Faculty Development Piloted

- In Madison VA and Univ Wisconsin
  - Organized by Alan Bridges COM, Craig Renner PSM
- Planned mixed with target of opportunities
  - Day One, AM → Case conference
    - Resident gave case; I was discussant
    - Used poster and one-page cognitive aids
  - Day One, PM → Fac Dev Session 1
    - How to run case conference, modulettes, consult service
  - Day Two, AM → Case Conference
    - I gave case (standardized); Chief Resident and Attending were discussant

Faculty Development Developed

- Several teleconferences with existing pioneers
  - Sept 2003-Jan2004
- One day face-to-face (Jan 2004)
  - Three physician teachers, two nurse teachers
- Now!!

Optional Pre-work

1) Participate in an RCA; or discuss with your patient safety manager
   - How might the event or proposed remedies affect residents?

2) Talk with residents about a close call
   - What kind of things prevented it from becoming an actual adverse event?

Conclusion

- Not huge consensus on content and formats
  - Mostly driven by pragmatics (requests to give a one hour talk...)
- Results from pilot testing are encouraging, but
  - Powerpoints are "evil"
  - Med students are likely harder audience
- Let's learn the module content together...
  - Before we judge
  - Recognize limitations to do the ideal

EBMの実践
-前立腺ガンの患者を例に-

(社)地域医療振興協会
名郷直樹
吉村 学

自己紹介

- 1986年 自治医大卒
- 同年 名古屋第二赤十字病院研修医
- 1988年 作手村国保診療所
- 1992年 自治医大地域医療学
- 1995年 作手村国保診療所
- 2003年 社団法人地域医療振興協会
  横須賀市立うわまち病院臨床研修センター
- 2004年 伊東市立伊東市民病院臨床研修センター
- 専門領域 地域医療、家庭医療、医学教育

このセッションの内容

- 眠くならないジャーナルクラブを体験する
- 治療にEBMの基本を学ぶ
  - EBMの5つのステップ
  - PECO
  - 歩きながら論文を読む
  - ACP Journal Clubと構造化抄録
  - 論文内容を患者にいかに説明するか実践する

患者シナリオ

- 72歳男性、海老原伝之輔さん。前立腺ガンの検診でPSA高値。泌尿器科で検査したところ、初期の前立腺ガンで手術すれば天皇陛下のように元気になりますよと、手術を勧められた。そこでセカンドオピニオンを求めて診療所を受診した。

あなたならどうする

- あなたがこの診療所医師であったら、どんなセカンドオピニオンを提供しますか？
- 隣同士で話し合ってみてください

EBMスタイルジャーナルクラブの掟

- 準備しない
- その場で読む
- みんなで読む
- 公式に沿って読む
  - 負担を最小限に
- 臨床現場でどう使うか議論
  - ロールプレイなどを使う
  - 二次資料も同時にチェック

EBMの5つのステップ

1. 問題の定式化
2. 問題についての情報収集
3. 得られた情報の批判的吟味 ←
4. 情報の患者への適用
5. 1-4のステップの評価

3分間で論文を読む

- A RANDOMIZED TRIAL COMPARING RADICAL PROSTATECTOMY WITH WATCHFUL WAITING IN EARLY PROSTATE CANCER. N Engl J Med 2002;347:781-9.
- まず3分で論文を読んで見ましょう
- 重要だと思う部分を書き抜きましょう
- 隣同士で見せ合って、どこが重要か話し合ってみましょう

批判的吟味の3原則

- 情報の表す3つのもの
  - 真実
  - バイアス
    - 研究デザインの吟味
  - 偶然
    - 統計学の適用の吟味

様々なバイアス

- 情報(測定)バイアス
  - 情報のあるところ、測るところにバイアスあり
- 選択バイアス
  - 選ぶところにバイアスあり
- 交絡因子
  - 間に入る因子にバイアスあり

情報バイアス

- 情報が入ると結果をゆがめる
  - 何の薬をのんでいるかわかっている
  - 実薬だとわかっていると効果を過大評価
  - プラセボだとわかっていると効果を過小評価
- マスキングで対処
  - 情報バイアスを避ける
  - プラセボの使用

選択バイアス

- 選ばれた対象が全体を代表していない
  - 薬好きが参加する
  - 新しい者好きが参加する
  - 大きな副作用の経験がない人が参加する
- ランダム抽出、悉皆調査で対処
  - 臨床試験では選択バイアスを避けられない
  - 観察研究では制御可能

交絡因子

- 間に入る因子に真の関連
  - 治療群の平均年齢が10歳以上若い
  - 100円ライターを持つと肺癌になりやすい
- ランダム化や多変量解析、マッチングで対処
  - 臨床試験ではランダム化、ITT解析
  - 観察研究では多変量解析、マッチング

バイアスと研究デザイン

- ランダム抽出により選択バイアスをコントロール
- 二重盲検により情報バイアスをコントロール
- ランダム化により交絡因子をコントロール
  - ランダム抽出二重盲検ランダム化試験で全てを考慮
  - 現実にランダム抽出は倫理的に不可能
  - 二重盲検ランダム化試験で治療効果を検討

3つの批判的吟味

- 研究方法は妥当か
- 結果は何か
- 患者に役立つか

批判的吟味パート1

研究方法は妥当か？

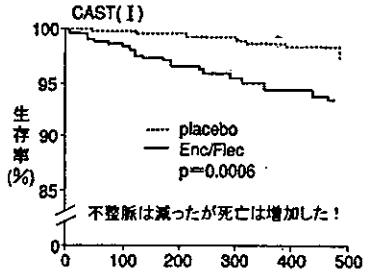
歩きながら論文を読む

- 研究方法は妥当か？
  - 論文のPECOを読む
  - ランダム化かどうか読む
  - ITT解析かどうか読む
    - 交絡因子のみはチェックする
- 結果は何か？
  - 一次アウトカムの結果を読む

PECO

- Patient:どんな患者に
- Exposure:どのような治療、検査をしたら
- Comparison:どんな治療、検査と比べ
- Outcome:どうなるか

