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16年度　総括・分担研究報告書

主任研究者　内藤　誠二

平成17（2005）年　3月

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厚生科学研究費補助金（がん臨床研究事業）

総括研究報告書

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
本研究の患者登録を開始した。

主任研究者氏名：　内藤誠二
所属機関名、職名：九州大学大学院医学研究院泌尿器科　教授

A. 研究目的

限局性前立腺癌に対する根治的前立腺摘除術後のPSA再発症例に対して、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。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、無増悪生存期間、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

登録時に次のA群(内分泌療法群)、B群(放射線療法群)とにランダム割付される。治療開始後、臨床的再発または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できなくなった場合、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外照射､その後のTTFに対する抗アンドロゲン療法､さらにその後のTTFに対するLH-RHアナログ療法をもってプロトコール治療とする。両群ともLH-RHアナログ療法が有効である間はLH-RHアナログ療法を継続するため「プロトコール治療完了」は定義しない。両群とも、登録後は、3ヵ月毎に血清PSA測定を行う。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

本年度の研究成果として 1) 当研究は Japan Clinical Oncology Group(JCOG)にプロトコール審査及び、データマネージメントを依頼し準備を進めている。H16年4月13日、審査を終了しプロトコール承認を受け、5月より、患者登録を開始した。H17年3月31日現在、登録症例数は7例である。

D. 考察

患者登録は各施設のIRB承認を得なければならないため、本年度は登録症例数が少ないが、今後積極的に患者登録を進めて行きたい。

E. 結論=JCOGにプロトコールの承認を受け、各施設の倫理委員会の承認を得て、患者登録を開始した。

F. 健康危険情報

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) Yamanaka H, Ito K, Naito S et al, Effectiveness of adjuvant intermittent endocrine therapy following neoadjuvant endocrine therapy and external beam radiation therapy in men with locally advanced prostate cancer. Prostate. 2005,63:56-64.

3) Akaza H, Usami M, Hinotsu S, et al. Characteristics of patients with prostate cancer who have initially been treated by hormone therapy in Japan: J-CaP surveillance. Jpn J Clin Oncol. 34:329-336, 2004.

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) 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かんする研究」2005 年 2 月 15 日、がん臨床研究成果発表会（研究者向け）にて発表。

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。

厚生科学研究費補助金（がん臨床研究事業）

分担研究報告書

分担研究者　横溝　晃

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

研究要旨
日本の限局性前立腺癌対する根治術後のアウトカム研究を行った。

分担研究者氏名：　横溝　晃
所属機関名、職名：九州大学大学院医学研究院泌尿器科　助手

A. 研究目的=限局性前立腺癌に対する根治的前立腺摘除術は、標準的な根治治療として広く行われているが、PSA 再発症例の頻度、時期、その後の治療法について、本邦における集積は行なわれていない。そのため、今回、全国より患者データの集積を行い、その治療成果と経過について解析を行なった。

B. 研究方法= H8 年 1 月～H14 年 6 月に臨床病期 T2 以下 N0M0 の限局性前立腺癌の診断にて、術前術後の補助療法を行わず、根治的前立腺摘除術が施行され、術後 PSA 値が一旦測定限界値まで低下した症例を対象とした。JCOG 泌尿器科腫瘍研究グループ 37 施設を対象に後ろ向き臨床調査を行い解析した。

C. 研究結果
総症例は 1192 症例、手術時年齢の中央値は 67 歳（48 歳～83 歳）、生検の Gleason score の中央値は 3＋3＝6 であった。臨床病期は I 期が 2.3%、II 期が 97.7%であった。全症例の観察期間は 3.8 年と比較的短いが、PSA 再発を来した症例が 25.1%あり、再発までの期間の中央値は術後 365 日であった。その後の治療法は、内分泌療法 23.2%、放射線療法 20.5%、両者 2.7%、経過観察のみ 22.8%、不明 30.8%であった。また、術後病理病期は pT3 以上 32.6%あり、欧米と同様に術前の臨床病期での under staging が問題と考えられた。予後に関しては、明らかな癌死は 7 名のみであり、極めて良好であった。

D. 考察
日本人は、欧米に比べ前立腺癌の発症頻度は低いことが知られているが、限局性前立腺癌対する根治術後のアウトカムは欧米のそれとほぼ同等の結果となっている。

E. 結論=根治的前立腺摘除術後のPSA再発を来した症例が25.1%あり、そのアウトカムは欧米と同等である。

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. 学会発表
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。2005年4月14日、第93回日本泌尿器科学会総会で発表予定。

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。

厚生科学研究費補助金（がん臨床研究事業）

分担研究報告書

分担研究者　山中英壽他

局所的進行前立腺癌患者における外照射放射線治療の後のアジュバント内分泌療法に関する研究

研究要旨
局所的進行前立腺癌患者における外照射放射線治療後のアジュバント内分泌療法で、間欠療法が有用である。

分担研究者氏名：山中英壽
所属機関名、職名：群馬大学医学部泌尿器科、教授

A. 研究目的
局所的進行前立腺癌患者における外照射放射線治療（EBRT）後のアジュバント内分泌療法の方法とその最適期間を明らかにする。

B. 研究方法
フレアアップ防止のための２週間の抗男性ホルモン治療後、6ヵ月間LHRHアゴニストを投与され、前立腺に対する 72Gy の EBRT 後、PSA が 10 ng/ml 以下になった患者を２群（持続性アンドロゲン除去群と間欠性アンドロゲン除去群）にランダム割した。

