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Report of the Consensus Workshop on Screening and Global Strategy for Prostate Cancer

Louis J. Denis, M.D., Gerald P. Murphy, M.D., and Fritz H. Schröder, M.D.

Introduction

The goals of the workshop, convened from March 5 to 7, 1994, were to bring together experts from Europe and North America to address the current situation with regard to the early detection of prostate cancer. The topics discussed included assessment of the epidemiology of this condition on a global basis, the accuracy of clinical diagnosis, the pathologic evaluation, the available laboratory tests, the methodology of detection and screening programs, and results and treatment. A workshop summary from each group was provided at the meeting, and adaptations of these are contained in this report. Providing answers to the following questions was the meeting's major goal.

1. Is there an acceptable method for early detection of prostate cancer available on a population basis?
2. Do the current results provide encouragement for proceeding to develop widespread, randomized trials?
3. What is the proper way to conduct such efforts and what other important issues should be considered?
4. What are the bases for the treatment of patients with prostate cancer when discovered?

These issues are addressed in a comprehensive fashion below.

Presented at the Consensus Workshop on Screening and Global Strategy for Prostate Cancer, held March 5 to 7, 1994, Antwerp, Belgium.

From the Flemish Advisory Commission on Cancer Prevention, the International Union Against Cancer, the American Cancer Society, the European Association for Research and the Treatment of Cancer, the European School of Oncology, the Association Contre le Cancer, and the Integrated Cancer Foundation, Antwerp, Belgium.

Sponsored by The Flemish Advisory Commission On Cancer Prevention (VACK), the International Union Against Cancer (UICC), the American Cancer Society (ACS), the European Association for Research and Treatment of Cancer (EORTC), the European School of Oncology (ESO), the Association Contre le Cancer, The Integrated Cancer Foundation Antwerp (IKSA).

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EPIDEMIOLOGY WORKGROUP

In many countries of the world, prostate cancer is the second most common form of cancer in men and in the United States it has recently overtaken lung cancer in terms of absolute incidence, although it remains second to lung cancer as a cause of death. Given that in several countries, a higher number of children born after 1945 will be in their mid-fifties in the early part of the 21st century (at which age cancer risk becomes an important consideration), coupled with the trend toward increased life expectancy, there will be an increase in the numbers of patients diagnosed with prostate cancer even if incidence rates remain fixed at 1980 levels. In the absence of treatment improvements, and with prospects for prevention by lifestyle modification only a remote hope in the current circumstances, it seems that there will also be an increase in the number of deaths from prostate cancer worldwide.

The situation could be further augmented by the presence of temporal trend toward increased risk of prostate cancer that is consistently reported in many

countries and that is unlikely to be entirely artifact. However, in many countries there has been little change in the mortality rate for prostate cancer, particularly at younger (< 70 years) ages since 1950 (Boyle P, Evstifeeva T, Maisonneuve P, Macfarlane EJ, Pagano F, unpublished data).

A major effort is required to reduce the impact of these changes and reduction of mortality by population screening has emerged as one possible way to accomplish this.[1] In this context, screening involves the examination of asymptomatic men to classify them as likely or unlikely to have prostate cancer. Men who appear likely to have the disease are investigated further to arrive at a final diagnosis and those who are found to have the disease are treated. Screening calls attention to the likelihood of disease before symptoms appear. The goal of a screening program is to reduce mortality from the disease among those screened by treatment of disease before symptoms appear. There have been criteria established to determine whether a screening activity could be justified in a particular circumstance[2] and at the present time, these criteria are almost completely fulfilled for prostate cancer.[3] The notable exceptions are the lack of detailed knowledge of the natural history of prostate cancer and lack of direct evidence that screening with the currently available modalities can lead to a reduction in prostate cancer mortality.

Although population screening for prostate cancer cannot be recommended as public health policy at the present time, there are strong arguments supporting the conduct of trials of screening (see Appendix 1 for this and other recommendations of this workgroup). It is recognized that possibilities for the conduct of such randomized trials are favorable in Europe at the present time. Such randomized trials need to be large and of long duration. They will be more complicated than trials of mammography and breast cancer screening as a result of several factors, including the nature of prostate cancer. In particular, there is a need to have reliable information about patterns of cancer care and treatment of prostate cancer in the study region. Men in an age group that is not treated according to local policy (older than 70 years of age in some areas) should not be recruited into screening trials as they are very unlikely to benefit from participation. Information is required about patterns of care in the study region. Patterns of health care for men enrolled in screening trials should be as similar as possible in both the screened and the unscreened group members. Cancer registries in the study region have an important role in identifying any interval cancers arising in the study participants, some of which may be missed, and in providing a backup to existing follow-up procedures. Cancer registries also provide an important resource of information regarding background incidence, mortality, and survival rates and follow-up for men who either refuse to participate in the trial or drop out during the study.

Care is required when dealing with aspects of the diagnosis of prostate cancer. A potential problem involves autopsy diagnosis, but this is only a relevant finding when it identifies the prostate as the primary site in the case of a man who died of metastatic disease whose primary origin was unknown (or wrongly attributed to another site) in life (occult cancer). In each trial, a committee should be established to determine whether prostate cancer was the underlying cause of death in study participants. Although death certificates appear to be reasonably reliable, there is need for detailed examination of each cause of death by clinicians who are expert in the disease in question. The need for large trials argues strongly for multicentred studies that probably will need to be conducted in international populations. Careful scrutiny of the reproducibility of the determination of prostate cancer as underlying cause of death in different countries is needed.

Screening trials require careful planning to ensure that the data can be used correctly for evaluation. The most reliable evaluation of screening activities is through the correct analysis of the randomized clinical trial data. However, modeling strategies have also proved useful and have a role in helping choose between the utility of different screening procedures.[4] The list of data required from a screening trial to allow evaluation is contained in Appendix 2.

As stated above, the goal of screening is to decrease the death rate from prostate cancer. Using death as the principle endpoint minimizes many possible biases and requires 10–20 years to complete. Regardless of the screening tests employed, the present climate of technologic advances offers the option of obtaining intermediate results in a shortened time by using prognostic indicators of death from prostate cancer. A decrease in the incidence rate of advanced cancer is the best intermediate indicator of a ultimate reduction in mortality. The use of intermediate endpoints at this time must be informal because they themselves require validation by mortality data from screening trials;[5] valid intermediate endpoints classify tumors into a number of categories within which survival is independent of mode of detection.

Using data from the Surveillance, Epidemiology, and End Results Program, available prognostic death indicators were ranked by their death potential with 7 to 18 years of follow-up. Gleason grade was found to be a strong indicator of the virulence of cancers in all stages and should also attempt to be gathered on all cancers.[6] There should be a uniform method of recording staging information on prostate cancer that is used

in all countries and can be compared through time (TNM is the most widely used scheme internationally).

Quality of life is a major issue, particularly when considering disease in older men. The criteria established by Wilson and Jungner, however, lack any criterion about quality of life. It is recommended that two important aspects of quality of life be measured in study participants: general quality of life and quality of urologic life, the latter, for example, including urinary symptomatology, annoyance of symptoms, interference with daily living, and sexual function. Quality of life assessment should be performed both for men free from prostate cancer and men with the disease in the screened and control groups. The measurements should be made at several stages of the disease course and also during eventual life-years gained. Much basic research work remains to be performed in this field before validated instruments will be available for use.

In conducting large scale screening trials, it is important to maximize the utility of this resource, for example by conducting etiologic studies within this assembled cohort. The establishment of a biologic data bank would maximize the value of this resource and help provide answers to several important research questions about prostate cancer that are complementary to the main question addressed by screening trials.

The potential list of data items is extremely long; this list represents the minimum data required for a thorough examination of the findings from screening trials.

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Appendix 1

Recommendations of the Epidemiologic Group on Prostate Cancer Screening

Widespread population screening for prostate cancer cannot be recommended as public health policy at the present time. Demonstration projects have provided valuable data and have assisted public education, providing very strong arguments in support of conducting randomized trials for screening.

Eligible men should have a life expectancy compatible with the expected duration of the study; and men to whom no curative treatment is given (in several countries, men older than 70 years of age) should not be eligible to participate in screening trials.

Patterns of health care for men enrolled in screening trials should be as similar as possible in both the screened and the unscreened group.

Comparable staging and diagnostic systems for prostate cancer should be used (e.g., TNM).

Information about patterns of care in the study regions should be available.

Incorporation of quality-of-life measurement in both screened and unscreened groups in randomized trials should be made. These should refer to both overall quality of life and to urologic quality of life specifically.

The opportunity offered by screening trials to conduct etiologic research should be noted.

Biologic material should be obtained and stored whenever possible for future analysis (of new markers for etiologic studies, etc.).

There should be a liaison between study coordinators and cancer tumor registries that is active in the region where screening trials are being conducted.

The principal method of evaluating screening trials is a correct statistical analysis of randomized trial data, but modeling is also of importance to help in the comparison of the utility and cost-effectiveness of different screening strategies.

Each study requires the establishment of a committee to evaluate the cause of death of study participants. There is a need for more research about the comparability of cause of death abstraction in different countries.