不整脈を治療したら……



真のアウトカム(エンドポイント)

- 陳旧性心筋梗塞患者
  - 代用のアウトカム:不整脈
  - 真のアウトカム:突然死、死亡
- 前立腺ガン患者
  - 代用のアウトカム:腫瘍の縮小率
  - 真のアウトカム:前立腺ガンによる死亡、死亡

歩きながら論文を読む:妥当か？

- PECO
  - 抄録から
- アウトカム
  - Primaryという単語を探す

グループワーク1

- PECOを読み込みましょう
- それぞれで読み込んだら、周囲の人と見せ合って確認しましょう

論文のPECO

- Patient:T1b、T1c、T2の前立腺ガン患者
- Exposure:根治的前立腺摘除術
- Comparison:注意深い経過観察と比べて
- Outcome:前立腺ガンによる死亡(primary outcome)
  全死亡、転移なく生存、局所での悪化
  (secondary outcome)

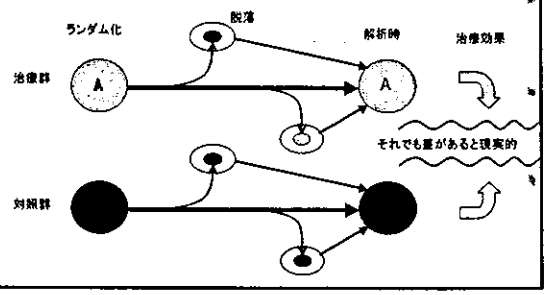
前立腺ガンによる死亡か、全死亡か

- どちらが重要なアウトカムと考えるか、周囲の人と議論しましょう
  - 死に直結する疾患の研究は死亡で判定すべき
  - 死に直結しない疾患は死亡では差が出ない
  - 胃潰瘍の治療の研究を死亡で評価することは困難

歩きながら論文を読む 治療編

- ランダム化比較試験か
- 解析時にもランダム化が守られているか
  - intention to treat analysis (ITT)

ITT(Intention To Treat)
:治療意図に基づく解析?



ランダム化、ITTについて読み込む

- まずは個人個人で
- 次に隣同士で
- 周囲の人で
  - どこに、どのように書かれていたか確認しましょう

歩きながら論文を読む:妥当か?2

- ランダム化
  - 表題から
- ITT解析
  - 図1から
  - 患者背景の表(通常table1)と解析の表の数字から

実際の論文で

- ランダム化比較試験
- ITT解析
  - どちらも満たす

批判的吟味パート2

結果は何か?

結果を評価する指標

- 相対指標：相対危険(Relative Risk:RR)
  - 割り算の指標
- 絶対指標：治療必要数
  (Number Needed to Treat:NNT)
  - 引き算の指標

RRとNNTでの治療効果の評価例

- 各群での脳卒中の発生率(例)
  治療群 5/1000 プラセボ群 10 /1000
  治療群 25 /100 プラセボ群 50 /100
- RRはどちらも 0.5
- NNTは 200と4
  両方での評価が重要

練習問題

- 介入群での心筋梗塞の発症 20%
- プラセボ群での発症 30%
  - RRとNNTを計算してみましょう
  - RR＝0.2／0.3＝0.67
  - RRR(相対危険減少)＝1－RR＝0.33
  - NNT＝1／(0.3－0.2)＝10
- それでは隣同士組になって、2題ずつ例題を出し合って見ましょう

RRとNNTを計算する

- 表の一次アウトカムの発症率のデータから、RRとNNTを計算してみましょう
  - 経過観察群 31/348 (8. 9%)
  - 手術群 16/347 (4. 6%)

論文結果のまとめ

- 一次アウトカム(前立腺ガンによる死亡)
  －RR 0.5 (0.27-0.91)
  －NNT 23 (12-173)

結果の批判的吟味の公式

- 研究仮説に沿って読む
- さまざまな指標で評価する
  - 相対指標：相対危険(Relative Risk:RR)
  - 絶対指標：治療必要数 (Number Needed to Treat:NNT)
- 確率的なものとして読む
  - 95%信頼区間
- 実数で評価する
  - 治療群でのイベント率、プラセボ群のイベントなしの率

結果3:EBM方式で結果を示す

- 相対危険 0.5 (0.27-0.91)
  - 50%前立腺ガンによる死亡を減らす
- 治療必要数 23 (12-173)
  - 22人は無駄に手術を受けた
- 治療しても4.6%が前立腺ガンで死亡
- 治療しないと8.9%が前立腺ガンで死亡
- 治療しなくても91.1%は前立腺ガンで死亡せず

ロールプレイ

- 隣同士でじゃんけんです
- 勝った人が医師役、負けた人が患者役です
- 論文結果を踏まえて、セカンドオピニオンの提供という視点でロールプレイしてみてください

歩きながら論文を読む

- 論文のPECOを読む
  - 抄録を利用する
- ランダム化かどうか読む
  - まず表題、次に抄録
- ITT解析かどうか読む
  - 追跡の流れ図から
  - 患者背景の表と結果の表から
- 一次アウトカムの結果を読む
  - Primaryという単語を探そう

二次資料を見る

- Clinical Evidence
  - 一般医向けEBMスタイルエビデンス集、年2回発行
  - 2001年9月に日本語版が発売
    - http://www.clinicalevidence.com/
  - 限局された早期の前立腺ガンに対し、明らかに有効な治療はない

批判的吟味パート3

結果は患者に役立つか？

EBMの5つのステップ

1. 問題の定式化
2. 問題についての情報収集
3. 得られた情報の批判的吟味
4. 情報の患者への適用 ←
5. 1-4のステップの評価

Step4. 患者への適用

- 自分の患者と論文の患者は異なっていないか？
- 臨床上重要なすべてのアウトカムが評価されたか？
- コストや害を上回る効果が期待できるか？

患者シナリオ

- 72歳男性、海老原伝之輔さん。前立腺ガンの検診でPSA高値。泌尿器科で検査したところ、初期の前立腺ガンで手術すれば天皇陛下のように元気になりますよと、手術を勧められた。そこでセカンドオピニオンを求めて診療所を受診した。

