厚生労働科学研究研究費補助金

がん臨床研究事業

早期前立腺がんにおける根治術後の再発に対する標準的治療法の確立に関する研究

平成17～19年度　総合研究報告書

主任研究者　内藤　誠二

平成20（2008）年　3月

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I　総合研究報告書

主任研究者　内藤誠二

早期前立腺がんにおける根治術後の再発に対する標準的治療法の確立に関する研究

研究要旨

限局性前立腺癌に対する標準的治療の一つとして根治的前立腺摘除術が広く行われている。しかし、術後、前立腺特異抗原（Prostate Specific Antigen : PSA）の再上昇で発見される 、いわゆるPSA 再発が15-25％の患者にみられ、その治療法は未だ確立していない。本研究では、根治術後の PSA 再発患者を対象に、内分泌療法群と内分泌療法に先行して局所放射線療法を行う群によるランダム化比較試験を行い、PSA 再発に対する標準的治療法の確立を目指す。現在、「早期前立腺がんにおける根治術後の再発に対する標準的治療法の確立に関する研究」（phase III 試験）を継続している。

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A. 研究目的

根治的前立腺摘除術後の再発は、通常まずPSAの再上昇（PSA再発）で発見されるが、その再発が局所か、遠隔転移か、さらには両者の合併かを画像的に同定することは困難である。一般的に局所再発であれば放射線療法、遠隔転移であれば内分泌療法が標準的な治療法になると思われるが、実際には再発部位の同定が困難であるため、明確な根拠もないままに治療法が選択され、現在までのところPSA再発患者に対する標準的治療法は確立されていない。そのため、限局性前立腺癌に対する根治的前立腺摘除術後のPSA再発患者に対して、内分泌療法前に放射線療法を行うことの臨床的有用性を、内分泌療法単独とのランダム化比較試験により評価する臨床試験を計画した。Primary endpointは抗アンドロゲン剤（ビカルタミド）のTime-to-Treatment Failure(TTF)とし、secondary endpointはプロトコール治療のTTF、全生存期間、臨床的無再発生存期間、放射線、抗アンドロゲン剤、LH-RHアナログの有害事象、QOLとした。

B. 研究方法

登録時に適格患者は以下のA群(内分泌療法群)かB群(放射線療法群)にランダム割付される。治療開始後、臨床再発またはPSA再発を認めた場合、または有害事象や患者拒否により治療継続が困難となった場合、Time to treatment failure (TTF)と判断する。A群では抗アンドロゲン剤による治療とその後のTTFに対するLH-RHアナログ治療をもってプロトコール治療とし、B群では前立腺床に対する64.8Gyの外照射、その後TTFを生じたらA群と同様の治療をもってプロトコール治療とする。登録期間は4年、追跡期間は登録終了後5年とし、総研究期間は9年とする。

C. 研究結果

1)当研究はJapan Clinical Oncology Group(JCOG)にデータマネージメント及び、効果・安全性評価を依頼し研究を遂行している。H20年3月19日現在、97名の登録が得られているが、重篤な有害事象は認めていない。放射線治療の品質管理も良好である。本研究は、H14－効果（がん）-030およびH17－がん臨床-003として採択され、H16年5月からの4年間に各群100名を目標に患者登録を開始した。登録症例数が予定を下回っていたことが問題であったが、全施設での適格患者の調査、参加施設の入れ替え、患者への説明医の固定、コアメンバーによる縮小班会議の定期的開催、説明パンフレットの作成、配布、カルテ用シール等の配布などの対策を行った結果、H19年3月からH20年3月19日現在までの約1年間に43例の登録があり、登録数は急増している。H19年9月の班会議の際に行った詳細な候補患者数に関する調査では、出席した25施設において、PSA上昇直線から1年以内に登録可能なPSA値である0.4ng/mlに到達しそうな患者が90名存在することが明らかとなった。これらの患者を確実にrecruitすることで登録が推進されるものと期待される

（倫理面への配慮）参加患者の安全性確保については、適格条件やプロトコール治療の中止変更規準を厳しく設けており、試験参加による不利益は最小化される。また、「臨床研究に関する倫理指針」およびヘルシンキ宣言などの国際的倫理原則に従い以下を遵守する。