Using death from prostate cancer as the principle endpoint in screening trials minimizes several possible biases but requires 10 to 20 years to complete. Intermediate results could be obtained by using prognostic indicators of death from prostate cancer (e.g., grading, stage, etc.).

Appendix 2

Minimal Information Required for Evaluation of Cancer Screening Trials

Target population
Invited population
Attendance

Nonparticipant characteristics
Screen-positive
Additional diagnostic tests (and results)
Additional invasive diagnostic tests
Lost to follow-up/assessment unknown
Cancers detected (by test)
Stages and other prognostic factors (T/N/M/grade/etc.)
Primary treatment of screen-detected cancers
Advanced disease in follow-up period (M1, regional recurrences)
Cancers diagnosed after negative screen
Deaths from other diseases
Similar detailed information on control group (diagnostic tests/screen tests/treatment/etc.)
Quality of life measurements
Cost measurements
Cost measurement analysis (screening/diagnosis and therapeutic phases)

Participants

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PATHOLOGY WORKGROUP

The Pathology Working Group (PWG) recognizes that screening programs have the authority and responsibility to specify conditions of quality control and quality assurance within the screening facility. However, once an abnormality is detected, the follow-up facilities for surgical excision and pathologic examination are not necessarily a part of the screening facility. Therefore, the PWG's objective was to develop criteria for the examination of prostate tissue specimens that would be generally acceptable to practicing surgical pathologists for the formulation of their consultation reports. The information included below is directed primarily to the consultative practice of pathology and is not specifically for research. Nevertheless, this information may be used in a clinical trial setting, and can be modified as appropriate for use in a specific protocol or institution. In this context, the participants of the PWG have formulated the following recommendations for the examination and surgical pathology consultation reports of prostate cancer specimens to document the extent of tissue removed, validate the diagnosis of cancer in the specimen (or its absence), and provide information that may be used for International Union Against Cancer/American Joint Committee on Cancer pTNM classification and staging, selection of therapy, and estimation of prognosis. The PWG therefore has included much of the data that have already been developed and reality tested by the Cancer Committee of the College of American Pathologists.[1]

The PWG made some general observations during the development of these recommendations. They unanimously agreed that prostate carcinomas should be assigned a histologic grade, and preferred a three-grade system; however, they also concurred that the grading system employed by a pathologist should be determined by her/his local medical practice environment. Therefore, the PWG include the following in the recommendation for histologic grading: "Any grading system as desired, such as Gleason's score"[1] (see below). Of course, the grading system used should include a verbal definition in the report such as ". . .moderately differentiated, grade 2."

The surgical pathology consultation report of a prostate specimen should include a statement confirming the presence (or absence) of carcinoma, or that it may not be possible to make a definitive diagnostic evaluation for carcinoma and state the reason (e.g., possibly due to limitations of the specimen). Prostate cancer associated lesions, such as prostatic intraepithelial neoplasia (PIN), atypical adenomatous hyperplasia (AAH), and the effects of therapy, may also be included. The PWG recommends that a group of pathologists develop a lexicon of definitions of terms, with appropriate related photomicrographs, to assist pathologists in the uniform application of the terminology specified in this report.

Recommendations follow for the information to be included in the surgical pathology consultation reports for four categories of specimens (1) needle biopsy, (2) transurethral resection of prostate (TURP), (3) suprapubic or retropubic prostate enucleation (subtotal prostatectomy), and (4) radical prostatectomy. Although prostate carcinoma can be diagnosed by fine needle aspiration cytology of the prostate gland with or without DNA analysis by flow cytometry or nuclear morphome-

try, this report is limited to solid tissue examination. There is repetition of information in the four categories of specimens because many of the data are common for all types of specimens; this deliberate repetition is intended for the convenience of the reader and for those who may wish to duplicate this material for use in their laboratory.

We cannot emphasize too strongly how important it is to provide basic clinical data to the pathologist for appropriate patient identification and clinical-pathologic correlation.

Recommendations for Data to be Included in the Surgical Pathology Consultation Report for the Four Types of Specimens

1. Needle biopsy

1.1 Clinical information provided to pathologist by the responsible physician

1.1.1 Patient identification (name/age/identification number)

1.1.2 Relevant history, including any previous diagnosis/therapy

1.1.3 Results of examinations

1.1.3.1 Laboratory (e.g., PSA or other significant findings)

1.1.3.2 Digital rectal examination

1.1.3.3 Imaging (e.g., ultrasound)

1.1.4 Clinical diagnosis

1.1.5 Type of surgical procedure (e.g., needle biopsy)

1.1.6 Anatomic site of specimen [site(s) of biopsy specified by surgeon, as appropriate]

1.1.6.1 Location in prostate gland [right or left lobe; base, mid, apex (as labeled by surgeon)]

1.1.6.2 Extraprostatic site(s) (e.g., right/left seminal vesicle(s), as labeled by surgeon)

1.2 Macroscopic examination (size/number of pieces)

1.3 Microscopic examination

1.3.1 Tumor characteristics

1.3.1.1 Histologic type (World Health Organization modified)

1.3.1.1.1 Adenocarcinoma (not otherwise specified)

1.3.1.1.2 Acinar adenocarcinoma

1.3.1.1.3 Ductal adenocarcinoma

1.3.1.1.4 Mucinous adenocarcinoma

1.3.1.1.5 Transitional cell carcinoma

1.3.1.1.6 Squamous cell carcinoma

1.3.1.1.7 Neuroendocrine tumor

1.3.1.1.8 Small cell anaplastic carcinoma

1.3.1.1.9 Undifferentiated carcinoma

1.3.1.1.10 Other cancer (specify)

1.3.1.2 Histologic grade of tumor (any grading system as desired, such as Gleason's histologic score; specify grading system used)

1.3.1.3 Extent of tumor

1.3.1.3.1 Proportion (%) of tissue involved

1.3.1.3.2 Lymphatic vessel invasion

1.3.1.3.3 Blood vessel invasion

1.3.1.3.4 Perineural invasion

1.3.1.3.5 Periprostatic tissue invasion (if appropriate)

1.3.1.3.6 Adjacent organs(s): specify

1.3.1.4 International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) pT category

1.3.2 Malignancy indeterminate (specify nature of the problem)

1.3.3 No tumor identified (if the tissue is not adequate for diagnostic evaluation for tumor, this should be noted)

1.3.4 Other findings, as appropriate

1.3.4.1 Prostatic intraepithelial neoplasia (PIN), and grade

1.3.4.2 Atypical adenomatous hyperplasia (AAH)

1.3.4.3 Prostatitis (granulomatous or other)

1.3.4.4 Benign prostatic hyperplasia

1.3.4.5 Basal cell hyperplasia

1.3.4.6 Postatrophy hyperplasia

1.3.4.7 Therapy related

1.4 Special studies [if special studies have been performed, they should be designated and the results included with the surgical pathology consultation report (e.g., histochemistry, immunohistochemistry, flow cytometry, or nuclear morphometry)].

2. Transurethral resection of prostate (TURP)

2.1 Clinical information provided to pathologist by the responsible physician

2.1.1 Patient identification (name/age/identification number)

2.1.2 Relevant history, including any previous diagnosis/therapy

2.1.3 Results of examinations

2.1.3.1 Laboratory (e.g., PSA or other significant findings)

2.1.3.2 Digital rectal examination

2.1.3.3 Imaging (e.g., ultrasound)

2.1.4 Clinical diagnosis

2.1.5 Type of surgical procedure (e.g., TURP)

2.1.6 Anatomic site of specimen (prostate gland)

2.2 Macroscopic examination

2.2.1 General characteristics of specimen

2.2.1.1 Weight

2.2.1.2 Significant gross features

2.2.2 Recommendations for selection of tissue for microscopic examination

2.2.2.1 Include any grossly suspicious chips

2.2.2.2 Specimens < 12 grams, embed totally

2.2.2.3 Specimens > 12 grams, embed at least 12 grams and approximately 1 additional cassette for every 10 grams

2.2.3 After diagnosis of a clinically unsuspected (incidental) carcinoma that involves 5% or less of the tissue, or high grade PIN, or atypical adenomatous hyperplasia, consider embedding (all) remaining tissue.