患者シナリオ続き

- 喫煙30本/日
- 過度の飲酒(1日2-3合)と肥満あり
- 高血圧、高コレステロール血症を合併
- 父が心筋梗塞で死亡
  - 前立腺ガンより心筋梗塞による死亡の危険のほうが高いかもしれない

コレステロールについて勉強する

- コレステロールの治療の論文を、歩きながら読む法で読んでみましょう
- PROSPER Lancet 2002; 360: 1623-30
- 上記論文の読みやすい要約がある
  - ACP Journal Club

ACP Journal Club と Evidence-Based Medicine

- 1991発刊(ACP):アメリカ内科学会
- 1995発刊(EBM):イギリス医師会
- 1論文1ページ
- 構造化抄録(Structured Abstract)
- 専門家のコメント
- 英語の主要雑誌のみを対象
- 2ヶ月に一度発行

構造化抄録(Structured Abstract)

- メニュー形式
- 総合医学誌が採用
  - AIM,JAMA,BMJなど
  - NEJM、Lancetは採用せず
- 論文を読む側に立った抄録

治療の論文の構造化抄録

- Design(研究デザイン) → ランダム化
- Setting(研究が行われた場所、設定)
- Patients(対象患者) → P
- Intervention(治療法) → E & C
- Outcomes(主なアウトカム) → O
- Main results(主な結果)
- Conclusion(結論)

歩きながら論文を読む

- 研究方法は妥当か？
  - 論文のPECOを読む
  - ランダム化かどうか読む
  - ITT解析かどうか読む
- 結果は何か？
  - 一次アウトカムの結果を読む

論文のPECOを読み込む(PROSPER)

P:血管疾患の危険が高い高齢者(年齢70－82歳、総コレステロール155～346mg/dl)

E:プラバスタチン40mg

C:プラセボ

O:非致死性心筋梗塞、あるいは冠動脈疾患死亡、致死性、非致死性の脳卒中

デザインと結果のまとめ

- ランダム化、ITT解析
  - デザインにランダム化、結果の最初にITT解析の記載あり
- 心筋梗塞について
  - 相対危険 0.87 (0.77－0.98)
  - 治療必要数 47 (25－359)
- 治療群で14%が心筋梗塞
- プラセボ群で16%が心筋梗塞
- プラセボ群でも84%は心筋梗塞を起こしていない

ロールプレイ2

- 医師役、患者役を交替しましょう
- コレステロールの論文結果も踏まえて、ロールプレイしてみてください

EBM実践による変化:治療編

- 問診、診察をより重視
  - 患者の問題が明らかになって初めて何を勉強すればよいのか明らかになる
  - 目の前の患者のリスクをより細かく検討
- 患者に治療を強要しない
  - 「手術を受けないと死んでしまいますよ！」という脅しをしなくなった

EBMとは？

- 個々の患者の医療判断の決定に、

  最新で最善の根拠を、良心的かつ明確に、

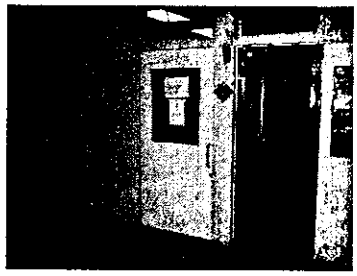
  思慮深く利用すること(Sackett, DL.)

私にとってのEBMの実践

- 目の前の患者の話をよく聞き、よく診察し（患者からのエビデンス）
- その患者によく似た患者についての研究結果をよく勉強し（外部のエビデンス）
- その二つの情報を統合し
  - 目の前の患者に現時点での最善の医療を提供すること

作手村診療所 1番診察室

海老原伝之助さん、
1番へどうぞ

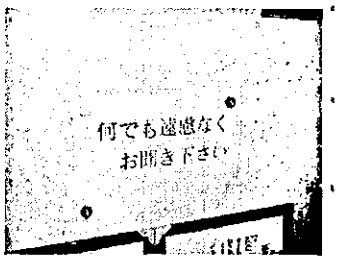


診察室へ入ると.....

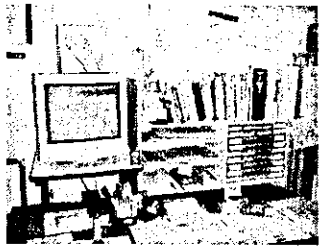
- 何が違う？
  - 肘掛椅子
  - コンピュータ
  - 張り紙

本音を聞き出すは大変ですが

- 手術は？
  - むつかしいなあ
- 脂っこいものは？
  - ひかえめに
- お酒は飲んでいい？
  - 少々なら
- たばこは？
  - 止めたほうが...

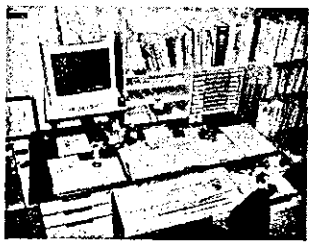


情報は診察室に



あなたに似た患者さんでは....

治療の効果を調べる



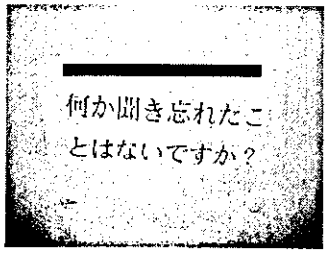
- これまでの研究では
  - 前立腺ガンによる死亡を50%減少
  - 数十人治療して治療のおかげで助かるのはそのうち一人

診察を終わって

- あわてる必要はないと思います
- もう少しゆっくり考えてはどうでしょう

あわてないでというのだけれど

- 今日も眠れそうにないなあ



最後に

- 実践してこそEBM
- EBMとは何かと問う前に、目の前の患者にとっての最善の医療は何かと自問しよう
- EBMが役に立つかどうかではなく、EBMを利用する自分自身が患者の役に立てるかどうか
- 論文に対して批判的になるだけでなく、自分自身に対してこそ批判的に

Pravastatin lowered coronary disease risk in elderly persons with or at risk for vascular disease

Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360:1623-30.

