival analysis based on the prognostic factors.
- All statistical analyses were conducted at a 5% significance level or 95% confidence interval, considering a P value less than 0.05 as statistically significant. The survival time of a patient is referred to as the number of months from the day the patient was diagnosed until he died or until the end of the study period.

Results

A total of 210 patients were diagnosed with prostate cancer from 2017 to 2023. After excluding the number of patients according to the research criteria, a total of 118 patients' data were analyzed for biochemical and structural relapse treated with post-prostatectomy SRT with ADT. Of these 118 relapse patients, 46 patients (39.0%) were aged 75 and above, 57 patients (48.3%) were 65 to 74 years old, and the rest 15 patients (12.7%) were less than or equal to 65 years. A total of 62 patients (52.53%) showed Gleason scores up to 7, and 56 patients (47.45%) had Gleason scores of 8 and above.

In terms of PSA, 9 patients (7.6%) had PSA of 20 ng/ml and above, 2 patients (1.7%) had PSA ranging between 10 to 19.9 ng/ml, and the rest 107 patients (90.7%) had less than or equal to 10 ng/ml. For the stage cancer distribution, 30 patients (25.4%) were diagnosed with early pT2 stage cancer, and a total of 88 patients (74.6%) were diagnosed with advanced stage pT3 and pT4 cancer. A total of 48 patients (40.67%) had involvement of lesions.

In this study, a total of 95 patients (80.50%) had involvement of lymph nodes, 51 patients (43.2%), and 65 patients (55.1) had Margins and Extra prostatic extensions positive, respectively indicating structural relapse along with biochemical relapse. The results also indicated that 23 patients (19.4%) died of prostate cancer (Table 1).

S.NO		N (%)
1	AGE AT RELAPSE	
	< 65	15 (12.7)
	65 - 74	57 (48.3)
	≥ 75	46 (39.0)
2	GLEASON SCORE	
	≤ 6	4 (3.38)
	7	58 (49.15)
	≥ 8	56 (47.45)
3	PSA (RELAPSE)	
	< 10.00	107 (90.7)
	10.00 - 19.99	2 (1.7)
	≥ 20.00	9 (7.6)
4	pT STAGE	
	T2	30 (25.4)
	T3	72 (61.0)

	T4	16 (13.6)
5	MARGIN	
	Negative	67 (56.8)
	Positive	51 (43.2)
6	EPE	
	Negative	53 (44.9)
	Positive	65 (55.1)
7	LYMPH NODES	
	NO	23 (19.49)
	YES	95 (80.50)
8	LESIONS	
	YES	48 (40.67)
	NO	70 (59.32)

Table 1: Baseline characteristics and treatment parameters.

The survival analysis of those 118 patients with biochemical and structural relapse was done based on the above-mentioned factors using Kaplan Meier and Log-rank tests in comparison with the survival status and the duration of Salvage RT with Androgen Deprivation Therapy. It was found that factors such as age, PSA, and regional involvement of lymph nodes had a greater impact on survival rate when compared to Gleason score, total radiation dose used, and involvement of lesions.

Kaplan Meier and log-rank test

The study demonstrated that the overall seven-year survival rate was 80.50% with a survival mean of about 5 and a half years. It was also found that factors such as age ($x^2 = 5.801$, $p < 0.05$), PSA ($x^2 = 28.676$, $p < 0.05$), involvement of regional lymph nodes ($x^2 = 0.473$, $p < 0.05$), showed statistical significance in survival rate, whereas Gleason score ($x^2 = 0.553$, $p > 0.05$), total radiation dose used ($x^2 = 0.540$, $p > 0.763$), involvement of lesions ($x^2 = 1.199$, $p > 0.05$) showed no significant difference in the survival rate.

