THE NATURAL HISTORY OF PROSTATIC CANCER
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Introduction

• **Definition:** (of ‘The Natural History’)
  • The evolving clinical and pathologic manifestations of the disease in the untreated host
  • can properly be regarded as a consequence of host-tumor interaction

• **Reasons** (for understanding this)
  • provides the basis for logical treatment
  • affords insight in assessing successes and failures
Although considerable confusion, both semantic and anatomic, persists, it is generally agreed that the majority of prostatic cancers arise in the peripheral portions of the gland, as distinguished from the central or periurethral portions of the gland which give rise to benign prostatic hyperplasia.\textsuperscript{1,12,17,25,33,42,43,57,59,60–63,88}
Things taken for granted

- Clear cut relationship between grade and aggressiveness of cancer

- Not all agreed with this
Whitmore Staging system

Stage A
- The clinically unapparent prostatic cancer, found incidentally by the pathologist either at autopsy or during examination of clinically removed prostatic tissue
- Without evidence of local extension beyond the prostatic capsule or of metastasis.

Stage B
- The clinically evident prostatic cancer, apparently confined within the prostatic capsule, and without evidence of metastasis

Stage C
- The clinically evident lesion with apparent local extension beyond the prostatic capsule but without evidence of metastasis.

Stage D
- Clinically metastatic prostatic cancer

Limitations to the staging system

- Pathologic stage often differs from clinical stage
- Staging implies a step-like progression of tumor growth rather than the continuum of tumor growth which more probably exists
- No provision for indicating growth rate or change in growth rate, even when such is known
• Different tumor characteristics within a stage
  • the “small” and the “large” Stage A, Stage B, or Stage C lesions
  • various patterns and extents of metastatic lesions (Stage D) the size and local extent of the primary tumor and the pattern and extent of metastatic spread (Stage D)
Simplistic model of progression

Fig. 1. Stage progression of prostatic cancer.
In support of a simplistic model

- The majority of deaths in Stage; to a lesser extent in Stage C
- Treatment of Stage B disease decreases Stage C and D disease incidence
- Successful treatment of Stage A decreases stage B incidence
Stage A

• Clinically unapparent tumor
• Most often from tissue removed for ‘BPO’
• Incidence is ~ ½ that of autopsy specimens
• Prevalence far exceeds mortality and morbidity

• Long course of disease
• Normal or ‘close to normal 5-yr ‘life-expectancy
  – Dependant on grade
    • Hanash, 1972
Stage A

- Autopsy incidence roughly 2X the clinical incidence
  - Peripheral location of lesions
  - Small size of lesions
  - Incompleteness of prostatectomy specimens
  - Extent of pathologic examination

- Multi-centricity
  - Common
  - Intra-gland metastases?
  - Extension of a single lesion?
  - However.....
    - long survival without treatment
    - Absence of identifiable dis. upon further treatment
Stage A

- Good clinical course of Stage A cancer
  - The operation may be curative
  - Natural history of the particular tumor predetermines a long survival

- TURP prevents CaP??
  - ‘Prostatectomy for benign prostatic hyperplasia offers no apparent prophylaxis against the subsequent development of cancer’

Stage A

- Are all Stage A cancers early?
  - The greater the size
    - the greater the size of the microscopic lesion,
    - the greater the tendency to dedifferentiate,
    - to involve prostatic capsule,
    - to involve nerve sheaths,
    - to produce local extensions within the gland, and
    - to form intragland metastases

- Poorly differentiated tumors a/w:
  - increase tumor size
  - Diffuse growth pattern
  - perineural spread
  - extension outside the prostatic capsule
    - patient who presents with diffuse metastases from a clinically inapparent prostatic growth


Stage B prognosis

• < 10% of ‘representive clinical experiences’
• Natural history poorly documented
• Stage B cancer is infrequently found because it infrequently or only transiently exists?
• Latency in tumors is not determined by size.
  – Franks, L. M., and Durh, M. B
  Lancet ii: 1037-1039, 1956

• 20% 5-year survival rate: large Stage B carcinomas treated only by transurethral resection.