2.3 Microscopic examination

2.3.1 Tumor characteristics

2.3.1.1 Histologic type (World Health Organization modified)

2.3.1.1.1 Adenocarcinoma (not otherwise specified)

2.3.1.1.1 Acinar adenocarcinoma

2.3.1.1.2 Ductal adenocarcinoma

2.3.1.1.3 Mucinous adenocarcinoma

2.3.1.1.4 Transitional cell carcinoma

2.3.1.1.5 Squamous cell carcinoma

2.3.1.1.6 Neuroendocrine tumor

2.3.1.1.7 Small cell anaplastic carcinoma

2.3.1.1.8 Undifferentiated carcinoma

2.3.1.1.9 Other cancer (specify)

2.3.1.2 Histologic Grade of Tumor (any grading system as desired such as Gleason's histologic score; specify grading system used)

2.3.1.3 Extent of tumor

2.3.1.3.1 Proportion (%) of tissue involved

2.3.1.3.2 Lymphatic vessel invasion

2.3.1.3.3 Blood vessel invasion

2.3.1.3.4 Perineural invasion

2.3.1.3.5 Periprostatic tissue invasion (if appropriate)

2.3.1.3.6 Direct extension to adjacent organs(s): specify

2.3.1.4 UICC/AJCC pT Category

2.3.2 Malignancy Indeterminate (specify nature of the problem)

2.3.3 No tumor identified (if the tissue is not adequate for diagnostic evaluation for tumor, this should be noted).

2.3.4 Other findings, as appropriate

2.3.4.1 PIN and grade

2.3.4.2 AAH

2.3.4.3 Prostatitis (granulomatous or other)

2.3.4.4 Benign prostatic hyperplasia

2.3.4.5 Basal cell hyperplasia

2.3.4.6 Postatrophy hyperplasia

2.3.4.7 Therapy related

2.4 Special studies [Designate special studies, if done, and include results with Surgical Pathology Consultation Report (e.g., histochemistry, immunohistochemistry, flow cytometry, nuclear morphometry)].

3. Suprapubic or retropubic enucleation specimen (subtotal prostatectomy)

3.1 Clinical information provided to pathologist by the responsible physician

3.1.1 Patient identification (name/age/identification number)

3.1.2 Relevant history, including any previous diagnosis/therapy

3.1.3 Results of Examinations

3.1.3.1 Laboratory (e.g., PSA or other significant findings)

3.1.3.2 Digital rectal examination

3.1.3.3 Imaging (e.g., ultrasound)

3.1.4 Clinical diagnosis

3.1.5 Type of surgical procedure (e.g., subtotal prostatectomy)

3.1.6 Anatomic site of specimen (prostate gland)

3.1.7 Orientation of the specimen as marked by the surgeon (e.g., area of possible invasion of margin)

3.2 Macroscopic examination

3.2.1 General characteristics of prostate specimen

3.2.1.1 Size, three dimensions

3.2.1.2 Weight

3.2.1.3 Size of carcinoma(s), if possible

3.2.1.4 Other significant gross features

3.2.1 Method of margin identification (e.g., india ink)

3.2.2 Recommendations for selection of tissue for microscopic examination

3.2.2.1 Approximately eight cassettes including:

3.2.2.1.1 Any areas suspicious for tumor, noting location (right, left lobe, etc.)

3.2.2.1.2 Extent, if possible

3.2.2.1.3 Other representative sections as appropriate

3.2.2.2 Additional sections may be needed for further evaluation after diagnosis of a neoplasm to evaluate tumor characteristics (see Microscopic features, below)

3.3 Microscopic examination

3.3.1 Tumor characteristics

3.3.1.1 Histologic Type (World Health Organization modified)

3.3.1.1.1 Adenocarcinoma (not otherwise specified)

3.3.1.1.2 Acinar adenocarcinoma

3.3.1.1.3 Ductal adenocarcinoma

3.3.1.1.4 Mucinous adenocarcinoma

3.3.1.1.5 Transitional cell carcinoma

3.3.1.1.6 Squamous cell carcinoma

3.3.1.1.7 Neuroendocrine tumor

3.3.1.1.8 Small cell anaplastic carcinoma

3.3.1.1.9 Undifferentiated carcinoma
3.3.1.1.10 Other cancer (specify)
3.3.1.2 Histologic Grade of Tumor (any grading system as desired, such as Gleason's histologic score; specify grading system used)
3.3.1.3 Extent of tumor
3.3.1.3.1 Distribution of tumor in the specimen (e.g. right lobe, left lobe)
3.3.1.3.2 Quantitation of tumor (determine from gross and/or microscopic findings)
3.3.1.3.3 Lymphatic vessel invasion
3.3.1.3.4 Blood vessel invasion
3.3.1.3.5 Perineural invasion
3.3.1.3.6 Periprostatic tissue invasion (if appropriate)
3.3.1.3.7 Direct extension to adjacent organs(s): specify
3.3.1.4 Status of margins, if possible
3.3.1.5 UICC/AJCC pT Category
3.3.2 Malignancy indeterminate (specify nature of the problem)
3.3.3 No Tumor Identified
3.3.4 Other findings, as appropriate
3.3.4.1 PIN and grade
3.3.4.2 AAH
3.3.4.3 Prostatitis (granulomatous or other)
3.3.4.4 Benign prostatic hyperplasia
3.3.4.5 Basal cell hyperplasia
3.3.4.6 Postatrophy hyperplasia
3.3.4.7 Therapy related
3.4 Special studies designate special studies, if done, and include results with surgical pathology consultation report (e.g., histochemistry, immunohistochemistry, flow cytometry, nuclear morphometry)].
4. Radical prostatectomy
4.1 Clinical information provided to pathologist by the responsible physician
4.1.1 Patient identification (name/age/identification number)
4.1.2 Relevant history, including any previous diagnosis/therapy
4.1.3 Results of examinations
4.1.3.1 Laboratory (e.g., PSA or other significant findings)
4.1.3.2 Digital rectal examination
4.1.3.3 Imaging (e.g., ultrasound)
4.1.4 Clinical diagnosis
4.1.5 Type of surgical procedure (specified by surgeon)
4.1.5.1 Perineal prostatectomy
4.1.5.2 Retropubic prostatectomy
4.1.5.3 Nerve-sparing prostatectomy (left/right/both)
4.1.5.4 Standard radical prostatectomy
4.1.5.5 Super-radical prostatectomy
4.1.6 Anatomic site of specimen:
4.1.6.1 Prostate gland
4.1.6.2 Regional lymph nodes (site and laterality specified by surgeon)
4.1.7 Orientation of the specimen as marked by the surgeon (e.g., area of possible invasion of margin)
4.2 Macroscopic examination
4.2.1 Prostatectomy
4.2.1.1 Structures included should be noted
4.2.1.1.1 Prostate
4.2.1.1.2 Seminal vesicles
4.2.1.1.3 Segments of vasa deferentia
4.2.1.1.4 All or portion of bladder
4.2.1.1.5 Other (specify)
4.2.1.2 Description of type of prostate specimen
4.2.1.2.1 Total
4.2.1.2.2 Subtotal prostate
4.2.1.2.3 Size, three dimensions
4.2.1.2.4 Weight
4.2.1.2.5 Size of carcinoma(s), if possible
4.2.1.2.6 Method of margin identification (e.g., india ink)
4.2.2 Regional (pelvic) lymph nodes
4.2.2.1 Site and laterality (as specified by surgeon)
4.2.2.2 Number
4.2.2.3 Location
4.2.2.4 Size of largest gross metastasis
4.2.3 Recommendations for selection of tissues for microscopic examination
4.2.3.1 Tumor (each grossly recognizable tumor)
4.2.3.1.1 Location (right, left lobe, etc.), and extent
4.2.3.1.2 Extent, if possible
4.2.3.2 Sections to determine extent of invasion and margins
4.2.3.2.1 Apex (urethral) margin
4.2.3.2.2 Base (bladder neck) margin
4.2.3.2.3 Prostatic "capsule"
4.2.3.2.4 Circumferential periprostatic margins adjacent to tumor, including neurovascular bundle, as appropriate.
4.2.3.2.5 Seminal vesicles
4.2.3.2.6 Periprostatic tissue about the bases of seminal vesicles
4.2.3.2.7 Additional sections to determine multicentricity
4.2.3.3 All lymph nodes (specify laterality and site as specified by surgeon)
4.3 Microscopic examination
4.3.1 Tumor characteristics
4.3.1.1 Histologic type (World Health Organization modified)
4.3.1.1.1 Adenocarcinoma (not otherwise specified)

4.3.1.1.2 Acinar adenocarcinoma
4.3.1.1.3 Ductal adenocarcinoma
4.3.1.1.4 Mucinous adenocarcinoma
4.3.1.1.5 Transitional cell carcinoma
4.3.1.1.6 Squamous cell carcinoma
4.3.1.1.7 Neuroendocrine tumor
4.3.1.1.8 Small cell anaplastic carcinoma
4.3.1.1.9 Undifferentiated carcinoma
4.3.1.1.10 Other cancer (specify)
4.3.1.2 Histologic grade of tumor (any grading system as desired, such as Gleason's histologic score; specify grading system used)
4.3.1.3 Extent of tumor
4.3.1.3.1 Distribution of tumor in the specimen (e.g., right lobe, left lobe)
4.3.1.3.2 Quantitation of tumor (determine from gross and/or microscopic findings)
4.3.1.3.3 Lymphatic vessel invasion
4.3.1.3.4 Blood vessel invasion
4.3.1.3.5 Perineural invasion
4.3.1.3.6 Periprostatic tissue invasion (if appropriate)
4.3.1.3.7 Direct extension to adjacent organs(s): specify
4.3.1.3.8 Seminal vesicle(s) invasion
4.3.1.4 Status of margins, if possible
4.3.1.5 UICC/AJCC pT category
4.3.2 Malignancy indeterminate (specify nature of the problem)
4.3.3 No tumor identified
4.3.4 Other findings, as appropriate
4.3.4.1 PIN and grade
4.3.4.2 AAH
4.3.4.3 Prostatitis (granulomatous or other)
4.3.4.4 Benign prostatic hyperplasia
4.3.4.5 Basal cell hyperplasia
4.3.4.6 Postatrophy hyperplasia
4.3.4.7 Therapy related
4.3.5 Lymph node examination
4.3.5.1 Total number of lymph nodes examined
4.3.5.2 Number with metastases
4.3.5.3 Size of largest metastasis
4.3.5.4 AJCC pN classification
4.4 Special studies designate special studies, if done, and include results with Surgical Pathology Consultation Report (e.g., histochemistry, immunohistochemistry, flow cytometry, nuclear morphometry)].

