Evaluation and Management of Prostate-specific Antigen Recurrence After Radical Prostatectomy for Localized Prostate Cancer

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A radical prostatectomy has been established as one of the standard management options for localized prostate cancer. However, a substantial proportion of patients who undergo a radical prostatectomy develop prostate-specific antigen (PSA) recurrence which is commonly defined as a PSA cut-off point value of 0.2 ng/ml. Although the management of PSA recurrence after radical prostatectomy may depend on the site of recurrence, it is quite difficult to identify the recurrent lesion accurately based on the currently available imaging technology. Patients who have surgical margin involvement or a Gleason score <7 based on the radical prostatectomy specimens, who do not have nodal or seminal vesicle involvement, and who develop a PSA recurrence >1–2 years after surgery with a doubling time of >1 year, and whose pre-treatment PSA is <1.0–1.5 ng/ml are considered to benefit from local treatment with at least 64 Gy of salvage radiotherapy. Patients with different characteristics are considered to have distant metastases or both local lesions and distant metastases, and thus may be candidates for hormonal manipulation rather than radiotherapy. Since local recurrent lesions are considered to be quite small at the early stage of PSA recurrence, hormonal manipulation may be sufficient to prevent disease progression instead of radiotherapy. However, the optimal type and timing of hormonal manipulation remain to be elucidated. As a result, no consensus regarding the treatment for PSA recurrence after radical prostatectomy has yet been reached.

Key words: prostate cancer – radical prostatectomy – prostate-specific antigen – recurrence – salvage radiotherapy – hormonal therapy

INTRODUCTION

A radical prostatectomy has been established as the primary curative procedure for the treatment of localized prostate cancer. However, despite a marked downward stage shift due to widespread serum prostate-specific antigen (PSA) screening and improvement in surgical techniques, approximately one-third of all patients still demonstrate disease recurrence after surgery (1–8). For the majority of these patients, the first sign of recurrent disease is a rising PSA level without either clinical or radiographic evidence of disease—the so-called ‘PSA recurrence’ or ‘biochemical failure’. Rising PSA levels after radical prostatectomy may be due to a local recurrence in the prostatic bed, occult distant metastases or a combination of both. Unfortunately, however, it is quite difficult to identify recurrent lesions accurately at an early stage of PSA recurrence. Local recurrence may be cured using salvage external-beam radiotherapy, whereas distant metastases cannot be cured with such local radiotherapy and such cases are instead indicated for systemic hormonal therapy. At present, there have been few studies comparing the outcomes of radiotherapy and endocrine therapy for PSA recurrence, and no consensus regarding the optimal treatment for PSA recurrence has yet been reached. The majority of patients with PSA recurrence after radical prostatectomy tend to be relatively young and healthy. Therefore, the treatment for PSA recurrence should aim not only to improve survival but also to preserve the quality of life. This review article discusses the evaluation and management of PSA recurrence after radical prostatectomy.
DEFINITION OF PSA RECURRENCE AFTER RADICAL PROSTATECTOMY

Since serum PSA is produced almost exclusively by prostatic epithelial cells and its half-life is 3.15 days (9), it should decline to 0.78% of the original value by seven half-lives, and therefore it usually reaches an undetectable level within 21–30 days after radical prostatectomy (10,11). As a result, persistently detectable or subsequent rising serum PSA levels after radical prostatectomy indicate either residual prostate cancer or recurrence.

In order to standardize the definition of PSA recurrence after radical prostatectomy, various PSA cut-off points, such as >0.1 ng/ml (12), >0.2 ng/ml (8,13,14), >0.4 ng/ml (15,16) and >0.5 ng/ml (17) have been investigated. Amling et al. (16) suggested that a PSA level of ≥0.4 ng/ml may be the most appropriate cut-off point to use since a significant number of patients with lower PSA did not have a subsequent PSA progression. Freedland et al. (18) reported the 1 and 3 year risk of additional PSA progression in patients with a post-operative PSA value >0.2 ng/ml to be 86 and 100%, respectively, and concluded that a PSA value >0.2 ng/ml is an appropriate cut-off point to define PSA recurrence after radical prostatectomy. Pound et al. (8) reported that serum PSA level increases >0.2 ng/ml demonstrated an exponential growth curve if observed without any treatment, and he thus defined PSA recurrence as a detectable PSA level of at least 0.2 ng/ml. In patients with pathological stage C prostate cancer and at least one post-operative serum PSA level of 0.1 ng/ml, Schild et al. (19) found the subsequent freedom from failure to be 80% at 23 months in comparison with only 13% in patients with at least one post-operative PSA level of 0.2 ng/ml. They therefore concluded that a serum PSA level of 0.2 ng/ml is reflective of residual prostate cancer. Regarding the European Association of Urology (EAU) guidelines on prostate cancer, Aus et al. (20) mentioned that a serum PSA level of >0.2 ng/ml is mostly associated with residual or recurrent disease. The European Consensus Group (21) also defined PSA recurrence after radical prostatectomy as a value of 0.2 ng/ml and one subsequent rise, and concluded that there is a major risk of progression when the PSA level reaches 0.4 ng/ml (Table 1).

