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Review Article

A meta-analysis on the use of radiotherapy after prostatectomy: adjuvant versus early salvage radiation

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ABSTRACT

To determine which method of radiotherapy proves more effective after prostatectomy: Adjuvant (ART) or early salvage (ESRT), we observed the pathologic and adverse risk factors of patients and their results from both treatments, looking specifically at biochemical-free survival rates, metastasis-free survival rates, and overall survival rates. Peer review articles containing their own data collected between 1986 and 2022 were reviewed. We reviewed 67 peer review articles and included 33 that met criteria. Studies focused on the adverse risk factors and the results of patients either before/after receiving adjuvant or early salvage/salvage radiotherapy were included in the analysis. Patient characteristics had an effect on what treatment a patient would receive; if a patient had more than one adverse risk factor such as a high Gleason score, prostate-specific antigen (PSA) level, T-stage, or positive margins, they would receive immediate radiation after prostatectomy, which would classify as ART. If the patient had no adverse risk factors after surgery, they would be placed in an observation period to follow their PSA and overall health, and only if necessary, undergo ESRT. Of the 33 studies, ART was proven to be only slightly more beneficial when relating to biochemical recurrence-free survival while ART and ESRT results were similar in metastasis-free survival and overall survival. ART and ESRT are overall comparable in their patient outcomes, despite their own unique pros and cons. The use of ESRT reduces overtreatment in men who may not experience biochemical recurrence. However, in those with very high-risk pathologic features, a multi-disciplinary approach should be utilized to best determine which mode of radiation therapy after surgery is recommended.

1. Introduction

Prostate cancer is the most common non-cutaneous cancer among men. Approximately one in nine men will be diagnosed with prostate cancer during his lifetime. Due to the coronavirus pandemic, new cases and deaths related to prostate cancer reported in the years 2020 and 2021 are likely an underestimate, since many people missed their cancer screenings. This would predict a sharp increase of new prostate cancer cases in 2022.

Prostatectomy remains the gold standard for treatment of clinically localized prostate cancer. After surgery, patients can choose to undergo adjuvant or salvage radiation treatment if deemed necessary. Adjuvant radiotherapy is received immediately (within 4–6 months) after prostatectomy while salvage radiotherapy is given after a period of observation and biochemical failure. This article will primarily focus on early salvage radiotherapy, which still contains an observation period, but is administered sooner than salvage radiation.

Adjuvant radiotherapy is given when patients pathology demonstrates a high risk for a localized recurrence, advanced stage, or node positive disease. Salvage radiotherapy is administered when there is a biochemical recurrence after a period of observation following prostatectomy.

There are benefits and drawbacks to both ART and SRT, and both produce varying outcomes. It has been shown that these differences are limited when comparing ART to ESRT versus SRT. ESRT has been proven to be superior to SRT by allowing for better cancer control. The advantages and disadvantages between ART and ESRT are measured in various ways in order to compare and contrast them. The more popular outcome metrics used are biochemical recurrence-free survival (BRFS), metastasis-free survival (MFS), and overall survival (OS). However, until recently, the Gleason score,

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stage, adverse pathologic risk factors and postoperative clinical condition of a patient all determine whether they receive ART or ESRT.[1]

2. Materials and methods

A systematic literature search was conducted on Google Scholar to evaluate peer review articles with topics of adjuvant, salvage, and early salvage radiotherapy. The search was completed between December of 2020 and January of 2022, and was performed by searching for articles relating to "adjuvant versus early salvage radiation," "benefits of adjuvant radiotherapy," "benefits of salvage radiotherapy," and "ART versus ESRT prostate cancer." We pooled data from 33,773 patients who received either adjuvant or early salvage/salvage radiotherapy. All studies included were completed between 1986 and 2021. Articles comparing early salvage radiotherapy to salvage radiotherapy were included. The survival benefits of ART versus ESRT (including SRT) were analyzed. Articles addressing medical complications and costs of treatments were excluded. We assessed 33 articles that met our inclusion criteria.