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DIAGNOSIS AND STAGING WORKGROUP

Overview

The group considered that:

1. The objective of screening for prostate cancer is the detection of clinically significant tumors that are potentially curable in patients who have a life expectancy of at least 10 years postscreening and are otherwise candidates for therapy.
2. Methods of screening are limited with regard to sensitivity and specificity and there is as yet no consensus on normal ranges of serum prostate specific antigen (PSA) in relation to prostate volume, PSA density, and patient's age.
3. Staging systems need flexibility to incorporate new technology and to reflect the histologic potential of cancers discovered by screening. Clinical staging falls short of pathologic staging because of limitations of current technology.

Digital Rectal Examination

Digital rectal Examination (DRE) is a simple, inexpensive, and direct method of assessing the prostate. When undertaken by a trained health care professional, the positive predictive value can be 25–50%.[1] Experience from Sweden indicated that it may be feasible to train nonphysicians to evaluate the prostate sensitively and effectively, but it was agreed that such a practice may be unacceptable in certain cultures. It was agreed that universal training of medical students to carry out DRE should be a goal of medical education. However, it must

not be forgotten that the finer interpretation of the results of DRE is best undertaken by a trained urologist, even though it is accepted that DRE is a subjective process that has limited value for diagnosis and staging. DRE, as a simple procedure, is inadequate for diagnosis and screening and inaccurate for staging.[2,3]

Tumor Markers

Prostate Acid Phosphatase

It was agreed that prostate acid phosphatase may have limited use in staging but not in diagnosis or screening. An elevated PAP is indicative of local or metastatic spread of prostate cancer and usually indicates noncurable disease.[4]

Prostate Specific Antigen

It was agreed that PSA is the most appropriate tumor marker to screen for prostate cancer but has limited accuracy in staging.[5–7] There was no argument about the absolute upper value of normality (4 ng/ml monoclonal); in Europe, prostate volume is considered to be important, but it was agreed that this is an important priority for the future. Data were presented that indicated that PSA generally is proportional to prostate (and tumor) volume, and that a PSA greater than 6 ng/ml is more commonly associated with a tumor volume that may not be curable.[8,9] Bostwick et al.'s data indicated that a tumor volume of 5 cc had a 10% chance of positive lymph nodes, whereas others have shown up to a 21% incidence of metastases in tumors with a volume of 4–16 cc (Fig. 1).[9]

The issue of the significance of PSA detected tumors should be addressed in designing screening trials,

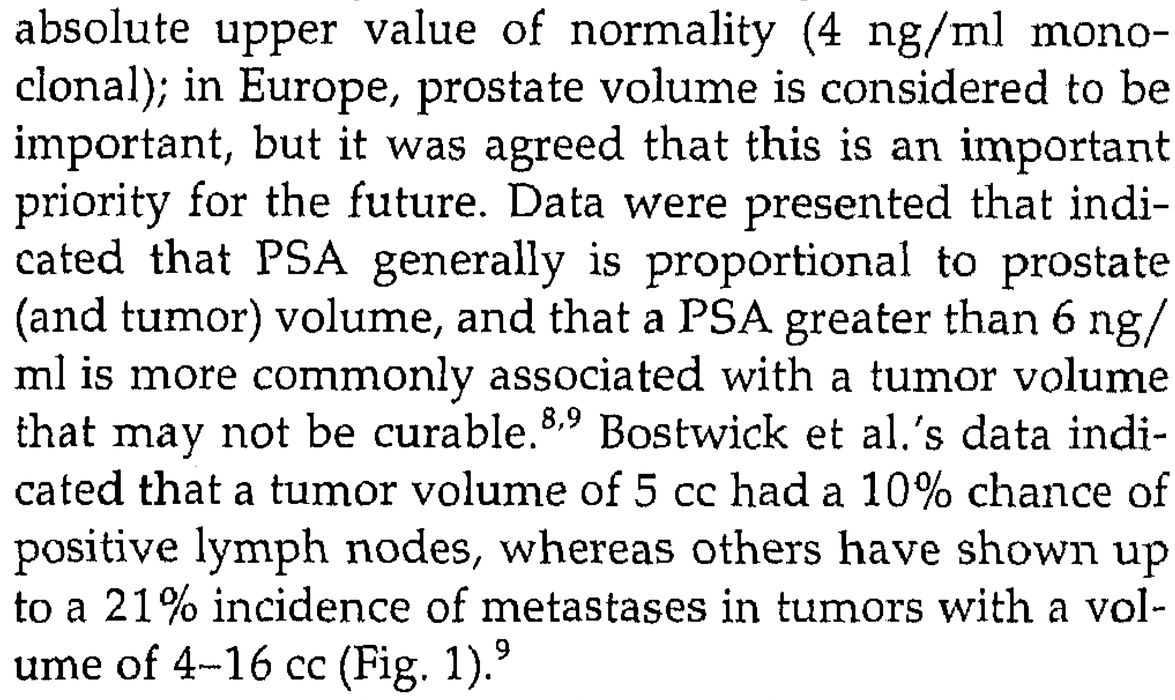

Figure 1. Relationship of tumor volume and PSA. Assuming a 5 cc. tumor volume is the upper limit of organ confined disease, the shaded area denotes the PSA range of maximum curability.

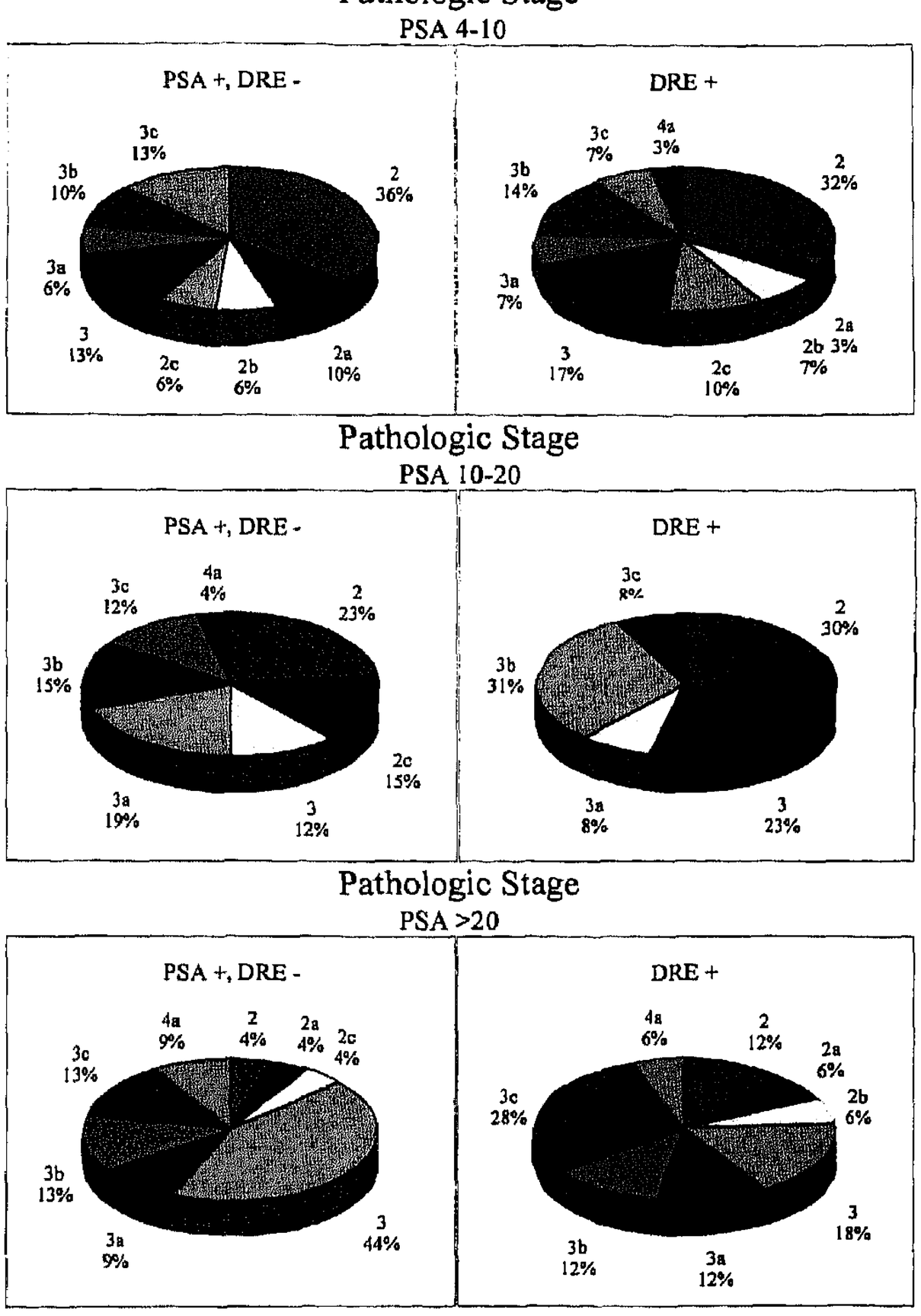

Figure 2. Comparison of T stage of radical prostatectomy specimens, controlled for PSA level, in PSA detected (DRE negative) vs. abnormal DRE. There is no significant difference in either group stratified for PSA.

because the intent is to impact only those tumors that are biologically significant. Data were presented indicating that tumors detected with a serum PSA of 4–10 ng/ml are associated with a 30–50% incidence of capsular involvement and up to 10% incidence of seminal vesicle involvement (Fig. 2).[10,11] All accepted that longitudinal PSA measurements are very promising for future study in screening, particularly when PSA is less than 10 ng/ml.