The PSA recurrence-free survival after radical prostatectomy may be influenced by the timing of PSA determination as well as the PSA cut-off point. Oh et al. (22) surveyed the follow-up strategies after radical prostatectomy of 4467 American Urological Association urologists and reported that 1050 (24%) who returned evaluable surveys generally recommended office visits with a digital rectal examination (DRE), serum PSA and urinalysis approximately 3 or 4 times yearly during post-operative year 1, gradually tapering off to once or twice yearly by post-operative years 5–10. According to the EAU guidelines for the follow-up of prostate cancer after treatment with curative intent, PSA measurement is recommended to be performed at 3, 6 and 12 months after treatment, then every 6 months until 3 years, and thereafter annually (20). Pound et al. (8) reported that in patients with PSA recurrence, 45% developed the condition in the first 2 years after radical prostatectomy, 76% within the first 5 years, and the remaining 23% >5 years after surgery. This indicates that a prolonged PSA follow-up is necessary after radical prostatectomy.

The introduction of ultrasensitive PSA assays has now made it possible to predict PSA recurrence earlier. Doherty et al. (23) reported that only 3% of patients who achieved an undetectable (<0.01 ng/ml) PSA nadir had additional PSA recurrence defined as three consecutive rises in PSA, whereas 76% of those who did not reach undetectable levels had PSA recurrence. Ellis et al. (24) also reported that ultrasensitive PSA assays could detect PSA recurrence with a significant lead time (12.7–22.5 months) over conventional assays on condition that PSA recurrence was defined as >0.008 ng/ml on

Table 1. Principal conclusions of the European Consensus Group on the management of PSA relapse in prostate cancer (21)

<table>
<thead>
<tr>
<th></th>
<th>Total prostate-specific antigen (PSA) is the most widely used detection tool for prostate cancer; in the PSA range 2–6 ng/ml.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>PSA relapse means treatment failure.</td>
</tr>
<tr>
<td>3.</td>
<td>PSA relapse after radical prostatectomy is defined as a value of 0.2 ng/ml and one subsequent rise. There is a major risk of progression when PSA reaches 0.4 ng/ml.</td>
</tr>
<tr>
<td>4.</td>
<td>The ultrasensitive PSA assay should be used for monitoring patients but not for decision making.</td>
</tr>
<tr>
<td>5.</td>
<td>Secondary treatment after local failure of surgery should be instigated before PSA levels reach 1.0–1.5 ng/ml.</td>
</tr>
<tr>
<td>6.</td>
<td>The ASTRO definition of PSA failure should be used after radiotherapy. An alternative definition that might be considered is three cumulative rises above nadir.</td>
</tr>
<tr>
<td>7.</td>
<td>Treatment of PSA failure after local therapy depends on whether progression is local or distant. This process is best carried out using a continuous assessment process in the form of a nomogram or artificial neural network.</td>
</tr>
<tr>
<td>8.</td>
<td>Treatment of distant failure involves hormonal manipulation; the type and timing of therapy are based on physician and patient preference.</td>
</tr>
<tr>
<td>9.</td>
<td>For treatment of local failure after radical prostatectomy, salvage radiotherapy can be considered with or without hormonal therapy.</td>
</tr>
<tr>
<td>10.</td>
<td>Treatment of radiotherapy failure will require prostate biopsy, with imaging conducted on patients with a positive biopsy to confirm absence of distant failure. Local failure should subsequently be treated in well-selected patients with a choice of salvage radical prostatectomy, high-intensity-focused ultrasound, cryotherapy or external beam radiotherapy.</td>
</tr>
<tr>
<td>11.</td>
<td>A PSA level of &lt;0.4 ng/ml after hormonal therapy can be considered an indicator of a positive response. The use of PSA to monitor second- or third-line interventions is not totally reliable.</td>
</tr>
<tr>
<td>12.</td>
<td>Remember that treating the patient, and not the PSA, remains the physician’s primary goal.</td>
</tr>
</tbody>
</table>
FACTORS PREDICTING PSA RECURRENCE AFTER RADICAL PROSTATECTOMY

