Prostate Cancer

Long-Term Rates of Undetectable PSA with Initial Observation and Delayed Salvage Radiotherapy after Radical Prostatectomy

Stacy Loeb, Kimberly A. Roehl, Davis P. Viprakasit, William J. Catalona

Department of Urology, Johns Hopkins Medical Institutions, Baltimore, MD, USA
Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA
Department of Urology, Northwestern Feinberg School of Medicine, Chicago, IL, USA

Abstract

Background: Randomized trials have shown an improvement in progression-free survival rates with adjuvant radiation therapy (ART) after radical prostatectomy for patients with a high risk of cancer recurrence. Less is known about the relative advantages and disadvantages of initial observation with delayed salvage radiation therapy (SRT).

Objective: To examine the results of SRT in a large single-surgeon radical prostatectomy series.

Design, Setting, and Participants: From a radical prostatectomy database, we identified 859 men with positive surgical margins (SM+), extracapsular tumor extension (ECE), or seminal vesicle invasion (SVI) who chose to defer ART. Following a period of initial observation, 192 ultimately received SRT for prostate-specific antigen (PSA) progression.

Measurements: Survival analysis was performed to examine the outcomes of initial observation followed by SRT.

Results and Limitations: In patients with SM+/ECE and SVI, the 7-yr PSA progression-free survival rates with observation were 62% and 32%, respectively. Among those who had PSA progression, 56% and 26%, respectively, maintained an undetectable PSA for 5 yr after SRT. The long-term rates of undetectable PSA associated with an SRT strategy were 83% and 50% for men with SM+/ECE and SVI, respectively. In the subset of 716 men who did not receive any hormonal therapy, the corresponding long-term rates of undetectable PSA were 91% and 75%, respectively.

Conclusions: Following radical prostatectomy, initial observation followed by delayed SRT at the time of PSA recurrence is an effective strategy for selected patients with SM+/ECE. Some patients with SVI may also benefit from this strategy. However, additional prospective studies are necessary to further examine the survival outcomes following SRT.

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* Corresponding author. 675 N. Saint Clair Street, Suite 20-150, Chicago, IL 60611, United States. Tel. +1 312 695 4471; Fax: +1 312 695 1482.
E-mail address: wcatalona@nmff.org (W.J. Catalona).
1. Introduction

Despite the stage migration that has occurred as a result of screening for prostate cancer based on prostate-specific antigen (PSA), a considerable proportion of patients have adverse pathologic features at the time of radical prostatectomy (RP). The preferred postoperative management for these patients is an important issue because the presence of adverse pathologic features portends a significantly worse prognosis.

For example, Karakiewicz et al examined the impact of positive surgical margins (SM+) in 5831 patients treated at eight institutions between 1983 and 2000 [1]. At a median follow-up of 25 mo, 16.4% had biochemical progression. The actuarial 10-yr progression-free survival (PFS) rate was 70.1% for patients with negative surgical margins compared to 36.1% with SM+. In the subset with SM+ without extracapsular extension (ECE), the 10-yr PFS rate was 61.4%. In a multivariate model with Gleason grade, seminal vesicle invasion (SVI), and lymph node metastases (LN+), SM+ were associated with a 3.7-fold increased risk of biochemical progression.

In another study by Hull et al, SM+ were associated with a significantly worse prognosis. For example, Karakiewicz et al examined the impact of positive surgical margins (SM+) in 5831 patients treated at eight institutions between 1983 and 2000 [1]. At a median follow-up of 25 mo, 16.4% had biochemical progression. The actuarial 10-yr progression-free survival (PFS) rate was 70.1% for patients with negative surgical margins compared to 36.1% with SM+. In the subset with SM+ without extracapsular extension (ECE), the 10-yr PFS rate was 61.4%. In a multivariate model with Gleason grade, seminal vesicle invasion (SVI), and lymph node metastases (LN+), SM+ were associated with a 3.7-fold increased risk of biochemical progression.