1）研究実施計画書のIRB承認が得られた施設のみから患者登録を行う。

2）すべての患者について登録前に充分な説明と理解に基づく自発的同意を本人より文書で得る。

3）データの取り扱い上、患者氏名等直接個人が識別できる情報を用いず、かつデータベースのセキュリティを確保し、個人情報（プライバシー）保護を厳守する。研究の第三者的監視：JCOGは厚生労働省がん研究助成金指定研究5班（17指-1～5）を中心に、同計画研究班6班および厚生労働科学研究費がん臨床研究事業22研究班、計33班の任意の集合体であり、JCOGに所属する研究班は共同で、Peer reviewと外部委員審査を併用した第三者的監視機構としての各種委員会を組織し、科学性と倫理性の確保に努めている。本研究も、JCOGのプロトコール審査委員会、効果・安全性評価委員会、監査委員会、放射線治療委員会などによる第三者的監視を受けることを通じて、科学性と倫理性の確保に努める。

D. 考察

登録患者数が当初の予定を下回っているが、H19年度は登録数が急増しており、さらなる登録推進のため参加施設の入れ替えや若手分担研究者の積極的な採用などの努力を積極的に行って、試験の円滑な進行を図りたい。なお、登録数が100例を超えた段階で中間解析を行う予定である。また、本研究の登録促進と根治的前立腺摘除術後のPSA再発の臨床背景を明らかにするため、各施設におけるPSA再発患者の後ろ向き臨床調査を行い、現在データ解析中である。

E. 結論

H20年3月19日現在までに97名の患者登録を行い、プロトコール治療を実施中であるが、両群ともに治療による重篤な有害事象は認めていない。

F. 健康危険情報

治療と関連するグレード3以上の有害事象は報告されていない。

G. 研究発表

1. 論文発表

1. Yokomizo A, Tobisu K, Kawamoto H, Nihei K, Ishizuka N, Naito S. Randomized

Controlled Trial to Evaluate Radiation plus Endocrine Therapy or Endocrine Therapy alone for PSA failure after radical prostatectomy: Japan Clinical Oncology Group Study JCOG 0401. Jpn J Clin Oncol, 35:34-36, 2005.

2. Naito S. Evaluation and management of prostate-specific antigen recurrence after radical prostatectomy for localized prostate cancer. Jpn J Clin Oncol 35:365-74, 2005.

3. Yokomizo A, Murai M, Baba S, Osamu Ogawa O, Tsukamoto T, Niwakawa M, Tobisu K, Kinukawa N and Naito S: Percentage of positive biopsy cores, preoperative prostate-specific antigen (PSA) level, pT and Gleason score as predictors of PSA recurrence after radical prostatectomy: a multi-institutional outcome study in Japan. BJU Int 98: 549-553, 2006.

2. 学会発表

1. Seiji Naito, TREATMENT OF PATIENTS WITH PSA RECURRENCE AFTER REDICAL PROSTATECTOMY. January 25, 2005. The 18th International Symposium of Foundation for Promotion of Cancer Research.

2. 横溝　晃、古賀寛史、鳶巣賢一、内藤誠二、JCOG泌尿器科腫瘍研究グループ.「日本の早期前立腺がん根治手術後の再発に関するアウトカム研究」第 93 回日本泌尿器科学会総会

3. 横溝　晃、古賀寛史、此元竜雄、内藤誠二、JCOG 泌尿器科腫瘍研究グループ. 早期前立腺がんにおける根治術後の再発に関する outcome study. 第 41 回日本癌治療学会総会