The local extent of disease on a DRE (T stage), serum PSA level and Gleason score from prostate biopsy specimens have all been considered to be important factors for predicting the pathological stage (pT stage) for patients with clinically localized prostate cancer (27,28). Regarding the pre-operative PSA level, Partin et al. (27) reported that 64, 50, 35 and 16% of patients with a serum PSA level <4, 4–10, 10–20 and >20 ng/ml, respectively, have pathologically organ-confined disease. Pelvic lymph node involvement is found in nearly 3, 9 and 17% of patients with a serum PSA level <10, 10–20 and >20 ng/ml, respectively. As a result, patients with a serum PSA level between 10 and 20 ng/ml are at an intermediate risk for PSA recurrence, while those with a serum PSA level >20 ng/ml represent a high-risk population for developing PSA recurrence after radical prostatectomy.

Regarding the Gleason score of biopsy specimens, Partin et al. (27) reported that 55, 29 and only 17% of the patients with a Gleason score of ≤6, of 7 and of ≥8 based on biopsy specimens, respectively, have pathologically organ-confined disease. Pelvic lymph node involvement is found in nearly 3, 10 and 20% of patients with a Gleason score of ≤6, of 7 and of ≥8, respectively. They (27,29,30) constructed a nomogram based on these pre-operative parameters (Partin tables) in the 1990s to assist urologists in pre-operatively predicting the final pathological stage. The Partin tables have recently been updated to reflect the dramatic change in the stage of prostate cancer at presentation during the past decade (28). Using the Partin tables, information regarding the probability of various pathological stages, such as organ-confined disease, extraprostatic extension, seminal vesicle or lymph node involvement, is provided pre-operatively. Such pathological stages can serve as an excellent surrogate for the outcome after radical prostatectomy.

The Gleason score of radical prostatectomy specimens is also an important factor for predicting PSA recurrence after radical prostatectomy (29,31). The presence of a Gleason grade ≥4, or a Gleason score >7 on radical prostatectomy specimens is predictive of a high-risk for PSA recurrence (31–33). Khan et al. (34) constructed a nomogram that was simple to use and divided the probability of long-term PSA recurrence-free survival into four groups according to the prostatectomy Gleason score, pathological stage and surgical margin status: namely, excellent, good, moderate and low (Table 2). Group 1 consists of patients who have an excellent PSA recurrence-free survival (95% at 10 years); they have a Gleason score of ≤6, organ-confined or extraprostatic extension of the disease and negative surgical margins. Group 2 includes patients who have a good PSA recurrence-free survival (72% at 10 years); they have a Gleason score of ≥7, organ-confined or extraprostatic extension of the disease and negative surgical margins, or a Gleason score of ≤6, organ-confined or extraprostatic extension of the disease and positive surgical margins. Group 3

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th>Gleason score</th>
<th>Surgical margin status</th>
<th>5-year bNED (%)</th>
<th>10-year bNED (%)</th>
<th>Prognosis group</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC or EPE</td>
<td>2–6</td>
<td>Negative</td>
<td>97 (95–98)</td>
<td>95 (92–96)</td>
<td>Excellent</td>
</tr>
<tr>
<td>OC or EPE</td>
<td>7</td>
<td>Negative</td>
<td>86 (82–90)</td>
<td>72 (62–80)</td>
<td>Good</td>
</tr>
<tr>
<td>OC or EPE</td>
<td>2–6</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OC</td>
<td>8–10</td>
<td>Positive/negative</td>
<td>62 (51–70)</td>
<td>41 (29–55)</td>
<td>Moderate</td>
</tr>
<tr>
<td>EPE</td>
<td>8–10</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPE</td>
<td>7–10</td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SV</td>
<td>2–10</td>
<td>Positive/negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LN</td>
<td>2–10</td>
<td>Positive/negative</td>
<td>37 (26–48)</td>
<td>13 (4–26)</td>
<td>Low</td>
</tr>
</tbody>
</table>

bNED, biochemical recurrence-free survival; OC, organ confined; EPE, extraprostatic extension; SV, positive seminal vesicles but negative lymph nodes; LN, positive lymph nodes. The numbers in parentheses are the 95% confidence intervals.