C. 研究結果
188 例（87%）が、プロトコール治療中である。登録時の PSA の中央値は 25.3ng/ml であった。EBRT で治療された 157 症例のうち、153 例(97.5%)で、17.3 ヵ月の平均追跡期間で PSA の上昇が見られなかった。

D. 考察
本研究は、EBRT後の間欠的内分泌療法の有用性を示唆する。しかし経過観察期間が短くて、結論好けるのは早急である。

E. 結論=局所的進行前立腺癌患者における外照射放射線治療の後のアジュバント内分泌療法に関して、間欠的アンドロゲン除去療法が有用化かも知れない。

G. 研究発表
1. 論文発表
Yamanaka H, Ito K, Naito S et al, Effectiveness of adjuvant intermittent endocrine therapy following neoadjuvant endocrine therapy and external beam radiation therapy in men with locally advanced prostate cancer. Prostate. 2005, 63:56-64.
2. 学会発表

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。

厚生科学研究費補助金（がん臨床研究事業）

分担研究報告書

分担研究者　高橋　公太

アンドロゲン除去療法による前立腺組織内テストステロンに関する研究

研究要旨
日本の限局性前立腺癌対する根治術後のアウトカム研究を行った。

分担研究者氏名：　高橋　公太
所属機関名、職名：新潟大学泌尿器科　教授

A. 研究目的
アンドロゲン除去療法が前立腺組織のジヒドロテストステロン（DHT）・レベルに与える影響は、明らかではない。そのため、我々は、アンドロゲン除去療法の前後に前立腺の組織でDHT濃度を分析した。

B. 研究方法=計 103 人の患者は、前立腺生検を受けた。34 人が癌なし、69 人の患者は前立腺癌と診断された。血清サンプルは、生検または前立腺切除の前に集められた。前立腺組織と血清の DHT 濃度は、液体クロマトグラフィ/エレクトロスプレー・イオン化-質量分析を使用して分析された。前立腺癌患者 30 人において、6 ヵ月間の MAB 後、再生検もしくは摘出標本から前立腺組織の DHT 濃度を、を実行することによってまたは去勢とフルタ測定された。

C. 研究結果
アンドロゲン除去治療後の前立腺の組織の DHT 濃度は、治療前の約 25%であった。血清の DHT 濃度は、治療後、約 7.5%に減少した。アンドロゲン除去治療前の前立腺の組織の中の DHT レベルは、テストステロンの血清レベルと相関していなかった。副腎アンドロゲンの血清レベルは、アンドロゲン剥奪治療の後、約 60%になった。

D. 考察
アンドロゲン除去治療後の前立腺組織のDHTは前立腺内でいわゆるintracrine生産される。そして、副腎アンドロゲンをDHTに変換する。アンドロゲン除去療法後にまだ前立腺内に残っているDHTは、5alpha-還元酵素阻害剤と抗男性ホルモン（去勢と同様に）の組合せのような新しい治療が必要となる可能性がある。
E. 結論=アンドロゲン除去療法による前立腺組織内DHT濃度は血清レベルより高い。

G. 研究発表
1. 論文発表
Nishiyama T, Hashimoto Y, Takahashi K. The influence of androgen deprivation therapy on dihydrotestosterone levels in the prostatic tissue of patients with prostate cancer. Clin Cancer Res. 10:7121-7126, 2004.

2. 学会発表
前立腺癌に対するアンドロゲン抑制療法に伴う前立腺組織内dihydrotestosterone level の変化、2004年９月27日、第62回日本癌学会総会

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。

厚生科学研究費補助金（がん臨床研究事業）

分担研究報告書

分担研究者　赤座英之

日本における前立腺癌の内分泌療法の治療成績に関する研究

研究要旨
日本の大多数の前立腺癌患者は、ホルモン療法を受けている。

分担研究者氏名：　赤座英之
所属機関名、職名：筑波大学大学院泌尿器科　教授

A. 研究目的

前立腺癌のホルモン療法は、広く日本に普及しているが、十分な治療効果判定はなされていない。今回、治療ガイドラインを確立するため、日本におけるホルモン療法の現状と患者背景を評価した。

B. 研究方法

初期治療としてホルモン療法が施行された前立腺癌患者は、J-CaP 登録システムを通して、登録された。今回は、背景因子を要約する。

C. 研究結果

2001 年 1 月から 2003 年 10 月まで、17,872 人の患者が、日本の 395 の施設から登録され、17,312 人の患者の背景因子が、分析された。T1、T2、T3 と T4 は、それぞれ、22.9、35.1、32.9 と 8.6%であった。ホルモン療法のうち、77.5%は、初期治療としてもホルモン療法であった。また、ネオアジュバント設定とアジュバント設定はそれぞれ、18.1 と 4.3%であった。ホルモン療法の約 60%は、LH-RHa と抗男性ホルモンを併用したホルモン療法であった。

D. 考察

この傾向が日本の泌尿器科医の単なる過去の治療経験の継続結果なのか、または、欧米での治療と比較して日本の患者の治療効果と有害事象の差に基づく結果であるのか評価が必要である。

E. 結論

患者の年齢、TNM、疾病のステージ、組織学的背景にかかわりなく、日本の大多数の前立腺癌患者は、ホルモン療法を受けている。

G. 研究発表

1. 論文発表

Akaza H, Usami M, Hinotsu S, et al. Characteristics of patients with prostate cancer who have initially been treated by hormone therapy in Japan: J-CaP surveillance. Jpn J Clin Oncol. 34:329-336, 2004.

