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Equivocal Test Results and Prognostic Staging Uncertainties in the Evaluation of Patients with Cancer of the Prostate

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In the staging of cancer, equivocal test results may occur in subjectively evaluated imaging procedures whose interpretations raise the possibility of metastases but are too uncertain to rule in or rule out metastatic spread, and in tests whose repetitions in the same patient yield conflicting results about dissemination. We assessed the frequency and prognostic correlates of test results giving equivocal evidence of disseminated (Stage IV) disease in an inception cohort of 280 patients receiving initial treatment for prostatic cancer between 1973–76.

Among tests used for clinical staging, lymphangiograms (equivocal in 28 percent of tested patients), bone scans (equivocal in 25 percent of tested patients), and bone radiographs (equivocal in 20 percent of tested patients) most frequently yielded interpretations that equivocally suggested metastatic spread. Eighty-three (45 percent) of the 185 patients without clear-cut dissemination (Stages I–III) had at least one equivocal test result that suggested dissemination and that remained unresolved at the time of selection of therapy. Five-year survival (30 percent) for the 20 patients with local extracapsular spread (Stage III) and multiple equivocal results suggesting dissemination was identical to that for patients with clear-cut dissemination. In contrast, other patients with equivocal dissemination in Stages I–III had survival rates similar to those patients in the same stage and lacking equivocal dissemination.

Unresolved equivocal staging results frequently complicate management decisions for patients with prostatic cancer. Survival analyses aid these decisions by demonstrating that equivocal findings of dissemination are prognostically unimportant unless they are multiple and occur in the context of unequivocal extracapsular spread.

INTRODUCTION

Diagnostic tests are used in the management of solid tumors to determine how far the cancer has spread so that an appropriate therapy can be selected. Yet for the majority of laboratory tests used for staging of cancer, such as radiographs and radionuclide scans, the interpretation of complex patterns is required, and the interpretation is frequently "possibly positive" or "possibly negative." Moreover, even a test with results that are expressed on a dimensional scale may become equivocal if it yields both "normal" and "abnormal" results when performed on multiple occasions in the same patient. But despite the well-known occurrence of such equivocal results, and despite the unsettling effect of these results upon clinical decision making, little is known about their prevalence and their meaning.

In this paper we consider the prevalence and prognostic importance of equivocal results from tests used in the clinical staging of patients with prostatic cancer. Prostatic cancer was chosen for this analysis for two reasons. First, the staging of prostatic

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cancer relies to a great extent upon the results of non-invasive tests requiring subjective interpretations [1]. Second, patients with prostatic cancer tend to be elderly and to have associated conditions that may mimic cancer metastases [2]. For both these reasons, the staging dilemmas created by equivocal results should be as pronounced for prostatic cancer as for any cancer.

METHODS

Prognostic Staging of Prostatic Cancer

We classified patients according to the combined anatomic-serum prostatic acid phosphatase system used for the Veterans Administration Cooperative Urological Research Group (VACURG) studies of prostatic cancer [3]. In this system, patients with a normal value for prostatic acid phosphatase are placed in Stage I if the cancer is clinically unsuspected and if it is localized within the prostatic capsule, in Stage II if the cancer is localized within the capsule but is clinically suspected, and in Stage III if the cancer extends beyond the capsule but has not spread to the pelvic lymph nodes or other distant sites. Patients who have an elevated value for serum prostatic acid phosphatase or patients who have evidence of distant spread are placed in Stage IV. When staging is determined on the basis of routine clinical tests and biopsies short of an operative retroperitoneal dissection, the stage is referred to as the "clinical stage," and when staging is based additionally upon the results of a retroperitoneal dissection, the stage is referred to as a "surgical stage" [4]. Since relatively few patients receive complete surgical staging, our major focus in this paper is the influence of equivocal staging results upon clinical staging. Moreover, since not all patients receive complete clinical staging evaluations in routine practice, we gave patients a modified VACURG stage in two circumstances. First, for patients who received no serum acid phosphatase determinations, a clinical stage was determined on the basis of anatomic findings. Second, for patients who received total serum acid phosphatase determinations rather than prostatic serum acid phosphatase determinations, the stage was determined on the basis of the total serum acid phosphatase.