QUESTION

In elderly persons with or at risk for vascular disease, what is the effectiveness and safety of pravastatin?

DESIGN

Randomized (allocation concealed*), blinded (clinicians, participants, data collectors, outcome assessors),* placebo-controlled trial with mean follow-up of 3.2 years (Prospective Study of Pravastatin in the Elderly at Risk [PROSPER]).

SETTING

Scotland, Ireland, and the Netherlands.

PARTICIPANTS

5804 participants between 70 and 82 years (mean age 75 y, 52% women) who had a history of vascular disease (coronary, cerebral, or peripheral) or risk factors for vascular disease (e.g., smoking, hypertension, or diabetes), a total plasma cholesterol level between 4.0 and 9.0 mmol/L, and a triglyceride level < 6.0 mmol/L. Participants with poor cognitive function (Mini Mental State Examination score < 24) were excluded. Follow-up was 100%.

INTERVENTION

Participants were allocated to pravastatin, 40 mg/d (n = 2891), or placebo (n = 2913).

MAIN OUTCOME MEASURES

Composite endpoint of coronary death, nonfatal myocardial infarction (MI), or fatal or nonfatal stroke (primary composite endpoint); composite endpoint of coronary death or nonfatal MI; composite endpoint of fatal or nonfatal stroke; and adverse events.

MAIN RESULTS

Analysis was by intention to treat. Pravastatin lowered the risk for the primary composite endpoint and the composite endpoint of coronary death or nonfatal MI (Table). The pravastatin and placebo groups did not differ for the composite endpoint of fatal or nonfatal stroke, but pravastatin was associated with a greater risk for having a new cancer diagnosis (Table).

CONCLUSION

In elderly persons with or at risk for vascular disease, pravastatin lowered the risk for coronary disease events.

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*See Glossary.

Pravastatin vs placebo in elderly persons with or at risk for vascular disease at mean 3.2 years†

Outcomes	Pravastatin	Placebo	RRR (95% CI)	NNT (CI)
Primary composite endpoint‡	14%	16%	13% (1.8 to 23)	47 (25 to 359)
Coronary death or nonfatal MI	10%	12%	17% (4 to 29)	47 (27 to 199)
			RRI (CI)	NNH
Fatal or nonfatal stroke	4.7%	4.5%	4% (−18 to 31)	Not significant
New cancer diagnoses	8.5%	6.8%	24% (4 to 48)	61 (33 to 362)

†MI = myocardial infarction. Other abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article.
‡Primary composite endpoint = coronary death, nonfatal MI, or fatal or nonfatal stroke.

COMMENTARY

With proof that lowering cholesterol levels decreases mortality in high-risk, middle-aged patients, it is appropriate to focus attention on the elderly. Beyond about 75 years of age, serum cholesterol levels contribute less to the risk for coronary heart disease than they do between the ages of 55 and 75 years, but coronary mortality is higher.

The results of the PROSPER study extend the results of a subgroup analysis of the Heart Protection Study (1) that showed significant effects of statin therapy on cardiovascular events in older patients. PROSPER failed to confirm decreased stroke rates with statin therapy, probably because of short follow-up and a lower-than-expected background stroke rate. Many participants in the study, however, had systolic hypertension at baseline (mean systolic blood pressure 155 mm Hg), and control of this risk factor might have lessened the effect of statin therapy on stroke (and MI) even more. The finding of increased malignancy rates in patients treated with statins should not be viewed as credible. This finding contradicts a larger body of evidence showing that no such increased risk exists and is more likely the result of chance.

Elderly patients and their caregivers often choose therapies that preserve functional status rather than those that decrease mortality. PROSPER failed to show reductions in cognitive and functional decline, but the measures used in the study were insensitive to change in persons with high levels of function.

On the whole, the results of PROSPER give providers and elderly patients data on which to individualize therapeutic decisions. Elderly patients who are highly functional, have vascular disease or high cholesterol levels and 1 other risk factor, and wish to maximize life span will probably choose statin therapy. Similar patients whose only goal is to preserve their current functional level will probably forgo therapy.

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Reference

1. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7-22.

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A RANDOMIZED TRIAL COMPARING RADICAL PROSTATECTOMY WITH WATCHFUL WAITING IN EARLY PROSTATE CANCER

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ABSTRACT

Background Radical prostatectomy is widely used in the treatment of early prostate cancer. The possible survival benefit of this treatment, however, is unclear. We conducted a randomized trial to address this question.

Methods From October 1989 through February 1999, 695 men with newly diagnosed prostate cancer in International Union against Cancer clinical stage T1b, T1c, or T2 were randomly assigned to watchful waiting or radical prostatectomy. We achieved complete follow-up through the year 2000 with blinded evaluation of causes of death. The primary end point was death due to prostate cancer, and the secondary end points were overall mortality, metastasis-free survival, and local progression.

Results During a median of 6.2 years of follow-up, 62 men in the watchful-waiting group and 53 in the radical-prostatectomy group died (P=0.31). Death due to prostate cancer occurred in 31 of 348 of those assigned to watchful waiting (8.9 percent) and in 16 of 347 of those assigned to radical prostatectomy (4.6 percent) (relative hazard, 0.50; 95 percent confidence interval, 0.27 to 0.91; P=0.02). Death due to other causes occurred in 31 of 348 men in the watchful-waiting group (8.9 percent) and in 37 of 347 men in the radical-prostatectomy group (10.6 percent). The men assigned to surgery had a lower relative risk of distant metastases than the men assigned to watchful waiting (relative hazard, 0.63; 95 percent confidence interval, 0.41 to 0.96).

Conclusions In this randomized trial, radical prostatectomy significantly reduced disease-specific mortality, but there was no significant difference between surgery and watchful waiting in terms of overall survival. (N Engl J Med 2002;347:781-9.)