2. 学会発表

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。

厚生科学研究費補助金（がん臨床研究事業）

分担研究報告書

分担研究者　篠原　信雄

日本の局所進行前立腺癌の治療成績に関する研究

研究要旨
局所進行前立腺癌に対する治療として根治手術、放射線療法およびホルモン療法で、治療成績に有意差はない。

分担研究者氏名：　篠原　信雄
所属機関名、職名：北海道大学大学院外科治療学
腎泌尿器外科学　講師

A. 研究目的

局所進行前立腺癌に対する診断と治療の日本のガイドラインを作成するため、1988 年から 2000 まで日本の東北地区の 6 つの学術機関で治療された局所進行前立腺癌患者を調査した。

B. 研究方法

根治的前立腺摘除術（RP）、放射線療法および初期ホルモン療法によって治療された局所進行前立腺癌患者 391 人を対象とした。疾患特異的生存率と臨床病理学的特徴や治療方法との関連について解析を行なった。統計解析法として、マン-ホイットニーU検定、クラスカル-ウォリス、カイ二乗とログランク検定が用いられた。

C. 研究結果

低 PSA 値（P = 0.023）と良いパフォーマンス状態（P = 0.001）*をもつ 128 人の患者は、RP を受けた。RP の前のネオアジュバント・ホルモン療法は、これらの 128 人の患者のうちの 68 人（53%）が受けていた。また、66 人（52%）は、即時のアジュバント・ホルモン療法を受けた。放射線療法で治療された 87 人の患者の内、75 人（86%）は密封小線源療法なしの外照射放射線療法（EBRT）を受けた、そして、12 人（14%）は主要な方法として密封小線源療法を受けた。ネオアジュバント・ホルモン療法は、87 人の患者（64%）のうちの 56 人に、また 48 人（55%）は、即時のアジュバント・ホルモン療法を受けた。単独で初期ホルモン療法を受けた 176 人の患者のうち、併用抗アンドロゲン療法（CAB）と外科的もしくは化学的去勢を受けた人はそれぞれ 76 人（43%）と 85 人（48%）であった。また RP、EBRT とホルモン療法で治療された患者の 5 年の疾患特異的生存率は、それぞれ、90%、98%と 89%であった。

D. 考察

今回の治療選択枝は欧州および米国のガイドラインで述べられるものと有意差がなかった。そして、各々の短期疾患特異的生存率は今までの報告と遜色なかった。局所的進行前立腺癌の日本のガイドラインを作成するため、更なる調査が、必要である。

E. 結論

局所進行前立腺癌に対する治療としてRP、放射線療法およびホルモン療法で、治療成績に有意差はない。

G. 研究発表

1. 論文発表

Hachiya T, Akakura K, Saito S, et al. A retrospective study of the treatment of locally advanced prostate cancer by six institutions in eastern and north-eastern Japan. BJU Int. 95:534-540, 2005.

2. 学会発表

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。

厚生科学研究費補助金（がん臨床研究事業）

分担研究報告書

分担研究者　井川　幹夫

前立腺癌細胞死に関する分子生物学的解析

研究要旨
前立腺癌において、パクリタキセルによるチミジンホスホリラーゼの誘導と細胞死の関連について解析した。

主任研究者氏名：　井川　幹夫
所属機関名、職名：島根大学医学部泌尿器科　教授

A. 研究目的

最近、パクリタキセル（PTX）を使用した化学療法の有用性とPTXによるチミジンホスホリラーゼ（TP）の誘導が報告されている。一方で、TPは生体外でカスパーゼ-8活性化の抑制を通して、腫瘍細胞に抗アポトーシスな効果がある。この分子機序を前立腺癌にて検討した。

B. 研究方法

=全ホルモン抵抗性前立腺癌症例８例と前立腺癌細胞株（PC-3、DU 145とLNCaP）において、PTXにより誘導されたTP発現や、アンチセンスTP処置によるアポトーシス関連分子の動態を解析した。

C. 研究結果

高いTP発現のあるホルモン抵抗性の前立腺癌症例６例で、化学療法後、切断されたカスパーゼ-8は発現されなかった。しかし前立腺癌細胞株（PC-3、DU 145とLNCaP）において、PTX処置の後のTP発現は、用量依存的に明らかに発現上昇していた。前立腺癌細胞株で、PTXとアンチセンスTP処置で細胞生存度は、単独PTX処置と比較して時間依存的と用量依存的に有意に低下していた。同様に、前立腺癌細胞株で、PTXとアンチセンスTP処置でアポトーシスインデックスは、PTX単独と比較すると有意に増加した。TPアンチセンス・トランスフェクションによって、PTX誘導されたTP翻訳を完全な抑制すると、カスパーゼ-3ポリ（ADPリボース）重合酵素の切断は増加した。そして、PTX用量依存的にカスパーゼ-8は活性化されていた。これらの結果は、PTX誘導されたTP誘導はカスパーゼ-8活性化の低下と関連することを示している。