Table 2. Estimation of 5 and 10-year likelihood of biochemical recurrence-free survival and four prognosis groups determined by pathological stage, surgical margin status and prostatectomy Gleason score (34)
consists of patients who have moderate PSA recurrence-free survival (41% at 10 years); they have a Gleason score of 7–10 with extraprostatic extension and positive surgical margins, or a Gleason score of 8–10 with extraprostatic extension, or positive seminal vesicle involvement. Group 4 consists of patients who have a low PSA recurrence-free survival (13% at 10 years); they have disease involvement in the pelvic lymph nodes.

In addition to standard pathological examinations, various histopathological determinants and molecular markers have been evaluated to predict PSA recurrence and survival. Bauer et al. (35) reported the p53 tumor suppressor gene expression and bcl-2 protooncogene expression to be significant risk factors for PSA recurrence after radical prostatectomy. However, the predictive value of these molecular markers remains controversial (36,37). The expression of Ki-67 (36) and p27 (38), apoptotic index (36), DNA ploidy (39) and tumor angiogenesis (microvessel density) (40) have also been reported to be possible predictive factors of PSA recurrence after radical prostatectomy.

**NATURAL HISTORY OF PSA RECURRENCE**

It has become apparent that the outcome of patients with PSA recurrence after radical prostatectomy is extremely heterogeneous, although there have only been a few reports providing direct information on the long-term natural history of PSA recurrence. Pound et al. (8) provided an excellent account of the natural history of PSA recurrence after radical prostatectomy by stratifying patients into varying risks for the development of metastatic disease or death. They (8) reviewed the outcome of 1997 patients, who received radical prostatectomy and pelvic lymphadenectomy by a single surgeon for clinically localized (stage T1, T2 and T3a) prostate cancer between 1982 and 1997, with a median follow-up of 5.3 years, and thus demonstrated that metastatic disease was predictive of the time until death. Men who developed metastases within 1–3 years following surgery tended to die from cancer at a higher rate than those who developed metastases >4 years after surgery.

Once patients developed metastatic disease, the median actuarial time to death was 5 years, and the cancer-specific survival at 10 and 15 years following surgery was 94 and 91%, respectively (8). The time interval from surgery to the development of metastatic disease was predictive of the time until death. Men who developed metastases within 1–3 years following surgery tended to die from cancer at a higher rate than those who developed metastases >4 years after surgery.

**SITE OF RECURRENCE**

It is important to distinguish whether an increase in the PSA level after radical prostatectomy is due to local recurrence, distant metastases or a combination of both, because the management regimen is determined according to the recurrence pattern. Pound et al. (4) reported that approximately one-third of the patients who eventually developed clinical recurrence had local evidence of disease and 70% had distant metastasis with or without local recurrence. Other investigators also estimated a low probability for local recurrence, ranging between 10 and 25% (11,43).

Many approaches have been attempted to identify the site of recurrence. Regarding a DRE, several investigators have demonstrated that >50% of the patients with biopsy-proven local recurrence have no abnormalities on DRE (44–46). Lightner et al. (47) mentioned that an induration in the prostatic fossa may be secondary to a benign scar rather than Table 3. Estimation of metastasis-free rates following PSA failure after radical prostatectomy (8)

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Metastasis-free survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 years</td>
</tr>
<tr>
<td>All men with PSA recurrence</td>
<td>78 (73–84)</td>
</tr>
<tr>
<td>Gleason score 5–7</td>
<td>86 (79–90)</td>
</tr>
<tr>
<td>PSA recurrence ≥2 years</td>
<td>89 (81–94)</td>
</tr>
<tr>
<td>PSA doubling time &gt;10 months</td>
<td>95 (83–96)</td>
</tr>
<tr>
<td>PSA doubling time ≤10 months</td>
<td>82 (54–94)</td>
</tr>
<tr>
<td>PSA recurrence &gt;2 years</td>
<td>80 (68–88)</td>
</tr>
<tr>
<td>PSA doubling time &gt;10 months</td>
<td>79 (65–88)</td>
</tr>
<tr>
<td>PSA doubling time ≤10 months</td>
<td>81 (57–93)</td>
</tr>
<tr>
<td>Gleason score 8–10</td>
<td>63 (52–73)</td>
</tr>
<tr>
<td>PSA recurrence &gt;2 years</td>
<td>77 (55–89)</td>
</tr>
<tr>
<td>PSA recurrence ≤2 years</td>
<td>53 (39–66)</td>
</tr>
</tbody>
</table>

PSA: prostate-specific antigen. Numbers in parentheses are 95% confidence intervals.