THE management of early prostate cancer is controversial. Radical prostatectomy has become widely used, but its possible benefit has not been adequately documented in a randomized trial. Early studies indicated a lower rate of progression after surgery than after external radiotherapy,[1] but no gain in overall survival after more than 20 years of follow-up, as compared with primary expectant management (watchful waiting).[2,3] Systematic overviews of observational studies reveal a lack of reliable data to support any specific recommendation for the treatment of early prostate cancer.[4-7]

We conducted a randomized trial in 695 men with early prostate cancer, who were assigned to either watchful waiting or radical prostatectomy. The median follow-up was 6.2 years. Our presentation follows the revised CONSORT recommendations.[8]

METHODS

The protocol (available at http://www.roc.se) was defined in 1988. Our main purpose was to determine whether mortality from

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prostate cancer was lower among patients treated with radical prostatectomy than among patients treated with watchful waiting. Secondary aims were to measure metastasis-free survival and the risk of local tumor progression. In March 1999, we added an analysis of deaths from all causes.[9]

Enrollment Criteria

Men under the age of 75 years with a primary, previously untreated, and newly diagnosed adenocarcinoma of the prostate verified by cytologic examination, histologic examination, or both were eligible. Further prerequisites were a general condition and mental status that were expected to permit a radical prostatectomy and follow-up for at least 10 years. Patients with other cancers were excluded.

To be eligible, the participants had to have a tumor in stage T0d, T1, or T2.[10] After 1994, men with T1c tumors — according to the revised 1987 International Union against Cancer classification[11] — were also eligible. All of these are early stages; the prostate cancer was either clinically inapparent (T0d, T1), confined to the prostate (T2), or diagnosed by needle biopsy performed because of an elevated prostate-specific antigen level (T1c). If the tumor was detected through transurethral resection only, at least six blocks of prostatic tissue had to have been studied. The tumor had to be graded as well- or moderately well differentiated, as judged according to the World Health Organization classification.[12] Men with a poorly differentiated tumor were not eligible. Patients whose condition was diagnosed with an extended biopsy protocol were accepted if less than 25 percent of the tumor was Gleason grade 4 and less than 5 percent was Gleason grade 5. It was further required that a preoperative bone scan show no signs of metastases, that a bone scan or a urographic examination show no signs of obstruction of the upper urinary tract, and that the prostate-specific antigen level be less than 50 ng per milliliter.

Randomization

Patients were randomly assigned to two parallel groups, the watchful-waiting group and the radical-prostatectomy group, with stratification according to degree of differentiation and center. The randomization was performed through a telephone service at offices outside the clinical units. The urologist responsible for the patient's care informed the patient and completed the case-record forms.

Interventions

Men assigned to watchful waiting received no immediate treatment apart from the transurethral resection some had already undergone. In the radical-prostatectomy group, surgery started with a dissection of the pelvic lymph nodes.[13] If no nodal metastases were found in a frozen section, a Walsh–Lepor radical prostatectomy[14] was carried out. The radical nature of the surgery was given priority over preservation of potency.

Adjuvant local or systemic treatment was not given. Transurethral resection was recommended in the watchful-waiting group as a treatment for local progression. For men with symptomatic local progression in the radical-prostatectomy group, orchidectomy or treatment with gonadotropin-releasing hormone analogues was recommended. Treatment for disseminated disease was the same for the two groups within each center.

Histopathological Review

Four pathologists who were unaware of the patients' outcomes reviewed the inclusion cytologic evidence (55 men had a cytologic examination only) and core-biopsy material (which was missing for 24 men). Each pathologist reviewed the samples from 150 to 200 men, with a similar number from each study group. The review re-evaluated the diagnosis of cancer and scored the tumors according to the method of Gleason.[15] In 48 randomly selected specimens, the rate of agreement among the pathologists was 60 percent for the classification of tumors as having Gleason scores less than, equal to, or more than 7, where a score of less than or equal to 7 indicates a well- or moderately well differentiated tumor.

Follow-up

Routine follow-up examination of all patients occurred twice a year for the first two years and then annually. On each occasion, a clinical examination was performed, and determination of hemoglobin, creatinine, prostate-specific antigen, and alkaline phosphatase levels was recommended. A bone scan and chest radiograph were obtained one year after randomization and then annually. After 1996, chest x-ray films were obtained annually for the first two years after randomization. From 1998 through March 2001, the records of all patients from the urology and oncology departments were reviewed, and an extended search for all available medical information for men who had died was carried out.

Outcomes and Definitions of Clinical Events

Cause of Death

Two of the investigators extracted data relevant to the clinical course of prostate cancer in a standardized format for all deceased participants. The group assignment and primary treatment mode were not revealed. An independent end-point committee of two urologists and one pathologist individually classified all deaths in one of six categories: 1, death from prostate cancer; 2, death from another main cause but with distant metastases present, regardless of local status; 3, death from another main cause with local progression but without distant metastases; 4, death from another main cause with local progression but with unknown status concerning distant disease; 5, death without evidence of tumor recurrence; and 6, death from another cause within the first month after randomization.

The end-point committee, whose members were unaware of the study results, used the following guidelines.[9] If the autopsy determined that death was due to prostate cancer or there were distant metastases that had progressed or had not responded to treatment, then the patient's death was attributed to prostate cancer. If the patient had distant recurrence that had responded to treatment with no or only minimal residual disease at autopsy, or if the patient had local tumor progression (watchful-waiting group) or a local recurrence (radical-prostatectomy group) without metastases, the patient was considered to have died with but not directly from prostate cancer and was assigned to category 2, 3, or 4 as appropriate. Otherwise, the patient was deemed to have died from a cause other than prostate cancer without recurrence.

Distant Metastases

Metastases were diagnosed when a bone scintigram or skeletal radiograph was positive, when a computed tomographic scan or pulmonary x-ray film demonstrated metastases, and when lymph nodes beyond the regional nodes showed cytologic or histologic evidence of prostate cancer.

Local Progression and Local Recurrence

In the watchful-waiting group, a patient was classified as having local progression if a transcapsular tumor growth was palpable, if he had symptoms of obstruction of the flow of urine that necessitated intervention, or both. In the radical-prostatectomy group, the criterion for progression and local recurrence was a histologically confirmed local tumor.