ECE and SVI are also associated with significantly worse outcomes after RP. For example, in the senior author’s series, the 10-yr PFS rate was 62% (95% confidence interval [CI], 51–72%) with ECE and negative surgical margins, and 53% (95%CI, 47–59%) for patients with both ECE and SM+ [3]. In men with SVI, the 10-yr PFS rate was only 26% (95%CI, 18–35%). Han et al similarly reported a low 15-yr PFS rate of 17% (95%CI, 5–35%) for men with SVI [4].

Although adverse surgical pathology findings clearly are associated with worse outcomes, the appropriate selection of patients for postoperative radiation therapy (RT) is an unresolved issue for many clinicians. Despite evidence from three multi-institutional phase 3 randomized controlled trials supporting the use of immediate adjuvant radiotherapy (ART) for men with unfavorable pathology in the RP specimen [5–7], it may lead to additional side effects, and a proportion of men could be overtreated. As a result, some physicians instead prefer initial observation with later salvage radiation therapy (SRT) at the time of PSA progression or clinical failure [8]. The purpose of our study was to examine the results of initial observation followed by SRT in men with adverse pathology from a large single-surgeon RP series.

2. Methods

From 1983 to 2005, >4000 men underwent RP by a single surgeon (W.J.C.). The clinical characteristics and pathologic features of these patients were prospectively entered into a database. From this population, we identified 1060 men with SM+/ECE or SVI or both. Our policy is to offer these patients a choice between ART and initial observation. All patients who chose to defer RT were followed with semiannual PSA measurements and yearly digital rectal examinations. SRT was offered to patients at the time of PSA progression (PSA ≥ 0.2 ng/ml). Among those patients who then received SRT, the average radiation dose was 6300 Gy. However, because the SRT was performed at numerous institutions throughout the country, no other treatment-related data were available.

For the purposes of analysis, we excluded men who underwent ART, leaving a final population of 859 men managed with initial observation. In these men, we calculated 7-yr biochemical PFS, cancer-specific survival (CSS), and overall survival (OS) rates as a function of pathologic features, using the Kaplan-Meier method. In men who received SRT, we also calculated the proportion who maintained an undetectable PSA level for 5 yr after SRT. These numbers were used to calculate long-term rates of undetectable PSA by adding together the 7-yr biochemical PFS rate with observation alone to the proportion of men who maintained an undetectable PSA level for 5 yr after SRT. Specifically, the following formula was used: long-term rate of undetectable PSA = 7-yr FFS + (% undetectable PSA 5 yr after SRT × [100 – (7-yr FFS)]). Finally, a multivariate Cox regression analysis was performed to evaluate predictors of progression among men who were managed with initial observation, wherein PSA was coded as a continuous variable.

Because the majority of these patients were managed at outside institutions at the time of progression, some were also given hormonal therapy at the discretion of their local physicians. Thus, our database did not have detailed information on the timing, duration, or type of hormonal therapy. To reduce potential confounding, we therefore repeated the same analyses for the subset of 716 (83%) men who did not receive any hormonal therapy. All statistical analysis was performed using SAS 8.2 for Linux.

3. Results

From a large surgical database, there were 859 men with adverse pathology in the RP specimen who did not receive ART. Table 1 shows the characteristics of the study population. The mean age was 62 yr and the majority of men were white (94%). The median preoperative PSA level was 6.6 ng/ml, and 97% of men had clinical stage T1c or T2 disease.

The Kaplan-Meier curves for PFS, CSS, and OS rates with observation are shown in Fig. 1, stratified by pathologic tumor features. The median follow-up was 67 mo (range: 0–233 mo) after RP. Among men with SM+/ECE, at 7 yr, 62% were free from
biochemical progression, with 98% CSS and 93% OS, with a median follow-up of 66 mo (range: 0–233 mo). For SVI, the 7-yr biochemical PFS rate was 32%, with 87% CSS and 75% OS, with a median follow-up of 71 mo (range: 0–213 mo) (Fig. 2).