...
malignancy. As a result, DRE is considered not to be very helpful in determining the site of recurrence (48). Despite its low sensitivity, however, serial DREs are non-invasive and cheap and thus may be potentially helpful in detecting subtle changes that may reflect local recurrence.

The usefulness of transrectal ultrasound (TRUS)-guided anastomotic biopsies is also unclear. Several studies have demonstrated the sensitivity of this technique to be quite poor in patients with a PSA <1.0 ng/ml, at which level salvage radiotherapy is most efficacious (46,49,50). Shekarriz et al. (50) found only 25% of the patients with a PSA ≤1.0 ng/ml to have a positive biopsy compared with 71% of those with a PSA >1.0 ng/ml. Furthermore, a positive anastomotic biopsy is not associated with an improved outcome after salvage radiotherapy (51) and 10–40% of the patients with a negative biopsy and a PSA <1.0 ng/ml show a PSA decrease after salvage radiotherapy, thus suggesting the presence of undetected local recurrence (52). As a result, since a negative biopsy does not always rule out local recurrence, and a positive result does not always exclude the presence of metastatic disease, the role of anastomotic biopsies remains ambiguous.

There is no imaging test to identify recurrent lesions accurately in patients demonstrating lower PSA levels. Cher et al. (53) found the probability of a positive bone scintigram to be <5% until the PSA value increased to 40–45 ng/ml. They concluded that serum PSA is the best predictor of the bone scintigram results in patients with rising serum PSA levels after radical prostatectomy, and bone scintigraphy is only of limited usefulness until the PSA level increases to >30–40 ng/ml. There is no consensus concerning the PSA level at which a bone scan should be performed, but recently a delay was recommended until the serum PSA reached 20 ng/ml, provided that the patient was asymptomatic. Despite the small likelihood of a positive finding, however, an evaluation by early bone scan may be necessary as a baseline for comparison purposes with future studies that are performed as the serum PSA ultimately continues to increase.

Computed tomography (CT) scans are not sufficiently sensitive for detecting local recurrence until the increasing rate of PSA becomes >20 ng/ml per year (54). The sensitivity and specificity of magnetic resonance imaging (MRI) and MR spectroscopy are improving and they are most useful for detecting nodal and bony metastases (55,56). However, they are also not sufficiently useful early in the course of PSA recurrence. Positron emission tomography (PET), a biochemical imaging modality, cannot accurately distinguish post-operative scars from local recurrence (42). Immuno-scintigraphy, a technique in which a radiolabelled monoclonal antibody against prostate-specific membrane antigen (PSMA) is used to bind to PSMA, is now being increasingly used to evaluate patients with a rising serum PSA after radical prostatectomy. By combining the results of Levesque et al. (57) and Kahn et al. (58), Lange et al. (59) showed promising data in which the response to salvage radiotherapy was 28% when scans revealed extraprostatic disease; however, this value rose to 70% when scan results demonstrated either activity in the prostatic fossa only or a normal scan. In those studies, however, the PSA level was high at the time of scanning. As a result, the true usefulness of this test in patients demonstrating a lower PSA level, when radiotherapy has the most potential to be beneficial, is unclear. This new technique is still in its early phase of use and further studies are required to evaluate its usefulness.