3. Results

Table 1 displays the total number, average, most frequent, or median characteristics of the patients involved in each study. For the total number characteristics, the number of patients from each given trial were added together. To calculate average and median characteristics, data from every given study were computed. The surgical margin status was recorded. The median follow-up range was 0.92–9.30 years for ART, 3.75–9.80 years for ESRT/SRT, and 2.71–13.33 years in studies that combined the follow-up for ART and ESRT/SRT. Gleason score, PSA level, tumor stage, and surgical margins were crucial factors since they contributed to whether a patient received ART or ESRT/SRT. Between all studies that incorporated these certain characteristics, Gleason score ranged between > 6–10, PSA levels varied between ≤ 0.1 and ≤ 10 ng/mL, and tumor stage spanned across pT2 to pT4a. Not all peer review articles contained each set of data necessary to determine these characteristics.

In order to collate ART versus ESRT/SRT, the following end results were computed. Table 2 shows the most recurring final products throughout all peer review articles. Mean percentages were calculated in order to grasp an understanding of the complications or free survival rates for ART and ESRT/SRT. For most of these data points, there were yearly marks after RT to keep track of the free survival rate after radiation. Not all peer review articles contained each set of data necessary to determine these features.

Table 1
Patient characteristics

Characteristics	
Total number of patients	33,773
Total number of ART patients	8424
Total number of ESRT and SRT patients	11,909
Average median follow-up	6.6 years
Average median age	64 years
Median Gleason score	≥ 7
Median PSA level	$\leq$0.5 ng/mL
Median tumor stage	pT3a
Median nodal status	pN0
Most frequent surgical margins	Positive
Median Gy	60–64

ART, adjuvant radiotherapy; ESRT, early-salvage radiotherapy; SRT, salvage radiotherapy; PSA, prostate-specific antigen

Fig. 1 displays the biochemical recurrence-free survival rate in both adjuvant and early salvage/salvage radiotherapy measured by the number of years after a patient received either RT. Over the years, there appears to be a decrease in survival rates for both radiation types. At two years, five years, and 12 years, the BRFS for ART was 91.40%, 82.90%, and 69.00%, compared to the BRFS for ESRT/SRT at the same time intervals, which was 88.90%, 76.90%, and 43.00%, respectively ($p = 0.504$). Even at years three and 10, ART led ESRT/SRT with 87.00% versus 68.80% and 61.00% versus 48.00%, respectively ($p = 0.171$). Year four was the only point in time where ESRT/SRT rates were higher (44.20%) compared to ART (43.40%) ($p = 0.539$). It must be noted that for the majority of the years, ART and ESRT/SRT's mean only had a couple percent difference. It is fair to identify that ART is associated with improved BRFS rates due to the large increase in certain years.

Fig. 2 compares the mean metastasis-free survival rates in ART and ESRT/SRT for studies that gave no yearly follow up but presented MFS in their results, and six and eight years after radiotherapy. Mean MFS for ART was 80.00% and 95.00%, and for ESRT/SRT was 78.50% and 89.00% for years N/A and six, respectively ($p = 0.721$). ART is more favorable at the six-year mark, although numbers remained constant and comparable throughout all years. Therefore, ART as compared to ESRT/SRT provide the same outcomes for MFS, and there is no clinically significant difference.

Fig. 3 compares ART versus ESRT/SRT in mean overall survival for studies that gave no yearly follow up but presented OS rates, plus six and eight years after receiving radiation. There is a 5% difference for the years N/A and six for ART (77.50% and 100.00%) versus ESRT/SRT (72.70% and 95.00%), where ART has increased OS ($p = 0.461$). As seen with MFS, numbers remained constant and comparable throughout the years. Therefore, both RT methods result in similar outcomes for OS.

4. Discussion

This meta-analysis sought to determine whether there is a difference between adjuvant and early salvage radiotherapy. ART and ESRT are independent radiation treatments used for different patient post-operative scenarios. However, our analysis supports the fact that there is little difference between ART and ESRT. Therefore, we recommend an ESRT approach to avoid overtreatment of patients with radiation in the adjuvant setting.

ART has been proven to increase biochemical recurrence-free survival.[2–11] ART had an increased biochemical recurrence-free survival mean for almost all years after prostatectomy. When comparing the population of patients that participated in BRFS studies for ART and ESRT/SRT, results were clinically significant, but did not reach statistical significance ($p = 0.08$). Therefore, there may be an effect that exists between ART and ESRT/SRT, however, it is not strong enough to be able to conclude that one method is superior to the other. Due to this, it can be concluded that these methods produce the same results when relating to BRFS rates. This supports ESRT over ART in an effort to avoid radiation in those patients who may not benefit.