Quality assurance of PSA assay is crucial for screening programs and it was agreed that this should be performed in Central Reference Laboratories. Also, PSA has a practical advantage over PAP in that it is stable at room temperature and therefore is suitable for batch processing and off-site collection (Dr. A. Lijia, personal communication). Caution was urged for some instances of mildly elevated PSA that increase due to infection

(prostatitis) and a consideration should be made for trial of antibiotics.

Transrectal Ultrasound

Transrectal ultrasound of the prostate is now generally reserved for the evaluation of abnormal DRE or PSA elevated beyond 4.0 ng/ml.[12–14] This helps select for higher risk patients and increases the predictive value for transrectal ultrasound abnormalities. Transrectal ultrasound appearance of prostate cancer follows the general morphologic breakdown of: 30% nodular, 50% nodular and infiltrative and 20% infiltrative.[15] This corresponds to a spectrum of very hypoechoic to isoechoic appearance, respectively. Both the anterior and posterior periphery of the prostate should be searched carefully for lesions 6 mm–2 cm in diameter, corresponding to approximate tumor volumes of 0.2 cc–5.0 cc. This leads to optimal localization of pathologically confined cancer for diagnosis. A volume obtained by height, width, and length measurements also provides correlation with PSA.[16]

Staging

The confirmation of transrectal ultrasound abnormalities have been simplified by transrectal automated 18 gauge biopsy. As cancers enlarge, their margins may become more ill-defined yet also cause adjacent architectural distortions by mass effect. Capsular bulging, especially near the periphery, should prompt closer evaluation of potential extracapsular extensions. Biopsy of extracapsular extension or adjacent seminal vesicles could produce histologic confirmation, not afforded by other staging modalities. The estimated tumor volume, or gland involvement, has also been suggested by the number of involved cores if systematic biopsy is performed.[17] Systematic biopsy may increase cancer yield, especially in patients with disproportionate PSA elevations (e.g. serum PSA > gland vol × 0.1 ng/ml/cc). PSA density also correlates with increasing probability for extracapsular extension.[16,18]

Pelvic Lymph Node Dissection

The committee noted that while pelvic lymph node dissection provided the most accurate means of assessing the pelvic lymph nodes, that it was not curative and the recurrence rates reported ranged from 23 to 30%.[19–21] There is a group of patients in whom pelvic lymph node dissection may be of limited benefit as the current incidence of positive nodes is <5%.

Computed Tomography Scan Magnetic Resonance Imaging

Computed tomography scan magnetic resonance imaging was agreed to provide limited usefulness in staging.

Cystoscopy

It was agreed that cytoscopy provides no usefulness in staging.

Radionuclide Bone Scan

Radionuclide bone scan is useful in assessing the bony extent of metastases. It is, however, rarely positive in patients with a serum PSA less than 20 ng/ml. In the absence of an elevated alkaline phosphatase or symptoms, it could be omitted in patients with clinically localized cancer, a serum PSA less than 20 ng/ml, and well to moderately differentiated (Gleason 2–7) cancer.[22]

Pathologic Predictors

In addition to the above-mentioned staging techniques, there are certain pathologic predictors of stage, including Gleason sum and tumor volume, that should be incorporated into the staging algorithm.

Conclusions

The committees agreed that screening may provide a significant impact upon the natural history of prostatic adenocarcinoma, but that the parameters should be well defined. Patients who undergo screening should do so only if they are expected to benefit from the alteration in therapy. This would include those men 1) in whom prostatic cancer is likely (over the age of 40 or 50), 2) who have an expectation of survival of 10 years or longer and, 3) who are otherwise candidates for therapy. There are current guidelines by the American Urologic Association and American Cancer Society as to when screening should begin, but these organizations specify no upper limits of age or health at which time screening becomes of little value.

The groups further agreed that the methodology for screening should be a combination of PSA and digital rectal examination. Transrectal ultrasound was felt to be a useful adjunct in the event of an abnormal examination. The frequency of examination was discussed, and although the general feeling was that annual examinations are optimal, there were no data presented to

support this stance. The level of "abnormal" PSA should be sufficiently low to allow optimal detection in terms of both numbers of significant tumors and curable tumors (defined as tumors confined to the prostate). This would correlate with a "window of opportunity" between a serum PSA of 2 and 6 ng/ml. Age-specific ranges were discussed and felt to be another attempt to increase the specificity and sensitivity of PSA, yet personal data of LaBrie refuted age-specific PSA.[23]

Staging systems were discussed and it was felt that because the stage was a reflection of the biologic hazard of the disease, the palpability of a lesion was a poor marker, as a large number of tumors were anterior or hidden in a large adenomatous gland. The best predictor of biologic hazard is the volume of the tumor, yet there currently is no technology available to accurately assess the volume preoperatively.

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LABORATORY EVALUATION WORKGROUP

It is now well established that the determination of the concentration of prostate specific antigen (PSA) in serum is of clinical value in monitoring the treatment of patients with prostatic cancer.[1] Moreover, there is now good evidence[2] that the determination of serum PSA levels will make a significant contribution to the new screening initiatives directed to the recognition of early prostate cancer. Such screening studies are currently the center of considerable controversy,[3] although a number of case control studies have established the potential of the serum PSA analysis and digital rectal examination as the currently available primary tests to identify early, probably organ-confined prostatic cancer. Transrectal ultrasonography is generally seen as the secondary procedure to be undertaken if either of the primary tests is positive.

Randomized screening studies are necessary to determine whether the use of such tests is appropriate and when used in populations of asymptomatic normal men, will reduce the mortality from prostate cancer. A range of serum PSA concentrations from 0 to 4.0 ng/ml has been seen for some time by the international urologic community as normal. Levels of serum PSA greater than 4.0 ng/ml therefore would be viewed with some suspicion with regard to the possibility of cancer. In a population of normal men older than 55 years, 2 to 3% would be expected to have levels of serum PSA greater than 10.0 ng/ml and about 10% would be in the 4.0–10.0 ng/ml range. A value of 10.0 ng/ml or greater should require serious clinical evaluation, with a large proportion of such subjects expected to have disseminated disease. On the basis of such studies, the American Cancer Society has recommended an annual digital rectal examination and PSA analysis for all men over the age of 50.

The arbitrary PSA value of 4.0 ng/m as a cutoff point for cancer dominated discussion related to screening for the last 5 years, with studies indicating that many men in the 4.0 to 10 ng/ml range have cancer confined to the prostate. Considerable emphasis is directed to the potential value of PSA analysis for the recognition of early cancer. Laboratory specialists have indicated, however, that PSA immunoassays can only provide a guideline as to the level of PSA in serum.[4] There is no internationally recognized PSA standard reference material against which the calibration of such immunoassays for PSA measurement can be validated. There is, moreover, no recognized procedure that would readily be accepted as the "definitive" assay. Different studies have shown the various immunoassay kits for the measurement of PSA, produced by a number of diagnostic companies, provided widely varying results from the same serum sample.

The consensus committee discussed the biochemistry relating to the production of PSA by the epithelial cells of the prostate. It is recognized[5] that the PSA molecule was essentially of the kallikrein family and as a serine proteinase, has the capacity to bind in the serum to the proteinase inhibitors α_1-antichymotrypsin and α_2-macroglobulin.[6] A major proportion (65–90%) of the PSA that is measured by PSA immunoassays is in the form of the PSA-α_1-antichymotrypsin complex. The PSA that is complexed with α_2-macroglobulin is not recognized by the antibodies currently used as components of any diagnostic PSA immunoassay kit.[6–8]

The PSA immunoassay kits therefore measure PSA that is in the free, unbound state, and also the PSA that is complexed to -α_1-antichymotrypsin. The sum of both indices provides the "total PSA" level in serum.[7] Depending on the antibody composition of the various kits, the total PSA value will vary according to whether the free PSA and complexed PSA are determined on an equimolar basis.[9] The experimental data suggest that few commercially available assays can measure free and complexed PSA in an almost equimolar equivalence pattern. The level of total PSA in serum, measured by procedures that determine the free and the complexed PSA on an equimolar basis, would be considered, at present, to provide the most likely accurate value. The Hybritech Tandem R assay was recognized by the committee as an acceptable provisional reference method. Many other kits do not appear to measure serum PSA components in this equimolar manner. The committee considered, therefore, that the varying levels obtained with different kits is a problem that could well relate to the capacity of the immunoassay under the specified analytical conditions, to measure free and complexed PSA.

