Influential factors in the response to salvage radiotherapy after radical prostatectomy


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KEYWORDS
Prostate neoplasm; Biochemical relapse; Radical prostatectomy; Salvage therapy; Radiation therapy; Prostate specific antigen

Abstract
Objective: To analyze the influential factors in the response in prostatectomized patients with subsequent biochemical relapse (BCR) and treated with salvage radiotherapy (RTP).

Materials and methods: We analyzed 313 patients with pT2/pT3 prostate cancer who were receiving salvage therapy due to biochemical relapse (from a series of 1310 radical prostatectomies between 1989 and 2012). Of the 313 patients, 159 (50.8%) only received androgen deprivation (AD), 63 (20.1%) radiotherapy (RTP) plus concomitant AD and 91 (29.1%) only RTP. Of these, 57 (62.6%) have maintained complete response and 34 (37.4%) had failure response with post-RTP BCR.

Results: Study of the group treated exclusively with salvage RTP. Ninety-one patients were treated with salvage RTP. Median follow-up was 6.4 years and median to recurrence 11 months. Post-RTP biochemical relapse-free survival (PRBRFS) was 68 ± 7% and 30 ± 10% in 5–10 years. Median PRBRFS was 7.3 years (6.3–8.3). Initial PSA (HR: 1.08; 95% CI: 1.01–1.1 P = 0.02) with best PSA cut-off point PSA > 20 ng/ml (HR: 13.6; 95% CI: 2.1–86 P = 0.005) and PSA pre-RTP (HR: 1.9; 95% CI: 1.2–3.3; P = 0.009), best PSA cut-off point PSA preRTP 0.92 ng/ml (HR: 4.5; 95% CI: 1.3–15.6; P = 0.01) showed independent influence in the response in the multivariate study. PRBRFS at 5 years was 81 ± 9% versus 58 ± 9% with initial PSA < 20 or >20 ng/ml (P = 0.03). PRBRFS at 5 years was 93 ± 5% versus 53 ± 10% according to PSA pre-RTP < 0.9 or >0.9 ng/ml (P = 0.02).

Conclusions: In patients treated with salvage RTP after radical prostatectomy, the preoperative PSA > 20 ng/ml and PSA preRTP > 0.92 ng/ml show an independent influence on the response.

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Factores influyentes en la respuesta al rescate con radioterapia tras prostatectomía radical

Resumen

Objetivo: Analizar en los pacientes prostectomizados con posterior progresión bioquímica (PB) y tratados con radioterapia de rescate (RTP) los factores influyentes en la respuesta. Material y métodos: Analizamos 313 pacientes con cáncer de próstata pT2/pT3 que reciben tratamiento de rescate por PB (de una serie de 1.310 pacientes operados entre 1989-2012). De los 313 pacientes 159 (50,8%) reciben solo depuración androgénica (DA), 63 (20,1%) radioterapia (RTP) más DA concomitante y 91 (29,1%) solo RTP, de los cuales 57 (62,6%) mantienen respuesta completa y 34 (37,4%) fracaso del tratamiento. Resultados: Estudio del grupo tratado solo con RTP de rescate: 91 pacientes son tratados con RTP de rescate. Mediana de seguimiento 6,4 años. Mediana hasta progresión 11 meses. La supervivencia libre de progresión bioquímica post-RTP (SLPBPR) es de 68±7% y 30±10% en 5 y 10 años y la mediana de SLPBPR 7,3 años (6,3-8,3). En el análisis multivariado presentan influencia independiente en la respuesta: el PSA inicial (HR: 1,08; IC 95%: 1,01-1,1; p = 0,02) con mejor punto de corte PSA > 20 ng/ml (HR: 13.6; IC 95%: 2.1-86; p = 0,005) y PSA pre-RTP (HR: 1,9; IC 95%: 1,2-3,3 p=0,009), mejor punto de corte PSA preRTP de 0,92 ng/ml (HR: 4.5; IC95% 1,3-15,6; p=0,01). SLPBPR a 5 años 81 ±9 frente a 58 ±9% con PSA inicial < 20 o > 20 ng/ml (p=0,03). SLPBPR a 5 años 93 ±5% frente a 53 ±10% según PSA pre-RTP < 0,9 o >0,9 ng/ml (p=0,02).