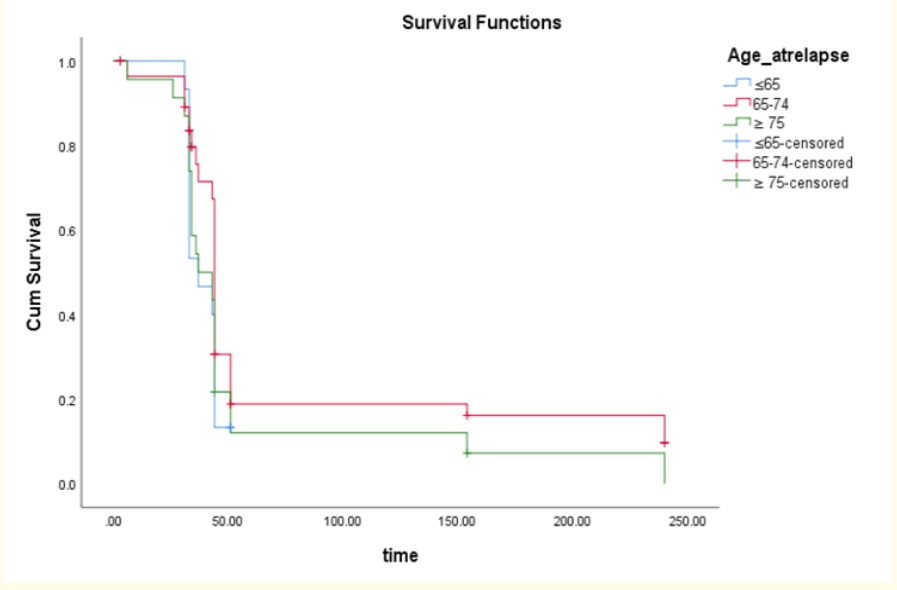

Figure 1: Prostate cancer survival curve based on age at relapse.

The above graph of the Kaplan- Meier, and Log-Rank test depicts that the patients aged 65 or younger exhibit relatively stable survival rates over time, with an average longevity of 3 years.

Patients aged 65 to 74 exhibit high initial mortality, but there is an improvement in survival over time, with an average of about 3 and a half years.

Patients aged 75 or older have initially high survival rates, with a slight decline over time, with an average longevity of 3 years.

The above graph of the Kaplan- Meier, and Log-Rank test depicts that the patients having less than 10 ng/mL of PSA at relapse show a relative decline in survival, indicating a notable impact of PSA levels on survival.

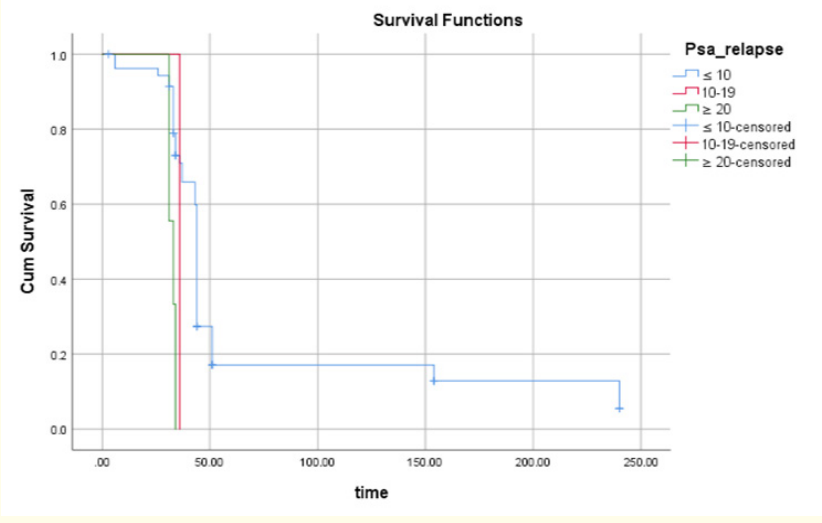

Figure 2: Prostate cancer survival curve based on PSA at relapse.

There is no marked correlation between the patients with PSA levels of 10-19 ng/mL at relapse and survival.

Patients with PSA levels greater than or equal to 20 at relapse exhibit a relatively steep decline in survival, reaching approximately 39.3% experiencing the event by the end of the observation period. The median survival is about 3 years.

The above graph of the Kaplan- Meier, and Log-Rank test depicts that patients with Gleason scores less than or equal to 6 exhibit high initial survival, with an average longevity of 3 years. A Gleason score of 7 infers high initial mortality, but the likelihood of survival improved over time, with an average longevity of 3 and a half years.

Gleason scores greater than or equal to 8 infer high initial mortality, but the probability of survival gradually improves over time, with an average longevity of 3 and a half years after Salvage RT with ADT.