Information was made available to the committee to indicate that when specific assays were established to separately determine the concentration of free PSA as well as the levels of PSA complexed to α_1-antichymotrypsin, the ratios of free PSA/total serum PSA, or of PSA-α_1-antichymotrypsin complex/total serum PSA, appear to provide sensitive parameters that would allow a more specific differentiation of patients with benign prostatic hyperplasia from those with cancer in the screening programs.[8,10,11] Such assays could reduce the false positive rate by about 50%.[10] It was noted by the committee, however, that these assays are not yet available for current screening studies.

The committee considered that it should be prag-

matic about the "laboratory requirements" necessary for the support of the screening studies and recommended that a short term and a longer term program should be established. The long term goal is to establish international PSA standard preparations, but in the short term, it will be necessary to prepare a provisional PSA standard that would be available for the Pan-European Screening Program.

Such a standard could be obtained as follows. First, samples of PSA isolated from seminal plasma should be obtained from sources that could provide evidence of acceptable purity and characterization. A PSA concentration would then be assigned to the preparation of PSA in buffer medium, by use of "the provisional reference assay." Samples would then be aliquoted into tubes for stability experiments, storing samples at varying temperatures, from 0°C down to minus 70°C, as a preliminary study to establish conditions for the storage of the European reference materials. A series of laboratories involved with the screening studies would perform the analytical work to assign the PSA concentration to the standard preparation. Furthermore, a series of "pools" of serum would be prepared containing levels of PSA in the range between 0 to 10 ng/ml. These pools would form the basis of a quality assurance program to monitor the performance of the laboratories involved in the determination of serum PSA for the screening studies. Randomly selected samples of different pools would be dispatched from a designated center to the laboratories at regular intervals and results reported to the quality assessment coordinator.

The committee also accepted that the laboratories would probably require an automated analytical system for the determination of PSA. Although the correlation was seen[10] to be excellent, but with a small negative bias, between data generated by the current Abbot IMX automated assay and the Hybritech Tandem R procedure from the analysis of a series of serum samples, evidence provided to the committee indicated that there may still be differences between the assays as to how well they measure the free PSA and complexed PSA on a molar equivalent basis. Such differences could be readily overcome by the selection of appropriate antibodies that can provide equivalence in the detection of different molecular forms of PSA in automated assay systems, although these may not yet be commercially available. It was recommended that if possible, all the laboratories concerned in the screening studies would use an automated assay.

Once evidence that other immunoassay systems were able to provide analytical equivalence and satisfactory precision, as documented by the quality assurance program, then they should be considered for use in the screening studies.

In the longer term, the application to the European Community for financial support for the cooperating laboratories to produce European reference materials containing PSA and PSA-α_1-antichymotrypsin complex would be submitted on April 14, 1994, the next acceptable date for such requests. Standardized isolation and characterization procedures would be established and such materials would be processed according to the standards of the European Community Bureau of Reference Materials, to produce the European standard preparations of both PSA and PSA-complex that could then be used for assay validation. It would be expected that diagnostic kits for total serum PSA analysis would determine the different molecular forms of PSA at molar equivalence. The complexed PSA would be made available for the development, establishment, and validation of the next generation of more specific assays for the determination of the free PSA, and the PSA-α_1-antichymotrypsin complex in serum. The European standard preparations would then be made available and distributed through the World Health Organization, if this was considered appropriate.

Although new markers for prostatic cancer will inevitably be developed for future years, a shorter-term goal is to establish the more specific assays for the measurement of the various molecular forms of PSA. At present, the determination of "total PSA" levels in serum provides the only practical and rational means available for the identification of early prostate cancer. These assays must be better monitored in the screening studies and assay precision established for the lower 0 to 10 ng/ml range to determine, more accurately, the relevance of the "cancer cut-off point," be it 3.0 or 4.0 ng PSA/ml serum.

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TREATMENT WORKGROUP

Introduction

Localized prostate cancer represents a disease spectrum of clinical stages from T_{1a} to T_3. Within each stage exist variations in malignant potential. Several clinical, biochemical, and radiographic factors are considered in the assessment of the individual T stage, including digital rectal examination, transrectal ultrasound, prostate specific antigen (PSA), PSA density, magnetic resonance imaging, tumor grade, ploidy, and lymph node status. For example, category T_3 includes both patients with minimal capsular penetration (as identified by digital rectal examination, transrectal ultrasound, or even needle biopsy) as well as patients who have bulky T_3 tumors with symptoms of an obstructive nature. Some of the former may still be localized and curable, whereas the majority of the latter will have nodal metastases. Despite the importance of T-staging, in some surgical series only 22% of patients have been staged accurately.[1,2]

The concept of "localized disease" implies that it is curable, with acceptable treatment mortality. Therefore, for the purpose of this workshop discussion, our definition encompasses a range of prognostic criteria that, for an individual patient, are considered to be synonymous with curability. Many parameters are used to assess curability; for example, a poorly differentiated Gleason sum grade 10 T_2 cancer is not likely to be cured, whereas a well differentiated Gleason grade 4 tumor is.

We are witnessing both a stage and intrastage migration in prostate cancer toward more favorable prognostic groups. This phenomenon may influence treatment selection and must be recognized when attempting to compare current treatment strategies with past experience.

The presence or absence of lymph node metastasis is an important prognostic factor. When considering treatment for localized disease, lymph node status should be ascertained with reasonable certainty. Despite this, many patients do not undergo lymph nodal assessment. In general, a relationship exists between tumor (Gleason) grade, PSA, and lymph node status.[1,3,4] (Tables 1 and 2) Patients with a PSA less than 20 ng/ml and a Gleason grade less than 7 have a low risk of

Table 1. Risk of Lymph Node Metastases Versus Gleason Grade

	Percent node positive		
Gleason sum	*Partin**	*Wolf*†	*Kleer*‡
1			
2			
3	1	0	8
4			
5	4		
6	8	9	26
7	20		
8		21	
9	42		
10			
Overall percent node positive	11	10	13
Total no. patients	703	164	975

* Journal of Urology 1993;150:110–4.
† Journal of Urology 1993;42:131–7.
‡ Journal of Urology 1993;41:207–16.

Table 2. Risk of Lymph Node Metastases Versus Preoperative Serum Prostate Specific Antigen

	Percent node positive		
PSA ng/ml	*Partin**	*Wolf*†	*Kleer*‡
0–4	1	8	3
4–10	12	5	6
10–20	18	—	16 (10–25 ng/ml)
20–30	26	—	—
30–40	42	31	25 (25–50 ng/ml)
40–50	25	—	—
>50	74	—	52
Overall percent node positive	11	10	13
Total no. patients	703	164	975

* Journal of Urology 1993;150:110–4.
† Journal of Urology 1993;42:131–7.
‡ Journal of Urology 1993;41:207–16.

lymph nodal metastases. However, a poorly differentiated (Gleason sum 8) with PSA of 15 ng/ml may have a 20% risk of nodal disease. The goal of any treatment for localized prostate cancer is to improve patient survival while preserving the best quality of life. In other words, giving the patient "the best chance of dying of something else." Thus, treatment should be considered for any man with prostate cancer whose survival, in the opinion of the clinician, will be shortened by the cancer. Usually, these are men with a life expectancy greater than 10 years and whose treatment would be expected to influence outcome. In this decade, economic issues as well as therapeutic efficacy are influencing such treatment decisions. Economically, curative treatment of early disease may be more attractive than treating advanced disease. However, it is not known what strategy is ethically and economically desirable.

Treatment Options

Having defined localized prostate cancer and whom to treat, we review the options available for treatment. The choice of therapy depends upon the T stage and, as previously discussed, the overall health of the patient. Watchful waiting may be very appropriate for an asymptomatic patient with a T_{1a} cancer whereas a high grade, Gleason 9 T_3 cancer may benefit from radiation therapy, even though the likelihood of cure could be remote. Treatment options should be discussed with the patient and in some cases second opinions sought from multiple specialties.

Treatment options for localized prostate cancer have been embraced with varying degrees of enthusiasm. Opinions and practices have changed considerably over the past decade. The list of therapeutic options includes time-honored methods of radical prostatectomy or radiation therapy as well as watchful waiting, brachytherapy, hormone manipulation, and cryotherapy. The major challenge facing the clinician regarding treatment options is the lack of data from randomized clinical trials.

Radical Prostatectomy

Radical prostatectomy is the gold standard for the treatment of localized prostate cancer. Through the early 1960s, the perineal surgical approach was the only curative procedure for highly selected patients with small nodules. As a result of greater understanding of the relevant anatomy and the refinement of the nerve-sparing retropubic radical prostatectomy, the complications of surgical treatment have decreased significantly.