D. 考察

本研究は、PTX誘導されたTP発現抑制がPTXで処理された前立腺癌細胞株でアポトーシスを誘導することを明らかにした最初の報告である。
我々の結果は、TPがPC細胞でPTXによって媒介されるアポプトーシスの作用を強化することで新しい分子標的になりうることを示している。

E. 結論

=前立腺癌において、パクリタキセルによるチミジンホスホリラーゼの誘導を阻害すると細胞死を促進し、それはカスパーゼ-8活性化と関連している。

G. 研究発表

1. 論文発表

Kikuno N, Moriyama-Gonda N, Yoshino T et al. Blockade of paclitaxel-induced thymidine phosphorylase expression can accelerate apoptosis in human prostate cancer cells. Cancer Res. 64:7526-7532, 2004.

2. 学会発表

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。

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
Yamanaka H, Ito K, Naito S et al	Effectiveness of adjuvant intermittent endocrine therapy following neoadjuvant endocrine therapy and external beam radiation therapy in men with locally advanced prostate cancer.	Prostate	63	56-64	2005
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Kikuno N, Moriyama-Gonda N, Yoshino T et al.	Blockade of paclitaxel-induced thymidine phosphorylase expression can accelerate apoptosis in human prostate cancer cells.	Cancer Res.	64	7526-7532	2004

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.

A. Yokomizo, Study Coordinator; H. Kawamoto, Protocol Coordinator; K. Nihei, Radiation Oncology Study Coordinator; N. Ishizuka, Study Statistician; Y. Kakehi, QOL Coordinator; K. Tobisu, Chair of Urologic Oncology Study Group; S. Naito, Study Chair.

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The Prostate 63:56 – 64 (2005)

Effectiveness of Adjuvant Intermittent Endocrine Therapy Following Neoadjuvant EndocrineTherapy and External Beam RadiationTherapy in Men With Locally Advanced Prostate Cancer

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PURPOSE. To clarify the optimal duration and methods for adjuvant endocrine therapy after external beam radiation therapy (EBRT) in patients with locally advanced prostate cancer.
MATERIALS AND METHODS. Between 2001 and 2003, 215 patients with locally advanced prostate cancer were enrolled in the study. Patients were registered as primary candidates of the study and were treated with 6 months of LHRH agonist, with short-term of antiandrogen treatment for flare-up prevention. Patients with PSA levels below 10 ng/ml after the 6-month endocrine treatment were randomly divided into two arms. Then, a total dose of 72 Gy was given to the prostate. After 14 months of the protocol treatment, patients were treated with continuous androgen ablation (arm 1) or intermittent androgen ablation (arm 2).
RESULTS. A total of 188 cases (87%) remained in the protocol. The median PSA level at entry was 25.3 ng/ml. The Gleason score was 2–6 in 32 cases (16%), 7 in 94 cases (48%), and 8–10 in 68 cases (35%). The median PSA level showed a remarkable decrease to 1.1, 0.2, and 0.1 ng/ml, after 6, 8, and 14 months of the protocol treatment, respectively. Of the 157 cases treated with EBRT, 153 cases (97.5%) had no biochemical failure in the mean follow-up of 17.3 months.

All authors are members of The National Research Project on Endocrine-Radiation Combination Therapy for Locally Advanced Prostate Cancer.

Grant sponsor: The Ministry of Health, Labor and Welfare in Japan (to Hidetoshi Yamanaka); Grant number: 12–14.

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Received 6 June 2004; Accepted 9 August 2004
DOI 10.1002/pros.20171
Published online 5 October 2004 in Wiley InterScience (www.interscience.wiley.com).

CONCLUSIONS. The present study may reveal the possibilities of intermittent endocrine therapy after EBRT. However, the follow-up interval is short and little can be said about the results observed so far, exception of acute tolerance and patient acceptance of the protocol. *Prostate 63: 56–64, 2005.* © 2004 Wiley-Liss, Inc.

KEY WORDS: **prostate cancer; intermittent hormonal therapy; external beam radiation therapy**

INTRODUCTION

Treatment of prostate cancer has been one of the most important issues for elderly males, especially in Western countries. In Japan, prostate cancer is the eighth leading life-threatening cancer in males [1]. However, in the past 10 years, the probability of cause of death from prostate cancer has increased and will increase rapidly in the future [1,2]. In the present study, we have conducted a prospective randomized control trial (RCT) for locally advanced prostate cancer in order to clarify how to treat it with adjuvant endocrine therapy after external beam radiation therapy (EBRT). The previous RCT for locally advanced prostate cancer already revealed that cancer causes of death and also all causes of death may decrease in men treated with both EBRT and endocrine therapy (neoadjuvant and/or adjuvant) in comparison with those treated with EBRT alone [3–5]. Bolla et al. [3] demonstrated that 5-year disease-free survival was higher at 85% in patients with locally advanced prostate cancer treated with EBRT and 3 years of endocrine therapy than in those treated with EBRT alone. However, the optimal timing and duration for endocrine therapy as adjuvant or neoadjuvant treatment with EBRT have not been solved. Furthermore, those issues should be discussed in terms of not only survival advantage, but also improvement of QOL.