In view of the limited role of such imaging tests to identify the site of recurrence, statistical models based on various clinical and pathological risk factors have been developed. Cadeddu et al. (60) reported that of 82 patients treated with radiation therapy for PSA recurrence, the patients with Gleason score ≥8, positive seminal vesicles or lymph nodes, or a PSA recurrence within the first year following surgery rarely benefit from radiotherapy. This finding suggests that PSA recurrence in such patients may be due to distant metastases or a combination of distant metastases and local recurrence. Conversely, PSA recurrence is more likely to be due to local recurrence alone if there is a Gleason score ≤7 or an absence of nodal or seminal vesicle involvement. Furthermore, Kupelian et al. (2) reported that surgical margin involvement was the only independent predictor of local failure. Partin et al. (61) mentioned that a serum PSA velocity ≥0.75 ng/ml/year was associated with an increased likelihood of metastatic disease. They concluded that the combination of the Gleason score, pathological stage and serum PSA velocity 1 year after surgery best distinguished local recurrence from distant metastases. Patel et al. (62) demonstrated that a PSADT of <6 months was most indicative of distant metastases, whereas local recurrence correlated with a long PSA doubling time. Trapasso et al. (6) reported the median PSADT to be 4.3 months for patients who were ultimately found to have metastatic disease compared with 11.7 months for patients with local recurrence alone. Pound et al. (8) demonstrated that PSADT (≤10 months), Gleason score (≥7) and time to PSA recurrence (≤2 years) were important in determining the probability of progression to distant metastases thereafter. Many studies therefore suggest that patients who develop PSA recurrence within 1–2 years of surgery, have a Gleason score of >7, positive seminal vesicles or lymph node involvement are more likely to have metastatic disease and are thus considered to be better candidates for systemic treatment (Table 4). For further confirmation, however, prospective studies concerning PSA parameters are necessary.

**TREATMENT OF PSA RECURRENCE**

The best way to treat PSA recurrence after radical prostatectomy may depend on the site of recurrence: namely local, systemic or a combination of both. The treatment options for presumed local recurrence include external beam radiotherapy and, for presumed distant metastasis, hormonal therapy. Observation only is also one of the treatment options regardless of the recurrence site. However, standard imaging
Table 4. Summary of clinicopathological factors that predict local or distant recurrence

<table>
<thead>
<tr>
<th>Local recurrence</th>
<th>Distant recurrence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSADT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6 months</td>
<td>&lt;6 months</td>
<td>62</td>
</tr>
<tr>
<td>&lt;10 months</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td><strong>PSA velocity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.75 ng/ml/year</td>
<td>≥0.75 ng/ml/year</td>
<td>61</td>
</tr>
<tr>
<td><strong>Time from RP to PSA recurrence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 year</td>
<td>&lt;1 year</td>
<td>60, 63</td>
</tr>
<tr>
<td>≤2 years</td>
<td></td>
<td>4, 8</td>
</tr>
<tr>
<td><strong>Gleason score on RP specimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8–10</td>
<td></td>
<td>4, 8, 60</td>
</tr>
<tr>
<td><strong>Surgical margin involvement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>SV or LN involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−)</td>
<td>(+)</td>
<td>4, 49, 60, 64</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen; PSADT, doubling time; RP, radical prostatectomy; SV, seminal vesicle; LN, lymph node.

tests cannot help to identify the site of recurrence until the PSA reaches 20–50 ng/ml, at which level the effectiveness of radiotherapy can no longer be expected. Therefore, treatment is mainly selected according to the pathological findings of the radical prostatectomy specimen and the post-operative serum PSA parameters.

**OBSERVATION**

According to a report by Pound et al. (8), the natural course from PSA recurrence to the development of metastatic disease or prostate cancer-specific death seems to be quite long. Frazier et al. (65) mentioned that the majority of patients (93%) with PSA recurrence had not failed clinically and concluded that PSA recurrence may not translate into disease-related death. As a result, observation with delayed hormonal therapy for symptomatic or metastatic disease can be one of the treatment options. According to the international survey on the management of PSA recurrence after radical prostatectomy, 54% of urologists preferred observation, whereas 31% opted for hormonal therapy and only 13% selected salvage radiotherapy (66).

**RADIATION THERAPY**

Salvage radiotherapy is the recommended terminology for curative-intended radiation for post-operative PSA recurrence as opposed to adjuvant radiotherapy administered shortly after radical prostatectomy based on adverse pathological findings (67). To be candidates for salvage radiation therapy, patients must have a life expectancy of >10 years, since the salvage radiation therapy is sometimes associated with high morbidity.