Notably, the prostatectomy Gleason score was significantly associated with the risk of adverse outcomes among men managed with initial observation postoperatively. The mean Gleason score was significantly higher among men who had biochemical progression (6.7 vs. 6.3,  \( p < 0.0001 \)), metastatic disease (7.5 vs. 6.4,  \( p = 0.0009 \)), or death from prostate cancer (7.3 vs. 6.5,  \( p = 0.01 \)).

We also performed multivariate analysis for the prediction of biochemical progression among men with adverse pathology managed with initial observation. Preoperative PSA (1.03; 95%CI, 1.02–1.04;  \( p < 0.0001 \)), SVI (hazard ratio [HR] 2.2; 95%CI 1.7–2.9;  \( p < 0.0001 \)), and a Gleason score \( \geq 7 \) (HR 1.7; 95%CI, 1.3–2.2,  \( p < 0.0001 \)) were significant independent predictors of failure during observation.

From the overall study population, 192 underwent SRT. The median PSA level was 0.7 ng/ml (range: 0.2–13.6 ng/ml) at the time of SRT initiation, and the average radiation dose was 6300 Gy. Table 2 shows the oncologic outcomes at a mean follow-up of 53 mo after SRT, stratified by pathologic tumor features. In men with SM+/ECE, 57 (56%) maintained an undetectable PSA 5 yr later. Among the men with SVI, 11 (26%) maintained an undetectable PSA after SRT and few men developed metastases or died from prostate cancer.

Among men who initiated SRT at a PSA level <1 ng/ml, 53 (58%) maintained an undetectable PSA 5 yr later compared to 12 (29%) who received SRT at a PSA level >1 ng/ml. Metastatic disease was also significantly less likely among men who initiated SRT at a PSA level <1 ng/ml (0% vs. 11%,  \( p = 0.003 \)), although the mortality rate was similar (0% vs. 4%,  \( p = 0.10 \)).

Finally, we calculated the overall long-term rates of undetectable PSA by adding together the proportion of men who remained free from progression with observation alone to the additional proportion who were successfully salvaged with postoperative RT. For example, in men with SM+/ECE who were observed, we added the 7-yr PFS of 62% for the observation group to the additional 56% who maintained an undetectable PSA after SRT, yielding a long-term rate of undetectable PSA of 83%. In men with SVI, the corresponding long-term rate of undetectable PSA was 50%.

Of the 859 men with adverse pathology, 716 (83%) underwent initial observation and did not receive hormonal therapy at any point during follow-up. This included 621 men with SM+/ECE and 95 with SVI. Table 3a shows the survival outcomes associated with observation alone in these men. Of the 716 men, 107 (15%) ultimately received SRT (Table 3b). The long-term rates of undetectable PSA were 91.3% and 75.4% for patients with SM+/ECE and SVI, respectively.

### 4. Discussion

The appropriate management for men with adverse pathology at the time of RP is controversial. Some patients with minimal adverse pathology may have a low progression rate without additional treatment. On the other end of the spectrum, some patients with high-risk features likely may have disseminated disease and will not benefit from additional local therapy. The issue is to define the intermediate group of patients who will truly benefit from postoperative radiation.

To date, three large randomized controlled trials have examined the efficacy of ART in this population [5–7]. In the European Organization for Research and Treatment of Cancer (EORTC) trial 22911, 1005
men with pT2 margin-positive or pT3 N0 M0 prostate cancer were randomized to ART or a ‘wait-and-see’ approach after RP [5]. The primary end point in this trial was PFS. At a median follow-up of 5 yr, the PFS rate was significantly higher in the irradiated group (74% vs. 52.6%, p < 0.0001). Clinical failure and locoregional failure were also significantly lower in the ART group. However, the duration of follow-up was insufficient to reliably evaluate more distant end points, such as metastases and death.

