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RETROSPECTIVE STUDY OF OUTCOMES OF SALVAGE RT WITH ADT IN PATIENTS OF CA PROSTATE WITH RELAPSE

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ABSTRACT

Background. Despite the success of Radical prostatectomy in many cases, a subset of patients experiences iochemical 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 Ca prostate relapse. **Methodology.** Survival probabilities were estimated using the Log-rank test, adjusted hazard ratios (HR) using the Cox proportional hazard regression model, genitourinary (GU) and gastrointestinal (GI) toxicities were analyzed using x2 test based on the radiation dose, and the correlation between radiation dose and quality of life was assessed. **Results.** The overall survival rate was 80.52% and it was found that factors such as age ($p < 0.05$), PSA ($p < 0.05$), involvement of regional lymph nodes ($p < 0.05$), showed statistical significance in survival rate and according to results of Cox regression, several factors like patient's age (HR= 1.368, 95% CI: 0.666-2.810), PSA (HR= 1.986, 95% CI: 1.18-3.319), Margins (HR= 0.563, 95% CI: 0.330-0.960), EPE (HR= 0.537, 95% CI: 0.291-0.989), T-stage (HR= 1.442, 95% CI: 0.952-2.186) were statistically significant, suggesting that more than one predictor variables are related to survival. Neither of the cohorts treated with SRT experienced acute or late grade 2 GU toxicities. Only 8% of the patients had experienced grade 2 GI toxicities and the patient's survival was also not completely associated with the total radiation dose, indicating an extremely weak and practically negligible correlation and higher ECOG status has a significant risk of mortality. **Conclusion.** Based on the findings it indicates that SRT along with ADT can improve survival. Thus, to increase the survival rate of patients with prostate cancer, early detection and treatment of recurrence should be implemented. Both the timing of postoperative radiotherapy and the duration of ADT have a greater impact on survival and improve both the time to salvage ADT and metastasis-free survival.

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 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]

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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. [1,2,3]

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 retrospective study for toxicities and outcomes in patients of CA prostate after surgery with structural or biochemical relapse treated with salvage RT+ADT.

Patient's data:

For the present study, we included

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

Exclusion criteria were

1. Patients on ADT before prostatectomy for > 6 months duration.
2. Neoadjuvant chemotherapy before or after prostatectomy
3. Patients underwent chemotherapy for any other disease condition within the last 5 years.
4. Patients underwent prior cryosurgery or brachytherapy of the prostate.
5. 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).
6. 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.
7. 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. [4,5,6]

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, short-term physician-scored genitourinary (GU) and gastrointestinal (GI) toxicities gastrointestinal toxicities data collected at each follow-up visit, ECOG performance status, prescribed ADT drugs, survival status and date of death were among the prognostic variables that were determined and studied.

Endpoint and Assessment

Estimating overall survival and evaluating the toxicities as well as outcomes of CA prostate patients after surgery with biochemical or structural relapse treated with Salvage RT along with ADT was the primary endpoint of this study. The secondary endpoint was to assess whether combining these therapies can enhance freedom from progression for five years in men post prostatectomy by maintaining PSA levels and to comprehensively evaluate the scope and duration of health-related quality of life about a specific disease.

Statistical Analysis

This data was analyzed using version 20 of SPSS software.

Log-Rank test was used for survival analysis based on the prognostic factors.

The prognostic factors for prostate cancer patients with biochemical and structural relapse were analyzed using the Cox proportional hazard regression model (Forward LR) test method.

The Chi-square test was used for analyzing the acute and late GU and GI toxicities based on the radiation dose administered.

The correlation for the quality-of-life data was done using Pearson's coefficient. The ADT drugs that were prescribed along with salvage RT were analyzed using a bar graph.

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 dies 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).

The survival analysis of those 118 patients with biochemical and structural relapse was done based on the above-mentioned factors using 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.

Predefined Gastrointestinal toxicities (GI) and Genitourinary toxicities (GU) were described based on types, grades, frequency, and percentages depending significantly on the treatment arms across all time points. The occurrence of acute and late-grade toxicity was compared between treatment arms using chi-square tests.

