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Timing of radiotherapy after radical prostatectomy adjuvant radiotherapy OR salvage radiotherapy

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Abstract: *Radical prostatectomy is currently one of the primary treatments for localized prostate cancer. However, some patients experience biochemical recurrence after the procedure, which can lead to disease progression and eventual death. The risk of biochemical recurrence is higher in patients with high risk factors, including extraperitoneal tumor invasion, positive surgical margins, and a high Gleason score. Previous research has demonstrated that adjuvant radiotherapy after radical prostatectomy can reduce the risk of biochemical recurrence and improve metastasis-free survival. However, it also increases the risk of urinary tract and intestinal-related side effects and may result in overtreatment of patients who do not experience biochemical recurrence. Salvage radiotherapy, which is administered following biochemical recurrence, can mitigate the risk of overtreatment in patients without biochemical recurrence. Additionally, some studies have pointed out that salvage radiotherapy offers comparable survival benefits to adjuvant radiotherapy while reducing toxic side effects. Therefore, opting for salvage radiotherapy instead of adjuvant radiotherapy after radical prostatectomy might be a reasonable option.*

Keywords: *Prostate cancer; Biochemical recurrence; Adjuvant radiotherapy (ART); radical prostatectomy (RP)*

1. Introduction

Prostate cancer is currently the second most common malignant tumor in men and the fifth leading cause of cancer-related mortality worldwide [1]. At present, the primary treatment for localized prostate cancer (PCa) is radical prostatectomy (RP). However, about one-quarter of patients experience biochemical recurrence (BCR) after RP [2]. Postoperative radiotherapy is a critical tool for managing local recurrence, and several trials have demonstrated that postoperative adjuvant radiotherapy(ART) improves disease progression-free survival, biochemical recurrence-free survival, and overall survival in high-risk of recurrence patients (defined as those with positive surgical margins, pathologic stage pT3-4, lymph node metastasis, or pathologic grade group 4–5) compared to observation alone [3] [4] [5] [6]. Consequently, adjuvant radiotherapy is recommended by some experts for this high-risk group. However, in the above trials, since approximately 40% of the patients in the observation group did not experience biochemical recurrence during the study [7], adjuvant radiotherapy may pose a risk of over-treatment and increased adverse effects. Based on the above background some researchers suggested that Early salvage radiotherapy (SRT) could be considered for these patients with high risk of recurrence after radical prostatectomy as an alternative to adjuvant radiotherapy.

2. Adjuvant radiotherapy

Adjuvant radiotherapy for prostate cancer involves administering radiation therapy to patients after radical prostatectomy but before BCR. In postoperative prostate cancer patients at high risk of recurrence, adjuvant radiotherapy is aimed at eliminating subclinical prostate cancer lesions, thereby reducing the risk of local recurrence and distant metastasis. Previous studies have demonstrated that adjuvant radiotherapy is effective in prolonging biochemical recurrence-free time and overall survival and improving distant metastasis-free survival in high-risk prostate cancer patients. However, it also increases the toxic effects in the urinary system and reduces the quality of long-term survival of patients. The clinical trial results comparing adjuvant radiotherapy with observation are illustrated in Table 1.

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Table 1: Summary of published trials for ART.

Trail	Number of people enrolled	median follow-up time	TNM	Primary Outcome	Secondary outcome
SWOG 8794	425	10.6year	pT3N0M0	MFS HR = 0.71(0.54,0.94);p=0.016	OS HR=0.72(0.55,0.96)p=0.023)
EORTC 22911	1005	10.6year	pT2R1-pT3N0orNxM0	BPFS HR=0.49 (0.41,0.590;p<0.0001	OS HR=1.18 (0.91,1.53);p=0.2024
ARO 96-02	307	53.7months	pT3-4N0	BPFS HR=0.53;(0.37,0.79);P = .0015	
FinnProstate group trial	250	9.3year	pT2R1-p3aN0M0	BPFS HR 0.26;(0.14–0.48);p <0.001	10yearOS:HR =0.69;(0.29–1.60);p =0.4

All four trials confirmed the benefit of adjuvant radiotherapy in improving biochemical progression-free survival among postoperative prostate cancer patients with high-risk pathologies, (high-risk pathologies include positive surgical margins, seminal vesicle invasion, etc.). These findings laid a theoretical foundation for the use of adjuvant radiotherapy. However, approximately 40% of patients in these studies did not experience biochemical recurrence. For this subset of patients who were eligible for adjuvant radiotherapy but did not experience biochemical recurrence over a prolonged period of time, adjuvant radiotherapy provided only relevant side effects without survival benefit. Therefore, strict adjuvant radiotherapy may pose a risk of over-treatment for patients with a high risk of recurrence, and it has become a matter of concern whether radiation therapy can be administered to patients after biochemical recurrence to achieve the same survival benefit without increasing the side effects of radiotherapy. Based on this assumption, three related clinical trails have provided a partial answer.