4. 横溝　晃、古賀寛史、此元竜雄、鳶巣賢一、 内藤誠二. 「早期前立腺がんに対する根治術後の PSA 再発症例の統計解析」第 19 回前立腺シンポジウム

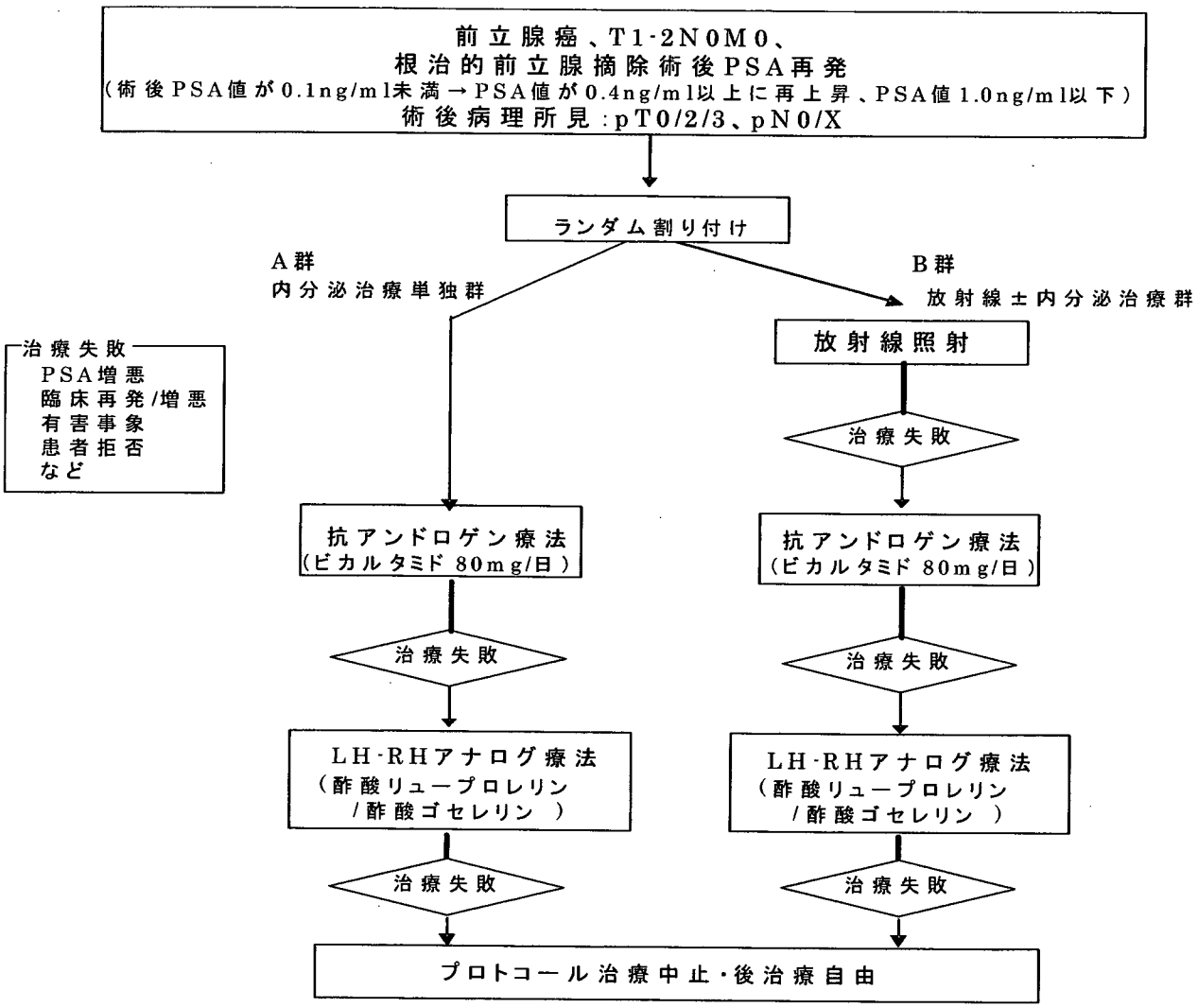
5. 横溝　晃.「早期前立腺癌に対する根治術後の PSA 再発の臨床的特徴」前立腺癌の病態・治療と DDS、第 20 回福岡がん懇話会

6. 内藤誠二、横溝　晃、古賀寛史、庭川　要、二瓶　圭二、鳶巣賢一. 「早期前立腺癌根治術後の PSA 再発に対する放射線照射と内分泌治療に関するランダム化比較試験 JCOG0401」　第 13 回福岡前立腺癌研究会

H. 知的財産権の出願・登録状況

1. 特許取得 なし
2. 実用新案登録　なし。

試験概要図


前立腺癌、T1-2N0M0、
根治的前立腺摘除術後PSA再発
(術後PSA値が0.1ng/ml未満→PSA値が0.4ng/ml以上に再上昇、PSA値1.0ng/ml以下)
術後病理所見:pT0/2/3、pN0/X
ランダム割り付け
A群
内分泌治療単独群
B群
放射線±内分泌治療群
治療失敗
PSA増悪
臨床再発/増悪
有害事象
患者拒否
など
放射線照射
治療失敗
抗アンドロゲン療法
(ビカルタミド 80mg/日)
抗アンドロゲン療法
(ビカルタミド 80mg/日)
治療失敗
治療失敗
LH-RHアナログ療法
(酢酸リュープロレリン
/酢酸ゴセレリン)
LH-RHアナログ療法
(酢酸リュープロレリン
/酢酸ゴセレリン)
治療失敗
治療失敗
プロトコール治療中止・後治療自由