Opinions on the more effective radiation therapy in regards to metastasis-free survival were divided. In multiple peer review articles, MFS had better results when a patient received ART.[2,3,7,9,10,12] One study supported ESRT to improve MFS.[13] Some articles were incapable of demonstrating a difference in either radiotherapy when it came to MFS rates, showing that either method was effective.[14,15] Through our literature review, ART and ESRT/SRT results when looking at MFS were similar. These results were not statistically significant ($p = 0.428$), and therefore provide strong evidence for the null hypothesis that there is no difference between ART and ESRT when observing MFS rates.

Table 2
Mean percentage of free survival and complication rates for years after radiotherapy comparing ART and ESRT/SRT

Mean	Year(s) after	ART	ESRT/SRT
Biochemical recurrence-free survival	2	91.4%	88.9%
	3	87.0%	61.0%
	4	43.4%	44.2%
	5	73.3%	76.9%
	8	81.5%	75.0%
	10	68.8%	48.0%
	12	69.0%	43.0%
Metastasis-free survival	N/A	74.8%	78.5%
	6	95.0%	89.0%
	8	92.0%	91.0%
Overall survival	N/A	77.9%	72.9%
	6	100.0%	95.0%
	8	89.0%	92.0%
Hormone therapy	N/A	84.0%	N/A
	5	92.0%	93.0%
Gastrointestinal toxicity	N/A	74.0%	N/A
		Grade $\geq$ 2: 5.7%	Grade $\geq$ 2: 14%
Genitourinary toxicity	N/A	26.0%	40.5%
	1	5.1%	3.4%
		Grade $\geq$ 2: 70%	Grade $\geq$ 2: 54%
Erectile dysfunction	N/A	28.0%	8.0%
	3	11.6%	29.0%
		Grade $\geq$ 2: 96%	98.0%
Event-free survival	N/A	89.0%	88.0%
	5	83.0%	61.7%

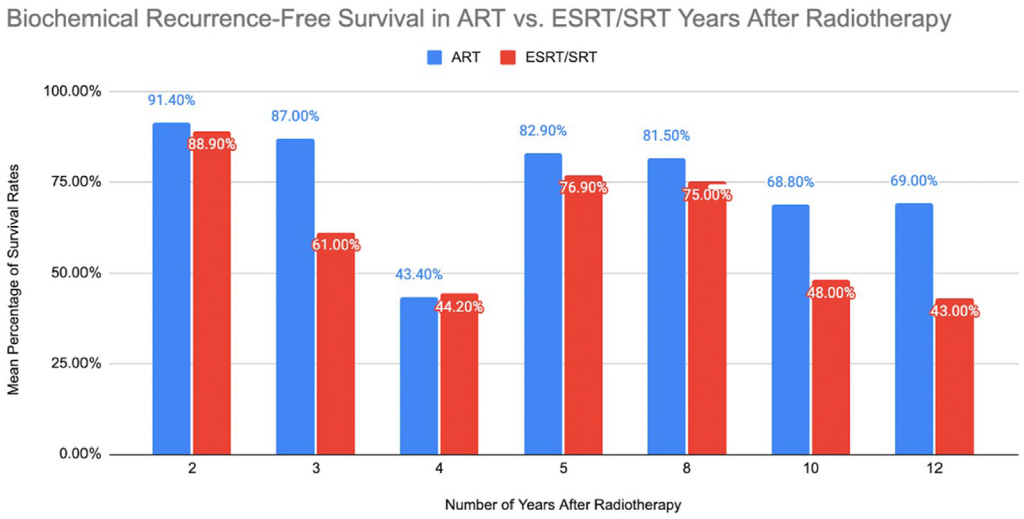

Fig. 1. Mean percentage of biochemical recurrence-free survival in ART versus ESRT/SRT years after radiotherapy ($p = 0.08$).