Alternatively, the concept of intermittent endocrine therapy was proposed as a possible treatment to prolong the hormone naïve status of prostate cancer. According to basic research on androgen-dependent Shionogi carcinoma in mice, androgen-dependent status recovered after endocrine treatment was stopped in hormone-independent prostate cancer. This phenomenon would result in induction of apoptosis several times during intermittent androgen deprivation [6]. Although the treatment efficacy of intermittent hormonal therapy has not been confirmed in clinical settings, there may be some advantages in the cost for treatment, prevention of osteoporosis development, and recovery of libido.

The present assessment of combination therapy with EBRT and endocrine therapy for locally advanced prostate cancer may be of positive concern. However, it may be difficult to answer how long neoadjuvant and/or adjuvant endocrine therapy should be used. Several RCTs have been carried out or are ongoing in Europe and the USA. However, there have been no RCTs comparing the treatment efficacy and QOL between long-term adjuvant endocrine therapy and intermittent adjuvant endocrine therapy after treatment with EBRT and neoadjuvant endocrine therapy for locally advanced prostate cancer. To answer uncertainties on the above issues, the present multi-center RCT was conducted as a national cancer research project, which has been supported by the Ministry of Health, Labor and Welfare in Japan.

The primary endpoint of this study is biochemical relapse-free survival and the secondary endpoints are overall survival, cancer-specific survival and longitudinal QOL assessment between two groups. It is expected that the survival advantage by means of biochemical relapse-free survival in the continuous adjuvant endocrine treatment group may be better than that in the intermittent endocrine treatment group. Alternatively, adverse effects in patients treated with long-term androgen deprivation may increase in comparison with those treated with intermittent androgen deprivation. After completing this RCT, we expect to be able to distinguish patients who can benefit more from continuous hormonal treatment by means of survival with minimized adverse effect from those who can benefit more from intermittent hormonal treatment by means of maintaining QOL without dying of prostate cancer or suffering cancer-related complications.

MATERIALS AND METHODS

Study Protocol

Patients were eligible to participate in the protocol at any of 15 medical centers if they had biopsy-proven untreated adenocarcinoma of the prostate with clinical stage T3N0M0 or T4N0M0 (bladder neck invasion alone) and were younger than 80-years-old. Clinical stage was confirmed according to UICC 1997 by digital rectal examination (DRE), transrectal ultrasonography (TRUS), chest X-ray, bone scan, abdominal-to-pelvic CT and pelvic MRI. Patients who were treated with antiandrogen or any adrenocortical steroid hormones, or had undergone subcapsular prostatectomy or transurethral resection of the prostate including laser ablation for benign prostatic hyperplasia, were

eliminated from this study. Pelvic MRI was conducted before or 3 months after prostate biopsy.

Patients were registered as primary candidates of the study and were treated with 2 weeks of steroidal antiandrogen (chlormadinone acetate; CMA), then with both luteinizing hormone-releasing hormone (LHRH) agonist (leuprorelin or goserelin) and another 2 weeks of antiandrogen, and thereafter with LHRH agonist alone. After 6 months of endocrine treatment with LHRH agonist, only patients with PSA levels lower than 10 ng/ml, with a PSA level lower than the pretreatment level and without clinically apparent metastatic disease were enrolled in the following protocol as final candidates (2nd-line registration). All Gleason scores were reviewed by one urologic pathologist (M.H.) before the 2nd-line registration. After the 2nd-line registration was done, the patients were randomly divided into two groups according to institutions, age (younger than 70, 70 years, or older), PSA levels after 6 months of endocrine treatment (4.0 ng/ml or lower, 4.1 ng/ml or greater), and Gleason score (7 or less, 8–10) as follows: (1) continuous androgen ablation group (arm 1), (2) intermittent androgen ablation group (hormonal therapy must be stopped 6 months after the day of final EBRT treatment) (arm 2) (Fig. 1). All of these patients were treated with EBRT immediately after completing 2nd-line registration.

Details on the procedures of radiation therapy were specified in the protocol as follows: (1) radiation field should be limited to the prostate in all cases, and the seminal vesicle should be included in radiation fields only in cases with seminal vesicle involvement being highly suspected by imaging. Elective pelvic lymph node irradiation is not performed. (2) Conformal radiation therapy, 4-field oblique or box technique, or pendulum methods are recommended in order to minimize adverse effects in the rectum and bladder. (3) A total dose of 72 Gy should be given in 36 fractions, 5 fractions per week. (4) Verification films should be taken at least two times during the radiation therapy. (5) The gross tumor volume (GTV) and clinical target volume (CTV) are the prostate gland in cases without seminal vesicle involvement. The planning target volume (PTV) margin is 10 mm from the CTV. In cases with seminal vesicle involvement, the GTV and CTV include the seminal vesicles in addition to the prostate gland. In multi-portal treatment, every portal should be irradiated in every treatment. (6) Only photon beam energy of 6 MV or more is accepted.