Conclusiones: En los pacientes prostatectomizados tratados con RTP de rescate el PSA preoperatorio > 20 ng/ml y el PSA preRTP > 0,92 ng/ml tienen influencia independiente en la respuesta. © 2013 AEU. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

Between 15 and 40% of patients treated with radical prostatectomy show biochemical progression (BP) in time. The indication for salvage radiotherapy (RTP) in patients treated with surgery is a much-discussed topic. Only in English more than 200 articles have been published since 1990. Regrettably, the general attitude is still relatively reluctant. It is estimated that 50% of urologists remain watchful waiting, 30% indicate salvage with androgen deprivation (AD) and the rest with RTP.

Among the various treatment options with RTP, it is the only potentially curative option. However, 10–61% of the irradiated ones show post-RTP BP due to treatment failure. It is essential to know the influential clinicopathologic factors in radiotherapy failure. The therapeutic approach is largely dependent on this knowledge in patients operated with BP.

Most published studies belong to the Anglo-Saxon world, with probably different connotations to ours. Thus, the objective of this study is to evaluate the factors influencing the response in patients undergoing radical prostatectomy with subsequent BP and treated with salvage RTP.

Materials and methods

We retrospectively analyzed 313 patients with pT2-pT3 prostate cancer (from a series of 1310) operated between January 1989 and December 2012 and receiving salvage treatment due to BP.
after completion of the treatment, then, every 6 months for a total of 3 years, and later every year. Following the guidelines of the PSA Working Group, we defined biochemical recurrence of PSA as that determination of PSA ≥0.4 ng/ml (Hybritech®) obtained at least 30 days after surgery, and then confirmed with an equal or greater value.

Only the patients who neutralize the PSA after radical prostatectomy and that subsequently show BP constantly receiving salvage treatment are included for the study. The patients with lymph node involvement and those who do not neutralize the PSA receive immediate adjuvancy, being excluded from all studies, since there are previous studies in which it is revealed that patients who do not get to neutralize the PSA show worse prognosis.12,13

We defined as complete response the negativization of the PSA figures after RTP and its persistence to the end of the study. We call the rest of the results (not maintained response, partial response, and no response) treatment failure.

Of the 313 (23.9%) patients finally included, 159 (50.8%) received only AD, 63 (20.1%) RTP plus concomitant AD, and 91 (29.1%) only RTP, of which 57 (62.6%) maintain complete response and 34 (37.4%) treatment failure.

Salvage radiotherapy was administered in sessions of 5 days per week for 8 weeks with a minimum dose of 65 Gy. Three-dimensional conformal radiotherapy (3DCRT) was applied in 4 fields on the prostate bed, including the theoretical area of the bladder neck, the tissue around the bed, and the theoretical location of seminal vesicles. There are no phase I studies evaluating the most appropriate dose. It seems that higher doses of 65 Gy provide better results14,15 but the American Society for Therapeutic Radiology and Oncology (ASTRO) after a consensus meeting16 recommends 64 Gy.

Full AD therapy was prescribed by means of quarterly or semiannual injections for a minimum of 2 years.

The criterion for selecting a particular salvage treatment depended on the personal decision of each responsible physician.

For the calculation of the PSA doubling time (PSA-DT in months) at least 2 determinations of PSA (ng/ml) were collected after biochemical progression, and it was calculated using the formula: Ln 2 × DT/Log PSA2 – Log PSA1.

To compare qualitative variables, contingency tables and Chi-square or Fisher’s exact F are used; Student’s ‘t’-test was used to compare quantitative variables and non-parametric tests (Mann Whitney U test) for those variables which do not follow a normal distribution. The normality of continuous quantitative variables was determined using the Kolmogorov–Smirnov and Shapiro–Wilk tests.

When determination of a cut-off point was required in continuous variables we used ROC curves.

Actuarial survival was studied with the Kaplan–Meier method and for the comparison of survival curves we used the Log-Rank test.

To determine influential variables on survival we used Cox regression (univariate and multivariate). The p values of statistical significance and hazard ratios with their respective confidence intervals were calculated and estimated respectively by means of the Bootstrapping technique with 1000 replications.

Study of the group treated only with salvage RTP. Factors influencing the response are: the median time from surgery to the BP for the 91 patients treated with RTP is 11 months (6–118); the median follow-up of the radiated group is 6.4 years (0.7–19); for the 34 (37.4%) with failure it is 8.2 years and 5.5 years for the 57 (62.6%) who maintain complete response to treatment.

The clinicopathologic characteristics of the radiated patients and the differences between those who show radiotherapy failure and those maintaining complete response during the study are summarized in Table 1.