II 研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yokomizo A, Tobisu K, Kawamoto H, et al.	Randomized Controlled Trial to Evaluate Radiation plus Endocrine Therapy or Endocrine Therapy alone for PSA failure after radical prostatectomy: Japan Clinical Oncology Group Study JCOG 0401	Jpn J Clin Oncol	35	34-36	2005
Naito S	Evaluation and management of prostate-specific antigen recurrence after radical prostatectomy for localized prostate cancer	Jpn J Clin Oncol	35	365-374	2005
Yoshida T, Kinoshita H, Segawa T, et al.	Antiandrogen bicalutamide promotes tumor growth in a novel androgen-dependent prostate cancer xenograft model derived from a bicalutamide-treated patient	Cancer Res	65	9611-961 s6	2005
Kuroda K, Horiguchi Y, Nakashima J, et al.	Prevention of cancer cachexia by a novel nuclear factor {kappa}B inhibitor in prostate cancer	Clin Cancer Res	11	5590-559 4	2005
Imamoto T, Suzuki H, Fukasawa S, et al.	Pretreatment serum testosterone level as a predictive factor of pathological stage in localized prostate cancer patients treated with radical prostatectomy	Eur Urol	47	308-312	2005
Enokida H, Shiina H, Urakami S, et al.	Multigene methylation analysis for detection and staging of prostate cancer	Clin Cancer Res	11	6582-658 8	2005
Enokida H, Shiina H, Urakami S, et al.	Smoking influences aberrant CpG hypermethylation of multiple genes in human prostate carcinoma	Cancer	106	79-86	2006

Yokomizo A, Murai M, Baba S, et al.	Percentage of positive biopsy cores, preoperative prostate-specific antigen (PSA) level, pT and Gleason score as predictors of PSA recurrence after radical prostatectomy: a multi-institutional outcome study in Japan	BJU Int.	98	549-553	2006
Akaza H, Hinotsu S, Usami M, et al.	The case for androgen deprivation as primary therapy for early stage disease: results from J-CaP and CaPSURE	J Urol	176	S47-49	2006
Tsuchiya N, Wang L, Suzuki H	Impact of IGF-I and CYP19 gene polymorphisms on the survival of patients with metastatic prostate cancer	J Clin Oncol	24	1982-1989	2006
Inoue T, Yoshida T, Shimizu Y, et al.	Requirement of androgen-dependent activation of PKC{zeta} for androgen-dependent cell proliferation in LNCaP cells and its roles in transition to androgen-independent cells	Mol Endocrinol	20	3053-69	2006
Miyake H, Hara I, Kurahashi T, et al.	Quantitative detection of micrometastases in pelvic lymph nodes in patients with clinically localized prostate cancer by real-time reverse transcriptase-PCR.	Clin. Cancer Res.	13	1192-1197	2007
Suzuki K, Nakamura K, Kato K, et al.	Exploration of target molecules for prostate cancer gene therapy	Prostate	67	1163-1173	2007
Namiki S, Saito S, Nakagawa H, et al.	Impact of unilateral sural nerve graft on recovery of potency and continence following radical prostatectomy: 3-year longitudinal study	J Urol	178	212-216	2007
Namiki S, Kwan L, Kagawa-Singer M, et al.	Sexual function reported by Japanese and American men	J Urol	179	245-249	2007

Abe T, Shinohara N, Harabayashi T, et al.	Postoperative inguinal hernia after radical prostatectomy for prostate cancer	Urology	69	326-329	2007
Saito T, Hara N, Kitamura Y, et al.	Prostate-specific antigen/prostatic acid phosphatase ratio is significant prognostic factor in patients with stage IV prostate cancer	Urology	70	702-705	2007
Fujimura T, Shinohara Y, Tissot B, et al.	Glycosylation status of haptoglobin in sera of patients with prostate cancer, vs. benign prostate disease or normal subjects	Int J Cancer	122	39-49	2008
Ide H, Nakagawa T, Terado Y, et al.	Tyk2 expression and its signaling enhances the invasiveness of prostate cancer cells	Biol Biophy Res Com		In press	2008

III 研究成果の刊行物・別刷

Jpn J Clin Oncol 2005;35(1)34–36
doi:10.1093/jjco/hyi007

Clinical Trial Note

Randomized Controlled Trial to Evaluate Radiotherapy ± Endocrine Therapy Versus Endocrine Therapy Alone for PSA Failure after Radical Prostatectomy: Japan Clinical Oncology Group Study JCOG 0401