Definition of End Points

Three end points were used. The first, disease-specific mortality, was defined by the time to death from prostate cancer (category 1), with deaths from other causes treated as censoring events. The sec-

ond, the rate of distant metastasis, was defined by the time to diagnosis of distant metastases, with deaths from causes other than prostate cancer treated as censoring events. For patients assigned to categories 1, 2, and 4, but without a prior clinical diagnosis of metastases, the date of death was considered the date of diagnosis of distant metastases. Overall mortality was defined by the time to death, regardless of cause.

Sample Size

Initially, the five-year, disease-specific survival rate in the watchful-waiting group was assumed to be 85 percent,[16] and we aimed to detect a reduction in mortality from prostate cancer due to radical prostatectomy that would yield a disease-specific survival of at least 95 percent. With the risk of a type I error at 5 percent (two-sided test) and the risk of a type II error at 20 percent, the initial target sample size was 520 patients. We planned two interim analyses, one after the enrollment of 300 patients and the other after the enrollment of 520. We decided to break the code and discuss the results in the steering committee if the P value was greater than 0.01 and less than or equal to 0.05 and to consider an early cessation for all patients if the P value was less than 0.01.

In the interim analyses, none of the prestipulated P values for breaking the code and revealing the results to the steering committee were reached; however, the overall mortality rate was lower than anticipated. Therefore, after the analysis of 520 patients, the target sample size was increased to 700 patients. With that sample size and the same risks of type I and type II errors, we would be able to detect an absolute difference in the survival rate of 6 percent between the two groups if the disease-specific survival rate was 95 percent in one group.

Ethical Considerations

The ethics committees at all participating centers approved the initial protocol and the increased target sample size. In all but two centers, a modified version of Zelen's randomization model[17] was allowed from 1988 to 1990, which implied that only men in the experimental group received complete information about the study before randomization, but that all patients were informed that they were taking part in a clinical study and gave their oral consent to participate. From 1990, when 68 men had been enrolled at these centers (with 33 assigned to watchful waiting), it became clear that Zelen's model was not necessary for randomization, and thus all men were fully informed thereafter.

Statistical Analysis

All analyses were prespecified, were performed according to the intention-to-treat principle, and were based on complete follow-up of all enrolled eligible men (Fig. 1). At the end of follow-up on December 31, 2000, 520 men had been followed for at least five years, when the first open analysis was to be undertaken according to the protocol. To acknowledge the presence of competing risks, we calculated cumulative cause-specific hazard rates[18] with the use of the negative log transformation of the Kaplan–Meier estimator for each end point. The 95 percent confidence intervals for the difference between the point estimates at five and eight years for the cumulative hazard rates for the study groups are reported.

The log-rank test was used for comparisons between groups, with a P value of less than 0.05 (two-sided) considered to indicate statistical significance. Relative hazards with 95 percent confidence intervals were estimated with the use of Cox proportional-hazards models. The influence of any imbalance in age, distribution of tumor stage, Gleason score as determined by the review, or prostate-specific antigen level was checked in a multivariate Cox model for disease-specific mortality. In the multivariate model, the tumor stage and Gleason grade were represented with dummy variables, and age was entered as a continuous variable. SAS statistical software was used for all calculations. No adjustments of P values or confidence intervals were made for the interim analysis.

RESULTS

Participation

Fourteen centers enrolled 2 to 182 patients each from October 1989 to February 1999. A total of 698 men were enrolled (Fig. 1), with 349 assigned to watchful waiting and 349 to radical prostatectomy. After the exclusion of 2 men wrongly given a diagnosis of prostate cancer and of 1 man with a prior diagnosis of Hodgkin's disease, 348 and 347 men (assigned to watchful waiting and prostatectomy, respectively) were included. During follow-up, 30 men in the watchful-waiting group were treated with curative intent and 25 men in the radical-prostatectomy group were followed without radical treatment (Fig. 1). No patient was lost to follow-up, and the median duration of follow-up was 6.2 years in both groups.

Characteristics at Base Line

The characteristics at base line were similar in the two study groups, with the exception of a somewhat higher proportion of men with stage T1b tumors in the watchful-waiting group (Table 1); however, most of the men had stage T2 tumors.

Number of Events

During follow-up, 115 men died (Table 2); 62 had been assigned to watchful waiting and 53 to radical prostatectomy. Before its consensus meeting, the end-point committee was unanimous in its classification of the causes of deaths of 94 men (53 in the watchful-waiting group and 41 in the radical-prostatectomy group). At a joint meeting, the committee reached a consensus about all causes of death.

Of the 115 men who died, 47 died of prostate cancer, only 1 of whom had no prior clinical diagnosis of distant metastatic disease; all had received hormonal treatment. There were 31 deaths related to prostate cancer in the watchful-waiting group and 16 in the radical-prostatectomy group. There were 37 deaths from other causes in the radical-prostatectomy group and 31 in the watchful-waiting group. Of the 23 men who died from other cancers (Table 2), 17 had a second cancer verified during surgery or at autopsy, and 2 had myeloma verified and treated before death.

Disease-Specific Mortality

The cumulative hazard functions for death from prostate cancer (Fig. 2) and the corresponding five-year and eight-year point estimates (Table 3) showed a difference that increased over time. The absolute difference, in favor of radical prostatectomy, was 2.0 percent (95 percent confidence interval, −0.8 to 4.8) at five years and 6.6 percent (95 percent confidence interval, 2.1 to 11.1) at eight years. The relative hazard for men assigned to prostatectomy as compared with