The PSA response to radiotherapy for PSA recurrence varies from 18 to 68% (68–71,73). The PSA level before radiation is critical in the response to salvage radiotherapy (69, 71–74). Schild et al. (71) reported patients with PSA levels of ≤1.1 ng/ml at the beginning of radiotherapy to have a 30 month actuarial freedom from failure of 78% in comparison with only 18% for those with higher pre-treatment PSA levels. Kooy et al. (72) reported the 8-year relapse-free survival of patients who received salvage radiotherapy to be 67, 39 and 42% in patients with a pre-radiotherapy PSA level of ≤1.0, 1.1–4 and >4 ng/ml, respectively. Nudel et al. (73) reported that patients who received salvage radiotherapy at PSA <1 ng/ml after radical prostatectomy and those who received radiotherapy as an adjuvant treatment to surgery had equivalent progression-free survival, but it was significantly worse if radiotherapy was delayed until the PSA reached a level >1 ng/ml. These reports suggest that a PSA cut-off point of 1 ng/ml is likely to confer the best chance of biochemical survival. Garg et al. (69) reported the 3-year disease-free survival rate to be 78% in patients with a PSA level of ≤2 ng/ml at the time of radiotherapy compared with 31% in those with a PSA level >2 ng/ml. Peschel et al. (74) reported the pre-operative PSA level, pre-radiotherapy PSA level and seminal vesicle involvement to be significant risk factors for actuarial biochemical disease-free survival following post-operative radiotherapy, and the most significant risk factor was the pre-radiotherapy PSA of >0.3 ng/ml. The American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Panel demonstrated a serum PSA level of 1.5 ng/ml to be the threshold level for optimal success rates (67). As most recently recommended by the European Consensus Group (21), a PSA level of 1.0–1.5 ng/ml is considered to be an appropriate cut-off point to initiate salvage radiotherapy for presumed local recurrence.

The dose of radiation is also an important factor influencing the response to PSA recurrence after radical prostatectomy. Schild et al. (71) reported that patients who received ≥64 Gy had a 30 month freedom from failure of 62% in comparison with 17% for those who had a smaller dose. The ASTRO Consensus Panel recommended that at least a dose of 64.8 Gy radiation should be administered to the prostatic bed (67). The European Consensus Group (21) also recommended that the minimum dose that should be delivered is 64 Gy with 1.8 or 2 Gy per fraction.

The response to salvage radiotherapy for PSA recurrence after radical prostatectomy may depend on the site of recurrence. Katz et al. (75) reported negative/close margins, an absence of extracapsular extension and the presence of seminal vesicle invasion to be independent predictors of PSA relapse following salvage conformal radiotherapy for PSA recurrence. Stephenson et al. (76) also reported a Gleason score of 8–10, a pre-radiotherapy PSA level ≥2.0 ng/ml, negative surgical margins, a PSA doubling time of ≤10 months and seminal vesicle invasion to be a predictor of disease progression following salvage radiotherapy. Therefore, patients with such clinicopathological characteristics may not be good candidates for salvage radiotherapy. Conversely, the long-term response may be expected for patients without such characteristics. However, further prospective studies are required to identify the candidates who can most benefit from salvage radiotherapy.
Hormonal therapy may increase the sensitivity to irradiation. Bolla et al. (77) showed that adjuvant hormonal therapy improved local recurrence, PSA-free survival and overall survival. Eulau et al. (78) also demonstrated that transient androgen deprivation around the time of salvage radiation therapy showed an improvement in the biochemical and clinical response rates. Katz et al. (75) also reported that neoadjuvant androgen deprivation improved the PSA relapse-free survival after salvage conformal radiotherapy in patients with any of the following factors, namely positive margins, extracapsular extension or seminal vesicle invasion. Androgen deprivation may be effective for possible distant metastases in such patients. However, the European Consensus Group (21) mentioned that hormonal therapy is not standard in patients receiving salvage radiotherapy (Table 1). A prospective randomized study is necessary for an accurate evaluation of the role of androgen derivation combined with salvage radiation therapy.

When counseling patients regarding the use of salvage radiation therapy after a radical prostatectomy, it is important to keep in mind potential complications, such as gastrointestinal symptoms, new or worsened urinary incontinence and erectile dysfunction, associated with this therapy, although the incidence of severe long-term toxicity is uncommon. Tsien et al. (79) reported that using three-dimensional conformal radiotherapy at a median dose of 64.8 Gy, the 5 year actuarial likelihood of grade ≥2 rectal toxicity was 8.9%. Peyromaure et al. (80) also reported that irritative urinary disorders, hematuria and rectal irritation were observed in 9.7, 8.1 and 6.4% of patients who received salvage radiotherapy at a dose of 65 Gy, but none of them was severe. However, since these findings are based on the findings of a retrospective study, the incidence reported may be an underestimation of the actual complication rate (81). Prospective quality of life studies are necessary to make a more precise evaluation.

In conclusion, the role of salvage radiotherapy in the management of PSA recurrence after radical prostatectomy remains inconclusive.