At the end of the study 34 out of 91 (37.4%) had treatment failure and show post-RTP BP. The median time from the salvage with RTP to post-RTP BP is 33 months (0–155). This group shows worse clinicopathologic characteristics (initial PSA [ng/ml], clinical Gleason, D’Amico groups, pT3b, Ki-67, PSA-DT [months], pre-RTP PSA [ng/ml]; p < 0.05) compared to the 57 (62.6%) maintaining a complete response.

The PRBDFS of the group treated with salvage radiotherapy (91 patients) is 68 ± 7% and 30 ± 10% in 5 and 10 years. Median PRBDFS is 7.3 years (6.3–8.3) (Fig. 1).

In the univariate analysis the following are influential in PRBDFS: initial PSA (ng/ml) (HR: 1.04; 95% CI: 1.003–1.09; p < 0.03), the best cut-off point being the PSA > 20 ng/ml (HR: 4.6, 95% CI: 1.3–16.6; p = 0.02), pT3b (HR: 2.9; 95% CI: 1.07–7.9; p = 0.03), PSA-DT (months) (HR: 0.8, 95% CI: 0.6–0.9; p = 0.05), best cut-off point 3 months (HR: 0.03,
Influential factors in the response to salvage radiotherapy

Table 1 Descriptive study of the group treated with radiotherapy. Comparison of the clinicopathologic characteristics according to the type of response.

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Radiated group 91 (100%)</th>
<th>Complete response 57 (62.6%)</th>
<th>Failure 34 (37.4%)</th>
<th>p≤*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 (48–80)</td>
<td>63.6 (48–77)</td>
<td>64.7 (49–80)</td>
<td>0.4</td>
</tr>
<tr>
<td>Initial PSA (ng/ml)</td>
<td>13.7 (4.2–65)</td>
<td>11.7 (4.2–54)</td>
<td>17.2 (4.2–65)</td>
<td>0.1</td>
</tr>
<tr>
<td>PSA &gt; 20 ng/ml</td>
<td>15 (16.5%)</td>
<td>4 (7%)</td>
<td>11 (32.3%)</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.1 (21.5–48)</td>
<td>28.6 (21.5–48)</td>
<td>26.7 (22–33)</td>
<td>0.6</td>
</tr>
<tr>
<td>Clinical Gleason</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–6</td>
<td>49 (53.8%)</td>
<td>34 (59.6%)</td>
<td>15 (44.1%)</td>
<td>0.05</td>
</tr>
<tr>
<td>7</td>
<td>22 (24.2%)</td>
<td>16 (28.1%)</td>
<td>6 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>8–10</td>
<td>20 (21.9%)</td>
<td>7 (12.3%)</td>
<td>13 (38.2%)</td>
<td></td>
</tr>
<tr>
<td>Risk groups (Dâmico)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>22 (24.2%)</td>
<td>18 (31.6%)</td>
<td>4 (11.7%)</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>42 (46.1%)</td>
<td>27 (47.3%)</td>
<td>15 (44.1%)</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>27 (29.6%)</td>
<td>12 (21%)</td>
<td>15 (44.1%)</td>
<td></td>
</tr>
<tr>
<td>Pathological variables</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pathological Gleason</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2–6</td>
<td>29 (31.8%)</td>
<td>22 (38.6%)</td>
<td>7 (20.6%)</td>
<td>0.6</td>
</tr>
<tr>
<td>7</td>
<td>30 (32.9%)</td>
<td>16 (28%)</td>
<td>14 (41.2%)</td>
<td></td>
</tr>
<tr>
<td>8–10</td>
<td>32 (35.2%)</td>
<td>19 (33.3%)</td>
<td>13 (38.2%)</td>
<td>0.2</td>
</tr>
<tr>
<td>pT2</td>
<td>43 (47.2%)</td>
<td>28 (49.1%)</td>
<td>15 (44.1%)</td>
<td></td>
</tr>
<tr>
<td>pT3a</td>
<td>27 (29.7%)</td>
<td>20 (35.1%)</td>
<td>7 (20.5%)</td>
<td>0.04</td>
</tr>
<tr>
<td>pT3b</td>
<td>21 (23.1%)</td>
<td>9 (15.8%)</td>
<td>12 (35.3%)</td>
<td></td>
</tr>
<tr>
<td>Affected surgical margin</td>
<td>52 (57.1%)</td>
<td>34 (59.6%)</td>
<td>18 (52.9%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Ki-67</td>
<td>10% (1–55)</td>
<td>5.5% (1–15)</td>
<td>12.7% (2–55)</td>
<td>0.02</td>
</tr>
<tr>
<td>preRTP PSA (ng/ml)</td>
<td>2.1 (0.4–23)</td>
<td>0.9 (0.4–4)</td>
<td>4.7 (0.4–23)</td>
<td>0.007</td>
</tr>
<tr>
<td>preRTP PSA &gt; 0.92 (ng/ml)</td>
<td>38 (41.8%)</td>
<td>18 (31.6%)</td>
<td>20 (58.8%)</td>
<td>0.006</td>
</tr>
<tr>
<td>PSA-DT (months)</td>
<td>10.1 (2–23.3)</td>
<td>11.7 (3.2–23.3)</td>
<td>5.4 (2–10.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>RTP dose (Gy)</td>
<td>66.4 (65–75)</td>
<td>65.5 (65–75)</td>
<td>66.1 (65–71)</td>
<td>0.7</td>
</tr>
<tr>
<td>Median to BP (months)</td>
<td>11.4 (6–120)</td>
<td>12.5 (6–120)</td>
<td>9.6 (6–117)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Data presented as median and range or number (%).
 Statistical significance for the comparison of means of the variables age (years), initial PSA (ng/ml), BMI (kg/m²), Ki-67, pre-RTP PSA (ng/ml), PSA-DT (months), RTP dose (Gy), and median to BP (months) has been determined using the non-parametric Mann Whitney U test. Ki-67 was determined in 47 patients, 23 from the group with complete response and 24 from the group with treatment failure. The result was expressed in percentage of stained cells.