• need for long followup in evaluating the possibility of cure
Stage B – prognosis and course

- Progressively diminishing 5, 10 and 15-year survival rates
- 25% of patients with clinical Stage B lesions may have regional
- Local recurrences or metastases or both
  - Have been reported 15 or more years after various forms of potentially curative or palliative therapy
- ‘Radical prostatectomy is usually performed on patients with small and low-grade lesions’
- End results in patients with high grade tumors are generally poor
- Majority of stage B cancers suitable for radical prostatectomy are of low grade
- Lesions 1 cm or more in diameter are usually of high grade and are often locally extensive

Stage B prognosis - good

- Natural and clinical selection for radical prostatectomy tumors
  - ‘Clinical’ by surgeon
  - ‘Natural’ by the low grade

- no difference in survival rates at 15 years between Stage A and Stage B lesions (nodules) treated conservatively
  - ? Different grade composition
  - ? ‘nodules have a more favorable prognosis then Fig 1 implies

Stage B prognosis - bad

- Pathologic study of total prostatectomy specimens often reveals the tumor to be more extensive locally than was clinically appreciated.

- up to 25% of patients with clinical Stage B lesions may have regional LN metastases
  - Castellino, R. A., JAMA 1973
  - Flocks, R et. al. Now alay 1959
  - Whitmore, W. F., Jr., and Mackenzie, A. R.:Cancer 1959
  - Whitmore, W. F., Jr., Hilaris, B., and Grabstald, H; J Urol 1972
Summary Stage B

1. Stage C or D cancers may not pass through Stage B

2. Small Stage B CaP may be low grade
   - Natural selection

3. Natural history Stage B poorly defined
   - Long evolution time
   - Circumstantial evidence from treatment

4. Malignant potential of some Stage B CaP
   - Mortality even after various treatments
   - Pathological evidence of local extension and LN positivity
Stage C

- Relatively common
  - 1/3 to 1/2 of ‘clinical experiences’
  - More common than Stage B
  - Produces symptoms

- Prognosis
  - 2 to 3 yrs life expectancy in the untreated patient
    - Obstructive symptoms
    - Classical DRE findings

- Pathology
  - Extensive local disease
  - Usually infiltrating prostate diffusely
  - SV and B/N invasion
  - Rectum and periprostatic soft tissues (capsular penetration)
  - “perineural lymphatic invasion” (actually perineural and not lymphatic)
Stage C

- LN involvement
  - Regional LN’s +ve in up to 60%
  - Correlation with
    • Size
    • Grade
  - ? Extra-pelvic nodes +ve more frequently than pelvic nodes

- “Selected lesions”
  - Stage C lesion not metastasized
  - Autopsy studies show that locally aggressive disease may occur without distant metastases
  - 20% (Arnheim study vide infra)
  - “Selected” lesion as there is a generally parallel relationship between size and local extension/metastases
  - “Natural selection could account for good results of
    • ‘super-radical surgery’
    • Combined ADT + Rad surgery
    • DXT

Stage C Summary

1. Not all ‘C’ pass through a ‘B’

2. Most ‘C’ lesions progress to ‘D’

3. Some don’t do this within the hosts lifetime
   - ‘Naturally selected’ tumors
Stage D

- About ½ of ‘clinical experiences’
- Majority of patient will have cancer specific mortality
- Survival of untreated patients about 1 yr

- Metastases
  - bone
  - Occasionally LN’s
    - Far more common than clinically recognized
  - Lung/liver uncommon but occur
  - Virtually no tissue/organ exempt
  - Factors determining patterns of spread unknown
Comment

• Tumor behavior

  1. Spontaneous regression not reported

  2. Growth rate
     • (in general) directly related to grade
     • Exceptions indicating other factors involved

  3. Local invasion and metastasis
     • A function of size
     • these two properties are not always linked
     • More common in high than low grade CaP

• HPE

  – Variations in anaplasia & architectural pattern between different areas
     • ‘discouraged efforts at grading’

  – Morphological heterogeneity
     • Varying responsiveness of diff, portions of the same CaP to ADT