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Received July 9, 2004; accepted November 3, 2004

A randomized controlled trial has started in Japan to evaluate radiotherapy and endocrine therapy for prostate-specific antigen (PSA) failure after radical prostatectomy. Patients who have PSA failure after radical prostatectomy for localized prostate cancer (T1–2N0M0) are randomized into treatment groups of either radiotherapy ± endocrine therapy or endocrine therapy alone. The Urologic Oncology Study Group (UOSG) in the Japan Clinical Oncology Group (JCOG) composed of 36 specialized institutions will recruit 200 patients. The primary end-point is time to treatment failure (TTF) of bicalutamide, and secondary end-points are TTF of protocol treatment, progression-free survival, overall survival, adverse events and quality of life (QOL). The Clinical Trial Review Committee of the JCOG approved the protocol on April 13, 2004, and the study was activated on May 17, 2004.

Key words: prostate cancer – prostatectomy – PSA failure – endocrine therapy – radiation

PROTOCOL DIGEST OF THE JCOG 0401

TRIAL BACKGROUNDS

In spite of improvements in both the detection of early prostate cancer and surgical techniques, ~35% of men develop prostate-specific antigen (PSA) failure after radical prostatectomy (1). Most of the recurrences after radical prostatectomy are detected only by a rise in the PSA level (2). Those who have local recurrence may benefit from radiation therapy, whereas those who have metastatic disease may benefit from systemic treatment, the most common of which is androgen deprivation (2). As computed tomography (CT) scans or bone scans usually cannot detect the recurrent sites, a standard has not yet been established for the treatment of PSA failure after prostatectomy.

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PURPOSE

The purpose of the trial was to evaluate radiotherapy ± endocrine therapy in comparison with endocrine therapy alone for PSA failure after radical prostatectomy.

STUDY SETTING

The study was a multi-institutional (36 specialized centers), randomized controlled trial.

RESOURCES

The study was supported by Health Sciences Research Grants for Clinical Research for Evidenced Based Medicine and Grants-in-Aid for Cancer Research (14S-4), from the Ministry of Health, Labor and Welfare, Japan.

END-POINTS

In general, overall survival (OS) is supposed to be the best primary end-point to compare the clinical advantage in

randomized trials. However, the 10 year overall survival rate is expected to be >80% in this study, therefore OS will not be a good candidate for the primary end-point. The clinical progression-free survival is also not adequate as the primary end-point for the same reason. Regarding 'PSA failure', it may be a potential candidate for the primary end-point, but PSA failure will occur at least three times more frequently in the experimental arm, which causes confusion in evaluation. Therefore, the adequate primary end-point would be time to treatment failure (TTF) of luteinizing hormone-releasing hormone (LH-RH) analog as a hormone-refractory state of prostate cancer. As the TTF of bicalutamide can be evaluated more quickly than that of LH-RH analog and thus should be its good surrogate end-point, the TTF of bicalutamide is selected as a primary end-point in this study. In summary, the primary end-point is the TTF of bicalutamide, and secondary end-points are TTF of protocol treatment, clinical progression-free survival, OS, adverse events and patient-reported quality of life (QOL).

Eligibility Criteria

Tumors are staged according to the General Rule for Clinical and Pathological Studies on Prostate Cancer (Japanese Urological Association, The Japanese Society of Pathology), which is the 1997 revision of the TNM Classification of Malignant Tumours by the International Union Against Cancer (UICC) (3).

Inclusion Criteria

(i) A diagnosis of localized prostate cancer (clinical stage T1–2N0M0) which was treated by radical prostatectomy; (ii) pathological stage: pT0/2/3 and pN0/x; (iii) the serum level of PSA once it has reached <0.1 ng/ml after radical prostatectomy and then increased to ≥0.4 ng/ml; (iv) a serum level of PSA ≤1.0 ng/ml at study entry; (v) no clinical recurrence based on abdominal and pelvic CT, and a bone scan; (vi) no history of chemotherapy, radiation therapy or endocrine therapy for any cancer; (vii) age ≥20 and ≤79 years; (viii) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (ix) no blood transfusion within 28 days of entry; (x) sufficient organ function within 28 days of entry; and (xi) written informed consent.

Exclusion Criteria

(i) Synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*; (ii) mental disease or mental symptoms which would affect the participant's decision to participate; (iii) continuous medication of steroids (exclude external use of steroids for skin); (iv) ischemic heart disease or arrhythmia which needs medical treatment; (v) poorly controlled hypertension; (vi) poorly controlled diabetes mellitus; (vii) history of cerebral infarction or myocardial infarction within 6 months; (viii) liver cirrhosis; and (ix) interstitial pneumonia which requires ventilation assistance, oxygen inhalation, steroids or diuretic medicine.