*p < 0.05.

95% CI: 0.020–0.3; p = 0.005), and pre-RTP PSA (ng/ml) (HR: 1.9; 95% CI: 1.2–3.1; p = 0.005). The best cut-off point is the pre-RTP PSA of 0.92 ng/ml (HR: 4.1; 95% CI: 1.4–11.6; p = 0.002).

In the multivariate one, the following have independent influence: the initial PSA (ng/ml) (HR: 1.08; 95% CI: 1.01–1.1; p = 0.02) with a better PSA cut-off point >20 ng/ml (HR: 13.6; 95% CI: 2.1–86; p = 0.005), and pre-RTP PSA (ng/ml) (HR: 1.9, 95% CI: 1.2–3.3; p = 0.009), better pre-RTP PSA cut-off point of 0.92 ng/ml (HR: 4.5, 95% CI: 1.3–15.6, p = 0.01) (Table 2).

The PRBFRS at 5 years is 93 ± 5% for the group with pre-RTP PSA <0.9 ng/ml (58.2%), and 53 ± 10% for the pre-RTP PSA group >0.9 ng/ml (41.8%) (p = 0.02). Patients with initial PSA <20 ng/ml (83.5%) have a PRBFRS at 5 years of 81 ± 9% versus 58 ± 9% of patients with initial PSA >20 ng/ml (16.5%) (p = 0.03).

Discussion

In the patients with localized prostate cancer treated surgically with subsequent BP there is no consensus based on scientific evidence on what the best type of treatment is. There have not been published to date randomized, double-blind studies with enough patients to make any statement.

There are 3 determining factors in choosing salvage RTP: the difficulty in determining whether the recurrence is local or systemic, the benign natural history of patients with BP, and the lack of evidence of improved survival. These three facts, despite being the only curative option for patients with recurrence, determine that less than 50% of those treated complementarily receive RTP.

We know that the rescue with RTP is not equally effective in all patients. Around 10–61% fail treatment and
show post-RTP BP. This is because there are factors that significantly influence this type of response.

In large series of patients operated and subsequently treated with salvage RTP, the preoperative PSA (ng/ml), the pre-RTP PSA (ng/ml), PSA-DT (months), Gleason 8–10, surgical margins, and seminal vesicle involvement have independent influence on PRBRFS. In our study, the initial PSA (ng/ml), the pre-RTP PSA (ng/ml), PSA-DT (months), and pathological stage T3b influence the univariate one, but only initial PSA (>20 ng/ml) and pre-RTP (>0.9 ng/ml) are influential in the multivariate one.

In most studies, patients with preoperative PSA > 20 ng/ml were excluded from treatment with salvage RTP because it is exceptional that they do not associate other negative risk factors. The ideal patient is that who has a presurgery PSA < 10 ng/ml. In our case, it was not an exclusion criterion and it is an independent influencing factor.