To avoid bias in determining the clinical stage, it is necessary to ascertain the extent of disease using only information accumulated up to a time in the clinical course that is comparable for each patient. This time, which we refer to as "zero-time," was defined as the inception of antineoplastic therapy for cancer of the prostate [5]. For the purposes of this study, "antineoplastic therapy" included radical prostatic surgery, radiotherapy, and hormonal therapy (estrogens or orchiectomy). When a decision was made to give such antineoplastic therapy, zero-time was taken as the first day of the therapy. If none of these therapies was given, but some non-radical surgical procedure (e.g., transurethral resection of the prostate) was administered as palliative therapy for cancer, the palliative therapy was considered the antineoplastic therapy. When therapy was intentionally withheld after a diagnosis of prostatic cancer was made, zero-time was taken as the date of the decision not to administer therapy. When no antineoplastic therapy was given but no clear anti-therapeutic decision was made, zero-time was the date of the histologic diagnosis of prostatic cancer.

Assembly of the Patient Population

The patient population for this study comprised all patients with a histologic diagnosis of prostatic cancer confirmed during life and with zero-time events occurring

at the Yale–New Haven Hospital (YNHH) between January 1, 1973, and December 31, 1976. The patient population was identified from three sources: the diagnostic registry of the YNHH medical record room, the Connecticut Tumor Registry, and the surgical pathology files of YNHH. The search yielded the names of 405 patients. After inspection of medical records and of data made available by the Connecticut Tumor Registry, 125 cases were excluded: 91 cases in which zero-time occurred at a hospital other than YNHH; 16 cases in which zero-time occurred at YNHH but not during the selection interval for the study; 12 cases for whom prostatic cancer was histologically confirmed; and six cases in which prostatic cancer was histologically confirmed only as a surprise diagnosis at necropsy. The remaining 280 patients are the subjects of this report.

Collection of the Data

Data from YNHH medical records, supplemented when necessary by information from the Connecticut Tumor Registry and from other sources such as other hospitals and personal physicians, were extracted on to a form specially constructed to provide a detailed account of the chronologic development and course of the illness, together with the formal reports of all pertinent laboratory tests used to evaluate the patients before therapy. Details of therapy as well as post-zero survival were recorded. Follow-up for the patient population terminated as of December 31, 1981. Complete follow-up at five years after zero-time was available for 267 of the patients: thirteen patients were lost to follow-up at post-zero intervals ranging from .01 year to 4.8 years. Data extraction was performed by a research assistant who was "blinded" to the nature of the research hypotheses.

Assessment of Equivocal Results

Because findings of distant metastases constitute the most important source of data arguing against radical antineoplastic therapy, the focus of this research was to evaluate the importance and the impact of laboratory results giving equivocal evidence for distant metastases. For test results expressed as qualitative descriptions (e.g., radiographic procedures), a test result was regarded as equivocal if the description of the result suggested that distant spread was possible, but could not be definitely established. Accordingly, such expressions as "atypical of, but not inconsistent with metastases," "equivocal evidence of metastases," "metastases cannot be ruled out," or statements supplemented by a qualification that further tests were required to resolve the diagnostic uncertainty were deemed equivocal. In contrast, statements indicating that metastases were either at least "probable," or "unlikely" were considered unequivocal. A test result was not considered equivocal if one anatomic area that was considered to be equivocal was accompanied by an additional area felt to represent metastatic spread. For each type of serum acid phosphatase (total and prostatic fraction) we considered the results to be equivocal if results both inside and outside of the range of normal values were obtained. All assessments about equivocal vs. non-equivocal results were made without knowledge of post-zero survival.

Evaluation of Equivocal Data in the Context of Multiple Test Results

When several tests were performed to evaluate the abnormality cited in an equivocal test result, it was necessary to make decisions about whether the composite of the test results remained equivocal for metastases. For equivocal results from tests which

permit visual evaluation of metastases, we considered the equivocal results as resolved to either metastasis or no metastasis, according to biopsy results for the corresponding area.

In lieu of histological evaluation, if the same imaging test was repeated and one or more of the results was regarded as equivocal for metastases, the composite of repeated tests was not considered equivocal unless *all* results were considered equivocal for metastases or unless the repeated testing yielded unequivocal interpretations that were conflicting (e.g., one result describing a definite metastasis and another result describing no metastasis in the same anatomic area). Although equivocal composites of repeated results could also result from conflicting unequivocal interpretations per se, such ensembles of repeated results were not observed in our series.

Without biopsy evidence, an equivocal result by one test that was designated as definite or probable metastasis by a different test was considered to be metastasis. When an equivocal metastasis shown in one test was not interpreted as a metastasis in a different test, we considered the composite interpretation for the anatomic area to be negative for metastasis if the normal result was derived from a test that was more sensitive in detecting metastases. In practice, this rule applied to the evaluation of retroperitoneal and pelvic nodal metastases, for which we regarded lymphangiography as more sensitive than intravenous pyelography, and to the evaluation of bone metastases, for which we considered radionuclide studies to be more sensitive than radiographs [6,7,8]. These rules for interpretating the results of multiple imaging tests should have yielded a conservative estimate of the prevalence of equivocal metastases, since it is not necessarily true that an equivocal result of one imaging test can be resolved by an additional, apparently clear-cut result obtained by repeating the same test or by performing different imaging tests.