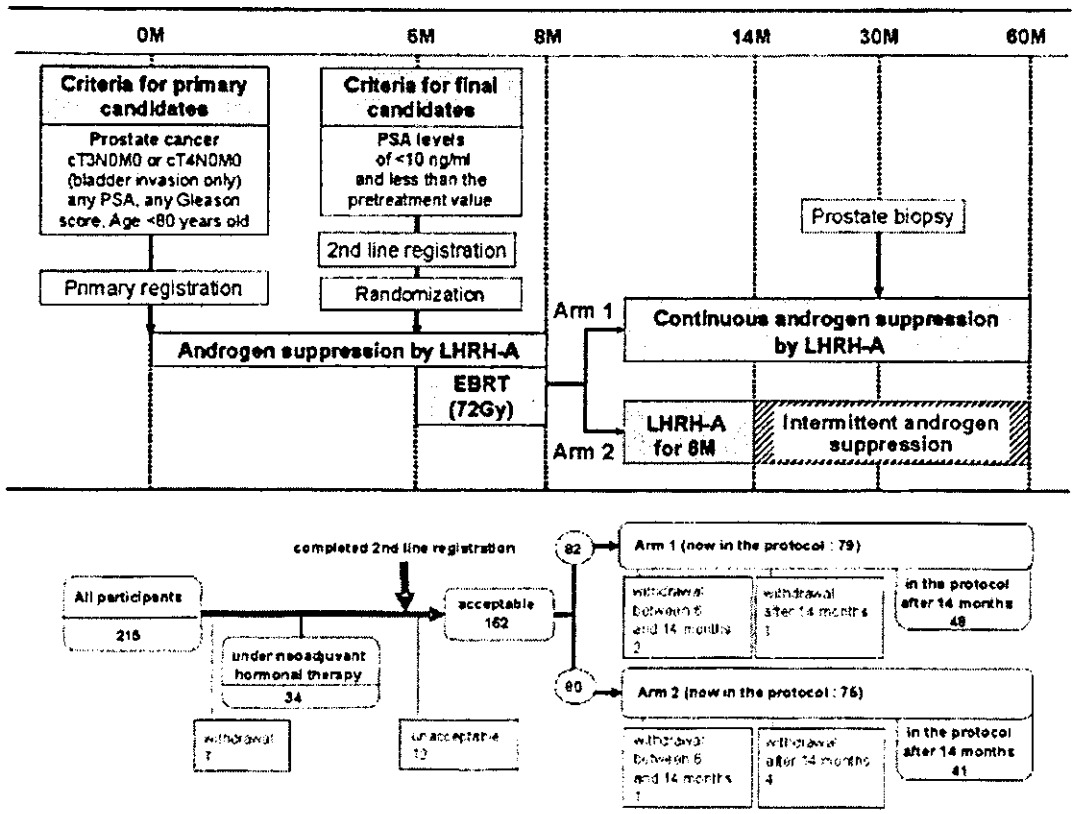

Fig. 1. Scheme of the study protocol, the number of patients registered and the present status of those patients in this study protocol. LHRH-A, LHRH agonist; EBRT, external beam radiation therapy.

Acute radiation morbidity should be evaluated by using common toxicity criteria of NCI within 90 days after radiation therapy, and late radiation morbidity should be evaluated by using the late radiation morbidity criteria of RTOG/EORTC.

Patients assigned to the intermittent androgen ablation group (arm 2) resumed hormonal therapy if they had PSA level of 10 ng/ml or greater or a clinical recurrence of disease. Resumed hormonal therapy would continue until the PSA levels decreased to below 1.0 ng/ml. If the PSA levels did not decrease to below 1.0 ng/ml, the possibility of biochemical recurrence of disease would be evaluated using the criteria in the study.

Biochemical failure was defined according to modified ASTRO criteria as follows: (1) three consecutive PSA increases in every 3-month interval and with a PSA velocity per 3 months of 0.5 ng/ml or greater, or (2) PSA levels increasing to 10 ng/ml or more. If three consecutive monthly-checked PSA levels increased rapidly at a PSA velocity per month of 0.17 ng/ml or greater, the researchers could designate that phenomenon a biochemical recurrence. The day of biochemical recurrence was defined between the day immediately before PSA increase and the day of initial PSA increase.

Clinical relapse was defined as progressive disease at a new site, an increase in the size of a nodule or cancer lesion on any images of the prostate, worse performance status, or body weight loss due to progression of prostate cancer.

Figure 2 shows the clinical assessment schedule of evaluation of treatment efficacy, QOL and adverse effects. PSA levels are measured monthly. Bone scan, abdominal-to-pelvic CT and chest X-ray must be conducted every 6 months for 1 year, and yearly thereafter. Pelvic MRI is conducted yearly. Prostate biopsy is recommended at around 2 years after the first date of EBRT. QOL can be assessed using FACT-P and part of the UCLA prostate cancer index before the initial endocrine therapy (0 months), immediately before EBRT (6 months), immediately after EBRT (8 months), 6 months after EBRT is completed (14 months), and 6 months after dividing the patients into two arms (20 months).

In the present study, treatment efficacy, adverse effects and QOL were compared between the two groups. The primary endpoint was biochemical (PSA) relapse-free survival. The secondary endpoints were overall survival, cause-specific survival, and longitudinal QOL assessment.

Cost effectiveness was also compared between men treated with continuous endocrine therapy and those with intermittent hormonal therapy.

The study protocol of this RCT and the documents of informed consent for the participants were approved by the IRB of all facilities, and a copy of the IRB approval document has been stored in the research bureau.