The involvement of the seminal vesicle is such a negative factor that it usually excludes RTP as well, and the same thing happens when Gleason is > 8. There is a recent study of patients with seminal vesicle involvement in which 47 T3b are treated with salvage RTP and the results are discouraging, at 4 years the PRBRFS is only 18%.

Our experience with the 21 T3b who received radiotherapy is not so negative, at 5 years the PRBRFS is 59 ± 12%, 9 patients remaining at risk (data not shown), and according to our results, the involvement of the seminal vesicle is an influential factor in the univariate study. The same cannot be said for the pathological Gleason. It is an historical series. We assume it is due to the evolution of the type of patient candidate for radical prostatectomy in the last 20 years, due to changes in the criteria for pathologic classification with a tendency to increase Gleason and the phenomena of migration of the clinicopathological stages that this disease has suffered.

As for the PSA-DT, there is a preliminary study with 1200 patients in which it is concluded that it has no independent influence. In our study, the PSA-DT only has an influence on the univariate one.

The PSA figure at the time of starting RTP is probably the most influential factor. It appears in all studies. We have not defined a strict cut-off point, it has gone down progressively. The first serious study (1997) established the cut-off point at 2.7 ng/ml, but the patients with a PSA > 2.7 ng/ml had a PRBRFS of 0%. Since then the cut-off point has been declining, and what the evidence of 16 studies published suggests is that the ideal number is 1 ng/ml (10 of them, which are the most recent, consider the cut-off point 1 ng/ml) and that a PSA > 2 ng/ml has a PRBRFS of 0–31% (mean: 10%) in 3 years. With a PSA < 1 ng/ml, the PRBRFS in 3 years is 40–75% and in 5 years is 30–50%.

The Consensus Conference of the ASTRO 1999, which concludes that we cannot determine risk groups with the clinicopathological variables, indicates that it is a recommended condition that the pre-RTP PSA does not exceed 1.5 ng/ml.

The most important retrospective study, with 1540 patients, multi-institutional with 17 tertiary centers, with a median follow-up of 54 months, shows that the PRBRFS is 32% in 6 years and it depends on pre-radiation PSA (if it is <0.5; 0.5–1; 1.5–5; >5.5) and the PRBRFS is 48, 40, 28 and 18%. The problem is that in that study 14% received concurrent AD.

The PRBRFS in our series of radiated groups is 68 and 30% in 5 and 10 years. Taylor et al. show at 5 years a PRBRFS of 66%, the results being consistent with what have been published. For these authors, the pre-RTP PSA (ng/ml) is the most influential prognostic factor, so their levels prior to RTP determine the type of response and, therefore, the survival rates, and they are not alone in attributing pre-RTP PSA a determining factor. Tiguert et al. obtained at 4 years a significantly decreased PRBRFS, from 74 to 22% when the pre-RTP PSA is >2 ng/ml. In our series, the PRBRFS in 5 years decreases from 93 to 53% when the pre-RTP PSA exceeds 0.92 ng/ml.

Recent studies also show a greater effectiveness of radiotherapy rescue when the pre-RTP PSA is <1 ng/ml. According to Nudell et al., when patients are treated with salvage RTP with a pre-RTP PSA lower than 1 ng/ml, the PRBRFS is similar to that of those treated with adjuvant RTP.

Salvage treatment with RTP has not shown improvement in overall survival (there are no randomized, prospective studies), it improves progression-free survival and may...
In influential factors in the response to salvage radiotherapy

decrease the risk of local recurrence. A paradigmatic example is a multicenter, retrospective study of 500 patients treated with salvage RTP in which SS is 90%, overall 85%, and PRBRFS 45% in 4 years. Median follow-up is 45 months and median to progression is 12.5 months.

According to our results, the SS in the radiated group at 5 and 10 years is 98 ± 1% and 82 ± 6% (data not shown). Our biggest limitation certainly lies in the median follow-up, since in prostate cancer we need to be cautious to talk about SS with a median lower than 12 years. At this point, our follow-up is still short.

Ki-67 has not been determined in all patients, only in 46.9% (147/313), and specifically in 51.6% (47/91) of the radiated group.

Furthermore, it is a single center study not centralized in which the small number of patients and the lack of randomization in the salvage treatment received prevents us from making strong statements.

Conclusions

In prostatectomized patients with subsequent BP treated with salvage RTP the PRBRFS is 68 ± 7% and 30 ± 10% at 5 and 10 years. In the multivariate study, the PSA > 20 ng/ml and the pre-RTP PSA > 0.9 ng/ml have independent influence on the response.

Conflict of interest

The authors declare that they have no conflict of interest.

References