3. Salvage radiotherapy

Salvage radiotherapy refers to radiotherapy after the biochemical recurrence of prostate cancer. Biochemical recurrence becomes an important indicator for judging salvage radiotherapy, and the commonly used criteria are: Following radical prostatectomy, the Panel recommends defining biochemical recurrence as an initial serum prostate specific antigen of > or =0.2 ng/mL, with a second confirmatory level of prostate specific antigen of >0.2 ng/mL [8]. However, some articles have also indicated that the point at which the occurrence of systemic progression is most strongly associated with psa values is PSA ≥ 0.4 ng/ml, and therefore the use of PSA values of 0.4 ng/ml or higher should be considered as a standard biochemical definition of recurrence [9]. A systematic review analyzing more than 5,000 postoperative prostate cancer patients yielded that for every 0.1 ng/mL increase in PSA at the start of SRT, there was a mean loss of 2.6% (95% CI, 2.2-3.1) in RFS (relapse-free survival) after SRT [10]. More than 50 definitions of BCR can be found in the previous literature [8], therefore, the criteria for biochemical recurrence in several studies comparing salvage radiotherapy with adjuvant radiotherapy are not uniform, and further studies are needed to support this [11] [12] [13].

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3.1. RAVES

A total of 333 postradical prostate cancer patients with high-risk factors (defined as positive surgical margins, extraprostatic extension, or seminal vesicle invasion) were enrolled in the study. These patients were randomly assigned to either the adjuvant radiotherapy group (166 patients) or the salvage radiotherapy group (167 patients), with a median follow-up of 6.1 years. Salvage radiotherapy was initiated in this study when PSA levels reached ≥0.2 ng/ml. The primary outcome measure was freedom from biochemical progression, with a 5-year freedom from biochemical progression rate was 86% in the adjuvant radiotherapy group and 87% in the salvage radiotherapy group (HR 1.12, 95% CI 0.65-1.90; p=0.15). The salvage radiotherapy group had a lower incidence of grade 2 and higher genitourinary toxicity than the adjuvant radiotherapy group, while the gastrointestinal toxicity rates were similar between the two groups. Secondary outcome indicators—including 5-year and 8-year freedom from locoregional or distant progression, as well as 5-year and 8-year overall survival—did not show statistically significant differences between the two groups. Based on these findings, this study recommends the early use of salvage radiotherapy rather than adjuvant radiotherapy in high-risk patients after radical prostatectomy [14].

3.2. GETUG-AFU-17

The study included 424 patients with high-risk factors (defined as pathologic stage pT3a, pT3b, or pT4a (with bladder neck infiltration), pNx (no pelvic lymph node dissection), or pN0 (negative lymph node dissection) and positive surgical margins). These patients were randomly assigned to either salvage or adjuvant radiotherapy groups, each consisting of 212 patients, with a median follow-up time of 75 months. Biochemical relapse before initiating salvage radiotherapy was defined as a PSA level greater than 0.2 ng/mL confirmed after 4 weeks. The primary outcome indicator was event-free survival, with a 5-year event-free survival rate of 92% in the adjuvant radiotherapy group and 90% in the salvage radiotherapy group (HR 0.81,95% CI 0.48-1.36; p=0.42); secondary outcome: 5-year overall survival in the adjuvant radiotherapy group was 96% and 5-year overall survival in the salvage radiotherapy group was 99% (HR=1.60,95% CI 0.71-3.60;p=0.25). Acute genitourinary toxicity and gastrointestinal adverse effects were higher in adjuvant radiotherapy than in the salvage radiotherapy group. Therefore salvage radiotherapy can prevent excessive radiotherapy in prostate cancer patients with high-risk factors and reduce the occurrence of radiotherapy-related adverse reactions [15].