The most important and significant early complication is postoperative mortality. In the age and health group of a screened population, the expected mortality in major centers will be approximately 1% (±0.9%) within 30 days and 1.2% within four months.[5–7] In some urologic practices, mortality rates are higher. A second early complication is rectal injury, with a reported frequency of approximately 3%.[8] This complication, however, has little long term importance. Strictures, incontinence, and impotence are the major late complications. None influence survival but all definitely affect quality of life. Stricture frequency is about 20% and relatively easy to handle. Incontinence and impotence are also age- and stage-related. Overall final incontinence rates should be less than 5%, although this is certainly a question of definition. Impotence is a major quality of life issue, but its frequency has decreased considerably with the adoption of nerve-sparing surgical techniques.[7] Treatment of incontinence and impotence can have considerable cost implications. These should be taken into account when performing financial cost-benefit analysis of screening programs.[8]

Perhaps for more than any other treatment modality, the outcome of radical prostatectomy is inextricably related to pathologic stage. If the malignancy is organ-confined, long term survival is indistinguishable from age-matched men without prostate cancer.[1,6] Fifteen-year survival rates in excess of 50% have been reported. The survival of men with locally advanced (T_3 or T_4) disease is considerably less.

The postoperative follow-up of men treated with radical prostatectomy has been revolutionized by the advent of assays for the detection of serum PSA. Measurable levels of PSA after radical prostatectomy are a harbinger of clinically evident persistence disease, although the prognostic value of this biochemical marker

is unknown with respect to individual morbidity or cancer-specific mortality. The impact of adjuvant therapy on incomplete surgical resection or postoperatively detectable serum PSA is unknown. Several trials have been initiated to study these issues. At the present time, there is insufficient data to support the use of postoperative hormone therapy as an adjuvant in the treatment of localized prostate cancer except in the context of clinical trials.

Neoadjuvant Hormone Therapy

Several studies are in progress evaluating neoadjuvant hormone ablation before radical prostatectomy or radiation therapy.[2,9–11] Labrie and others[2] demonstrated a significant reduction of positive margins in men receiving three months of an antiandrogen plus luteinizing hormone-releasing hormone agonist before radical prostatectomy compared with men undergoing immediate surgery without hormone therapy. Similarly, the Canadian Anadron Trial and the Radiation Therapy Oncology Group have reported significant decrease in local recurrence and improvement in disease free survival in men with T_3 prostate cancer receiving neoadjuvant hormone ablation.[11]

Cryotherapy

There has been a resurgence of interest in cryoablation owing to improved delivery systems and, particularly, to the ability to visualize tissue freezing by transrectal ultrasound. These factors have contributed to a significant reduction in morbidity. Long term outcome data are lacking, but in one recent series, 62% of men had negative biopsy at three months.[12] The ability to freeze beyond to the prostate capsule makes this modality appealing for some patients with clinical stage T_3 disease. In addition, this approach holds promise for some patients failing primary radiotherapy.

Morbidity does occur with this method of treatment. Rectal fistula, sloughing of urethral tissue, impotence, penile edema, and voiding difficulty have all been reported.[12] Long term follow-up of patients undergoing cryoablation will be required before the efficacy and morbidity of this procedure can be determined. At the present time, this treatment should only be used in the context of a clinical trial.

Radiotherapy

Radical external beam radiotherapy has become possible with the development of high energy radiation equipment, earlier with cobalt 60 treatment units and with linear accelerators beginning in the 1960s. The pattern of care study (PCS)[13] reported radiotherapy treatment results for localized prostate cancer from a large number of research and nonresearch centers. The aim of this review was to produce data that were unlikely to be biased by any single institution. Sixteen-year overall survival of T_1N_o patients was similar to a healthy age-matched population. Survival of T_2N_o was 22% lower than the age-matched controls. Survival of T_3/T_4N_o was about 15% lower than T_2N_o at 10 years but was identical at 16 years. Other single institution series report essentially similar results.[14,15] Pooled data from the literature report 0.2% fatal complications after radiotherapy. The overall incidence of significant urinary or rectosigmoid sequelae is approximately 3% and 7–10% for severe and moderate complications, respectively. The most frequent urinary sequelae are radiation cystitis with intermittent hematuria and urethral strictures. The incidence of severe anal/rectal injury requiring colostomy is less than 1%. These complications are related to treatment technique. A sexual dysfunction has been described in 14 to 50% for patients depending upon age, time of assessment, and technique of irradiation. However, prospective data comparing postradiotherapy impotence with the natural evolution of sexual dysfunction are presently lacking.[14]

Progress in radiation computer technology (either with conventional radiation or proton beams) and imaging as well as in the physics of radiation have modified the practice of radiotherapy considerably. Emerging data for three-dimensional conformal radiotherapy indicate that higher doses can be delivered safely to the prostate gland without increasing treatment morbidity.[16,17] This observation assumes particular importance in view of the strong relationship existing between radiation dose, local control, and survival.[15] The same rationale supports the renewed interest in prostate cancer brachytherapy[18] although the consensus of this workshop is that the technical difficulties of brachytherapy may limit its role and make it less attractive than 3-D conformal radiotherapy. Long term data on local control and survival of localized prostate cancer with these sophisticated modern imaging therapies are not yet available.

Recent data indicate that pretreatment PSA levels, when considered together with clinical stage and grade, will help to define patient subgroups with different probabilities of local control and disease free survival after radiotherapy. Poor prognostic groups on which to focus clinical trials that employ more intensive local treatment or adjuvant systemic therapy including hormones can be identified by these means. There are also indications that postradiotherapy PSA levels will help to identify at an early stage those patients who are likely

to relapse and who should be considered for salvage therapy.[19,20]

Treatment of Tumor Relapse

Many men treated for localized prostate cancer will demonstrate local recurrence despite the curative intent of the treatment. Recurrence may be identified by several parameters, including palpable local recurrence, positive biopsy, detectable serum PSA after radical prostatectomy, or rising PSA after achieving a nadir in men treated with other modalities. The therapeutic options for tumor relapse are predicated on the primary therapy administered. Radiation therapy may be offered to a patient who develops local relapse after radical prostatectomy. The benefit of such treatment is presently unknown. Salvage prostatectomy after radiotherapy failure is feasible but rarely successful. Hormone therapy is usually effective in altering biochemical markers (PSA); however, its impact on altering survival is unknown. Recently, cryotherapy has been suggested as an alternative for patients failing radiation.

Watchful Waiting

Several studies have provided long term follow-up for watchful waiting of localized prostate cancer indicating a favorable outcome.[21–24] These studies have been criticized for various biases, but their overall conclusion should not be ignored. For many patients with significant comorbidity, watchful waiting may be appropriate because the probability of noncancer death could be high.

The question that remains is whether watchful waiting is equivalent to immediate treatment for healthy patients with a long life expectancy. Four important factors raised by these studies need to be considered:

Death from Prostate Cancer

These studies reported that death from prostate cancer within 10 years was 7 to 8.5%, compared with 31 to 47% from other causes. Longer follow-up data are lacking. This survival differential may change, suggesting that the present data should be applied to younger men with caution.

Progression

In most patients, once progression has been observed, cure is no longer possible. One exception is that progression from T_{1c} to T_2 may still be curable. Local progression to T_3 occurred in 22 to 55% of patients, but this causes concern to the physician more frequently than the patient. Patients who need treatment for local progression are usually few. Distant metastases developed in 12 to 14% during watchful waiting. At this time treatment can only be palliative.

Quality of Life

Assessment of quality of life in patients with localized prostate cancer must be evaluated in terms of "health" rather than "disease." Although the review by Fleming and others[23] was based on such a conception, it did not address the patient's own perception of living with cancer.

Treatment Decisions

Watchful waiting implies treatment for progression. If palliative treatment only is planned, it may be argued that follow-up is not necessary. However, if immediate treatment is considered necessary at the time of progression, therapy will depend upon the type of progression. Should a rising PSA be treated? If so, at what PSA level? Furthermore, what constitutes "local progression?"

Summary

There are advantages and disadvantages to each of the treatment modalities available for localized prostate cancer. For individual patients, treatment selection should consider all these factors in concert with the patient's acceptance of the side effects and the expected results of each treatment choice.

Readers should note the absence of a table comparing the outcome of different treatments. This is not an oversight but illustrates the workshop view that adequate randomized trials of treatment for localized prostate cancer have not been performed and that data deriving from different treatment modalities are not comparable. The most pressing issue for the treatment of localized prostate cancer is the development of reliable prognostic markers that will allow the separation of those men who will die of prostate cancer from those who will not. Thereafter, the impact of intervention must be determined.

Meanwhile, the organization of prospective trials is necessary if informed decisions are to be made in the future. In designing such trials, the endpoints must be identified clearly and must include overall survival, time to progression, and quality of life. For this purpose, the assessment of comparative treatment morbidity requires refinement for use in clinical trials.

Constant monitoring will be needed, and evaluation analysis must consider not only the trial itself but also any progress in developing therapeutic methods.

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TRIAL ORGANIZATION WORKGROUP

The committee on trial organization agreed that at this time there is insufficient evidence of potential benefit to support the use of widespread population screening tests for prostate cancer outside of research studies. Meanwhile, there are different criteria upon which to base evaluations of screening programs, depending on the objectives to be achieved; for example, demonstration projects for feasibility purposes or randomized con-

trolled trials for effectiveness evaluation. The committee mainly considered questions related to the latter.