Furthermore, overall survival rates were the most indistinguishable between adjuvant and early salvage radiotherapies. Certain studies have claimed ART superiority since it can obtain better control of prostate cancer.[2,3,7,9,10,12] Despite the fact that ART was seen as the preferable treatment in many of the peer review articles, a great deal of studies supported either method by demonstrating that ART and ESRT/SRT shared no statistically significant differences relating to OS.[14–18] To further provide evidence for this point, this review discovered that even when comparing data with other studies, OS rates in ART and ESRT/SRT were almost equivalent. These results were also insufficient in concluding that one method is better than the other, since the evidence was not strong enough to suggest that an effect exists between ART and ESRT/SRT ($p = 0.770$). Therefore, for OS, ART, and ESRT/SRT produce very similar results, again supporting the use of ESRT over ART to avoid overtreating patients.

There are other determinants of the more beneficial RT method besides these particular courses of action. A higher pathological T-stage, Gleason score, PSA level, higher rate of positive margins, and men with seminal vesicle invasion are all associated with a patient at higher risk of death after RP.[19] These men may require RT upfront and therefore were qualified to receive adjuvant radiotherapy. On the other hand, lower adverse risk factors lead to an observation period before a patient receives ESRT, if necessary. Delayed radiotherapy can spare men from overtreatment of RT and its associated adverse events.[15,20,21] ESRT allows for better functional outcomes after surgery, especially considering that the longer the time interval between RP and RT, the more time for a potential recovery of urinary function and potency.[22] A major downside to ART is that it increases the risk of urinary incontinence rates, genitourinary toxicity, gastrointestinal toxicity, and erectile dysfunction.[20,22,23,24]

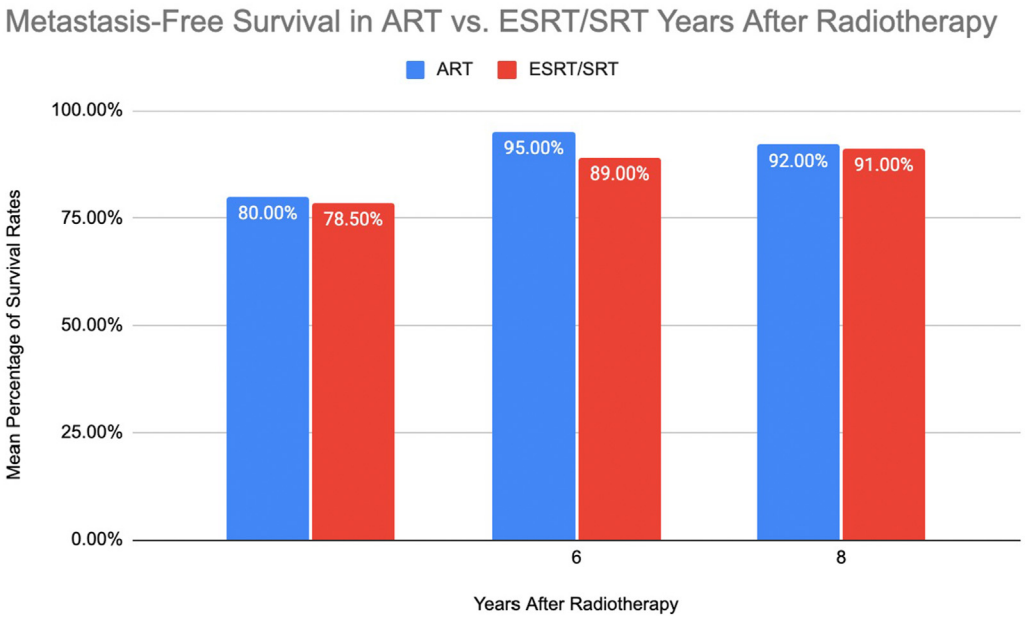

Fig. 2. Mean percentage of metastasis-free survival in ART versus ESRT/SRT years after radiotherapy ($p = 0.428$).