**Hormonal Therapy**

Although androgen deprivation therapy by surgical (82) or medical castration using a luteinizing hormone-releasing hormone (LH-RH) agonist (83,84) or antiandrogens (85–87) has been widely used for the treatment of prostate cancer, the early use of such hormonal therapy for PSA recurrence after radical prostatectomy remains controversial. It has been extensively debated regarding whether or not giving early hormonal treatment is of any benefit compared with delayed treatment applied only when symptomatic progression occurs. The PSA level at which hormonal therapy should be initiated remains to be elucidated. Messing et al. (88) compared immediate versus deferred androgen deprivation therapy with surgical or medical castration by LH-RH agonist in patients who underwent radical prostatectomy and pelvic lymphadenectomy and were found to have nodal metastases. They demonstrated that immediate hormonal treatment led to a better overall survival, prostate cancer-specific survival and also progression-free survival. The aim of this study focused on the significance of adjuvant hormonal therapy for patients at high risk of disease progression after radical prostatectomy, but not on the significance of treatment for those with PSA recurrence after radical prostatectomy. However, this result suggests the possible survival benefit by androgen deprivation therapy for the treatment of PSA recurrence after radical prostatectomy.

Recently, Wirth et al. (89) reported the results of an interim analysis of the Early Prostate Cancer (EPC) program which consists of three randomized, double blind, placebo-controlled trials prospectively designed for combined analysis. In this program, a total of 8113 patients with localized or locally advanced prostate cancer were randomized to a pure antiandrogen (bicalutamide 150 mg/day) group or a placebo group in addition to standard care including watchful waiting, radical prostatectomy and radiation therapy. At a median 5.4 years of follow-up, a significant benefit due to bicalutamide in the progression-free survival was demonstrated in radical prostatectomy patients with locally advanced disease. Bicalutamide provides a similar survival outcome to castration including a bilateral orchiectomy or LH-RH agonist in previously untreated patients with locally advanced prostate cancer, and confers a statistically significant benefit over castration with respect to sexual interest and physical capacity (85,86). Another recent study comparing flutamide, another non-steroidal antiandrogen, versus no adjuvant treatment also showed that flutamide induced a better recurrence-free survival after radical prostatectomy for locally advanced, lymph node-negative prostate cancer with a median follow-up of 6.1 years, although there were no differences in terms of overall survival, and considerable toxicity was also observed in the flutamide arm (90). Since local recurrent lesions at an early stage of PSA recurrence is considered to be quite small, pure antiandrogens may be sufficient to prevent disease progression. Recently, the Japan Clinical Oncology Group (91) started a randomized controlled trial (JCOG 0401) to evaluate radiotherapy ± hormonal therapy with bicalutamide versus hormonal therapy alone for PSA recurrence after radical prostatectomy. The usefulness of bicalutamide or irradiation for the treatment of PSA recurrence after radical prostatectomy is thus expected to be clarified.

In order to avoid the side effects of hormonal therapy, the concept of the intermittent administration of hormonal therapy has been advocated (92). Despite the potential benefits of intermittent hormonal therapy, its long-term efficacy remains to be demonstrated. Confirmation of the efficacy of intermittent hormonal therapy by controlled clinical trials in comparison with standard consecutive hormonal therapy may be necessary before we can clinically recommend this treatment for PSA recurrence after radical prostatectomy. From the viewpoint of side effects, the 5α-reductase inhibitor, finasteride, has recently attracted much attention. Finasteride may have an ability to delay disease progression by itself in patients with PSA recurrence after radical prostatectomy (93). However,
Further confirmation by longer and larger studies is required for the use of finasteride as a treatment option for patients with PSA recurrence after radical prostatectomy.

Eventually, the treatment of PSA recurrence by suspected distant metastasis involves hormonal manipulation, but at present the type and timing of such treatment are still based on physician and patient preference.

**CONCLUSIONS**

A significant proportion of patients who undergo a radical prostatectomy for localized prostate cancer develop PSA recurrence. In terms of the treatment for such PSA recurrence, some patients may be good candidates for local radiotherapy, whereas others may be indicated to undergo hormonal manipulation rather than radiotherapy. Although the pathological findings and post-operative serum PSA parameters may be useful for predicting the pattern of recurrence, it is still quite difficult to identify the most appropriate candidates for each type of treatment. The optimal type and timing of hormonal manipulation have yet to be elucidated. Further prospective randomized trials are thus still necessary to reach a consensus regarding the ideal treatment protocols for PSA recurrence after radical prostatectomy.

**References**