Similarly, Wiegel et al reported the preliminary results of a phase 3 trial that randomized 385 men with pT3 prostate cancer to either 60 Gy ART or a wait-and-see approach [7]. At 4 yr, biochemical progression-free survival (the primary end point) was 81% in the ART arm versus 60% for the wait-and-see arm (p < 0.0001; HR = 0.45).

More recently, Thompson et al reported the results of the Southwest Oncology Group (SWOG) 8794 trial [6]. Beginning in 1988, 425 men with adverse pathology in the RP specimen were randomized to either ART or initial observation. Similar to the EORTC 22911, they reported a significantly lower progression rate in the ART group at a median follow-up of 10.9 yr (34.9% vs. 64%). There was also a nonsignificant trend toward a higher metastasis-free survival rate in the adjuvant group. Patients who received ART were also significantly less likely to receive hormonal therapy by 5 yr (HR = 0.45; 95%CI, 0.29–0.68; p < 0.001). At 10 yr, 35.5% of irradiated men had metastatic disease or died compared to 41.3% of men in the observation group (p = 0.06). OS was also not significantly different between the groups (HR = 0.80; 95%CI, 0.58–1.09; p = 0.16). However, it is noteworthy that in both studies men who relapsed during observation were offered secondary active treatment, which may have obscured any survival differences between the groups.

Another important issue is treatment-related morbidity. In the SWOG study, a significantly higher overall rate of adverse events was found in the ART group (28.8% vs. 11.9%), including rectal toxicity,
urethral strictures, and incontinence [6]. However, other studies have failed to show a significant increase in side effects with ART. For example, Van Cangh et al compared the results of pad tests along with personal interviews about continence among 48 men treated with ART and 52 men who were followed expectantly [9]. At a mean follow-up of 24 mo after RP, the overall continence rate and proportion of patients with grade 3 (major) incontinence was similar between groups. In EORTC 22911, the cumulative incidence of grade 3 toxicity between the irradiation and wait-and-see groups by 5 yr was statistically similar (4.2% vs. 2.6%; p = 0.07), and no instances of grade 4 toxicity occurred [5]. Interestingly, although the SWOG 8794 study was analyzed in an intent-to-treat fashion, it is noteworthy that 70 patients who were randomized to observation crossed over and received RT [6]. In 63 of these men, the radiation was given as salvage for recurrence. Unfortunately, no information was reported regarding the PSA level at the time of SRT or other clinical characteristics of this population that might influence the likelihood of response. In addition, no data were reported on the proportion that subsequently maintained an undetectable PSA level after SRT or a comparison of the complications profile. Although these factors do not permit a detailed comparison of the results of SRT in this population, the SWOG results nonetheless have important implications. For example, at 5 and 10 yr of follow-up, the observation group had actuarial metastasis-free survival rates of 84% and 63%, respectively. Correspondingly, the median metastasis-free survival was 13.2 yr in the observation group, suggesting that initial observation followed by delayed salvage may be a reasonable alternative.

Table 2 – Results of salvage radiation therapy in men with positive surgical margins, extracapsular extension, or seminal vesicle invasion in the radical prostatectomy specimen (n = 192)

<table>
<thead>
<tr>
<th></th>
<th>Maintain undetectable PSA</th>
<th>Metastatic disease</th>
<th>PCa death</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM+/ECE</td>
<td>57 (56%)</td>
<td>6 (5%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>SVI</td>
<td>11 (26%)</td>
<td>18 (29%)</td>
<td>13 (21%)</td>
</tr>
<tr>
<td>p value</td>
<td>0.0009</td>
<td>&lt;0.0001</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

SM+ = positive surgical margins; ECE = extracapsular extension; SVI = seminal vesicle invasion; PSA = prostate-specific antigen; PCa = prostate cancer.