3.3. RADICALS-RT

The randomized controlled trial included 1,396 patients who had undergone radical prostatectomy for prostate cancer and exhibited at least one risk factor (including pathologic T stage 3 or 4, Gleason score of 7-10, positive surgical margins, or preoperative PSA ≥10 ng/mL). These patients were randomly assigned to the adjuvant radiotherapy group (including 697 patients) and the salvage radiotherapy group (including 699 patients) for observation, with follow-up data available until December 2021 and a median follow-up period of 7.8 years. PSA failure in this study was defined as two consecutive PSA elevations with PSA >0.1 ng/mL or three consecutive PSA elevations. The study found no significant difference in the primary outcome measure of early efficacy, with a 5-year biochemical progression-free survival rate of 85% for the adjuvant radiotherapy group and 88% for the salvage radiotherapy group. There was no evidence of significant improvement in the primary outcome measure of freedom from distant metastases(FFDM), with 10-year FFDM was 93% in the adjuvant radiotherapy group and 90% in the salvage radiotherapy group: (HR=0.68, 95% CI 0.43-1.07, P=0.095). However, adjuvant radiotherapy was associated with a higher incidence of urinary and intestinal adverse events, and fecal incontinence remained significant after 10 years (P=0.017). Therefore, based on the above results, it is concluded that salvage radiotherapy should be the recommended treatment option for high-risk patients after radical prostatectomy for prostate cancer [16].

These studies, which included postoperative prostate cancer patients with at least one risk factor, demonstrated that salvage radiotherapy has the same near- and long-term efficacy as adjuvant radiotherapy, with a lower incidence of adverse effects. However, the populations included in the above three studies were of European ethnicity, and the majority of the subjects had Gleason scores ≤7. PCa in Asian populations usually shows a high likelihood of advanced clinical stages compared to Western populations. The majority of patients in China had high-grade PCa (Gleason score > 7) [17]. It has been shown that the Gleason score is an independent predictor of biochemical relapse [18]. Therefore, for high-risk patients with a Gleason score of 8 and above, the aforementioned studies offer limited reference

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value. Further research is needed to determine whether salvage radiotherapy can serve as a substitute for adjuvant radiotherapy.

4. Radiation therapy combined with hormones

Hormone therapy plays a crucial role in the management of prostate cancer. Androgen deprivation therapy (ADT) for prostate cancer (PCa) is widely used in patients with metastatic prostate cancer with remarkable efficacy [19],and is commonly combined with surgery and radiotherapy to enhance local control. RTOG 0534 and GETUG-AFU 16 Randomised controlled trial pointed out that the addition of a short-term (4-6 months) of ADT in patients who underwent salvage radiotherapy after prostatectomy slowed down the progression of the disease[20], and prolonged progression-free survival [21]. The results of the RTOG 9601 trial showed that in patients undergoing advanced SRT (PSA >0.6 ng/mL), the addition of a long course (24 months) of ADT not only improved metastasis-free survival, but also improved overall survival [22]. Therefore, either short- or long-term ADT treatment combined with salvage radiotherapy offers substantial benefits to patients. However, these studies did not directly compare the efficacy of short-course versus long-course ADT, indicating a need for further clinical trials to determine the optimal duration of ADT treatment.

The recently published results of the RADICALS-HD phase III trial, which compared postoperative radiotherapy combined with either short-term or long-term androgen deprivation therapy (ADT) for prostate cancer, provide significant insights. A total of 1,523 patients were randomized into two groups: a short-term ADT group (6 months, n=761) and a long-term ADT group (24 months, n=762) following radical prostatectomy, with a median follow-up time of 8.9 years. The findings indicated that long-term ADT improved metastasis-free survival compared to short-term ADT (HR 0.773; 95% CI 0.612-0.975; p=0.029). Specifically, the 10-year metastasis-free survival rates were 71.9% for the short-term ADT group and 78.1% for the long-term ADT group. Additionally, the incidence of grade 3 or higher toxicity was 5% lower in the short-term ADT group compared to the long-term ADT group (p=0.025), with no reported treatment-related deaths. Notably, most patients receiving postoperative radiotherapy were classified as undergoing early salvage radiotherapy, and the efficacy of the treatment was not influenced by pretreatment PSA levels. Consequently, the use of long-term ADT combined with postoperative radiotherapy is recommended for well-tolerated patients [23].