Table 2. Multivariate analysis of prognostic factors influencing survival of patients

FACTORS	NUMBER OF PATIENTS		B	S. E	95% CI	HR	Wald (d.f)	P -value
	Alive	Death						
AGE AT RELAPSE			0.313	0.367	0.666-2.810	1.368	0.727(1)	0.394
< 65	13 (11%)	2 (1.69%)						
65 – 74	41 (34.7%)	16 (13.5%)						
≥ 75	41 (34.7%)	5 (4.23%)						
GLEASON SCORE								
≤ 6	4 (3.38%)	0						
7	49(41.52%)	9 (7.62%)						
≥ 8	42 (35.5%)	14 (11.8%)						
PSA AT RELAPSE			0.686	0.262	1.188-3.319	1.986	6.852 (1)	0.009
< 10.00	84 (71.18%)	23 19.49%)						
10.00 – 19.99	2 (1.69%)	0						
≥ 20.00	9 (7.62%)	0						
pT STAGE			0.366	0.212	0.952-2.186	1.442	2.980 (1)	0.084
T2	23 (19.49%)	7 (5.93%)						
T3	62 (52.54%)	10 (8.47%)						
T4	10 (8.47%)	6 (5.08%)						
MARGIN			0.575	0.272	0.330-0.960	0.563	4.458 (1)	0.035
Negative	55 (46.6%)	12 (10.16%)						
Positive	40 (33.89%)	11 (9.32%)						
EPE			-0.622	0.312	0.291-0.989	0.537	3.982 (1)	0.046
Negative	47 (39.83%)	6 (5.08%)						
Positive	48 (40.67%)	17 (14.4%)						
LYMPH NODES								
NO	37 (31.35%)	6 (5.08%)						
YES	58 (49.15%)	17 (14.4%)						
LESIONS								
YES	41 (34.74%)	7 (5.93%)						
NO	54 (45.76%)	16 (13.55%)						

Prognostic Factors

The prognostic factors for prostate cancer patients with biochemical and structural relapse were analyzed using the Cox proportional hazard regression model (Forward LR) test method. The analysis found that several factors contributed significantly to the survival analysis and had an impact on survival. Those were the patient's age (HR= 1.368, 95% CI: 0.666-2.810), PSA (HR= 1.986, 95% CI: 1.18-3.319), Margins (HR= 0.563, 95% CI: 0.330-0.960), EPE (HR= 0.537, 95% CI: 0.291-0.989), T-stage (HR= 1.442, 95% CI: 0.952-2.186). The "Omnibus Tests of Model Coefficients" section provides information on the overall fit of the model suggesting that the

overall model is statistically significant, meaning that more than one of the predictor variables is related to survival time.

Toxicities

Toxicities of SRT are subdivided primarily into GU and GI toxicities. These toxicities are then graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and the American Urology Association Symptoms Index (AUA-SI). According to CTCAE classification, the toxicities grades are given from grade 1 (mild) to grade 5 (death).

Table 3. Genitourinary toxicities

TOXICITY	≤ 66 Gy group	> 66 Gy group	P value
URINARY TRACT PAIN 0 1 2	 67 29 0	 15 7 2	0.541
URINARY TRACT OBSTRUCTION 0 1 2	 67 29 0	 16 6 0	0.764
URINE RETENTION 0 1 2	 81 15 0	 14 8 0	0.003
URINARY URGENCY 0 1 2	 86 11 0	 17 3 0	0.487

Gu Toxicities

GU toxicity events mainly include urinary tract pain, urinary tract obstruction, urinary urgency, and urine retention. For radiation dose ≤ 66Gy and above, the incidence of grade 0 and grade 1 urinary tract pain are 81.3%, and 20.4 % respectively indicating that there is no statistical association between urinary tract pain grade and total radiation dose of Salvage RT (p= 0.541).

The incidence of grade 0 and grade 1 urinary tract obstruction is 81.4%, and 18.6% respectively indicating that there is no statistical association between urinary tract obstruction and total radiation dose of Salvage RT (p=0.764).

The incidence of grade 0 and grade 1 urine retention is 80.4%, and 18.6% respectively indicating that there is a statistical association between urine retention and total radiation dose of Salvage RT (p=0.003).

The incidence of grade 0 and grade 1 urinary urgency is 82.5%, and 17.5% respectively indicating that there is no statistical association between urinary urgency and total radiation dose of Salvage RT (p=0.487).

There were no grade 2 GU toxicities in any of the groups of cohorts treated with Salvage RT and ADT but the patients with grade 0 and grade 1 urinary urgency were found to have higher mortality risk when compared to others.

GI Toxicities

GI toxicity events are mainly manifested as adverse reactions in the lower digestive tract, which include Abdominal distention, Constipation, Nausea, Vomiting, diarrhoea, and rectal pain.

The incidence of grade 0 and grade 1 abdominal distention was 81.3%, and 16.9% for radiation dose ≤ 66Gy and above, respectively indicating that there is no statistical association between abdominal distention and total radiation dose of Salvage RT (p= 0.647).