The above graph of the Kaplan- Meier, and Log-Rank test depicts that Patients with lymph node involvement exhibit initial mortality, followed by a trend of improvement in survival, with an average longevity of 3 and a half years but survival patterns are comparable to those without lymph node involvement showing subsequent improvement in survival over time, with an average longevity of 3 and a half years after Salvage RT with ADT.

The above graph of the Kaplan- Meier, and Log-Rank test depicts that Patients with no structural relapse exhibit high survival rates, with an average longevity of 3 and a half years when compared to those with structural relapse showing a decline in survival followed by a trend of improvement in survival with an average longevity of 3 and a half years after Salvage RT with ADT.

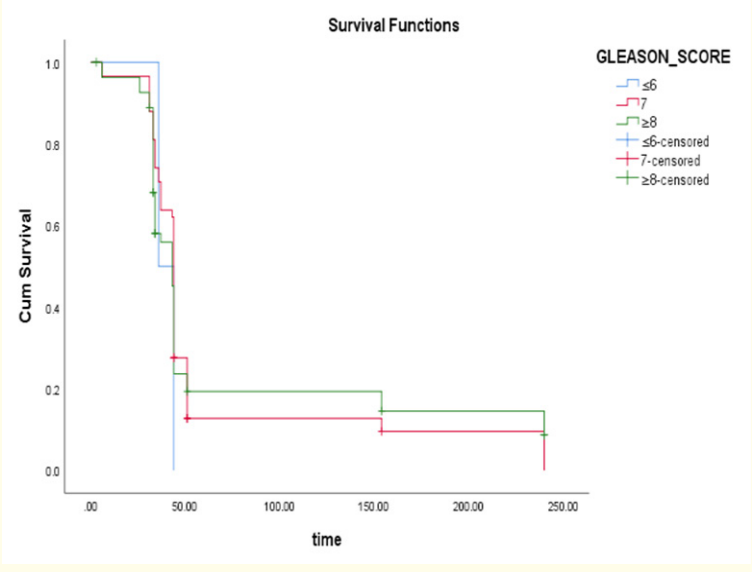

Figure 3: Prostate cancer survival curve based on Gleason score.

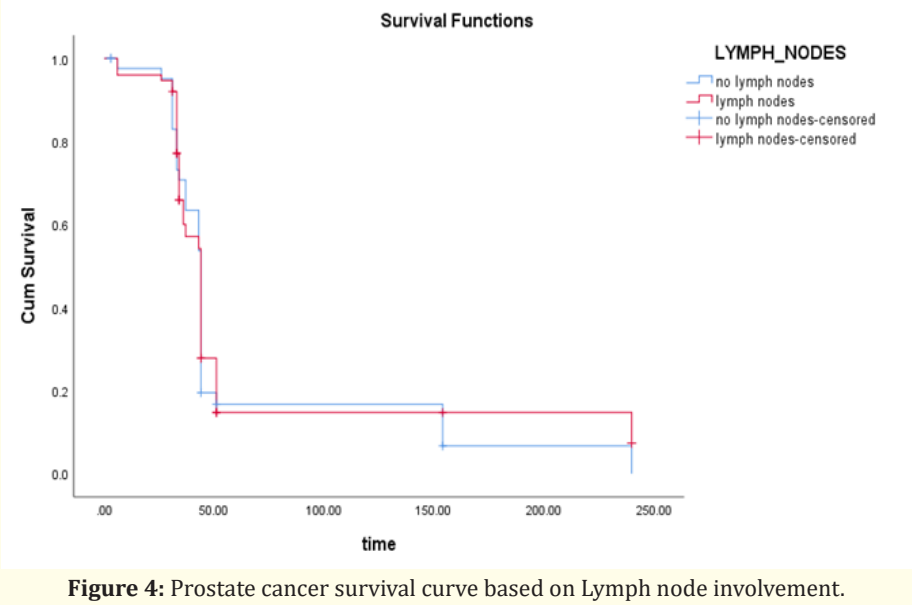

Figure 4: Prostate cancer survival curve based on Lymph node involvement.