Randomization

Using telephone or fax contact with the JCOG Data Center after confirmation of the above criteria, patients are randomized by the minimization method of balancing the groups according to the Gleason score of the radical prostatectomy specimen, period from operation to PSA failure, and institution.

Treatment Methods

Endocrine therapy alone group (standard arm). The protocol treatment includes the bicalutamide medication (80 mg/day). After TTF of bicalutamide, it is followed by LH-RH analog (leuprorelin acetate 3.75 mg/4 weeks or 11.25 mg/12 weeks, goserelin acetate 3.6 mg/4 weeks or 10.8 mg/12 weeks).

Radiotherapy ± endocrine therapy group (experimental arm). The total dose of 64.8 Gy/36 Fr (50 days) external beam irradiation is delivered to the prostatic bed. If the patient has no treatment failure, no additional therapy will be given. In case of treatment failure of radiation therapy, bicalutamide medication will be started in the same way as in the standard arm. After the treatment failure of bicalutamide, a LH-RH analog is given to the patients as in the case of endocrine therapy alone.

Definition of Treatment Failure

(i) PSA increase beyond 0.4 ng/ml if previous value is <0.4 ng/ml
(ii) Any PSA increase if previous value is ≤0.4 ng/ml
(iii) Clinical progression or clinical recurrence
(iv) Adverse event
(v) Patient refusal to continue treatment
(vi) Any cause of death
(vii) Poor compliance (less than two-thirds of planned dose) of oral bicalutamide at two consecutive visits (only for bicalutamide treatment failure)

Follow-Up

All patients are followed-up by their urologist at least every 3 months for more than 5 years. Blood tests including PSA and urinalysis are performed during the follow-up interval. Abdominal and pelvic CT, chest X-ray and bone scan are carried out every 12 months. The symptoms and adverse events are surveyed at each visit.

Study Design and Statistical Methods

This trial is designed to evaluate the superiority of radiotherapy ± endocrine therapy to endocrine therapy alone in terms of the TTF. Almost half of the patients can be cured by radiation therapy alone (4–6), therefore, these patients are

expected to have a greatly prolonged TTF after radiation (radiation responder). In contrast, the other half of the patients irradiated are expected to have a treatment failure of radiation therapy (non-responder) and they will have a TTF not significantly shorter than that of those on bicalutamide therapy. In the standard arm, there have been no published data concerning the TTF of bicalutamide for PSA failure after radical prostatectomy. Therefore, we assumed the TTF of bicalutamide therapy in this study to be 4–5 years, based on the report in which the median TTF of bicalutamide therapy for localized prostate cancer was 63.5 months (7). The median TTF in the experimental arm can be calculated on the assumption that the TTF in a radiation responder (50% of the experimental arm) is prolonged three times more than in the non-radiation responders (50% of the experimental arm). Therefore, the median TTF in the experimental arm will be 6.6 years (4.0 years in non-responders and 12.0 years in responders) and 8.3 years (5.0 years in non-responders and 15.0 years in responders). We calculated sample sizes based on Shoenfeld and Richter's methods (8) with 5 year follow-up after 4 years of accrual. If the TTF in the standard arm is 4.0 years, the detectable difference in TTF and sample size per arm will be 2.6 years and 83 cases, respectively. If TTF in the standard arm is 5.0 years, the detectable difference in TTF and sample size per arm will be 3.3 years and 93 cases, respectively. This will provide an 80% power to detect the difference between the assumed TTF in the experimental arm and the TTF in the standard arm (non-responder in the experimental arm compatible) at a 5% one-sided alpha level. Based on these data, the planned sample size is 100 cases in one arm.

QOL

All the patients are enrolled prospectively in a QOL survey using a validated assessment tool and are evaluated before the treatment and 1-year after the treatment. The health-related QOL is assessed using the Japanese version of the RAND Health-Item Short Form 36 (SF-36) version 2.0 (9), and cause-specific QOL is analyzed by the UCLA Prostate Cancer Index which was established by Litwin et al. (10). The Japanese version of SF-36 and that of UCLA PCI were assessed as described previously (11–13).