  – ? Grade and/or growth rate remain uniform during the natural history – unknown

  – Tumor ploidy
     • Strong correlation with behavior
     • Potential useful parameter
     • Tvares et al, J Urol 1973
Grading

• no universal agreement on a specific system of grading (at that time)

• no attempt has been made to specify a system of grading although reference is made to low-grade and high grade tumors (at that time)
Limitations of the original stage progression schema (fig 1)

Fact: 17,000 deaths/yr from ‘C’ and ‘D’ CaP

Successful treatment of ‘B’ should by definition eliminate ‘C’ and ‘D’
  ? Re: proportion of ‘C’ and ‘D’ which have a ‘B’ phase
  Some ‘B’ lesions are already in ‘C’ or ‘D’
  ? Role of ‘natural’ and clinical ‘selection’ on the end-results of treatments

“Effective” treatment of ‘A’ would by definition eliminate ‘B’, ‘C’ and ‘D’ from that ‘segment’ of ‘A’ population but:
Many/most ‘A’ low-grade patients have a low threat of impaired life expectancy (over-treatment)
High grade ‘A’: significant mortality risk; clinical trials needed (remember no PSA)
Modified natural history schema

Fig. 2. Stage progression of prostatic cancer.
Modified stage-progression schema

- Stage A may
  - Go to ‘B’
  - Remain ‘A’ for the natural history of the host
  - Bypass ‘B’ and progress to ‘C’ or ‘D’ before the primary lesion is known

- Stage B may
  - Go to ‘C’
  - Remain ‘B’ for the host’s lifetime
  - Bypass ‘C’ and go directly to ‘D’

- Stage ‘C’ may
  - Remain a ‘C’
  - Progress to ‘D’

- Stage D
  - Extent/pattern of metastases not known
  - Size of lesion positively correlates with metastases but the two do not ‘parallel’ one another
The Host

Host influence on behavior of tumor not exactly known

1. Endocrine status of the host
   - Influences natural history if not genesis of the tumor
     • Based on biologic responsiveness of CaP’s to various forms of endocrine therapy
   - Evidence is wanting; other than CaP being rare in Eunuch’s

2. Host’s immunologic competence
   - Host – Tumor behavior relationship research ‘beginning’ but data not yet available

3. Age
   - Relationship controversial
   - ? More aggressive CaP in ‘younger’ hosts but some studies don’t support this
   - Progressively more common > 50yrs
   - Any consideration on management must consider life expectancy
   - Analysis of mortality causes in CaP shows significant mortality from ‘other causes’
Discussion (Summary)

1. Important aspects of the natural history of CaP remain incompletely defined
   – But enough data to reveal inadequacies of the model in Fig 1
   – Potential use of the more complex model in Fig 2

2. Behavior patterns in the total spectrum of CaP not well defined
   – A priori behavior pattern in the individual host

3. Difficult decision-making
   – Occurrence of CaP at a time of life showing reducing life expectancy
   – Multiple treatment choices
   – Natural history of the tumor
Discussion (Summary)

4. ‘Uncontrolled treatment regimens’
   - End results prone to varying interpretations due to variable/unpredictable natural history
   - Morally and ethically impossible to get data regarding the natural history of CaP in the ‘present era’
   - Controlled clinical trials needed to answer therapeutic questions

5. Appropriate treatment requirements
   - Avoiding ‘unnecessary’ and ‘ineffective’ treatments
   - Providing a qualitatively and quantitatively normal life
   - Need not necessarily mean a cure
   - Recognizing the ‘Human nature’ of care-givers
     - Good results are from treatment and bad results from the CaP ignoring the natural history factor in good and bad outcomes

6. Clinical judgment involves
   - Appropriate treatment for a particular CaP in an individual patient
Conclusion

1. Better means of defining the natural history of CaP

2. More sophisticated means of estimating life expectancy

3. Good data on the effects of treatment modalities on the quality & quantity of survival in patients with appropriately stratified tumors

4. “Inject more science into the extant art of CaP treatment, and substitute an era of cold fact for the present era of heated opinion”