Statistical Consideration on Primary Endpoint of the Study

There has been no conclusive information on the optimal treatment strategy of adjuvant endocrine therapy after EBRT in patients with locally advanced prostate cancer. Therefore, the present study was conducted on the basis of the following two hypotheses. First, there was the non-recessive hypothesis, that the cumulative biochemical relapse-free survival rate in the intermittent endocrine therapy group (arm 2) would not be remarkably worse than that in the

Variables	Months after enrollment																				
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
PSA measurement	◎	← monthly check-up →																			◎
Digital rectal examination	◎	○	◎	○	◎	○	◎	○	◎	○	◎	○	◎	○	◎	○	◎	○	◎	○	◎
Transrectal ultrasonography	◎	○	◎	○	◎	○	◎	○	◎	○	◎	○	◎	○	◎	○	◎	○	◎	○	◎
Abdominal and pelvic CT	◎		◎		◎				◎				◎				◎				◎
Pelvic or endorectal MRI	◎				◎				◎				◎				◎				◎
Bone scintigraphy	◎		◎		◎				◎				◎				◎				◎
Chest X-P or Chest CT	◎		◎		◎				◎				◎				◎				◎
Prostate biopsy	◎										◎										◎
QOL assessment	◎		◎	◎(8M)		◎(14M)		◎(20M)													
Uroflowmetry	○				○				○				○				○				○
Residual urine	○				○				○				○				○				○
Blood test	◎	◎	◎	◎	◎		◎		◎		◎		◎		◎		◎		◎		◎
Performance status	◎				◎				◎				◎				◎				◎

◎ Essential assessment
○ Recommended assessment

Fig. 2. Assessment protocol for treatment effects, adverse effects and QOL in the study.

continuous endocrine therapy group (arm 1). If intermittent endocrine therapy after definitive EBRT is acceptable, the present study may be worthwhile from social, economic, and QOL points of view. The study would verify that the cumulative biochemical relapse-free survival rate in the continuous endocrine therapy group (arm 1) can be significantly better than that in the intermittent endocrine therapy group (arm 2). The second hypothesis was that continuous androgen suppression after EBRT may be worthwhile in terms of treatment efficacy, because of the specific characteristics of treatment for prostate cancer, which is famous for being hormone-naïve for a while in most cases. It would be possible to verify both of the above-mentioned hypotheses simultaneously by investigating the interval estimation of the hazard ratio, if the linearity can assume either hypothesis by carrying out the interval estimation of the hazard ratio, if the linearity can assume the recurrence hazard. Then, the 90% confidence interval for the hazard ratio (intermittent group/continuous group) can be calculated at both sides. If the upper limit is within the acceptable threshold, then the non-recessive hypothesis has been verified. On the other hand, the survival rate of the continuous group (arm 1) would be considered significantly excellent if the lower limit surpasses 1.

The main subjects for the analyses are qualified patients from whom the protocol treatments have been properly conducted. The analysis is limited to cases without remarkable contravention and deviation is carried out. The survival curve and recurrence-free survival will be estimated using Kaplan–Meier methods, and the confidence interval of the proportion at 3 and 5 years calculated by the formula of Greenwood. The hazard ratio is estimated by score statistic values from the log rank test results. Supplemental, by the hazard ratio is estimated by the Cox's proportional hazard model using the allocated factors at the 2nd registry, except for that of the facilities. The verification of the proportion hazard is done by double logarithm plotting, and the necessary analysis is carried out for the interpretation of results, such as the appliance of the Cox's proportional hazard model for time-dependent changes of the effects, when there is a remarkable dissociation from the proportion hazard. Prognostic factors which seem to be important are analyzed by means of each allocated factor at the 2nd registry except for that of the facilities, and the uniformity of differences between the two groups is examined. If necessary, the interaction between each facility and its remaining allocated factors at the 2nd registry will be analyzed, and also the differences between one facility and another.

The upper limits for the determination of non-recessiveness are 1.5 and 1.333. These upper limits may be acceptable if the hazard for combination treatment with EBRT and long-term endocrine therapy is outlining these thresholds compared with that for EBRT alone. These consequences have already been clarified by Bolla et al. [3], in which the confidence interval of hazard for disease-free survival was demonstrated between 1/0.15 and 1/0.32. According to the results of the Bolla study [3], an upper limit for the determination of non-recessiveness of 1.5 may be acceptable. On the other hand, the upper limit of 1.333 will also be used for an alternative analysis, because it may be a reference threshold for RCTs comparing treatment efficacy for other cancers.

Intermediate Assessment and the Possibility of Withdrawal of This Protocol

At the time when the number of enrolled cases reaches half of the expected adequate number of cases, an intermediate analysis will be performed to investigate whether the main purpose of the test has already been achieved, and another at the time when the expected adequate number of cases is fully registered. The intermediate analysis will be investigated blind by one statistician (Y.O.) at the registration center of the study in Tokyo University. If the disease-free survival in one group is significantly worse than that in the other group after careful consideration of the intermediate analysis, it will be decided whether the study protocol should continue or not.