Table 3 – (a) 7-yr progression-free, cancer-specific, and overall survival rates for men with positive surgical margins, extracapsular extension, or seminal vesicle invasion managed with initial observation (n = 716) and (b) the results of salvage radiation therapy in the subset of men who did not receive hormonal therapy (n = 107)

<table>
<thead>
<tr>
<th></th>
<th>7-yr PFS</th>
<th>7-yr CSS</th>
<th>7-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Observation alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SM+/ECE</td>
<td>70%</td>
<td>99%</td>
<td>94%</td>
</tr>
<tr>
<td>SVI</td>
<td>59%</td>
<td>97%</td>
<td>76%</td>
</tr>
<tr>
<td>p value</td>
<td>0.01</td>
<td>0.02</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Undetectable PSA</th>
<th>Metastases</th>
<th>PCa death</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b) Results of salvage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SM+/ECE</td>
<td>50 (71%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>SVI</td>
<td>6 (40%)</td>
<td>3 (16%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>p value</td>
<td>0.03</td>
<td>0.02</td>
<td>0.08</td>
</tr>
</tbody>
</table>

SM+ = positive surgical margins; ECE = extracapsular extension; SVI = seminal vesicle invasion; PFS = progression-free survival; CSS = cancer-specific survival; OS = overall survival; PSA = prostate-specific antigen; PCa = prostate cancer.
On the whole, less is known about the results of SRT in the contemporary era. Song et al reported the results of SRT in 61 men with a persistent or rising PSA after RP [10]. Although their study was not limited to men with adverse surgical pathology, the majority of men did have ECE or SM+. Overall, 59% of patients had an undetectable PSA after SRT. The estimated 4-yr biochemical PFS, metastasis-free survival, and OS rates were 39%, 82%, and 95%, respectively. In their series, men with a pre-radiation PSA level $>$1 ng/ml and Gleason score $>$8 were significantly more likely to have a failure of SRT.

In 2004, Stephenson et al reported on a multi-institutional cohort of 501 patients treated with SRT [11]. Of the overall population, 67% had a complete response to SRT, defined as a PSA nadir $\leq$0.1 ng/ml. At a median follow-up of 45 mo, 50% developed disease progression, 10% had distant metastases, and 4% died from prostate cancer. On multivariate analysis, the strongest predictors of progression after SRT were a Gleason score of 8–10, PSA level $>$2 ng/ml before RT, negative surgical margins, and SVI. In their study, ECE and lymph node metastases were not significant predictors of progression after RT.

More recently, Stephenson et al created a nomogram to aid in patient selection for SRT based on a large multi-institutional cohort [12]. Overall, they reported a 6-yr progression-free probability of 32% (95%CI, 28–35%) after SRT. In their nomogram, the most important factors to predict the outcome of SRT were the pre-radiation PSA level, Gleason score, PSA doubling time, surgical margin status, hormonal therapy, and lymph node metastases.

In the present study, we found that men with SM+/ECE had an 80% 7-yr PFS rate with observation alone, and 55% of those who failed were then successfully salvaged with RT. Thus, it would be difficult to surpass the 83% long-term rate of undetectable PSA in this group. Taken together with the findings of Stephenson et al, this suggests that a strategy of initial observation followed by SRT is effective for selected low-risk men with these features.

Both our study and that of Stephenson et al found that patients with SVI had a significantly higher progression rate with observation alone. Similarly, SVI was a significant risk factor for biochemical progression among men in the “wait-and-see” arm of the EORTC 22911 trial [13]. Although in our study these men were less likely to respond to SRT, deferring RT until evidence of progression still had favorable results in some of these men.

Several limitations of our study deserve mention. Foremost, it was not a randomized trial; therefore, both patient preferences and physician counseling were reflected in the decision to undergo or defer ART. In addition, other confounding variables likely affected the results, such as hormonal therapy, for which detailed information on its timing was not available in all patients. Because this makes the analysis of treatment effect more difficult, we also included the results separately for men who did not receive hormonal therapy at any time. In addition, detailed information about the RT technique was not available in our database, such as the target definition for various situations. Furthermore, it is possible that using newer radiation techniques or a higher dose, a greater proportion of men may have maintained an undetectable PSA level after SRT. As with surgery, the results of RT may also be influenced by the expertise of the radiation oncologist, and quality assurance is important.