For the evaluation of multiple acid phosphatase determinations, we regarded the serum prostatic acid phosphatase as the "gold standard" for determining serum acid phosphatase. When both total and prostatic acid phosphatase values were ascertained, we considered the serum acid phosphatase to be equivocal only if the serum prostatic acid phosphatase values were conflicting (inside and outside the range of normal values). When serum prostatic acid phosphatase values were not ascertained, we considered the serum acid phosphatase to be equivocal if the serum total acid phosphatase determinations were conflicting.

Prognostic Analyses of Equivocal Staging Results

Because patients infrequently received biopsies to evaluate anatomic regions containing equivocal evidence of metastases, and because possible dissemination cannot be directly refuted by a negative biopsy result when the evidence for dissemination consists of equivocally elevated values for serum acid phosphatase, we assessed the prognostic correlates of equivocal dissemination. In this analysis, we compared the survival of patients with and without equivocal results for disseminated cancer, controlling for the degree of spread evident from unequivocal staging data. We chose five-year survival as the target for survival analyses because the median survival for patients in our series was approximately five years, and because five-year survival rates commonly form the basis for prognostic and therapeutic evaluations of prostatic carcinoma. Differences in five-year survival rates were statistically appraised with chi-square tests, interpreted in a two-tail fashion, for 2×2 contingency tables in which

TABLE 1
Five-Year Survival Rates for the Study Population According to Clinical Stage

Clinical Stage[a]	Number in Stage[b]	Number (%) Surviving Five Years
I	50	37 (74)
II	72	51 (71)
III	54	28 (52)
IV	91	27 (30)
Total	267	143 (54)

[a]Defined according to criteria described in the text
[b]13 patients for whom five-year follow-up was incomplete are excluded.

each expected cell frequency was ≥ 5. For 2×2 tables in which smaller frequencies were expected, the Fisher exact test was employed.

RESULTS

Characteristics of the Study Population

All 280 patients had adenocarcinoma of the prostate. The median age for the study population was 70 years. Approximately equal numbers of patients met the eligibility requirements for the study during each of the four years constituting the selection interval. Five-year survival rates for the 267 patients with complete follow-up are given in Table 1. When patients were classified by clinical stage according to unequivocal staging results, five-year survival rates ranged from 74 percent in Stage I to 30 percent in Stage IV.

Prevalence of Equivocal Results Suggesting Metastatic Spread of Cancer

During the era in which the study population was treated, the basic tests used to detect distant metastases in clinical staging included serum acid phosphatase (total and prostatic fraction), radiographs and radionuclide scans for the evaluation of bone metastases, intravenous pyelography and lymphangiography to assess pelvic lymph node metastases, and chest radiographs to detect pulmonary metastases. Table 2 shows the number of patients receiving each of these basic tests and the number of patients having equivocal evidence for metastases according to each type of test result. In Table 2 test results that were equivocal by one type of test, but which were resolved by the results of different tests, are still considered equivocal, so that the overall frequency of equivocal results provided by each type of staging test can be appreciated. Strikingly high frequencies of equivocal results, occurring in excess of 20 percent of patients receiving the test, were found for bone scans, lymphangiograms, and bone radiographs. Equivocal results were less frequent, but not uncommon, for the remainder of the tests. Table 3 shows the staging ambiguities created by equivocal findings of metastatic spread that remained unresolved at zero-time. Eighty-three (30 percent) of the 280 patients had at least one equivocal result which was unresolved at zero-time and which created uncertainty as to whether the cancer was non-disseminated (Stages I–III) or disseminated (Stage IV). The proportion of patients having such equivocal evidence of dissemination increased with the clinical stage determined on the basis of unequivocal

TABLE 2
Frequency of Equivocal Evidence of Distant Cancer by Individual Staging Tests

Type of Test	Number of Patients Receiving Test	Number (%) of Patients Receiving Test in Whom Test Yielded Equivocal Results
Serum acid phosphatase[a] (total)	249	5 (2) [a]
Serum acid phosphatase (prostatic fraction)	240	19 (8)
Bone scan	119	30 (25)
Bone radiograph	256	52 (20)
Intravenous pyelogram	227	13 (6)
Lymphangiogram	53	15 (28)
Chest radiograph	259	29 (11)