Interim Analysis and Monitoring

An interim analysis is planned to be performed once, taking into account multiplicity using the Lan and DeMets approach. The Data and Safety Monitoring Committee (DSMC) of the JCOG independently reviews the interim analysis report, and an early termination of the trial may be considered at that stage. In-house interim monitoring is performed by the Data Center to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. The monitoring reports are submitted to and reviewed by the UOSG and the DSMC every 6 months.

PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)

Hokkaido University, Sapporo Medical University, Tohoku University, Miyagi Cancer Center, Akita University, Tsukuba University, Tochigi Cancer Center, Gunma University, Chiba Cancer Center, Chiba University, National Cancer Center Hospital, Tokyo Women's Medical School, Keio University, The Jikei University, Nippon Medical School, Kitasato University, Niigata Cancer Center Hospital, Niigata University, Yamanashi University, Shinshu University, Hamamatsu Medical School, Shizuoka Cancer Center, Nagoya University, Mie University, Kyoto University, Osaka Medical Center for Cancer and Cardiovascular Diseases, Kobe University, Nara Medical University, Shimane University, Kurashiki Central Hospital, Okayama University, Kagawa University, National Shikoku Cancer Center, Kyushu University, Kurume University and Kagoshima University.

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References

1. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *J Am Med Assoc* 1999;281:1591–7.
2. Carroll P. Rising PSA after a radical treatment. *Eur Urol* 2001; 40:Suppl 2:9–16.
3. International Union Against Cancer, Urological tumours. In: Sobin LH, Wittekind C, editors. *TNM Classification of Malignant Tumours*. 5th edn. New York: Wiley-Liss 1997;170–3.
4. Morris MM, Dallow KC, Zietman AL, Park J, Althausen A, Heney NM, et al. Adjuvant and salvage irradiation following radical prostatectomy for prostate cancer. *Int J Radiat Oncol Biol Phys* 1997;38:731–6.
5. Pisansky TM, Kozelsky TF, Myers RP, Hillman DW, Blute ML, Buskirk SJ, et al. Radiotherapy for isolated serum prostate specific antigen elevation after prostatectomy for prostate cancer. *J Urol* 2000;163:845–50.
6. Anscher MS, Clough R, Dodge R. Radiotherapy for a rising prostate-specific antigen after radical prostatectomy: the first 10 years. *Int J Radiat Oncol Biol Phys* 2000;48:369–75.
7. Iversen P, Tyrrell CJ, Kaisary AV, Anderson JB, Van Poppel H, Tammela TL, et al. Bicalutamide monotherapy compared with castration in patients with nonmetastatic locally advanced prostate cancer: 6.3 years of followup. *J Urol* 2000;164:1579–82.
8. Shoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometrics* 1982;38:163–70.
9. Ware JE, Kosinski M, Turner-Bowker DM, Gandek B. *How to Score Version 2 of the SF-12® Health Survey (With a Supplement Documenting Version 1)*. Lincoln, RI: Quality Metric Incorporated, 2002.
10. Litwin MS, Hays RD, Fink A, Ganz PA, Leake B, Brook RH. The UCLA Prostate Cancer Index: development, reliability, and validity of a health-related quality of life measure. *Med Care* 1999;36:1002–12.
11. Fukuhara S, Ware JE Jr, Kosinski M, Wada S, Gandek B. Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. *J Clin Epidemiol* 1998;51:1045–53.
12. Kakehi Y, Kamoto T, Ogawa O, Arai Y, Litwin MS, Suzukamo Y, et al. Development of Japanese version of the UCLA Prostate Cancer Index: a pilot validation study. *Int J Clin Oncol* 2002;7:306–11.
13. Suzukamo Y, Kakehi Y, Kamoto T, Arai Y, Ogawa O, Fukuhara S. Translation and adaptation of the UCLA prostate cancer index for use in Japan. *Nippon Hinyokika Gakkai Zasshi* 2002;93:659–68 (in Japanese).

Jpn J Clin Oncol 2005;35(7)365–374
doi:10.1093/jjco/hyi113

Review Article

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

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Received April 20, 2005; accepted May 15, 2005; published online June 23, 2005

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.