Also, in our database SM+ and ECE were grouped together, so it was not possible to separate these groups for this analysis. Collette et al previously showed that men with SM+/ECE−, SM−/ECE+, and SM+/ECE− had similar biochemical progression rates with a “wait-and-see” approach [13]. However, after pathologic review of a subgroup from the EORTC 22911 trial, a recent update suggested that the greatest treatment effect with ART over observation occurred in patients with SM+ [14].

Other limitations are that many pathologists were involved in reviewing the prostatectomy specimens, and pathologic findings were reported as present or absent in our database. However, the presence of focal versus extensive ECE or the extent and location of SM+ may have affected both the outcomes and clinical decision-making. For example, a man with only a focal microscopic SM+ or, alternatively, minimal ECE with a negative surgical margin may have been more likely to defer initial ART. Thus, further studies with more detailed information on pathologic features would be helpful to further evaluate the utility of ART compared to observation.

In addition, the median follow-up of 53 mo after SRT was relatively short. Additional follow-up is necessary to better assess more distant outcomes, such as metastasis and death. Also, our method for calculating long-term rates of undetectable PSA has not been previously validated. Although we included this calculation to help further elucidate the results of SRT, it is possible that the numbers would have been different using an alternate calculation.

Finally, data on complications after SRT were not available in our database. This information is relevant for treatment decisions and may also be different with the use of modern RT techniques.
5. Conclusions

For men with adverse pathology features in the RP specimen, the necessity and timing for subsequent RT are controversial. Patients with SM+/ECE had a 62% 7-yr PFS survival rate with observation alone, and 56% of those who failed maintained an undetectable PSA level for 5 yr after SRT. The 83% long-term rate of undetectable PSA makes initial observation followed by delayed SRT an excellent strategy for men with these pathologic features. The long-term rate of undetectable PSA was a more modest 50% for men with SVI. Overall, future randomized controlled trials are needed to directly compare the results of adjuvant and salvage radiation strategies for men with adverse surgical pathology.

Author contributions: William J. Catalona had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Loeb, Catalona.
Acquisition of data: Viprakasit, Roehl.
Analysis and interpretation of data: Loeb, Roehl.
Drafting of the manuscript: Loeb, Catalona.
Critical revision of the manuscript for important intellectual content: Loeb, Catalona.
Statistical analysis: Roehl.
Obtaining funding: Catalona.
Administrative, technical, or material support: Viprakasit.
Supervision: Catalona.
Other (specify): None.

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References

Editorial Comment on: Long-Term Rates of Undetectable PSA with Initial Observation and Delayed Salvage Radiotherapy After Radical Prostatectomy
Massimo Maffezzini
Ospedali Galliera, Genova, Italy
massimo.maffezzini@galliera.it

The assumption that isolated, occult local recurrence or persistence of prostate cancer after radical retropubic prostatectomy (RRP) might represent the most likely scenario for patients with adverse pathological features (ie, extracapsular extension (ECE) or positive surgical margins (M+), poor risk, or locally advanced disease) constituted the rationale for studies of radiation therapy (RT) after surgery. The most appropriate timing of the administration of RT—immediately following surgery in an adjuvant setting or delayed until evidence of (biochemical) recurrence appeared in a salvage setting—is a subject for debate.

In randomised studies, adjuvant irradiation showed efficacy in decreasing the risk of prostate-specific antigen (PSA) progression by 50% at 10 yr. Conversely, when considering cancer-specific survival (CSS) and overall survival (OS) as end points, no difference was observed (reference [6] in Loeb et al [1]), although it must be noted that irradiation was also offered to men undergoing progression in the observation arm.