5. Prediction of biochemical recurrence after radical prostatectomy

With the use of ultrasensitive PSA tests, PSA values can be measured with an accuracy of 0.001 ng/ml, which allows for a more refined level of prostate cancer-specific antigen monitoring and management. Biochemical recurrence of prostate cancer is associated with increased risk of clinical progression, metastasis, and prostate cancer-specific mortality [24]. Early biochemical recurrence is associated with poorer oncological outcomes for patients [25]. Predicting biochemical recurrence after radical prostatectomy is crucial for optimizing postoperative management and initiating salvage therapy in time to achieve the desired cancer-specific survival. We can assess patients' risk of BCR after radical prostatectomy by preoperative prostate cancer-specific antigen values, Gleason score, tumor stage, and surgical margin (SM) status [26]. Among the preoperative factors, PSA value and Gleason score exert a more significant influence on BCR, and studies indicate that patients with preoperative PSA>=20 ng/ml are more than three times more likely to develop BCR than patients with preoperative PSA <6 ng/ml [27].Among postoperative factors, a higher nadir PSA value is associated with an increased risk of BCR. A PSA value exceeding 0.03 ng/mL at 3 months after RP indicates a higher risk of recurrent and occult prostate cancer. If the first PSA value >0.03 ng/mL is detected at 3 months postoperatively in a prostate cancer patient with risk factors, salvage radiotherapy is recommended and combined endocrine therapy is also required [28] [29]. Another important PSA-related metric is the PSA doubling time (PSA-DT), which is frequently used to evaluate recurrence and prognosis. It is not only associated with biochemical recurrence but also a predictor of prostate cancer-specific mortality. Most current studies have used 3 months as a cut-off point to categorize post-RP patients into low-risk and high-risk groups. A PSA-DT of less than 3 months is linked to higher prostate cancer-specific mortality, with a median survival of just 6 years for this group, therefore, aggressive therapy is needed for this population [30]. However, it has also been suggested that PSA-DT monitoring has a lag in guiding treatment, with patients waiting 6-24 months for sufficient PSA values to accurately calculate PSA-DT, and that these factors limit the clinical utility of PSA-DT in determining the need for additional localized therapy [31].

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6. Discussion

The results of the above clinical studies show that salvage radiotherapy does not reduce biochemical recurrence-free survival and distant metastasis-free survival, and the incidence of radiotherapy-related adverse effects is less than that in the adjuvant radiotherapy group. Consequently, salvage radiotherapy appears to be a reasonable option for patients at high risk of recurrence after radical prostatectomy, rather than adjuvant radiotherapy. However, the proportion of high-grade PCa patients with Gleason score greater than 7 varies among different countries and regions. For Asian populations, such as China, the proportion of patients with Gleason score of 8 or higher is larger, and such populations have a higher probability of postoperative biochemical recurrence, and there is a lack of clinical studies on whether salvage radiotherapy can be used as an alternative to adjuvant radiotherapy for these patients. Therefore, it is suggested that early salvage radiotherapy is feasible for patients with a Gleson score of less than or equal to 7, while patients with a high Gleason score can choose whether to have adjuvant radiotherapy or not according to the patient's condition.

Unfortunately, the three studies mentioned lacked standardization in determining the PSA value at the start of salvage radiotherapy. Among them, the RADICALS-RT study, which had the largest patient cohort and the longest follow-up time, was supported by the data of the long-term efficacy outcome index: freedom from distant metastases, making its PSA value at the initiation of salvage radiotherapy a useful reference. Nonetheless, a uniform standard is lacking; As PSA testing becomes more precise, the standard PSA value at the beginning of salvage radiotherapy continues to decrease, narrowing the distinction between salvage radiotherapy and adjuvant radiotherapy. Thus, it is advisable to consider the patient's lowest postoperative PSA value, PSA-DT, and other relevant indicators for a comprehensive assessment of the optimal timing for starting salvage radiotherapy. Postoperative PSA levels serve as the primary indicator for detecting prostate cancer recurrence and a direct indicator for determining the biochemical recurrence of prostate cancer. Studies have proved that the detection of the first PSA value >0.03 ng/ml at 3 months postoperatively increases the risk of occult prostate cancer. Additionally, an elevated PSA level at the commencement of SRT correlates with a decreased recurrence-free survival rate following the treatment. Therefore, the PSA monitoring is very important, and patients need to undergo rigorous PSA monitoring postoperatively to detect biochemical recurrence as early as possible, which requires a high level of patient compliance and easy access to healthcare resources.

Combined androgen deprivation therapy during salvage radiotherapy has a survival benefit for patients but leads to an increase in treatment-related side effects. A long course of ADT lasting 24 months improves metastasis-free survival compared with a short course of ADT lasting 6 months. Thus, patients in good health who are willing to accept the risks of extended hormonal treatment may opt for long-course ADT combined with salvage radiotherapy for optimal efficacy.

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