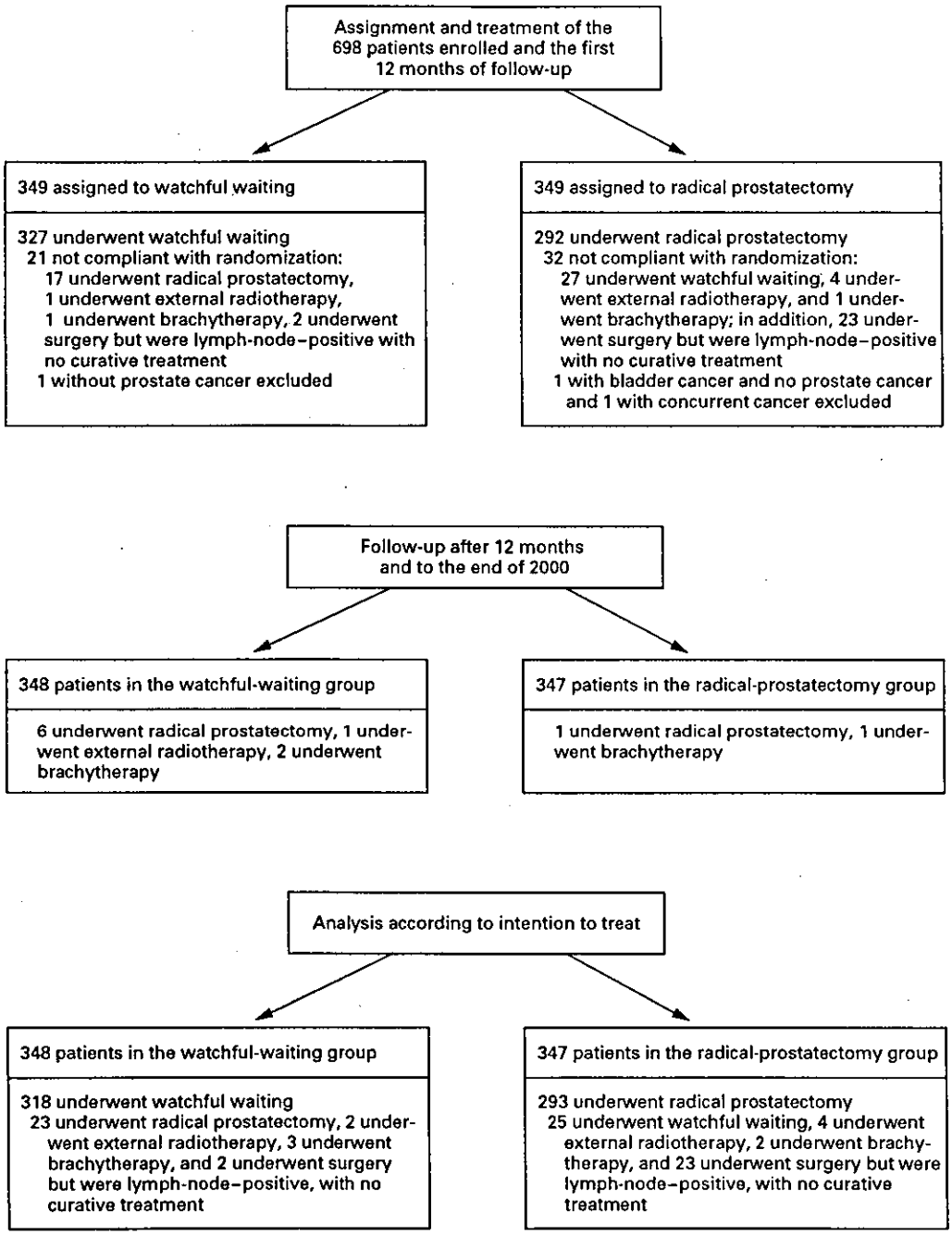


Figure 1. Flow Diagram of Treatment Assignment and Follow-up.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 695 MEN ENROLLED IN THE STUDY.

CHARACTERISTIC	WATCHFUL WAITING (N=348)	RADICAL PROSTATECTOMY (N=347)
Age (yr)*	64.7±5.1	64.7±5.1
Mean prostate-specific antigen level (mg/ml)	12.3	13.5
	no. (%)	
Tumor stage†		
T1b	50 (14.4)	33 (9.5)
T1c	38 (10.9)	43 (12.4)
T2	259 (74.4)	270 (77.8)
Unknown	1 (0.3)	1 (0.3)
World Health Organization grade		
1	166 (47.7)	168 (48.4)
2	182 (52.3)	178 (51.3)
Unknown	0	1 (0.3)
Gleason score‡		
2–4	46 (13.2)	45 (13.0)
5–6	166 (47.7)	165 (47.6)
7	82 (23.6)	77 (22.2)
8–10	21 (6.0)	14 (4.0)
Unknown§	33 (9.5)	46 (13.3)
Method of detection		
Screening	18 (5.2)	18 (5.2)
Coincidental	91 (26.1)	87 (25.1)
Transurethral resection of the prostate	56 (16.1)	40 (11.5)
Symptoms	138 (39.7)	152 (43.8)
Other	44 (12.6)	49 (14.1)
Unknown	1 (0.3)	1 (0.3)
Prostate-specific antigen level		
<4 ng/ml	63 (18.1)	43 (12.4)
4–6.9 ng/ml	60 (17.2)	60 (17.3)
7–10 ng/ml	67 (19.3)	68 (19.6)
10.1–20 ng/ml	95 (27.3)	100 (28.8)
>20 ng/ml	60 (17.2)	69 (19.9)
Unknown	3 (0.9)	7 (2.0)

*Plus–minus values are means ±SE.

†In incidental prostate cancer, stage T1b indicates an incidental histologic finding in more than 5 percent of tissue resected (in 1978, this was classified as stage T0d); stage T1c indicates a tumor identified by needle biopsy because of elevated serum prostate-specific antigen levels (in 1978, this classification did not exist). In palpable or visible carcinoma confined to the prostate, stage T2 indicates a tumor confined within the prostate (in 1978, this was classified as stage T1 or T2).

‡This score was assigned during histopathological review.

§Diagnosis was made by cytologic examination only in 55 patients; a biopsy specimen could not be retrieved in 24 patients.

TABLE 2. CAUSE OF DEATH ACCORDING TO THE FINAL CONSENSUS MEETING OF THE END-POINT COMMITTEE.