[a]Equivocal values for total serum acid phosphatase and for prostatic serum acid phosphatase occurred when more than one result was obtained with a mixture of normal ($\leq$1.5 International Units for prostatic acid phosphatase and $\leq$8.0 International Units for total acid phosphatase) and abnormal results.

information, reaching a maximum of 63 percent of patients in whom all unequivocal data indicated Stage III disease. Among the 83 patients with unresolved ambiguities about dissemination at zero-time, the ambiguities were attributable to bone studies in 51 patients (61 percent), to lymph node studies in 22 patients (27 percent), to lung radiographs in 16 patients (19 percent), and to acid phosphatase determinations in 15 patients (18 percent). Ten of the patients in the series received biopsies to resolve these major uncertainties about distant metastases. One patient with equivocal bone studies received a bone biopsy which revealed no tumor, and nine patients with equivocal lymph node studies underwent subsequent surgical staging with retroperitoneal node exploration. Only one of these nine patients had demonstrable nodal metastases upon exploration.

Survival Correlates of Equivocal Metastatic Spread

Table 4 compares five-year survival rates for patients whose only evidence for metastatic spread was equivocal and for patients lacking such equivocal data. Within each clinical stage, defined on the basis of unequivocal staging data, no statistically significant differences in survival were apparent between patients having and patients

TABLE 3
Frequency of Equivocal Results Causing Ambiguity Between a Non-Disseminated and Disseminated Stage

Stage Based on Unequivocal Data	Number of Patients in Stage	Number (%) of Patients with Equivocal Dissemination
I	55	14 (25)
II	74	34 (46)
III	56	35 (63)
IV	95	—
Total	280	83 (30)

TABLE 4
Five-Year Survival According to Unequivocal Clinical Stage and to the Presence or Absence of Equivocal Dissemination

Clinical Stage Based on Unequivocal Results	Equivocal Dissemination	Proportion (%) Surviving Five Years[a]
I	No	29/39 (74)***
	Yes	8/11 (73)**
II	No	27/39 (69)***
	Yes	24/33 (73)***
III	No	13/21 (62)**
	Yes	15/33 (45)
IV	—[b]	27/91 (30)

**$p < .01$ ***$p < .001$ for the differences between five-year survival rate for the cited stage and that for Stage IV

[a]13 patients with incomplete follow-up at five years excluded from survival calculations

[b]Equivocal findings not considered since they did not affect assessment of whether dissemination was present or absent

lacking equivocal metastases. For patients in Stages I and II, the five-year survival rates were virtually identical, irrespective of equivocal dissemination, and the rates of survival in patients with equivocal dissemination were significantly higher than rates for patients having clear-cut dissemination (Stage IV). In contrast, the survival rate for patients in Stage III with equivocal dissemination was between the survival rate for Stage III patients lacking equivocal dissemination and the rate for Stage IV patients.

We also attempted to identify additional characteristics of equivocal dissemination that delineated a subgroup whose survival was similar to that for patients in Stage IV. Analysis of survival according to the particular site of the equivocal results (e.g., bone, lymph nodes, lungs) failed to identify such a subgroup. When we classified patients according to the number of sources of equivocal evidence for metastases—where a "source" is defined as an anatomic site with an equivocal metastasis or as an equivocal ensemble of values for serum acid phosphatase—patients in Stages I and II had virtually identical rates of survival regardless of the number of sources of evidence for equivocal metastases (Table 5). Similarly, patients in Stage III with a single source of evidence for equivocal dissemination had a survival rate similar to that of the patients in Stage III without any equivocal evidence of dissemination. However, patients in Stage III with more than one source of evidence for equivocal dissemination had a survival rate that was virtually identical to the survival rate of patients in Stage IV.

DISCUSSION

Our data demonstrate that equivocal results obtained in the course of the clinical staging of prostatic cancer create frequent ambiguities in assessing whether the cancer has become disseminated. Among the 185 patients in whom unequivocal staging results demonstrated no more than contiguous extracapsular extension, 83 (45 percent) had additional unresolved equivocal evidence of distant metastases at the time that antineoplastic therapy was selected.