What Is the Most Appropriate Design to Study the Effectiveness of Prostate Cancer Screening?

The design must avoid biases caused by selection, lead time, and length. This can be best achieved by a controlled trial in which an identified study population of sufficient size is randomized into two arms. One is offered screening tests, and the other receives routine health care. Both arms are to be followed up from the date of randomization and total prostate cancer mortality recorded. Analysis must be on an "intention to treat" basis.[1] Within this basic framework, randomization may precede consent (the target population is the same as the study population) or follow consent (the study population is smaller than the target population). If there are ethical objections because the control arm receives no potential benefit, then it would be possible to offer screening to the control group after a delay of several years.[2,3]

Lessons from breast cancer screening trials show that individual randomization is to be preferred.[4]

Details Concerning Randomized Controlled Screening Trials

Age Range

The selection of the age group is influenced by the incidence rates and by life expectancy.[5] Therefore the committee recommended selecting a target group ages 55 to 70 years at entry to the trial. There are no good arguments for starting screening under the age of 50. Although some individual men between the ages of 50 to 54 years might have most benefit in terms of years of life gained, the costs for each additional year will be extremely high.

Interscreening Interval

Recent results from the Canadian[6] and the US ACS-NCDCP[7] demonstration screening projects show interesting results based on annual prostate specific antigen (PSA) tests, obtaining detection rates of greater than 2.0% to 3.0% after 1, 2, and 3 years screening. Conversely, this short time period may not provide enough relevant data on interval cancer cases to investigate the natural history of the disease under study. In addition, annual screening may be less likely to be cost-effective and could probably result in high costs per additional cancer case detected. Therefore the majority of the committee recommended a rescreening period of at least 3 years for randomized controlled trials. Supporting this design are the recent results from the Canadian project.[6] Reports from the American Cancer Society Project in the USA support the cost-effectiveness of annual screening.[7,8]

Screening Tests

Despite evidence that PSA, or PSA combined with DRE, as primary screening tests, could be an effective choice, the use of the 3 screening tests (digital rectal examination, PSA, and TRUS) is recommended at the start of the European trial.[8–10] At present time there is not enough information available from the European pilot studies to delete one of them as being of poor cost-effectiveness for the detection of early cancer cases when a rescreening interval of more than 3 years is proposed. For scientific purposes it is recommended that serum samples are taken from each individual and stored. Strict objective criteria that could be easily applied should be defined for the selection of suspected cases on DRE and TRUS. Biopsy should be taken from patients with suspected cases as agreed by the diagnostic and laboratory committees.

Outcome Measures

The primary outcome measure of the trial will be prostate cancer mortality reduction. Quality of life measurements and cost parameters must also be included as intrinsic components of this trial design. To measure cost-effectiveness of different screening strategies and costs per prostate cancer death avoided, it is recommended that resource use in both arms is recorded. The data can be collected for the total group or in a subsample of individuals.

Whether analyzing duration of survival, quality of life, or cost parameters, all measurements should be stratified retrospectively for important prognostic factors, such as advanced disease.

What about Recruitment?

European pilot studies in Rotterdam and Antwerp show that between 36 and 42% of men from the target population are willing to join the study population of randomized screening trial. Fortunately, screening trials with low rates of recruitment could yield unbiased results so long as randomization is applied after recruitment. High compliance rates within both arms of this study population will increase statistical power. Possible specific ways to increase those rates could be the use

of professional media techniques and personal mailings.[1] Generalization of the results to the target population will be more straightforward if high recruitment rates have been achieved (or if the study population is representative of the target population). However, promotion of screening is very complex because it may enhance contamination of the control arm by the use of screening tests. In screening demonstration projects such as conducted in the US, (ACS-NPCDP)[7] higher recruitment rates may be achieved because the message to the population promises potential benefits. This is difficult to promote in the context of a randomized controlled trial.

Is Overdiagnosis a Concern?

The term "overdiagnosis" refers to the possibility that screening detects excess numbers of small volume (0.05 to 1.00 ml) tumors. Evidence is accumulating in the literature that PSA screening, even when accompanied by an aggressive biopsy policy, does not lead to overdiagnosis in this sense.[11,12] Overdiagnosis can also be interpreted as detection and treatment of tumors which, although classified as biologically important, would not have become life threatening. Epidemiologic data on incidence and mortality of prostate cancer, particularly from the US, show that despite a tremendous incidence increase during the last decade, mortality has remained relatively constant.[13] This suggests that screening may lead to overdiagnosis in this latter sense. It could also mean that current screening is finding significant cancers, preventing an increase in mortality despite an increase in incidence. It will be essential to monitor cumulative incidence of prostate cancer in the two arms of the trial to determine whatever occurs.

Trial Committees

Several trial committees are required: the causes of death committee, quality control committee, and an independent data monitoring committee that will establish stopping rules, apply ethical standards to interim results, and if necessary, review early mortality results.

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CHAIRMEN'S SUMMARY

During this workshop we received confirmation that there has been a progressive rise of a significant degree in prostate cancer incidence in North America and Western Europe, for at least the last 8 years. Although the mortality rates are not necessarily the same in both regions, it appears that they have not increased greatly.

This has been suggested to be similar to the situation in the 1970s when mammography and other associated tests were being introduced for breast cancer screening in the United States. There is no current basis for projecting how long the increased prostate cancer incidence will be observed, nor when it might drop with or without a change in mortality rates. Proposed public health interventions, if conducted, must be evaluated in the presence of such features. Intervention action by demonstration projects or randomized trials seems desirable.

The workshop presentations and discussions have focused rightly on the conduct of prostate detection trials. Lessons from trials of other cancer sites are available to be learned. Quality of assessment and uniformity of processing are essential features of any pathologic evaluation. The nature and extent of the cancers detected are very important in these projects. The care given the pathologic evaluation of the tumors found can be said to be one of the most important features of any good trial. That is certainly the case in the United States.

The reports dealing with the methods and process of staging and diagnosis of prostate cancer emphasized the use of the currently available TNM system. There is no need for agreement as to which techniques of diagnosis (prostate specific antigen blood test, digital rectal examination, and transrectal ultrasound trials) must be used either primarily or secondarily. The fact that there are and will be differences in this feature of trial design will be useful in comparing the results obtained in the various efforts. It is also certainly true that the cost of any trial can be considerable, and may have an impact on which diagnostic tests are chosen for primary or secondary use. We can only learn, based on the outcomes over time, how these features play out. There is no sure answer at this point.

An area of major concern is the quality assessment and performance of prostate specific antigen blood determinations. As reported, there are differences among the available tests and there obviously can occur variations in test performance. Comparison of prostate specific antigen results between participating hospitals or institutions, variations over time, or after specimen storage, present interpretation problems. There will also be variations between trials. These differences could be significant. It is hoped that by working with industry researchers and scientists this important concern presently can be addressed. Because detection trials are expected to obtain values from participants that are in the normal or near normal range, where a small variation might cause a significant diagnostic or therapeutic procedural change, this is a most important current concern. Several of the European and North American laboratories are working to provide possible solutions to this issue, but some time will be necessary. Knowledge of this issue is critical for those instituting any trial, and should be considered by anyone conducting a current trial.

The trial organization for prostate cancer detection has and will differ, to some degree, based on whether the effort is a prospective randomized trial or a demonstration project. Both methods provide valid and useful information that can be evaluated employing epidemiologic and statistical techniques using other concurrent regional tumor registry data that can provide population-based information on the screened or nonscreened population for comparisons. The types of cancers and other clinical features will doubtless prove to be similar despite differences in trial design. This feature is readily apparent based on the multiyear results available in the United States, where in the aggregate the following has been seen: 1) The majority of the tumors are clinically significant (85–90%); 2) The tumors are usually treated not observed; 3) The tumor size or volume, or tumor grades observed are comparable to those tumors being concurrently clinically observed or treated. It was also observed that small volume well differentiated tumors are not detected in great numbers. These clinically insignificant tumors are generally observed and, if treated, they do not show poor clinical results with high morbidity and mortality from the treatment. The emerging data from multiple trials are putting to rest the speculations of some health economists in this regard.

Any conducted trial should be performed with the intention to treat those tumors found, and to do so in a similar fashion to those otherwise being treated. The treatment group reaffirmed this feature, and has provided a fair and comprehensive summary of the current available treatment options. This workshop has provided a very good basis for the evaluation of the current situation regarding the early detection and treatment of prostate cancer on a global basis, and we are grateful to the participants and the sponsoring organizations for their support and active participation.

The workshop goals have dealt generously and fairly with features of epidemiology, pathology, diagnosis, staging, laboratory evaluation, treatment, and trial organization. The reader is commended to this current assessment of these factors as they might affect screening for prostate cancer.

Chairmen

L.J. Denis, Chairman Flemish Advisory Commission on Cancer Prevention; G.P. Murphy, Secretary-General, International Union Against Cancer; F.H. Schröder, Coordinator Pan-European Screening Trial for Prostate Diseases.