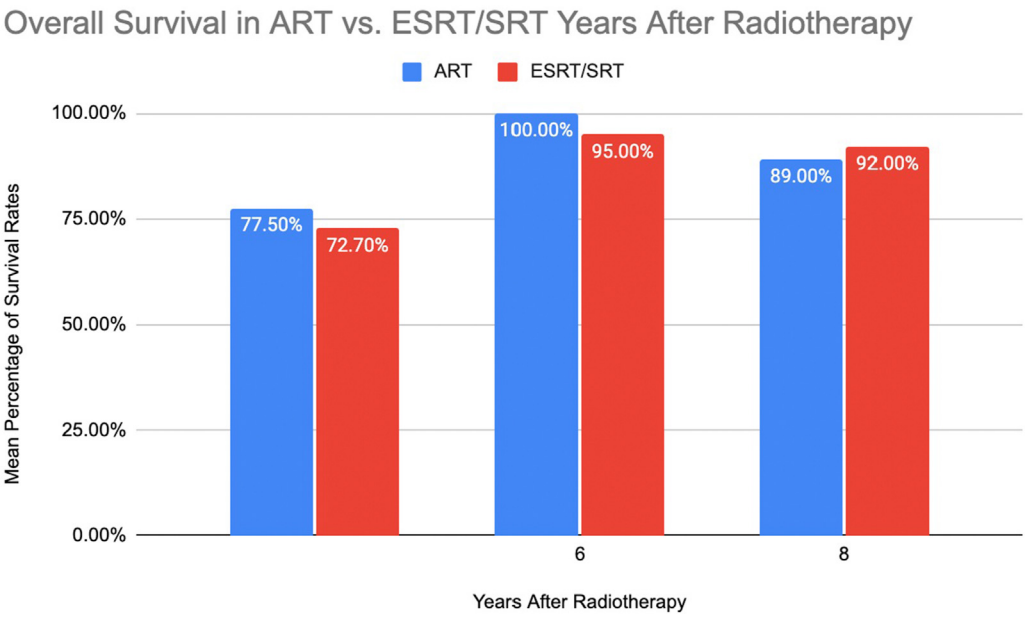

Fig. 3. Mean percentage of overall survival in ART versus ESRT/SRT years after radiotherapy ($p = 0.770$).

Given the documented morbidity of ART compared to ESRT, the decision to proceed with ART over ESRT must be made cautiously.

Of all 33 scholarly articles that were assessed and resulted in either treatment, the answer to our question came to a conclusion. A few peer review articles concluded that ART was the preferred method since it yielded significantly better outcomes.[2,7,9,10,11,13] Meanwhile ESRT was noted as the better treatment option in 8 articles since it reduces the risk of overtreatment.[15,20,21,22,24,25,26,27] Lastly, there were some articles that discovered ART and ESRT were just as effective as the other, and the radiation treatment a patient receives really depends on each patient's risk-benefit ratio.[1,12,19,28] The data we configured ultimately supports the use of ESRT, given the fact that there is no clinically significant difference compared to ART, but potentially less risk for overtreatment. Although ART may appear to improve BRFS, adjuvant and early salvage radiotherapies appear to be equally effective under all circumstances.

Recent publications have suggested that the adoption of ESRT may still result in overtreatment of a significant number of men. The concern being that ESRT may still result in unnecessary radiation toxicities. Delaying radiation further may "preserve the oncologic benefits of RT and spare many patients radiation toxicities." Further, their analysis demonstrated that 74% of patients who were eligible for ESRT did not recur with observation and there was no difference in survival noted.[29]

Limitations to our study are the differences between the methods in the manuscripts reviewed. This is a result of our retrospective approach, which contains intrinsic selection bias. The evidence supports an ESRT approach given equivalent outcomes with potentially less overtreatment. However, in patients with the highest risk factors for recurrence such as pathologic Gleason 8–10, T3/T4 disease, and node positive disease, ART should be considered given the possibility that a significant reduction in all-cause mortality exists.[30] Due to the complexity in treatment decision making, we advocate for a multi-disciplinary approach including urology, medical oncology, and radiation oncology.

5. Conclusion

This meta-analysis supports an ESRT approach to the majority of men post-prostatectomy given that there was no statistically significant difference between ART and ESRT. The use of ESRT is felt to reduce overtreatment in men who may not experience a biochemical recurrence. However, in those with very high-risk pathologic features, a multi-disciplinary approach should be utilized to best determine which mode of radiation therapy after surgery is recommended.

Conflicts of interest

There are no conflicts of interest to the related topic.

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