Our results also demonstrate that since patients with equivocal staging data uncommonly receive definitive histologic evaluations of equivocal sites (ten patients in

TABLE 5
Five-Year Survival According to Unequivocal Clinical Stage and to the Presence and Number of Sources of Equivocal Dissemination

Clinical Stage Based on Unequivocal Results	Equivocal Dissemination	Number of Sources of Equivocal Dissemination[a]	Proportion (%) Surviving Five Years[b]
I	No	—	29/39 (74)
	Yes	1	3/5 (60)
	Yes	>1	5/6 (83)
II	No	—	27/39 (69)
	Yes	1	8/12 (75)
	Yes	>1	16/21 (76)
III	No	—	13/21 (62)
	Yes	1	9/13 (69)*
	Yes	>1	6/20 (30)
IV	—	—	27/91 (30)

*$p < .05$ for the difference in five-year survival rates between Stage III patients with one source of equivocal metastases and Stage III patients with >1 sources of equivocal metastases

[a]Defined in text

[b]13 patients with incomplete follow-up at five years are excluded from this analysis.

our series), correlations between such equivocal staging results and corresponding results from invasive tests are susceptible to giving a biased impression of the "true" diagnostic meaning of equivocal metastases. This infrequency of concurrent gold-standard testing made it desirable to evaluate the implications of equivocal metastases indirectly through the analysis of survival. Our analysis suggests that for patients in whom all unequivocal evidence suggests only intracapsular disease (Stages I and II), equivocal results for dissemination do not portend survival that differs quantitatively or statistically from survival associated with clearly negative results for dissemination. For patients in whom all unequivocal evidence indicates extracapsular but not distant spread (Stage III), a single source of evidence for dissemination also corresponds to a rate of survival that is no different from the rate for patients with negative evaluations, but multiple equivocalities predict a rate of survival that is identical to the rate for patients with clear-cut metastases.

Biological and Pragmatic Implications of Equivocal Metastatic Spread

Because isolated equivocal metastases are prognostically unimportant and multiple equivocal metastases portend poor survival in the setting of Stage III disease, it is tempting to speculate that any equivocal metastases in Stages I–II disease and isolated equivocal metastases in Stage III disease usually represent false-positive metastases, whereas multiple equivocal metastases in Stage III disease usually correspond to true dissemination. However, we do not believe that it is possible to deduce from survival analyses whether equivocal metastases in fact represent true dissemination. Several workers have established that the likelihood of inapparent dissemination increases as the extent of local spread progresses from Stages I to III [9,10,11]. In our series we observed correspondingly higher frequencies of both single and multiple equivocal metastases with increasing degrees of unequivocal local spread (Table 5). This

parallelism might suggest an alternative explanation for our findings: equivocal metastases may represent true metastases, and the prognostic correlates observed in our study merely reflect variations in the biological aggressiveness of the dissemination.

Despite our inability to draw conclusions about whether equivocal metastases represent true metastases, the relationships in our prognostic analyses have substantial practical importance. In the management of individual patients, knowledge of the prognostic implications of equivocal test results may assist selection of appropriate therapies and tests, and can provide reassurance to both physicians and patients. In addition, our data indicate that studies of therapies for prostatic cancer must arrange for appropriate classification and analysis of equivocal staging results to assure that the therapies are compared in patients with equivalent baseline prognoses and to enable extrapolation of the results to patients encountered in clinical practice.

Limitations of the Data

Since we depended upon routine readings of tests reported qualitatively in diagnostic test reports, it was impossible to discern which particular features of the results made them "equivocal." Moreover, there may be wide variations in the meaning that different physicians attach to the expressions which we used to define "equivocal." Thus, strictly speaking, our results pertain to equivocalities described in laboratory reports rather than equivocalities as interpreted by clinicians.

Another limitation arises from the changing technologies used to stage the patients. For the assessment of distant metastases, substantial changes have occurred in the assessment of lymph node metastases with the introduction of computerized tomography and transcutaneous thin needle biopsies [12]. Moreover, surgical staging has become more common, although it has not become universal because of the substantial morbidity and mortality associated with this form of staging [13]. On the other hand, methods for evaluation of bone metastases have not changed, and although more sensitive methods of assaying serum acid phosphatase have become available, they are not in widespread use. Since the problem of equivocal results for these newer tests has not been addressed, it is difficult to predict what impact these technological changes have had on the prevalence and prognostic correlates of equivocal dissemination. Nevertheless, because of the continued substantial reliance on non-invasive tests, it would be surprising if changing technologies have significantly diminished the problem of equivocal staging results in the management of prostatic cancer.

Future Research

Our study emphasizes the need for prospective research into the definition of which features make tests seem equivocal for metastases rather than clearly positive or negative. Because of the high frequency of equivocal metastases, it is also important to understand how clinicians incorporate equivocal data into management plans and why clinicians so rarely perform tests to resolve the equivocalities. With rapidly changing technologies, it is also important to evaluate the impact of newer techniques both in creating and in resolving ambiguities in staging. Finally, because it is unlikely that the problem of equivocal results in staging is limited to prostatic cancer, the problem of equivocal results in staging should be assessed for other cancers.

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