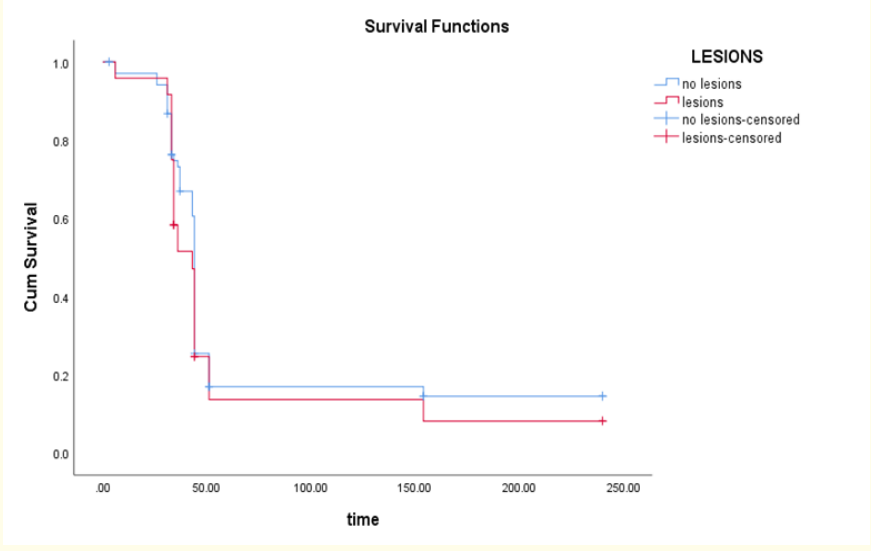

Figure 5: Prostate cancer survival curve based on Lesions involvement.

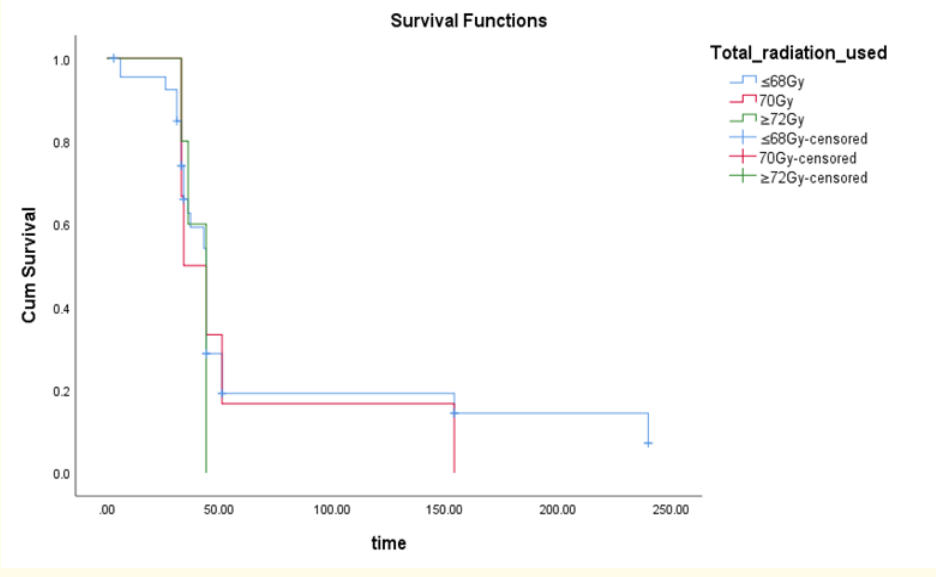

Figure 6: Prostate cancer survival curve based on Total radiation dose used.

The above graph of the Kaplan- Meier, and Log-Rank test depicts that an initially high mortality is observed when a radiation dose of 65 Gy or lower is given, but there is a gradual improvement in survival over time, with an average longevity of 3 and a half years.

Patients receiving 70 Gy radiation dose have an initial mortality, followed by a trend of improvement in survival. The median survival time is relatively less compared to other groups i.e., about 3 years.

Patients receiving 72 Gy or more show high initial survival rates, and this group survived throughout the observation period median survival time is not reached.

Discussion

Prostate cancer is a major health issue affecting men worldwide, often resulting in significant morbidity and mortality, posing a health burden and demanding constant research to enhance treatment strategies and improve patient outcomes. Radical prostatectomy is a popular curative approach for localized prostate cancer, offering the potential for long-term disease control and increased survival rates. However, in some cases, patients may experience biochemical or structural relapse, which is indicated by rising levels of prostate-specific antigen (PSA) or evidence of disease recurrence by involvement of lymph nodes with or without margins.