CAUSE OF DEATH	WATCHFUL WAITING (N=348)	RADICAL PROSTATECTOMY (N=347)
	number	
Prostate cancer	31	16
Other causes	31	37
Other main cause with metastases	3*	1†
Other main cause without metastases but with local progression or recurrence	8*	6†
Other main cause with no evidence of metastases or local progression or recurrence	19‡	29§
Other main cause within first mo after randomization	1	1
All causes	62	53

*Of these 11 men, 3 died from another cancer.

†Of these 7 men, 3 died from another cancer.

‡Of these 19 men, 5 died from another cancer.

§Of these 29 men, 12 died from another cancer.

those assigned to watchful waiting was 0.50 (95 percent confidence interval, 0.27 to 0.91). A multivariate analysis that adjusted for age at randomization, tumor stage, and Gleason score according to the pathologists' review yielded a relative hazard of 0.45 (95 percent confidence interval, 0.25 to 0.84).

Rate of Development of Distant Metastases

Analyses of the cumulative hazard rate for distant metastases (Fig. 3 and Table 3) also showed a time-dependent pattern, with similar results in the two groups at five years but an absolute difference at eight years of about 14 percent in favor of prostatectomy. The results of log-rank tests were statistically significant (P=0.03), and the relative hazard was 0.63 (95 percent confidence interval, 0.41 to 0.96).

Rate of Local Progression

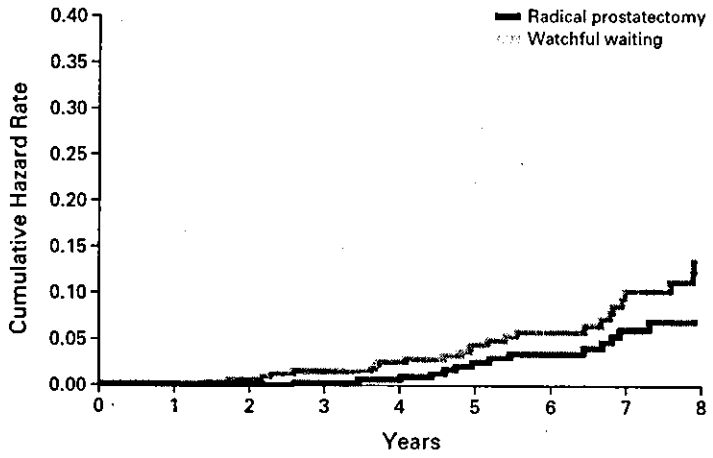
The cumulative hazard rate of local progression (Table 3) was significantly different in the two groups at five years. At eight years, the risk of a local recurrence verified by biopsy was almost 20 percent in the prostatectomy group but was approximately 60 percent in the watchful-waiting group.

Overall Mortality

Two men died within one month after randomization. One man assigned to watchful waiting died at home without signs of progression. One man in the radical-prostatectomy group died postoperatively. If his death is classified as due to prostate cancer, the absolute difference in disease-specific end points changes marginally (Table 3). Sixty-two men in the watchful-waiting group and 53 in the radical-prostatectomy group died; this corresponded to a relative hazard of death from any cause of 0.83 (95 percent confidence interval, 0.57 to 1.2; P=0.31) (Fig. 4).

Hormonal Treatment, Palliative Irradiation, and Laminectomy

Overall, 116 men in the watchful-waiting group (24.7 percent) and 80 men in the radical-prostatecto-



No. at Risk									
Radical prostatectomy	347	343	339	308	281	233	185	134	89
Watchful waiting	348	346	337	302	275	231	185	121	82

Figure 2. Cumulative Hazard Rate of Death from Prostate Cancer.

Table 3. Cumulative Hazard Rates, Difference between the Cumulative Hazard Rates, and Relative Hazards from Cox Models for the Main End Points.*

Variable	Watchful Waiting (N=348)	Radical Prostatectomy (N=347)	Difference
Disease-specific mortality			
Total no. of events	31	16	
Mean follow-up — yr	6.1	6.2	
Five years of follow-up — % (95% CI)	4.6 (2.1 to 7.2)	2.6 (0.7 to 4.6)	2.0 (−0.8 to 4.8)
Eight years of follow-up — % (95% CI)	13.6 (7.9 to 19.7)	7.1 (3.3 to 11.0)	6.6 (2.1 to 11.1)
Relative hazard — % (95% CI)			0.50 (0.27 to 0.91)†
P value by log-rank test			0.02
Rate of development of distant metastases			
Total no. of events	54	35	
Mean follow-up — yr	5.8	6.0	
Five years of follow-up — % (95% CI)	11.0 (7.1 to 15.0)	8.6 (5.3 to 12.0)	2.3 (−2.1 to 6.8)
Eight years of follow-up — % (95% CI)	27.3 (19.4 to 36.0)	13.4 (8.6 to 18.5)	13.9 (8.0 to 19.8)
Relative hazard — % (95% CI)			0.63 (0.41 to 0.96)‡
P value by log-rank test			0.03
Rate of local progression			
Total no. of events	108	40	
Mean follow-up — yr	4.4	5.2	
Five years of follow-up — % (95% CI)	35.5 (28.0 to 43.7)	9.4 (5.8 to 13.1)	26.2 (20.3 to 32.0)
Eight years of follow-up — % (95% CI)	61.1 (47.8 to 76.4)	19.3 (12.7 to 26.4)	41.8 (35.2 to 48.4)
Relative hazard — % (95% CI)			0.31 (0.22 to 0.44)
P value by log-rank test			<0.001
Overall mortality			
Total no. of events	62	53	
Mean follow-up — yr	6.1	6.2	
Five years of follow-up — % (95% CI)	10.3 (6.6 to 14.0)	8.7 (5.3 to 12.2)	1.5 (−2.8 to 5.9)
Eight years of follow-up — % (95% CI)	28.3 (20.2 to 37.1)	22.0 (15.3 to 29.1)	6.3 (−0.2 to 12.7)
Relative hazard — % (95% CI)			0.83 (0.57 to 1.2)
P value by log-rank test			0.31

*CI denotes confidence interval.

†This estimate changes to 0.53 if one postoperative death is defined as due to prostate cancer.

‡This estimate changes to 0.64 if one postoperative death is defined as due to prostate cancer.