The incidence of grade 0 and grade 1 nausea and is 76.3%, 23.7% respectively with no grade 2 toxicities at the given doses indicating that there is no statistical association between nausea and total radiation doses of Salvage RT (p=0.381).

The incidence of grade 0 and grade 1 vomiting is 79.3%, and 19.4% respectively with only 5 patients showing grade 2 toxicities above 66Gy radiation dose indicating that there is no statistical association between vomiting and total radiation doses of Salvage RT (p= 0.0773).

The incidence of grade 0 and grade 1 diarrhoea is 79.4%, and 15.2% respectively with only 3 patients showing grade 2 toxicities at less than or equal to 66Gy radiation dose indicating that there is no statistical association between diarrhoea and total radiation doses of Salvage RT (p= 0.539).

The incidence of grade 0, and 1 rectal pain is 81.5%, and 18.5% respectively with no grade 2 toxicities at the given doses indicating that there is no statistical association between rectal pain and total radiation doses of Salvage RT (p=0.303).

TOXICITY	≤ 66 Gy group	>66 Gy group	P value
ABDOMINAL DISTENTION 0 1 2	 59 37 0	 15 5 0	0.647
CONSTIPATION 0 1 2	 78 15 3	 18 2 2	0.129
NAUSEA 0 1 2	 71 19 0	 19 9 0	0.381
VOMITING 0 1 2	 87 9 0	 20 3 5	0.0773
DIARRHEA 0 1 2	 68 14 3	 16 2 0	0.539
RECTAL PAIN 0 1 2	 85 15 0	 20 2 0	0.303

The incidence of grades 0, 1, and 2 of constipation was 81%,

8.5%, and 10% respectively indicating that there is no statistical association between constipation and total radiation dose of Salvage RT (p=0.129). *Table 4. Gastrointestinal toxicities*

Quality of Life

Baseline performance status (PS) of each patient of this study was assessed using the Eastern Cooperative Oncology Group (ECOG) score of performance status also called Zubrod performance status. According to the research criteria, only patients showing ECOG performance status of 0-1 were considered.

Based on the results of the Cox proportional hazard model and Pearson's correlation (coefficient r = -0.009), the patient's survival was not completely associated with the total radiation dose, indicating an extremely weak and practically negligible correlation and higher ECOG status i.e., low-performance status has a significant risk of mortality.

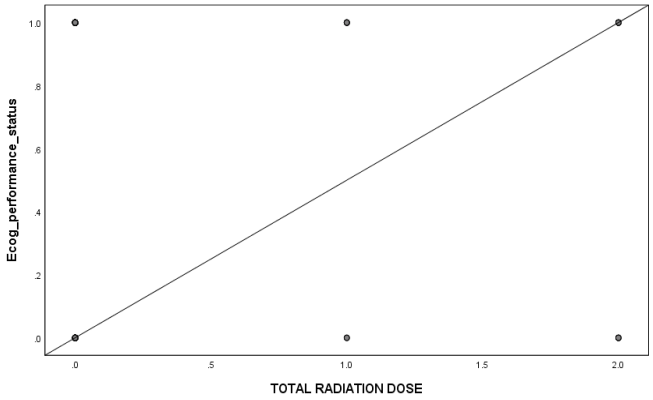

Figure 7. Correlation between ECOG performance status and Total radiation dose

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.[8] 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, on the other hand, 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.

Based on the results of RADICALS -HD trials both the timing of postoperative radiotherapy (immediate or early) and the duration of hormone therapy (short-term or long-term) have a greater impact on survival.[9] In patients having post-operative radiotherapy after radical prostatectomy, 24 months ADT vs 6 months ADT improved both times to salvage ADT and metastasis-free survival. In contrast, 6 months ADT vs no ADT improved the time to salvage ADT but did not improve metastasis-free survival.[10] Thus, to increase the survival rate of patients with prostate cancer, preventative measures including early detection and treatment of recurrence should be implemented.[11]

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. It was also found that neither of the cohorts treated with Salvage RT in combination with ADT experienced acute or late grade 2 GU toxicities. Out of all, only 8% of the patients had experienced grade 2 GI toxicities, and the patient's survival was not completely associated with the total radiation dose, indicating an extremely weak and practically negligible correlation and higher ECOG status i.e., low-performance status has a significant risk of mortality.

Keywords: Structural relapse, Salvage Radiotherapy, ADT, Radical prostatectomy, Survival, Toxicities

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