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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)

1.	Total prostate-specific antigen (PSA) is the most widely used detection tool for prostate cancer; in the PSA range 2–6 ng/ml.
2.	PSA relapse means treatment failure.
3.	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.
4.	The ultrasensitive PSA assay should be used for monitoring patients but not for decision making.
5.	Secondary treatment after local failure of surgery should be instigated before PSA levels reach 1.0–1.5 ng/ml.
6.	The ASTRO definition of PSA failure should be used after radiotherapy. An alternative definition that might be considered is three cumulative rises above nadir.
7.	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.
8.	Treatment of distant failure involves hormonal manipulation; the type and timing of therapy are based on physician and patient preference.
9.	For treatment of local failure after radical prostatectomy, salvage radiotherapy can be considered with or without hormonal therapy.
10.	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.
11.	A PSA level of <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.
12.	Remember that treating the patient, and not the PSA, remains the physician's primary goal.

ultrasensitive asssays and as >0.1 ng/ml on conventional assays, respectively. However, not all patients who show PSA recurrence, based on ultrasensitive assays, develop clinical progression as well as an additional PSA recurrence over time (24,26). The determination of such a low level of PSA may be influenced by either the residual benign prostatic glands or non-prostatic tissues such as the periurethral glands (24–26). Therefore, there may be a risk in treating the residual benign glands only, if treatment is initiated at such a lower level of PSA. Furthermore, the patients' awareness of PSA rising even at extremely low levels has a considerable effect on the emotional quality of life, and there is no definite evidence that early intervention may decrease future morbidity and prolong the overall survival. The European Consensus Group (21) recommended that the ultrasensitive PSA assay should be used for monitoring patients but not for decision making (Table 1).

As a result, although there is no definite consensus regarding the PSA cut-off point for defining PSA recurrence after radical prostatectomy, a PSA level of 0.2 ng/ml on conventional assays seems to be the most acceptable cut-off point for PSA recurrence based on a clinical point of view.

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, had 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, and 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 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)

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

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.

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.

Table 3. Estimation of metastasis-free rates following PSA failure after radical prostatectomy (8)

Prognostic factors	Metastasis-free survival (%)		
	3 years	5 years	7 years
All men with PSA recurrence	78 (73–84)	63 (56–70)	52 (44–60)
Gleason score 5–7	86 (79–90)	73 (65–80)	62 (52–71)
PSA recurrence >2 years	89 (81–94)	82 (71–94)	77 (65–86)
PSA doubling time >10 months	95 (83–96)	86 (74–92)	82 (69–90)
PSA doubling time ≤10 months	82 (54–94)	69 (40–86)	60 (32–80)
PSA recurrence ≤2 years	80 (68–88)	62 (49–73)	47 (33–60)
PSA doubling time >10 months	79 (65–88)	76 (61–86)	59 (40–73)
PSA doubling time ≤10 months	81 (57–93)	35 (16–56)	15 (4–33)
Gleason score 8–10	63 (52–73)	40 (28–54)	29 (16–43)
PSA recurrence >2 years	77 (55–89)	60 (33–79)	47 (17–72)
PSA recurrence ≤2 years	53 (39–66)	31 (17–45)	21 (9–35)

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

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 reported PSA recurrence to develop in 315 (15%) patients. In this series, the patients with PSA recurrence were observed until there was evidence of clinical metastatic progression, and then hormonal therapy was initiated. Eleven patients who received early hormonal therapy after an increase in their PSA level were excluded from the analysis. Of the remaining 304 patients, 103 (34%) developed metastatic disease. The median actuarial time from the development of PSA recurrence to the identification of metastases was 8 years, and the 5-year metastasis-free rate was 63%. The Gleason score on radical prostatectomy specimens (5–7 versus 8–10), the time from the radical prostatectomy to PSA recurrence (≤2 versus >2 years) and the PSA doubling time (PSADT; ≤10 versus >10 months) were all found to be predictive of the probability and time to the subsequent development of metastatic disease. To enhance its clinical applicability, they (8) developed an algorithm for estimating a patient's probability of remaining free of metastatic disease at 3, 5 and 7 years (Table 3). Using this algorithm, patients who are likely to have an indolent course can be identified and spared the potential morbidity of additional therapy. Conversely, patients with a high risk of disease progression can be identified early and thus more quickly be administered hormonal therapy (41,42). Although this algorithm undoubtedly provides the most comprehensive information to date, its availability will be enhanced even more by adding data concerning patients with a Gleason score from 8 to 10 and new parameters such as molecular markers.

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

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 efficatious (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). Immunoscintigraphy, 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 radiation therapy. 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) (2,4,8,49,60,63,64). 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

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

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 (bicaltamide 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 bicaltamide in the progression-free survival was demonstrated in radical prostatectomy patients with locally advanced disease. Bicaltamide 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 bicaltamide versus hormonal therapy alone for PSA recurrence after radical prostatectomy. The usefulness of bicaltamide 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 view point 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,