In an analysis of the European Organization for Research and Treatment of Cancer (EORTC) study, it was observed that the hazard ratio for biochemical progression was 0.38 for immediate irradiation and 0.88 for the observation arm (reference [14] in Loeb et al [1]). It is of note that the point where the Kaplan-Meyer curves of the two groups begin to separate falls shortly before the end of the first year of follow-up; in other words, progression in the observation arm was not immediate (see Fig. 3 in Loeb et al [1]).

The study by Loeb and co-authors addresses the approach of initial observation followed by delayed salvage irradiation at the time of progression [1]. The study results are comparable to similar studies of patients treated with salvage radiotherapy (SRT). For example, Loeb et al’s [1] and Stephenson’s (reference [11] in Loeb et al) studies are compared in Table 1.

Loeb et al [1] honestly acknowledged some points that contribute to weakness, at least in part, in this article (and others):

- Randomisation: absent
- Physician counselling and patients’ choice: the chicken or the egg?
- Hormonal treatment in subgroups: blurs results
- Central pathology review: absent
- Long-term, undetectable PSA rate calculation: not validated
- Info on RT unavailable: makes generalisation questionable
- Toxicity from RT, acute, long term: unknown.

Selection bias is not behind the scenes; it is probably onstage already.

We are left with another difficult question to be answered by a clinical trial of patients with comparable pathologic risk features who are randomly assigned to adjuvant radiotherapy (ART) or to SRT. Since the amplitude of the difference of the expected results dictates the numbers of patients to be entered in such a trial, and given that a smashing difference cannot be reasonably anticipated based on the current literature, the trial will be of some complexity.

In the meantime, that piece of information will be increasingly needed as radical prostatectomy is considered for (locally) advanced disease [2]. Although we are still far from port, manuscripts like the one presented here might point to the right heading.

These are the essential problems:

- The sensitivity of PSA—biochemical relapse—is insufficient to locate the disease (deep pelvis, distant sites, or both).
- The addition of RT might be useful only for patients with isolated disease recurrence (or persistence) in the pelvis, whereas it is unnecessary (and potentially harmful) for those with other conditions.
- Radiation toxicity, acute and long term, has to be taken into account when planning treatment.
- In most cases, disease does not progress all of a sudden.

Table 1 – Comparison of studies by Loeb et al [1] and Stephenson (reference [11] in Loeb et al [1])

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Good intermediate risk</th>
<th>M+/ ECE</th>
<th>Dose (Gy)</th>
<th>7-y CSS</th>
<th>7-y OS</th>
</tr>
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<tbody>
<tr>
<td>Stephenson 501</td>
<td>73%</td>
<td>56%</td>
<td>64.8</td>
<td>90%</td>
<td>86%</td>
</tr>
<tr>
<td>Loeb 716</td>
<td>85%</td>
<td>86%</td>
<td>63</td>
<td>98%</td>
<td>93%</td>
</tr>
</tbody>
</table>
In addition to the most acknowledged risk factors, many of which are incorporated into specific tools (reference [12] in Loeb et al [1]), we are beginning to consider other factors, such as serum PSA before diagnosis, the tertiary Gleason pattern, or the presence of cancer-cell clusters within the lymphovascular spaces, and their potential influence on prognosis. Fast PSA kinetics preceding diagnosis [3] and highest tertiary Gleason fractions (ie, any amount of 4 or 5) [4] are likely to herald systemic progression, whereas slow, prediagnosis PSA kinetics, no tertiary Gleason 4 or 5, positive margins, and clusters of cancer cells within the lymphovascular spaces [5] are probably the telltale signs of periprostatic spread. ART may represent an option for patients at risk of persistence or recurrence of disease in the prostatic fossa, and systemic treatment might be an option for patients at risk for distant progression. In the remaining cases, careful follow-up that builds an accurate curve for PSA doubling time (PSA-DT) and takes into account three equally spaced readings (eg, a few weeks after surgery, at 6 mo, and at 12 mo) [6] may guide the choice between SRT and systemic treatment at biochemical recurrence.

References


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