Number of Cases Required for the Study, When to Close the Registration, and the Follow-Up Period

Considering that the cumulative PSA recurrence rate within 5 years in treatment with endocrine monotherapy for locally advanced prostate cancer in Japanese was demonstrated at about 40% [7], and that in combination therapy with EBRT and endocrine therapy was demonstrated between 15 and 64% [3,4], the cumulative PSA recurrence rate within 5 years in men treated with 3 years of adjuvant endocrine therapy and EBRT, in the present study, was assumed to be 30% [3]. For non-recessive verification using a hazard ratio of 1.5 as an upper limit, 75 events are necessary in each group in order to have 80% statistical power on the basis of the alternative hypothesis, in which there is no difference in the disease-free survival rate between both groups. Alternatively, on the basis of the alternative hypothesis which uses a hazard ratio of 2, the necessary event number for the dominance verification in both groups is 55, for 80% statistical power. There may be 90–100 events in 300 patients in the protocol during 5 years of observation. Therefore, if the cumulative disease-free survival rate in the continuous endocrine group is better with a hazard ratio of 2 or

more than that in the intermittent endocrine group, it may be possible to verify the dominance with high probability, which would be 93–95% if the number of the events is 90–100. Alternatively, if the cumulative rates for disease-free survival are similar between the two groups, pursuing non-recessive verification can not be avoided. In fact, the power decreases to 61–65% if there are 90–100 events.

It is worthwhile to consider that the significance of the study is the reevaluation by meta analysis with other clinical researchers around the world, who have almost the same hypothesis for verification, when non-recessiveness and dominance can not be verified. On the other hand, it is also possible to continue registration for another few years in some cooperative facilities, because randomization to one of two arms may be permitted even in the ethics target. Furthermore, it would also be possible to conduct a multi-factorial experiment, containing the LHRH administration period as a factor, and then performing a meta analysis.

The number of expected registered cases was set at 300 and the registration period 3 years in the protocol.

Patient Characteristics Registered

Between February 2001 and November 2003, 215 patients were registered in the protocol. Table I shows the clinicopathological features of patients registered in the present study. Age ranged from 54 to 79 years (70.6 ± 5.6, mean ± SD; 72.0, median). The median PSA level at entry was 25.3 ng/ml (45.1 ± 64.3; mean ± SD). The clinical stage was T3N0M0 in 202 (94.0%) and T4N0M0 in 13 (6.0%). The Gleason score diagnosed by the central urologic pathologist was 2–6 in 32 cases (16%), 7 in 94 cases (48%), and 8–10 in 68 cases (35%).

Details in the progression of this protocol in all participants are shown in Figure 1. On November 15, 2003, 188 patients (87.4%) were still in the protocol and 27 patients (12.6%) had withdrawn from the protocol. A total of 19, 3, and 5 cases were excluded from the protocol during 0–6 months, 6–14 months, and after 14 months of the protocol treatment, respectively. Of the 27 cases excluded from the protocol, 3 cases (11%) had adverse effects, 6 cases (22%) withdrew their agreement to this protocol, 1 case (4%) had other life-threatening cancer during the protocol treatment, 4 cases (15%) had recurrence of disease, 12 cases (44%) did not meet the criteria at the 2nd registration, and 1 case (4%) was excluded from the protocol by a contravention issue.

Of the 188 cases in the protocol, 34 patients (18%) received neoadjuvant hormonal therapy between 0 and 6 months of the protocol treatment, 64 patients (34%) were treated with EBRT and adjuvant endocrine therapy between 6 and 14 months, and 90 patients (48%) were treated with continuous or intermittent androgen ablation after 14 months of the protocol treatment.

Of the 95 cases who continued the protocol treatment after 14 months, 49 were treated with continuous endocrine treatment (arm 1) and 46 were treated with intermittent endocrine treatment (arm 2). The mean follow-up duration was 22.2 months (ranged from 14 to 30 months) in arm 1 and 23.0 months (ranged from 14 to 30 months) in arm 2. Of the 49 patients registered in arm 1, 1 case (2.0%) was excluded from the protocol because of recurrence of disease. Of the 46 cases registered in arm 2, 4 cases (8.7%) were excluded from the protocol treatment, because of recurrence of disease in 2 cases, contravention of the protocol in 1 case, and their own decision in 1 case.

TABLE I. Clinicopathological Features at Entry

Age	
Mean ± SD	70.6 ± 5.6
Median	72
Age distribution	
54–59	7 (3.3%)
60–64	28 (13.0%)
65–69	38 (17.7%)
70–74	80 (37.2%)
75–79	62 (28.8%)
PSA level (ng/ml)	
Mean ± SD	45.1 ± 64.3
Median	25.3
PSA distribution	
0.0–4.0	3 (1.4%)
4.1–10.0	38 (17.7%)
10.1–20.0	41 (19.1%)
20.1–50.0	79 (36.7%)
50.1–100.0	33 (15.3%)
100.1–∞	21 (9.8%)
Gleason score by (hospital pathologists)	
2–6	26 (12.1%)
7	106 (49.3%)
8–10	83 (38.6%)
Primary Gleason grade (hospital pathologists)	
–3	92 (42.8%)
4–5	123 (57.2%)
Clinical stage	
T3N0M0	202 (94.0%)
T4N0M0	13 (6.0%)
Gleason score by (central pathologist)	
2–6	32 (16.5%)
7	94 (48.5%)
8–10	68 (35.1%)
Primary Gleason grade (central pathologist)	
–3	99 (51.0%)
4–5	95 (49.0%)