This study demonstrates the survival outcomes in patients with prostate cancer who underwent surgery but experienced relapse and were treated with SRT and ADT based on various parameters, like Age at diagnosis, Age at surgery, Age at relapse, PSA level at diagnosis, PSA levels post-surgery, PSA levels at relapse, TNM staging, Grade group, Margins, Extraprostatic extension (EPE), ECOG performance status.

A total of 210 patients were diagnosed with prostate cancer out of which 118 were analyzed for biochemical and structural relapse. They were categorized based on age as younger or equal to 65, between 65 and 74, and those who are 75 and above. The study showed that patients aged 65 or younger show relatively stable survival rates over time, while patients between 65 and 74 years experience an improvement in survival over time. The ones aged 75 years or above may show a slight decline. The study also indicates that only 19.4% (23 patients) died of prostate cancer.

About 7.6% (9 patients) had a PSA level of 20 ng/mL and above, 1.7% (2 patients) had a PSA level ranging between 10 to 19.9ng/mL, and the remaining 90.7% (107 patients) had a PSA below 10ng/mL. This study indicated a notable impact of PSA on survival. Patients with less than 10ng/mL of PSA show a relative decline in survival, patients with PSA level of 10-19 ng/mL show no correlation with survival, and patients with PSA levels of >20 ng/mL at relapse tend to have a shorter median survival indicating that PSA levels play a crucial role in predicting the survival time of patients.

In terms of Gleason score, a total of 52.53% (62 patients), and 47.45% (56 patients) showed a score of up to 7, 8, or above respectively. Patients with a Gleason score of 7 exhibit high initial mortality but the likelihood of survival improved over time and those with a Gleason score greater than or equal to 8 have high initial mortality. Still, the probability of survival gradually improved after Salvage RT with ADT.

Out of all the patients, 80.5% (95 patients) showed involvement of regional lymph nodes, 43.2% (51 patients) and 55.1% (65 patients) had margins and extra-prostatic extensions positive, respectively indicating both biochemical as well as structural relapse. Patients with lymph node involvement exhibit initial mortality, followed by an increase in survival rate for about 3 and a half years after Salvage RT with ADT. When compared to patients with structural relapse, who show a decline in survival followed by a trend of improvement in survival with an average longevity of 3.5 years after Salvage RT with ADT, patients without structural relapse have high survival rates, with an average longevity of 3.5 years.

The study shows no significant difference in survival distributions based on the total radiation dose received. Patients receiving less than or equal to 68Gy, and 70Gy radiation doses have an initial high mortality but observed a gradual improvement in survival over time of about 3 and a half years and 3 years respectively. While the patients receiving 72Gy or more showed a high initial survival rate. Thus, the total dose of radiation does not show a significant difference in survival.

Conclusion

Salvage radiotherapy in combination with ADT administered within 2 years of biochemical or structural relapse is associated with an increase in prostate cancer-specific survival among men with a PSA doubling time which is independent of other prognostic

factors like Gleason score, Total radiation dose, and involvement of lesions [11]. Biochemical recurrence which often occurs post-prostatectomy prompts salvage radiotherapy, and based on the findings of our study which showed an 80.5% overall survival rate in the last 7 years of patient data indicates that salvage radiotherapy along with ADT can improve survival and factors such as age ($x^2 = 5.801$, $p < 0.05$), PSA ($x^2 = 28.676$, $p < 0.05$), involvement of regional lymph nodes ($x^2 = 0.473$, $p < 0.05$), showed statistical significance in survival rate, which was in accordance with the results of previous clinical research works, indicating age greater than or equal to 75 years, PSA levels greater than 20 ng/mL, and lymph node involvement were the prognostic factors of prostate cancer survival, whereas Gleason score ($x^2 = 0.553$, $p > 0.05$), total radiation dose used ($x^2 = 0.540$, $p > 0.763$), and involvement of lesions ($x^2 = 1.199$, $p > 0.05$) showed no significant difference in the survival rate.

Salvage RT when combined with ADT can have beneficial outcomes depending on the pathological characteristics of the patient; those with more aggressive disease appeared to benefit from hormone therapy.

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Conflicts of Interest

No conflicts of interest.

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